Global evidence on the potential of some Ugandan herbal medicines to mitigate antibiotic resistance: a systematic review and meta-analysis from 1996 to 2021

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Abstract

Background

Diarrheal and respiratory ailments are major causes of global deaths, and are mostly escalated by antibiotic-resistant bacteria (ARB), warranting novel therapies against ARB. In Uganda, plants like *C. pyrrhopappa, E. abyssinica*, *C. limon*, *M. foetida*, *C. flexuosus*, and *C. citrinus* are often used to treat diarrhea and/or cough. Some of these are reported to demonstrate antibacterial properties in some countries, but the evidence is limited due to fragmented studies. We evaluated global antibacterial research on these plants, to derive practical insights, able to stimulate new thinking and inform drug development.

Methods

Electronic articles on antibacterial effects of the named plants (with a special focus on efficacy against ARB), were identified from 14 electronic databases. The eligible articles were examined using Standard Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Sensitive ARB to the plant-extracts, Cochran's Q test, and heterogeneity were evaluated with MedCalcs software, using a random-effects model. Sources of heterogeneity were examined through sensitivity analysis, subgroup analysis, and meta-regression ($p < 0.05$). Publication bias was assessed using Begg's test and funnel plot asymmetry.

Results

Sixty-one articles met the inclusion criteria. Of these, 20 assessed the plants against 237 ARB *invitro*. *C. flexuosus* had the greatest efficacy (89.8%), while *C. pyrrhopappa* had the least (0.0%). Efficacy differences between *C. flexuosus* (the most efficacious species), and the rest of the plants were not significant except for *M. foetida* and *C. pyrrhopappa* (χ^2, $p < 0.05$). The multidrug-resistant strains (resistant to at least three drug-classes), with 100% sensitivity to plant extracts included *A. baumannii, S. aureus*, and *P. aeruginosa*. Heterogeneity was high ($I^2 = 86.85\%$), with no evidence of publication bias, hence suggesting robust results.

Conclusion

Some herbal medicines in Uganda have vast potential to avert the global antibacterial resistance menace. Their efficacy against globally circulating bacteria that are resistant to vital drugs, such as carbapenems, shows possible treatment success if these species are used in drug development. More research is desired, especially on the potential efficacy of these plants against the world's leading strains of resistant bacteria like *K. pneumoniae* and *E. coli*. Also, *in-vivo* studies are recommended due to their importance in drug discovery.

1.0 Background

Antimicrobial resistance (AMR), is rapidly escalating all over the world (1). Without urgent stewardship interventions, AMR is feared to become the next global pandemic (2). This medical challenge is associated with devastating consequences such as increased morbidity and mortality, prolonged hospital stays, and high cost of health care (3). At present, AMR is reported to cause over 700,000 global annual deaths, but the burden is projected to rise above 10 million deaths per annum by the year 2050 (4–6). The widespread inappropriate use of antibacterial drugs has made antibiotic resistance a dominant form of AMR globally (7). In most countries around the world, antibiotic resistance is already alarming in some bacteria, such as *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella spp*, *Acinetobacter baumannii*, and *Staphylococcus aureus* among others (5,7–14). The resistance of these strains to the existing conventional drugs, with no known reports of new medicines discovered in the last three decades, puts the world at risk of sliding back into the pre-antibiotic era (15).

Historically, medicinal plants are so linked to human treatment, that most of the drugs in current use were discovered following hints from plant species (16). As such, herbal medicines (HM) have saved humanity against the destruction of killer diseases, including deadly pandemics, across centuries (17–23). Globally, HM is used to manage numerous complications, ranging from emergencies like snakebites to chronic non-communicable diseases like cancers and diabetes. The HM is also used to manage infectious diseases like diarrhea and cough among others (24–28). Currently, the global prevalence of HM use ranges between 50% and 95% (29,30). The consumption rate is highest in Africa and Asia, both at 80% (31). In Africa, Ethiopia tops the list with a consumption rate of 90%, followed by Mali (75%), Rwanda (70%), Tanzania (60%), and Uganda (60%) (32). In Europe, Germany tops the list with 80%, followed by Canada (70%) and France (49%) (32).

Some of the global diarrheal and respiratory diseases that can be treated using HM may be caused by bacteria (33,34). In Uganda, cough and diarrhea are commonly managed using HM (35–39). The bacteria associated with these diseases include; *E. coli*, *S. pneumoniae*, *K pneumoniae*, and *S aureus*. The critical role of these bacteria in the global spread of antibiotic resistance has been reported (40–42). The use of some herbal medicines in the management of diseases potentially caused by these bacteria points to the possibility that such plants possess antibacterial potency; they can therefore provide clues for the discovery of new antibacterial drugs. Some of the plant species that are frequently used against cough and/or diarrhea in Uganda include; *Entada abyssinica*, *Citrus limon*, *Momordica foetida*, *Cymbopogon flexuosus*, *Callistemon citrinus*, and *Conyza pyrrhopappa* among others (35–37,39,43,44). Some of these plants have been reported to exhibit *in-vitro* bactericidal activity (45–50), but the evidence, especially against drug-resistant bacteria remains unclear since the studies are scattered across a few countries. This impedes the systematic consideration of such plants in the national and international healthcare systems, more so for the development of novel remedies that could avert the global antibiotic resistance threat. Here, recent studies on antibacterial efficacy on the named plant species were evaluated, to support the optimal use of HM as antibacterial resources that might replace or synergize with conventional drugs. The rationale was to consolidate the evidence and generate actionable insights, able to influence future research and drug discovery across the world.

2.0 Methods

Study area

This meta-analysis included all the 195 countries in the world, as described by the United Nations (51,52).

Protocol registration, and Journal article search strategy

The protocol which was used to write this meta-analysis was jointly developed by all the authors and submitted for registration to the International Prospective Register of Systematic Reviews (registration ID; PROSPERO-300460) (53). Appropriate key terms were used (initially separately and later combined with linking words like, “plus”, “and”, “or”, “with”), to search fourteen electronic databases for published articles relating to the antibacterial efficacy of the six selected plant species, *viz*; *Entada abyssinica*, *Citrus limon*, *Momordica foetida*, *Cymbopogon flexuosus*, *Callistemon citrinus*, and *Conyza pyrrhopappa* in all the 195 countries of the world (51,52). Primary studies that investigated the efficacy of the selected plants against bacterial pathogens, published between January 1996 to December 2021, were identified by searching the following databases; Google scholar, HerbMed, PubMed, Science Direct, Scifinder Scholar, Medline, EMBASE, African Journal Online (AJOL), Cochrane Library, International Pharmaceutical Abstracts, Commonwealth Agricultural Bureau Abstracts, and Biological Abstracts, Scopus, and Willy. The search was done by the three researchers (AW, SA, HMK) between 1st and 31st August 2021 using key terms related to the efficacy of the selected plants against bacterial pathogens.

