

## **Q.1 Give a detailed note on principles and methods of plant disease management.**

**Ans.:** It conveys a concept of continuous process which is based not only on the principle of eradication of the pathogen but mainly on the principle of minimizing the damage or loss below economic injury level.

**Importance:** Plant diseases are important because of the losses (qualitative and quantitative) they cause. Loss may occur at any time between sowing of the crop and consumption of the produce. Measures taken to prevent the incidence of the disease, reduce the amount of inoculum that initiates and spreads the disease and finally minimize the loss caused by the disease are called as management practices.

### **Essential considerations in plant disease Management:**

1. Benefit-cost ratio
2. Procedures for disease control should fit into general schedule of operations of crop production
3. Control measures should be adopted on a **co-operative basis** over large adjoining areas. This reduces frequency of applications, cost of control and increases chances of success of control measures
4. Knowledge aspects of disease development is essential for effective economical control. Information is needed on the following aspects
  - a. Cause of a disease
  - b. Mode of survival and dissemination of the pathogen
  - c. Host parasite relationship
  - d. Effect of environment on pathogenesis in the plant or spread in plant population
5. Prevention of disease depends on management of primary inoculum
6. Integration of different approaches of disease management is always recommended

### **General principles of plant disease management**

1. **Avoidance:** Avoiding disease by planting at times when, or in areas where, inoculum is ineffective due to environmental conditions, or is rare or absent
2. **Exclusion of inoculum:** Preventing the inoculum from entering or establishing in the field or area where it does not exist
3. **Eradication:** Reducing, inactivating, eliminating or destroying inoculum at the source, either from a region or from an individual plant in which it is already established
4. **Protection:** Preventing infection by creating a chemical toxic barrier between the plant surface and the pathogen
5. **Disease resistance (Immunization):** Preventing infection or reducing effect of infection by managing the host through improvement of resistance in it by genetic manipulation or by chemical therapy.

**I. Avoidance of the pathogen:** These methods aim at avoiding the contact between the pathogen and susceptible stage of the crop. This is achieved by

- a. Proper selection of geographical area b.  
Proper selection of the field
- c. Adjusting time of sowing d.  
Disease escaping varieties
- e. Proper selection of seed and planting material

**a) Proper selection of geographical area:** Many fungal and bacterial diseases are more severe in wet areas than in dry areas. Cultivation of bajra in wet areas is not profitable due to the diseases, smut (*Tolyposporium penicillariae*) and ergot (*Claviceps microcephala*).

**b) Proper selection of the field:** Proper selection of field will help in the management of many diseases, especially the soil borne diseases. Raising of a particular crop year after year in the same field makes the soil sick, where disease incidence and severity may be more.

Ex: Wilt of redgram, late blight of potato (*Phytophthora infestans*), green ear of bajra (*Sclerospora graminicola*), etc.

**c) Time of sowing:** Generally pathogens are able to infect the susceptible plants under certain environmental conditions. Alteration of date of sowing can help in avoidance of favourable conditions for pathogen.

Ex: *Rhizoctonia* root rot of redgram is more severe in the crop sown immediately after the rains. Delayed sowing will help in reducing the incidence of disease.

Ex: Infection of black stem rust of wheat (*Puccinia graminis tritici*) is more in late sowing, hence, early sowing helps in reduction of stem rust incidence.

**d) Disease escaping varieties:** Certain varieties of crops escape the disease damage because of their growth characteristics. Ex: Early maturing varieties of wheat or pea escape the damage due to *Puccinia graminis tritici* and *Erysiphe polygoni*, respectively.

**e) Proper selection of seed and planting material:** Selection of seed and seedling material from healthy sources will effectively manage the diseases such as loose smut of wheat (*Ustilago nuda tritici*), bunchy top of banana (*Banana virus-1*), Panama wilt of banana (*Fusarium oxysporum f.sp. cubense*) and whip smut of sugarcane (*Ustilago scitaminae*). Potato seed certification or tuber indexing is followed for obtaining virus free seed tubers. Citrus bud wood certification programme will help in obtaining virus free planting material.

**II. Exclusion of the pathogen:** These measures aim at preventing the inoculum from entering or establishing in the field or area where it does not exist. Different methods of exclusion are seed treatment, seed inspection & certification, and plant quarantine regulation.

**a) Seed inspection and certification:** Crops grown for seed purpose are inspected periodically for the presence of diseases that are disseminated by seed. Necessary precautions are to be taken to remove the diseased plants in early stages, and then the crop is certified as disease free. This practice will help in the prevention of inter and intra regional spread of seed borne diseases.

**b) Plant quarantine regulation:** Plant quarantine is defined as “ a legal restriction on the movement of agricultural commodities for the purpose of exclusion, prevention or delaying the spread of the plant pests and diseases in uninfected areas”.

Plant quarantine laws were first enacted in **France** (1660), followed by Denmark (1903) and USA (1912). These rules were aimed at the rapid destruction or eradication of barbery bush which is an alternate host of *Puccinia graminis tritici*.

In India, plant quarantine rules and regulations were issued under **Destructive Insects and Pests Act (DIPA)** in 1914. In India, 16 plant quarantine stations are in operation by the “Directorate of plant protection and quarantine” under the ministry of food and agriculture, government of India.

Plant quarantine measures are of 3 types.

**1. Domestic quarantine:** Rules and regulations issued prohibiting the movement of insects and diseases and their hosts from one state to another state in India is called domestic quarantine. Domestic quarantine in India exists for two pests (Rooted scale and Sanjose scale) and three diseases (Bunchy top of banana, banana mosaic and wart of potato).

**Bunchy top of banana:** It is present in Kerala, Assam, Bihar, West Bengal and Orissa. Transport of any part of *Musa* species excluding the fruit is prohibited from these states to other states in India.

**Banana mosaic:** It is present in Maharashtra and Gujarat. Transport of any part of *Musa* species excluding the fruit is prohibited from these states to other states in India.

**Wart of potato:** It is endemic in Darjeeling area of West Bengal, therefore seed tubers are not to be imported from West Bengal to other states.

**2. Foreign quarantine:** Rules and regulations issued prohibiting the import of plants, plant materials, insects and fungi into India from foreign countries by air, sea and land. Foreign quarantine rules may be general or specific. General rules aim at prevention of introduction of pests and diseases into a country, where as the specific rules aim at specific diseases and insect pests. The plant materials are to be imported only through the prescribed ports of entry.

1. **Airports:** Bombay (Santacruz), Calcutta (Dum Dum), Madras (Meenambakam), New delhi (Palam, Safdarjung) and Tiruchurapally.

2. **Sea ports:** Bombay, Calcutta, Vishakapatnam, Trivandrum, Madras, Tuticorin, Cochin and Dhanushkoti.

3. **Land frontiers:** Hussainiwala (Ferozpur district of Punjab), Kharla (Amritsar district of Punjab) and Sukhiapokri (Darjeeling district of West Bengal)

3. **Total embargoes:** Total restriction on import and export of agricultural commodities.

**Phytosanitary certificate:** It is an official certificate from the country of origin, which should accompany the consignment without which the material may be refused from entry.

Plant diseases introduced into India before/after enforcement of plant quarantine laws:

S.No.	Disease	Year	Introduced into	From
1	Late blight of potato	1883	India	Europe
2	Coffee rust	1879	India	Srilanka
3	Flag smut of wheat	1906	India	Australia
4	Downy mildew of grapes	1910	India	Europe
5	Bacterial blight of rice	1964	India	Phillippines
6	Rice blast	1918	India (Madras)	South East Asia
7	Downy mildew of maize	1912	India (Madras)	Java
8	Ergot of bajra	1957	India (Bombay)	Africa
9	Panama wilt of banana	1920	India	Panama canal
10	Bunchy top of banana	1940	India	Srilanka
11	Wart of potato	1953	India	Netherlands
12	Golden cyst nematode of potato	1961	India	Europe

**Diseases not entered into India:** Swollen shoot of cocoa, leaf blight of rubber and many viral diseases.

**III. Eradication:** These methods aim at breaking the infection chain by removing the foci of infection and starvation of the pathogen (i.e., elimination of the pathogen from the area by destruction of sources of primary and secondary inoculum). It is achieved by

**a) Rouging:** Removal of diseased plants or their affected organs from field, which prevent the dissemination of plant pathogens.

Ex: Loose smut of wheat and barley, whip smut of sugarcane, red rot of sugarcane, ergot of bajra, yellow vein mosaic of bhendi, khatte disease of cardamom, etc. During 1927-

1935, to eradicate citrus canker bacterium in USA, 3 million trees were cut down and burnt.

**b) Eradication of alternate and collateral hosts:** Eradication of alternate hosts will help in management of many plant diseases.

Ex: Barbery eradication programme in France and USA reduced the severity of black stem rust of wheat

Ex: Eradication of *Thalictrum* species in USA to manage leaf rust of wheat caused by *Puccinia recondita*.

Eradication of collateral hosts, such as *Panicum repens*, *Digitaria marginata* will help in the management of rice blast disease (*Pyricularia oryzae*)

**c) Crop rotation:** Continuous cultivation of the same crop in the same field helps in the perpetuation of the pathogen in the soil. Soils which are saturated by the pathogen are often referred as **sick soils**. To reduce the incidence and severity of many soil borne diseases, crop rotation is adopted. Crop rotation is applicable to only root inhabitants and facultative saprophytes, and may not work with soil inhabitants.

Ex: Panama wilt of banana (long crop rotation), wheat soil borne mosaic (6 yrs) and club root of cabbage (6-10 yrs), etc.

**d) Crop sanitation:** Collection and destruction of plant debris from soil will help in the management of soil borne facultative saprophytes as most of these survive in plant debris. Collection and destruction of plant debris is an important method to reduce the primary inoculum.

**e) Manures and fertilizers:** The deficiency or excess of a nutrient may predispose a plant to some diseases. Excessive nitrogen application aggravates diseases like stem rot, bacterial leaf blight and blast of rice. Nitrate form of nitrogen increases many diseases, whereas, phosphorous and potash application increases the resistance of the host. Addition of farm yard manure or organic manures such as green manure, 60-100 t/ha, helps to manage the diseases like cotton wilt, Ganoderma root rot of citrus, coconut, etc.

**f) Mixed cropping:** Root rot of cotton (*Phymatotrichum omnivorum*) is reduced when cotton is grown along with sorghum. Intercropping sorghum in cluster bean reduces the incidence of root rot and wilt (*Rhizoctonia solani*)

**g) Summer ploughing:** Ploughing the soil during summer months expose soil to hot weather which will eradicate heat sensitive soil borne pathogens.

**h) Soil amendments:** Application of organic amendments like saw dust, straw, oil cake, etc., will effectively manage the diseases caused by *Pythium*, *Phytophthora*, *Verticillium*, *Macrophomina*, *Phymatotrichum* and *Aphanomyces*. Beneficial micro-organisms increases in soil and helps in suppression of pathogenic microbes.

Ex: Application of lime (2500 Kg/ha) reduces the club root of cabbage by increasing soil pH to 8.5

Ex: Application of Sulphur (900 Kg/ha) to soil brings the soil pH to 5.2 and reduces the incidence of common scab of potato (*Streptomyces scabies*).

**ij) Changing time of sowing:** Pathogens are able to infect susceptible plants under certain environmental conditions. Alternation in date of sowing can help avoidance of favourable conditions for the pathogens.

Ex: Rice blast can be managed by changing planting season from June to September/October.

**j) Seed rate and plant density:** Close spacing raises atmospheric humidity and favours sporulation by many pathogenic fungi. A spacing of 8'X8' instead of 7'X7' reduces sigatoka disease of banana due to better ventilation and reduced humidity. High density planting in chillies leads to high incidence of damping off in nurseries.

