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Review article

Antibacterial activity of medicinal plants against ESKAPE: An update

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ABSTRACT

Antibiotic resistance has emerged as a threat to global health, food security, and development today. Antibiotic resistance can occur naturally but mainly due to misuse or overuse of antibiotics, which results in recalcitrant infections and Antimicrobial Resistance (AMR) among bacterial pathogens.

These mainly include the MDR strains (multi-drug resistant) of ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species). These bacterial pathogens have the potential to "escape" antibiotics and other traditional therapies. These bacterial pathogens are responsible for the major cases of Hospital-Acquired Infections (HAI) globally. ESKAPE Pathogens have been placed in the list of 12 bacteria by World Health Organisation (WHO), against which development of new antibiotics is vital. It not only results in prolonged hospital stays but also higher medical costs and higher mortality. Therefore, new antimicrobials need to be developed to battle the rapidly evolving pathogens. Plants are known to synthesize an array of secondary metabolites referred as phytochemicals that have disease prevention properties. Potential efficacy and minimum to no side effects are the key advantages of plant-derived products, making them suitable choices for medical treatments. Hence, this review attempts to highlight and discuss the application of plant-derived compounds and extracts against ESKAPE Pathogens.

1. Introduction

Many new antibiotics have been produced in the last four decades by pharmacological industries, and resistance by microorganisms to these drugs have been accelerated due to impetuous use of antibiotics. A report submitted to the United Nations in 2019, expects that infections caused by antibiotic resistant bacteria would cause 10 million deaths per annum and an economic crisis just like the 2008–2009 global financial collapse by 2050 [1]. Antimicrobial Resistance (AMR) can be conferred in bacteria via genetic mutation and Horizontal Gene Transfer (HGT) through chromosomes, plasmids, transposons and other mobile genetic elements [2]. AMR is a natural prevalence that is connected to a rise in "mortality, morbidity and economic burden" of nations worldwide [3]. Till date, there have been no evidences for effective antimicrobial compounds against the AMR bacteria caused infections [4, 5]. Thus, there is an immediate need for novel treatment methods targeting the issues caused by AMR.

Global priority pathogen list (PPL) was released by the World Health Organization (WHO) in 2016 to guide the researcher in discovery, and development of new antibiotics [6]. In this sequence the five-year NAP (National Action Plan) for the control of AMR (2017–2021) that was developed by the Indian Ministry of Health and Family Welfare in April 2017, was presented at the 70th World Health Assembly (WHA) held at Geneva in May 2017. It geared towards increasing awareness, surveillance and investment in research to combat the spread of AMR. However, there are many hurdles to overcome such as lack of funding, strict implementation and ethical commercial practices [7].

The prime class of opportunistic pathogens that are a universal threat to humankind are entitled as 'ESKAPE' (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.) as they are known to "escape" antibiotics and other traditional treatments [8]. ***This imminent health threat has activated the development of novel antimicrobial therapies, where better care of the patient and improved governance happens to be the requirement of the hour.***

The European Center for Disease Control (ECDC) and the Center for Disease Control (CDC) in USA gave the subsequent standardized definitions for multidrug resistant (MDR), extensively drug resistant (XDR),

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and pan drug resistant (PDR) bacteria: multidrug resistance (MDR) is defined as acquired non-susceptibility to a minimum of one agent in three or more antimicrobial categories. Extensively drug resistance (XDR) is defined as non-susceptibility to a minimum of one agent altogether but two or fewer antimicrobial categories (i.e., bacterial isolates remain vulnerable to just one or two antimicrobial categories). The non-susceptibility to all agents in all antimicrobial categories is called Pan Drug Resistance (PDR) [9].

For a long period of time people of India have been using many plant species as traditional medicines for a variety of ailments, including treatment of infectious diseases [10]. Discovery of novel drugs can be accomplished with the use of plants extracts, which is a reservoir of broad-spectrum secondary metabolites [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23]. Plants have proven themselves to be effective in preventing and treating the toxicity induced by other toxins or drugs. The efficacy of plant extracts and their derivatives in terms of their antimicrobial activities have paved the way for the exploration of new and effective treatments against MDR-ESKAPE. This review targets the use of such diverse traditional medicinal plants, which are capable of being used effectively as anti-ESKAPE drugs.

2. ESKAPE: a threat to public health

Antimicrobial resistance represents a global threat to human health. AMR is found in both Gram-positive and Gram-negative strains of bacteria. India's AMR rates are alarmingly high when compared to other nations. For instance, the percentage of clinical isolates of MRSA (Methicillin Resistant *Staphylococcus aureus*) nearly doubled over a period of just 6 years (2008–2014) from 29% to 47%. Other nations reported a decline in the percentage of MRSA as a result of extensive antibiotic stewardship and awareness practices [24]. The Carbapenem resistant *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *E. faecium,* Methicillin resistant, vancomycin intermediate/resistant *S. aureus* and other members of *Enterobacteriaceae* are [25] known as "superbugs" or ESKAPE. The above mentioned pathogens are responsible for lethal infections amongst critically ill and immunocompromised individuals as a result of lack of treatment [26]. Thus the consequences of ESKAPE could be devastating.

