Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
https://www.plantsjournal.com
JMPS 2023; 11(3): 01-13

Received: 01-03-2023
Accepted: 07-04-2023

Santosh Kodgire
Reliance Industries Ltd, Jamnagar, Gujarat, India

Chandrashekharaiah PS
Reliance Industries Ltd, Jamnagar, Gujarat, India

Jatinkumar Solanki
Reliance Industries Ltd, Jamnagar, Gujarat, India

Debanjan Sanyal
Reliance Industries Ltd, Jamnagar, Gujarat, India

Santanu Dasgupta
Reliance Industries Ltd, Reliance Corporate Park, Ghansoli, Mumbai, Maharashtra India

Corresponding Author:
Debanjan Sanyal
Reliance Industries Ltd, Jamnagar, Gujarat, India

Broad-spectrum antimicrobial activity of medicinal herbs: A potential solution towards microbial drug resistance

Santosh Kodgire, Chandrashekharaiah PS, Jatinkumar Solanki, Debanjan Sanyal and Santanu Dasgupta

DOI: https://doi.org/10.22271/plants.2023.v11.i3a.1548

Abstract
Infectious diseases are major threats to humankind and are main reasons for mass mortality. As a survival mechanism microbes continuously evolve and change their genetic make up to gain resistance against the drugs which they come in contact. Hence, there is a growing interest in identifying alternative and safe medicines to overcome microbial drug resistance. The use of medicinal plants against various diseases has been mentioned in Ayurveda and the knowledge of usage has been transferred over the generation through oral tradition. The active principles behind the medicinal property of plants were not studied in traditional medicine. With the advent of modern tools, the active principals behind the broad-spectrum anti-microbial activity of medicinal plants were attributed to the presence of variety of bioactive compounds. The formulations or the extracts containing mixture of bioactive compounds are considered as GRAS and each one has various therapeutic applications. The bioactive compounds are secondary metabolites which play a pivotal role in solving the issues of microbial drug resistance and other ailments. In this review five medicinal crops (*Aloe vera*, *Cynodon*, *Datura*, *Euphorbia*, and *Ocimum*) were selected to review the significance of these crops in alternative medicine. The cause and mechanisms of microbial resistance to commonly used drugs are discussed. The historical aspects, the bioactive compounds, the broad-spectrum antimicrobial property and market potential of these crops are reviewed in the context of alternative medicine.

Keywords: Alternative medicines, antimicrobial properties, antimicrobial resistance, medicinal herbs

1. Introduction
The infectious diseases cause threat to human kind [1]. Currently, there are many targeted drugs available in the market to treat deadly infectious diseases and the new ones have continuously been discovered [2]. The pathogens are winning over drugs due to their continuous evolution and acquisition of resistance to multiple mono drugs [3]. It has been reported that the development of microbial drug resistance would take a ten million lives per year and is expected to cause hundred trillion-dollar loss to the economy [4]. Solving the issue of microbial drug resistance under the mono drug treatment system is a challenging task and is increasing the health issues and mortality at the global level.

Plants have been recognized as a source of medicines [5] and are widely used in curing human diseases for more than 5000 years in traditional medicine [6]. The traditional medicine is widely followed in many countries, to maintain health and to prevent/treat physical/mental illness. The techniques of traditional medicine is purely based on indigenous knowledge, skills, practises, and these vary with culture to culture (WHO). More than 80% of the population residing in developing countries depends on plants for their medicine [7] and this dependency is mainly due to the safety, and cost-effectiveness[8]. In the last decade, more than 50% of the newly developed drugs approved by Food and Drug Administration (FDA) were from plant sources [9].

Plants which have medicinal properties are called medicinal plants and are rich sources of various phytochemicals. In traditional medicine, the plant parts or their products are used in preparation of formulations to treat multiple ailments [10, 11]. The products/formulations prepared from plants are considered as GRAS (Generally regarded as safe) and play a pivotal role in ethnomedical treatment [12]. The extract of the plants is known to contain many bioactive compounds with therapeutic applications [13] and these bioactive compounds act in synergy to break the AMR [14].

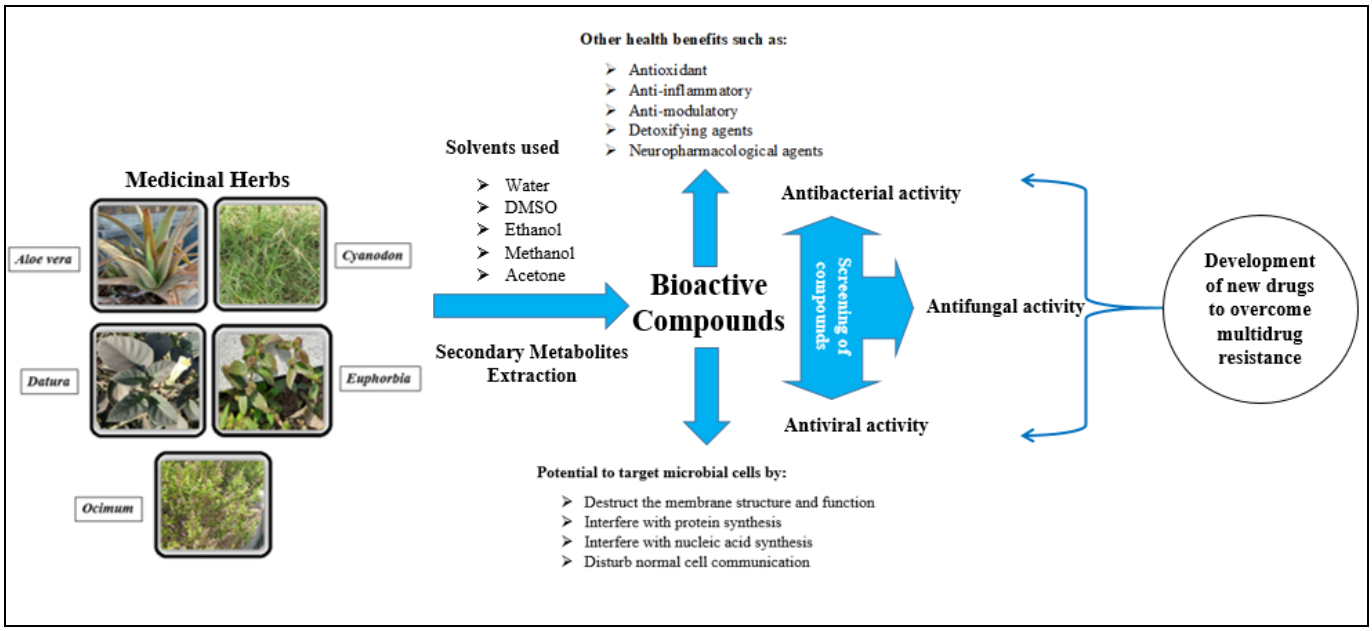
Apart from that, these have other properties such as antioxidants, anti-inflammatory, anti-modulatory, detoxifying, and neuropharmacological agents there by helps in overall health improvement [15].

Now a days there is growing research in the field of ethnomedicine and poly-pharmacology to find a novel molecule from various medicinal plants to overcome AMR and to use in primary health care [16]. Due to this the medicinal plants are gaining importance as an alternative to synthetic drugs and the global market for medicinal plant products is growing and it is valued at $100 billion [17]. Most of the medicinal plants which have pharmacological significance are wild and needs domestication for round year cultivation with improved yield. The medicinal plants which can grow in rain fed or marginal land would be of interest to farmers to grow as cash crops. This review summarizes the broad-spectrum antimicrobial activity of medicinal plants such as *Aloe vera*, *Cynodon*, *Datura*, *Euphorbia*, and *Ocimum* on disease causing micro-organisms in humans. Also discussed the role of these medicinal plants in solving the AMR and their market potential.

2. Historical aspects of medicinal plants in the context of traditional medicine

The first written report on the medicinal use of *Aloe vera* is available in the Egyptian document [18]. The use of *Aloe vera* for wound treatment was mentioned in Bible. In 16th century, the Indian tribes were familiar with the healing properties of *Aloe vera*. They were using aloe juice on skin as an insect repellent [19]. In 1935, Collins and Collins reported the beneficial role of *Aloe vera* for treating severe roentgen (radiation) dermatitis [20]. Because of many beneficial aspects, *Aloe vera* is used in consumption purpose, and it is a FDA approved food supplement and flavoring agent [21]. *Cynodon* is recognized as the devil's grass and is commonly cultivated in Hindu homes. It is useful in the treatment of hysteria and epilepsy. It is known to efficiently arrest the bleeding in infectious diseases, dysentery, diarrhoea, piles, and raktapitta, etc. The first medicinal use of *Datura* was mentioned in Sanskrit literature [22]. Before fifteen century, the use of this plant was also mentioned in Mongolian and ancient Tibetan texts. In ancient China, before consumption of wine it was a general practice to steep the flowers of *Datura* in wine [23]. In recent literature, this plant has been reported to have several pharmacological properties such as analgesic, antiepileptic, anti-asthmatic, antimicrobial, antioxidant, insecticidal, and repellent activities [24]. *Euphorbia* is known as asthma plant, reported to useful in treating respiratory and digestive disorders. In India, *Ocimum* (Tulsi) is used in Ayurveda over the years for the treatment of cold, headache, malaria, and heart disease.

Graphical Abstract



3. Emergence of antimicrobial resistance

The antimicrobial compounds are generally used to kill various pathogenic microbes, which cause diseases in humans and animals. However, most of the microbes (bacteria, fungi, and viruses) slowly develop resistance towards various groups of drugs and this process is generally termed antimicrobial resistance. The antimicrobial resistance phenomenon was first observed in *Staphylococcus aureus* against penicillin antibiotics [25, 26]. *S. aureus* inactivates penicillin by producing the enzyme penicillinase. The penicillinase enzyme breaks down the core beta-lactam ring of penicillin, which is required for binding with the penicillin-binding proteins (PBPs) of bacteria. Since then, the resistance to antimicrobial compounds was observed in various other bacterial species such as *Shigella dysenteriae*, *Salmonella typhi*, *Mycobacterium tuberculosis*, *Enterococcus*, methicillin-resistant *S. aureus*, *Streptococcus pneumonia*, and *Haemophilus influenza* [26, 27]. Generally, bacteria use mechanisms such as modification in the drug target, less permeability to a drug, inactivation of drugs by enzymes, use of an alternative pathway, and increased efflux of the drug to develop the resistance. Drug resistance is also a common phenomenon in numerous fungal pathogens such as *Aspergillus fumigatus*, *Candida glabrata*, *Candida albicans*, and *Cryptococcus neoformans* [28]. The fungi mainly use mechanisms such as alterations in the drug target, metabolic bypasses, and reduction of active drug concentration to gain resistance [28]. The viruses such as Cytomegalovirus, Hepatitis

B virus, Herpes simplex virus, and Varicella zoster virus also have shown resistance against antiviral drugs [29]. The viral resistance to a particular drug is mainly due to the mutations in the target gene or protein [29]. Due to the antimicrobial resistance, the current drugs may fail in effective control of disease, which requires the usage of multiple drugs, higher dosage, or new molecule of drugs [30].

