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Review Article

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Antibiotics classification, uses, resistance and their alternates

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Abstract

Antibiotics discovery is deliberated one of the most significant achievements of science in 20th century. It modernized both veterinary and human medicine to treat infectious diseases. All the drugs used to combat bacterial infection in both human and animals are termed as antibiotics. Antibiotics can be obtained from natural sources like plants & prokaryotes, and can be synthesized in vitro. Antibiotics are classified into bacteriostatic (cure infection by inhibiting bacterial growth) and bactericidal (cure infection by killing prokaryotes) on the basis of their mechanism of action. Further classification of antibiotics based on their site of action within prokaryotic cells. Use of antibiotics to treat infections in human and animals has become very common in previous century. Prophylactic use of antibiotics in humans, animals, and antibiotic persistence in environment has provoked antibiotic resistant in pathogenic bacteria. Due to increase in bacterial resistance against antibiotics, scientists developed alternatives of antibiotics to combat with infectious diseases. Probiotics, antimicrobial proteins, bacteriophages and plant-derived compounds are promising substitute of antibiotics to prevent and cure infectious diseases. Antibiotic persistence in environment and prophylactic use of antibiotics in humans and animals are the major factors that develop remittance against antibiotics in pathogenic bacteria. The healthy food is the best alternate to antibiotics and other medicines. This review articles focuses on history of antibiotics discovery, their uses to treat infectious medicine, antibiotic classification, antibiotic resistant and alternatives of antibiotics.

Keywords: Antibiotics, Antibiotics Classification; Infectious diseases; Antibiotic resistance; Alternatives to antibiotics

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1. ANTIBIOTICS HISTORY

In 1928, Alexander Fleming, a Scottish bacteriologist discovered the first antibiotic named as penicillin produced by a fungus, *Penicillium notatum* [1]. Few years latter Ernst Chain a British biochemist, Howard Florey an Australian pathologist both find some materials (e.g penicillin) that were highly effective against various highly pathogenic bacteria [2].

In 1950s, semisynthetic antibiotics were prepared by adding different chemical groups in the core penicillin. Various types of penicillin antibiotics used against streptococci, gonococci, staphylococci, and spirochete were available at the end of 1950s [2]. Mycobacterium tuberculosis was resistant to the penicillin, but it was sensitive to the streptomycin, another antibiotic secreted by Streptomyces griseous. Streptomycin was effective against the bacterium of typhoid fever [3].

Tyrocidin, and gramicidin antibiotics were discovered in 1939, Rene Dubos, a French born American microbiologist. These antibiotics were used to treat topical infection. These are toxic if used internally [4]. In 1950s, scientists also discovered another type of antibiotics secreted by cephalosporin acrimonious, termed as Cephalosporin. Quinolones were also discovered in the same decades [5]. Quinolones inhibit the DNA- synthesis that is a critical step in bacterial replication. Hence quinolones are very effective to treat infectious diarrhea, infections that involves bones and WBCs, UTI infection[6].

The time period of 1940-1950 is considered the golden age of antibiotics discovery. After World War II, a vast variety of antibiotics was discovered by different scientists[7]. For instance, Professor Selman Waksman and his graduate pupil Albert Schatz discovered streptomycin in 1944 [8]. Similarly, tetracycline was discovered by Benjamin Minge Duggar in 1940s [9]

The era of 1950s-1960s is considered, the era of cosmopolitan usage of antibiotics. During this time period, antibiotics usage was very common to treat infectious diseases both in humans and animals [10].

Excessive use of antibiotics against prokaryotes leads to antibiotic resistance. Hence, antibiotic resistance became a prominent issue for health workers during 1980s-1990s [11]. In the 2000s, advancement in knowledge of molecular biology and genetics has helped us a lot to understand the mechanism of action of antibiotics against various bacteria [12]. During the first decade of 21st century, multi- drug resistant bacteria commonly known as "superbugs" had become a global health issue. Since the emergence of resistance in bacteria against antibiotics, scientists are trying to overcome this problem by using various alternatives like vaccines, probiotics, prebiotics etc [13].

2. ANTIBIOTIC DEFINITION

The term antibiotics means against life. Antibiotics are chemical substances produced by living organisms or semisynthetic chemicals that kill pathogens, stop their growth and spread and replication [14]. Before the use of antibiotics, mortality rate due to bacterial infection e.g. T.B, STDs and pneumonia was very high [15].

