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Use of plant derived antimicrobials as an alternative to antibiotics

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Abstract
Antibiotics are marvelous drugs. They fight against various infectious diseases and saved millions of lives. However the recent failure of antibiotics due to drug resistant pathogens and rapid spread of new infections, pressurize the health organizations and pharmaceutical industries to change their strategy and stop going slow growing production of more synthetic antibiotics against the fast growing antibiotic resistant organisms. There are considerable alternative sources of natural antimicrobials from plant with different mode of actions and was found to have competitive effects compared to commercial antibiotics. This reviews shows the plant derived antimicrobials as alternative source for synthetic antimicrobials.

Keywords: Antibiotics, antibiotic resistant, medicinal plant, plant derived antimicrobials, antimicrobial activity, traditional medicines

Introduction
INSPITE of presence of lots of advancements in medicinal industries, bacteria are biggest problem causing agents to human health. There are different and number of highly potent antibiotics are present to fight against bacteria. Penicillin was the first antibiotic which was discovered by Flemimg in 1929 [28] (Fleming, 1929) [28]. These microbial derived antibiotics fully revolutionized bacterial therapy. Even penicillin became the main therapeutic option for infectious disease. After this, large number of medicines was discovered against bacterial and fungal infection.

As the discovery of antibiotics increased, the microorganisms continue to developed resistance to these antibiotics (Davies *et al*., 2010) [20]. The multidrug resistance (MDR) also occurs due to prolonged use of antibiotics (Abraham *et al*.,1940, Rammelkamp *et al*.,1942) [5, 73]. Multidrug resistant microorganisms are capable to resist the effects of three or more antibiotics (Styers *et al*., 2006). The strains of *Mycobacterium tuberculosis*, resistant to virtually all classes of antimicrobials have been identified (Gandhi *et al*. 2006), a typical example of extremely drug resistant tuberculosis (XDR TB) reported in 64 countries to date (World Health Organization 2011). Due to increased incidence of bacterial resistance to antibiotics there has been a corresponding decrease in antimicrobial discovery. This situation attract the researchers toward alternative therapies like traditional plant based medicines, bacteriophage therapies and combinational therapies. Traditional medicines (use of plant, plant products and plant extracts) are the attractive method to combat antibiotic resistant pathogens. The total estimated plant species on earth is 250,000 to 5,00,000 species. Among these species, only 1-10% species are used by animal and humans (Osman *et al*., 2012, Borris *et al*., 1996) [67, 9].

There are 7500 species are known medicinal plant. Out of these, 4635 species are commercially used to a fairly large scale. Inspite of greater advancement in synthetic organic chemistry of twentieth century, over 25% prescribed medicines are derived directly or indirectly from plants (Punjabi *et al*., 2014) [71].

Development of Antibiotic Resistance
Antibiotic resistant is a big issue to health organizations. Even, the theme of World Health Day 2011 was "Antimicrobial Resistance: No action today, No cure tomorrow."

Antibiotic resistance is the ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once sensitive. The microbes know how to develop resistance against antibiotics. Bacteria become resistant to antibiotics by adapting their structures and functions in some way as a defense mechanism (Levy, 1998, Morar *et al*., 2010, Dever *et al*., 1991) [48, 61, 22].

Fig 1: The timeline of antibiotic development and evolution of antibiotic resistant given here (Dahal *et al*., 2018) [18].

The adaptation can happen in several ways. Bacteria can:

- Pump out the antibiotic from
- Cell (efflux pumps).
- Change the site or receptor where the antibiotic normally works (targ*et al*teration).
- Neutralize the antibiotic before has a "killing" effect (produce inactivating enzymes)
- Decrease antibiotic uptake.
- Share genetic material with other bacteria to also make them resistant.

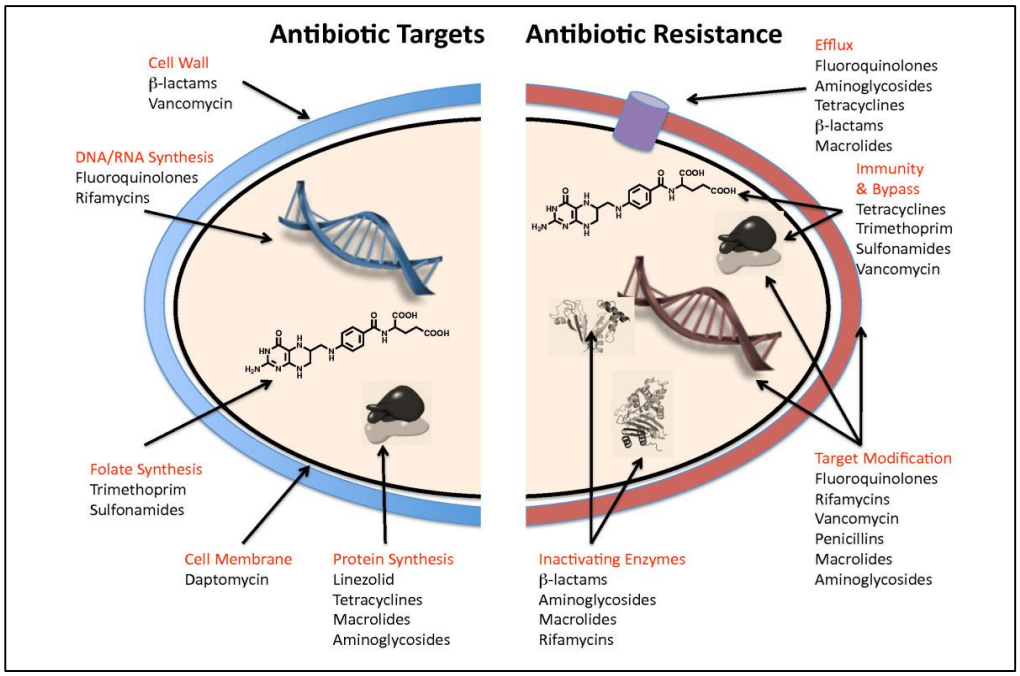

Fig 2: Antibiotic Targets and Antibiotic Resistance (Wright, 2005) [95].