**k) Irrigation and drainage:** The amount, frequency and method of irrigation may affect the dissemination of certain plant pathogens. Many pathogens, including, *Pseudomonas solanacearum*, *X. campestris pv. oryzae* and *Colletotrichum falcatum* are readily disseminated through irrigation water. High soil moisture favours root knot and other nematodes and the root rots caused by species of *Sclerotium*, *Rhizoctonia*, *Pythium*, *Phytophthora*, *Phymatotrichum*, etc.

**PHYSICAL METHODS:** Physical methods include soil solarization and hot water treatments.

**i. Soil solarization:** Soil solarization or slow soil pasteurization is the hydro/thermal soil heating accomplished by covering moist soil with polyethylene sheets as soil mulch during summer months for 4-6 weeks. Soil solarization was developed for the first time in Israel (Egley and Katan) for the management of plant pathogenic pests, diseases and weeds.

**ii. Soil sterilization:** Soil can be sterilized in green houses and sometimes in seed beds by aerated steam or hot water. At about 50<sup>0</sup>C, nematodes, some oomycetous fungi and other water molds are killed. At about 60 and 72<sup>0</sup>C, most of the plant pathogenic fungi and bacteria are killed. At about 82<sup>0</sup>C, most weeds, plant pathogenic bacteria and insects are killed. Heat tolerant weed seeds and some plant viruses, such as TMV are killed at or near the boiling point (95-100<sup>0</sup>C).

**iii. Hot water or Hot air treatment:** Hot water treatment or hot air treatment will prevent the seed borne and sett borne infectious diseases. Hot water treatment of certain seeds, bulbs and nursery stock is done to kill many pathogens present in or on the seed and other propagating materials. Hot water treatment is used for controlling sett borne diseases of sugarcane [whip smut, grassy shoot and red rot of sugarcane (52<sup>0</sup>C for 30 min)] and loose smut of wheat (52<sup>0</sup>C for 10 min).

### **Biological methods:**

**Def:** Biological control of plant disease is a condition or practice whereby survival or activity of a pathogen is reduced through the agency of any other living organism (except human beings), with the result that there is reduction in incidence of the disease caused by the pathogen (Garett, 1965).

**Def:** Biological control is the reduction of inoculum density or disease producing activity of a pathogen or a parasite in its active or dormant state by one or more organisms accomplished naturally or through manipulation of the environment of host or antagonist by mass introduction of one or more antagonists (Baker and Cook, 1974)

### **Mechanisms of biological control**

**1. Competition:** Most of the biocontrol agents are fast growing and they compete with plant pathogens for space, organic nutrients and minerals. Most aerobic and facultative anaerobic micro-organisms respond to low iron stress by producing extracellular, low molecular weight (500-1000 daltons) iron transport agents, designated as **Siderophores**, which selectively make complex with iron (Fe<sup>3+</sup>) with very high affinity. Siderophore producing strains are able to utilize Fe<sup>3+</sup> -

Siderophore complex and restrict the growth of deleterious micro-organisms mostly at the plant roots. Iron starvation prevents the germination of spores of fungal pathogens in rhizosphere as well as rhizoplane. Siderophores produced by

*Pseudomonas fluorescens* (known as **pseudobactins** or **pyoverdins**) helps in the control of soft rot bacterium, *Erwinia caratovora*.

**2. Antibiosis:** Antagonism mediated by specific or non-specific metabolites of microbial origin, by lytic agents, enzymes, volatile compounds or other toxic substances is known as antibiosis.

a. **Antibiotics:** Antibiotics are generally considered to be organic compounds of low molecular weight produced by microbes. At low concentrations, antibiotics are deleterious to the growth or metabolic activities of other micro-organisms.

Ex: *Gliocladium virens* produces **gliotoxin** that was responsible for the death of *Rhizoctonia solani* on potato tubers.

Ex: Colonization of pea seeds by *Trichoderma viride* resulted in the accumulation of significant amount of the antibiotic **viridin** in the seeds, thus controlling *Pythium ultimum*.

Ex: Some strains of *Pseudomonas fluorescens* produce a range of compounds, viz., 2,4- diacetyl phloroglucinol (DAPG), phenazines, pyocyanin, which have broad spectrum activity against many plant pathogenic bacteria and fungi

b. **Bacteriocins:** These are antibiotic like compounds with bactericidal specificity closely related to the bacteriocin producer. Ex: The control of crown gall (caused by *Agrobacterium tumefaciens*) by the related *Agrobacterium radiobacter* strain K 84 is by the production of bacteriocin, **Agrocin K84**.

c. **Volatile compounds:** Antibiosis mediated by volatile compounds has been observed in the management of soil borne pathogens, viz., *Pythium ultimum*, *Rhizoctonia solani* and *Verticillium dahlia*, by *Enterobacter cloacae*. The volatile fraction responsible for inhibition was identified as ammonia.

**3. Hyperparasitism:** Direct parasitism or lysis and death of the pathogen by another micro-organism when the pathogen is in parasitic phase is known as hyperparasitism.

Ex: *T. harzianum* parasitize and lyse the mycelia of *Rhizoctonia* and *Sclerotium*.

### Biocontrol agents for the management of plant pathogens

Biocontrol agent	Pathogen/disease
1. <i>Ampelomyces quisqualis</i>	Powdery mildew fungi
2. <i>Darluca filum</i> , <i>Verticillium lecanii</i>	Rust fungi
3. <i>Pichia gulliermondii</i>	<i>Botrytis</i> , <i>Penicillium</i>

## **Biocontrol agent**

1. *Pasteuria penetrans* (Bacteria)
2. *Paecilomyces lilacinus* (Fungus)

## **Nematode**

- Juvenile parasite of root knot nematode
- Egg parasite of *Meloidogyne incognita*

### **Important fungal biocontrol agents:**

Most of the species of Trichoderma, viz., *T. harzianum*, *T. viride*, *T. virens* (*Gliocladium virens*) are used as biocontrol agents against soil borne diseases, such as, root rots, seedling rots, collar rots, damping off and wilts caused by the species of Pythium, Fusarium, Rhizoctonia, Macrophomina, Sclerotium, Verticillium, etc.

Formulations of biocontrol agents available: *T. viride* (**Ecofit**, **Bioderma** in India), *G. virens* (**GlioGard** in USA), *T. harzianum* (**F-Stop** in USA) and *T. polysporum* (**BINAB- T**)

### **Important bacterial biocontrol agents:**

1. *Pseudomonas fluorescens* (**Dagger-G** against damping off of cotton seedlings in USA)
2. *Bacillus subtilis* (**Kodiak** against damping off and soft rot in USA)
3. *Agrobacterium radiobacter* K-84 (**Gallex** or **Galltrol** against crown gall of stone fruits caused by *Agrobacterium tumefaciens*)

### **Plant growth promoting Rhizobacteria (PGPR):**

Rhizosphere bacteria that favourably affect plant growth and yield of commercially important crops are designated as plant growth promoting rhizobacteria. The growth promoting ability of PGPR is due to their ability to produce phytohormones, Siderophores, Hydrogen cyanide (HCN), chitinases, volatile compounds or antibiotics which will reduce infection of host through phyto-pathogenic micro-organisms.

Many bacterial species, viz., *Bacillus subtilis*, *Pseudomonas fluorescens*, etc., are usually used for the management of plant pathogenic microbes. *Bacillus* has ecological advantages as it produces endospores that are tolerant to extreme environmental conditions. *Pseudomonas fluorescens* have been extensively used to manage soil borne plant pathogenic fungi due to their ability to use many carbon sources that exude from the roots and to compete with microflora by the production of antibiotics, HCN and Siderophores that suppress plant root pathogens.

## **Q. 2 Give a detailed description of Integrated Plant Disease Management (IPDM)**

**Ans** - Integrated plant disease management can be defined as a decision-based process involving coordinated use of multiple tactics for optimizing the control of pathogen in an ecologically and economically. The implications are:

- ✓ Simultaneous management of multiple pathogens
- ✓ Regular monitoring of pathogen effects, and their natural enemies and antagonists as well
- ✓ Use of economic or treatment thresholds when applying chemicals
- ✓ Integrated use of multiple, suppressive tactics.

### **Principles of Plant Disease Control**

1. **Avoidance**—prevents disease by selecting a time of the year or a site where there is no inoculum or where the environment is not favorable for infection.
2. **Exclusion**—prevents the introduction of inoculum.
3. **Eradication**—eliminates, destroy, or inactivate the inoculum.
4. **Protection**—prevents infection by means of a toxicant or some other barrier to infection.
5. **Resistance**—utilizes cultivars that are resistant to or tolerant of infection.
6. **Therapy**—cure plants that are already infected

### **Factors affecting occurrences**

Factors which affect Plant diseases are micro-organisms, including fungi, bacteria, viruses, mycoplasmas, etc. or may be incited by physiological causes including high or low temperatures, lack or excess of soil moisture and aeration, deficiency or excess of plant nutrients, soil acidity or alkalinity, etc. Factors that limit the rate of disease development are the relatively low amounts of inoculum in the lag stage and the paucity of healthy plants available to the inoculum in the stationary stage.

The causative agents of disease in green plants number in a tens of thousands and include almost every form of life. But primary agents of disease may also be inanimate. Thus nonliving (abiotic) agents of disease include mineral deficiencies and excesses, air pollutants, biologically produced toxicants, improperly used pesticidal chemicals, and such other environmental factors as wind, water, temperature, and sunlight. Nonliving things certainly qualify as primary agents of disease; they continuously irritate plant cells and tissues; they are harmful to the physiological processes of the plant; and they evoke pathological responses that manifest as the symptoms characteristic of the several diseases. But the abiotic agents of disease in plants. The abiotic

agents of plant disease are termed noninfectious, and the diseases they cause are termed noninfectious diseases.

### **Micro-organisms**

The micro-organisms obtain their food either by breaking down dead plant and animal remains (saprophytes) or by attacking living plants and animals (parasites). In order to obtain nutrients, the parasitic organisms excrete enzymes or toxins and kill the cells of the tissues of the host plant, as a result of which either the whole plant or a part of it is damaged or killed, or considerable disturbance takes place in its normal metabolic processes.

### **Parasites**

One of the factors causing plant diseases is parasites, those living organisms that can colonize the tissues of their host-plant victims and can be transmitted from plant to plant. These biotic agents are, therefore, infectious, and the diseases they cause are termed infectious diseases. The infectious agents of plant diseases are treated in the standard textbooks on plant pathology. **Ability to produce an inoculum**

The parasitic pest must produce an inoculum, some structure that is adapted for transmission to a healthy plant and this can either parasitize the host directly or develop another structure that can establish a parasitic relationship with the host. For example, inocula for viruses are the viral particles (virions); for bacteria, the bacterial cells; for fungi, various kinds of spores or the hyphal threads of mold; for nematodes, eggs or second-stage larvae.

### **Agents/ Media for transportation of inoculum**

The inoculum must be transported from its source to a part of a host plant that can be infected. This dispersal of inoculum to susceptible tissue is termed inoculation. Agents of inoculation may be insects (for most viruses and mycoplasma-like organisms and for some bacteria and fungi), wind (for many fungi), and splashing rain (for many fungi).

### **Wounds, Natural openings**

The parasite must enter the host plant, which it can do (depending on the organism) in one or more of three ways; through wounds, through natural openings, or by growing directly through the unbroken protecting surface of the host. Viruses are literally injected into the plant as the homopterous insect carrier probes and feeds within its host. Bacteria depend on wounds or natural openings (for example, stomates, hydathodes, and lenticels) for entrance, but many

fungi can penetrate plant parts by growing directly through plant surfaces, exerting enormous mechanical pressure and possibly softening host surfaces by enzymatic action.