3. SOURCES OF ANTIBIOTICS

Initially discovered antibiotics were naturally synthesized by living organisms e.g. penicillin by fungus, streptomycin and tetracycline synthesized by soil bacteria [16]. To enhance the yield of antibiotics produced by these microbes, they were treated by the mutagens e.g. X-rays, chemical mutagens and UV rays. The copies of genes yielding the enzymes that are involved in antibiotics production are also inserted into host cells by vectors to get more and more antibiotics [17].

Different fungi produce antibiotics e.g. Cephalosporins synthesized Acremonium chrysogenum, Geldanamycin secreted by Streptomyces hygroscopicus naturally [18]. Streptomyces erythreus mostly known as Saccharopolyspora erythraea synthesized an antibiotic called erythromycin [19]. Different microbes produced different antibiotics for instance streptomyces aureofaciens synthesizes tetracycline, Streptomyces griseus produce streptomycin and streptomycines orientalis commonly known as Amycolatopsis synthesizes Vancomycin [19].

4. CLASSIFICATION OF ANTIBIOTICS

4.1 Classification of antibiotics on the basis of spectrum

Based on their spectrum (ability of an antibiotic to affect various number of microbes), antibiotics can be divided into three major groups[20].

4.1.1 Broad-spectrum antibiotics: These types of antibiotics can affect a wide range of pathogenic microbes and routinely used in the treatment of infection when causative agent of the infection is unknown [21].

4.1.2 Narrow spectrum antibiotics: These types of antibiotics are used in the treatment of specific infection whose causative agent is known. These antibiotics are highly effective against the specific pathogen but ineffective on other pathogens [22].

This is according to the mechanism of action of antibiotics used. For instance, Bactericidal antibiotics (Beta-lactam antibiotics e.g. Penicillin) kills bacteria by stopping their cell wall formation. Monobactems, carbapenus, Cephalosporins (cephems)and vancomycin. Telithromycin, metronidazole, deptomycin, nitrofurantoin, fluroquinolones, and co-trimoxazole are also bactericidal [23].

4.1.3 Bacteriostatic Antibiotics: These antibiotics inhibit bacterial growth by stopping DNA replication, bacterial metabolism and protein synthesis. They also work with our immune system in synergistic mechanism to eliminate microbes from our body [24]. There is no complete distinction between bacteriostatic and bactericidal antibiotics. As a high amount of bacteriostatic can act as bactericidal. Whereas low concentration of bactericidal antibiotics work as bacteriostatic instead of bactericidal [25]. Macrolides, trimethoprim, sulfonamides, chloramphenicol, tetracycline, and lincosamides are the best examples of bacteriostatic antibiotics [26].

Antibiotics are also classified based on their chemical structure. For instance, cephalosporins includes cephalexin and penicillin include penicillin and amoxicillin [27].clarithromycin, azithromycin and erythromycin are the members of macrolides class of antibiotics [28]. While members of the fluoroquinolones class of antibiotics are ofloxacin, levofloxacin, and ciprofloxacin [29]. Proloprim,

Bactrim, co-trimethoprim, and trimethoprim are the members of sulfonamides class of antibiotics [30]. Doxycycline, tetracycline, and vibramycin are the members of tetracycline's class of antibiotics while tobramycin and gentamycin are the members of aminoglycosides class of antibiotics [31].

4.2 Classification of antibiotics on the basis of mode of action

4.2.1 Beta-Lactams: Beta lactams are broad-spectrum antibiotics its first member (penicillin) was discovered by Alexander Fleming in 1928. These antibiotics contain beta lactam ring in the core of their chemical structure [32]. Penicillin e.g. cephalosporin and amoxicillin are inhibit the synthesis of peptidoglycan, necessary component of bacterial cell wall structure, and are most effective to cure Gram positive bacterial infection [33]. Though, bacteria have developed resistance against beta lactams by developing and enzyme named as beta lactamase that destroy the beta lactam ring of these antibiotics [34].