2.1. Enterococcus faecium (E. faecium)

E. faecium is a Gram-positive spherical (cocci) bacterium that occurs in pairs or chains, commonly involved in nosocomial infections amongst immunocompromised patients. β-lactam antibiotics such as penicillin and other last resort antibiotics have no effect on *E. faecium.* [27]. Resistance to Vancomycin, in particular, has led to a significant increase in Vancomycin resistant Enterococci (VRE) strains [27]. A gene of VRE encodes for a putative Enterococcal Surface Protein that aids in the formation of thicker biofilms [28]. Infections caused by it include urinary tract infections (UTI), bacteremia, intra-abdominal infections, and endocarditis. Enterococci are now the third most common nosocomial pathogen that caused 14% of hospital-acquired infections in the United States between 2011 and 2014, compared to 11% in 2007. Aside from nosocomial infections, enterococci are responsible for 5–20% of community-acquired endocarditis [29].

2.2. Staphylococcus aureus (S. aureus)

S. aureus is a Gram-positive spherical (coccus) bacteria that's commonly found in human skin microbiota and is typically harmful only in immunocompromised individuals. Being a part of normal microflora of skin, it usually causes infections when it invades the regions that it typically does not inhabit, such as bruises and wounds. *S. aureus* is capable of causing infections on medical implants and forming biofilms that poses a challenge in antibiotics mediated treatment. Moreover, approximately 25% of *S. aureus* strains secrete the TSST-1 exotoxin which is responsible for causing toxic shock syndrome. Methicillin-resistant *S. aureus* (MRSA), a special strain of *S. aureus,* is known to have evolved resistance against β-lactam antibiotics [27]. They confer resistance to β-lactam antibiotics by the expression of *mecA* that encodes a low penicillin binding affinity protein (PBP 2a) [30]. They are associated with an increasing number of health care related infections, particularly seen in infective endocarditis and prosthetic device infections. Also, strains with particular virulence factors and resistance to β-lactam antibiotics are some of the major causes of community-associated skin and soft tissue infections [31]. Certain *S. aureus* strains have been identified as resistant to Vancomycin-intermediate owing to the overuse of the drug for the treatment of *S. aureus* [32].

2.3. Klebsiella pneumoniae (K. pneumoniae)

K. pneumoniae is a Gram-negative rod-shaped (bacillus). According to Shiri et al., about one-third of all Gram negative infections such as UTI, Septicemia, Surgical Wound Infections, Cystitis, Pneumonia and endocarditis can be attributed to this organism. It is also known to cause necrotizing pneumonia, pyogenic liver abscesses and endogenous endophthalmitis. *K. pneumoniae* infections account for its high mortality rates, extended hospitalization, coupled with expensive treatments. A significant rise in the occurrence of multidrug-resistant (MDR) and extremely drug-resistant (XDR) pathogens of the *Enterobacteriaceae* group is posing a global economic threat nowadays. Certain strains have been classified as carbapenem-resistant *K. pneumoniae* (CRKP), because of the development of β-lactamases, which makes them resistant to commonly used antibiotics, such as carbapenems. There are only a few antibiotics in development which will treat infection [27, 33, 34].

2.4. Acinetobacter baumannii (A. baumannii)

A. baumannii is a Gram-negative, strictly aerobic, non-fermenting, non-fastidious, catalase-positive, oxidase-negative coccobacillus or pleomorphic bacterium that is responsible for almost 2 per cent of all nosocomial infections in the US and Europe and twice as high in Asia and the Middle East. 45% of all isolates of this deadly, opportunistic pathogen around the world have been reported as Multidrug Resistant (MDR). The most usual types of infections caused by this bacterium are Central line-associated bloodstream infections and ventilator-associated pneumonia. The ability to resist desiccation, form biofilms and presence of fundamental virulence factors, such as surface adhesins, glycoconjugates and secretion systems help *A. baumannii* to thrive in this environment [35].

2.5. Pseudomonas aeruginosa (P. aeruginosa)

P. aeruginosa is a Gram-negative, gamma-proteobacterium possessing a lowly permeable outer membrane and multiple transport systems that provide it innate resistance to many antibiotics. It also employs a variety of mechanisms such as alterations in porin channels, efflux pumps, target modifications, and β-lactamases that allow it to develop resistance to antimicrobial agents [36]. Cystic fibrosis (CF) patients are at a particularly high risk of acquiring this infection because of its ability to form biofilms and persister cells in the lungs [37]. Point mutations on DNA gyrase/Topoisomerase IV provide immense resistance against Fluoroquinolones to *P. aeruginosa* [38].

2.6. Enterobacter spp.

***Enterobacter* spp.** are Gram-negative, facultatively anaerobic, rod-shaped bacteria that are members of the *Enterobacteriaceae* family. Immunocompromised patients such as those on mechanical ventilation or implanted with IMD are most susceptible to urinary or respiratory tract infections by this pathogen. *E. cloacae* is the most commonly found species in patients causing 4%–5% of all nosocomial bacteraemia,

Table 1. Plant-derived compounds and plant extracts reported during 2006–2020 against ESKAPE.

