Use of plant derived antimicrobials as an alternative to antibiotics

Monika, Dr. Shreshtha Sharma and Dr. Nitin Kumar

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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

INSPIRTE 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 Fleming 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, 4653 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].
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 (target alteration).
- Neutralize the antibiotic before it has a “killing” effect (produce inactivating enzymes).
- Decrease antibiotic uptake.
- Share genetic material with other bacteria to also make them resistant.

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

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].

| Antibiotic Class | Examples | Drug Target | Resistance Mode |
|------------------|----------|-------------|-----------------|
| β-lactams | Penicillins (Ampicillin) | Peptidoglycan biosynthesis | Hydrolysis, Efflux, Altered target |
| | Cephalosporins (cephamycin) | | |
| | Penems (meropenem) | | |
| | Monobactams (aztreonam) | | |
| Aminoglycosides | Gentamicin | Translocation | Phosphorylation, Acetylation, Nucleotidylation, Efflux, Altered target |
| | Streptomycin | | |
| | Spectinomycin | | |
| Glycopeptides | Vancomycin | Peptidoglycan biosynthesis | Reprogramming of peptidoglycan biosynthesis |
| | Teicoplanin | | |
| Tetracyclines | Minocycline | Translation | Monoxygenation, Efflux, Altered target |
| | Tigecycline | | |
| Macrolides | Erythromycin | Translation | Hydrolysis, Glycosylation, Phosphorylation, Efflux, Altered target |
| | Azithromycin | | |
| 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 | Examples | Selected Antimicrobial Spectrum | References |
|------------------------------|----------|---------------------------------|------------|
| **Flavonoids** | Phenolics And Polyphenols | Listeria monocytogenes, Staphylococcus aureus, Escherichia coli, Salmonella enterica, Vibrio cholera, Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, Aspergillus flavus, Penicillium Sp., Cladosporium Sp. | Beecher, 2003 [29]; chye and Hoh, 2007 [28]; Orhan et al., 2010 [10]; 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 [73]; 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, Agasillin | Staphylococcus aureus, Listeria monocytogenes, E. coli, Salmonella typhimurium, Salmonella enteritidis, Vibrio para-haemolyticus | Basile et al., 2009 [15]; Ulate-Rodriguez et al., 1997 [48]; Venugopala et al., 2013 [19]; Saleem et al., 2010 [52]; Cowan, 1999 [51]. |
| **Terpenoids** | Carotenoids, Terpinene | St. aureus, Pseudomonas aeruginosa | Ulubelen, 2013 [70]; Bach et al., 2011 [77]. |

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.
Phenolics and Polyphenols
These are the diverse group of aromatic secondary metabolites. They consist of Flavonoids, Quinones, Tannins and Coumarins (Savoa, 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 (Savoa, 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) [23].

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         | 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 : 32 µg/ml      | (Lechner, Gibbons, & Bucar, 2008) [66]   |
| Naringeninin | Pure             | Escherichia coli              | MIC : 2 µg/ml       | (Smejkal et al., 2008) [10]              |
| Lupinifolin  | Mundulea sericea | Bacillus subtilis Escherichia coli | MIC : 0.5 µg      | (Mazimba et al., 2012) [59]             |

Flavonoids 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 polyepptides 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 bacteriostic action against pathogen bacteria such as Bacillus anthracis, Corynebacterium pseudodiphtherium and Pseudomonas aeruginosa. It shows bactericidal against Burkholderia pseudomallei (Kazm, 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 : 6.25-400 µg/ml |
| Rheum rhabarbarum | Aeromonas hydrophilia       | MIC : 50-200 µg/ml  |
| Rheum rhamnopicum  | Staphylococcus saprophyticus | MIC : 125-250 µg/ml |
| Rheum palmatum     | Staphylococcus aureus    | MIC : 1.56-25 µg/ml |
| Cassia species    | Bacillus subtilis      | MIC : 7.8 µg/ml     |
|                 | Staphylococcus aureus  | MIC : 3.9 µg/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, 60].

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 urapathogenic E. coli (Okuda, 2005).

The main sources for tannins which are studied are Catharanthus roseus, Terminalia arjuna and Piper betel (Kurhekar, 2016) [44].
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 compounds which shows antimicrobial activity. Some of these are given below with their minimum inhibitory concentration (Khan et al., 2019, Smania, 2005).

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

| Name of bacteria   | Catharanthus roseus Aqueous extract | Catharanthus roseus Acetone extract | Piper betel Aqueous extract | Piper betel Acetone extract | Terminalia arjuna Aqueous extract | Terminalia arjuna Acetone extract |
|--------------------|-------------------------------------|------------------------------------|-----------------------------|-----------------------------|----------------------------------|----------------------------------|
| B. subtilis        | -                                   | 11.83 ± 0.98                       | -                           | 11.66 ± 1.03                |                                  |                                  |
| S. aureus         | -                                   | 15.33 ± 2.16                       | 14.83 ± 2.04                | 14.5 ± 1.04                 |                                  |                                  |
| Ent. fecalis      | 14.83 ± 1.47                        | -                                  | -                           | -                           | 16.83 ± 1.16                     |                                  |
| M. luteus         | 19.16 ± 1.94                        | -                                  | -                           | 15.83 ± 1.47                | 19.33 ± 1.03                     | 20 ± 1.26                       |
| K. pneumoniae     | 21.66 ± 2.33                        | -                                  | -                           | -                           |                                  |                                  |
| 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. marcescens   | -                                   | 15.33 ± 2.73                       | -                           | -                           |                                  |                                  |
| O.C. albicans     | 14.83 ± 1.16                        | 10.33 ± 1.03                       | -                           | -                           |                                  |                                  |
| Asp. niger        | -                                   | -                                  | -                           | -                           |                                  |                                  |

### Table 5: coumarin compounds with minimum inhibitory concentration

| Coumarin compounds | Minimum inhibitory concentration (mg/ml) | Test strains |
|--------------------|------------------------------------------|--------------|
|                    | A. niger A. fumigatus A. flavus Rhizopus Mucor Penicillium E. coli |
| Coumarin (1)       | 500 | >1000 | 500 | 1000 | 1000 | 500 | 750 |
| 6-methylcoumarin (2) | 500 | 1000 | 1000 | 1000 | 1000 | 500 | 750 |
| 6-hydroxycoumarin (3) | 500 | 750 | 250 | 500 | 250 | 500 | 250 |
| 6-0-acteyloumarin (4) | 1000 | 125 | <125 | 125 | 250 | 500 | 250 |
| 6-methoxycoumarin (5) | 1000 | 750 | 125 | <125 | 250 | 500 | 250 |
| 6-chlorocoumarin (6) | 1000 | 750 | 250 | 500 | 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 | 1000 | 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 Ranunculaceae 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 (Mabhuza 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 effects for alkaloid like barberry, exert direct antibacterial and antivirulence effects. Alkaloids that inhibit bacterial virulence without inhibiting growth or viability, these could potentially be developed as antiviral 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 sesquiterpenes (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 (Termanzi 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) [45].

| 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            |
| Sulfolaminamide   | -                | 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) [31].

Mechanism of action: Antimicrobial mechanism of lectin and polypeptide 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, Entercoccus hirae, Candida albicans (fungi). Lectin such as MAP30 from bitter melon (Huang et al., 1995) [47], GAP31 from Gelonium mutilflorum (Bourinbairai 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) [57].

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.

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