The search terms used included; “Antibacterial efficacy of *Entada abyssinica*, *Citrus limon*, *Momordica foetida*, *Cymbopogon flexuosus*, *Callistemon citrinus*, and *Conyza pyrrhopappa*”, “Bactericidal effects of *Citrus limon*, *Momordica foetida*, *Entada abyssinica*, *Cymbopogon flexuosus*, *Callistemon citrinus*, and *Conyza pyrrhopappa*”, “Herbal medicine for diarrhea and cough”, “medicinal plants for diarrhea and cough”, “Drug resistant bacteria”, “Diarrhea”, “Cough”, “Asia”, “Africa”, “North America”, “Europe”, “South America”, “Uganda”, “Nigeria”, “Ethiopia”, “Egypt”, “Democratic Republic of Congo”, “Tanzania”, “South Africa”, “Kenya”, “Algeria”, “Sudan”, “Morocco”, “Angola”, “Mozambique”, “Ghana”, “Madagascar”, “Cameroon”, “Cote d'Ivoire”, “Niger”, “Burkina Faso”, “Mali”, “Malawi”, “Zambia”, “Senegal”, “Chad”, “Somalia”, “Zimbabwe”, “Guinea”, “Rwanda”, “Benin”, “Burundi”, “Tunisia”, “South Sudan”, “Togo”, “Sierra Leon”, “Libya”, “Congo”, “Liberia”, “Central African Republic”, “Mauritania”, “Eritrea”, “Namibia”, “Gambia”, “Botswana”, “Gabon”, “Lesotho”, “Guinea-Bissau”, “Equatorial Guinea”, “Mauritius”, “Eswatini”, “Djibouti”, “Comoros”, “Cabo Verde”, “Sao Tome and Principe”, “Seychelles”, “China”, “India”, “United States of America”, “Indonesia”, “Pakistan”, “Brazil”, “Bangladesh”, “Russia”, “Mexico”, “Japan”, “Philippines”, “Vietnam”, “Turkey”, “Iran”, “Germany”, “Thailand”, “United Kingdom”, “France”, “Italy”, “Myanmar”, “South Korea”, “Colombia”, “Spain”, “Argentina”, “Ukraine”, “Iraq”, “Afghanistan”, “Poland”, “Canada”, “Saud Arabia”, “Uzbekistan”, “Peru”, “Yemen”, “Nepal”, “Malaysia”, “Venezuela”, “North Korea”, “Australia”, “Siri Lanka”, “Romania”, “Chile”, “Kazakhstan”, “Guatemala”, “Ecuador”, “Netherlands”, “Cambodia”, “Bolivia”, “Belgium”, “Haiti”, “Cuba”, “Dominican Republic”, “Czech Republic”, “Greece”, “Jordan”, “Portugal”, “Azerbaijan”, “Sweden”, “Honduras”, “United Arab Emirates”, “Hungary”, “Tajikistan”, “Belarus”, “Austria”, “Papua New Guinea”, “Serbia”, “Israel”, “Switzerland”, “Laos”, “Paraguay”, “Bulgaria”, “Lebanon”, “Nicaragua”, “Kyrgyzstan”, “El Salvador”, “Turkmenistan”, “Singapore”, “Denmark”, “Finland”, “Slovakia”, “Norway”, “Oman”, “Palestine”, “Costa Rica”, “Ireland”, “New Zealand”, “Mauritania”, “Panama”, “Kuwait”, “Croatia”, “Moldova”, “Georgia”, “Uruguay”, “Bosnia and Herzegovina”, “Mongolia”, “Armenia”, “Jamaica”, “Qatar”, “Albania”, “Lithuania”, “North Macedonia”, “Slovenia”, “Latvia”, “Bahrain”, “Trinidad and Tobago”, “Estonia”, “Timor-Leste”, “Mauritius”, “Cyprus”, “Eswatini”, “Djibouti”, “Fiji”, “Guyana”, “Bhutan”, “Solomon Islands”, “Montenegro”, “Luxembourg”, “Suriname”, “Cabo Verde”, “Micronesia”, “Maldives”, “Malta”, “Brunei”, “Belize”, “Bahamas”, “Iceland”, “Vanuatu”, “Barbados”, “Sao Tome & Principe”, “Samoa”, “Saint Lucia”, “Kiribati”, “Grenada”, “St. Vincent & Grenadines”, “Tonga”, “Antigua and Barbuda”, “Andorra”, “Dominica”, “Marshall Islands”, “Saint Kitts & Nevis”, “Monaco”, “San Marina”, “Palau”, “Tuvalu”, and “Nauru”.

Between August 1st – 6th 2021, AW, SA, and HMK searched PubMed, HerbMed, and Google scholar using the aforementioned terms. We also carried out a snowball search to identify additional studies by searching the references of the publications that were eligible for full text review using Google scholar, to identify and screen the studies citing them. From August 8th -15th 2021, HMK and AW conducted a search of three data bases namely, Science Direct, Scifinder Scholar, and Medline using the aforesaid terms. As with the search from the Google scholar, HerbMed, and PubMed databases above, a snowball search to identify additional studies by searching the references of the publications eligible for full text review, was done. On August 17th – 25th 2021, HMK, AW and SA searched the Cochrane Library, EMBASE, and African Journal Online (AJOL) using the aforementioned search terms. Through the use of the same strategy of snowball search, we also identified the studies from the references of the eligible articles. Similar searches using the aforementioned strategies were conducted by HMK and AW in the International Pharmaceutical Abstracts, Commonwealth Agricultural Bureau Abstracts, Biological Abstracts, Scopus, and Willy libraries on 26th, 27th, 28th, 29th and 30th 2021 respectively. Finally, we updated the database search and the snowball on August 31st 2021 using the same search strategy but narrowing the search to only 2010 onwards (Table 1). The literature search was limited to articles published between January 1996 and August 2021 (across 2½ decades). The total output from all the databases was 24,767 citations.

Table 1
Databases consulted, date of the search and period covered

Data base	Date the search was done	Period covered
Google scholar, HerbMed, and PubMed	August 1st – 6th 2021	1996 to 2020
Science Direct, Scifinder Scholar, and Medline	August 8th – 15th 2021	1996 to 2021
EMBASE, African Journal Online (AJOL), Cochrane Library	August 17th – 25th 2021	1996 to 2020
International Pharmaceutical Abstracts, Commonwealth Agricultural Bureau Abstracts, Biological Abstracts, Scopus, and Willy	August 26th – 30th 2021	1996 to 2021
All databases	August 31st 2021	2010 to 2021
Key: EMBASE; Excerpta Medica Database, AJOL; African Journal Online.		

Selection criteria

Initially, all published literature related to the antibacterial efficacy of the six selected plants worldwide was collected irrespective of the quality, research design used, and the attributes of the herbal medicines, such as formulation, method of preparation, and dosage among others. The final selection and inclusion of the publications were done using standardized protocols (54). Studies that were included met the following conditions: they must have been full-text articles published in the English language; in peer-reviewed journals; published between 1996 and 2021; and must have subjected the extracts of each of the six plants (*Citrus limon*, *Momordica foetida*, *Cymbopogon flexuosus*, *Callistemon citrinus*, *Conyza pyrrhopappa*, and *Entada abyssinica*), either singly or in combination, to efficacy experiments against bacteria, with a particular focus on drug-resistant bacterial strains that are potentially associated with diarrhea and/or cough in any part of the world. The exclusion was based on: research conducted on other plants beside the six species of interest, research investigating efficacy against other microbial pathogens besides bacteria, review articles, and research published before January 1996.

Review process

Data extraction from the journal articles

Four reviewers (AW, SA, HMK, DA), extracted data independently from the 61 eligible articles. Each researcher individually entered the data in spreadsheets, capturing these attributes: plant species, first author, year of publication, country, disease(s) treated, plant organ(s) used as medicine, method of efficacy testing used, all microbes tested, drug-resistant bacterial strains tested, drug resistance profiles of bacteria tested, number of resistant bacterial strains tested (sample size), number of resistant bacteria that were sensitive to the plant extracts (prevalence of drug-resistant bacteria that were sensitive to the plant extracts), nature/source of the drug-resistant bacterial isolates tested, and overall conclusion about the potency of the plant(s). The reviewers compared their records weekly to remove any duplicates and reconcile their data through a consensus.