S. No.	Scientific Name	Common Names	Parts used	Traditional uses	Extract prepared in	Anti -microbial activity against	References
1	*Cinnamomum glaucescens*	Sugandhakokila	Leaves	Skin and throat infection	Acetone	**MRSA**	Panda et al., 2020 [48]
2	*Smilax zeylanica*	Kumarika	Leaves	Ulcers treatment	Acetone	**MRSA**	Panda et al., 2020 [48]
3	*Syzygium praecox*	N/A	Leaves	Skin infection	Acetone	**MRSA**	Panda et al., 2020 [48]
4	*Trema orientalis*	Charcoal tree	Leaves	Sore throat, boils, wound infections	Acetone	**MDR-S**	Panda et al., 2020 [48]
5	*Bischofia javanica*	Java cedar	Leaves	Skin diseases	Acetone	**MDR-S**	Panda et al., 2020 [48]
6	*Elaeocarpus serratus*	Ceylon olive	Flower	Acts as a diuretic and cardiovascular stimulant	Water	**MDR-S**	Panda et al., 2020 [48]
7	*Acacia pennata*	Climbing acacia	Leaves	Effective against dysentery, diarrhoea and lowers body cholesterol	Ethanol	**MRSA**	Panda et al., 2020 [48]
8	*Holigarna caustica*	Long-leaf varnish tree	Fruit	Skin diseases	Ethanol	**MRSA**	Panda et al., 2020 [48]
9	*Murraya paniculata*	Orange jessamine	Leaves	Cure to cardiovascular disorders	Ethanol	**MRSA**	Panda et al., 2020 [48]
10	*Pterygota alata*	Buddha coconut	Bark	Skin diseases	Ethanol	**MDR-S**	Panda et al., 2020 [48]
11	*Kalanchoe fedtschenkoi*	Lavender scallops	Woody stems	Used as an analgesic (Cumberbatch, 2011) [49]	Ethanol	**S,A,P**	Richwagen et al., 2019 [50]
12	*Bridelia micrantha*	Coastal golden leaf	Stem bark	Used in Cameroon to treat amoebic dysentery, cough diarrhoea, gastric ulcer, eye diseases, infertility and tapeworms. Has antibacterial, hepatoprotective, antioxidant, antitumor and antiviral activities	Methanol	**S, K, P, MRSA, Ea**	Ngane et al., 2019 [51]
13	*Prunus cerasifera*	Cherry plum	Fruit	Astringent, antioxidant, sudorific, antipyretic, axative and diuretic properties	Methanol	**K,S,P**	Pallah et al., 2019 [52]
14	*Ribes nidigrolaria*	Jostaberry	Fruit	Anti-aging, cataracts, cardiovascular disease, immunity.	Methanol	**P,S**	Pallah et al., 2019 [52]
15	*Prunus avium*	Sweet Cherry	Fruit	Cancer, osteoarthritis and cardiovascular disease	Methanol	**K,S,P**	Pallah et al., 2019 [52]
16	*Prunus subg. Prunus*	Plum	Fruit	Antioxidant, anti-inflammatory, and memory-boosting properties	Methanol	**K,S,P**	Pallah, et al., 2019 [52]
17	*Ribes rubrum*	Red Currant	Fruit	To treat scurvy, relieve constipation, digestive and urination issues, laxative	Methanol	**K,S,P**	Pallah et al., 2019 [52]
18	*Adiantum capillus-veneris*	Maiden hair fern	Whole plant	Urinary tract infections (UTIs); also used as an astringent, demulcent, antitussive and diuretic (Ishaq et al., 2014) [53]	Ethanol	**Ef,S**	Khan et al., 2018 [54]
19	*Artemisia absinthium*	Worm wood	Aerial parts	Pruritus and inflammatory and infectious skin disorders, (Khan and Khatoon, 2008) [55] Drugs against malaria and typhoid (Hayat et al., 2009) [56]	Ethanol	**Ef,S**	Khan et al., 2018 [54]
20	*Martynia annua*	Bichoo	Fruit	Wound healing, skin conditions and sore throats (Santram and Singhai, 2011; Dhingra et al., 2013) [57,58]	Ethanol	**K,A,Ef,S**	Khan et al., 2018 [54]
21	*Swertia chirata*	Chirayita	Whole plant	Hepatitis, inflammation and digestive diseases. Other indications include chronic fever, malaria, skin disease and bronchial infections (Kumar and Van Staden, 2016) [59].	Ethanol	**S**	Khan et al., 2018 [54]
22	*Zanthoxylum armatum*	Timber	Fruit	Cancer and digestive ailments such as cholera and dysentery, dental infections and oral sores (Ahmad et al., 2014; Alam and Saqib, 2017) [60, 61].	Ethanol	**Ef,S**	Khan et al., 2018 [54]
23	*Berberis lycium* Royle	Indian Lycium	Root	Bark infusions are traditionally used for oral infections, toothaches and earaches (Abbasi et al., 2010) [62]. Traditionally used to treat diarrhea, cholera and piles (Malik et al., 2017) [63].	Ethanolic and Aqueous	**Ef**	Khan et al., 2018 [54]

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Table 1 (*continued*)

