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# General Veterinary Pharmacology and Drugs Used for Treatment of Bacteria, Virus, Fungus and Parasites in Animals.

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**Abstract:-**Veterinary pharmacology is study of chemical substances (drugs) and it is deals with interaction between drugs and living tissue. Pharmacology has sub division such as: Pharmacognosy, Pharmacodynamics, Pharmacokinetics, Pharmacotherapy, Therapeutics, Chemotherapy, Posology and so on. Key Terminology of pharmacology includes the Drugs, biological, Poison, dose, dosage, dosage regimen dosage intervals and so on. Antibacterial drugs can be either Cidal or static and can be either narrow spectrum or broad spectrum. Antimicrobial resistance is the ability of a microbe to resist the effects of medication. Viruses are obligate intracellular parasite, Viruses contain a single type of nucleic acid (DNA or RNA) and a protein coat, sometimes enclosed by an envelope composed of lipids, proteins, and carbohydrates. Antifungal (antimycotics): are medications used to treat fungal infections like: Dermatophytosis (ring worm), Aspergillosis and Candidiasis, Epizootic lymphangitis, Sporotrichosis and Serious systemic infections, such as cryptococcal meningitis. Antiparasitics are a class of medications which are indicated for the treatment of parasitic diseases caused by: Nematodes, Cestodes, Trematodes, Protozoan infections and Arthropod infestations. Antiparasitic agents can be grouped depending on the parasite where they act as: anthelmintics, antiprotozoa and acaricides and insecticides.
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**Key words: -** Bacteria, drugs, fungus and parasites, pharmacology and virus.

## 1. Introduction

Veterinary Pharmacology is study of chemical substances (drugs), deals with interaction between drugs and living tissue, deals with drugs action upon animal & animal action upon drugs and changes produced in living organisms by drugs. In general pharmacology deals with the knowledge of: - The source of drugs (pharmacognosy), Action and fate of body (pharmacodynamics), Use in the treatment (Rx), diagnosis (Dx) and prevention of disease and Poisonous effect (toxicology) [2].

Sub division of pharmacology includes the 1) Pharmacognosy is concerned with the study of the source, identification and property of drugs in Natural origin, 2) Pharmacodynamics is the study of physiological and biological effect of drugs, it defines drug mechanisms of action and it deals with what the drug does to the body, 3) Pharmacokinetics is the study of absorption, distribution, accumulation, biotransformation(metabolism) and excretion of the drugs and it deals with what the body does to the drugs, 4) Pharmacotherapy is use of drugs in treatment of diseases, 5) Therapeutics is treatment of disease in general and includes use of drugs, surgery, radiation, behavioral medication and other modalities, 6) Pharmacy is concerned with collection, identification, purification, isolation, synthesis, standardization and quality control of drugs and it is a place where drugs are prepared and dispensed, 7) Chemotherapy is deals with a specific drug that selectively inhibit/destroy specific agent of disease such as bacteria, virus, parasite, fungi, 8)Posology is the study of medicine dosage which varies with species of animals, 9) Metrology is the study of weight and measures, 10) Toxicology is the study of poisons and their adverse effects, 11)Clinical pharmacology studies about controlled evolution of efficacy and safety drugs in patients, 12) Pharmacoegenetics is the study of genetic influence on response to drugs and 13) Pharmacoepidemiology

is the study of drug effect on population and Concerned with variability of drug effects b/n individuals in population and b/n populations [1].

Key Terminology of pharmacology includes the:- 1) Drugs are all particles intended to be used the diagnosis, mitigation, treatment and prevention of disease in human and animals, 2) Pharmaceuticals is drug preparations, 3) Biologicals are drugs derived from infectious agent/living tissue Eg, vaccine, toxoids, antitoxin, 4) Poison is harmful or toxic substances, 5) Toxins are poisons derived from infectious agent released by endogenous bacteria, 6) Dose is the quantity of drug to be administer at one time to bring a therapeutic response in patient and expressed in mg/kg or IU/kg, 7) Dosage is determination and regulation of doses, 8)Dosage regimen refers to the dose size, frequency, duration and route of drug administration, 9) Dosage interval is the time b/n successive doses, 10) Prescription drugs: a drug that limited to use under a supervision of veterinarians because of potential danger, difficulty of administration or other consideration, 11) Over the counter drugs: a drug that simply buy from pharmacy without prescription like: pain killers, 12) Residue: is an amount of drug that still present in animal tissue or products (meat, milk and eggs) at particular point (slaughter), 13) Withdrawal time: the length of time it takes for a drug to be eliminated from the animal tissue or products, 14) Adverse drug reaction: an undesirable response of drugs to a drug by a patient, 15) Agonist : a drug that brings about a specific action by binding with appropriate receptors, 16) Antagonist ; a drug that inhibit a specific action by binding with a particular receptors, 17) Efficacy :the extent to which a drug causes the intended effect in a patient, 18) Metabolism ; the biological process that alters a drug from active form to inactive form or that can be eliminated from the body and 19) Oral : route of administration of oral drugs [3].