### **Availability of food**

For occurrence of disease one of the factor affecting is, availability of nourishment to grow within its host. This act of colonizations is termed infection. Certainly the parasite damages the cytoplasmic membranes of the host cells, making those membranes freely permeable to solutes that would nourish the parasite. And parasitism certainly results from enzymatic attacks by the parasite upon carbohydrates, proteins, and lipids inside the host cell. The breakdown products of such complex molecules would diffuse across the damaged host-cell membranes and be absorbed by the parasite in the form of sugars, amino acids, and the like. Air-borne parasites of foliage, flower, and fruit.

### **Preventive and control measures**

#### **A. PREVENTIVE MEASURES**

##### **Cultural practices**

Cultural practices usually influence the development of disease in plants by affecting the environment. Such practices are intended to make the atmospheric, edaphic, or biological surroundings favorable to the crop plant, unfavorable to its parasites. Cultural practices that leads to disease control have little effect on the climate of a region but can exert significant influence on the microclimate of the crop plants in a field. Three stages of parasite's life cycle namely, Survival between crops, production of inoculum for the primary cycle and inoculation can be control by following preventive measures.

##### **Survival between Crops**

Organisms that survive in the soil can often be controlled by crop rotations with unsusceptible species. Depending on the system, either of two effects results. Catch crops have been used to control certain nematodes and other soil-borne pathogens. Soil-borne plant pathogens can be controlled by biological methods. Plant parasites may be controlled by antagonistic organisms that can be encouraged to grow luxuriantly by such cultural practices as green manuring and the use of appropriate soil additives. The soil-invading parasite thus becomes an amensal in association with its antagonist. Soil-borne plant parasites may also be killed during their over-seasoning stages by such cultural practices as deep ploughing (as for the pathogen of southern leaf blight of corn), flooding (as for the cottony-rot pathogen and some nematodes), and frequent cultivation and fallow (as for the control of weeds that harbor plant viruses). Plant diseases caused by organisms that survive as parasites within perennial hosts or within the seed of annual plants may be controlled therapeutically. Therapeutic treatments of

heat and surgery are applicable here; those involving the use of chemicals will be mentioned later. Removal of cankered limbs (surgery) helps control fire blight of pears, and the hot-water treatment of cabbage seed controls the bacterial disease known as black rot. Heat therapy is also used to rid perennial hosts of plant-parasitic nematodes.

### **Production of Inoculum for the Primary Cycle**

Environmental factors (particularly temperature, water, and organic and inorganic nutrients) significantly affect Inoculum production. Warm temperature usually breaks dormancy of overseasoning structures; rain may leach growth inhibitors from the soil and permit germination of resting spores; and special nutrients may stimulate the growth of overseasoning structures that produce inoculum.

### **Dispersal of inoculum and inoculation**

Cultural practices that exemplify avoidance are sometimes used to prevent effective dissemination. A second hierarchy of regulatory disease control is plant quarantine, the legally enforced stoppage of plant pathogens at points of entry into political subdivisions. The Plant Quarantine Act of the United States governs importation of plant materials into the country and requires the state govt. to enforce particular measures. Also, states make regulations concerning the movement of plant materials into them or within them. E.g., Florida imposes quarantine against the citrus-canker bacterium, which was eliminated from the state earlier by means of cooperative efforts led by the Florida Department of Agriculture.

### **Sample inspection**

One of the preventive measures to control the diseases is the use of sample inspection method. Laboratory evaluation of the representative sample drawn by the certification agency for the determination of germination, moisture content, weed seed content, admixture, purity, seed-borne pathogens.

## **B. Control Measures**

### **Chemical Control**

The pesticidal chemicals that control plant diseases may be used in very different ways, depending on the parasite to be controlled and on the circumstances it requires for parasitic activities. E.g., a water-soluble eradicated spray is applied once to dormant peach trees to rid them of the overwintering spores of the fungus of peach-leaf curl, whereas relatively insoluble protective fungicides are applied repeatedly to the green leaves of potato plants to safeguard them from penetration by the fungus of late blight. Also, systemic fungicidal chemicals may be used therapeutically.

The oxathiin derivatives that kill the smut fungi that infect embryos are therapeutic, as is benomyl (which has systemic action against powdery mildews and other leaf infecting fungi). Volatile fungicides are often useful as soil-fumigating chemicals that have eradicated action. The chemical control of plant diseases is classified in three categories: seed treatments, soil treatments, and protective sprays and dusts.

### **Seed Treatments**

Chemical treatments of seed may be effective in controlling plant pathogens in, on, and around planted seed. Seed treatment is therapeutic when it kills bacteria or fungi that infect embryos, cotyledons, or endosperms under the seed coat, eradicated when it kills spores of fungi that contaminate seed surfaces, and protective when it prevents penetration of soil-borne fungi into seedling stems. Certified seed is usually given treatment necessary for the control of certain diseases. Seed treatment is of two types; viz., physical and chemical. Physical treatments include hot-water treatment, solar-heat treatment (loose smut of wheat), and the like. Chemical treatments include use of fungicides and bactericides. These fungicides are applied to seed by different methods. In one method, the seed in small lots is treated in simple seed-treaters. The seed-dip method involves preparing fungicide suspension in water, often at field rates, and then dipping the seed in it for a specified time.

## Some chemicals commonly used to control plant diseases

Chemical and use	Relative toxicity	
	Oral	Dermal
<b>Seed treatments (all fungicides)</b>		
Chloraneb	Low	Low
Dichlone	Low	High
Thiram	Moderate	High
Carboxin (systemic and therapeutic)	Low	Low
<b>Soil treatments</b>		
Methyl bromide <sup>b</sup> (general pesticide)	Very high	Very high
PCNB (fungicide)	Low	Moderate
SMDC [vapam] (fungicide, nematicide)	Moderate	Moderate
MIT ["Vorlex"] (fungicide, nematicide)	Moderate	Moderate
D-D mixture (nematicide)	Moderate	Low
<b>Plant-protective treatments</b>		
Copper compounds (fungicides, bactericides)	Moderate	Low
Sulfur (fungicide)	Low	Moderate
Maneb (fungicide)	Very low	Low
Zineb (fungicide)	Very low	Low
Captan (fungicide)	Very low	Very low
Dinocap (fungicide for powdery mildews)	Low	Low
Streptomycin (bactericidal antibiotic)	Very low	Low
Cyclohexamide <sup>b</sup> (fungicidal antibiotic)	Very high	Very high
Benomyl (protective and therapeutic fungicide)	Very low	Very low

The oxathiins (carboxin, DMOC) used to kill embryo infecting smuts of cereal grains have little effect on other organisms, most eradicated and protective chemicals have a wide range of fungicidal activity; they are effective against most seed-infesting and seedling-blight fungi. But specific seed-treatment chemicals often work best to control a given disease of a

single crop-plant species. Moreover, the toxicity of chemicals to seeds varies, and farmers should use only the compounds recommended by the Cooperative Extension Service of their country and state.

Copper and mercury-containing compounds were first used as seed-treating chemicals. But copper is toxic to most seeds and seedlings, and mercury has been banned from use in seed treatments because of the danger it poses to humans and animals. Organic compounds now widely used as protective and eradicated seed treatments include thiram, chloraneb, dichlone, dexton, and captan.

### **Soil Treatments**

Soil-borne plant pathogens greatly increase their populations as soils are cropped continuously, and finally reach such levels that contaminated soils are unfit for crop production. Chemical treatments of soil that eradicate the plant pathogens therein offer the opportunity of rapid reclamation of infested soils for agricultural uses. Preplanting chemical treatment of field soils for the control of nematode-induced diseases, and fumigation of seedbed and greenhouse soils (with methyl bromide, for example) is commonly practiced to eradicate weeds, insects, and plant pathogens. Field applications of soil-treatment chemicals for fungus control are usually restricted to treatments of furrows. Formaldehyde or captan applied is effective against sclerotia-producing fungi that cause seedling blights, stem rots, and root rots of many field crops. Other soil-treatment fungicides are vapam and "Vorlex." Soil treatments made at the time of planting are most effective against parasitic attacks that come early in the growing season.

### **Protective sprays and dust**

Protective fungicides prevent germination, growth, and penetration. In order to use protective fungicides effectively, the farmer must not only select the right fungicide for the job, but also apply it in the right amount, at the right times, and in the right way. Too little fungicide fails to control disease; too much may be toxic to the plants to be protected. The farmer and applicator, therefore, must always follow use instructions to the letter. Timing of applications is also critical.

### **Advantages**

Integrated approach integrates preventive and corrective measures to keep pathogen from causing significant problems, with minimum risk or hazard to human and desirable components of their environment.

Some of the benefits of an integrated approach are as follows:

- Promotes sound structures and healthy plants
- Promotes the sustainable bio based disease management alternatives.
- Reduces the environmental risk associated with management by encouraging the adoption of more ecologically benign control tactics
- Reduces the potential for air and ground water contamination
- Protects the non-target species through reduced impact of plant disease management activities.
- Reduces the need for pesticides and fungicides by using several management methods
- Reduces or eliminates issues related to pesticide residue
- Reduces or eliminates re-entry interval restrictions
- Decreases workers, tenants and public exposure to chemicals
- Alleviates concern of the public about pest & pesticide related practices.
- Maintains or increases the cost-effectiveness of disease management programs

### **Nature, chemical combination, classification, mode of action and formulation of fungicides.**

Use of chemicals for the control of plant diseases is generally referred to as protection or therapy.

**Protection:** The prevention of the pathogen from entering the host or checking the further development in already infected plants by the application of chemicals is called protection and the chemicals used are called protectants.

**Therapy** means cure of a disease, in which fungicide is applied after the pathogen is in contact with the host. Chemicals used are called therapeutants.

Fungicide: Any agent (chemical) that kills the fungus

**Fungistat:** Some chemicals which do not kill fungi, but simply inhibit the fungus growth temporarily.

**Antisporulant:** The chemical which inhibits spore production without affecting vegetative growth of the fungus.

Fungicides are classified into three categories: Protectants, eradicants and therapeutants.

**1. Protectants:** These are the chemicals which are effective only when used before infection (prophylactic in behavior). Contact fungicides which kill the pathogen present on the host surface when it comes in contact with the host are called protectants. These are applied to seeds, plant surfaces or soil. These are non-systemic in action (i.e, they cannot penetrate plant tissues). Ex: Zineb,sulphur, captan, Thiram, etc.

**2. Eradicants:** Those chemicals which eradicate the dormant or active pathogen from the host. They can remain on/in the host for some time. Ex: Lime sulphur, Dodine.

**3. Therapeutants:** These are the agents that inhibit the development of a disease syndrome in a plant when applied after infection by a pathogen. Therapy can be by physical means (solar and hot water treatment) and chemical means (by use of systemic fungicides, i.e., chemotherapy).