S. No.	Scientific Name	Common Names	Parts used	Traditional uses	Extract prepared in	Anti -microbial activity against	References
24	*Anacardium occidentale*	Cashew	leaves	Venereal diseases, stomach issues, skin diseases, stomatitis, bronchitis, psoriasis, toothaches, and gum problems	Ethanol	**K, P, S**	Shobha et al., 2018 [64]
25	*Piper longum*	Pipli	Root	Antioxidant potential and anti-inflammatory properties	Aqueous	**Ef, A**	Chandrasekharan et al., 2018 [65]
26	*Cymbopogon citratus*	Lemon grass	Leaves	Treatment against hypertension, epilepsy, gastrointestinal, central nervous system disorders	Hexane	**P, Ec**	Chandrasekharan et al., 2018 [65]
27	*Aloe vera*	Medicinal aloe	Leaves	Help with skin injuries caused by burning, irritations, cuts, actively repairs damaged skin	Aqueous	**S**	Chandrasekharan et al., 2018 [65]
28	*Cynodon dactylon*	Bermuda grass	Leaves	Laxative, coolant, brain and heart tonic	Ethanol	**K**	Chandrasekharan et al., 2018 [65]
29	*Theobroma cacao*	Cocoa	Seeds Leaves	Stimulates nervous system, low blood pressure and softens damaged skin. Effective against anemia, diarrhea and bruises	Methanol	**K** **Ea**	Nayim et al., 2018 [66]
30	*Ipomoea batatas*	Sweet potato	Leaves	Treatment of diabetes, hypertension, and stomach related issues, arthritis, rheumatoid diseases, meningitis, kidney ailments, and inflammations.	Methanol	**Ea**	Nayim et al., 2018 [66]
31	*Azadirachta indica*	Neem tree	Bark	Used to treat teeth-related issues and disorders of the GI tract, malaria fevers, skin diseases, and as insect repellent	Methanol	**Ea, K**	Nayim et al., 2018 [66]
32	*Citrus grandis*	Pomelo	Leaves	To treat epilepsy, chorea, Convulsive cough and also in the treatment of hemorrhage disease.	Methanol	**K**	Nayim et al., 2018 [66]
33	*Cucurbita maxima*	Winter squash	Beans	Treat intestinal infections and kidney problems and to fight tapeworms	Methanol	**K**	Nayim et al., 2018 [66]
34	*Dacryodes edulis*	Bush butter tree	Leaves seeds	Gargle and mouth wash to treat tonsillitis	Methanol	**Ea, Ec** **Ea, P**	Nayim et al., 2018 [66]
35	*Hibiscus esculentus*	Okra	Leaves	Used in the treatment of nose and throat related infections, urine associated issues and gonorrhoea	Methanol	**Ea**	Nayim et al., 2018 [66]
36	*Phaseolus vulgaris*	Common bean	Leaves	Consumed orally for weight loss and obesity. Taken for diabetes as well	Methanol	**Ea, P**	Nayim et al., 2018 [66]
37	*Lantana camara*	Lantana	Leaves	Antispasmodic, anti-tumor, anti-inflammatory, anti-malarial,anti-ulcerogenic	Dichloromethane, methanol, petroleum ether, chloroform, ethyl acetate, acetone, ethanol and water	**MRSA, MDR-A, VRE, P**	Subramani et al., 2017 [67]
38	*Butea monosperma*	Palash	Leaves	Stimulation of diuresis and menstrual flow.	Petroleum ether, acetone, methanol, ethanol and water	**MRSA, VRS**	Subramani et al., 2017 [67]
39	*Terminalia chebula*	Myrobalan	Dried seedless ripe fruits	Treats High cholesterol and digestive disorders, dysentery	Cold and hot aqueous and ethanol	**MRSA**	Subramani et al., 2017 [67]
40	*Anthocephalus cadamba* and *Pterocarpus santalinus*	Burflower tree and red sandalwood	Leaves and bark	Treatment of fever, uterine complaints, skin diseases, inflammation. Antipyretic, dysentery, antihyperglycaemic	Ethanol and water	**MDR-A species, P**	Subramani et al., 2017 [67]
41	*Andrographis paniculata*	Green chireta	-	Anti-cancer, anti-diabetic, helps overcome high blood pressure, ulcer, lung related issues, skin diseases	Chloroform and chloroform + HCl	**MRSA**	Subramani et al., 2017 [67]
42	*Callistemon rigidus*	Stiff bottlebrush	Leaves	Treatment of diarrhea, dysentery, rheumatism, anticough and antibronchitis	Methanol	**MRSA**	Subramani et al., 2017 [67]
43	*Myrtus communis*	Myrtle	Leaves	Diabetes, ulcers, hypertension, dysentery, rheumatism, cancer, inflammations and diarrhea	Hydro-alcoholic	**P, S**	Masoumian and Zandi, 2017 [68]

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Table 1 (*continued*)