Quality assessment

Quality assessment for the eligible studies was independently performed by three reviewers (AW, SA, JES), and a quality score ranging from 0 to 10 was awarded to each study. Quality scoring was done based on three dimensions namely; sample collection, comparability, outcome, and statistical analysis, as described in guidelines of the New Castle-Ottawa scale (54). Studies with a score of 9–10 were described as very good, 7–8 as good study, 5–6 as satisfactory study, and less than 5 as unsatisfactory. Consistency in quality assessment of the articles was supervised by three co-authors not involved in the scoring, i.e. (JLN, AKT, and EKK).

Data analysis

The number of eligible studies, the species and combined frequencies of drug-resistant bacteria that were sensitive to the plant extracts, drug resistance phenotypes of the test bacterial isolates, plant species, and plant organs used as medicine were evaluated and presented using graphs and tables. A random-effects model was used to determine the prevalence of bacterial sensitivity to the plant extracts in the studies where heterogeneity was high; however, a fixed-effects model was used in cases where heterogeneity of the respective studies was low (55). The results were presented using forest plots. The prevalence of bacterial sensitivity to plant extracts was compared for association with different variables during the subgroup analysis and the *p*-values were determined at a 95% confidence interval (CI). Cochran's Q test and the I^2 statistic were evaluated to examine the heterogeneity of the eligible studies for our meta-analysis. Publication bias was examined using both Begg's test, and funnel plots. Funnel plots exhibit a lack of publication bias when they demonstrate symmetrical spread; while Begg's test uses Kendall's rank correlation coefficient between the meta-analysis effect size and the study weight (56). In Begg's test, $P > 0.05$ is an indicator of no evidence (absence) of a significant publication bias.

Sources of heterogeneity of the eligible studies were evaluated by conducting sensitivity analysis, subgroup analysis, and meta-regression. All the analyses were performed using statistical software called MedCalcs (https://www.medcalc.org/), and $p < 0.05$ was considered significant in all cases. Three authors (AW, JES, DA), were involved in the data analysis.

3.0 Results

Screening for eligible studies

A standard search strategy, i.e., the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), was used to screen for eligibility of the research articles published worldwide, on the antibacterial effects of the six plants, from 1996 to 2021 (57). Sixty-one research articles met our inclusion criteria. Of these, 20 studies examined the efficacy of the plant extracts on drug-resistant isolates. Those that used drug-susceptible bacteria were 41 (Fig. 1). The studies were found in 23 countries all around the world (Fig. 2).

3.9.2 Characteristics of eligible studies on the antibacterial-efficacy of C. limon, M. foetida, C. flexuosus, C. citrinus, C. pyrrhopappa, **and** E. abyssinica **from 1996 to 2021**

The characteristics of eligible studies are summarized (Table 2). Overall, 61 studies were eligible and thus included in this meta-analysis. Most of them (35, 57.4%), were published from the year 2007 to 2017, and the minority in 1996 to 2006 (5, 8.2%). The studies were found in 23 countries across all continents except North America; mostly in Africa and Asia (27, 44.3% each) (Fig. 2). India had the majority of the eligible studies (14, 23.0%), followed by Cameroon (6, 9.8%), and South Africa (5, 8.2%). Leaves (38, 62.3%), and fruits (19, 31.1%) were the commonest organs used; while water (41, 67.2%), and methanol (19, 31.1%), were the most frequently used solvents (Table 2). Except for the biofilm inhibition method used by Shehabeldine *et al*, 2020 in Egypt (58), all studies employed culture-based techniques like Disk Diffusion (36, 59.0%), and Agar Dilution (8, 13.1%), to deduce efficacy. Each study reported the overall antibacterial potency of plants (n = 61) as; high (54, 88.5%), moderate (2, 3.3%), and none (5, 8.2%) (Table 2). Diseases treated using the plants were related to the gastrointestinal tract (34 citations), mostly diarrhea (6, 8.0%), unspecified GIT illnesses (6, 8.0%), and stomachache (3, 3.9%); the respiratory tract (15 citations), and others (26 citations) (Table. 2).

The minority (N = 20, 32.8%), of the 61 eligible studies, used antibiotic-resistant bacteria (ARB) to examine the medicinal efficacy of plant extracts (45–50,58,65,83,86,91–93,95–97,103,104,106,109). These studies were found in 12 countries, mainly India (7, 11.5%), Kenya (2, 3.3%), and Cameroon (2, 3.3%); and they mostly examined bacteria that were resistant to aminoglycosides (9, 14.8%), and penicillin drugs (9, 14.8%), among others (Fig. 3). The total sample size of ARB tested was 237; from 15 genera and 19 species (Fig. 4). Most of these studies (10, 16.4%), adopted *S. aureus* and *P. aeruginosa* (6, 9.8%), while the minority used *S. flexneri* and *Acinetobacter* spp (1, 1.6% each). A study by Dharmik *et al*, 2016 in India had the largest sample size of ARB (70 strains) (96), while Mabhiza *et al* 2016 in Zimbabwe had the least (2 strains) (48). Ten studies obtained the ARB from the American Type Culture Collection (ATCC); four studies used clinical isolates; three used both clinical isolates and ATCC, while the isolates from hospital wastes and unspecified sources were each used by one study.

Antibacterial potency of C. limon, M. foetida, C. flexuosus, C. citrinus, C. pyrrhopappa, **and** E. abyssinica **globally from 1996 to 2021**

Among the 20 studies that examined drug resistant bacteria, 17 (85%) reported significant bactericidal efficacy of the plants. *C. flexuosus* exhibited the greatest potency rate to the ARB (88.9%), followed by *C. limon* (86.1%). *C. pyrrhopappa* showed the least (0.0%), while no eligible studies on ARB were found for *M. foetida* (Table. 3). A chi-square test revealed no significant difference in the % efficacy against ARB, between *C. flexuosus*, and *E. abyssinica, C. limon*, as well as *C. citrinus* ($p < 0.05$) (Table. 3). Though *S. aureus*, a gram-positive species, was the commonest ARB reported to be exceptionally sensitive to plant extracts (7 of 20 citations), the majority of the bacteria in this category were gram-negatives such as; *A. baumannii* (3 citations), *K. pneumoniae*, and *P. aeruginosa* (2 citations each) among others (Table. 3). The ARB species that were reported to exhibit absolute resistance to the plants (no sensitive strains observed), included *B. subtilis* (5 citations), *E. coli* (4 citations), and *S. epidermidis* (2 citations) among others (Fig. 4).