### CLASSIFICATION OF FUNGICIDES BASED ON CHEMICAL NATURE

Many fungicides have been developed for purpose of managing crop diseases which may be used as sprays, dusts, paints, pastes, fumigants, etc. The discovery of Bordeaux mixture in 1882 by Professor Millardet, University of Bordeaux, France led to the development of fungicides. Major group of fungicides used include salts of toxic metals and organic acids, organic compounds of sulphur and mercury, quinones and heterocyclic nitrogenous compounds. Copper, mercury, zinc, tin and nickel are some of the metals used as base for inorganic and organic fungicides. The non metal substances include, sulphur, chlorine, phosphorous etc. The fungicides have been classified based on their chemical nature as follows

**COPPER FUNGICIDES:** Copper fungicides can be classified as preparatory and proprietary copper compounds.

### PREPARATORY COPPER FUNGICIDES

Common name	Chemical composition	Diseases managed
1. Bordeaux mixture	It is prepared by suspending 5 Kg of copper sulphate and 5 Kg of lime in 500 liters of water (1%)	Downy mildew of grapes, Coffee rust, Tikka leaf spot of groundnut, citrus canker, citrus scab, etc.
2. Bordeaux paste	It is prepared by mixing 1 Kg of copper sulphate and 1 Kg of lime in 10 liters of water	It is a wound dressing fungicide and can be applied to the pruned parts of the host plants such as fruit crops and ornamentals. Ex: Citrus gummosis, Stem bleeding of coconut, Bud rot of coconut, etc.
3. Burgundy mixture	Sodium carbonate is used in place of lime. It is prepared by mixing 1 Kg of copper sulphate and 1 Kg of sodium carbonate in 100 liters of water	Downy mildew of grapes, Coffee rust, Tikka leaf spot of groundnut, citrus canker, citrus scab
4. Cheshunt compound	It is a compound prepared by mixing 2 parts of copper sulphate and 11 parts of ammonium carbonate	It is used for soil drenching only. Sclerotial wilt diseases of chilli, tomato and groundnut. Fusarial wilt diseases. Damping-off diseases of solanaceous crops.
5. Chaubattia paste	It is a compound prepared by mixing 800g of copper sulphate and 800g of red lead in 1 liter of lanolin or linseed oil	Pink disease of citrus, stem canker and collar rot of apple and pears

Proprietary copper fungicides or Fixed or insoluble copper fungicides: In the fixed or insoluble copper compounds, the copper ion is less soluble than in Bordeaux mixture. So, these are less phytotoxic than Bordeaux mixture but are effective as fungicides.

Common name	Trade name	Dosage	Disease managed
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1. Copper oxy chloride	Blitox-50, Blue copper-50, Cupramar-50	0.3 to 0.5% for foliar application, 25 to 35 Kg/ha for dusting	Anthracnose of grapevine, Tikka leaf spot of groundnut, Sigatoka leaf spot of banana, citrus canker, black arm of cotton
2. Cuprous oxide	Fungimar and Perenox	0.3% for foliar spray	Anthracnose of grapevine, Tikka leaf spot of groundnut, Sigatoka leaf spot of banana, citrus canker, black arm of cotton
3. Copper hydroxide	Kocide	0.3% for foliar spray	Blister blight of tea, False smut of rice, Tikka leaf spot of groundnut

## SULPHUR FUNGICIDES

Sulphur is probably the oldest chemical used in plant disease management for the control of powdery mildews and can be classified as inorganic sulphur and organic sulphur. Inorganic sulphur fungicides include lime sulphur and elemental sulphur fungicides. Organic sulphur fungicides, also called as carbamate fungicides, are the derivatives of dithiocarbamic acid.

## INORGANIC SULPHUR FUNGICIDES

Common name	Trade name	Dosage	Disease managed
<b>Preparatory sulphur compounds</b>			
1. Lime sulphur	It is prepared by mixing 20 Kg of rock lime and 15 Kg of sulphur in	10-15 liters in 500 liters of water	Powdery mildew of apple, Apple scab, bean rust
2. Sulphur dust	Kolo dust, Mico-999	4-5g/Kg seed for ST, 10-30 Kg/ha for dusting on crops, 100 Kg /ha for soil application in tobacco, 500	Common scab of potato, Grain smut of jowar, Powdery mildew of tobacco, chilli, rose, mango, grapes, etc.
3. Wettable sulphur	Sulfex, Thiovit,	0.2-0.4 % for foliar	Powdery mildews of

## ORGANIC SULPHUR COMPOUNDS

Organic sulphur compounds are derived from dithiocarbamic acid and are widely used as spray fungicides. In 1931, Tisdale and Williams were the first to describe the fungicidal nature of Dithiocarbamates. Dithiocarbamates can be categorized into two groups, viz., dialkyl dithiocarbamates (ziram, ferbam and thiram) and monoalkyl dithiocarbamates (nabam, zineb, vapam and maneb).

Common name	Trade name	Dosage	Diseases managed
<b>Dialkyl Dithiocarbamates</b>			
1. Ziram	Ziride, Hexazir, Milbam, Zerlate	0.15 to 0.25% for foliar spray	Anthracnose of pulses, tomato, beans, tobacco, etc., bean rust

2. Ferbam	Coromet, Ferbam, Fermate, Fermocide, Hexaferb, Karbam Black	0.15 to 0.25% for foliar spray	Fungal pathogens of fruits and vegetables, leaf curl of peaches, apple scab, downy mildew of tobacco
3. Thiram	Arasan, Hexathir, Tersan, Thiram, Thiride	0.15 to 0.2% as foliar spray, 0.2-0.3% as dry seed treatment, 15-25Kg/ha as soil application	Soil borne diseases caused by <i>Pythium</i> , <i>Rhizoctonia solani</i> , <i>Fusarium</i> , etc. Rust of ornamental crops, Scab on pears and <i>Botrytis</i> spp. on lettuce
<b>Monoalkyl dithiocarbamates</b>			
1. Nabam	Chembam, Dithane D-14, Dithane A-40 and Parzate liquid	0.2% as foliar spray	Used as foliar spray against leaf spot diseases of fruits and vegetables. Also used against soil borne pathogens, <i>Fusarium</i> , <i>Pythium</i> and <i>Phytophthora</i>
2. Zineb	Dithane Z-78, Hexathana, Lanocol and Parzate	0.1 to 0.3% for foliar application	Chilli die-back and fruit rot, Apple scab, Maize leaf blight, early blight of potato
3. Vapam or Metham sodium	Chem-vape, vapam, vitafume, VPM	1.5 to 2.5 liters per 10 m <sup>2</sup> area	Fungicide with fungicidal, nematicidal and insecticidal properties. Soil fungal pathogens like <i>Fusarium</i> , <i>Puthium</i> , <i>Sclerotium</i> and <i>Rhizoctonia</i> .
4. Maneb	Dithane M22, Manzate and MEB. Mancozeb (78% Maneb + 2% zinc ion): Dithane M 45, Indofil M 45	0.2% to 0.3% as foliar application	Early and late blight of potato and tomato, rust diseases of field and fruit crops

## HETROCYCLIC NITROGENOUS COMPOUNDS

Common	Trade name	Dosage	Diseases managed
1. Captan (Kittleson's killer)	Captan 50W, Captan 75 W, Esso fungicide, Orthocide 406, Hexacap, Vancide 89	0.2 to 0.3% for dry seed treatment, 0.2 to 0.3% for foliar spray, 25 to 30 Kg/ha for furrow application	Onion smut, Chilli die-back and fruit rot, Damping off of beans, chilli and tomato, seed rots and seedling blights of maize
2. Folpet	Phaltan	0.1 to 0.2% for spraying	Apple scab, tobacco brown spot, rose

3. Captafol	Difosan, Difolaton, Sanspor, Foltaf	0.15 to 0.2% for spraying, 0.25% for seed treatment, 0.15% for soil drenching	Sorghum anthracnose, cotton seedling diseases, seed rot and seedling diseases of rice, downy mildew of crucifers, apple scab
4. Iprodione	Rovral, Glycophene	0.1 to 0.2% for foliar application	Diseases caused by Botrytis, Monilinia, Alternaria, Sclerotinia, Helminthosporium and Rhizoctonia
5. Vinclozolin	Ornalin, Ronilan, Vorlan	0.1 to 0.2% for foliar application	Effective against sclerotia forming fungi like Botrytis, Monilinia and Sclerotinia

The group of heterogeneous fungicides includes some of the best fungicides like captan, folpet, captafol, vinclozoline and Iprodione. Captan, folpet and captafol belong to dicarboximides and are known as phthalamide fungicides. The new members of dicarboximide group are Iprodione, vinclozolin, etc.

#### MISCELLANEOUS FUNGICIDES

Common	Trade name	Dosage	Diseases managed
1. Chlorothalonil	Bravo, Daconil, Kavach, Thermil, Exotherm, Safeguard	0.2 to 0.3% for foliar application	A broad spectrum contact fungicide often used in greenhouses for control of <i>Botrytis</i> on ornamentals and for several molds and blights of tomato. Also used for the control of sigatoka leaf spot of banana, onion purple blotch, tikka leaf spot and rust of groundnut
2. Dinocap	Karathane, Arathane, Capryl, Mildex, Mildont and crotothane	0.1 to 0.2% for spraying	It is a good acaricide and contact fungicide and it controls powdery mildews of fruits and ornamentals effectively. This can be safely used on sulphur sensitive crops like cucurbits and apple varieties for control of powdery mildews
3. Dodine	Cyprex, Melprex, Guanidol and Syllit	0.075% for spraying	Apple scab, black spot of roses and cherry leaf spot

#### SYSTEMIC FUNGICIDES

The systemic fungicides were first introduced by Von Schelming and Marshall Kulka in 1966. The discovery of Oxathiin fungicides was soon followed by confirmation of systemic activity of pyrimidines and benzimidazoles. A systemic fungicide is capable of managing a pathogen remote from the point of application. On the basis of chemical nature these fungicides are classified as follows

Common name	Trade name	Dosage	Diseases managed
<b>ACYLALANINES</b>			

1. Metalaxyl	Ridomil 25 % WP, Apron 35 SD, Subdue, Ridomil MZ-72WP	3-6 g/Kg seed for seed treatment, 1 to 1.5 Kg a.i/ha for soil application, 0.1 to 0.2% for foliar spray	It is highly effective against <i>Pythium</i> , <i>Phytophthora</i> and many downy mildew fungi
2. Benalaxyl	Galben 25% WP and 5% G	0.1 to 0.2% for foliar spray, 1 to 1.5 Kg a.i/ha for soil application	Blue mold of tobacco, late blight of potato and tomato, downy mildew of grapevine
<b>AROMATIC HYDROCARBONS</b>			
1. Chloroneb	Demosan	0.2% for seed treatment	Seedling diseases of cotton, peanut, peas and cucurbits caused by species of <i>Pythium</i> , <i>Phytophthora</i> , <i>Rhizoctonia</i> and <i>Sclerotium</i>
<b>BENZIMIDAZOLES</b>			
1. Carbendazim	Bavistin 50WP, MBC, Derosol 60WP, Agrozim, Zoom	0.1% for foliar spray, 0.1% for soil drench, 0.25% for ST, 500-1000ppm for post-harvest dip of fruits	Effectively controls anthracnose, powdery mildews and rusts caused by various fungi. It is also used as a soil drench against wilt diseases and for post harvest treatment of fruits
2. Benomyl	Benlate 50WP	0.1 to 0.2% for ST, 50-60g/100 L for foliar spray, 50-200ppm for soil drenching, 12-45 Kg a.i/ha for soil broadcast, 100-500 ppm for post harvest fruit dip	Effective against powdery mildews of cucurbits, cereals and legumes. It is highly effective against diseases caused by the species of <i>Rhizoctonia</i> , <i>Theilaviopsis</i> and <i>Cephalosporium</i> . Benomyl has no effect against Oomycetes and some dark coloured fungi such as <i>Alternaria</i> and <i>Helminthosporium</i>
3. Thiabendazole	Mertect 60WP, Mycozol, Arbotect, Tecto and Storite	0.2 to 0.3% for spraying, 1000 ppm for fruit dip	Blue and green molds of citrus, loose smut of wheat, Tikka leaf spot of groundnut

<b>ALIPHATICS</b>			
1. Prothiocarb	Previcur, Dynone	5.6 Kg a.i/ha for soil application	Highly active against soil borne Oomycetes like <i>Pythium</i> and <i>Phytophthora</i>
2. Propamocarb	Previcur-N, Dynone-N, Prevex, Benol	3.4 and 4.8 Kg a.i/ha for soil application	Effective against soil borne Oomycetes like <i>Pythium</i> and <i>Phytophthora</i>
<b>OXATHINS or CARBOXIMIDES</b>			