Definition of chemotherapy is Treatment of bacterial, viral, fungal and parasitic diseases by chemical substances (drugs). Selective toxicity is kills or inhibits the growth of microbes while causing minimal or no harm to the host. It happens by contacting with targets and the target must be a structure or physiological process (s) which is essential for the agent/pathogen however, absent or less important for the host.

### 1.1. Cidal versus static drugs

Bacteriostatic agents, such as tetracycline, inhibit the growth and multiplication of bacteria. A bacteriostatic agent, cells in a susceptible population stop dividing. However if the agent is removed, the cells once again multiply [6].

Bactericidal agents, such as fluoroquinolones, not only inhibit the growth of cells but also trigger pathways within the cell that lead to cell death. The actions of bactericidal drugs are irreversible so once susceptible cells are exposed to a bactericidal agent, they die.

### 1.2. Broad and Narrow Spectrum Antibiotics

Antibiotics that are limited to treat specific infections are known as **narrow spectrum** while those that can treat a wide range of infections are called **broad spectrum. Narrow-spectrum** drugs are sometimes preferred because they target a specific pathogen without disturbing the normal flora of the gut or respiratory tract and **Broad-spectrum** drugs are sometimes preferred for the initial treatment of an infection when the causative pathogen is not yet identified [7].

Assessing antimicrobial activity of a drug includes the 1) Minimum Inhibitory Concentration (MIC) is minimum concentration of antibiotic required to inhibit the growth of the test organism, 2) Minimum Bactericidal Concentration (MBC)is minimum concentration of antibiotic required to kill the test organism, 3) Concentration dependent killing (CDK) are those drugs which are considered to have a different kind of bacterial killing effect based on the concentration and 4) Post antibiotic effect (PAE): is defined as persistent suppression of bacterial growth after exposure of bacteria to an antibiotics.

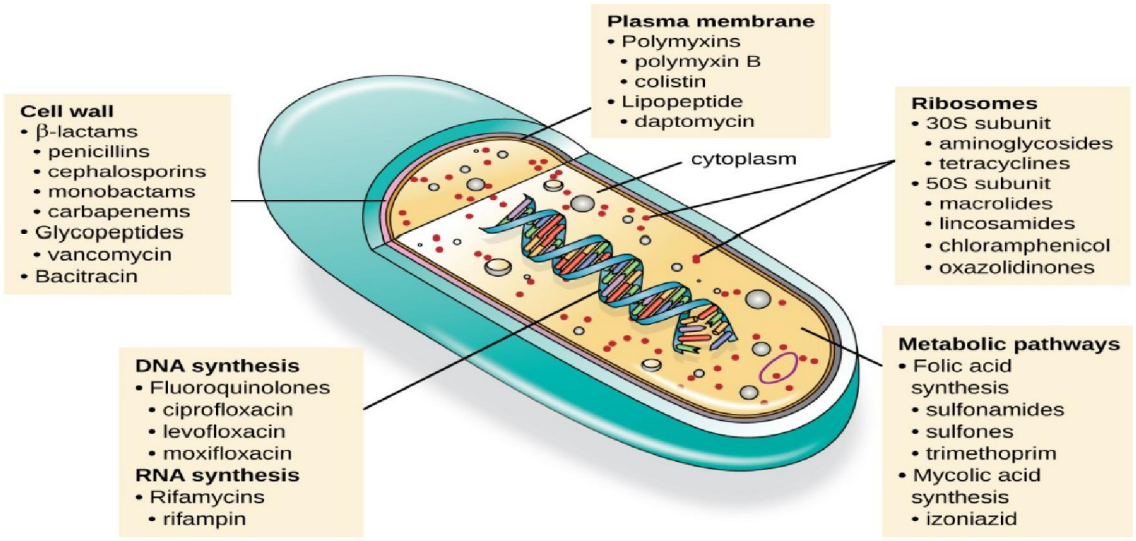


Figure 1:- Mechanism of action of chemotherapeutics/antibiotics/

**1.3. Antimicrobial resistance** is the ability of a microbe to resist the effects of medication. Resistance can be natural in certain types of microbes or acquired in another. The WHO defines antimicrobial resistance as a microorganism's resistance to an antimicrobial drug that was once able to treat an infection by that microorganism. A person cannot become resistant to antibiotics. Resistance is a property of the microbe, not a person or other organism infected by a microbe.

Pathogens often become resistant by: i) By preventing entrance of the drug into the envelope's membrane, ii) by pumping the drug out of the membrane after it has entered (translocases), iii) by inactivating drugs through chemical modification (hydrolysis), iv) by modification of target enzyme or organelle so that is no longer susceptible to the drug and v) they may either use an alternate pathway to bypass the sequence inhibited by the agent or increase the production of target metabolite.