Table 3

Bactericidal effects of the selected plants against drug-resistant bacteria

Plant species	Total ARB tested; Source	Total ARB sensitive to plants, n (%)	Most sensitive ARB, No of citation reports (Type)	χ^2	*p*-value	References
Cymbopogon flexuosus	9; ATCC (n = 3), Clinical (n = 2), NS (n = 4)	8 (88.9%) (REF)	*A. baumannii*, 2 (GN)			(106,109)
Entada abyssinica	33; ATCC (n = 18), NCTC (n = 5), Clinical (n = 10)	13 (39.4%)	*K. pneumoniae*, 1 (GN) *S. typhi*, 1 (GN) *S. aureus*, 1 (GP)	4.752	0.0293	(45,46,65)
Momordica foetida	0 (n = 0)	NA	NA	NA	NA	None
Citrus limon	165; ATCC (n = 3), Clinical (n = 119), NS (n = 8), HW (n = 5)	142 (86.1%)	*S. aureus*, 4 (GP) *P. aeruginosa*, 2 (GN) *Acinetobacter* spp, 1 (GN) *S. flexneri*, 1 (GN) *V. cholerae*, 1 (GN) *S. typhi*, 1 (GN) *K. pneumoniae*, 1 (GN) *M. luteus*, 1 (GP) *E. faecalis*, 1 (GP)	0.0497	0.8235	(50,51,103,106, 108,85,89,91,93,95,98,100,101)
Conyza pyrrhopappa	11; ATCC (n = 11)	0 (0%)	None	NA	NA	(47)
Callistemon citrinus	19; ATCC (n = 19)	14 (73.7)	*S. aureus*, 2 (GP) *A. baumannii*, 1 (GN)	0.682	0.4088	(48,58,83)

Key: ARB; Antibiotic-resistant bacteria, χ^2; Chi-Square, ATCC; American Type Culture Collection, NCTC; NCTC = National Collection of Type Cultures (England), NA; Not Applicable, NS; Not Specified, HW; Hospital Wastes, No; Number, GN; Gram-negative, GP; Gram-positive

The highest efficacy rates against ARB were reported by four authors, namely; Adukwu *et al* 2016 in England, for *C. flexuosus* against *A. baumannii* (100%, 95% CI = 47.818 to 100.000%) (106); Mabhiza *et al*, 2016 in Zimbabwe for *C. citrinus* against *S. aureus* and *P. aeruginosa* (100%, 95% CI = 15.811 to 100.000%) (48); Liya *et al*, 2018 in Bangladesh for *C. limon* against *P. aeruginosa* (100%, 95% CI = 47.818 to 100.000%) (49), and AL-Oqaili *et al*, 2014 in Iraq for *C. limon* against *S. aureus* (100%, 88.430 to 100.000%) (91) (Fig. 5a). Bitchagno *et al*, 2019 in Cameroon reported the lowest efficacy rate against ARB (0.0%), triggered by *Conyza pyrrhopappa* against *S. aureus* (0.0%, 0.000 to 28. 491%) (47), as well as Rathour *et al*, 2020 (0.0%, 0.000 to 70.760%) for *C. limon* against *B. subtilis* in India (97) (Fig. 5a). A funnel plot was constructed to analyze the publication bias. Despite the significant heterogeneity ($p < 0.0001$), the funnel plot displayed symmetrical spread in terms of relative weight and effect size, hence demonstrating no evidence of significant publication bias (Fig. 5b). This was confirmed by the Begg's test at $p < 0.05$, i.e. (Kendall's Tau = -0.1151, $p = 0.4779$), implying that the results are reliable.

Meta-analysis of sub-groups

Since the eligible studies on the efficacy of the selected plants against ARB were highly heterogeneous, the analysis was sub-divided into six sub-groups which included; the plant species used, country of study, year of publication, source of bacterial isolates tested, plant organ used, and type of solvent used (Table 4). In each of the six categories, the results reported by only a single study were excluded from the subgroup meta-analysis. In all the categories adopted for sub-group meta-analysis, heterogeneity (I^2) declined, below the value ($I^2 = 86.85\%$, $p < 0.0001$) which was reported by the overall meta-analysis (Fig. 5a). At the country level, the highest and lowest proportions of drug-resistant bacteria that were sensitive to plant extracts were reported in India, 84.0% (95% CI = 75.6 to 90.4%) and Cameroon 15.8% (3.4 to 39.6%) respectively (Table 4). There was no evidence of publication bias in the countries (Cameroon, Kenya, and India) that were eligible for consideration in this category. The prevalence of ARB sensitivity to the plant extracts in Cameroon was significantly different from that in India ($p < 0.0028$), but not from that in Kenya ($p < 0.4572$) (Table 4).

About the variation of ARB sensitivity to the plant extracts by years of publication, the period between the year 1996 to 2017 (n = 11) registered the highest prevalence rate of sensitive bacteria (81.0%, 95% CI = 74.2 to 86.6%) as compared to 59.4% (95% CI = 46.9 to 71.1%) reported from 2018 to 2021 (n = 9). The proportions of sensitive bacteria were significantly different ($p < 0.0046$), during the two time periods (Table 4). Regarding the analysis by the source of ARB isolates used, the highest prevalence of sensitivity to plant extracts was reported in the bacteria of clinical origin (85.2%, 95% CI = 78.5 to 90.5%), and the lowest (57.4%, 95% CI = 47.2 to 67.2%) in the ARB obtained from the American Type Culture Collection (ATCC). The prevalence of sensitivity to plant extracts was significantly different between clinical isolates and those from ATCC ($p < 0.0001$), but not from those obtained from unspecified sources ($p = 0.0610$) (Table. 4).

The most effective plant organ was the fruit (89.7%, 95% CI = 83.6 to 94.1%), and the corresponding ARB sensitivity was significantly different from that triggered by the other plant organs such as the stem barks ($p < 0.0138$), and the leaves ($p < 0.0001$), as shown in Table 4. With regard to the type of solvent used, aqueous extracts elicited the greatest antibacterial activity (80.2%, 95% CI = 73.1 to 86.0%), while the least was 58.9% (95% CI = 45.0 to 71.9%) for ethanol. The largest proportion of ARB was sensitive to *C. flexuosus* extracts (88.9%, 95% CI = 51.8 to 99.7), and this was not significantly different from the rest of the plant species except *E. abyssinica* (39.4%, 95ci = 22.9 to 57.9%; $p < 0.0001$) (Table 4).

Table 4: Sub-group analysis of the proportions of drug-resistant bacteria that were sensitive to the extracts of selected plants

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Variable		Analysis			
	Number of studies	The proportion of sensitive bacteria, % (95%CI)	*P-value*	I^2 (%) (95% CI)	*P* het
Sensitive bacteria per plant species used					
C. flexuosus	2	88.9 (51.8 to 99.7) REF		77.8% (-2.52 to 92.03)	0.0823
C. limon	11	80.0 (73.1 to 85.8)	0.5387	60.0% (41.9 to 71.8)	< 0.0001
C. citrinus	3	73.7 (48.8 to 90.9)	0.0734	47.4% (-1.31 to 73.37)	0.0691
E. abyssinica	3	39.4 (22.9 to 57.9)	< 0.0001	21.2% (-12.38 to 48.88)	0.2407
Sensitive bacteria per country of study					
Cameroon	2	15.8 (3.4 to 39.6) REF		68.6% (10.76 to 86.31)	0.0162
India	7	84.0 (75.6 to 90.4)	0.0028	68.0% (43.1 to 80.30)	<0.0162
Kenya	2	40.0 (21.1 to 61.3)	0.4572	20.0% (-17.6 to 50.70)	0.3367
Sensitive bacteria per years of publication					
1996 to 2017	11	81.0 (74.2 to 86.6) REF		62.0% (43.80 to 73.50)	< 0.0001
2018 to 2021	9	59.4 (46.9 to 71.1)	0.0046	18.80% (-7.36 to 41.56)	0.1707
Sensitive bacteria per source of isolates used					
Clinical	7	85.2 (78.5 to 90.5) REF		70.4% (49.25 to 81.13)	<0.0001
ATCC	12	57.4 (47.2 to 67.2)	< 0.0001	14.8% (-4.75 to 32.83)	0.1432
Unspecified	3	58.3 (27.7 to 84.8)	0.0610	16.6% (-32.09 to 55.99)	0.5871
Sensitive bacteria per plant organ used					
Fruit	8	89.7 (83.6 to 94.1) REF		79.4% (54.54 to 88.26)	< 0.0001
Stem bark	3	66.7 (43.0 to 85.4)	0.0138	33.4% (-9.73 to 62.77)	0.1565
Leaf	8	58.9 (45.0 to 71.9)	< 0.0001	17.8% (-8.29 to 40.75)	0.1938
Unspecified	3	57.9 (33.5 to 79.7)	0.0025	15.8% (-25.32 to 50.37)	0.5079
Sensitive bacteria per solvent used					
Water/aqueous	12	80.2 (73.1 to 86.0) REF		60.4% (42.35 to 72.08)	< 0.0001
Methanol	5	59.2 (44.2 to 73.0)	0.0160	18.4% (-9.41 to 42.56)	0.2099
Ethanol	7	77.6 (63.4 to 88.3)	0.7262	55.2% (21.89 to 73.62)	0.0008