1. Carboxin	Vitavax 75WP, Vitaflow	0.15 to 0.2% for seed treatment, 0.5% for spraying	Highly effective against smut diseases. Commonly used for the control of loose smut of wheat, onion smut, grain smut of sorghum. As a soil drench it is used for the control of diseases caused by <i>Rhizoctonia solani</i> and <i>Macrophomina phaseolina</i> .
2. Oxycarboxin	Plantavax 75 WP, Plantavax 20EC, Plantavax 5% liquid	0.1 to 0.2% for foliar spray, 0.2 to 0.5% for ST	Highly effective against rust diseases. Commonly used for the control of rusts of wheat, sorghum, safflower, legumes, etc.
<b>IMIDAZOLES</b>			
1. Imazalil	Fungaflor, Bromazil and Nuzone	0.1 % as post harvest dip	Blue and green molds of citrus
2. Fanapanil	Sistane 25 EC	0.05% foliar spray	Spot blotch of barley, loose and covered smut of barley
<b>MORPHOLINES</b>			
1. Tridemorph	Calixin 75EC, Bardew, Beacon	0.1% for foliar spray	Powdery mildew of cereals, vegetables and ornamentals. Rusts of pulses, groundnut and coffee, Sigatoka leaf spot of banana, pink disease of rubber, Ganoderma root rot & wilt
<b>ORGANOPHOSPHATES</b>			
1. Iprobenphos	Kitazin 48EC, Kitazin 17G, Kitazin 2% D	30-45 Kg of granules/ha, 1 to 1.5 liters of 48% EC in 1000 ml of water for foliar spray	Fungicide with insecticidal properties. Highly specific against rice blast, stem rot and sheath blight of rice
2. Ediphenphos	Hinosan 30 and 50% EC, Hinosan 2%D	400 to 500 ppm for spraying, 30 to 40 Kg/ha	Highly specific against rice blast, stem rot and sheath blight of rice
<b>ALKYL PHOSPHONATES</b>			
1. Fosetyl-Al or Aluminium Tris	Aliette 80WP	0.15% for foliar spray, 0.2% for soil drench	Ambimobile fungicide. Specific against Oomycetes fungi

<b>PYRIMIDINES</b>			
1. Fenarimol	Rubigan 50% WP, 12%EC	2g/Kg seed as ST, 20 to 40 ml/100 liters of water for spraying	Powdery mildew of cucurbits, apple, mango, roses, grapes and ornamental crops
<b>THIOPHANATES</b>			
1. Thiophanate	Topsin 50WP, Cercobin 50WP	0.1 to 0.2% for spraying	Powdery mildew of cucurbits and apple, club root of crucifers, rice blast

2.Thiophanate methyl	Topsin M 70WP, Cercobin M 70WP	0.1% spraying for	Blast and sheath blight of rice, sigatoka leaf spot of banana, powdery mildew of beans, chilli, peas and cucurbits
<b>TRIAZOLES</b>			
1. Triadimefon	Bayleton, Amiral	0.1 to 0.2% for spraying, 0.1% for seed treatment	Highly effective against powdery mildews and rusts of several crops. Effective against diseases caused by species of <i>Erysiphe</i> , <i>Sphaerotheca</i> , <i>Puccinia</i> , <i>Uromyces</i> , <i>Phakopsora</i> , <i>Hemileia</i> and <i>Gymnosporangium</i>
2. Tricyclazole	Beam 75WP, Baan 75WP, Trooper 75WP	2g/Kg seed for ST, 0.06% for spraying	Highly effective against blast of rice
3. Bitertanol	Baycor and Sibutol	0.05 to 0.1% for foliar spray	Powdery mildews and rusts of various crops, apple scab, <i>Monilinia</i> on fruit crops, late leaf spot of groundnut and sigatoka leaf spot of banana
4. Hexaconazole	Contaf 5%EC, Anvil	0.2% for spraying	Sheath blight of rice, powdery mildew and rust of apple, rust and tikka leaf spot of groundnut
5. Propiconazole	Tilt, 25% EC, Desmel	0.1% for foliar application	Sheath blight of rice, Sigatoka leaf spot of banana, brown rust of wheat
6. Myclobutanil	Systhane 10WP	0.1 to 0.2% for spraying	Apple scab, cedar apple rust and powdery mildew of apple
<b>STROBILURINS</b>			
1. Azoxystrobin	Amistar, Quadris	0.1% spraying for	Broad spectrum fungicide
2.Kresoxim methyl	Ergon, Discus, Stroby	0.1% spraying for	Commonly used for control of ornamental diseases

### **CLASSIFICATION OF FUNGICIDES BASED ON METHOD OF APPLICATION**

The fungicides can also be classified based on the nature of their use in managing the diseases.

1. Seed protectants: Ex. Captan, thiram, carbendazim, carboxin etc.
2. Soil fungicides (preplant): Ex. Bordeaux mixture, copper oxy chloride, Chloropicrin, Formaldehyde, Vapam, etc.
3. Soil fungicides: Ex. Bordeaux mixture, copper oxy chloride, Captan, PCNB, thiram etc.
4. Foliage and blossom: Ex. Capton, ferbam, zineb, mancozeb, chlorothalonil etc.
5. Fruit protectants: Eg. Captan, maneb, carbendazim, mancozeb etc.
6. Eradicants: EX. Lime sulphur
7. Tree wound dressers: Ex. Boreaux paste, chaubattia paste, etc.
8. General purpose sprays and dust formulations.

## Disease Resistance

### HOST PLANT RESISTANCE (IMMUNIZATION)

Disease resistance: It is the ability of a plant to overcome completely or in some degree the effect of a pathogen or damaging factor.

**Susceptibility:** The inability of a plant to resist the effect of a pathogen or other damaging factor.

#### Advantages of resistant varieties:

1. Resistant varieties can be the most simple, practical, effective and economical method of plant disease management.
2. They not only ensure protection against plant diseases but also save the time, energy and money spent on other measures of control
3. Resistant varieties, if evolved can be the only practical method of control of diseases such as wilts, viral diseases, rusts, etc.
4. They are non-toxic to human beings, animals and wild life and do not pollute the environment
5. They are effective only against the target organisms, whereas, chemical methods are not only effective against target organisms but also effective against non-target organisms.
6. The resistance gene, once introduced, is inherited and therefore permanent at no extra cost.

#### Disadvantages:

1. Breeding of resistant varieties is a slow and expensive process
2. Resistance of the cultivar may be broken down with the evolution of the pathogen

#### Types of resistance:

**1. Vertical resistance:** When a variety is more resistant to some races of the pathogen than others, the resistance is called vertical resistance (race-specific resistance, qualitative resistance, discriminatory resistance). Vertical resistance is usually governed by single gene and is unstable.

**2. Horizontal resistance:** When the resistance is uniformly spread against all the races of a pathogen, then it is called horizontal/generalized/non-specific/field/qualitative resistance. Horizontal resistance is usually governed by several genes and is more stable.

**3. Monogenic resistance:** When the defense mechanism is controlled by a single gene pair, it is called monogenic resistance.

**4. Oligogenic resistance:** when the defense mechanism is governed by a few gene pairs, it is called oligogenic resistance.

**5. Polygenic resistance:** When the defense mechanism is controlled by many genes or more groups of supplementary genes, it is called polygenic resistance.

**Cross protection:** The phenomenon in which plant tissues infected with mild strain of a virus are protected from infection by other severe strains of the same virus. This strategy is used in the management of severe strains of Citrus Tristeza virus.

## Antibiotics.

The term antibiotic was coined from the word „antibiosis“ which literally means „against life“. In the past, antibiotics were considered to be organic compounds produced by one microorganism which are toxic to other microorganisms (Russell, 2004). As a result of this notion, an antibiotic was originally, broadly defined as a substance, produced by one microorganism (Denyer et al., 2004), or of biological origin (Schlegel, 2003) which at low concentrations can inhibit the growth of, or are lethal to other microorganisms (Russell, 2004). However, this definition has been modified in modern times, to include antimicrobials that are also produced partly or wholly

through synthetic means. Whilst some antibiotics are able to completely kill other bacteria, some are only able to inhibit their growth. Those that kill bacteria are termed bactericidal while those that inhibit bacterial growth are termed bacteriostatic (Walsh, 2003). Although antibiotic generally refers to antibacterial, antibiotic compounds are differentiated as antibacterials, antifungals and antivirals to reflect the group of microorganisms they antagonize (Brooks et al., 2004; Russell, 2004).

Penicillin was the first antibiotic discovered in September 1928 by an English Bacteriologist, late Sir Alexander Fleming who accidentally obtained the antibiotic from a soil inhabiting fungus *Penicillium notatum* but its discovery was first reported in 1929 (Aminov, 2010), and clinical trials first conducted on humans in 1940 (Russell, 2004; Schlegel, 2003).

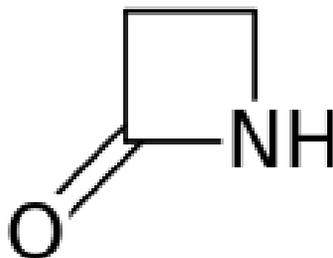
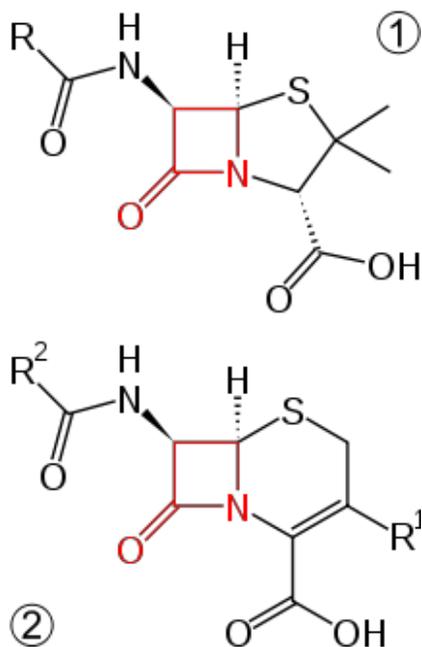


Figure 1. Chemical structure of a beta-lactam ring (Tidwell, 2008).



**Figure 2.** Chemical structure of beta- lactam structure. Core structure of [penicillins](#) (top) and cephalosporins (bottom) (Holten and Onusko, 2000).

The discovery and development of the first significant antibiotic “penicillin” in 1920’s, and subsequent introduction into man’s health care system in the 1940’s has continued to transform the management and fight against bacterial infections (White and Cox, 2013). However, antibiotics are not totally selective in their antibacterial activity. Whilst antagonizing disease causing bacteria, they also antagonize the normal and useful microbiota that we all have and need in our systems as those in the gastrointestinal tract (Walsh, 2003). Prescription and administration of any given antibiotics is

therefore predicated on the overall intended benefit, taking into consideration the attendant side effects. For this reason, it is pertinent to understand the mechanism of action of every identified antibiotic before introduction into our health care delivery system, and recent molecular biological approaches have played very significant roles to elucidate our understanding in this regard.

Hence this paper aimed to review the classification of antibiotics and their mode of action with emphasis on molecular perspectives.

## CLASSIFICATION OF ANTIBIOTICS

There are several ways of classifying antibiotics but the most common classification schemes are based on their molecular structures, mode of action and spectrum of activity (Calderon and Sabundayo, 2007). Others include route of administration (injectable, oral and topical). Antibiotics within the same structural class will generally show similar pattern of effectiveness, toxicity and allergic- potential side effects.