Bacteria have different mode of resistance to different antibiotics. There are lots of antibiotics which are in clinical use and bacteria shows resistant to them by different modes. A table is listed below which shows antibiotic in clinical use and modes of resistance (Cheesman *et al*., 2017) [13].

Table 1: Antibiotic in clinical use and modes of resistance.

Antibiotic Class	Examples	Drug Target	Resistance Mode
β-lactams	Penicillins (Ampicillin) Cephalosporins (cephamycin) Penems (meropenem) Monobactams (aztreonam)	Peptidoglycan biosynthesis	Hydrolysis Efflux Altered target
Aminoglycosides	Gentamicin Streptomycin Spectinomycin	Translocation	Phosphorylation Acetylation Nucleotidylation Efflux Altered target
Glycopeptides	Vancomycin Teicoplanin	Peptidoglycan biosynthesis	Reprogramming of peptidoglycan biosynthesis
Tetracyclines	Minocycline Tigecycline	Translation	Monooxygenation Efflux Altered target
Macrolides	Erythromycin Azithromycin	Translation	Hydrolysis Glycosylation Phosphorylation Efflux Altered target
Phenicols	Chloramphenicol	Translation	Acetylation Efflux Altered target
Quinolones	Ciprofloxacin	DNA replication	Acetylation Efflux Altered target
Pyrimidines	Trimethoprim	C1 metabolism	Efflux Altered target
Sulfonamides	Sulfamethoxazole	C1 metabolism	Efflux Altered target

Plant derived antimicrobials are used as an alternative to antibiotics because they have different and numerous mode of actions to kill microorganisms (Upadhyay *et al*. 2014) [87].

Plant Derived Antimicrobials

Most plant derived antimicrobials are produced as secondary metabolites. They can be classified based on their chemical structure, which also influences their antimicrobial property.

The major groups of phytochemicals are listed here

Plant-Derived Antimicrobials	Examples	Selected Antimicrobial Spectrum	References
Flavonoids	**Phenolics And Polyphenols** Flavones (Rutin) Flavonones (Naringenin) Catechins (Catechin, Epicatechin) Anthocyanins (Cyaniding)	*Listeria monocytogenes* *Staphylococcus aureus* *Escherichia coli* *Salmonella enterica* *Vibrio cholera* *Pseudomonas aeruginosa* *Acinetobacter baumannii* *Klebsiella pneumonia* *Aspergillus flavus* *Penicillin* Sp. Cladosporium Sp.	Beecher, 2003 [29] [263]; chye and Hoh, 2007 [24] [264]; Orhan *et al*., 2010 [16] [265]; Rattanachaikunsopon *et al*., 2010 [69] Ozcelik *et al*., 2008 [7]; Cushnie and Lamb, 2005 [54].
Quinones	Anthraquinone Benzoquinone Naphthoquinone Plastoquinone Pyrroloquinoline Quinone	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Bacillus subtilis* *Cryptococcus neoformans*	Ignacimuthu *et al*., 2009 [46]; Singh *et al*., 2006 [17]; Cowan, 1999 [51].
Tannins	Tannic Acid Gallic Acid Proanthocyanidins	*Staphylococcus aureus* *Bacillus cereus* *Listeria monocytogenes* *Salmonella enterica* *Campylobacter jejuni*	Engels *et al*., 2009 [11]; Scalbert, 1991 [2, 80].
Coumarins	Ammoresinol Ostruthin Anthogenol Agasyllin	*Staphylococcus aureus* *Listeria monocytogenes* *E. coli* *Salmonella typhimurium* *Salmonella enteritidis* *Vibrio parahaemolyticus*	Basile *et al*., 2009 [1]; Ulate-Rodriguez *et al*., 1997 [40]; Venugopala *et al*., 2013 [38]; Saleem *et al*., 2010 [52]; Cowan, 1999 [51].
Terpenoids	Carotenoids Terpinene	*S. aureus* *Pseudomonas aeruginosa*	Ulubelen, 2013 [3]; Bach *et al*., 2011 [77];

	Isopentenyl Pyrophosphate	*Vibrio cholera* *Salmonella typhi*	Batista *et al*., 1994 [65]; Mathabe *et al*., 2008 [50].
Lectins And Polypeptides	Concanavalin A Wheat Germ Agglutinin(WGA) Aleuria Aurantia Lectin(AAL)	*Staphylococcus aureus* *Bacillus subtilis* *Escherichia coli* *P. aeruginosa* *Candida albicans*	Hardman And Ainsworth, 1972 [37]; Petnual *et al*., 2010 [68]; Kheeree *et al*., 2010 [62]; Peumans And Van Damme, 1995 [90].

Phenolics and Polyphenols

These are the diverse group of aromatic secondary metabolites. They consist of Flavonoids, Quinones, Tannins and Coumarins (Savoia, 2012, Cowan, 1999, Kurek *et al*. 2011) [79, 51, 43].