To overcome this risk of antimicrobial resistance, it is required to use broad-spectrum antimicrobial compounds that are safe and effective on many different genera of microbes. This could be achieved only by screening various bioactive compounds from traditional medicinal plants against various diseases. The therapeutic potential of many medicinal plants has been already mentioned in the history of Ayurveda and followed traditionally by many people from different parts of the world. However, a systematic scientific study is required to prove the broad-spectrum activity and safeness. In the below sections the important medicinal herbs with their broad-spectrum antimicrobial activities and commercial aspects are discussed.

4. Medicinal herbs and their antimicrobial properties

Plants produces various secondary metabolites for their defense against pathogens (fungus, virus, and bacteria) and these metabolites have great potential as natural drugs [31]. The phytochemicals and secondary metabolites are classified into phenolics, polyphenols, alkaloids, tannins, terpenes, flavonoids, quinones, coumarins, lectins, polypeptides, saponins, etc [32]. These metabolites act as antimicrobial agents and possess unique mode of action. Some of these compounds specifically disrupt membrane/structure, interfere with metabolism, genetic material synthesis, and quorum sensing of the pathogen [33]. The bioactive compound needs to be extracted from plant to use as drug or any formulations. Extraction of the bioactive compounds depends on timely collection of plants, drying, grinding, type of solvent used, temperature during extraction, pH of the media, and ratio between solvent to sample. The polar solvents such as water, methanol, and ethanol are used in extraction of polar compound and the non-polar compounds are extracted using hexane and dichloromethane [34]. The various solvents used in extraction of bioactive compounds is shown in table 1 and the broad-spectrum antimicrobial activities of selected medicinal plants extracts prepared using various solvents are discussed in detail.

Table 1: Solvents used in extraction of various bioactive compounds from plants

Name of compound	Boiling point	Solvents used in extraction
Aloin	752.60 °C	Water, Dimethyl sulphoxide (DMSO), ethanol, and methanol
Acemannan	1521.1 ºC	Water
Chrysophanic Acid	357.45 °C	DMSO and dimethyl formamide (DMF)
Aloe-emodin	568.8 °C	DMSO and DMF
Alpha tocopherol	235 °C	Ether, acetone, chloroform, and ethanol
Phytol	204 °C	Ethanol, DMSO, and DMF
Oleic acid	360 °C	Ethanol, ether, acetone, chloroform, DMF, and DMSO
Linoleic acid	230 °C	Water and acetone
Atropine	429.8 °C	Water
DHP	86 °C	Ethanol, methanol, and acetonitrile
Rutin	983.1 °C	DMSO and DMF
Quercetin	642 °C	Ethanol, DMSO, and DMF
Kaempferol	582.1 °C	Ethanol, DMSO, and DMF
Gallic acid	501.1 °C	Ethanol, DMSO, and DMF
Camphor	209 °C	Alcohol, ether, acetone, and benzene
Eugenol	254 °C	Water, alcohol, chloroform, and ether
Linalool	198 °C	Paraffin oil and propylene glycol
Ursolic acid	556.9 °C	Ethanol, DMSO, and DMF
Apigenin	555.50 °C	Ethanol, DMSO, and DMF
Plumbagin	383.9 °C	Methanol, ethanol, and DMSO

5. *Aloe vera*

5.1.1 Antibacterial activity

Several studies were published on antibacterial activity of *Aloe vera* gel and leaf extracts against human pathogens. In 2009, Arunkumar and Muthuselvam determined the impact of various solvent (ethanol, aqueous, and acetone) extracts on *A. barbadensis* leaf against *Streptococcus pyogens*, *Escherichia coli*, *S. aureus*, and *P. aeruginosa* [35]. The acetone extract had shown the highest zone of inhibition *viz*., 20±0.35 mm, 12±0.45 mm, 15±0.38 mm, and 20±0.57 mm against these pathogens respectively as compared to other extracts. Thiruppathi *et al*. (2010) [36] studied the various solvent extracts (Petroleum ether, ethyl acetate, hexane, and ethanol) of *A. barbadensis* against *Bacillus subtilis*, *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *and P. aeruginosa* [36]. In the study, ethanol extract had shown the highest inhibition activity (ZOI: 7-12 mm) followed by ethyl acetate (ZOI: 1-9 mm) as compared to others [36].

Malar *et al*. 2012 evaluated the dimethyl sulphoxide (DMSO) crude extract of *A. barbadensis* gel against S. *typhi*, *B. subtilis*, *E. coli*, *S. aureus*, and *Proteus vulgaris*. The highest ZOI was observed against *E. coli* (13 mm) [37]. In the same year, another group of scientists Fani and Kohanteb evaluated inhibitory activity of *A. barbadensis* on *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Streptococcus mutans*, and *Bacteroides fragilis* [38]. The highest inhibitory activity was observed against *S. mutans* (MIC of 12.5 µg/mL). Dharajiya *et al*. (2017) investigated the antibacterial activity of different solvent extracts (methanol, hexane, water, and ethyl acetate) of leaves of *A. barbadensis* [39]. The hexane extract had shown the highest zone of inhibition (ZOI) (13.67±0.57 mm) against *Serratia marcescens* (MIC: 6.25 mg/mL). The phytochemical analysis of hexane extract revealed the presence of phenol, sterols, saponins, and alkaloids as active compounds.

5.1.2 Antifungal activity

Various studies have been published to assess the antifungal

activity of *Aloe vera*. Arunkumar and Muthuselvam (2009) [35] determined the antifungal activity of three solvent extracts (acetone, water, and ethanol) of *Aloe vera* leaf using the disc diffusion method [35]. Among these, acetone extracts have reported highest inhibition of *Aspergillus flavus* (15±0.73 mm) and *Aspergillus niger* (8±0.37 mm) as compared to others. In 2012, Malar and colleagues evaluated the effect of DMSO extract of *A. barbadensis* gel against *Candida albicans*, *Aspergillus fumigatus*, and *Penicillium* sp. [37]. The highest inhibitory activity was observed with *C. albicans* (ZOI: 11 mm) followed by *Penicillium* sp. (ZOI: 9 mm) [37]. The ethanol extract of *A. barbadensis* shown significant inhibitory activity against *C. albicans* at 1000 µg/mL concentration (ZOI: 14 mm) [40].

Saniasiaya *et al*. (2017) tested water and ethanol extract of *A. barbadensis* leaves against *C. albicans* and *A. niger* [35]. In the study only *A. niger* growth was inhibited by both the extracts (Ethanol: MIC 4.4 and Water: 5.1 g/mL) and both the extracts were failed to inhibit *Candida* growth [41].

5.1.3 Antiviral activity

Rezazadeh *et al*. (2016) evaluated the antiviral activity of various concentrations (0.2, 0.5, 1, 2, and 5%) of DMSO extracted *Aloe vera* gel on Herpex Simplex virus 1 (HSV-1) in verda reno (Vero) cell lines[42]. These concentrations were found non cytotoxic and inhibition toxicity was found dose dependent.

The Acemannan a type of aloe poly saccharide (APS) prepared from *Aloe vera* is an USFDA (United States Food and Drug Administration) approved drug to treat acquired immunodeficiency syndrome (AIDS) [43]. The Acemannan affects AIDS virus replication by modifying the glycosylation of the infected host cell. In *in vivo* studies, these were known to increase the specific antibodies against other viruses such as Coxsackievirus B3 [44]. Sun *et al*. (2018), studied the antiviral effect of APS (20-640 µg/mL) on Influenza A virus in Madin-Darby canine kidney (MDCK) cell lines of Mice [45]. The viral replication kinetic assay showed the inhibition of viral replication at all the tested concentrations. The transmission electron microscopic (TEM) analysis showed the reduced viral load/adsorption on cell surface as compared to untreated infected cell lines.

Choi *et al*. (2019) evaluated the *Aloe vera* ethanol extract on influenza virus (green fluorescent labelled) in MDK cell lines [46]. After the post-treatment, the infected cells (MDK) have shown reduced viral matrix proteins (M1 and M2), mRNA synthesis, hemagglutinin, and autophagy. The catechin hydrate, quercetin, and kaempferol were reported as active ingredients in ethanol extract. Sydiskis *et al*. (1991) evaluated the antiviral activity of glycerine leaf extract of *Aloe vera* containing anthraquinone [47]. The antiviral activities of this extract were attributed to the presence of active components such as de-glycosylated Aloin and Aloe-emodin. The Aloe-emodin was found effective against only enveloped RNA and DNA viruses (Ex., Influenza virus, Pseudorabies virus, HSV type 1 and 2). Parvez *et al*. (2019) demonstrated the targeted activity of Aloe-emodin on Herpes B virus with cytochrome p450 activity[48]. Li *et al*. (2014) studied the antiviral effect of Aloe-emodin on influenza virus [49]. It was known to affect the virus by acting on Toll-like receptor 4 protein, casein kinase 2, Nuclear factor-kappa (NF-KB), interferon - γ pathways, signal transducer and activator of transcription (STAT), virus entry and replication.

Borges-Argaez *et al*. (2019) evaluated the antiviral effects of *Aloe vera* root isolates and their derivatives [50]. The acetylation or addition of tetra-O-acetyl-β-D-glucopyranosyl at C3-position of aloesaponarin-1 had increased the effectiveness on influenza A H1N1 [51]. The various bioactive compounds of *Aloe vera* have shown antiviral properties. The lectins were found to inhibit the multiplication of Cytomegalovirus (CMC) in cell cultures [52, 53], Chrysophanic acid showed 50% inhibition of type 2 and type 3 polioviruses. The Aloin has been widely characterized and was known to affect Haemorrhagic Rhadovirus Septicaemia [52, 54]. Keivan *et al*. (2007) shown antiviral activity of glycerine extract of *Aloe vera* gel on HSV2 virus in Vero cell lines[53]. The extract found to affect the adsorption and various stages of the virus post-infection. The extract at 428 and 536 µg/mL was found to reduce the viral load by 50% before and after attachment to the cell lines. Kahlon *et al*. [56], shown that acemannan extract of *Aloe vera* acts independently and synergistically with acyclovir and azidothymidine to block the AIDS and herpes virus [56].

5.2 *Cynodon*

5.2.1 Antibacterial activity

Rao and colleagues (2011) studied the aqueous extracts of *C. dactylon* whole plant against *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. aureus*, and *Proteus mirabilis* [59]. The aqueous extract shown highest inhibitory activity against *E. coli* and *P. aeruginosa* with 14 mm ZOI. The phytochemical analysis of water extract revealed the presence of flavonoids, saponins, steroids, and tannins in aqueous extracts [59]. Pandey *et al*. (2016) reported the antibacterial activity of different solvent (acetone, chloroform, water, and ethanol) leaf extracts of *C. dactylon* against *E. coli* using the disc diffusion method [60]. The ethanol extract showed highest activity (ZOI: 11.33 mm±0.570) at 1 mg/L as compared to other extracts. Phytochemical analysis of the ethanol extract of *C. dactylon* showed the presence of flavonoids, cardiac glycosides, saponins, tannins, and carbohydrates [60].