S. No.	Scientific Name	Common Names	Parts used	Traditional uses	Extract prepared in	Anti -microbial activity against	References
44	*Cinnamomun zeylanicum*	Cinnamon	Bark	Antioxidant, anti-inflammatory, anti-diabetic properties	Water	**P, S**	Masoumian and Zandi, 2017 [68]
45	*Mentha sp.*	Mint	Leaves	Effective against cold, irritable bowel syndrome, indigestion	Aqueous hydro-alcoholic	**P S**	Masoumian and Zandi, 2017 [68]
46	*Lawsonia inermis*	Henna	Leaves	Heals wounds and burns, used for skin infections, hair health	Aqueous	**P, S**	Masoumian and Zandi, 2017 [68]
47	*Aloe vera*	Medicinal aloe	Leaves	Burns, acne, oral and digestive problems	Aqueous	**P, S**	Masoumian and Zandi, 2017 [68]
48	*Zingiber officinale*	Ginger	Roots	Nausea, vomiting, anti-cancer	Hydro-alcoholic	**P, S**	Masoumian and Zandi, 2017 [68]
49	*Bulbine frutescens*	Snake flower	Leaves and bulbs	Skin and wound conditions. (Van Wyk et al., 2009; Diederichs et al., 2009) [69, 70]	Chloroform and methanol	**S,P**	Ghuman et al., 2016 [71]
50	*Aloe ferox*	Bitter Aloe	Leaves	Skin conditions (Van Wyk et al., 2009; Diederichs et al., 2009) [69, 70]	Chloroform	**S,P,K**	Ghuman et al., 2016 [71]
51	*Mentha longifolia*	Horse mint	Aerial parts	Throat irritation, mouth and sore throat (Al-Bayati, 2009) [72]	Ethanol	**VRE**	Agarwal et al., 2016 [73]
52	*Phyllanthus emblica*	Amla	Aerial parts	Antimicrobial, anti-inflammatory, antioxidant, anti pyretic, analgesic, adaptogenic, hepatoprotective (Gulati et al., 1995; Baliga et al.,2012) [74, 75]	Ethanol	**MRSA, VRE**	Agarwal et al., 2016 [73]
53	*Aloe arborescens*	Tree Aloe	Leaves	Skin, digestive and respiratory conditions (Hutchings et al., 1996; Crouch et al., 2006; Klos et al., 2009; Van Wyk et al., 2009) [69, 76, 77, 78]	Dichloromethane	**S,P**	Ghuman et al., 2016 [71]
54	*Hypericum aethiopicum*	N/A	Leaves	Skin and gastrointestinal issues. (Rood, 1994; Bruneton, 1995; Hutchings et al., 1996; Van Wyk et al., 2009) [69, 76, 79, 80]	Dichloromethane, Chloroform, Methanol.	**S,K**	Ghuman et al., 2016 [71]
55	*Aframomum corrorima*	Ethiopian Cardamom	Fruit	Substitute medication for the regional community and scientific research in search for substitute drugs to overcome challenges associated with the rising antimicrobial resistance	_	**S**	Bacha et al., 2016 [81]
56	*Camellia sinensis*	Green Tea	Leaves	Anticancer activity, Cardiovascular Diseases (Miura et al., 2000; Smith and Dou, 2001) [30, 82]	Ethanol	**MRSA**	Agarwal et al., 2016 [73]
57	*Mentha longifolia*	Horse mint	Aerial parts	Throat irritation, mouth and sore throat (Al-Bayati, 2009) [72]	Ethanol	**VRE**	Agarwal et al., 2016 [73]
58	*Phyllanthus emblica*	Amla	Aerial parts	Antimicrobial, anti-inflammatory, antioxidant, anti pyretic, analgesic, adaptogenic, hepatoprotective (Gulati et al., 1995; Baliga et al., 2012) [74, 75]	Ethanol	**MRSA, VRE**	Agarwal et al., 2016 [73]
59	*Oxalis corniculata*	Yellow sorrel	Leaves	Digestion, chronic dysentery, diarrhea, headaches, intoxication, fever, inflammations, jaundice, pain, scurvy, anti-helminthic, analgesic, astringent, diuretic	Methanol	**K,S**	Manandhar et al., 2015 [83]
60	*Cinnamomum tamala*	Bay leaf	Leaves	Diabetes, Digestion, Cardiovascular Benefits, Cold and Infection, Pain, Anti-cancer, Menstrual Problems	Methanol	**S**	Manandhar et al., 2015 [83]
61	*Ageratina adenophora*	Cotton weed	Leaves	Cuts, wounds, boils, antiseptic	Methanol	**S**	Manandhar et al., 2015 [83]
62	*Artemesia vulgaris*	Mugwort	Aerial parts	Antiseptic, diarrhea, dysmenorrhea, asthma, antihelminthic, stomach ulcer, anorexia,	Methanol	**S**	Manandhar et al., 2015 [83]

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Table 1 (*continued*)