Flavonoids

Flavonoids are pigmented compounds. They mainly consists of flavones, flavonones, flavanols and anthocyanidins (Cowan, 1999, Kurek *et al*., 2011) [51, 43]. There are 14 classes of flavonoids (Savoia, 2012) [79].

Mechanism of action: The antimicrobial property against a variety of bacterial and fungal pathogens is mediated by their action on the microbial cell membranes (Kramer *et al*., 1984, Davidson *et al*., 2000)). They interact with membrane proteins which are present on the bacterial cell wall leading to increased membrane permeability and disruption. They have ability to form complexes with both extracellular and soluble proteins.

Other mode of actions are biofilm formation, inhibition of cell envelop synthesis, inhibition of nucleic acid synthesis, inhibition of electron transport chain and ATP synthesis.

Some flavonoids which shows antimicrobacterial activity are Morin, Rutin, Quercetin, Myricetin, Naringenin, Lupinifolin etc (Farhadi *et al*., 2018) [25].

Table 2: Antibacterial effect of flavonoids

Compounds	Source	Bacteria	Activity	References
Morin	*Psidium guajava*	*Aeromonas salmonicida*	MIC : 150-200 µg/ml	(Rattanachaikunsopon & Phumkhachorn, 2007) [75]
Rutin	*Litchi chinesis*	*Staphylococcus aureus* *Escherichia coli Shigella dysenteriae*	MIC : 62.5 µg/ml	(Wen *et al*., 2014) [91]
Quercetin	*Diospyrs virginiana*	*Staphylococcus aureus*	MIC : 50 µg/ml	(Rashed *et al*., 2014) [74]
Myricetin	Pure	*Mycobacterium*	MIC : 32µg/ml	(Lechner, Gibbons, & Bucar, 2008) [46]
Naringenin	Pure	*Escherichia coli Bacillus subtilis*	MIC : 2µg/ml	(Šmejkal *et al*., 2008) [82]
Lupinifolin	*Mundulea sericea*	*Staphylococcus aureus* *Bacillus subtilis Escherichia coli*	MIC : 0.5µg	(Mazimba *et al*., 2012) [59]

Flanonoids also contain antioxidant, anti-inflammatory, anticancer and antiviral properties.

Quinones

QUINONES are organic compounds that contains aromatic rings with two ketone substitutions.

Mechanism of action: they form complex irreversibly with nucleophilic amino acids in protein, often leading to their inactivation and loss of function (Sher, 2004) [1]. The major targets in microbial cells are surface exposed adhesion proteins, cell wall polypeptides and membrane bound enzymes, consequently leading to death of pathogens (Ciocan *et al*., 2007) [15].

Quinone such as Anthraquinone is obtained from *Cassia italica* shows bacteriostsic action against pathogen bacteria such as *Bacillus anthracis*, *Corynebacterium pseudodiphtherium* and Pseudomonas aeruginosa. It shows bactericidal against *Burkholderia pseudomallei* (Kazmi *et al*., 1994) [39] Mariyam Malmir *et al* studied antimicrobial activity of Anthraquinone against various microorganisms (Malmir, 2017.) [57].

Table 3: Antimicrobial activity of Anthraquinone

Source	Bacteria	Activity
Aloe vera	*Helicobacter pylori*	MIC : 6.25-400µg/ml
Rheum rhabarbarum	*Aeromonas hydrophilia*	MIC : 50-200µg/ml
Rheum rhaponticum	*Staphylococcus saprophyticus*	MIC : 125-250µg/ml
Rheum palmatum	*Staphylococcus aureus*	MIC : 1.56-25µg/ml
Cassia species	*Bacillus subtilis*	MIC : 7.8µg/ml
	Staphylococcus aureus	MIC : 3.9µg/ml

Tannins

Tannins are a group of polymeric phenolic compounds. They are found in almost every part of plant including bark, leave, fruit and roots (Scalbert, 1991) [2, 80].

Mechanism of action: The mode of antimicrobial activity of tannin is potentially due to inactivation of microbial adhesion, enzymes, cell envelop and transport protein (Calixto *et al*., 2009, Ya *et al*., 1998, Haslam, 1996) [78, 96, 33].

Hydrolysable and condensed tannins, obtained from flavanols and known as proanthocyanidins, exert antimicrobial effect by by antiperoxidation properties inhibiting in particular the growth of uropathogenic *E. coli* (Okuda, 2005).

The main sources for tannins which are studied are Catharanthus roseus, Terminalia arjuna and Piper betel (Kurhekar, 2016) [44].