4.2.2 Sulfonamides: Protosil is the first member of sulfonamides that is commercially available since 1932. These are also broad-spectrum antibiotics and are correspondingly effective against both gram negative and gram-positive bacteria [35]. These antibiotics do not work as bactericidal. Instead of it they stop the growth of bacteria by inhibiting the synthesis of B vitamin folate that is necessary for bacterial replication. These antibiotics work as bacteriostatic [36]. Several bacteria have developed antibiotic resistance against this class of antibiotic. The use of this class of antibiotics to treat infection is now very limited due to antibiotic resistance and hepatotoxicity [37].

4.2.3 Aminoglycosides: These antibiotics act as bactericidal by stopping the protein translation. They are effective against few gram-positive as well as gram-negative prokaryotes. These antibiotics do not absorb from digestive system into blood stream, so they are injected intravenously [38]. Streptomycin is a member of aminoglycosides class of antibiotics that is effective against Mycobacterium tuberculosis but its use is prohibited due to hepatotoxicity [39].

4.2.4 Tetracycline: Broad-spectrum antibiotics/tetracycline, are equally effective against both gram negative and gram-positive types prokaryotes. They also act as bacteriostatic by interfering in protein translation just like sulfonamides, and inhibit bacterial growth [40]. They are commonly used to treat UTI, chlamydia infections and respiratory infections. As these antibiotics can easily bind with food, so doctors recommend their intake before or after two hours of eating [41].

4.2.5 Chloramphenicol: Cephalosporin are broad-spectrum antibiotics that act as bacteriostatic by stopping protein synthesis and bactericidal for specific bacteria. Bacteria have developed resistance against this class of antibiotics and their use has been limited [35]. They are only used to treat life-threatening infections. It is mostly used to treat conjunctiva infections. In developing countries, this class of antibiotics is used as first choice of therapy against meningitis and is recommended by WHO [42].

4.2.6 Macrolides: Macrolides resembles with beta lactams and act as bacteriostatic against gram positive bacteria by inhibiting protein translation in them. They are more effective than penicillin and can be used to treat the bacterial infection whose causative agents are resistant to penicillin [43]. Bacteria also have developed resistance against macrolides. Erythromycins the most common antibiotic of this class to treat different infection in NHS [44].

4.2.7 Glycopeptides: Vancomycin, drug of last resort, is the member of glycopeptides class of antibiotic and is used to treat severe infection caused by the prokaryotes that are unaffected by most of the antibiotics [45]. It is used as last option to treat infections. MRSA infections are treated by glycopeptides. These antibiotics inhibit bacterial growth and replication and do not act as bactericidal [46].

4.2.8 Oxazolidinones: Oxazolidinones , inhibit the growth and replication of gram-positive bacteria by stopping their protein translation [47]. Linezolid, and cycloserine, second line therapy of T.B are the most popular members of this class of antibiotics. Bacteria have developed less resistance against this class of antibiotics [48].

4.2.9 Ansamycins: These antibiotics are usually prescribed as drug of choice to infections caused by any type of prokaryotes. They inhibit bacterial growth by arresting the transcription process of bacterial central dogma that leads to bacterial death. Rifamycin a subclass of antibiotics is used to treat leprosy and T.B. Ansamycins show anti-viral activity.

4.2.10 Quinolones: Quinolones are bactericidal drugs that interrupt the transcription and replication of DNA in bacteria cells. These broad-spectrum antibiotics are extensively used for UTI, as well as other hospital-acquired infections that had developed resistance to older classes of antibiotics [49]. Moreover, their use for animals is most common; a use that has been pointed in some quarters for hastening the development of resistance. Bacteria have developed resistance against quinolones in USAbecause of their prophylactic use [50].

4.2.11 Streptogramins: Streptogramins are mostly injected as a combination of two antibiotics from the various classes within the class. For example, streptogramin B and streptogramin A. They are bacteriostatic but in combination form, they act as bactericidal [51]. They are mostly used to cure resistant infections, however resistance to the streptogramins against them has also been developed [52].

4.2.12 Lipopeptides: These antibiotics were discovered in 1987. Lipopeptides are the modern class of antibiotics, and are kill Gram-positive bacteria [53]. Daptomycin is the most popular member of this class; it has a special mechanism of action, interfere with various aspects of cell membrane actions in bacteria [54]. This special mechanism of action also seems to be beneficial in that, present, events of resistance to the antibiotics seem to be rare – however they have been highlighted. It is given through injectable, and routinely used to cure infections in the dermis and tissue [55]. More details about antibiotics classification can be found in Table 1.