Raj and colleagues in 2017 studied the antibacterial activity of different solvent extracts (methanol, acetone, chloroform, ethanol, and water) prepared from leaves of *C. dactylon*[61] against bacterial pathogens. The ethanol extracts showed significant inhibition of *B. subtilis* (ZOI: 13 mm) and *S. aureus* (ZOI: 16 mm). Whereas, acetone extract was found active against *P. aeruginosa* and *B. subtilis* with 13 mm and 12 mm ZOI respectively. The phytochemical analysis showed the presence of flavonoids, protein, and carbohydrates in ethanol extract and only flavonoids were found in acetone extract [61]. Savadi *et al*. (2020) investigated the antibacterial activity of *C. dactylon* rhizome methanolic extract [62]. The highest ZOI was observed with methanolic extract against *Bacillus cereus* (18.3±0.4 mm) and *E. coli* (16.8±0.5 mm). The methanolic extract was found to contain palmitic acid (36.40%), oleic acid (28.26%), linoleic acid (17.01%), alpha tocopherol (151.39 mg/kg), phenols (917.08 mg/kg), and sitosterol (3199.62 mg/kg) [62].

5.2.2 Antifungal activity

Several literature studies reported the antifungal activity of *C. dactylon*. Kanimozhi *et al*. (2012) tested the various solvent extracts (Ethanol, acetone, chloroform, methanol, petroleum ether, and hexane) of *C. dactylon* against fungal pathogens such as *Candida tropicalis*, *Candida kefyr*, and *A. niger*[63]. All the extracts have shown antifungal activity, however, the extracts of ethanol showed higher ZOI against *A. niger* (12.23±0.21 mm) followed by *C. albicans* (11.0±0.20 mm) as compared to other solvent extracts.

The whole plant hydroalcoholic extract of *C. dactylon* was used to study the antifungal activity against the deadly keratogenic fungi such as *Epidermophyton floccosum* and *Microsporum gypseum* [64]. Out of the two concentrations tested (1000 and 750 µg/mL), 1000 µg/mL showed 19 mm and 16 mm ZOI on *E. floccosum* and *M. gypseum* respectively and this was found higher than 750 µg/mL concentration. The antifungal activity of *C. dactylon* was attributed to the presence of triterpenoid and saponins in hydroalcoholic extract fraction. Hence, it can be used as a natural agent in the preparation of various formulations against dermatophytic infections. Savadi *et al*. (2020) studied the composition and antifungal activity of methanolic extract of rhizomes of *C. dactylon* [62]. The methanolic extract at 1000 mg/L was found to inhibit the *A. niger* and showed 14.4 ± 0.45 mm inhibition zone.

5.2.3 Antiviral activity

Pringproa *et al*. (2014) studied the *in vitro* virucidal activity of *C. dactylon* crude extract on Porcine reproductive and respiratory syndrome virus (PRRSV) [65]. The whole plant crude extract of *C. dactylon* prepared in DMSO was found to inhibit PRRSV at 0.78 mg/L after 24 hours of post-infection in the Meat Animal Research Centre-145 (MARC-145) cell line. At this concentration the crude extract did not show any cytotoxic effect on cell lines, however, it had completely inactivated PRRSV. The authors have recommended the use of *C. dactylon* extract as a natural potential antiviral agent to control PRRSV.

The whole plant ethanolic extract of *C. dactylon* rich in luteolin and apigenin was evaluated for cytotoxicity and antiviral properties using Vero cells and the Chikungunya virus. The fraction was known to affect the mRNA synthesis of the virus at 50 µg/mL concentration and exhibited significant virucidal activity (98%) [66]. These studies confirms that *C. dactylon* has broad-spectrum antimicrobial properties and can be used in the development of formulations against various pathogens.

5.3 *Datura*

5.3.1 Antibacterial activity

Several groups of researchers have investigated the antibacterial properties of crude solvent extracts of *D. metel* against human pathogens. Okwu and Igara (2009) extracted and characterized antibacterial agents from *D. metel* leaves. The compound was identified as 5^1, 7^1-dimethyl 6^1- hydroxy 3^1, phenyl 3 α - amine β - yne sitosterol 1 (alkaloid) by nuclear magnetic resonance, infrared spectroscopy, and mass spectroscopy. The compound showed antibacterial activity (ZOI) in the decreasing order from *P. aeruginosa* (11.0±0.20), *B. Subtilis* (10.0±0.02), *K. pneumonia* (7.0±0.20), *S. typhi* (7.0±0.11), *S. aureus* (6.0±0.02), and *P. mirabilis* (5.0±0.10) [74]. Akharaiyi in 2011, tested the crude aqueous and ethanol extracts of *D. metel* leaf, stem bark, and roots against eight clinical pathogens (*Streptococcus beta-hemolytic*, *Streptococcus dysenteriae*, *P. aeruginosa*, *S. aureus*, *E. coli*, *B. cereus*, *K. pneumoniae*, and *S. typhi*) using agar well diffusion technique[75]. Ethanol leaf extracts showed the highest ZOI (> 30 mm) against *P. aeruginosa*, *K. pneumonia*, and *B. cereus*. Phytochemical analysis of ethanol extracts of *Datura* showed the presence of alkaloids, saponins, glycosides, flavonoids, and phenolics as bioactive compounds [75].

Muthusamy *et al*. (2014) tested acetone, water, and chloroform extracts of *D. metel* leaves against three human pathogens *B. subtilis*, *E. coli*, and *S. typhi* using agar disc and well diffusion techniques [76]. Their study showed that acetone extracts were more effective than water and chloroform extracts. The acetone extract showed the highest ZOI against *E. coli* (24 mm) and *S. typhi* (19 mm). The phytochemical analysis of acetone extract showed the presence of compounds such as terpenoids, alkaloids, steroids, saponins, flavonoids, glycosides, and phenolics [76]. Krishnan and colleagues (2017) analyzed the antibacterial activity of solvent extracts of *D. metel* leaves against four pathogenic bacteria *B. cereus*, *B. subtilis*, *E. coli*, and *S. typhi* by agar diffusion method [77]. In the study, ethanolic extract was effective against *B. subtilis* (ZOI: 26 mm), *B. cereus* (ZOI: 24 mm), *S. typhi* (ZOI: 24 mm), and *E. coli* (ZOI: 21 mm). The phytochemical analysis of the ethanolic extract revealed the presence of compounds such as flavonoid, alkaloid, tannin, saponins, amino acids, and glucosides [77]. Lim *et al*. (2020) evaluated the antibacterial activity of fruit extract of *D. metel* against *S. aureus* and *E. coli* by disc diffusion method [78]. The fruit extracts were found effective against *S. aureus* (ZOI: 7.3 mm) and *E. coli* (ZOI: 9.0 mm). The antibacterial activity of the extract was related to the presence of terpenoids, alkaloids, steroids, and tannins [78].

Venkanna *et al*. (2013), investigated the antibacterial activity of ethyl acetate and methanolic extracts of *Datura stramonium* flowers and leaves against methicillin-resistant *S. aureus* (MRSA) using the agar well diffusion technique [79]. The ethyl acetate extract of leaves showed the highest inhibitory activity against MRSA (28±1) and the MIC was found to be 0.156±0.02 mg/mL. The thin layer and silica gel chromatography of ethyl acetate extract of leaves showed the presence of phenolics, alkaloids, steroids, terpenoids, tannins, and saponins [79]. Shagal and colleagues (2012) investigated the antibacterial activity of aqueous and ethanolic extract of stem-bark of *D. stramonium* [80]. The bacterial species used for the study were *S. typhi*, *S. aureus*, *Shigella* sp., *K. pneumonia*, *E. coli*, and *Neisseria gonorrhea*. The study showed that the ethanolic extract was found more effective than aqueous extract and exhibited antibacterial activity against all the tested species except *N. gonorrhea*. However, the aqueous extract was found only effective against *S. aureus*. In the ethanolic extract, the highest ZOI was observed against *K. pneumoniae* (13 mm). The phytochemical screening of ethanolic extracts showed the presence of alkaloids, flavonoids, glycosides, saponins, and steroids as bioactive compounds [80].

5.3.2 Antifungal activity

Antifungal activity of *D. metel* was reported in various literature. Sharma, (2002) investigated the antifungal activity of different solvent extracts (methanol, chloroform, hexane, and acetone) of *D. metel*[83]. In the study, *A. flavus*, *A. niger*, and *A. fumigatus* were used as test organisms. The chloroform fraction of *D. metel* inhibited the growth of all three species of fungus at MIC of 625 µg/mL [81]. Dabur *et al*. (2004) examined methanolic extract of *D. metel* against three pathogenic *Aspergillus* species using the disc diffusion method [82]. The methanolic extracts of the plant showed significant inhibitory activity against *A. flavus*, *A. niger*, and *A. fumigatus* at 0.062 mg/disc concentration.

Dabur *et al*. (2005) evaluated the antifungal activity of 2-(3, 4-dimethyl-2, 5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate (DHP) a completely unique compound extracted from *D. metel* against *A. fumigatus*, *A. niger*, *A. flavus*, *C. tropicalis*, and *C. albicans* [83]. The results showed that the

compound dissolved in DMSO was found effective (90%) against all the tested species. The MIC90 of this extract was in the range of 21.87 to 43.75 µg/mL against all these fungi [83]. Dabur and colleagues (2007) studied the post-antifungal effect (PAFE) of DHP on *A. fumigatus*. They have reported that DHP dissolved in DMSO was found to inhibit the secretory proteins such as metalloprotease, which plays a critical role in virulence of the pathogen [84].

5.3.3 Antiviral activity
Numerous studies were published on evaluating the antiviral properties of *D. metel*. Roy *et al*. (2016) conducted *in vitro* studies to prove the efficacy of soxhlet and cold extracts of *Datura metel* (fruit and seed) on rabies virus using Vero cell lines [85]. The cell line was infected with the rabies virus at a standard concentration of 10^{-4} titer (RVCS) and treated with various concentrations of the extract. The fruit and seed extract at 2.5 mg/mL and 1.5 mg/mL have shown 50% inhibition of RVCS respectively. This study proves that the extract has potential for treating rabies virus under *in vitro* conditions. Roy *et al*. (2018) evaluated the anti-rabies activities of soxhlet and cold extracts of *D. metel* [86] *in vivo* using albino mice infected with rabies virus (LD50). The oral administration of extract of *Datura* at 60 mg/30 g of body weight of mice (intracerebrally) showed that the extract was nontoxic to albino mice. In the pre-exposure group treatment, 20% of infected mice were survived. Whereas 100% mortality of the mice was observed in the post-exposure treatment. This *in vivo* studies proves that the *Datura* has potential antirabies properties.
The atropine bioactive compound extracted from *Datura* was evaluated against New castle disease virus, HSV, Japanese encephalitis, Adenovirus, Influenza virus, and Sindbis virus. The Primary monkey-kidney cells, chick embryo, and HeLa S3 were used to culture the viruses. Atropine was found to affect the growth and formation of enveloped viruses, by interfering with the glycosylation. Most of the viruses, which were multiplied in presence of atropine, were found avirulent [87-89]. These published studies indicate that *Datura* is a potential antimicrobial plant.