Table 4: effect of extract of Catharanthus roseus, Piper betel, Terminalia arjuna on microorganisns, in terms of Zone of inhibition in mm (mean ±

	Catharanthus roseus		Piper betel		Terminalia arjuna	
Name of bacteria	**Aqueous extract**	**Acetone extract**	**Aqueous extract**	**Acetone extract**	**Aqueous extract**	**Acetone extract**
B. subtilis	-	-		11.83 ± 0.98	-	11.66 ± 1.03
S. aureua	-	-	15.33 ± 2.16	-	14.83 ± 2.04	14.5 ± 1.04
Ent. fecalis	14.83 ± 1.47	-	-	-	-	16.83 ± 1.16
M. luteus	-	-	-	-	15.83 ± 1.47	19.33 ± 1.03
E. coli	19.16 ± 1.94	-	-	-	-	20 ± 1.26
K. pneumoniae	21.66 ± 2.33	-		-	-	21.33 ± 1.03
Sal. typhi	-	-	-	-	-	14.83 ± 0.75
Sal. paratyphi B	-	-	19 ± 2.28	11.16 ± 1.16	-	16.66 ± 1.21
Sh. flexneri	-	-	16.66 ± 1.21	12.5 ± 1.04		13 ± 1.41
Ps. aeruginosa	-	-	-	-		-
P. vulgaris	-	-	15.33 ± 1.86	15.16 ± 0.75		-
Ser. marsescens	-	-	15.33 ± 2.73	-		-
0C. *albicans*	14.83 ± 1.16	-	10.33 ± 1.03	-		-
Asp. niger	-	-	-	-	-	-

Tannins are widely used in leather industry, food industry and in healthcare industry (as antimicrobials). They also show inhibitory action on fungi and yeast (Calixto *et al*., 2009) [78].

Coumarins

These consisting of fused benzene and alpha pyrone rings (Kennedy *et al*., 1997) [40]. Hydroxylated derivative of coumarins like phytoalexines shows antimicrobial activity and also antifungal activity.

Mechanism of action: The mode of antimicrobial action of tannins appear to be related to the inhibition of extracellular microbial enzymes, deprivation of the substrates required for microbial growth or direct action on microbial metabolism by inhibition of oxidative phosphorylation.

There are various coumarin compounda which shows antimicrobial activity. Some of these are given below with their minimum inhibitory concentration (Khan *et al*., 2019, Smania, 2005).

Table 5: coumarin compounds with minimum inhibitory concentration

Coumarin compounds	Minimum inhibitory concentration (mg/ml) Test strains						
	A. nigar	**A. fumigatus**	**A. flavus**	**Rhizopus**	**Mucor**	**Pennicillium**	**E. coli**
Coumarin (1)	500	>1000	500	1000	1000	500	750
6-methylocoumarin (2)	500	>1000	1000	1000	1000	750	1000
6-hydroxycoumarin (3)	500	750	250	500	250	500	250
6-o-acetylocoumarin (4)	1000	125	<125	125	250	750	250
6-methoxycoumarin (5)	500	125	125	<125	1000	750	250
6-chlorocoumarin (6)	1000	250	500	1000	250	500	250
6-iodocoumarin (7)	750	750	250	750	500	750	1000
6-aminocoumarin (8)	750	>1000	750	1000	1000	>1000	750
6-carboxycoumarin (9)	1000	>1000	750	750	1000	500	750
6-cyanocoumarin (10)	1000	1000	250	500	250	500	250

Approximately 1300 coumarin have been identified since 1996 (Ciocan *et al*., 2007) [15] and these are used as antithrombotic and anti-inflammatory compounds.

Coumarins such as Scopoletin and chalcones have been isolated from *Fatoua pilosa* are used as anti-tubercular constituents. Allium genus in traditional medicine indicating the importance of aroma precursors (cysteine sulphoxide) for a potent biological activity.

Alkaloids

Alkaloid are heterocyclic nitrogen compounds. They have broad antimicrobial activity. The analysis of leaf extracts of Gymnema montanum and ethanolic extract of *Tabernaemontana catherinensis* root bark are found to be possess antimicrobial activity (Ramkumar *et al*., 2007, Medeiros *et al*., 2011) [72]. Diterpenoid alkaloids which are isolated from Ranuculaceae or buttercup family of plants revealed an antibacterial property (Rahman *et al*., 1995) [6].

Mechanism of action: They are able to intercalate with DNA thereby resulting in impaired cell division and cell death (Savoia, 2012) [79].

The extracts of C. citrinus and V. adoensis were studied by carrying out antibacterial susceptibility tests, minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) determinations (Mabhiza *et al*., 2016) [53].

Table 6: MIC and MBC of alkaloid extracts

Bacteria	G+/G-	Alkaloid Extract	MIC (mg/mL)	MBC (mg/ML)
S. aureus	G+	*Callistemon citrus*	0.0025	0.835
		Vernonia adoensis	0.21	-
P. aeruginosa	G-	*Callistemon citrus*	0.21	-
		Vernonia adoensis	0.42	-

Some alkaloids also have antivirulence effect.for alkaloid like barberine exert direct antibacterial and antivirulence effects. Alkaloids those inhibit bacterial virulence without inhibiting growth or viability, these could potentially be developed as antivirulence drugs (Lasarre *et al*., 2013) [45].

Terpenoids

Terpenoids are naturally occurring organic chemicals derived from terpenes. Most are multicyclic structures with oxygen containing functional group. Approximate 60% of known natural products are terpenoids. The major group consist of diterpenes, triterpenes, tetraterpenes as well as hemiterpenes and susquiterpenes (Kurek *et al*., 2011) [43].

Mechanism of action: the mechanism of antimicrobial action of terpenoids are not clearly known but it is estimated that these involve membrane disruption in microorganism by the lipophilic compounds (Termentzi *et al*., 2011).

Sesquiterpenes isolated from different plants are known to exhibit bactericidal activity against gram positive bacteria, including *M. tuberculosis* (Kurek *et al*., 2011, Garcia *et al*., 2012) [43].

Table 7: Minimum bactericidal concentrations (mg/mL) of the compounds.