5. USES OF ANTIBIOTICS FOR TREATMENT

The major foremost antibiotic usage is to make sure that the enduring gets one to which the mark prokaryote is sensitive. An adequate attention should be taken that antibiotics do not have any side effects. Complete eradication of infection by use of antibiotics is compulsory [56]. Antibiotics differ due to variability in their target site. A few are perfectly exact. While others, like the tetracycline, work in contradiction of a comprehensive spectrum of diverse prokaryotes. These are mainly helpful in fighting miscellaneous infections and curing contagions when there is shortage of time to behavior compassion tests. Whereas different antibiotics, like semisynthetic penicillin as well as the quinolones, may be intake via mouth, others can be inserted by intravenous or intramuscular[57].

Table 1. Classification of antibiotics.

Aminoglycosides (inhibit protein translation)	
Gentamicin	It treats urinary tract infection, blood and abdominal cavity infections, respiratory infections and pelvic infections.
Tobramycin	It is used to treat pelvic demagogic infections, UTI infections, respirational infections, and abdominal cavity infections. [58]
Cephalosporin (stop cell wall formation)	
Cefaclor	It is used to cure otitis, infection of respiratory tract, urinary tract infection and dermal infections.
Cefamandole	It is used for the treatment of skin infections, blood peritonitis, UTI infections and bones and joints infections,
Cefazolin	It cures endocarditis, bone and joint infections, genitourinary infections, dermal infections and respiratory infections. [59]
Ceftriaxone	This antibiotic is used to treat the infection of skin, bone and joints infections, gonorrhea and meningitis, respiratory tract, urinary tract, bacteremia, pelvic inflammatory diseases other body infections.,
Cefuroxime	This antibiotic treats respiratory infections, bones, skins and joint infections and bacteremia.
Cephalexin	This drug is used to cure otitis media, excretory system infections, nasopharyngeal infections, ossein, and joint infections. [32]
Chloramphenicols (stop protein formation)	
Chloramphenicol	This antibiotic is mostly used to treat eyes, ears, and skins infections. It is also used to cure minor wounds and cystic fibrosis.
Fluoroquinolones (Interrupt DNA replication in bacterial cells)	
Ciprofloxacin	This antibiotic treats most of the infection like sinusitis, gonorrhea, diarrhea, pneumonia, prostatitis, abdominal cavity, anthrax and bone and joint infections.
Norfloxacin	They treat UTI infections, STDs, optic and ear and other topical infections. [60]
Lincosamides (Stop protein synthesis)	
Clindamycin	This drug treats air passageways infections, skin infections, gut cavity,pubic provocative infections and acne. [60]
Macrolides (Halt protein translation)	
Azithromycin	Otitis media, Pneumonia, STDs, COPD, skin and air passageways infections.
Clarithromycin	This drug cures otitis media, respiratory tract infections, skin infection.

Erythromycin	This antibiotic is used to treat the infection of skin, bone and joints infections, gonorrhea and meningitis, respiratory tract, urinary tract, bacteremia, pelvic inflammatory diseases other body infections., [29]
[61](destroy necessary cell components)	
Nitrofurantoin	UTI infections treatment
Penicillin's (Stop cell wall formation)	
Amoxicillin	This drug treats different staphylococcal and streptococcal infections.
Ampicillin	Ampicillin cures meningitis, respiratory tract infection, gonococcal infection, endocarditis, skin infections, bone infections
Penicillin G	Staphylococcal and streptococcal infections
Piperacillin	Genitourinary tract infections, skin infections, abdominal cavity infections, bacteremia, skin and bone infections.
Ticarcillin	Infections of the nasopharyngeal, impetigo, otitis media, meningitis and gut infection; tonsillitis, streptococcal and pseudomonas and gonorrhea infections; Lyme disease; [62]
Tetracycline (Taboo protein formation)	
Tetracycline	Chlamydia, pneumonia, gut amebiasis, rickettsia, acne and cure in minor injuries, rickettsia, pneumonia, chlamydia, [63]
Assorted antibiotics	
Aztreonam	Septicity of the urinary, respiratory and genital tracts, skin, gut cavity, and blood
Imipenem –cilastatin	infections of the urinary, air passageways and genital tracts, bones and joints, skin, intestinal cavity, endocarditis and blood.
Isoniazid	Infection due to *Mycobacterium tuberculosis*
Metronidazole	Vaginal Intestinal tract infection
Rifampine	T.B infection
trimethoprim- sulfamethoxazole	Otitis media, traveler's diarrhea UTI infections, and bronchitis
Vancomycin	Penicillin and cephalosporin resilient infections.[64]