CI = Confidence Interval, het = Heterogeneity

Meta-regression

Meta-regression analysis was performed to examine the continuous variables of sample size (number of ARB tested), the years of publication, and the prevalence of ARB that showed sensitivity to the plant extracts. The results revealed that sample sizes were not significantly associated with years of publication (p = 0.658) and with the prevalence of ARB that were sensitive to plant extracts (p = 0.335) (Fig. 6).

The removal of one study which had the largest sample size (96), maintained high heterogeneity (I^2 = 84.59%, p < 0.0001), with no demonstrable evidence of publication bias as exhibited by the symmetrical nature of the funnel plot (Fig. 7b), and confirmed by Begg's test at p < 0.05, i.e. (Kendall's Tau = -0.03672, p = 0.8261).

Discussion

We report a total of sixty-one original scientific studies that investigated the antibacterial efficacy of *E. abyssinica, C. pyrrhopappa, M. foetida, C. citrinus, C. limon*, and *C. flexuosus* globally, and published the findings online from the year 1996 to 2021. The consideration of these plants in this meta-analysis was inspired by their high frequencies of a citation for the treatment of diarrhea and/or cough in Uganda (35–37,43,44,113–115). These species were also found to be used in the management of many more ailments across the world. Such ailments ranged from infectious diseases of all etiologies (parasites, viruses, bacteria, and fungi) (58,66,81,82,84), to non-communicable complications such as diabetes, hemorrhoids, and snakebites among others (27,45,67,82). This therapeutic heterogeneity is indicative of the enormous roles these plants can play in advancing global health and economic development.

The commonest organs used as medicine were the; leaves, fruits, and stem barks. The cautious use of these organs is commendable, because it somewhat supports conservative harvesting, hence permitting long-term survival of the plant species (35,116). The findings revealed that in most of the cases where *C. limon* was adopted as medicine, the fruit peels were used (87,88,90,94,98,99,101,102). These peelings are normally discarded as wastes (117). The citrus fruit peels contain bioactive compounds such as flavonoids, essential oils, pectin, and citric acid (118). The direct release of these wastes in the environment is hence associated with escalation of global environmental challenges, like; disease spread, bad odor, deterioration of water quality, and loss of lives among others (117). The use of *C. limon* fruit peels as medicine, or even in the development of other value-added products is hence a brilliant practice, given its eco-friendly and cost-effective nature.

In total, over 88% of the 61 eligible studies reported high antibacterial efficacy of the plant extracts, while 3.3% reported moderate bactericidal potency. Reports on antibacterial efficacy of plants were; high (54, 88.5%), moderate (2, 3.3%), and none (5, 8.2%) (Table 2). Of the 61 eligible studies, only 20 tested the plant extracts for potential efficacy against drug-resistant bacterial strains. The 20 studies were conducted in Asia, Africa, Europe, South America, and Australia; in only 13 (6.7%) of the 195 countries in the world (51,52). The total sample size of "237" drug-resistant bacteria tested is considerably small for worldwide coverage. The studies were highly heterogeneous (I^2 = 86.85%, p < 0.0001). Though heterogeneity declined for all the sub-group meta-analyses, there was no demonstrable evidence of publication bias. The quantitative synthesis of these 20 studies in the current meta-analysis, could inform the design of plant-based strategies, able to stall the global antibiotic resistance menace.

Despite being among the most frequently tested ARB, *B. sabtilis* and *E. coli* turned out to be the most resistant to the plant extracts. Other strains in this category were *P. aeruginosa*, *K. pnuemoniae,* and *S. epidermidis*. This is worrying because most of these bacteria, especially; *P. aeruginosa*, *K. pnuemoniae,* and *E. coli*, are among the critically resistant pathogens which the World Health Organization has identified, that need urgent drug discoveries, and prioritization in AMR research (40). Therefore, there is a necessity for more efficacy experiments on these bacteria, using a wider variety of medicinal plant species. Furthermore, some ARB that have commonly been implicated in respiratory and/or diarrheal disease outbreaks in different parts of the world, such as *S. pneumoniae* (119–123), *Salmonella* spp, and *Shigella* spp (124–128), were conspicuously missing among the strains investigated by the eligible studies. This points to the need to refocus the selection of ARB strains that are prioritized in studies of this nature all over the world.

Most of the tested isolates were resistant to Penicillins and aminoglycosides, while the rest of the antibacterial drug classes were grossly underrepresented. Interestingly, aqueous extracts possessed the greatest efficacy against multidrug-resistant bacteria, as compared to the extracts of other solvents. The implication is that water was possibly the most effective solvent for the bactericidal active ingredients present in the tested plant species. This is advantageous to the communities because water is generally cheaper, more readily available, and easier to handle and store, compared to other solvents like ethanol. In addition, unlike ethanol, pure water does not possess antimicrobial properties which would otherwise cofound the observed antibacterial efficacy of the plants. On the other hand, water being an ionic solvent does not readily dissolve most organic, active Phyto-ingredients (129), yet such compounds might have augmented the reported efficacy of plants against ARB. The organic bioactive phytochemicals with perceived antibacterial properties, that may be more readily extracted using organic solvents include terpenoids, flavonoids, saponins, and essential oils among others (130).

Most of the studies were conducted between 1996 and 2017, as compared to those conducted from 2018 to 2021. Consequently, the efficacy of the plant extracts against ARB was highest between 1996 and 2017, but it later declined significantly between 2018 and 2021 (p = 0.0046). The factors that could explain this temporal decline remain unknown, however, it might partly be attributed to, (i) differences in the bacterial species tested during the two periods; (ii) the potential evolution of herbal drug resistance, of which a similar phenomenon was reported earlier by Vadhana *et al*, 2015 in India (15); (iii) variation in ecological parameters of the places where most eligible studies occurred during the two time periods. The differences in geographical and ecological features like temperature, rainfall, and soil factors, have also been reported to affect the biochemistry of plants and the associated biological functions such as medicinal efficacy (131–135). There is need for more research to resolve these disparities still.

India had the greatest number of studies that tested plant extracts against drug-resistant bacterial strains, followed by Kenya and Cameroon. Unfortunately, no such studies were found in the countries which the World Health Organization has reported as the world's leading consumers of herbal medicine; such as Ethiopia, Germany, Mali, Canada, Rwanda, Uganda, and Tanzania, among others. Though minimal antibacterial studies on the selected plants were found in some of these countries, like; Uganda (71–73), and Ethiopia (68–70), the bacteria used in these investigations were of unknown drug resistance traits. This deters the application of findings from such studies in the discovery and development of novel drugs suited for multidrug-resistant pathogens.