Factors promoting drug resistance are:- Exposure to sub-optimal levels of antimicrobial, exposure to microbes carrying resistance genes, inappropriate drug use, lack of quality control in manufacture or outdated antimicrobial, inadequate surveillance or defective susceptibility assays, poverty or war, use of antibiotics in foods and antibiotics are used in animal feeds and sprayed on plants to prevent infection.

Mechanism to Reduce Bacterial Resistance are:-Appropriate diagnosis and proper selection of antibiotics**,** rational use of antibiotics**,** proper hygienic and other disease prevention practices and cycling the usage of antibiotic [9].

## 2. Anti viral chemotherapy

### 2.1.Introduction

Viruses are obligate intracellular parasite, Viruses contain a single type of nucleic acid (DNA or RNA) and a protein coat, sometimes enclosed by an envelope composed of lipids, proteins, and carbohydrates, Their replication and metabolism depends on the host, Mutation occurs more frequently, difficult to find drugs that are selective target to treat viral diseases, However, there are some enzymes or processes that are virus specific and are potential targets for drugs [3].

### 2.2. Viral cycle

The step of viral cycle includes the: - 1) Viral Binding, 2) Uncoating , 3) Viral Entry /genome + some viral proteins/, 4) Viral replication, 5) Viral Assembly Maturation, 6) Viral shedding /Release/ and 7) Viral latency.

There are three possible alternatives to prevent and control viral diseases, these includes 1) Prophylactic immunization (vaccination), 2) Use of endogenous antiviral substances (e.g. interferon), increasing host defense and use antiviral drugs.

| | | |
|---|---|---|
| 1. amantadine<br>2. rimantadine<br>3. acyclovir<br>4. valcyclovir<br>5. famciclovir<br>6. penciclovir<br>7. ganciclovir<br>8. foscarnet<br>9. sorivudine<br>10. idoxuridine<br>11. vidarabine<br>12. trifluridine<br>13. ribavarine | **Anti- HIV Agents**<br>**NRTI's**<br>1. retrovir<br>2. didanosine<br>3. zalcitabine<br>4. stavudine<br>5. lamivudine<br>6. abacavar<br>7. tenofovir<br>8. emtricitabine | **Protease Inhibitors**<br>1. saquinavir<br>2. ritonovir<br>3. indiavir<br>4. nelfinavir<br>5. amprenavir<br><br>**NNRTI's**<br>1. nevirapine<br>2. delavirdine<br>3. efavirenz |

Figure 2:- Antiviral drug list

**2.3. Disadvantages and common characteristics of antiviral drugs includes the:**

1) Restricted spectrum, 2) No standardized in-vitro susceptibility tests, 3) Most inhibit replication, 4) Cure depends on host immune system to eradicate. If patients are immunocompromized, may have recurrences compromised, 5) Resistance development is common in some viruses, 6) Many of them need to be activated by viral or cellular enzymes before exerting antiviral effect and Activity of enzymes and concentration of substrates will influence the efficacy.

**2.4. Antiviral agents** are **divided into five groups depending on the mechanism of action, these are:-**

1) Inhibitors of viral adsorption and penetration into the host cells; e.g. γ globulin (non-specific), enfuvirtide (HIV), 2) Inhibitors of the uncoating of the viral protein coat e.g Amantadine and rimantadine (Influenza virus A), 3) Antiviral agents that interfere with nucleic acid synthesis, most antiviral drugs are in this group that is nucleoside analogues e.g. acyclovir (used for the treatment of herpes simplex virus infections), Nucleotide analogues e.g. cidofovir (for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS)and Reverse transcriptase inhibitors e.g. Zidovudine (ZDV or Azidothymidine, AZT), didanosine (HIV), 4) Suppression of viral protein synthesis or maturation (protease inhibitors) e.g. Ritonavir, indinavir, amprenavir, tipranavir, saquinavir (most are effectve against HIV) and 5) Drugs that interfere with the release of virus from the host cell, e.g. Amantadine.

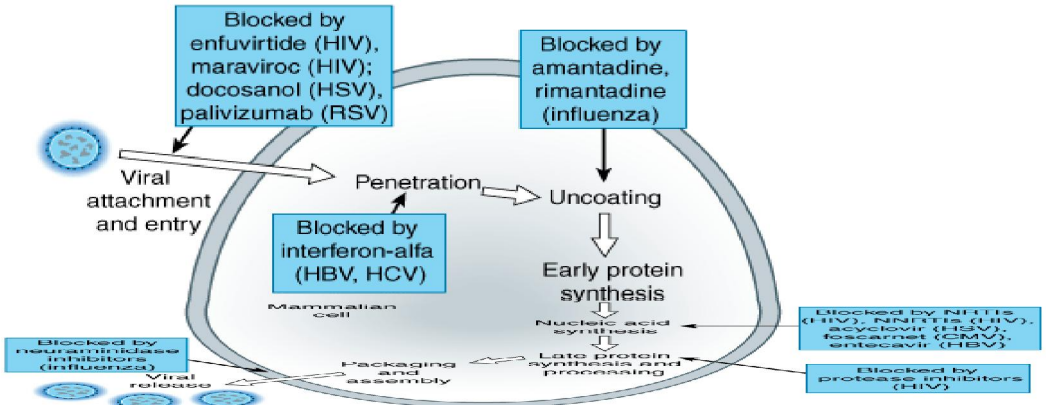


Figure 3: Viral drugs and Drug Targets

Amantadine has the following properties: Prevents uncoating &/or assembly, CNS Toxicity due to dopaminergic action, Given as prophylaxis for influenza A during epidemics, If used within 48 hours, it may help cure Influenza infections, Rimantadine: analog with less CNS toxicity.