S. No.	Scientific Name	Common Names	Parts used	Traditional uses	Extract prepared in	Anti -microbial activity against	References
				heartburn, hyperacidity, spasm of digestive organs, epilepsy			
63	*Cynodon dactylon*	Bermudagrass, Doob grass	Whole plant	Cuts, wounds, indigestion,genitourinary disorders (Rajbhandari., 2001; Manandhar, 2002; Singh et al., 2012) [84, 85, 86]	Ethanol, Chloroform	**MRSA, IRP, ESBL-K**	Quinn et al., 2015 [87]
64	*Curcuma longa*	Turmeric	Rhizomes	Antiseptic, cuts, wounds, as anthelmintic, jaundice, liver disorders (Rajbhandari., 2001; Manandhar, 2002; Singh et al., 2012) [84, 85, 86]	Ethanol and Chloroform	**MRSA, Ef**	Quinn et al., 2015 [87]
65	*Ginkgo biloba*	Ginkgo	Leaves	As antiaging, used to treat Alzheimer's disease, as anticoldness, as antinumbness (Rajbhandari, 2001; Manandhar, 2002) [84, 85]	Ethanol and Chloroform	**S,Ef**	Quinn et al., 2015 [87]
66	*Rauwolfia serpentine*	Serpentine (Sarpagandha)	Root	As antidysenteric, as antidote to snakebite, cuts, wounds, and boils (Rajbhandari., 2001; Manandhar, 2002; Singh et al., 2012) [84, 85, 86]	Ethanol and Chloroform	**MRSA,S, Ef, IRP, ESBL- K**	Quinn et al., 2015 [87]
67	*Croton macrostachyus* Del.	Rushfoil	Leaves	Veterinary: diarrhea (dysentery), external parasites etc. (Adedapo et al., 2008) [88]	Methanol and Chloroform	**S,P**	Romha et al., 2015 [89]
68	*Calpurnia aurea*	Wild laburnum	Leaves	Human: diarrhea, dysentery, and stomach disorder (Wagate et al., 2010) [90]	Methanol and Chloroform	**S,P**	Romha et al., 2015 [89]
69	*W. somnifera* L.	winter cherry	Roots	Human: extended flow of menstruation/ menometrorrhagia (bark & leaf), gallstone (root & leaf) (Alam et al., 2012) [91]	Methanol and Chloroform	**P**	Romha et al., 2015 [89]
70	*Nicotiana tabacum* L.	Tobacco	Leaf	Used to treat infected wounds, hair treatment to prevent baldness, used in case of chills, snake bites	Methanol and chloroform	**S, P**	Romha et al., 2015 [89]
71	*Phyllanthus niruri*	Sampa-sampalukan	Leaves, aerial parts	Problems of stomach, genitourinary system, liver, kidney and spleen, and to treat chronic fever (Kamruzzaman and Obydul Hoq, 2016) [92]	Ethanol	**MRSA, VRE, S**	Demetrio et al., 2015 [93]
72	*Psidium guajava*	Bayabas	Leaves	Anti-diarrhoeal, to treat gastroenteritis, dysentery, stomach problems (Martha et al., 2008) [94]	Ethanol	**MRSA, VRE, S**	Demetrio et al., 2015 [93]
73	*Piper betle*	Ikmo	Leaves	Mouth freshener, effective against parasitic worms, antibacterial, antifungal, antioxidant and anti-inflammatory activities (Fazal et al., 2014) [95]	Ethanol	**MRSA, MβL A, MβL P, VRE, ESBL-KP, S, K,P**	Demetrio et al., 2015 [93]
74	*Ehretia microphylla*	Tsaang gubat	Leaves	Antibacterial, antioxidant, anti-allergic as well as anti-snake venom properties (Shukla et al., 2018) [96]	Ethanol	**MRSA, MβL A, VRE, S, P**	Demetrio et al., 2015 [93]
75	*Tabebuia impetiginosa*	Tahuari	Whole plant	Treatment of rheumatism and, wounds, bronchitis and diarrhea.	Ethanol	**P**	Ulloa-Urizar et al., 2015 [97]
76	*Maytenus macrocarpa*	Chuchuhuasi	Whole plant	Urine related issues, anti-cancerous, syphylis, gasterointestinal problems, diabetes	Ethanol	**P**	Ulloa-Urizar et al., 2015 [97]
77	*Eucalyptus camaldulensis*	River red gum	-	Hot water extracts of dried leaves used as analgesic, anti-inflammatory and antipyretic remedies for the symptoms0 of respiratory infections, such as cold,	Ethanol	**P**	Amenu, 2014 [99]

(*continued on next page*)

Table 1 (*continued*)

S. No.	Scientific Name	Common Names	Parts used	Traditional uses	Extract prepared in	Anti -microbial activity against	References
				flu, and sinus congestion. (Darwish and Aburjai, 2010) [98].			
78	*Ficus sycomorus*	Sycamore fig	Leaves	*Ficus sycomorus* have been suspected to possessanti-diarrhoeal activities and sedative and anticonvulsant properties of this plant have also been reported. (Cuaresma et al.,2008) [100]	Methanol and Aqueous	**S**	Amenu, 2014 [99]
79	*Entada abyssinica*	Splinter bean	Leaves and roots	Coughs, fever, rheumatic, abdominal pains, and diarrhea, prevent miscarriage, gonorrhea, Bronchite, eyes inflammation, snake bite, sleeping sickness	Methanol	**S, K**	Tchana et al., 2014 [101]
80	*Carica papaya*	Papaya	Seeds	Typhoid fever, parasitic diseases, hepatic affections, dyspepsia, colic, gastric ulcer, toothache, analgesic, amebicide, antibacterial, febrifuge, hypotensive, laxative	Ethanol and aqueous	**K, P**	Tchana et al., 2014 [101]
81	*Carapa procera*	Carapa	Bark	Wound infections	Ethanol	**P**	Tchana et al., 2014 [101]
82	*Persea americana*	Avocado	Stones	Diarrhea, dysentery, toothache, intestinal parasites, hypertension, cancer, menstrual problems, inflammation, wounds	Methanol, ethyl acetate and chloroform	**K, P**	Tchana et al., 2014 [101]
83	*Adansonia digitata*	African baobab	Pulps, Fruits, leaves, Pip, Bark	Analgesic, anti-diarrheal, smallpox, rubella, antipyretic, fever, dysenteria, anti-inflammatory, astringent (Tanko et al., 2008; Kaboré et al., 2011) [102,103]	Ethanol and Aqueous Extract	**S,P**	Djeussi et al., 2013 [104]
84	*Aframomum polyanthum*	Matunguru	Fruits	-	Methanol	**S**	Djeussi et al., 2013 [104]
85	*Hibiscus sabdarifa*	Roselle	Flowers	Diuretic, stomachic, laxative, aphrodisiac, antiseptic, astringent, cholagogue, sedative, hypertension and other cardiac diseases (Olaleye, 2007) [105]	Ethanol, Methanol,Aqueous	**S,K,P**	Djeussi et al., 2013 [104]
86	*K. pinnata*	Cathedral bells	Leaves	Healing of Wounds caused by S and P, anti-microbial properties	95% Ethanolic, 60% Methanolic and Aqueous	**S,P**	Pattewar et al., 2013 [106]
87	*Acacia karroo*	Sweet thorn	Stem	Mouth ulcers, oral thrush, diarrhea, dysenteries, colic, colds, other Acacia pecies: asthma, bronchitis, cough, phithisis, fever, leprosy, chest and respiratory ailments (Watt and Breyer -Brandwijk, 1962; Johnson, 1999; Van Wyk et al., 2006) [107, 108, 109]	Methanol	**ARKP**	Nielsen et al., 2012 [110]
88	*Curtisia dentate*	Assegaai tree	Stem bark	Stomach ailments, diarrhea, blood purifier, afrodisiac, tanning, chewing sticks (Watt and Breyer-Brandwijk, 1962; Van Wyk et al., 2006) [107, 109]	Methanol	**MRSA**	Nielsen et al., 2012 [110]
89	*Erythrophleum lasianthum*	Sasswood	Stem and leaves	Headaches, fever, Erythrophleum species: heart problem, dermatitis, wounds, rheumatism, syphilis, gonorrhea, leprosy, tuberculosis, bronchitis, angina, ordeal and hunting poison (Palgrave et al., 1988; Neuwinger, 1996; Johnson, 1999) [108, 111, 112]	Methanol	**MRSA**	Nielsen et al., 2012 [110]