5.4 *Euphorbia*
5.4.1 Antibacterial activity
Kumarasamy *et al*. (2008) reported the efficacy of aqueous leaf extract of *E. hirta* against *E. coli*, *S. aureus*, *P. aeruginosa*, and *B. subtilis*[91]. Singh and Kumar (2013) evaluated effect of free and bound (covalently bound to plant matrix) form of flavonoids from *E. hirta*[92]. The free flavonoid of root showed the highest inhibitory activity against *S. aureus* (IZ: 18.33 mm, MIC: 0.039, Minimum bactericidal concentration (MBC): 0.078). The bound fruits flavonoid showed significant activity against *P. mirabilis* (ZI: 17 mm, MIC: 0.039, MBC: 0.039). However, bound stem extract flavonoid showed activity against all tested bacteria. Phytochemical screening of bound stem extract of *E. hirta* shown the presence of two flavonoids kaempferol and quercetin.
Kumari and Pandey (2017) tested the antibacterial activity of different plant parts of *E. hirta* (bud, leaf, and stem) [93]. Water, methanol, and ethanol solvent extracts were used to test antibacterial activity against *S. aureus*. The highest ZOI (20 mm) was observed in methanol leaf extract followed by ethanol (15 mm) and water (13 mm) extracts [93]. Saravanan *et al*. (2012) tested ethanol and petroleum ether extracts of different parts (leaf, stem, and bud) of *E. hirta* against several bacterial pathogens [94]. The results showed that ethanol extract was found more inhibitory than petroleum ether and shown the highest zone of inhibition against *E. coli* (28 mm) and *S. typhi* (33 mm) at 75 µg/mL concentration and at 100 µg/mL against *S. typhi* (ZOI: 25.3 mm).

5.4.2 Antifungal activity
Rao and colleagues (2010) reported the antifungal activity of ethanolic extract of the *E. hirta* leaves collected from August to December against *A. niger* with 13.90±0.11 mm ZOI [95]. Singh and Kumar (2013) examined the antifungal activity of the free and bound form of flavonoid obtained from *E. hirta*[92] against *C. albicans*, *A. niger*, *A. flavus*, and *T. mentagrophytes*. The bound flavonoid obtained from root of the plants showed highest inhibitory activity against *C. albicans* with 27.66 mm ZOI. The MIC and minimum fungicidal concentration (MFC) were determined as 0.039 mg/mL for this organism.
Gupta and colleagues (2018) investigated the antifungal activity of different solvent (petroleum ether, water, chloroform: methanol and ethanol) extracts of *E. hirta* (flowers and leaves)[96]. The ethanol extract of leaves showed maximum inhibitory activity against *C. albicans* (ZOI: 17±0.1 mm) and 12.5 mg/mL. The phytochemical analysis of the ethanol extract revealed the presence of terpenoids, tannins, steroids, flavonoids, alkaloids, glycosides, and carbohydrates.

5.4.3 Antiviral activity
Traditionally, *E. hirta* was used in curing dengue fever in the rural areas of many countries. The leaves of this plant are commonly called gatas-gatas or Tawa-tawa and are used in the preparation of formulation to cure fever symptoms caused by viral infections [97]. Tayone *et al*. (2014) studied the anti-dengue effect of whole plant ethyl acetate fraction (EAF) of *E. hirta* [98]. The EAF fraction had significantly reduced the plaque-forming capacity of dengue virus serotype 1 by 85%. In another study, the ethanol extract of *E. hirta* inhibited serotype 2 of the dengue virus by 34.7% [99].
Gyuris *et al*. (2009) studied the antiretroviral properties of *E. hirta* on HIV1, HIV2, and Simian immunodeficiency virus (SIVmac251) in metallothionein 4 (MT4) human T lymphocyte cell line [100]. The concentration of 442 µg/mL was determined as cytotoxic inhibitory concentration. The direct aqueous extract of aerial parts of *E. hirta* was found to inhibit the reverse transcriptase activity of the virus HIV1, HIV2, and SIVmac251 with IC50 values of 38, 22, and 177 µg/mL respectively. In further studies, the 50% methanol and aqueous extracts were studied on HIV1, both the extracts have exhibited a higher level of antiviral activities with an IC 50 value of 5 and 9 µg/mL respectively. In another treatment, when the tannins were removed from the aqueous extract, the antiviral activity was drastically reduced, and the author concluded that tannins were responsible for the antiretroviral activity.
Rotavirus causes diarrhea in children below 5 years. Even though the vaccine is available for rotavirus, the efficacy was not proven on various strains and there is a concern on various side effects and health issues. To develop the phytomedicine Arun *et al*. (2019) studied the anti-rotavirus properties of acetone extract prepared from whole plant of *E. hirta* under *in vitro* conditions using MA104 (African Green Monkey fetal kidney) cell line [101]. The results showed that the higher antiviral activity was observed after incubation of cell line with extract before infection. The antiviral activity was reduced by 50% after infection and antiviral properties was attributed to the presence of bioactive compounds such as

steroids, flavonoids, alkaloids, phenolics, and tannins.
Siva Ganesh *et al*. (2015) conducted molecular docking studies to find out the anti-dengue bioactive compounds from the *E. hirta* [102]. The bioactive compounds such as myricetin, rutin, quercetin, protocatechuic acid, kaempferol, and gallic acid from *E. hirta* have been subjected to docking study using Lead IT (FlexX) and Maestro (Glide) software. The dengue methyltransferase (2P40) and dengue protease (2FOM) virus have been used as target sites for modulation study. Out of these bioactive compounds, quercetin shown strong binding activity with both the targets and found potential to develop drug against the dengue viruses.

5.5 *Ocimum*
5.5.1 Antibacterial activity
Geeta and colleagues (2001) analysed the antibacterial activity of aqueous and alcoholic extracts of *Ocimum sanctum* leaves [109]. The aqueous extract showed the highest ZOI (> 20 mm) against *Klebsiella aerogens, S. typhi*, and *S. aureus*. Whereas the alcoholic extract showed the highest inhibitory activity against *Vibrio cholera*. Singh *et al*. (2005) evaluated the antibacterial activity of fixed oil extracted from *O. sanctum* L using petroleum ether against *Bacillus pumilus, S. aureus, and P. aeruginosa* [110]. The linolenic acid was found effective against *S. aureus*. Naik and colleagues (2015) tested antibacterial activity of methanol, acetone, and hexane leaf extracts of *O. tenuiflorum* [111]. The acetone and methanol extract have shown the highest inhibitory activity against *E. coli* with a 7 mm zone of inhibition.
Yamani *et al*. (2016) tested the effect of essential oils extracted from leaves and inflorescence of *O. tenuiflorum* against bacterial pathogens [112]. The essential oils at 2.25% and 4.5% concentration were found to inhibit the growth of MRSA and *E. coli* respectively. The gas chromatography-mass spectrometry (GC-MS) analysis revealed the presence of eucalyptol, camphor, and eugenol compounds. The Mallikarjun *et al*. (2016) evaluated the ethanolic leaf extract of Tulsi against periodontal pathogens [113]. The extract showed the highest ZOI (>35 mm) against *A. actinomycetemcomitans* at 5% and 10% concentrations. Saravanakumar *et al*. (2018) evaluated the antibacterial activity of ethanol, methanol, and acetone extracts of *O. tenuiflorum* leaf using the agar well diffusion method[114]. In the study ethanol extract showed the growth inhibition of *Salmonella gallinarum* (ZOI: 18mm±1.25).

5.5.2 Antifungal activity
Khan *et al*. (2010) evaluated the antifungal activity of water extracts and essential oil of five medicinal plants [115]. In the study, Tulsi essential oil (TEO) showed effective inhibition against *C. tropicalis* and *C. albicans* with MIC90 value of 0.024% v/v. The GC-MS profile of TEO revealed the presence of compounds linalool (44.3%), 1, 8-cineole (21.7%), methyl eugenol (6.3%), and eugenol (4.4%). Gupta and colleagues, (2014) examined the antifungal activity of water extracts prepared from leaves of *O.* sanctum [116] against *A. niger*, *Cladpsporium* sp., *Curvularia lunata*, and *Rizopous*. The results showed extract at 40% concentration was found to inhibit ~75% growth of *A. niger*, *Cladpsporium* sp., and *Rizopous*. Whereas 30% extract was found to inhibit the growth of *C. lunata* by 75% [116].
Gopalkrishna *et al*. (2016) tested the antifungal activity of *O. sanctum* seed oil extract prepared using petroleum ether against fungal oral pathogens such as *C. albicans* ATCC 90028, *Candida dubliniensis* MYA 646, *Candida glabrata* 90030, *Candida krusei* 6258, *Candida parapsilosis* 22019, and *C. tropicalis* 13803 [117]. Seed oil, at 7 µl concentration showed 61 mm zone of inhibition against *C. krusei* 6258. The neutral lipids (NL) fraction and unsaponifiable matter (UM) of seed extract showed 2.5 µL as MIC value against *C. albicans* and *C. krusei*. The mixtures of phospholipids (PL) and unsaponifiable matter (UM), at 1.25 µL was determined as MIC against *C. albicans* and *C. krusei*.

5.5.3 Antiviral activity
Ghoke *et al*. (2018) studied the antiviral properties of *O. sanctum* leaf hydro-methanolic extract on the influenza H92 virus[118]. The authors have tested the different extracts of the plant (polyphenols, crude extract, and terpenoids) on virus in chicken eggs model. All the extracts have shown antiviral properties, however significant ($p < 0.001$-0.01) reduction of viral nucleic acid was observed at the lowest concentration of crude and terpenoids fraction and maintained the antiviral activity for > 72 hours. Jayati *et al*. (2013) studied the hot water extract prepared from leaves of *O. sanctum* against New castle disease virus (NCDV) in chicken embryo fibroblast monolayer culture (CEFMC) [119]. The dose at 10 mg/mL was found nontoxic to cells and a brought virus titer to the lowest concentration. The absence of non-cytopathic effect and lower virus titer in CEFMC were the indicative and confirmative results for antiviral properties.
Chiang *et al*. (2005) evaluated the antiviral properties of purified ethanol and water extracts of *Ocimum basilicum* on various RNA (enterovirus 71 (EV71), coxsackievirus B1 (CVB1)) and DNA viruses (hepatitis B virus (HBV), adenoviruses (ADV), and HSV) [120]. In the study, the purified components such as linalool, ursolic acid, apigenin showed broad-spectrum inhibitory activity against various viruses. Out of these purified compounds the ursolic acid shown the strongest antiviral activity against HSV-1, ADV-8, CVB1, and EV71 with an EC50 of 6.6 mg/L, 4.2 mg/L, 0.4 mg/L, and 0.5 mg/L; selective index of 15.2, 23.8, 251.3, and 201 respectively. The linalool was found potent against ADV-11 with EC50 of 16.9 mg/L and selective index of 10.5. Whereas the apigenin was found inhibiting HSV-2, ADV-III, and HBV with an EC50 of 9.7 mg/L, 11.1 mg/L, 7.1 mg/L, with a selective index of 6.2, 5.4, and 2.3 respectively.
Kapewangolo *et al*. (2017) studied the antiviral activity of ethanol extract and isolated component (pheophytin a) obtained from leaves of *O. labiatum* on HIV1 expression [121]. At, the IC50 value of 49.8±0.4 µg/mL, the crude extract inhibited HIV1-protease activity and showed milder inhibition (20%) of HIV-1 reverse transcriptase. The extract showed a cytotoxic effect on U1 cells at 42.0±0.13 µg/mL and affected the replication of HIV1 at 25 µg/mL. The active compound from the crude extract was isolated and identified as pheophytin and tested against the HIV1-protease. Pheophytin was found to inhibit HIV-1PR at 44.4±1.5 µg/mL, (C50) and shown a CC50 value of 51.3±1.0 µg/mL in U1 cells. The leaf extract of *O. sanctum* is known to contain many secondary metabolites (linalool, apigenin, ursolic acid, and eugenol) and which are proven, antiviral agents. The essential oil and various parts of aqueous extract of *O. sanctum* were evaluated on encephalitis patients [122]. The essential oil and the extract shown antiviral activities on poliovirus type-3 [123], WSSV, infectious pancreatic necrosis virus [124], HBV, and RNA viruses (CVB1, HSV, ADV, and EV) [125, 126].
Joshi *et al*. (2014) demonstrated the anti-H1N1 activity of using leaf ethanol extract of *O. sanctum* in MDCK cells [127. The extract showed a low cytotoxic effect and reported CC50 value of 726.2±3.1 µg/mL. For 0.1, 1, 5, and 10 multiplicity