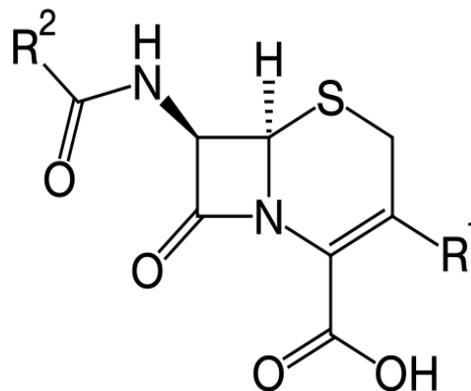
Some common classes of antibiotics based on chemical or molecular structures include Beta-lactams, Macrolides, Tetracyclines, Quinolones, Aminoglycosides, Sulphonamides, Glycopeptides and Oxazolidinones (van Hoek et al., 2011; Frank and Tacconelli, 2012; Adzitey, 2015).

## Beta-lactams

Members of this class of antibiotics contain a 3-carbon and 1-nitrogen ring that is highly reactive (Figures 1 and 2). They interfere with proteins essential for synthesis of bacterial cell wall, and in the process either kills or inhibits their growth. More succinctly, certain bacterial enzymes termed penicillin-binding protein (PBP) are responsible for cross linking peptide units during synthesis of peptidoglycan. Members of beta-lactam antibiotics are able to bind themselves to these PBP enzymes, and in the process, they interfere with the synthesis of peptidoglycan resulting to lysis and cell death (Heesemann, 1993). The most prominent representatives of the beta-lactam class include Penicillins, Cephalosporins, Monobactams and Carbapenems.

## Penicillins

The first antibiotic, penicillin, which was first discovered and reported in 1929 by Alexander Fleming was later found to be among several other antibiotic compounds called the penicillins. (McGeer et al., 2001). Penicillins



**Figure 3.** Structure of Cephalosporins (Pegler and Healy, 2007).

are involved in a class of diverse group of compounds, most of which end in the suffix -cillin. They are beta-lactam compounds containing a nucleus of 6- aminopenicillanic acid (lactam plus thiazolidine) ring and other ring side chains (Zahner and Maas, 1972).

Members of Penicillin class include Penicillin G, Penicillin V, Oxacillin (dicloxacillin), Methicillin, Nafcillin, Ampicillin, Amoxicillin, Carbenicillin, Piperacillin, Mezlocillin and Ticarcillin (Boundless, 2016). Penicillin G was the first to be produced amongst this group of antibiotics, and in fact of all antibiotics. Although penicillin G was discovered by Alexander Fleming in the 1920's, it took the efforts of several other workers such as Ernst Chain, Edward Abraham, Norman Heatley and Howard Florey in 1945 to understand the cultural requirements of the fungus and its clinical effectiveness. Furthermore, although Penicillin G was originally discovered and isolated from the fungus *P. notatum* by Alexander Flemming, a close relative *Penicillium chrysogenum* is the preferred choice of source. Also, producing the antibiotics through biochemical microbial fermentation more cost effective as compared to synthesizing it from raw materials (Talaro and Chess, 2008). There is no gainsaying that the discovery of this drug heralded the introduction of antibiotics into our health care delivery system. Sadly, however, Penicillin G has a narrow spectrum; only Gram positive bacteria (streptococci) and some Gram-negative bacteria such as *Treponema pallidum* causative agent for syphilis, and meningococci are sensitive to it (Talaro and Chess, 2008).

As with every biological interaction systems where living systems seek to protect itself from attack, certain bacteria are able to counter the activity of antibiotics by encoding enzymes. In view of this, some antibiotics such as ampicillin, carbenicillin and amoxicillin have been developed semi-synthetically with different side-chains. These side chains confer on the antibiotics the ability to evade the degradative capacity of certain enzymes produced by certain bacterial strains as well as facilitating the movement of antibiotics across the outer membrane of such bacterial cell walls. This double-pronged capability increases their spectrum of activity against Gram-negative bacteria. In particular, some penicillins such as Augmentin are produced in combination with non-antibiotic compound that are able to inhibit the activity of bacterial penicillinase enzyme. Augmentin is actually a drug comprising amoxicillin (antibiotic) and clavulanic acid a non-antibiotic compound. Clavulanic acid is able to inhibit beta-lactamase enzyme thereby prolonging the antibacterial activity of the amoxicillin component of Augmentin even amongst penicillinase producing bacteria (Poirel et al., 2005).

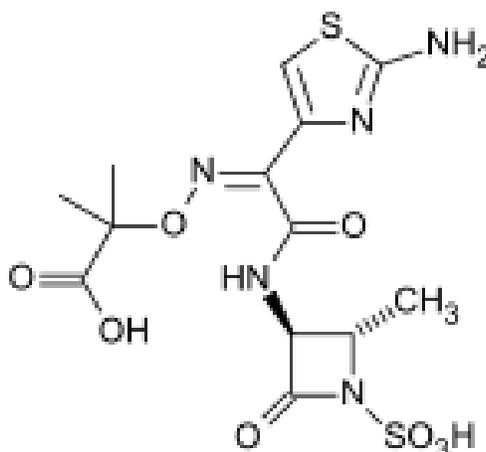
### Cephalosporin

Members of this group of antibiotics are similar to penicillin in their structure and mode of action. They form part of the most commonly prescribed and administered antibiotics; more succinctly, they account for one-third of all antibiotics prescribed and administered by the National Health Scheme in the United Kingdom (Talaro and Chess, 2008). The first known member of this group of antibiotics was first isolated by Guiseppe Brotzu in 1945 from the fungus *Cephalosporium acremonium*. Although the drug was first isolated by Guiseppe Brotzu, it was Edward Abraham who got the credit to patent it having been able to extract the compound. Cephalosporins contain 7-aminocephalosporanic acid nucleus and side chain containing 3,6-dihydro-2 H-1,3- thiazane rings (Figure 3). Cephalosporins are used in the treatment of bacterial infections and diseases arising from Penicillinase-producing, Methicillin-susceptible Staphylococci and Streptococci, *Proteus mirabilis*, some *Escherichia coli*, *Klebsiella pneumonia*, *Haemophilus influenza*, *Enterobacter aerogenes* and some *Neisseria* (Pegler and Healy, 2007).

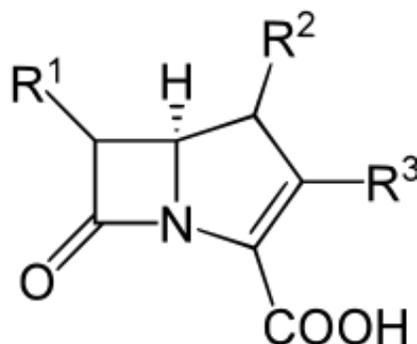
They are subdivided into generations (1st-5th) in accordance to their target organism but later versions are increasingly more effective against Gram-negative pathogens. Cephalosporins have a variety of side chains that enable them get attach to different penicillin-binding proteins (PBPs), to circumvent blood brain barrier, resist breakdown by penicillinase producing bacterial strains and ionize to facilitate entry into Gram-negative bacterial cells (Abraham, 1987).

### Monobactams

The discovery of this class of antibiotics was first reported by Skyes and co-workers. The antibiotic was obtained from the bacterium *Chromobacterium violaceum*. They are part of beta-lactam compounds but unlike most other



**Figure 4.** Structure of Monobactam (Bonner and Sykes, 1984).



**Figure 5.** Structure of Carbapenem (Papp-Wallace et al., 2011).

beta-lactams, the beta-lactam ring of monobactams stand alone and is not fused to another ring (Figure 4) (Bonner and Sykes, 1984; Sykes and Bonner, 1985). Aztreonam is the only commercially available monobactam antibiotic, with a narrow spectrum of activity. Aztreonam is active only against aerobic Gram-negative bacteria such as *Neisseria* and *Pseudomonas*; used for treating pneumonia, septicemia and urinary tract infections caused by these groups of bacteria. The monobactams are not effective against Gram-positive bacteria or anaerobes. They are used as injectables and inhalers (Sykes et al., 1981).

### ***Carbapenems***

This class of antibiotics, represented in Figure 5, was discovered out of necessity in 1976. Prior to this time in the late 1960's the effectiveness of penicillin was greatly threatened owing to the emergence of beta-lactamase in bacteria. Bacterial beta-lactamases conferred resistance on bacteria against penicillin (Papp-Wallace et al., 2011). This seemingly ugly scenario led scientists to embark on a massive search for beta-lactamase inhibitors. Their efforts yielded result in 1976 when olivanic acids, produced by a Gram-positive bacterium *Streptomyces clavuligerus*, was noted to inhibit beta-lactamase (Brown et al., 1976; Butterworth et al., 1979). Unfortunately, these acids were chemically unstable and could not easily penetrate the bacterial cell. These setbacks slowed down further works on the olivanic acids (Reading and Farmer, 1984), but interestingly, shortly afterwards, two superior beta-lactamase inhibitors were discovered. These were clavulanic acid obtained also from *S. clavuligerus* (Brown et al., 1976), and thienamycin isolated from *Streptomyces cattleya* (Kropp et al., 1976). Thienamycin is reportedly considered to be the first "carbapenem" and serves as a standard for every other carbapenem (Papp-Wallace et al., 2011). A good number of other carbapenems have also been identified (Cassidy et al, 1981; Kobayashi et al., 1982).

Carbapenems occupy a very important place in our fight against bacterial infections. This is because they are able to resist the hydrolytic action of beta-lactamase enzyme. Among the several hundreds of known beta-lactams, carbapenems possess the broadest spectrum of activity and greatest potency against Gram-positive and Gram-negative bacteria. As a result, they are often called "antibiotics of last resort" and are administered when patients with infections become gravely ill or are suspected of harboring resistant bacteria (Torres et al., 2007). Examples of carbapenem are:

- i.** Imipenem – a broad spectrum effective against aerobic and anaerobic pathogens, usually taken orally and active in low concentrations, with minimal allergy side effects;
- ii.** Meropenem – a broad spectrum effective against non-fermentative Gram-negative bacilli particularly against acquired infections;

iii. Ertapenem – a broad spectrum with limited activity against non-fermentative Gram-negative bacilli (Brink et al., 2004).

Sadly, emergence of bacterial pathogens resistant to this life saving class of antibiotics has been reported. More worrisome is the fact that bacterial resistance to carbapenems is on the increase globally (Livermore et al., 2011; Patel and Bonomo, 2011) and is fast becoming an international concern (Papp-Wallace et al., 2011).

### Macrolides

The first antibiotic belonging to this class was first discovered and isolated in 1952 by J. M. McGuire as a

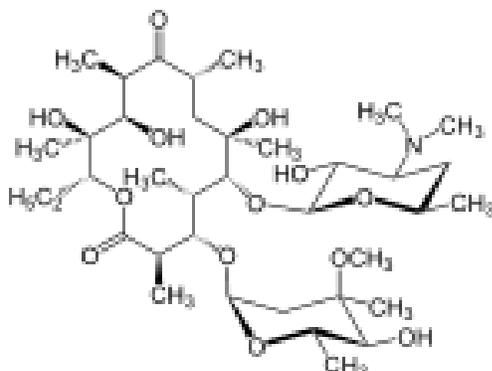


Figure 6. Structure of Macrolide (Hamilton-Miller, 1973).

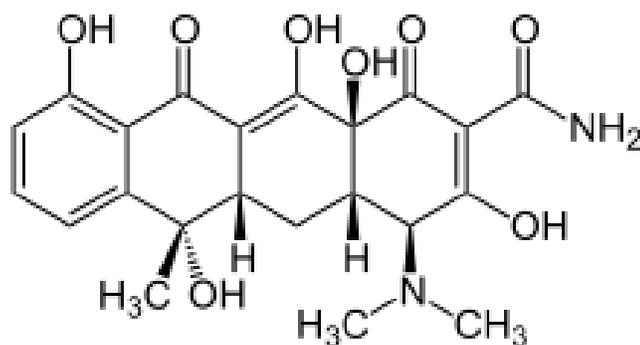


Figure 7. Structure of Tetracycline (Chopra and Roberts, 2001).

metabolic product of a soil inhabiting fungus *Saccharopolyspora erythraea*. This fungus was formerly known as *Streptomyces erythraeus* belonging to the genus *Saccharopolyspora* of actinomycete bacteria (Moore, 2015).