Interferon has the following properties: Antiviral, anticancer and immunomodulating agents, several sites of action in viral cycle but mainly inhibit translation of viral proteins and Toxicity: flu-like syndrome, BM suppression; CNS[3].

Table 1: Preparation, Dose, Route, and Frequency of viral drugs

| Drug | Preparation | Dose, route and frequency | Indication |
|---|---|---|---|
| Idoxuridine | 0.1% ophthalmic solution, | 1 drop, topical, every 5-6 hr | herpes virus infection |
| | 0.5% ophthalmic solution | 1 drop, topical, every 1-2 hr | |
| Trifluridine | 1% ophthalmic solution | 1 drop, topical, every 2 hr initially (2 days) then 3-8 times daily | Ocular herpesvirus infection |
| Vidarabine | 3% ophthalmic solution | 0.4-1 cm ointment, topical, every 5-6 hr; 3-6 times daily | Ocular herpesvirus Infection |
| Acyclovir | 200-mg capsules or Tablets | 200 mg, PO, qid, every 4 hr, or 5 times/day | Feline herpesvirus |
| Ganciclovir | 500 mg/vial powder | 2-5 , IV, bid-tid | |
| Ribavirin | 6 g/100 mL vial powder | 11 mg/kg, IV, sid for 7 days | Susceptible viral Infections |
| Amantadine | 100- and 500-mg capsules | 100 mg total (humans), PO, sid bid | |
| Rimantadine | | 200-300 mg total (humans), PO, sid | |

Anti-influenza Agents includes the Amantadine, Oseltamivir, Peramivir, Rimantadine and Zanamivir. Anti-herpesvirus agents includes the Acyclovir, Cidofovir, Docosanol, Famciclovir, Foscarnet, Fomivirsen, Ganciclovir, Idoxuridine, Penciclovir, Trifluridine, Tromantadine, Valaciclovir, Valganciclovir and Vidarabine.

Antiretroviral Agents are a). NRTIs: Zidovudine, Didanosine, Stavudine, Zalcitabine, Lamivudine Abacavir, Tenofovir, b). NNRTI's: - Nevirapine, Efavirenz, Delavirdine and C). PIs: Saquinavir, Indinavir, Atazanavir, Ritonavir, Nelfinavir, Amprenavir, Lopinavir, Tipranavir.

Other antiviral agents are Fomivirsen, Enfuvirtide, Imiquimod, Interferon, Ribavirin and Viramidine.

Conclusion:- With further understanding of Virus Genomes and virus' receptors antiviral drugs will be more effective, Antiviral drugs are very experimental as of right now and hopefully with further discoveries, new processes of synthesis will be discovered and Most antiviral drugs end with **vir.**

## 3. Antifungal (antimycotics) Chemotherapy

Are medications used to treat fungal infections like: Dermatophytosis (ring worm), Aspergillosis, Candidiasis, Epizootic lymphangitis, Sporotrichosis and Serious systemic infections such as cryptococcal meningitis [7].

### 3.1. Challenges in Fungal Chemotherapy

1) The incidence of fungal diseases and the therapeutic results are highly associated with **the strength of immunity of the patient and removal of the predisposing factor(s)**, 2) Fungal organisms grow slowly and fungal infections often occur in tissues that are poorly penetrated by antimicrobial agents (e.g., devitalized or a vascular tissues), 3) There are less number of antifungal than antibacterial agents, 4) Both fungi and animals are eukaryotes, thus fungal and animal's cells are much closer at molecular level than bacterial cells, 5) The fungal cell wall is rigid and contains **chitin,** which along with polysaccharides, acts as a barrier to drug penetration, 6) Antifungal are more toxic than antibacterial agents (mostly used topically due to their toxicity) and Most fungi are resistant to conventional antimicrobial agents [3].

Therapy of fungal infections usually requires: - Prolonged treatment, Removal of predisposing factors, strengthening the immunity of the host and Use of combined therapy to enhance antifungal efficacy, reduce resistance and toxicity [4].

Potential targets for antifungal agents, which means criteria for good target (basis for selective toxicity) are:1) Unique on the disease causing agent, 2) Less important on the host and if the host has mechanism to cope with.

### 3.2. Common structures on mammalian and fungal cells

Both are eukaryotic therefore macromolecules like ribosome's and DNA topoisomerase are more similar but, Unique structures of fungi are**:** 1) Fungi have cell walls, which contain chitin and 1,3-β glucan polysaccharides 2) The synthesis of cell wall polysaccharide can be a target, 3)Fungal cell membranes contain ergosterol instead of cholesterol and the ergosterol-containing bilayer itself, are targeted by antifungal agents.