of infection (MOI) of the virus, the IC50 value of 38.6±2.2, 44.7±0.7, 54.1±1.4, and 55.5±0.9 µg/mL were observed respectively. In the study, it was found that post-infection treatment was found more effective than the simultaneous and pre-treatment mode. The extract was mainly found to affect replication and protein synthesis. The important bioactive compounds of the all medicinal plants mentioned in this review and their mode of action are listed in table 2.

Table 2: Bioactive compounds of all medicinal plants and their mode of action

Group	Bioactive compound	Medicinal plant	Mode of action	References
Anthraquinone	Aloin	*A. vera*	Destruct the phospholipid bilayer of the virus	54
	Aloin	*A. vera*	Proteolytic activity on 3C replicase of the virus	53, 55
	Acemannan	*A. vera*	Glycosylation of viral protein and also affects the cell fusion and virus release	52
	Chrysophanic Acid	*A. vera*	Affects the penetration, initial cleavage of translation of viral RNA	53, 54
	Aloe-emodin	*A. vera*	Affects the synthesis of nucleic acid	58
Alkaloids	Lectins	*A. vera*	Affects the protein synthesis	57
	Atropine	*D. metel*	Inhibits the growth of enveloped viruses by blocking the process of protein glycosylation	87
		D. metel	Inhibits spore germination	81
	5',7' dimethyl 6'-hydroxy 3', phenyl 3 α-amine β-yne Sitosterol	*D. metel*	Affect the synthesis of peptidoglycan layer of bacterial cell wall which leads to osmotic shock and cell death	74
		E. hirta	Creates surface cracks which may relate to cell collapse and loss of function	103
Terpenoid	Alpha tocopherol	*C. dactylon*	Increases the permeability of the bacterial cell membrane	67
	Phytol	*C. dactylon*	Inducing oxidative stress response	68
		O. sanctum	Disturbs bacterial and fungal cell and cytoplasmic membrane. Inhibits virus replication	130
	Camphor	*O. sanctum*	Destabilization of membrane phospholipids, enzymes and proteins	132
	Linalool	*O. sanctum*	Interfere with the integrity of cell and cytoplasmic membrane	134
	Ursolic acid	*O. sanctum*	Suppress viral p65 phosphorylation to prevent nuclear factor κB (NF-κB) pathway (control of virus replication)	135
Flavanoids	Catechin	*C. dactylon*	Inhibits the entry step of several viruses	73
		D. metel	Disturbs the permeability of bacterial cell membrane which leads to cell lysis	90
	Quercetin	*E. hirta*	Increases the permeability of bacterial cytoplasmic membrane	105
	Kaempferol	*E. hirta*	Inhibits ATPase activity by binding to bacterial DNA helicase	106
		O. sanctum	Inhibits nucleic acid synthesis	128
	Apigenin	*O. sanctum*	Interact with bacterial membrane and lead to cell lysis. Inhibits bacterial DNA gyrase.	136, 137
Saponins		*C. dactylon*	Causing leakage of proteins and certain enzymes from the cell	72
Tannins		*E. hirta*	Inhibits viral replication	100
		O. sanctum	Inactivates transport proteins of cell envelope	129
Glycoside	Rutin	*E. hirta*	Damage to cell membrane which could result in leakage of cellular proteins	104
Steroids		*C. dactylon*	Associate with membrane lipid and exerts its action by causing leakages from liposomes	71
Fatty acid	Oleic acid	*C. dactylon*	Inhibits bacterial attachment	69
	Linoleic acid	*C. dactylon*	Induce autolysis of bacterial cell walls	70
DHP		*D. metel*	Inhibits secretory protein	84
Phenolic acid	Gallic acid	*E. hirta*	Inhibits efflux pumps, which are involved in generating resistance bacteria	107
	Gallic acid	*E. hirta*	Damage to cell membrane which results in leakage of essential intracellular constituents	108
Polyphenols		*O. sanctum*	Disrupts fungal cell wall by forming complexes with soluble proteins	131
Phenylpropanoid	Eugenol	*O. sanctum*	Deterioration, lysis, protein and lipid leakage of bacterial cell wall	133

6. Medicinal plants and their application in overcoming multidrug resistance of microbes

The resistance of pathogenic microbes to various drugs is a global concern. As per the estimate by 2050, AMR will cause ~10 M deaths at an expense of hundred trillion dollar [138]. The excess and irrational use of antimicrobial agents (antibacterial/antiviral/antifungal) has led to the evolution of resistant strains. The AMR properties from resistant strains are transferred to the progeny through gene transfer (horizontal/vertical). The inheritance of these drug resistance genes causes the development of microbes which are resistant to various new drugs hence, AMR is a huge socio-economic concern. Plants have been a source of therapeutic agents (antimicrobial, analgesic, antineoplastics, and cardio protective agents) from many years and secondary metabolites of plants are the most important products[139]. The phytochemical extracts of plant are complex mixture of various chemicals, therefore it's very difficult for a microbe to develop resistance against these extracts [140]. The phytochemical extract of plants kill microbes and prevent the disease by various actions such as inhibiting protein interactions, cell signalling, multiplication, infection process, cell wall structure, DNA/RNA synthesis, intermediary metabolism, cytoplasmic constituents and also can modulate immune responses [141]. Fresh *A. vera* gel was used by Banu *et al.* [142], against MDR bacteria at 200 µg/ml MIC concentration to prevent wound infection caused by MDR *Pseudomonas aeruginosa* [143]. Grimaudo *et al.* [144], tested antitumor effects of aglycon aloe-emodin from *A. vera* on human MDR leukemia cell line. Aloe-emodin was found to cause cytostasis and inhibit cell cycles (S and G2-M). A flavonoid, kaempferol showed a cytotoxic effect on leukemia cells and induced apoptosis by inhibiting the MDR protein [145, 146] and also increased the Bax/Bcl-2 ratio. A carboxylic fatty acid isolated from *A. barbadensis* formulated as an ointment was tested against MDR, *K. pneumoniae*, *E. coli*, *S. aureus*, *P. aeruginosa*, *Talaromyces flavus*, and *C. albicans*. In the study formulated ointment exhibited anti-infective activity and found effective wound healing agent [147]. Shokeen *et al.* [148], tested antigonorrhoeal activity of eugenol (85-256 mg/L) extracted from *O. sanctum* against various MDR *Neisseria gonorrhoeae*. The hydroalcoholic root extract of *C. dactylon*, showed significant growth inhibition of MDR *P. aeruginosa* [149].

7. Market demand and the commercial products of the selected medicinal plants

Medicinal plants play a vital role in pharmacological research and drug development due to the presence of various phytochemicals and bioactive compounds. As per World Health Organisation (WHO), around 25% of modern drugs are derived from medicinal plants.

The international market demand for medicinal plants is growing at a rate of 7% annually. The annual export of Indian medicinal flora is worth of 1200 million rupees. The worldwide alternative medicine marketplace is projected to reach 296.3 billion US dollars by 2027 and is growing at a compound annual growth rate (CAGR) of 19.9%. The Indian traditional medicine market is estimated to reach INR 710.87 billion by 2024, with a CAGR of ~16.06% [150].

All the medicinal herbs selected for this study are having large market demand and commercial importance. The worldwide *Aloe vera* extract market was 1.60 billion USD in 2018 and is predicted to grow at a CAGR of 7.6% from 2018 to 2025 [151]. The companies such as Aloe Laboratories Inc., Patanjali Ayurved, India, Herbalife International of America, Lily of the Desert, and Terry Laboratories Inc are working on Aloe vera extract.

Various Ayurvedic products of of *E. hirta* are sanjivani vati, Chhoti dudhi juice, Chhoti dudhi ras, *E. hirta* powder, and Vrikka sanjivini vati. Also, *Datura* extracts are used in the manufacturing of pain relief drugs and asthma. Topical pain relief market size is projected to reach 11.78 billion USD by 2025, at a 6.25% CAGR[152]. As per Fior Markets, the worldwide asthma spacers marketplace is predicted to raise from 1.44 billion USD in 2017 to 2.05 billion USD by 2025 at a CAGR of 4.14% [153].

Tulsi is categorized as a high-value crop. The key companies working on Tulsi extracts are, Ambuj Naturals, Frontier Natural Products, Greenwell Overseas, Mountain Rose Herbs, Rosa Food Products, and Sajeevan Organic. The various products of Tulsi plants are Tulsi drops, juice, ghan vati, face wash, Ginger tea, Chyawanprash, Tulasi tablets, and Immunocharge pill.

8. Conclusion and future perspective

Plants and their products were used for medicinal purposes for a very long time. Without any knowledge, and as a practice, many plants were consumed and used in treating diseases caused by pathogenic microbes. With the advancement of science and technology, the research on various medicinal plants and their antimicrobial properties were systematically studied and bioactive compounds from the plants were accurately identified and used for the development of concentrated drugs. The drugs, which were developed from medicinal plants, were found safe, more potent without any side effects, less cytotoxic, and broad-spectrum. Because of these properties in recent years, plant medicines are gaining more focus. Several antimicrobial studies with various solvent or crude extracts of these selected medicinal herbs or bioactive compounds showed promising antimicrobial activity against various types of bacteria, fungi, and viral pathogens of mammals. Hence, the drugs developed from these herbs can act as alternative medicines to synthetic drugs and could be a potential solution for the emerging antimicrobial resistance problem. Since there is a huge demand for natural medicines in the global market, farmers can consider and cultivate these medicinal crops in marginal lands to increase their income. Even though there are several advantages with plant-based antimicrobial agents, certain challenges such as bioavailability, the appropriate concentration, and tissue penetration need to be addressed. The scientific communities need to carry out further research on these selected plants to identify novel compounds and should conduct detailed *In vivo* and *In vitro* studies to prove the efficacy and to develop new therapeutics for emerging diseases.