Gram-negative drug-resistant bacteria such as *P. aeruginosa* and *Acinetobacter* spp were more frequently utilized by the eligible studies, and these bacteria made a great majority of those sensitive to the plant extracts. This is contrary to the findings of an earlier systematic review (136), which reported gram-positive bacteria such as *Streptococcus mutans* and *Lactobacillus* spp as the most frequently tested isolates. The unbalanced choice of test ARB strains in such studies is inappropriate, because the current global increase in the emergence of medically important ARB includes both gram positives and gram negatives (137,138). Though earlier studies reported that the extracts of other plant species such as *Hypericum roeperianum*, *Cremaspora trifloral*, and *Ochna species*, were more efficacious on gram-negative bacteria than the gram-positives, the differences were not statistically significant (139,140). Therefore, subsequent studies that aim at curbing the ARB burden by using plant extracts could need to address the two bacterial categories to ascertain potential efficacy contrasts. The potential differences in the sensitivity of gram-negative and gram-positive bacteria to antimicrobial compounds may to some extent be attributed to the dissimilarity in their cell wall structure. The gram-positive bacterial cell wall contains 70–100 layers of peptidoglycans (139). Peptidoglycan comprises two polysaccharides, N-acetyl-muramic acid and N-acetyl-glucosamine cross-linked by peptide side chains and cross bridges. This structural design is certainly not the absolute explanation for drug resistance or susceptibility levels in these bacteria, but other mechanisms possibly play a role. For the case of gram-negative bacteria, resistance against antimicrobial agents such as penicillin drugs is often attributed to the secretion of the Lactamase enzyme in the periplasmic space located between the cytoplasmic membrane and the thin outer membrane (141).

In the current meta-analysis, a great majority of the studies used standard strains, especially those from the American Type Culture Collection (ATCC). The fact that the emergence of new antibacterial resistance traits is frequently linked to unsuitable human and/or agricultural use of antibiotics (142–144), points to the need for prioritization of clinical and/or veterinary bacterial strains in subsequent studies on this subject.

Limitations of the study

Despite numerous antibacterial-efficacy studies on the plants considered in this meta-analysis, those that performed experiments on drug-resistant bacteria were minimal. The study was further limited by, (i) the small number of countries with eligible studies focusing on ARB (only 12 out of the 195 countries possessed studies that used drug-resistant bacteria), and (ii) the language (only English studies were available online among the eligible studies).

Conclusions

Some herbal medicines in Uganda have vast potential to avert the global antibiotic resistance threat because they possess considerable efficacy against drug-resistant bacteria circulating globally. *Cymbopogon flexuosus* was the most promising species regarding medicinal potency against antibiotic-resistant bacteria; but it was not significantly different from *Entada abyssinica*, *Citrus limon*, *Momordica foetida*, and *Callistemon citrinus*. We recommend, (i) More research, especially on the world's critical strains of resistant bacteria like *K. pneumoniae* and *E. coli*; and (ii) *In-vivo* studies, to fill the evidence gaps and potentially pave way for the industrial phase of herbal drug development.

Abbreviations

ARB; Antibiotic-Resistant Bacteria, PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-analyses, ATCC; American Type Culture Collection, CCUG; Culture Collection of the University of Gothenburg, CCIC; China Center of Industrial Culture Collection.

Declarations

Ethical Approval and Consent to participate

Since our study units in this research were already published articles in the public domain, the study did not require any ethical approvals and clearance.

Consent for publication

Not applicable

Availability of data and materials

Datasets generated and analyzed during this meta-analysis are available from the corresponding author on request.

Competing interests

The authors declared no competing interests in this study.

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Authors' contributions

AW, AKT, and SA conceived the research idea, participated in designing the study, searching and reviewing the research articles, data analysis, and drafting of the manuscript. HMK, JES and DA participated in searching and reviewing the research articles, data analysis, and drafting of the manuscript. EKK and JLN performed the overall supervision of this meta-analysis and manuscript writing. All authors read and approved the final manuscript.

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Table 2

Table 2 is available in the Supplemental Files section

Figures

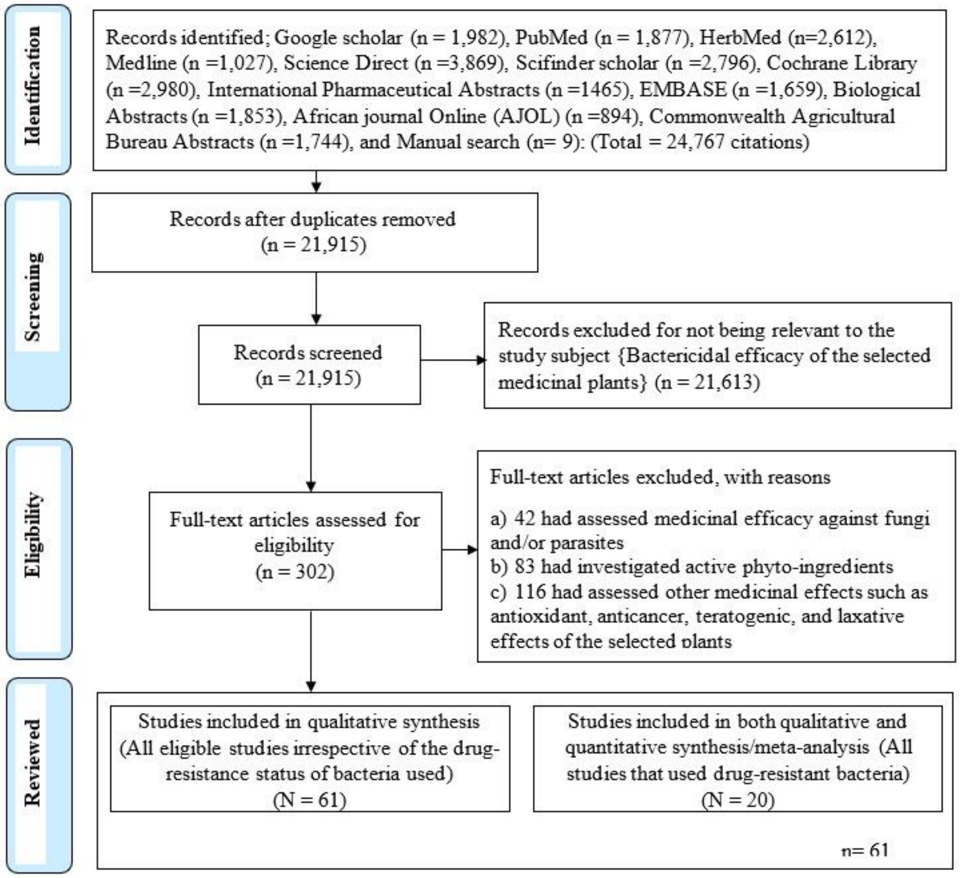

Figure 1

Flow chart for eligibility screening of the research articles related to the bactericidal-efficacy of E. *abyssinica, C. pyrrhopappa, M. foetida, C. citrinus, C. limon*, and *C. flexuosus* globally from 1996 t0 2021

Figure 2

Location of studies on antibacterial efficacy of *C. limon*, *M. foetida*, *C. flexuosus*, *C. citrinus*, *C. pyrrhopappa*, and *E. abyssinica*: Numbers in rectangular box = total of studies; Numbers in circles = number of studies that used drug-resistant bacteria.