Compound	*B. cereus*	*S. typhimurium*	*E. coli*	*S. aureus*
(-)-Borneol	0.12	0.12	0.25	0.03
(+)-Borneal	0.25	800	0.25	0.25
(±) Camphor	0.25	0.25	0.25	0.015
Carvacrol	0.03	0.015	0.03	0.015
L-Carveol	0.12	0.03	0.06	0.03
L- Carvone	0.25	0.12	0.06	0.25
m-Cymene	0.25	0.25	0.25	0.06
Citral	0.06	0.07	0.06	0.25
Citronellol	0.12	0.12	0.25	0.03
β-Citronellol	0.12	0.12	0.25	0.003
Eugenol	0.07	0.07	0.03	0.03
Trans-Geraniol	0.07	0.03	0.06	0.25
R-(+)-Limonene	0.25	0.06	0.25	0.25
Linalool	0.25	0.25	0.25	0.25
Terpineol	0.12	0.12	0.06	0.03
Thymol	0.007	0.003	0.007	0.007
Sulfanilamide	-	0.06	0.03	0.06

Lectins and Polypeptides

These are most potent antimicrobials. The inhibition of bacteria and fungi by these molecule has long been known but recent interest has chiefly focused on study anti-HIV peptides and lectins (Bolle *et al*., 1996) [21].

Mechanism of action: Antimicrobial mechanism of lectin and polypeptides include the pore formation ability, followed by changes in the cell permeability and latter, indicates interaction with the bacterial cell wall components. Their mode of action also assumed due to competitive inhibition of microbial protein to host polysaccharide receptor.

Lectins and Polypeptides shows antimicrobial activity against *E. coli, Pseudomonas Aeruginosa, Enterococcus hirae, Candida albicans* (fungi).

Lectin such as MAP30 from bitter melon (Huang *et al*., 1995) [47], GAP31 from *Gelonium multiflorum* (Bourinbaiar *et al*., 1996) [10], and Jacalin (Favero *et al*., 1993) [26] are inhibitory on viral proliferation, including HIV and Cytomegalovirus by potentially inhibiting viral interaction with critical host cell component.

With potent antimicrobials, polypeptides are also act as effective modulators of inflammation or neutralizers of pathogenic toxins (Mahlapuu *et al*., 2016) [55].

Benefits of plant derived antimicrobials over antibiotics

- They don't show side effects often associated with use of synthetic chemicals.
- No report of antimicrobial resistance has been documented to these phytochemical (plant derived antimicrobials) because they have multiple mechanism of action.
- Due to multiple mode of actions, they potentially prevent the selection of resistant strains of bacteria.
- Affordability of these compounds.

The marked antimicrobial effect, nontoxic nature and affordability of these compounds potentiate their use as growth promoters in livestock and poultry industry, effective antimicrobial and disinfectants in food industry, component of herbal therapy in veterinary medicine and source for development of novel antibiotics in pharmaceutics (Upadhyay *et al*., 2014) [87].

Conclusion

In 21st century antibiotic resistant is a major problem which is increasing day by day. We have to understand that the battle against these infection causing microorganism is never ending, but we can beat them by changing our strategy and by using active ingredients from plants that survived against microbes since scores of years.

Currently after observing microbial resistance to antibiotics, number of studies have been conducted on antimicrobial activity of medicinal plants. The interest of extracting drugs from medicinal plants would help to solve the problem of antibiotic resistant in present or future days. Hopefully, the area of antimicrobial research based on medicinal plant might be prove beneficial.

References

1. Basile S, Sorbo V, Spadaro *et al*. Antimicrobial and antioxidant activities of coumarins from the roots of *Ferulago campestris* (Apiaceae), Molecules, 2009; 14(3):939-952,
2. Scalbert. Antimicrobial properties of tannins," Phytochemistry, 1991; 30(12):3875-3883.
3. Ulubelen. Cardioactive and antibacterial terpenoids from some Salvia species," Phytochemistry. 2003; 64(2):395-399,
4. Abdallah ME. Plants: An alternative source for antimicrobials, journal of applied pharmaceutical science 2011; 01(06):16-20.
5. Abraham EP, Chain E. An enzyme from bacteria able to destroy penicillin. Nature. 1940; 146:837.
6. Atta-ur-Rahman, Chaudhary MI. Diterpenoid and steroidal alkaloids. Nat. Prod. Rep. 1995; 12:361-379
7. Ozc¸elik DD, Orhan S Ozgen, Ergun F. Antimicrobial activity of flavonoids against extended-spectrum *β*-lactamase (ES*β*L)-producing Klebsiella pneumoniae, Tropical Journal of Pharmaceutical Research. 2008; 7:1151-1157,
8. Balzarini J, Schols D, Neyts J, van Damme E, Peumans W, de Clercq E. α-(1–3)- and α-(1–6)-D-mannose-specific plant lectins are markedly inhibitory to human immunodeficiency virus and cytomegalovirus