9. Acknowledgements

We would like to acknowledge Dr Ajit Sapre Group President, Research and Technology, Reliance Industries Limited for giving approval to write this review article.

10. Competing interests

The authors declare that there is no conflict of interest for this publication.

11. Highlights

This review discusses about the antimicrobial resistance and the possible mechanisms. Systematically reviewed the broad-spectrum antimicrobial properties (bacterial, fungal, and viral) of five medicinal herbs and their importance in alternative drug development.

12. Traditionality

Alternative medicines are in line with the traditional medicines. The selected herbs were used for treating many ailments and are cited in the history of Ayurveda.

13. Abbreviations

AMR, antimicrobial resistance; MBC, minimum bactericidal concentration; MDR, multidrug resistance; MFC, minimum fungicidal concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus* (MRSA); TIM, traditional Indian medicine; ZOI, zone of inhibition.

14. References

1. Bloom DE, Cadarette D. Infectious disease threats in the twenty-first century: Strengthening the global response. Front Immunol. 2019;10:549.
2. Aminov RI. A Brief history of the antibiotic era: Lessons learned and challenges for the future. Front Microbiol. 2010;1:134.
3. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-318.
4. De Kraker MEA, Stewardson J, Harbath S. Will 10 million people die a year due to antimicrobial resistance by 2050? PLoS Med. 2016;13(11):e1002184.
5. Jamshidi-Kia F, Lorigooini Z, Amini-Khoei H. Medicinal plants: Past history and future perspective. J Herbmed Pharmacol. 2018;7(1):1-7.
6. Brown ED, Wright GD. Antibacterial drug discovery in the resistance era. Nature. 2016;529(7586):336-343.
7. Chin YW, Balunas MJ, Chai HB, *et al*. Drug discovery from natural sources. AAPS J. 2006;8:E239-E253.
8. Asase A, Kokubun T, Grayer RJ, *et al*. Chemical constituents and antimicrobial activity of medicinal plants from Ghana: *Cassia sieberiana*, *Haematostaphis barteri*, *Mitragyna inermis* and *Pseudocedrela kotschyi*. Phytother Res. 2008;22(8):1013-1016.
9. Chavan SS, Damale MG, Devanand B. Antibacterial and antifungal drugs from natural source: A Review of clinical development. Natural Products in Clin Trials. 2018;1:114.

10. Pandey MM, Rastogi S, Rawat AKS. Indian traditional Ayurvedic system of medicine and nutritional supplementation. Evidence-Based Compl and Alter Med; c2013. Article ID 376327.
11. Mintah SO, Asafo-Agyei T, Archer MA, *et al*. Medicinal plants for treatment of prevalent diseases. Pharmacognosy - Medicinal Plants; c2019. DOI:10.5772/intechopen.82049.
12. Chandra H, Bishnoi P, Yadav A, *et al*. Antimicrobial resistance and the alternative resources with special emphasis on plant-based antimicrobials-A Review. Plants. 2017;6(2):16.
13. Dhama K, Tiwari R, Chakrabort S, *et al*. Evidence based antibacterial potentials of medicinal plants and herbs countering bacterial pathogens especially in the era of emerging drug resistance: an integrated update. Inter J Pharmacol. 2014;10(1):1-43.
14. Oladosu S, Balogun O, Zhi-Qiang L. Chemical constituents of *Allophylus africanus*. Chinese J Natural Med. 2015;13(2):133-141.
15. Kennedy DO, Wightman EL. Herbal extracts and phytochemicals: plant secondary metabolites and the enhancement of human brain function. Adv in Nutr. 2011;2(1):32-50.
16. Adeeyo AO, Odiyo J, Odelade K. Chemical profiling and antimicrobial properties of phyto-active extracts fromTerminalia glaucescens stem against water microbial contaminants. Open Biotechnol J. 2018, 12(1).
17. Singh A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. African J Trad Complemen Altern Med. 2013;10(5):210-229.
18. Aloe Cure. The History of Aloe vera. American Global Health Group; c2021.
19. Susanne S. Medicinal plants of ancient. Aloe Medical Group International; c2021.
20. Collins E, Collins C. Roentgen dermatitis treated with fresh whole leaf of *Aloe vera*. American J Roentgenol. 1935;33(3):396-7.
21. Lanka S. A review on Aloe vera-the wonder medicinal plant. J Drug Deliver Therapeu. 2018;8(5):94-99.
22. Firdaus N, Uzma V, Munawwar HK. Potential and pharmacological actions of *Dhatura safed* (*Datura metel* l.): as a deadly poison and as a drug: an overview. Intern J Pharmaceu Sci Res. 2020;11(7):3123-3137.
23. Christian R. The Encyclopaedia of psychoactive plants: ethnopharmacology and its applications. Rochester Park Street Press; c1998.
24. Ali ES. Medical importance of *Datura fastuosa* (syn: *Datura metel*) and *Datura stramonium* - A review. IOSR J Pharmacy. 2017;7(2):43-58.
25. Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev. 1999;12(4):564-582.
26. WHO, World Health Report. World Health Organization, Geneva, Switzerland, WHO Publications Office; c2003. p. 1-50.
27. Witte W, Cuny C, Strommenger B, *et al*. Emergence of a new community acquired MRSA strain in Germany. Euro Surveill. 2004;9(1):1-2.
28. Sanglard D. Emerging threats in antifungal-resistant fungal pathogens. Front Med. 2016;3:11.
29. Strasfeld L, Chou S. Antiviral Drug Resistance: Mechanisms and Clinical Implications. Infect Dis Clin North Am. 2010;24(2):413-437.
30. Michael CA, Dominey-Howes D, Labbate M. The antibiotic resistance crisis: causes, consequences, and management. Front Public Health. 2014;2:145.
31. Boy HI, Rutilla AJ, Santos KA, Ty AM, Alicia IY, Mahboob T, *et al*. Recommended Medicinal Plants as Source of Natural Products: A Review. Digit Chin Med. 2018;1(2):131-142.
32. Alamgir ANM. Pharmacognostical Botany: Classification of Medicinal and Aromatic Plants (MAPs), Botanical Taxonomy, Morphology, and Anatomy of Drug Plants. In Therapeutic Use of Medicinal Plants and Their Extracts; Springer: Cham, Switzerland. 2017;1:177-293.
33. Chitemerere TA, Mukanganyama S. Evaluation of cell membrane integrity as a potential antimicrobial target for plant products. BMC Complement Altern Med 2014;14:278.
34. Das K, Tiwari RK, Shrivastava DK. Techniques for evaluation of medicinal plant products as antimicrobial agents: Current methods and future trends. J Med Plants Res. 2010;4(2):104-11.
35. Arunkumar S, Muthuselvam M. Analysis of phytochemical constituents and antimicrobial activities of Aloe vera L. against clinical pathogens. World J of Agri Sci. 2009;5(5):572-6.
36. Thiruppathi S, Ramasubramanian V, Sivakumar T, *et al*. Antimicrobial activity of Aloe vera (L.) Burm. f. against pathogenic microorganisms. J Bio sci Res. 2010;1(4):251-8.
37. Malar RT, Johnson M, Nancy Beaulah S, *et al*. Anti-bacterial and antifungal activity of aloe vera gel extract. Intern J Biomed and Advance Res. 2012;3(3):184-187.
38. Fani M, Kohanteb J. Inhibitory activity of aloe vera gel on some clinically isolated cariogenic and periodontopathic bacteria. J Oral Sci. 2012;54(1):15-21.
39. Dharajiya D, Pagi N, Jasani H, *et al*. Antimicrobial activity and phytochemical screening of Aloe vera (Aloe barbadensis Miller); Inter J of Curr Microbiol and Appl Sci ISSN: 2319-7706. 2017;6(3):2152-2162.
40. Shireen F, Manipal S, Prabu D. Anti-fungal activity of Aloe vera: *In vitro* study. SRM J of Res in Dental Sci. 2015;6(2):92-95.
41. Saniasiaya J, Salim R, Mohamad I, *et al*. Antifungal effect of Malaysian Aloe vera leaf extract on selected fungal species of pathogenic Otomycosis species *in vitro* culture medium. Oman Medical J. 2017;32(1):41-46.
42. Rezazadeh F, Moshaverinia M, Motamedifar M, *et al*. Assessment of Anti HSV-1 activity of Aloe vera gel extract: An *In vitro* study. J Dent (Shiraz) 2016;17(1):49-54.
43. Kahlon JB, Kemp MC, Carpenter RH, *et al*. Inhibition of AIDS virus replication by acemannan *in vitro*. Mol Biother. 1991a;3(3):127-35.
44. Gauntt CJ, Wood HJ, McDaniel HR, *et al*. Aloe polymannose enhances anti-coxsackievirus antibody titres in mice. Phytother Res. 2000;14(4):261-266.
45. Sun Z, Yu C, Wang W, *et al*. Aloe polysaccharides inhibit Influenza A virus infection-A promising natural anti-flu drug. Front Microbiol. 2018;9:2338.
46. Choi JG, Lee H, Kim YS, *et al*. Aloe vera and its components inhibit influenza A virus-induced autophagy and replication. Am J Chin Med. 2019;47(6):1307-1324.
47. Sydiskis RJ, Owen DG, Lohr JL, *et al*. Inactivation of enveloped viruses by anthraquinones extracted from plants. Antimicrob agents and Chemother. 1991;35(12):2463-2466.
48. Parvez MK, Al-Dosari MS, Alam P, *et al*. The anti-hepatitis B virus therapeutic potential of anthraquinones derived from Aloe vera. Phytother Res. 2019;33(11):2960-2970.
49. Li SW, Yang TC, Lai CC, *et al*. Anti-viral activity of