Antifungal agents are generally classified based on: -I) Chemical structure: A) Polyene antibiotics: (Amphotericin B and Nystatin), B) Azoles: (Imidazoles: ketoconazole, miconazole, Triazoles: itraconazole, fluconazole and C) Others (Griseofulvin and 5-fluorocytosine, II) Site of action or use: (Local/topical and Systemic) and III) Effect on the fungus ( fungicidal and fungistatics ). Most antifungal drugs are static but some are still Cidal depending on the organism and the concentration of the drug [4].

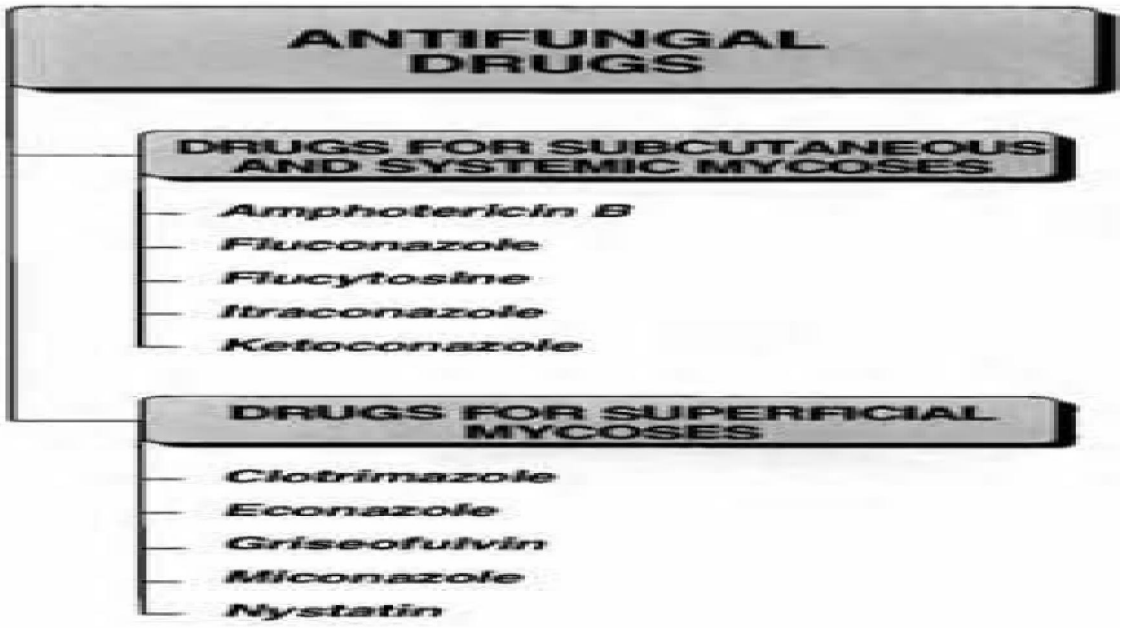


Figure 4: Site of action of fungal drugs.

Polyene antifungal agents: A polyene is a molecule with multiple conjugated double bonds, they also have hydroxylated region on the ring opposite the conjugated system and this makes polyene antifungals amphiphilic. The polyene antimycotics bind with ergosterol in the fungal cell membrane and two well known polyenes are Amphotericin B and Nystatin [1].

1) Amphotericin B is a polyene antibiotic. It is produced by Streptomyces nodosus and Discovered in 1956. It is indicated for treatment of severe, potentially life threatening fungal infections and also applied in the treatment of leishmaniasis. It has a broad spectrum of activities and the name of amphotericin originates from the chemicals amphoteric [8].