infections *in vitro*. Antimicrobial Agents and Chemotherapy. 1991; 35(3):410-416.
9. Borris RP. Natural products research: perspectives from a major pharmaceutical company. J. Ethnopharmacol. 1996; 51:29-38
10. Bourinbaiar AS, Lee-Huang S. The activity of plant-derived antiretroviral proteins MAP30 and GAP31 against herpes simplex virus infection *in vitro*. Biochemical and Biophysical Research Communications. 1996; 219(3):923-929.
11. Engels M, Knodler YY, Zhao R, Carle MGG. Anzle, ¨ Schieber A. "Antimicrobial activity of gallotannins isolated from mango (*Mangifera indica* L.) kernels," Journal of Agricultural and Food Chemistry. 2009; 57(17):7712-7718,
12. Cazarolli LH, Zanatta L, Alberton EH *et al*. Flavonoids: prospective drug candidates. Mini Reviews in Medicinal Chemistry. 2008; 8(13):1429-1440.
13. Cheesman JM, Ilanko A *et al*. developing new antimicrobial therapies: are synergistic combinations of plant extracts/compound with conventional antibiotics the solution?, pharmacognosy review 2017; 11(22):57-72.
14. Chung KT, Wong TY, Wei CI, Huang YW, Lin Y. Tannins and human health: a review. Critical Reviews in Food Science and Nutrition. 1998; 38(6):421-464.
15. Ciocan D, Bara I. Plant products as antimicrobial agents. Analele Ştiinţifice ale Universităţii "Alexandru Ioan Cuza" din Iaşi II A: Genetica si Biologie Moleculara. 2007; 8:151-156.
16. Orhan D, Ozc B¸ elik S, Ozgen, Ergun F. "Antibacterial, antifungal, and antiviral activities of some flavonoids," Microbiological Research. 2010; 165(6):496-504,
17. Singh N, Verma N, Raghuwanshi S, Shukla PK, Kulshreshtha DK. Antifungal anthraquinones from *Saprosma fragrans*, Bioorganic and Medicinal Chemistry Letters, 2006; 16(17):4512-4514
18. Dahal H Ram, Chaudhary K Dhiraj. Microbial Infections and Antimicrobial Resistance in Nepal: Current Trends and Recommendations, Review Article, 2018.
19. Davidson PM, Naidu AS. Natural Food Antimicrobial Systems. CRC Press; Phytophenols, 2000, 265-293.
20. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010; 74:417-33.
21. De Bolle MFC, Osborn RW, Goderis IJ *et al*. Antimicrobial peptides from *Mirabilis jalapa* and *Amaranthus caudatus*: expression, processing, localization and biological activity in transgenic tobacco. Plant Molecular Biology. 1996; 31(5):993-1008.
22. Dever LA, Dermody TS. Mechanisms of bacterial resistance to antibiotics. Arch Intern Med. 1991; 151:886-95.
23. Dixon RA, Steele CL. Flavonoids and isoflavonoids-a gold mine for metabolic engineering. Trends in Plant Science. 1999; 4(10):394-400.
24. Chye Y, Hoh SN. Antimicrobial activity of flavonoid extracts from Sabah tea (*Camellia sinensis*) against Escherichia coli and Listeria monocytogenes," Journal of Tropical Food Science. 2007; 35:245-251.
25. Farhadi Faeghen, Antimicrobial activity of flavonoids and their structure activity relationship: an update review, review article, published on, 2018.
26. Favero J, Corbeau P, Nicolas M *et al*. Inhibition of human immunodeficiency virus infection by the lectin jacalin and by a derived peptide showing a sequence similarity with GP120. European Journal of Immunology. 1993; 23(1):179-185.
27. Fischbach MA, Walsh CT. Antibiotics for emerging pathogens. Science. 2009; 325:1089-1093
28. Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. Br J Exp Pathol. 1929; 10:226.
29. Beecher R. Overview of dietary flavonoids: nomenclature, occurrence and intake," Journal of Nutrition, 2003; 133(10):3248S-3254S,
30. García A, Bocanegra-García V, Palma-Nicolás JP, Rivera G. Recent advances in antitubercular natural products. European Journal of Medicinal Chemistry. 2012; 49:1-23.
31. Gill SR, Pop M, DeBoy RT, Eckburg PB, Turnbaugh PJ, Samuel BS *et al*. Metagenomic analysis of the human distal gut microbiome. Science. 2016; 312:1355-9.
32. Guimaraes C. Aline *et al*, antibacterial activity of terpenes and terpenoids present in essential oil, review article, published on, 2019.
33. Haslam E. Natural polyphenols (vegetable tannins) as drugs: possible modes of action. Journal of Natural Products. 1996; 59(2):205-215.
34. Ulate-Rodr´ıguez J, Schafer HW, Zottola EA, Davidson PM. "Inhibition of *Listeria monocytogenes*, *Escherichia coli* O157:H7, and *Micrococcus luteus* by linear furanocoumarins in a model food system," Journal of Food Protection, 1997; 60(9):1050-1054,
35. Juneja VK, Dwivedi HP, Yan X. Novel natural food antimicrobials*. Annual Review of Food Science and Technology. 2012; 3(1):381-403.
36. Junior Smania Artur. Antimicrobial activity of coumarin, review article, 2005.
37. Hardman KD, Ainsworth CF. Structure of concanavalin A at 2.4-A resolution, ˚ Biochemistry, 1972; 11(26):4910-4919,
38. Venugopala KN, Rashmi V, Odhav B. Review on natural coumarin lead compounds for their pharmacological activity," BioMed Research International, Article ID 963248, 2013, 14
39. Kazmi MH, Malik A, Hameed S, Akhtar N, Ali SN. An anthraquinone derivative from *Cassia italica*. Phytochemistry. 1994; 36(3):761-763.
40. Kennedy OR, Thornes RD, editors. *Coumarins:* Biology, Applications and Mode of Action. New York, NY, USA: John Wiley & Sons, 1997.
41. Khan SM, Tarannum N, Design, synthesis and validation of antimicrobial coumarin derivatives: An efficient green approach, Review article, 2019.
42. Krämer RP, Hindorf H, Jha HC, Kallage J, Zilliken F. Antifungal activity of soybean and chickpea isoflavones and their reduced derivatives. Phytochemistry. 1984; 23(10):2203-2205.
43. Kurek A, Grudniak AM, Kraczkiewicz-Dowjat A, Wolska KI. New antibacterial therapeutics and strategies. Polish Journal of Microbiology. 2011; 60(1):3-12.
44. Kurhekar V. Jaya, Tannins-antimicrobial chemical components, review article, 2016.
45. Lasarre B, Federle MJ. Exploiting quorum sensing to confuse bacterial pathogens. Microbial Mol Biol rev. 2013; 77:73-111.
46. Lechner D, Gibbons S, Bucar F. Modulation of isoniazid susceptibility by flavonoids in Mycobacterium. Phytochemistry Letters, 2008; 1(2):71-75.