Macrolides are characterized by 14-, 15-, or 16- membered macrocyclic lactone rings with unusual deoxy sugars L-cladinose and D-desosamine attached (Figure 6). They have a wider spectrum of antibiotic activity than Penicillins and are often administered to patients allergic to penicillin (Moore, 2015).

Macrolides either kill or inhibit microorganisms by effectively inhibiting bacterial protein synthesis. They do so by binding to bacterial ribosome, and in the process, prevent the addition of amino acid to polypeptide chains

during protein synthesis. Macrolides tend to build up in the body because the liver is able to recycle it into the bile. They also have the capacity to cause inflammation.

As a result, clinicians usually recommend administering low doses. Although, Macrolides are generally broad spectrum, some bacterial species such as *Streptococcus pneumoniae* have resistance against the antibiotics. Example of members includes Erythromycin, Azithromycin and Clarithromycin (Hamilton-Miller, 1973).

## **Tetracyclines**

Tetracycline was discovered in 1945 from a soil bacterium of the genus *Streptomyces* by Benjamin Duggar (Sanchez et al., 2004). The first member of this class was chlorotetracycline (Aureomycin). Members of this class have four (4) hydrocarbon rings (Figure 7) and they are known by name with the suffix „-cycline“.

Historically, members of this class of antibiotics are grouped into different generations based on the method of synthesis. Those obtained by biosynthesis are said to be First generation. Members include Tetracycline, Chlortetecycline, Oxytetracycline and Demeclocycline. Members such as Doxycycline, Lymecycline, Meclon

cycline, Methacycline, Minocycline, and Rolitetracycline are considered Second generation because they are derivatives of semi-synthesis. Those obtained from total synthesis such as Tigecycline are considered to be Third generation (Fuoco, 2012).

Their target of antimicrobial activity in bacteria is the ribosome. They disrupt the addition of amino acids to polypeptide chains during protein synthesis in this

bacterial organelle (Medical News Today, 2015). Patients are advised to take tetracyclines at least two hours before or after meals for better absorption. All tetracyclines are

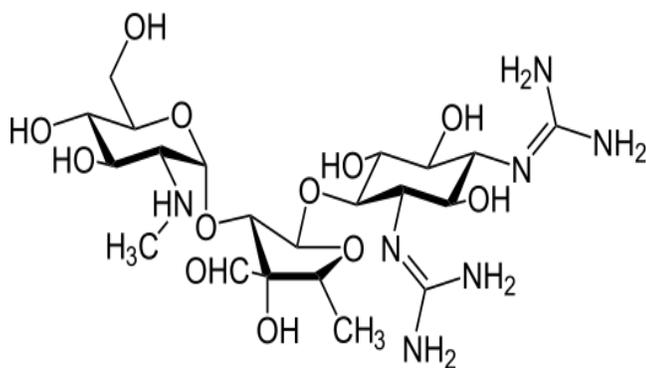
recommended for patients above eight (8) years because

the drugs have shown to cause teeth discoloration among patients below this age can be used in treating malaria, elephantiasis, amoebic parasites and rickettsia (Sanchez et al., 2004).

In the past, antibiotics belonging to this class were very much the envy of numerous Clinicians owing to their wide antimicrobial spectrum but this is no longer the case because numerous bacteria are now able to resist them (Chopra and Roberts, 2001).

## **Quinolones**

This class of antibiotics was first discovered as nalidixic acid by Scientists involved in search of antimalarial drugs. Nalidixic acid was discovered as an impurity during the development of quinine in the early sixties. They are able to interfere with DNA replication and transcription in bacteria. Two major groups of compounds have been developed from the basic molecule: quinolones and naphthyridones which include cinoxacin, norfloxacin, ofloxacin, ciproxacin, temafloxacin,



**Figure 8.** Structure of Aminoglycoside (Streptomycin) (Mingeot-Leclercq et al., 1999).

sparfloxacin, nalidixic acid, enoxacin etc. (Domagala, 1994). Their structure generally consists of two rings but recent generations of quinolones possess an added ring structure which enables them to extend their spectrum of antimicrobial activity to some bacteria, particularly anaerobic bacteria that were hitherto resistant to quinolone.

Since its discovery in the early 1960's, several modifications have been made to its parent structure and this has led to the development and synthesis of many derivatives with tested antibiotic potency. The nomenclature of members of this class of antibiotics is complex (Domagala, 1994) but members are often known by the suffix-oxacin, such as floxacin, ciprofloxacin and levofloxacin.

Modifications in the basic structure of quinolones are reported to have improved their bioavailability and increased both their spectrum of activity and potency; enhancing their performance in the treatment of various forms of illnesses such as urinary, systemic and respiratory tract infections. Notwithstanding these notable feats, there still exist safety concerns with some members of this class of antibiotics which has led to the withdrawal of grepafloxacin, sparfloxacin, temafloxacin, trovafloxacin etc., all belonging to the class quinolones, from the market (Domagala, 1994). Although a good deal of progress is being made in terms of *in vitro* studies and pharmacodynamics, knowledge of the dynamics of toxicity amongst some of this class of antibiotics is yet inconclusive.

### **Aminoglycosides**

The first drug to be discovered among members of this class of antibiotics was streptomycin, first isolated in 1943 (Mahajan and Balachandran, 2012). Streptomycin has been greatly used against *Mycobacterium tuberculosis*, the causal agent of tuberculosis among humans. The aminoglycosides are compounds of usually 3-amino sugars connected by glycosidic bonds (Figure 8). They are obtained from soil Actinomycetes.

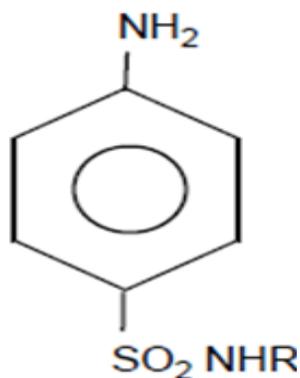
Aminoglycoside have a broad spectrum of antibacterial activity. They are able to inhibit the protein synthesis in bacteria by binding to one of the ribosomal subunits (Peterson, 2008), and are effective against aerobic Gram-negative rods and certain Gram-positive bacteria. The oldest known aminoglycoside, as earlier inferred is Streptomycin which has been used severally in treating bubonic plague, tularemia and tuberculosis (Talaro and Chess, 2008). Notwithstanding its effectiveness against a wide array of infections, streptomycin was found to be highly toxic. This unfortunate feature of the drug necessitated the need to search for new members of aminoglycosides that would still be effective against bacteria but less toxic to humans. The search was fruitful with the discoveries of antibiotics such as Gentamicin, Neomycin, Tobramycin and Amikacin. Gentamicin is less toxic and is widely used for infections caused by Gram- negative rods (Escherichia, Pseudomonas, Shigella and Salmonella). Tobramycin, in particular, is used in treating Pseudomonas infections in cystic fibrosis patients (Gilbert, 2000).

### **Sulphonamides**

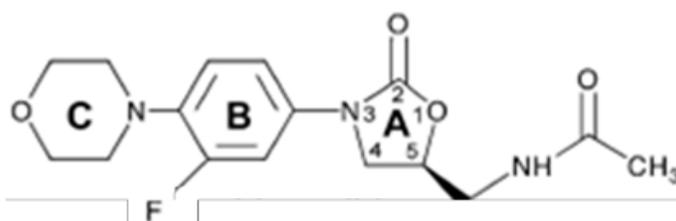
Sulphonamides are reportedly, the first group of antibiotics used in therapeutic medicine, and they still play very important role in medicine and veterinary practice (Eyssen et al., 1971). Sulphonamides inhibit both Gram-positive and Gram-negative bacteria such as Nocardia, E. coli, Klebsiella, Salmonella, Shigella and Enterobacter, Chlamydia trachomatis and some Protozoa, and are widely used in the treatment of various infections including tonsillitis, septicemia, meningococcal meningitis, bacillary dysentery and some urinary tract infections (Eyssen et al., 1971). Studies have shown that Sulphonamides are also able to impede cancerous cell agents (Stawinski et al., 2013; Xu et al., 2014). The original antibacterial sulphonamide (also spelt sulfonamide by some Workers), are synthetic antimicrobial agents that contain the sulphonamide group (Figure 9) (Henry, 1943).

Sulphonamides are generally thought to be bacteriostatic rather than bactericidal. However, Henry (1943) in his thorough early work opined that sulphonamides may become bactericidal if their concentration is sufficiently high or if the presence of any sulfonamide concentration is accompanied by other environmental conditions unfavourable to bacteria. Such unfavourable conditions would include poor cultural conditions, adverse temperature, antibodies, toxic proteolytic product etc.

Although sulphonamides are adjudged good and effective in treating various diseases and infections, they



**Figure 9.** General structure of Sulphamides (Henry, 1943).



**Figure 10.** Structure of Linezolid (Leach et al., 2007).

are recommended and administered with caution because of their toxicity and side effects, some of which include urinary tract disorders, haemolytic anaemia, porphyria, and hypersensitivity reactions (Slatore and Tilles, 2004; Choquet-Kastylevsky et al., 2002).

## Glycopeptides

Glycopeptide antibiotics generally abbreviated as GPAs were originally obtained as natural products, but the last 20 years witnessed the emergence of semi-synthetic derivatives with improved activity and pharmacokinetic properties (Kahne et al., 2005; Van Bambeke et al., 2004; Van Bambeke, 2004). Naturally, glycopeptides are made of a cyclic peptide of 7 amino acids, to which are bound 2 sugars, hence the name glycopeptides (Kang and Park, 2015). Structures of various forms of glycopeptides are well presented by Yim and Associates (2014). Binding of the antibiotic to its target occurs via the formation of 5 hydrogen bonds with the peptidic backbone of the drug. Sometimes, an additional chlorine and/or sugar is/are attached to the backbone of the drug (as is the case in oritavancin) during synthesis. Drugs with such additional attachments are known to bind more efficiently to the target (Allen and Nikas, 2003; Beauregard et al., 1995). Similarly, a lipophilic side chain antibacterial potency and prolongs half-life of glycopeptides.

## **Oxazolidinones**

Oxazolidinones are a group of synthetic antibiotics approved only recently for use. Linezolid (Figure 10) which represents the first member to be synthesized was approved for clinical application only in the year 2000. Although the mechanism of action of oxazolidinone is not yet fully understood, they are reported to interfere with protein synthesis. Oxazolidinones inhibit protein synthesis by binding to the P site of the ribosomal 50S subunit (Shinabarger et al., 1997; Bozdogan and Appelbaum, 2004). They have a broad spectrum of activity against Gram-positive bacteria including methicillin- and vancomycin-resistant staphylococci, vancomycin-resistant enterococci, penicillin-resistant pneumococci and anaerobes (Bozdogan and Appelbaum, 2004).

Linezolid is used for treatment of respiratory tract and skin infections caused by Gram-positive bacterial pathogens (Moellering, 2003). Oxazolidinones constitute the choice drug in dealing with surgical infections because they easily penetrate and accumulate in the tissue including bone, lung, vegetations (plant-like growth in tissues), haematoma and cerebrospinal fluid (Bozdogan and Appelbaum, 2004). Although adhering to normal standard routines of linezolid administration are usually safe, side effects such as myelosuppression, resulting to anemia and thrombocytopenia are often encountered in cases when treatment is prolonged (Kuter and Tillotson, 2001).