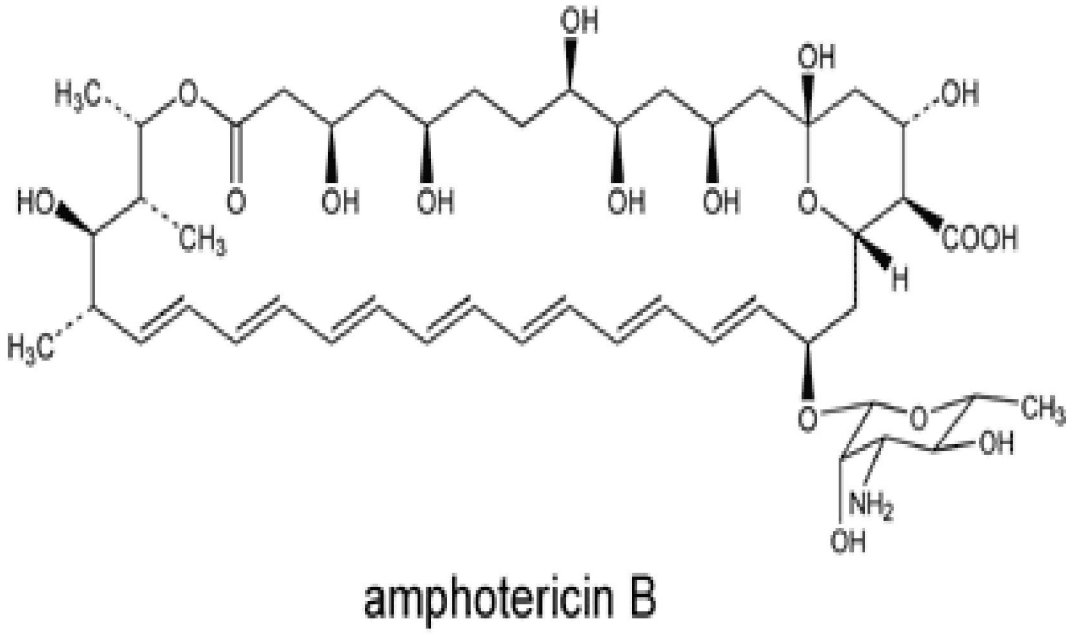


Figure 5: Structure of amphotericin.

Mechanism of action: Amphotericin B bind with ergosterol of fungal cell membrane and form a pore or channel that leads to $K^+$ leakage and fungal cell death (fungicidal). Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible and Most fungal species, except dermatophytes are sensitive to amphotericin B.

Therapeutics uses: -Used to treat systemic fungal infection in cats, horses, dogs and birds. Can be combined with other systemic antifungal agents to increase potency and reduce toxicity.

Side effects of Amphotericin B includes the: Nephrotoxic, Should not be used with other nephrotoxic drugs such as aminoglycosides, Should not also be used together with Ketoconazole (contraindicated) and Anemia (↓ erythropoietin) [9].

2) Nystatin is isolated from streptomyces noursei in 1951. It is the first clinically used polyene and it is used for local therapy only (not absorbed). Nystatin is a polyene antifungal drug to which many **mold** and **yeast** infections are sensitive, including **candida** species.

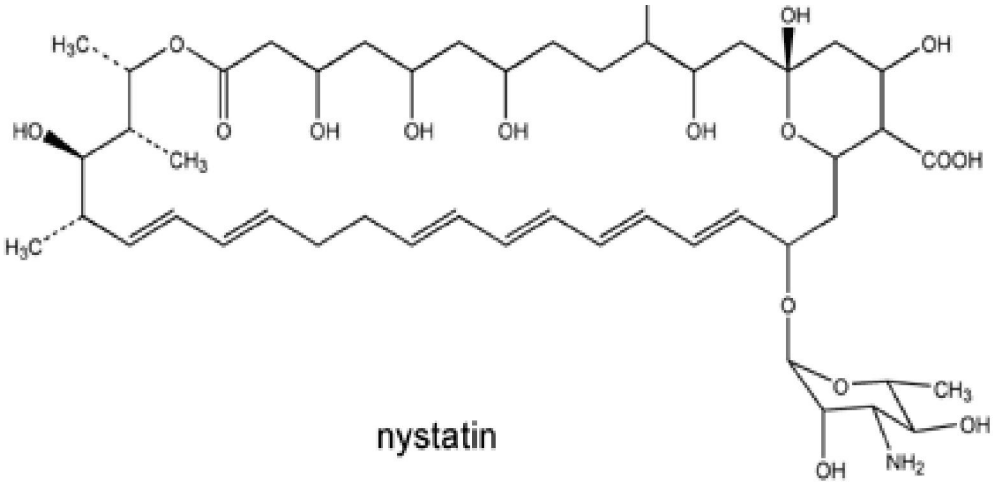


Figure 6: Structure of nystatin.

Azole Antifungal Agents: There are **two** types of azoles, An imidazole (two nitrogen atoms) and a triazole (three nitrogen atoms). More than 20 types are available in the market. **Imidazole includes** clotrimazole, miconazole, Ketoconazole and **Triazole** includes Itroconazole, Fluconazole, voriconazole. Triazoles are more potent, less toxic than imidazole. Azoles are used either **systemically** or **locally** based on the preparation and toxicity.

Mechanism of action: All azoles exert antifungal activity by inhibiting an enzyme (cytocrome P450 lanosterol demethalase) responsible for the demethylation of lanosterol to ergosterol. Mammalian cells can incorporate already formed cholesterol; fungi have to synthesize ergosterol.

Miscellaneous Antifungal: a) Griseofulvin: is a cyclohexene benzofuran antibiotic.Isolated from Penicillium griseofulvum in 1939. It is insoluble in water and it is Fungistatic.