47. Lee-Huang S, Huang PL, Chen H-C, *et al*. Anti-HIV and anti-tumor activities of recombinant MAP30 from bitter melon. *Gene*. 1995; 161(2):151–156.
48. Levy SB. The challenge of antibiotic resistance. Sci Am. 1998; 278:46-53.
49. Locher CP, Burch MT, Mower HF *et al*. Anti-microbial activity and anti-complement activity of extracts obtained from selected Hawaiian medicinal plants. Journal of Ethnopharmacology. 1995; 49(1):23-32.
50. Mathabe MC, Hussein AA, Nikolova RV, Basson AE, Meyer JJM, Lall N. Antibacterial activities and cytotoxicity of terpenoids isolated from *Spirostachys africana*, Journal of Ethnopharmacology. 2008; 116(1):194-197.
51. Cowan MM. "Plant products as antimicrobial agents," Clinical Microbiology Reviews, 1999; 12(4):564-582,
52. Saleem M, Nazir M, Ali MS *et al*., "Antimicrobial natural products: an update on future antibiotic drug candidates," Natural Product Reports, 2010; 27(2):238-254.
53. Mabhiza D, Chitemerere T, Mukanganyama S. Antibacterial properties of alkaloid extracts from *Callistemon citrus* and *Vernonia adoensis* against *Staphylococcus aureua* and *Pseudomonas aeruginosa*, Review article, 2016.
54. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG *et al*. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012; 18:268-81.
55. Mahlapuu Margit. Antimicrobial pepetides : An emerging category of therapeutic agents, review article, 27 december, 2016.
56. Maimone TJ, Baran PS. Modern synthetic efforts toward biologically active terpenes. Nature Chemical Biology. 2007; 3(7):396-407.
57. Malmir Maryam. Anthraquinones as potential antimicrobial agents- a review, review article published on august, 2017.
58. Martinez JL, Rojo F, Vila J. Are nonlethal targets useful for developing novel antimicrobials? Future Microbiol. 2011; 6:605-607
59. Mazimba O, Masesane IB, Majinda RR. A flavanone and antimicrobial activities of the constituents of extracts from *Mundulea sericea.* Natural Product Research, 2012; 26(19):1817-1823.
60. Medeiros MR, Prado LA, Fernandes VC *et al*. Antimicrobial activity of indole alkaloids from *Tabarnaemontana catharinensis*. Nat. Prod. Commun. 2011; 6:193-196
61. Morar M, Wright GD. The genomic enzymology of antibiotic resistance. Annu Rev Genet. 2010; 44:25-51.
62. Kheeree N, Sangvanich P, Puthong S, Karnchanatat A. "Antifungal and antiproliferative activities of lectin from the rhizomes of *Curcuma amarissima* Roscoe," Applied Biochemistry and Biotechnology, 2010; 162(3):912-925,
63. Namba T, Morita O, Huang SL, Goshima K, Hattori M, Kakiuchi N. Studies on cardio-active crude drugs; I. Effect of coumarins on cultured myocardial cells. Planta Medica. 1988; 54(4):277-282.
64. Negi PS. Plant extracts for the control of bacterial growth: efficacy, stability and safety issues for food application. International Journal of Food Microbiology. 2012; 156(1):7-17.
65. Batista O, Duarte A, Nascimento J, Simoes MF. "Structure and antimicrobial activity of diterpenes from the roots of *Plectranthus hereroensis*," Journal of Natural Products, 1994; 57(6):858-861.
66. Omulokoli E, Khan B, Chhabra SC. Antiplasmodial activity of four Kenyan medicinal plants. Journal of Ethnopharmacology. 1997; 56(2):133-137.
67. Osman K, Evangelopoulos D, Basavannacharya C *et al*. An antibacterial from *Hypericum acmosepalum* inhibits ATP-dependent MurE ligase from *Mycobacterium tuberculosis*. Intern. J Antimicrob. Agents. 2012; 39:124-129
68. Petnual P, Sangvanich P, Karnchanatat A. "A lectin from the rhizomes of turmeric (*Curcuma longa* L.) and its antifungal, antibacterial, and *α*-glucosidase inhibitory activities," Food Science and Biotechnology, 2010; 19(4):907-916,
69. Rattanachaikunsopon P, Phumkhachorn P. Contents and antibacterial activity of flavonoids extracted from leaves of *Psidium guajava*," Journal of Medicinal Plants Research, 2010; 4(5):393-396,
70. Pitman SK, Drew RH, Perfect JR. Addressing current medical needs in invasive fungal infection prevention and treatment with new antifungal agents, strategies and formulations. Expert Opin. Emerg. Drugs. 2011; 16:559-586
71. Punjabi Y. Antibacterial activity of flower extracts of *Nymphaea nouchali*, original research paper, 2014.
72. Ramkumar KM, Rajaguru P, Ananthan R. Antimicrobial properties and phytochemical constituents of an antidiabetic plant *Gymnema montanum*. Adv. Biolog. Res. 2007; 1:67-71
73. Rammelkamp CH, Maxon T. Resistance of *Staphylococcus aureus* to the action of penicillin. Exp Biol Med. 1942; 51:386-9.
74. Rashed K, Ćirić A, Glamočlija J, Soković M. Antibacterial and antifungal activities of methanol extract and phenolic compounds from *Diospyros virginiana* L. Industrial Crops and Products, 2014; 59:210-215.
75. Rattanachaikunsopon P, Phumkhachorn P. Bacteriostatic effect of flavonoids isolated from leaves of *Psidium guajava* on fish pathogens. Fitoterapia, 2007; 78(6):434-436.
76. Ignacimuthu S, Pavunraj M, Duraipandiyan V, Raja N, Muthu C. "Antibacterial activity of a novel quinone from the leaves of *Pergularia daemia* (Forsk., a traditional medicinal plant," Asian Journal of Traditional Medicines, 2009; 4:36-40,
77. Bach SM, Fortuna MA, Attarian R *et al*., "Antibacterial and cytotoxic activities of the sesquiterpene lactones cnicin and onopordopicrin," Natural Product Communications, 2011; 6(2):163-166,
78. Saura-Calixto F, Pérez-Jiménez J. Tannins: bioavailability and mechanisms of action. In: Knasmüller S, DeMarini DM, Johnson I, Gerhäuser C, editors. Chemoprevention of Cancer and DNA Damage by Dietary Factors. Weinheim, Germany: Wiley-VCH, 2009.
79. Savoia D. Plant-derived antimicrobial compounds: alternatives to antibiotics. Future Microbiology. 2012; 7(8):979-990.
80. Scalbert A. Antimicrobial properties of tannins. Phytochemistry. 1991; 30(12):3875-3883.