## **ANTIBIOTICS MODE OF ACTION**

The antimicrobial potency of most classes of antibiotic are directed at some unique feature of the bacterial structure or their metabolic processes. The most common targets of antibiotics are illustrated in Figure 11. The mechanism of antibiotic actions are as follows:

- Inhibition of cell wall synthesis
- Breakdown of cell membrane structure or function
- Inhibition of the structure and function of nucleic acids
- Inhibition of protein synthesis
- Blockage of key metabolic pathways

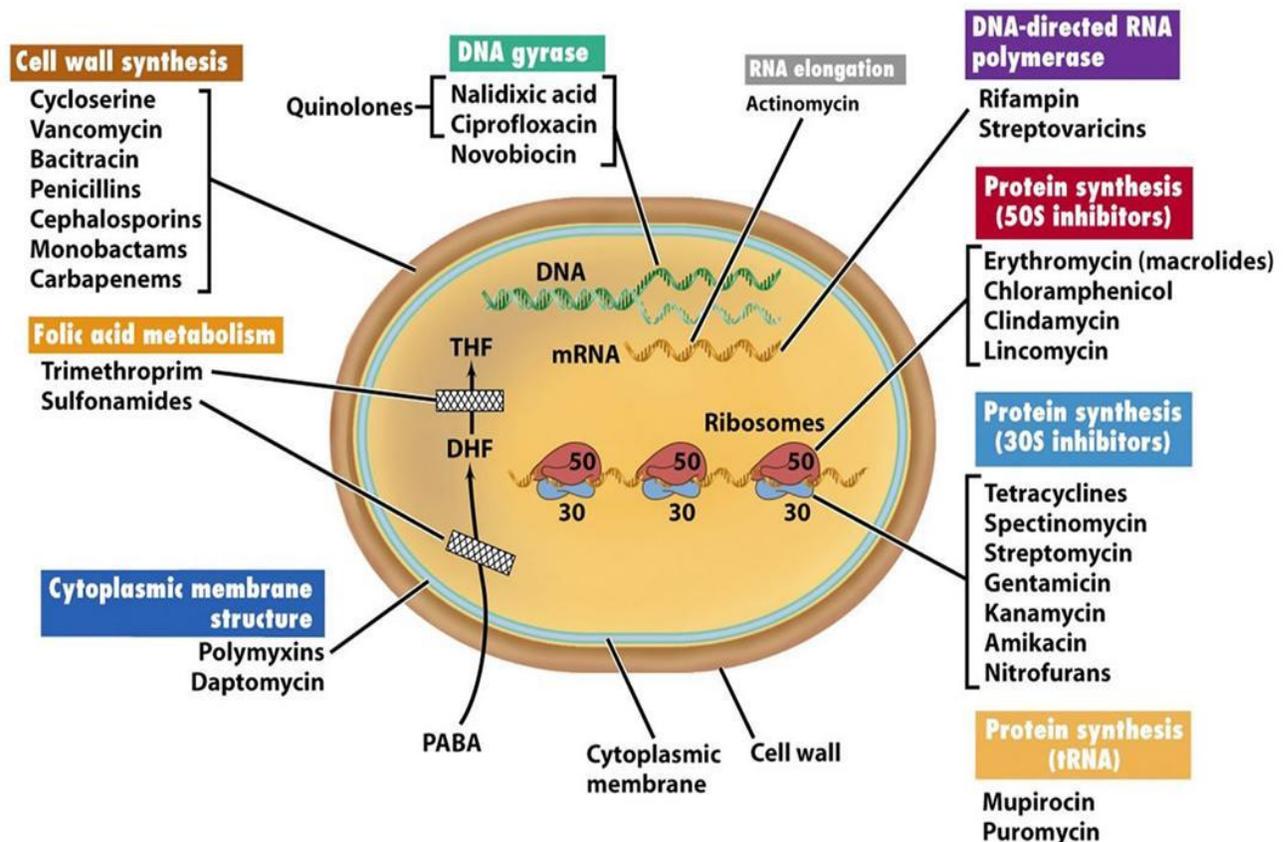
(Talaro and Chess, 2008; Madigan and Martinko, 2006; Wright, 2010)

### **Inhibition of cell wall synthesis**

Most bacterial cells are encased by a rigid layer of peptidoglycan (PG), also called murein in older sources) which both protect the cells in the face of prevailing osmotic pressure consistent

with the often-harsh environment and conditions under which they exist. Peptidoglycan has a degree of cross-linking peptide bonds called  $\beta$ -(1-4) -N- acetyl Hexosamine (Bugg and Walsh, 1992; Holtje, 1998). To stay alive, bacteria must of necessity synthesize peptidoglycan; they do this by the activity of PBPs which are transglycosylases and transpeptidases. These two enzymes play very pivotal roles by adding disaccharide pentapeptides to extend the glycan strands of existing peptidoglycan molecule and also cross-link strands of immature peptidoglycan units (Park and Uehara, 2008). Drugs like penicillins, carbapenems and cephalosporins are able to block the cross-linking of peptidoglycan units by inhibiting the peptide bond formation catalyzed by PBPs (Josephine et al., 2004).

Most antibiotics belonging to the glycopeptide class of antibiotics (for example, vancomycin) are able to inhibit bacterial growth by inhibiting the synthesis of PG. They inhibit the synthesis of PG by binding themselves to PG units, as well as blocking transglycosylase and transpeptidase activity (Kahne et al., 2005).



**Figure 11.** Antibiotic target sites (Madigan and Martinko, 2006).

## **Breakdown of the cell membrane structure or function**

The classes of antibiotics that damage cell membranes of bacteria are specific in each microbial group based on the differences in the types of lipids in their cell membranes. For example, Daptomycin depolarizes calcium-dependent membrane, and that leads to the cessation of macromolecular synthesis and disruption of the cellular membrane in bacteria (Alborn et al., 1991). The polymyxins cause disintegration of bacterial cell membrane by effectively binding to the lipid moiety of the lipopolysaccharide in the bacterial cell (Falagas et al., 2010).

## **Inhibition of nucleic acid synthesis**

The metabolic pathways that result in synthesis of nucleic acids are very essential; disruption of nucleic acid synthesis is inimical to both the survival and posterity of bacterial cells. Antibiotics interfere with nucleic acid synthesis by blocking replication or stopping transcription. DNA replication involves the unwinding of the traditional

double helix structure, a process facilitated by the helicase enzymes (Gale et al., 1981). The quinolones group of antibiotics, for example, do interfere with the functionality of the helicase enzyme thereby disrupts the enzyme from playing its function of unwinding DNA. This antibiotic action of the quinolones ultimately truncates the process of DNA replication and repair amongst susceptible bacteria (Chen et al., 1996). Antibiotics whose mode of action is inhibition of nucleic acid synthesis also target topoisomerase II and topoisomerase IV of bacteria. Disrupting the activities of these enzymes in bacteria adversely affects RNA polymerase which in turn prevents RNA synthesis. Quinolones that inhibit bacterial nucleic acid synthesis in this way do not interact with mammalian RNA polymerase, making them specifically antagonistic to Gram-positive bacteria and some Gram-negative bacteria.

## **Inhibition of protein synthesis**

Living things including bacteria are defined by the amount and type of proteins they are composed of, and continually produce. Proteins are responsible for the structural composition, metabolic and physiological processes, and response to adverse conditions, amongst other roles. However, the type and amount of proteins produced by a bacterium at any given time is dependent on information contained in yet another very important biomolecule – Deoxyribonucleic acid (DNA). DNA determines the type of protein a bacterial cell produces through certain information it harbors within itself. The information is a set of genetic codes called codons, handed down to an identical biomolecule – Ribonucleic acid (RNA), specifically messenger RNA (mRNA). Transfer RNA (tRNA), a similar biomolecule is also formed under the directive of DNA. This biomolecule together with mRNA travels to the ribosomes – the factory for protein synthesis in a living cell. The tRNA then deciphers the codons contained in the mRNA and facilitates the translation of the sequence of codons to a sequence of amino acids which are the building blocks of proteins (Etebu, 2013).

The translation of mRNA into proteins occurs over three sequential phases (initiation, elongation and termination) involving the ribosome and a host of cytoplasmic accessory factors (Gualerzi et al., 2000). Ribosomes are made up of RNA and proteins, and are generally called RIBONUCLEOPROTEINS. The RNA component is what is referred to as Ribosomal RNA (rRNA), and comprises two subunits, one small subunit (SSU) and the other large subunit (LSU). These two subunits are usually described in terms of their sedimentation coefficients (that is, their rate of sedimentation is an ultracentrifuge), and are measured in

Svedberg units (symbols) termed the 30S and 50S, respectively (Nissen et al., 2000). Bacterial possess 5S, 16S and 23S genes on their rRNA (Moore, 2001). The 16S rRNA gene resides as a single RNA gene in their SSU (16S) whilst the other two rRNA genes (23S and 5S) occur on the LSU of the bacterial ribosome (Lafontaine and Tollervey, 2001). There is huge difference between prokaryotic and eukaryotic rRNA, and this feat has greatly enabled Scientists to develop antibiotics that would target rRNA of a wide spectrum of pathogenic bacteria (Hong et al., 2014).

Given the importance of proteins in the metabolic and life processes of all living organisms, whatever disrupts the process of its synthesis in a bacterial cell would ultimately incapacitate the cell; inhibit its growth or even kill it completely. Drugs that inhibit protein synthesis are among the broadest classes of antibiotics and can be divided into two subclasses: the 50S inhibitors and 30S inhibitors.

Antibiotics such as erythromycin, clindamycin, lincomycin, chloramphenicol, linezolid etc. have been shown to be among the 50S ribosome inhibitors (Douthwaite, 1992; Katz and Ashley, 2005). In general terms, antibiotics that inhibit 50S ribosome do so by physically blocking either the initiation phase of protein translation or the elongation phase of protein synthesis where the incoming amino acid is linked up with the growing nascent peptide chain (Patel et al., 2001; Vannuffel and Cocito, 1996; Menninger and Otto, 1982). Examples of antibiotic that block initiation of protein translation are members of Oxazolidinones (Patel et al., 2001) whilst macrolides such as lincosamide and streptogramin block protein synthesis by inhibiting the elongation phase of mRNA translation (Vannuffel and Cocito, 1996; Menninger and Otto, 1982). These latter groups of antibiotics are therefore reportedly ineffective when elongation has progressed beyond a critical length (Tenson et al., 2003).

The 30S ribosome-inhibitors principally work by blocking the access of aminoacyl-tRNAs to the ribosome. Examples of antibiotics that function in this manner include the tetracycline, streptomycin, spectinomycin, etc. (Hong et al., 2014; Chopra and Roberts, 2001). It is worthy to note that some earlier works have shown that tetracycline also inhibits some proteins at the 50S ribosomes (Epe and Woolley, 1984).

Among ribosome inhibitors, the naturally-derived aminoglycoside subclass is the only one that is broadly bactericidal. Macrolides, streptogramins, spectinomycin, tetracyclines and chloramphenicol are typically bacteriostatic. However, some of these ribosome inhibitory antibiotics that are typically bacteriostatic in action could be bactericidal under certain conditions relating to species- or treatment-specific fashion. For example, chloramphenicol known typically to be

### **Blockage of key metabolic pathways**

Some antibiotics like sulphonamides and trimethoprim have been shown to mimic a substrate needed for cellular metabolism of bacteria. This deception cause bacterial enzymes to attach themselves to the antibiotic related glycopeptide antibiotics. Sulphonamides act like tetrahydrofolate which is required for the synthesis of folic acid in bacterial cells (Talaro and Chess, 2008). Folic acid is vital in the metabolism of nucleic acid and amino acids; for this reason, sulphonamides ultimately disrupt the production of nucleic acids (DNA and RNA) and amino acids, as they mimic substrates required for folic acid metabolism (Talaro and chess, 2008).