6. PROPHYLACTIC USE OF ANTIBIOTICS

Term prophylaxis means antibiotics utilization before operation or a dental process to stop a prokaryotic septicity. Prophylactic use of antibiotics has been reduced as compared to its usage 10 years ago [65]. This is because of:

- Enhanced antibiotic resistance in prokaryotes
- Mutations in infectious prokaryotes

- developments in infections diagnostic tools [66]

Though, prophylaxis is still a common practice among people who are at risk of septicity. Professional protocols endorse antibiotic consumption before processes having an extraordinary danger of bacteriological septicity [67]. These contain:

- Neck and cranium cancer operations.
- GIT tract surgeries
- C-section delivery
- Implantation of medical devices e.g. defibrillator, pacemaker etc, via operation.
- cardiac surgeries like bypass grafting in coronary artery, heart valve transplantation, and heart transplantation [68].

6.1 Drugs for antibiotic prophylaxis: Commonly used drugs before operations are cephalosporins like cefuroxime and cefazolin. Patients who are allergic to cephalosporin are prescribed vancomycine as drug of choice. Your medic may suggest vancomycin if you are sensitive to cephalosporins. In case of antibiotic resistance vancomycine is recommended as drug of choice.[68]. For dental treatment, most probably ampicillin or amoxicillin will be prescribed by your dentist. [69]

6.2 Reasons for usage: Individuals who require drugs as prophylaxis mostly have factors that lay them at higher menace of septicity during operation than the general populace. These factors comprise:

- childhood or very old age
- male nourishment
- chubbiness
- high blood sugar level
- smoking, along with smoking history
- prevailing septicity, even at a various body parts where the operation will be done
- contemporary operation
- prolonged clinical sojourn before the operation
- certain hereditary cardiac situations, means ones that have occurred since labor [70]

Prophylactic use of antibiotics for dental treatment can be applicable for individuals having:

- conceded immunity
- synthetic cardiac valves
- Infective endocarditis (inflammation in internal lining of heart).

- heart transplants that may cause male-functioning of cardiac valves [71]

6.3 Administration: The medicine formulation and intake mostly base on the kind of process you will suffer. Before operation, a healthcare worker usually provides antibiotic via a catheter that they have injected into one of your blood vessels. Or they can recommend some tablets. You often engulf the capsule almost 20-60 min before your operation. If the operation involves your optic, your medic may recommend you paste or eye drops. These paste or eye drops will be applied on your optics directly.[72]. Afore dental treatments, your dentist will most probably suggest tablets that you take orally. If you overlook to fill your medicament or to take your medicine afore your visit to doctor, he may recommend you antibiotics during or after the process [73].

7. ANTIBIOTIC RESISTANCE

Antibiotics are drugs used to cure and treat bacterial septicity. Antibiotic resistance arises when prokaryotes alter their response against antibiotics used as drug of choice to cure infection caused by them. Unlike bacteria, other organisms e.g., animals or human do not develop any resistance against antibiotics. Infections caused by antibiotic resistant prokaryotes are harder to cure as compared to infections caused by non-resistant prokaryotes. [74]. Losses due to anti-biotic resistant developed in prokaryotes includes too much healthcare expenses, lengthy stay in hospital, and augmented mortality rate. There is an urgent need to alter the way antibiotics are being used or prescribed [75]. Threats aroused by the antibiotic resistant cannot be minimized by developing new drugs until or unless we change our behavior in their usage. Here are some behavioral changes like hand washing, usage of hygienic food, vaccination, and safer sex practices reduces infectious rate and it can help us to overcome the problem of antibiotic resistance. [75].