81. Sher A. Antimicrobial activity of natural products from medicinal plants. Gomal Journal of Medical Sciences. 2004; 7(1):65-67.
82. Šmejkal K, Chudík S, Kloucek P, Marek R, Cvacka J, Urbanová M *et al*. Antibacterial C- geranylflavonoids from *Paulownia tomentosa* fruits. Journal of Natural Products, 2008; 71(4):706-709.
83. Srivastava J, Chandra H, Nautiyal RA, Kalra SJS. Antimicrobial resistance (AMR) and plant derived antimicrobials as an alternative drug line to control infections, review article, published on, 2013.
84. Cushnie TP, Lamb AJ. "Antimicrobial activity of flavonoids," International Journal of Antimicrobial Agents, 2005; 26(5):343-356.
85. Taylor PW, Hamilton-Miller JMT, Stapleton PD. Antimicrobial properties of green tea catechins. Food Science & Technology Bulletin. 2005; 2:71-81.
86. Termentzi A, Fokialakis N, Skaltsounis AL. Natural resins and bioactive natural products as potential antimicrobial agents. Current Medicinal Chemistry. 2012; 19:2292-2302.
87. Upadhyay A, Upadhyaya I *et al*. combating pathogenic microorganisms using plant-derived antimicrobials: a minireview of the Mechanistic Basis, Review article, published on, 2014.
88. van Wyk BE, Gericke N. People's Plants. Pretoria, South Africa: Briza Publications, 2000.
89. Vlieger AM, Blink M, Tromp E, Benninga MA. Use of complementary and alternative medicine by pediatric patients with functional and organic gastrointestinal diseases: Results from a multicenter survey. Pediatrics 2008; 122:e451. DOI: 1O.1542/peds.2008-0266.
90. Peumans WJ, van Damme EJ. "Lectins as plant defense proteins," Plant Physiology, 1995; 109(2):347-352,
91. Wen L, Wu D, Jiang Y, Prasad KN, Lin S, Jiang G *et al*. Identification of flavonoids in litchi (*Litchi chinensis* Sonn.) leaf and evaluation of anticancer activities. Journal of Functional Foods. 2014; 6:555-563.
92. WHO. Traditional medicine-growing needs and potential. World Health Organization policy perspective on medicines. 2002; 1:6.
93. WHO. Antimicrobial Resistance. World Health Organization; 2016. [Last cited on 2017 May 10]. Available from: http://www.who.int/mediacentre/factsheets/fs194/en/.
94. Wise R. BSAC Working Party on the Urgent Need: Regenerating Antibacterial Drug Discovery and Development. The urgent need for new antibacterial agents. J. Antimicrob. Chemother. 2011; 66:1939-1940
95. Wright GD. Bacterial resistance to antibiotics: enzymatic degradation and modification. Adv Drug Deliv Rev, 2005; 57:1451-1470.
96. Ya C, Gaffney SH, Lilley TH, Haslam E. Carbohydrate-polyphenol and complexation. In: Hemingway RW, Karchesy JJ, editors. Chemistry and Significance of Condensed Tannins. New York, NY, USA: Plenum Press; 1998, 553.
97. Zeng F, Wang W, Wu Y *et al*. Two prenylated and C-methylated flavonoids from *Tripterygium wilfordii*. Planta Medica. 2010; 76(14):1596-1599