(*continued on next page*)

Table 1 (*continued*)

S. No.	Scientific Name	Common Names	Parts used	Traditional uses	Extract prepared in	Anti -microbial activity against	References
90	*Salvia africana-lutea*	Golden sage	Aerial parts	Colds, flu, bronchitis, abdominal and uterine troubles, cough, chest troubles, other Salvia species: night sweat tuberculosis, respiratory and pulmonary ailments (Watt and Breyer-Brandwijk, 1962; Johnson, 1999; Van Wyk et al., 2006) [107, 108, 109]	Methanol	**MRSA**	Nielsen et al., 2012 [110]
91	*Toddalia asiatica*	Orange climber	Leaves	Traditionally used to treat malaria and cough; indigestion and influenza and the leaves are used to treat lung diseases and rheumatism.	Ethyl acetate	**K, Ea**	Karunai Raj et al., 2012 [113]
92	*Kalanchoe pinnata*	Patharkuchi	Stems and leaves	Diarrhea, dysentery and gastrointestinal disturbances. (Pal et al., 1991) [114]	Ethanol	**S,P**	Biswas et al., 2011 [115]
93	*Acacia nilotica*	Gum Arabic Tree	Leaves	Antimicrobial, antihyperglycemic and antiplasmodial properties	Ethanol	**K**	Khan et al., 2009 [116]
94	*Cinnamum zeylanicum*	Cinnamon	Barks	Antipyretic activity, antibacterial, antioxidant and antifungal properties	Ethanol	**K**	Khan et al., 2009 [116]
95	*Syzygium aromaticum*	Clove	Bud	Antipyretic activity, antibacterial, antifungal, anti-inflammatory and anticarcinogenic effects	Ethanol	**K**	Khan et al., 2009 [116]
96	*Syzygium lineare*	Malai naaval	Leaves	Diuretic, stomachic, tonic and astringent (Nadkarni, 1976; Rastogi and Mehrotra, 1990–1994; Narasimhan, 2003) [117, 118, 119]	Hexane and Methanol	**S**	Duraipandiyan et al., 2006 [120]
97	*Acalypha fruticosa*	Chinni chedi	Aerial parts	Stomachic, attenuate (Nadkarni, 1976; Rastogi and Mehrotra, 1990–1994; Narasimhan, 2003) [117, 118, 119]	Hexane	**P,S**	Duraipandiyan et al., 2006 [120]
98	*Syzygium cumini*	Naval pazham	Seed	Astringent, stomachic, diuretic, tonic and anti-diabetic (Nadkarni, 1976; Rastogi and Mehrotra, 1990–1994; Narasimhan, 2003) [117, 118, 119]	Methanol	**S,K**	Duraipandiyan et al., 2006 [120]
99	*Olax scandens*	Kaattu pavalam	Leaves	Febrifuge (Nadkarni, 1976; Rastogi and Mehrotra, 1990–1994; Narasimhan, 2003) [117, 118, 119]	Hexane	**K**	Duraipandiyan et al., 2006 [120]
100	*Peltophorum pterocarpum*	Malai porasu	Flower	Applied topically to treat wounds (Nadkarni, 1976; Rastogi and Mehrotra, 1990–1994; Narasimhan, 2003) [117, 118, 119]	Methanol	**K**	Duraipandiyan et al., 2006 [120]

KEY TO ABBREVIATIONS: Ef = *Enterococcus faecium*, K = *Klebsiella pneumoniae*, P = *Pseudomonas aeruginosa*, S = *Staphylococcus aureus* A = *Acinetobacter baumannii*, MRSA = Methicilin resistant *Staphylococcus aureus*, IRPA = Imipenem resistant *Pseudomonas aeruginosa*, ESBL-KP = Extended spectrum β lactamase producing *Klebsiella pneumoniae*, ARKP = Ampicillin resistant *Klebsiella pneumoniae*, Ec = *E. cloacae*, MDR-A = Multidrug resistant *Acinetobacter baumannii*, VRE = Vancomycin resistant *E. faecium*, Ea = *E. aerogenes*,* MβL P = metallo-β-lactamase-producing *Pseudomonas aeruginosa*, MβL A = metallo-β-lactamase-producing *Acinetobacter baumannii*, VRE = vancomycin-resistant *Enterococcus*, VRS = vancomycin-resistant *S. aureus*, MDR-S = Multidrug resistant *Staphylococcus aureus*.