7.1. Scope of this issue: Resistance against antibiotics is increasing to dramatically high levels in all over the world. Novel resistance method is up surging and spreading all over the world, frightening our capacity to cure routine infectious disorders. A developing list of contagions – for example gonorrhea, foodborne disease, blood intoxication, pneumonia, and tuberculosis – are pretty sever, and very often incredible, to cure as antibiotics ineffective against their causative agents [76].

When antibiotic can be taken for animal or human usage deprived of instructions, the upsurge and propagation of resistance is become worse. Correspondingly, in states without standard therapy protocols, antibiotics are usually over-prescribed by vetenarians and healthcare practitioners and miss-used by the community. Without taking crucial measures, we are searching for a post-antibiotic epoch, in which routine contagions and minor wounds can once again kill [77].

7.2 Control and prevention: Resistance against antibiotics is enhanced by the misuse and prophylactic use of antibiotics, as well as underprivileged infection inhibition and control. We should take measures at all levels of community to reduce the propagation of antibiotic resistance [78].

8. Effect of antibiotic resistance on human and animal health: Once upon a time when everybody was chatting about the progress and upgrading of accessible antibiotics in the name of redeemable human and animal life from misery and clinicians and veterinarians kept on recommending the antibiotics without seeing the antibiotic resistance [79]. This practice has brought us at this time that we want to get

rid of antibiotics but the microbes are not allowing us to do so. This situation seems like the falling curve of bell graph of medical science [80]. In rising curve everyone was talking about increased life expectancy with the development of strong antibiotics and cure from diseases within less time. But now the situation is very different [81]. The microbes have developed resistance against many of antibiotics. Only few of the antibiotics are left useful. This condition has brought a lot of health risks for humans as well as animals [82]. Now if a person catches a simple infection the physician would suggest him a strong antibiotic, and next time the same infection will not be treated by a low potency antibiotic ,which will prolong the disease course and definitely involving other organs of the body as everyone knows that if some infectious agent remains in body for a longer time period it may cause systemic infection and not treated so easily [83]. It is also noticed that the people or infants who have no history of exposure to antibiotics also show antibiotic resistance. This resistance comes from antibiotic exposure by using dairy products or meat of animal where abuse of antibiotics is not a big deal [84]. The veterinary side has aggravated this situation by using antibiotics without considering the withdrawal period of antibiotics as this brings economics losses to dairy of beef producers. This practice has affected the animal health a lot in a bad way. It results in emergence of new disease with strong impact on the health of the animals [85]. These antibiotics remain in the blood of the animal and secreted in the milk which is consumed by humans. So exposure to antibiotics in a very minute quantity results in antibiotic resistance, where mild infections may be life threatening. So if this practice kept on going a time will come when no antibiotic will be effective for mild diseases and the life expectancy will fall down [86]. So if one wants to deal with antibiotic resistance, he has to consider the use of antibiotics in humans as well as in animals which are used as food for humans. Mostly the quackery in both sides is also playing its part in this problem causing health risk to life of humans as well as animals [87].

9. ALTERNATES OF ANTIBIOTICS

The antibiotic resistance is major reason for discouraging the use of antibiotics. So the world has started thinking about the alternate of antibiotics and started trials in this regard [88]. The rational use of antibiotics without considering future outcomes of antibiotics has brought the world to an edge where it has become very difficult for scientists to develop strong alternate of antibiotics at this time [89]. The simple and easiest escape from this problem is to live simple and organic lifestyle and check the further use of antibiotics in humans or animals. The good food is the best alternate to antibiotics and other medicines [90]. The food you ingest can be the cure of your disease if taken properly. The way food is produced and processed also defines the direction of food. Either it will heal your body if grown in organic way and free of any synthetic fertilizers and unwanted pesticides or be the cause of some serious diseases in body [91]. All of this seems so easy and practicable then why still not achievable. The main reason this pharmaceutical industry. If the world chooses an organic life it means the collapse of this industry which is not acceptable pharmaceutical company owners. However pharmaceutical have developed a lollypop by the name of probiotics which they will keep on producing instead of antibiotics [92]. The factory must keep on running no matter what it is producing either antibiotic or alternate to antibiotic [93]. It's time for people to decide about their future, either discussing the pros and cons of antibiotics at the cost of their health or simply change their lifestyle and quit the use of antibiotics [94] .

The simple formula of alternate to antibiotics is stop taking antibiotics and start taking good food. Right food is the best remedy for any disease and best alternate to any medicine [95].