aloe-emodin against influenza A virus via galectin 3 up-regulation. Eur J Pharmacol. 2014;738:125-132.
50. Borges-Argaez R, Chan-Balan R, Cetina-Montejo L, *et al*. *In vitro* evaluation of anthraquinones from aloe vera roots and several derivatives against strains of influenza virus. Indus Crops and Prod. 2019;132:468-475.
51. Yagi A, Makino K, Nishioka I. Studies on the constituents of Aloe saponaria Haw. I. The structures of tetrahydroanthracene derivatives and the related anthraquinones. Chem and Pharma Bulletin. 1974;22(5):1159-1166.
52. Sharrif MM, Sandeep KV. Aloe vera their chemicals composition and applications: A review. Int J Biol Med Res. 2011;2(1):466-471.
53. Morin E. Aloe vera (L.) Burm. f.: Aspects pharmacologiques et cliniques. These dedoctorat en pharmacie, Faculté de Pharmacie, Université de Nantes; c2008, 224.
54. Alves DS, Perez-Fons L, Estepa A, *et al*. Membrane-related effects underlying the biological activity of the anthraquinones emolin and barbaloin. Biochem pharmacol. 2004;68(3):549-561.
55. Keivan Z, Moloud AZ, Kohzad S, *et al*. Antiviral activity of Aloe vera against herpes simplex virus type 2: An *in vitro* study. African J of Biotechnol. 2007;6(15):1770-1773.
56. Kahlon JB, Kemp MC, Yawei N, *et al*. *In vitro* evaluation of the synergistic antiviral effects of acemannan in combination with azidothymidine and acyclovir. Mol Biother. 1991b;3(4):214-23.
57. Wynn RL. Aloe vera gel: Update for dentistry. General Dentistry. 2005;53(1):6-9.
58. Mpiana PT, Ngbolua KT, Tshibangu DS, *et al*. *Aloe vera* (L.) Burm. F. as a potential anti-COVID-19 plant: A mini-review of its antiviral activity. Europ J Medicin Plant. 2020;31(8):86-93.
59. Rao AS, Nayanatara AK, Rashmi KS, *et al*. Potential antibacterial and antinfungal activity of aqueous extract of *Cynodon Dactylon*. Int J Pha Res. 2011;2(11):2889-2893.
60. Pandey K, Singh CS, Prasad RK, *et al*. Studies of anti-microbial activity using leaf extract of *Cynodon dactylon*. Der Pharmacia Lettre. 2016;8(3):325-330.
61. Raj VN, Almalki MA, Varghese R, *et al*. Phytochemical screening and antibacterial activity of *Cynodon dactylon* against human pathogens. Int J Adv Res. 2017;5(10):124-128.
62. Savadi S, Vazifedoost M, Didar Z, *et al*. Phytochemical analysis and antimicrobial/antioxidant activity of *Cynodon dactylon* (L.) Pers. rhizome methanolic extract. Jou Food Quality; c2020, 10.
63. Kanimozhi D, Ratha bai V. Evaluation of anti-microbial activity of *Cynodon dactylon*. Int J Res Phar. 2012;2(2):34-43.
64. Sudan P, Goswami M, Singh J. Antifungal activity of hydroalcholic extract of *Cynodon dactylon* against dermatophytes. Int J Res Phar; c2020. https://doi.org/10.26452/ijrps.v11i1.1784.
65. Pringproa K, Khonghiran O, Kunanoppadol S, *et al*. *In vitro* virucidal and virustatic properties of the crude extract of *Cynodon dactylon* against Porcine reproductive and respiratory syndrome virus. Vet Med Int. 2014;(1):947589.
66. Murali KS, Sivasubramanian S, Vincent S, *et al*. Anti-chikungunya activity of luteolin and apigenin rich fraction from *Cynodon dactylon*. Asian Pac J Trop Med. 2015;8(5):352-358.
67. Andrade JC, Morais-Braga MF, Guedes GM, *et al*. Biomed Pharmacother. 2014;68(8):1065-1069.
68. Lee W, Woo ER, Lee DG. Phytol has antibacterial property by inducing oxidative stress response in *Pseudomonas aeruginosa*. Free Radical Res. 2016;50(12):1309-1318, Doi:10.1080/10715762.2016.1241395.
69. Stenz L, François P, Fischer A, *et al*. Impact of oleic acid (cis-9-octadecenoic acid) on bacterial viability and biofilm production in *Staphylococcus aureus*. FEMS Microbiol Lett. 2008;287(2):149-155.
70. Kenny JG, Ward D, Josefsson E, *et al*. The *Staphylococcus aureus* response to 31 unsaturated long chain free fatty acids: survival mechanisms and virulence implications. PLoS One. 2009;4(2):e4344.
71. Raquel F. Epand: Bacterial lipid composition and the antimicrobial efficacy of cationic steroid compounds. Biochimica Biophysica Acta; c2007. p. 2500-2509.
72. Zablotowicz RM, Hoagland RE, Wagner SC. Effect of saponins on the growth and activity of rhizosphere bacteria. Adv Exp Med Biol. 1996;(405):83-95.
73. Song JM, Lee KH, Song BL. Antiviral effect of catechins in green tea on influenza virus. Antiviral Res. 2005;68(2):66-74.
74. Okwu DE, Igara EC. Isolation, characterization and antibacterial activity of alkaloid from *Datura metel* Linn leaves. Afr J of Phar Phar. 2009;3(5):277-281.
75. Akharaiyi FC. Antibacterial, Phytochemical and Antioxidant activities of *Datura metel*. Int J of PharmTech Res. 2011;3(1):478-483.
76. Muthusamy A, Punitha M, Beslin LG. Phytochemical screening of *Datura Metel* Linn and its antimicrobial activity on selected human pathogens. Int J of Bio. 2014;3(11):3474-3478.
77. Krishnan J, George M, Ajesh G. Phytochemical status, antibacterial activity and antioxidant property of *Datura metel* L. Int J Curr Pharm Res. 2017;9(3):106-110.
78. Lim KMC, Dagalea FMS, Vicencio MCG. Antibacterial activity of *Datura metel* Linn. (TALONG-PUNAY) fruit extract. Jou of Pharm Res Int. 2020;32(21):96-101.
79. Venkanna B, Uma A, Suvarnalaxmi C, *et al*. Antimicrobial property of *Datura* leaf extract against Methicillin-resistant *Staphylococcus aureus* isolated from Urethral and Skin Suppurative Infections. Curr Tren Biote Phar. 2013;7(3):782-792.
80. Shagal MH, Modibbo UU, Liman AB. Pharmacological justification for the ethnomedical use of *Datura stramonium* stem-bark extract in treatment of diseases caused by some pathogenic bacteria. Int Res Pharm Pharmacol. 2012;2(1):16-19.
81. Sharma RGL. Studies on antimycotic properties of *Datura metel*. J Ethno. 2002;80(2-3):193-197.
82. Dabur R, Singh H, Chhillar AK. Antifungal potential of Indian medicinal plants. Fitoterapia. 2004;75(3-4):389-91.
83. Dabur R, Chhillar AK, Yadav V, *et al*. *In vitro* antifungal activity of 2-(3, 4-dimethyl- 2, 5-dihydro-1H-pyrrol-2-yl)-1- methylethyl pentanoate, a dihydropyrrole derivative. J Med Microbiol. 2005;54(6):549-552.
84. Dabur R, Mandal K, Sharma GL. Post-antifungal effects of the antifungal compound2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate on *Aspergillus fumigatus*. J Med Microbiol. 2007;56(6):815-818.
85. Roy S, Mukherjee S, Pawar S, *et al*. Evaluation of *In vitro* antiviral activity of *Datura metel* Linn. against rabies virus. Phcog Res. 2016;8(4):265-9.
86. Roy S, Samant L, Ganjhu R, *et al*. Assessment of *In vivo*

Antiviral Potential of *Datura metel* Linn. extracts against Rabies Virus. Pharm Res. 2018;10(1):109-112.
87. Yamazaki Z, Tagaya I. Antiviral effects of atropine and caffeine. J Gen Virol. 1980;50(2):429-431
88. Alarcon B, Gonzalez ME, Carrasco L. Antiherpesvirus action of atropine. Antimi Age Chemo. 1984;26(5):702-706.
89. Al-Snafi AE. Medical importance of *Datura fastuosa* (syn: *Datura metel*) and *Datura stramonium* - A review. IOSR Jou of Phar. 2017;7(2):43-58.
90. Tagousop CN, Tamokou JD, Ekom SE, *et al*. Antimicrobial activities of flavonoid glycosides from *Graptophyllum grandulosum* and their mechanism of antibacterial action. BMC Complemen Altern Med. 2018;18(1):1-10. Doi: 10.1186/s12906-018-2321-7.
91. Kumarasamy S, Deepa P, Harisaranraj R, *et al*. Antimicrobial and phytochemical investigation of the leaves of *Carica papaya* L., *Cynodon dactylon* (L.) Pers., *Euphorbia hirta* L., *Melia azedarach* L. and *Psidium guajava* L. Ethno Leaf. 2008;12:1184-9.
92. Singh G, Kumar P. Phytochemical study and screening for antimicrobial activity of flavonoids of *Euphorbia hirta*. Int J Appl Basic Med Res. 2013;3(2):111-116.
93. Kumari I, Pandey RK. Antibacterial Activity of *Euphorbia hirta* L. Appli of Biote for Sust Dev; c2017. DOI: 10.1007/978-981-10-5538-6_1.
94. Saravanan R, Dhachinamoorthi D, Senthilkumar K, *et al*. Antibacterial activity of *Euphorbia hirta* extracts. Inter J Res Ayurv and Pharm. 2012;3(3):439-441.
95. Rao KVB, Karthik L, Elumalai EK, *et al*. Antibacterial and antifungal activity of *Euphorbia hirta* l. Leaves: A comparative study. Jou of Pha Res. 2010;3(3):548-549.
96. Gupta D, Kumar M, Gupta V. An *in vitro* investigation of antimicrobial efficacy of *Euphorbia hirta* and *Murraya koenigii* against selected pathogenic microorganisms. Asian J Pharm Clin Res. 2018;11(5):359-363.
97. Abd Kadir SL, Yaakob H, Zulkifli RM. Potential anti-dengue medicinal plants: A review. Jou of Nat Medi. 2013;67(4):677-689.
98. Tayone WC, Tayone JC, Hashimoto M. Isolation and structure elucidation of potential anti-Dengue metabolites from Tawa-Tawa (*Euphorbia hirta* Linn.). Walailak Jou of Sci and Tech. 2014;11(10):825-832.
99. Saptawati LR, Febrinasari P, Yudhani RD, *et al*. *In vitro* study of eight Indonesian plants extracts as anti-Dengue virus. Health Sci Jou of Indo. 2017;8(1):12-18.
100. Gyuris A, Szlaviki L, Minarovits J, *et al*. Antiviral activities of extracts of *Euphorbia hirta* L. against HIV-1, HIV-2 and SIVmac251. *In vivo*. 2009;23(3):429-432.
101. Arun P, Krishnasamic K, Gunasekeranc P, *et al*. Phytochemical analysis of *Euphorbia Hirta* and cytotoxic activity on Ma104. Prog Asp in Pediatric & Neonat. 2019;2(1):116-120.
102. Siva Ganesh M, Awasthi P, Timiri AK, *et al*. A novel approach for rationale selection of medicinal plants against viruses via molecular docking studies. Oak jubilee volume; c2015. The pharmaceutical society ISSN 2347-6001.
103. Rajeh MA, Zuraini Z, Sasidharan S, *et al*. Assessment of *Euphorbia hirta* L. leaf, flower, stem and root extracts for their antibacterial and antifungal activity and brine shrimp lethality. Molecules. 2010;15(9):6008-6018.
104. Gayathri A, Ramesh KV. Antifungal activity of *Euphorbia hirta* L. inflorescence extract against *Aspergillus flavus*- A mode of action study. Int J Curr Microbiol App Sci. 2013;2(4):31-37.
105. Siriwong S, Thumanu K, Hengpratom T, *et al*. Synergy and mode of action of ceftazidime plus quercetin or luteolin on *Streptococcus pyogenes*. Evidence-based Complem. Altern. Med, 2015, 759459.
106. Huang YH, Huang CC, Chen CC, *et al*. Inhibition of *Staphylococcus aureus* PriA helicase by flavonol kaempferol. Protein J. 2015;(34):169-172.
107. Simoes M, Bennett RN, Rosa EA. Understanding antimicrobial activities of phytochemicals against multidrug resistant bacteria and biofilms. Nat Prod Rep 2009;26(6):746-757. DOI: 10.1039/b821648g.
108. Borges A, Ferreira C, Saavedra MJ, *et al*. Antibacterial activity and mode of action of Ferulic and Gallic acids against pathogenic bacteria. Microb Drug Resis. 2013;19(4):256-265. DOI:10.1089/mdr.2012.0244.
109. Geeta, Vasudevan DM, Kedlaya R, *et al*. Activity of *Ocimum sanctum* (the traditional Indian medicinal plant) against the enteric pathogens. Indian J Med Sci. 2001;55(8):34-438.
110. Singh S, Malhotra M, Majumdar DK. Antibacterial activity of *Ocimum sanctum* L. fixed oil. Indian J Exp Biol. 2005;43(9):835-837.
111. Naik LS, Shyam P, Paul MK, *et al*. Antimicrobial activity and phytochemical analysis of *Ocimum tenuiflorum* leaf extract. Int Jou of Pharm Tech Res. 2015;8(1):88-95.
112. Yamani HA, Pang EC, Mantri N, *et al*. Antimicrobial activity of Tulsi (*Ocimum tenuiflorum*) essential oil and their major constituents against three species of bacteria. Front Micro 2016;7:681.
113. Mallikarjun S, Rao A, Gururaghavendran R, *et al*. Antimicrobial efficacy of Tulsi leaf (*Ocimum sanctum*) extract on periodontal pathogens: An *in vitro* study. J Ind Soc Peri. 2016;20(2):145-150.
114. Shahi P, Mandal RA, Mathema AB. Assessing the impact of climate change on medicinal herbs in Humla district. Int. J Geogr. Geol. Environ 2020;2(2):11-17.
115. Khan A, Ahmad A, Manzoor N, *et al*. Antifungal activities of *Ocimum sanctum* essential oil and its lead molecules. Nat Prod Com. 2010;5(2):345-349.
116. Gupta SP, Rana KS, Sharma K, *et al*. Antifungal activity of aqueous leaf extract of *Ocimum sanctum* on dominant fungal species of monuments. Eur Chem Bull. 2014;2(6):609-611.
117. Gopalkrishna AH, Seshagiri M, Muddaiah S, *et al*. *In vitro* antifungal activity of different components of *Centratherum anthelminticum* and *Ocimum sanctum* seed oils and their synergism against oral pathogenic fungi. Jou of Den Res Dent Clini Dent Pros. 2016;10(2):92-98.
118. Ghoke SS, Sood R, Kumar N, *et al*. Evaluation of antiviral activity of *Ocimum sanctum* and *Acacia arabica* leaves extracts against H9N2 virus using embryonated chicken egg model. BMC Complem and Altern Med. 2018;18(1):174.
119. Jayati, Bhatia AK, Kumar A, *et al*. *In vitro* antiviral potential of *Ocimum sanctum* leaves extract against New castle disease virus of poultry. Int Jou of Micr and Immu Res. 2013;2(7):051-055.
120. Chiang LC, Cheng PW, Ching W, *et al*. Antiviral activities of extracts and selected pure constituents of *Ocimum basilicum*. Clin and Exp phar and phy; c2005. p. 1440-1681.
121. Kapewangolo P, Kandawa-Schulz M, Meyer D. Anti-HIV Activity of *Ocimum labiatum* extract and isolated Pheophytin-a. Molecules. 2017;22(11):1763.
122. Rajeshwari S. *Ocimum sanctum*: The Indian home remedy. In Current Medical Scene, Cipla Ltd., Bombay Central, Bombay; c1992.
123. Parida MM, Pandya G, Bhargava R, *et al*. Assessment of