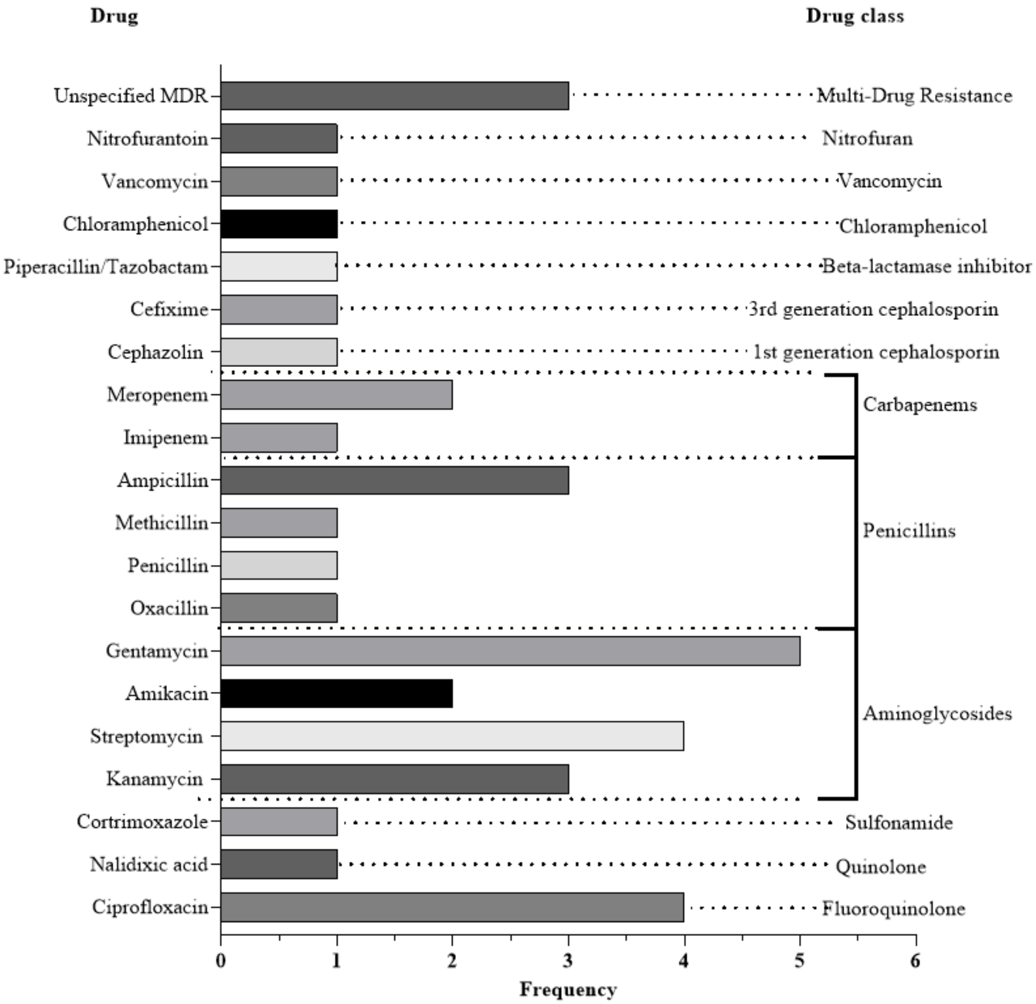

Figure 3

Drug-resistance profiles of bacteria subjected to efficacy tests using extracts of *C. limon*, *M. foetida*, *C. flexuosus*, *C. citrinus*, *C. pyrrhopappa*, and *E. abyssinica*

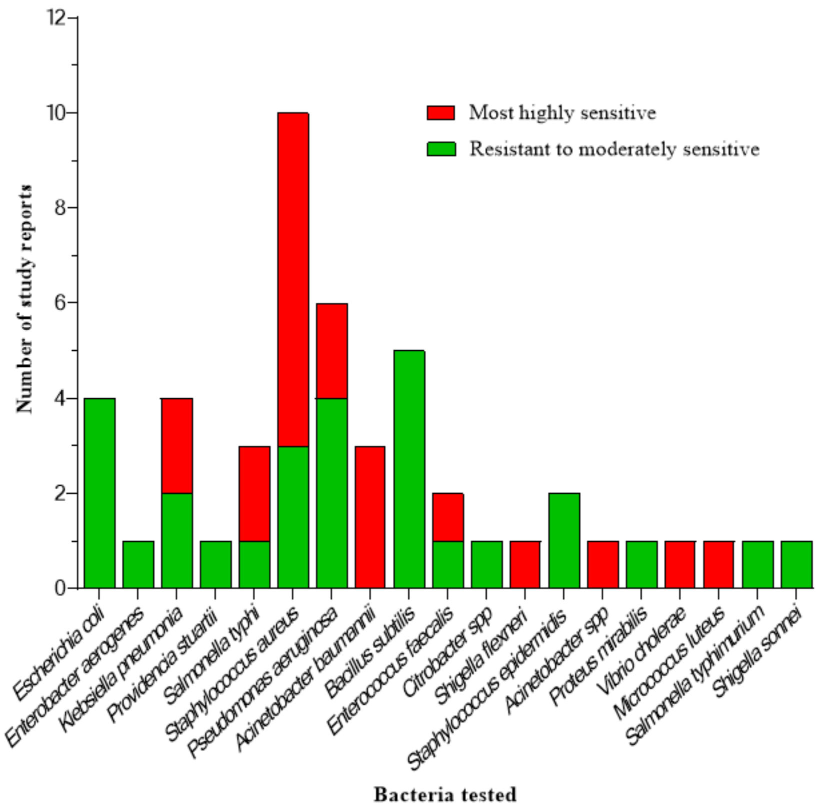

Figure 4

Species of drug-resistant bacteria that were tested for sensitivity to extracts of *C. limon*, *M. foetida*, *C. flexuosus*, *C. citrinus*, *C. pyrrhopappa*, and *E. abyssinica*