Mechanism of action: Binds to polymerize microtubules and disrupts mitosis.Effective against dermatophytes, microsporum and trichophyton. Metabolized by the liver and eliminated as a glucuronide conjugate in the urine. It induces the hepatic microsomal enzyme system.Contraindicated for pregnant animal due to its teratogenic effect in some species (cats). b) 5-Fluorocytosine /Flucytosine/ : Flucytosine is a fluorinated pyrimidine analogue of cytosine first synthesized to be used as antineoplastic agent. Deaminated by fungi (not by mammalian cell) to 5-flurouracil which is a potent antimetabolite. Inhibit thymidylate synthase (used to synthesize DNA and RNA synthesis) in susceptible fungi. Absorbed well after oral administrations. Distributed widely including CNS. It is excreted unchanged via urine. Fungistatic, used to treat cryptococcosis (including meningeal) in dogs and cats. It is also used to treat aspegillosis and candidiasis in birds.Can be used in combination with amphotericin for the treatment of systemic mycoses and meningitis. Toxicity is generally low, mild GI disturbance and rarely bone marrow suppression has been reported [9].

Table 2:Mechanism of action and selective toxicity of fungal drugs.

| Antifungal Agent | Mechanism of Action | Bases for selective toxicity |
|---|---|---|
| Azole Fungicides:<br>✓ Itraconazole<br>✓ Voriconzaole<br>✓ Posaconazole<br>✓ Fluconazole | •Inhibit ergosterol biosynthesis affect cell membranes | Mammalian cell contain Cholesterol. Can use already formed cholesterol |
| **Echinocandins:**<br>•Caspofungin<br>•Micafungin | •Inhibit 1,3-betaglucan synthase, affects cell wall<br>•Broad spectrum, low toxicity | •Absence of cell wall in mammals |
| **Fluorinated Pyrimidines:**<br>•Flucytosine (5FTC) | •Inhibit nucleic acid synthesis | •Absence of activation enzyme in mammals |
| **Polyenes:**<br>•Amphotericin B<br>•Nystatin | •Forms Pores in membranes by interacting with ergosterol, Toxic | •Mammalian cell contain Cholesterol |

Antifungal drug resistance: Drug resistance is the reduction in effectiveness of a drug in curing a disease or a condition. It occurs when the drug is unable to inhibit or kill the disease causing organism due to the development of a mechanism to cope the effect of the drug and Drug resistance is a growing and serious threat to the treatment and control of fungal infection

Possible Mechanisms of Resistance:1)The target enzyme is overproduced, so that the drug does not inhibit the biochemical reaction completely, 2) The drug target is altered so that the drug cannot bind to the target, 3) The drug is pumped out by an efflux pump, 4) The entry of the drug is prevented at the cell membrane/cell wall level, 5) The cell has a bypass pathway that compensates for the loss-of-function inhibition due to the drug activity, 6) Some fungal "enzymes" that convert an inactive drug to its active form are inhibited and the cell secretes some enzymes to the extracellular medium, which degrade the drug [9] .

Measures to be taken to reduce anti fungal drug resistance (AFDR): 1) Avoid prudent use of antifungals, 2) Appropriate dosing with special emphasis on (Avoiding treatment with low dosage, Avoiding interruption of treatment and keeping appropriate frequency of treatment), 3) Therapy with combinations of existing agents, 4) Treatment with the appropriate antifungal, 5) Use of surveillance studies to determine the true frequency of antifungal resistance and appropriate diagnosis and selection of proper antifungal agent [3].

**4. Antiparasitic agents**

Antiparasitics are a class of medications which are indicated for the treatment of parasitic diseases caused by: Nematodes, Cestodes, Trematodes, Protozoan infections and Arthropod infestations.

For effective treatment of parasitic diseases the following general principles are important: 1) Understanding the feature of parasite life cycle (Availability intermediate host(s) and Factors affecting the life cycle), 2) Education of client (about possible contaminants, Presence of other animals (cross contamination) and Dose, frequency, time of treatment), 3) Safety and effectiveness of the anti-parasitic agent (Safe for the host and professionals /clients/, Safe for the environment /biodegradable/, Effective to all stages of the parasite (larvae, adult, hibernated) and Cheap and easy to apply and caution use in old, young, debilitated, or pregnant animals Antiparasitic agents can be grouped depending on the parasite where they act as: **1) Anthelmintics, 2) Antiprotozoa and Acaricides and insecticides**.

**1) Anthelmintics**: Anthelmintics or antihelminthics are drugs used for the treatment of helminths (nemathelminths (nematode) and platyhelminths (trematodes and cestodes) infestations. Anti = against, Helminth = worm. They expel these parasitic worms from the body, by either stunning or killing them so they may be called vermifuges (stunning) or vermicides (killing). There are several classes of anthelmintics, which may include: 1) Benzimidazoles, Imidazothiazole, 3) Tetrahydropyrimidines, 4) Antibiotics, 5) Organosphates and others [6].

1) Benzimidazoles: Contain similar structure which is made up of fusion of benzene and imidazole. Chemically related and their mechanism is similar, but, different in spectrum of activity. Benzimidazole anthelmintics include: 1) Albendazole, 2) Mebendazole, 3) Fenbendazole, 4) Triclabendazole, 5) Oxibendazole, 6) Febantel and Thiabendazole.