* *E. aerogenes* has been changed to *Klebsiella aerogenes*.

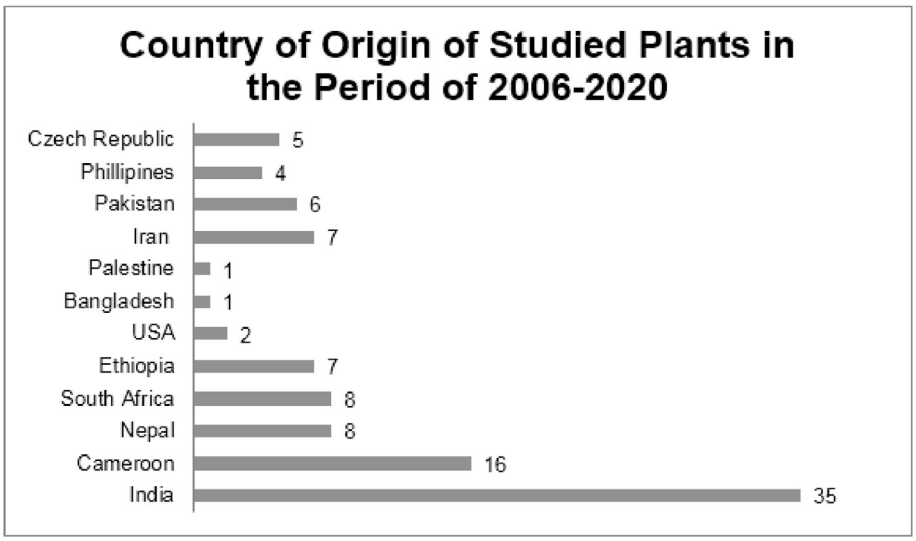

Chart 1. The above chart shows the number of plants with potential antimicrobial properties collected from each country during the period of 2006–2020.

pneumonia and urinary tract infections [39]. They show broad resistance to antimicrobials by plasmid encoded ESBLs, carbapenems [4].

3. Plant derived compounds and extracts against ESKAPE

Conventional medicinal practices utilize plants against various infections for over thousands of years now [40, 41, 42, 43]. 80% of the population in the developing nations are dependent upon the easily accessible traditional medications to fulfil their primary medical needs, [44, 45]. Indeed, plants are known to synthesize a wide array of compounds known as secondary metabolites or phytochemicals such as quinones, tannins, terpenoids, alkaloids, flavonoids, and polyphenols which have disease prevention properties and aid them in their self-defense and communication with other organisms in their environment [46]. Plant extracts as medicines are inevitable substitutions for antibiotics prescribed by physicians [47] Plant derived compounds and extracts are commonly used in self-medication due to its easy availability, competence and nil side effects [47].

Table 1 shows a total of 100 plants that were reported to show significant antimicrobial activity against ESKAPE pathogens during the period of 2006–2020. These plants were reported from 12 countries from Asia, Africa, Europe, North America and South America. India reported the highest number (35) of plants (Chart 1).

The plant-derived extracts mentioned in this review were prepared in deionised water and/or diverse organic solvents such as methanol, chloroform, hexane, ethyl acetate, and so on. Alcoholic extracts of ethanol and methanol were the most common extracts used and they showed the highest antimicrobial properties. Antimicrobial assays such as Kirby Bauer Disc Diffusion and Agar well diffusion were performed to determine the Minimum Inhibitory Concentration (MIC) to test the effectiveness of the extracts in MDR bacterial strains. MIC values of the extracts of the same solvent were varied even though all the extracts possessed similar antibacterial efficacy. This was seen because the bacterial inhibition activity is majorly dependent on the bioactive compound present in the extract. So, a difference in MIC between two plant extracts can be attributed to the presence of a different bioactive compound or different concentrations of the same bioactive compound. These bioactive compounds are essentially phytochemicals such as flavonoids, tannins, coumarins, triterpenes, alkaloids, phenylpropanoids, sterols and terpenoids.

Most of the plants showed specific inhibitory effects against one or two members of ESKAPE. However, a few displayed significant broad-spectrum antibacterial activity. These were: ***Martynia annua, Cynodon dactylon, Rauwolfia serpentine, Piper betle, Ehretia microphylla, Lantana camara,*** and ***Bridelia micrantha.***

Therefore, it is vital to perform additional chemical analysis of the aforementioned plant extracts to determine their chemical composition and pin-point the exact phytocompounds responsible for antimicrobial activity. The plant extracts should be subjected to a series of pharmacological tests to ascertain their *in vivo* efficacy, cytotoxicity, interactions and any harmful side-effects.

4. Conclusion

Emergence of "superbugs" is a serious health problem due to escaping of antibiotics used for their treatment. Therefore, there is a need for the medicinal plants being exploited as a source for alternative medicines ***Studies focusing on the use of phytochemicals and plant extracts from different countries for the treatment of infections caused by ESKAPE pathogens, have been highlighted in this review***.

However, further research needs be carried out regarding plant-derived active principles, for this knowledge to be translated into potential therapeutic drugs.

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