If you find this approach inefficient then go for the medicinal use of plants and start using them without manipulating them in a synthetic way. Some people are also suggesting the prevention of microbial infections by vaccine [96]. Researchers have done a millions of research in the development of alternates of antibiotics but most of them have been ignored and pharmaceutical industry is pretending to be serious about development of alternates but progress in this field indicates their real intensions [97]. Till the pharmaceutical industry find some profitable alternate of antibiotics this discussion will not come true. Till then try to avoid the use of antibiotics and other medicines. If you suffer a mild disease without using any antibiotic, you are saving your body against a greater suffering [98]. However, Probiotics, anti-microbial proteins, prophages and plant-based substances are used as favorable alternatives of anti-biotic.

9.1 Antimicrobial Proteins: Almost every species produces antimicrobials proteins as first form of its natural immune system against microbial pathogens. These anti-microbial proteins (AMPs) are classified into various groups on the basis of their structure and activity [99]. Direct killing and immune modulation are the two major mechanism of actions of AMPs against microbial pathogens [100]. Direct killing of bacterial pathogen may be membrane killing or non-membrane killing. Antimicrobial proteins can destroy membrane of pathogenic bacteria by interacting with membrane receptors [101]. AMPs synthesized by eukaryotes are receptor independent to disrupt membrane of pathogenic bacteria. AMPs kill bacteria by making pores in membrane of pathogen bacteria that causes leakage of cytoplasmic fluid of bacterial cell [102]. [103]. Small size (e.g. 15-50 amino acids), hydrophobicity, and positive charge (+2-+9) due to presence of cationic arginine are the general features of AMPs naturally produced by both prokaryotes and eukaryotes[104]. AMPs interaction with negatively charged cell wall of Gram-positive bacteria involve binding of peptides with peptidoglycan and lipotechoic acid, binding with the negatively charged lipids situated on outer side of membrane while removing divalent ions [105]. While in case of Gram-negative bacteria membrane killing by AMPs involve displacement of divalent ions and reaction with LPS [106]. AMPs are isolated from fungi, animals, plants and insects. α-defensin, protamine, ll-37, pleurocidin, lactoferrin, fibrinogen, α-poly-L-arginine, casecidin and isracidin, salmon sperm (salmine sulfate), α-poly-l-lysin, protamine from herring sperm, and salmine lb-AMP1 peptide are common AMPs produced by eukaryotes [107].

9.2 Bacteriophages: Viruses acting as natural killers of bacteria and capable of replicating only inside prokaryotic cells are termed as bacteriophages “bacteria eater” [108]. Bacteriophages are used to treat infectious diseases of human, plants and animals. Phages can be used as biosensor to detect lethal food borne pathogens e.g. salmonella [109].

It is supposed that phages are the most abundant organisms present on the earth. Number of phages estimated in biosphere is up to 10^[30-31] that is ten times higher than the number of prokaryotic cells in biosphere [110]. Due to pan-drug and multi-drug evolution in bacteria, antibiotics i.e. phages are used to kill bacteria by targeting them at site of infection. Phage therapy is well tolerated because of inherent adaptation of phages into human microbiota [111]. On the basis of morphological symmetry, Phages are categorized into three groups complex phages, icosahedron phages, and filamentous phages

[112]. Size of phages genome varies from few thousands to 498Kbs, and it can be RNA/DNA either single stranded or double (ssRNA/dsRNA, ssDNA/dsDNA) [113]. Phages may be classified into virulent phages that causes lysis of prokaryotic cell during its reproduction within host cell, and temperate phages that incorporated their genome into host cell genome and replicate along with host cells until the induction of lytic phase of their replication cycle [114]. Mostly phages are host specific and their host specificity depends on both host immunity (physical & genetic) against viruses and receptors for phages on host cell surface. Specificity of phages is much higher than antibiotics specificity [115]. No doubt phages are good alternates of antibiotics to treat infectious diseases (Table 2) but we are facing phage resistant bacteria that cause infection in human. Pseudomonas aeruginosa is resistant to both antibiotics and phages (i.e. phage 14/1) [116].

Table 2. Classification of phages.