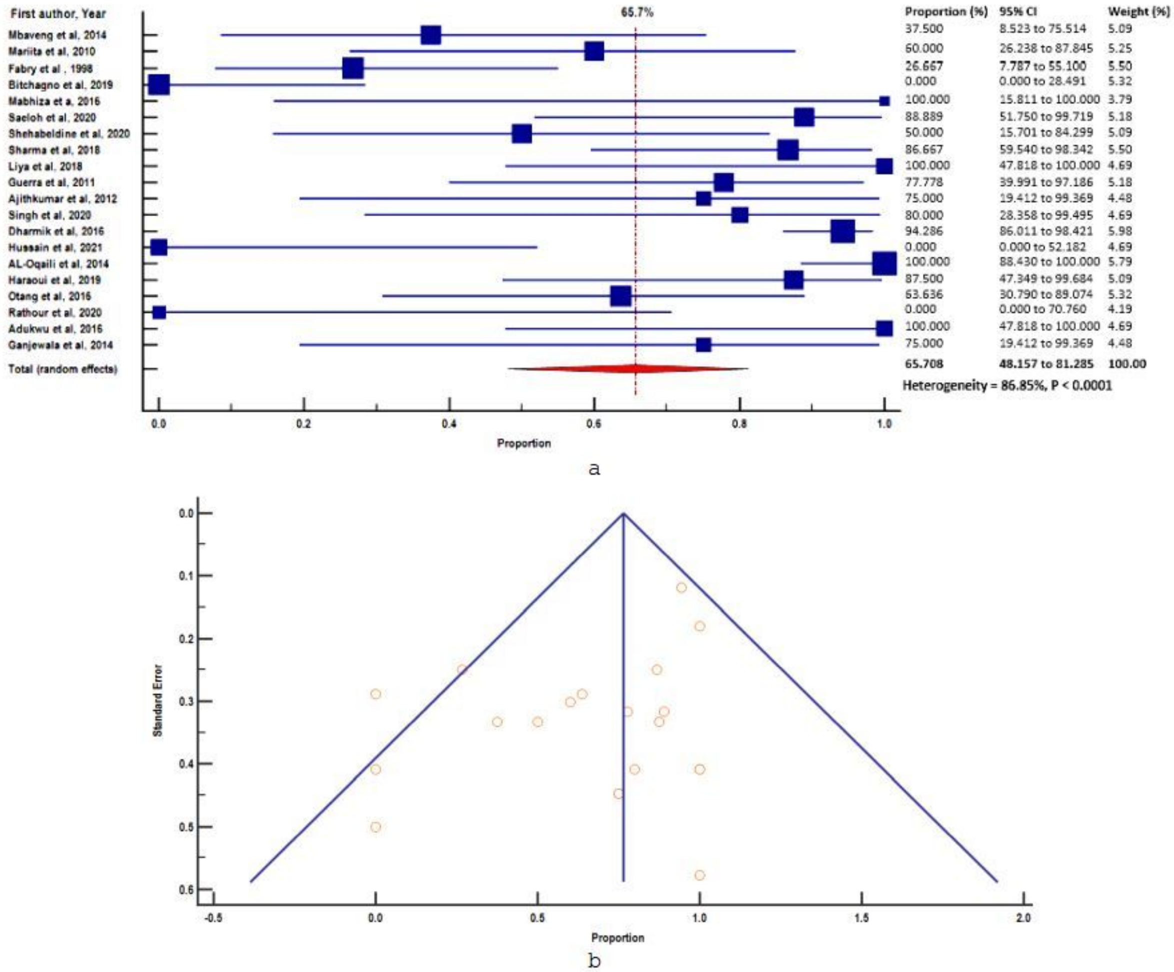

Figure 5

(a): Prevalence estimates of the drug-resistant bacteria that were sensitive to the extracts of *C. limon*, *M. foetida*, *C. flexuosus*, *C. citrinus*, *C. pyrrhopappa*, and *E. abyssinica*, using a random-effects model.

(b): Bias assessment plot of studies that reported the efficacy of *C. limon*, *M. foetida*, *C. flexuosus*, *C. citrinus*, *C. pyrrhopappa*, and *E. abyssinica* against drug-resistant bacteria

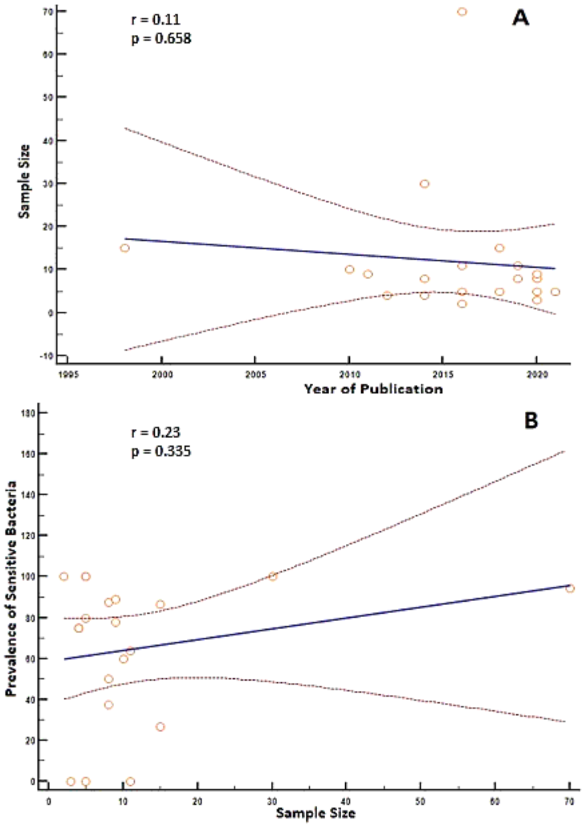

Figure 6

Meta-regression analysis by sample size and years of publication (A), and by the prevalence of drug-resistant bacteria that were sensitive to the extracts of the six selected plants (B)

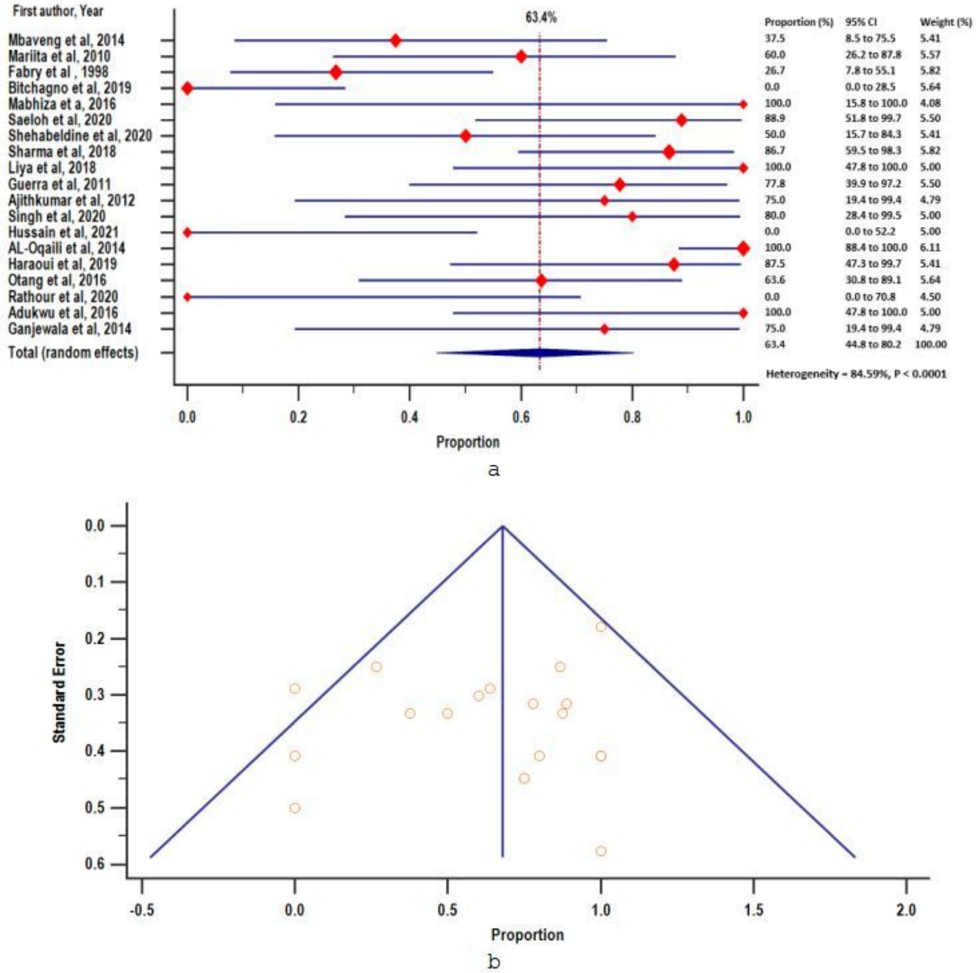

Figure 7

a: Forest plot showing sensitivity analysis of the proportions of drug-resistant bacteria that were sensitive to the selected medicinal plants globally from 1996 to 2021, using a random-effects model.

b: Bias assessment plot of studies that reported the medicinal efficacy of selected plants against drug-resistant bacterial globally from 1996 to 2021.

Supplementary Files

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- Table2.docx