in vitro antiviral activity of certain indigenous plants against polio virus type-3. Ind J Vitro. 1997;13(2):101-105.
124. Direkbusarakom S, Herunsalee A, Yoshimizu M, *et al*. Antiviral activity of several Thai traditional herb extracts against fish pathogenic viruses. Fish Pathol. 1996;31(4):209-213.
125. Bhatia JAK, Gupta A, Goel A, *et al*. Antiviral activity of hot aqueous extract of *Ocimum sanctum* leaves against New castle disease virus. Xith Indian Vety. Congress and XIIth Ann Conf of IAAVR and National symp on vety sciences and education on move: critical gaps and need, 2011, 163.
126. Joseph B, Dar MA, Kumar V. Bioefficacy of plant extracts to control *Fusarium solani, F.* sp., *Melongenae incitant* of Brinjal wilt. Global J Biote Biochem, 2008;3(2):56-59.
127. Joshi G, Sharma S, Acharya J, *et al*. Assesment of *in vitro* antiviral activity of *Ocimum sanctum* (Tulsi) against pandemic swine flu H1N1 virus infection. World Res J Antimi Agen, 2014;3(1):62-67.
128. Xie Y, Yang W, Tang F, *et al*. Antibacterial activities of flavonoids: Structure-activity relationship and mechanism. Curr Med Chem. 2015;22(1):132-149.
129. Ya C, Gaffney SH, Lilley TH, *et al*. Carbohydrate polyphenol complexation. In R. W. Hemingway and J. J. Karchesy (ed.), Chemistry and significance of condensed tannins. Plenum Press, New York, 1988, 553.
130. Kumara Swamy M, Mohd SA, Uma RS. Antimicrobial properties of plant essential oils against Human pathogens and their mode of action: An updated review. Evidence-based Complemen Altern Med, 2016, 21.
131. Rodríguez MA, Troncoso RR, Sánchez EA, *et al*. Efecto antifúngico de extractos fenólicos y de carotenoides de chiltepín (*Capsicum annum* var. glabriusculum) en *Alternaria alternata* y *Fusarium oxysporum*. Revista Argentina De Microbiol. 2015;47(1):72-77, https://doi.org/10.1016/j.ram.2014.12.005.
132. Xu H, Nathaniel TB, David EC. Camphor activates and strongly desensitizes the transient receptor potential vanilloid subtype 1 channel in a vanilloid-independent mechanism. The J Neurosci. 2005;25(39):8924-8937.
133. Oyedemi SO, Okoh AI, Mabinya LV, *et al*. The proposed mechanism of bactericidal action of eugenol, α-terpineol and γ-terpinene against *Listeria monocytogenes*, *Streptococcus pyogenes*, *Proteus vulgaris* and *Escherichia coli*. African J Biotech. 2009;8(7):1280-1286.
134. Greay SJ, Hammer KA. Recent developments in the bioactivity of mono- and diterpenes: anticancer and antimicrobial activity. Phytochem Rev; c2011.
135. Mlala S, Adebola O, Mavuto G, *et al*. Ursolic acid and its derivatives as bioactive agents. Molecules 2019;(24):2751. DOI: 10.3390/molecules24152751.
136. Banerjee K, Banerjee S, Das S, *et al*. Probing the potential of apigenin liposomes in enhancing bacterial membrane perturbation and integrity loss. J Colloid Interface Sci. 2015;(453):48-59.
137. Ohemeng KA, Schwender CF, Fu KP, *et al*. DNA gyrase inhibitory and antibacterial activity of some flavones. Bioorg Med Chem Lett. 1993;3(2):225-230.
138. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations–The Review on Antimicrobial Resistance Chaired by Jim O'Neill; c2016. Wellcome Trust; HM Government; London, UK.
139. Robinson MM, Zhang X. The World Medicines Situation. Traditional Medicines: Global Situation, Issues and Challenges. World Health Organization; Geneva, Switzerland; c2011. p. 1-4.
140. Ody P. The Complete Medicinal Herbal: A Practical Guide to the Healing Properties of Herbs. Skyhorse Publishing Inc.; New York, NY, USA; c2017.
141. Chitemerere TA, Mukanganyama S. Evaluation of cell membrane integrity as a potential antimicrobial target for plant products. BMC Complement. Altern. Med. 2014;14:278. Doi: 10.1186/1472-6882-14-278.
142. Banu A, Sathyanarayana B, Chattannavar G. Efficacy of fresh Aloe vera gel against multi- drug resistant bacteria in infected leg ulcers. Australas Med J. 2012;5(6):305-9.
143. Goudarzi M, Fazeli M, Azad M, Seyedjavadi SS, Mousavi R. *Aloe vera* Gel: Effective Therapeutic Agent against Multidrug-Resistant *Pseudomonas aeruginosa* Isolates Recovered from Burn Wound Infections. Chemot Res Prac; c2015. p. 1-6.
144. Grimaudo S, Tolomeo M, Gancitano RA, D'Alessandro N, Aiello E. Effects of highly purified anthraquinoid compounds form Aloe vera on sensitive and multidrug-resistant leukemia cells. Oncol Rep. 1997;4(2):341-343.
145. Moradzadeh M, Tabarraei A, Sadeghnia HR, Ghorbani A, Mohamadkhani A, Erfanian S, *et al*. Kaempferol increases apoptosis in human acute promyelocytic leukemia cells and inhibits multidrug resistance genes. J Cell Biochem. 2018;119(2):2288-2297.
146. Mogosanu GD, Grumezescu AM, Huang KS, Bejenaru LE, Bejenaru C. Prevention of microbial communities: Novel approaches based natural products. Curr. Pharm. Biotechnol. 2015;16(2):94-111. DOI: 10.2174/1389201016021501121459l6.
147. Donkor MN, Kuubabongnaa N, Donkor AM. Effectiveness of isolated compound from *Aloe barbadensis* Miller and its formulated ointment against bacteria and fungi. J Appl Biotechnol Bioeng. 2021;8(2):47-53.
148. Shokeen P, Bala M, Singh M, Tandon V. *In vitro* activity of eugenol, an active component from *Ocimum sanctum*, against multiresistant and susceptible strains of *Neisseria gonorrhoeae*. Intern J Antimicrob Agents. 2008;32(2):174-179.
149. Jazani NH, Mikaili P, Shayegh J, Haghighi N, Aghamohammadi N, Zartoshti M. Evaluation of Antibacterial Activity of *Cynodon dactylon* on Multi-Drug Resistant Bacterial Isolates in Comparing with Ciprofloxacin. Journal of American Science. 2011;7(6).
150. Dublin. The "Ayurveda market in India 2019". 2020; Research and Markets.com.
151. Grand view research. Global *Aloe vera* extract market size report 2019-2025. 2019; Report ID: GVR-2-68038-883-1.
152. Furion Analytics Research and Consulting. 2019; Report Code: HCR 93908
153. Avinash D. The global asthma spacers market. Fior Market Research; c2020.
154. Saravanakumar P, Thangapandiyan S, Dharanipriya R, *et al*. Phytochemical analysis and antimicrobial activity of *Ocimum tenuiflorum* (Tulsi), a known Indian folk medicinal plant. Int J Pharm Sci Rev Res. 2018;53(2):24-28.