Family	**Phage name**	**Morphology**	**Genome**	**Therapeutic use**	**Refrences**
Myoviridae	Tailed phage T4	Non-enveloped virus with contractile tail	Linear dsDNA	*E. coli*	[117]
Siphoviridae	Phage λ	Non-enveloped virus with long non-contractile tail	Linear dsDNA	*E. coli*	[118]
Podoviridae	Coliphage T7	Non-enveloped virus with short non-contractile tail	Linear dsDNA	*E. coli*	[119]
Tectiviridae	Phage PRD1	Non-enveloped, isometric virus	Linear dsDNA	Enterobacteria	[120]
Lipotherixviridae	Thermoproteous ϕ phage 1	Enveloped, rod shape virus	Linear dsDNA		[121]
Corticoviridae	PM2	Non-enveloped, isometric virus	Circular dsDNA	Pseudoalteromonas	[122]

Plasmaviridae	Acholeplasma phage	Enveloped, pleomorphic virus	Circular dsDNA	Acholeplasma	[112]
Rudiviridae	Rudivirus	Non-Enveloped, rod shape virus	Linear dsDNA	Archae bacteria	[123]
Fuselloviridae	SSV-1	Non-Enveloped, lemon-shaped virus	Circular dsDNA	Archae bacteria	[124]
Inoviridae	Coliphage fd, MS2, ϕX174	Non-Enveloped, filamentous virus	Circular ssDNA	*E.coli*	[125]
Cystoviridae	Φ66	Enveloped, spherical virus	Segmented dsRNA	Staphylococcus aureus	[126]
Microviridae	Spiroplasma phages	Non-Enveloped, isometric virus	Circular ssDNA	Spiroplasma	[127]
Leviviridae	Coliphage Qβ	Non-Enveloped, isometric virus	Linear ssRNA	Infect coliform bacteria	[128]

9.3 Plant derived-antimicrobial compounds: Use of plants extract as antimicrobial compounds for treatment of infectious diseases is very common. Plant derived compounds are promising substitute of antibiotics for the resistant prokaryotes [129]. Naturally plants are major source of biologically active compounds. With the passage of time plants developed various strategies to combat with microbial attack on them [130]. Due to lack of cell mediated immunity, plant had to develop some other means to combat with prokaryotes [131]. Plants derived antimicrobial compounds contain various functional compounds like phytochemicals, phenols, essential oils, polyphenols, and micronutrients. These plant based compounds are used as photobiotics in animal nutrition [132]. These compounds have antimicrobial as well as antioxidant properties. More than 30,000 active antimicrobial compounds have been derived from plants [133]. Antimicrobial activity of essential oils derived from herbs because of terpenoids and phenolic [134]. These lipophilic compounds kill bacteria by accumulating in prokaryotic cell membrane and causing disturbance in cell membrane [135]. These lipophilic compounds are chemically divided into three

major groups e.g. phenolic, essential oils and, alkaloids [136]. These phytochemicals are the best alternatives of antibiotics to treat bacterial infections (Table 3).

Table 3. Plant based antimicrobial compounds.

Plant	Antimicrobial compounds	Mode of action	Activity against	Reference
Eugenia caryophillus (Clove)	Essential oils	Denaturation of membrane proteins, Cell lysis	*E. coli*, *S. aureus* L. monocytogenes	[137]
Armoracia rusticana (Horseradish)	Organosulfar compounds (allyl isothiocycnate)	Compromise the integrity of prokaryotic membrand, React with sulhydryl groups of enzymes	*S. enterica sr. enteritidus* *E. coli, S.aureus* *L. monocytogenes*	[138]
Cymbopogan citratus (lemongrass)	Essential oils	Denaturation of membrane proteins, Cell lysis	*S. enterica sr. enteritidus* *E. coli, S.aureus* *L. monocytogenes*	[139]
Allium sativum (Garlic)	Organosulfar compounds (diallyl sulfides, allicin) Phenolic compounds	Compromise the integrity of prokaryotic membrand, React with sulhydryl groups of enzymes	*S. enterica sr. enteritidus* *E. coli, S.aureus* *L. monocytogenes*	[139]
Ocimum basilicum (Basil)	Essential oils	Denaturation of membrane proteins, Cell lysis	*S. enterica sr. enteritidus* *E. coli, S.aureus* *L. monocytogenes*	[140]

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