Albendazole is abroad spectrum oral anthelmintic. Pharmacokinetics: The oral absorption is quite variable and affected by food in the GIT. Fatty meal facilitates its absorption. It is metabolized in the liver to active metabolite with wide distribution including bile, CSF and hydatid cyst. The elimination half-life is 8-12 hrs. The albendazole and its metabolites are excreted via urine

Mechanism of action: Albendazole inhibits microtubule synthesis so stopping cell division and glucose uptake in helminths reduced stores of ATP.Clinical use: It can be employed to treat intestinal nematodes, cestodes and liver fluke (adult). The dose should be increased for cestode infestations (tape worms and hydatid disease).Adverse effect: Albendazole is well tolerated and side effects are rare under recommended doses. It is reported to be teratogenic in some animals so during pregnancy, it should be avoided [9].

Mebendazole is a benzimidazole drug that is used to treat infestations by worms including: 1) Strongyloides, 2) Whipworms (Trichuris trichiura), 3) Hookworms (Ancylostoma) and tapeworms (cestodes).Double the doses for cestodes. Pharmacokinetics: Same as albendazole.

Mechanism of action: Mebendazole causes slow immobilization and death of the worms by selectively and irreversibly blocking uptake of glucose and other nutrients and ATP depletion. Clinical use. It is also broad spectrum anthelmintics. Active against nematodes, cestode (Taenia saginata). Adverse effect: Limited to GIT disturbance, contraindicated during pregnancy due to possible embryotoxicity [5].

Triclabendazole: has no therapeutic activity against round worms and tapeworms. It is the first

choice for liver fluke. It displays high efficacy against both immature and adult liver fluke. Commonly sold as Fasinex. Generally accepted to bind to beta-tubulin and prevent the polymerisation of the microtubules

Fenbendazole (brand names Panacur) is a broad spectrum benzimidazole anthelmintic used against gastrointestinal nematodes and the taenia species of tapeworms. It can be administered to sheep, cattle, horses, dogs and cats [10].

Oxibendazole is a benzimidazole drug that is used to protect against roundworms like: strongyles, threadworms, pinworms and lungworm infestations in horses and some domestic pets.

Febantel is a probenzemidazole that will be converted into fenbendazole and oxifendazole in vivo. It is similar to pyrantel by anthlmentics activity which interferences with the carbohydrate metabolism of the worm, leading to energy exchange breakdown and inhibit glucose uptake. The worms become weak or die and then eliminated by peristaltic action of the intestine. NB: cross resistance occurs in all benzimidazoles.

2) Imidazothiazole :(Tetramisole(Nicotine like nematocides and Levamisole): a) Levamisole is a levo-isomer of tetramisole and it is more active than tetramisole. It is used to treat GIT nematodes and lungworms. Both larva (immature) and adult stage of the parasite are effectively removed by levamisole. Oral and parenteral preparations are available and both have almost equal efficacy.

Mechanism of action: Levamisole paralyzes worms by selectively activating nematode nicotinic acetylcholine receptors (agonist), allowing entry of Na+, Ca2+, for excessive muscle contraction and finally induces paralysis. Absorption is rapid after oral absorption Levamisole has immunostimulant effects at dosage rates higher than the dose used for anthelmintic activity.

It is metabolized by the liver and excreted by the kidney mainly but small quantity is also excreted with faeces [7].

**Side effect**: Levamisole is one of the most toxic anthelmintics, (It is out of market in some countries.), It has a low safety of margin, especially when given by injection, signs of toxicity include parasympathetic stimulation, convulsion, CNS depression and asphyxia which are primarily the result of respiratory muscle paralysis.

3) Tetrahydropyrimidines:This group include Pyrantel, morantel, Oxantel. 1) Pyrantel is an imidazothiazole derivative. It loses its potency when exposed to light due photoisomerization. Pyrantel is a depolarizing neuromuscular blocking agent. It acts on the cholinergic receptors of the nematode resulting in **spastic paralysis**. This has the result of causing the worm to "lose its grip" on the intestinal wall and be passed out of the system by natural process. It is effective against most gastrointestinal nematodes. Repeated doses are needed; because the drug kills only adult hookworms but not migrating larvae. Pyrantel pamoate salt is poorly absorbed from the gastrointestinal tract of the host. This property of the drug contributes to its selective action on gastrointestinal nematodes and its less toxicity. Morantel and oxantel are analogues of pyrantel with closer mechanism of action and activities [8].

4) Antibiotic–anthelmintics: 1) Ivermectin is a semisynthetic derivative of avermectin which was isolated from Streptomyces avermitilis. Ivermectin kills the parasite by interfering with nervous system and muscle function, in particular by enhancing inhibitory neurotransmission**.** It acts as a (Gama aminobutyric acid) GABA agonist, causing paralysis in susceptible **arthropods and nematodes.** It doesn't cross BBB (blood brain barrier), GABA is neurotransmitter only in the CNS of higher animals.

Therapeutic uses: It is effective against all major GIT nematodes and lungworms, effective against all ectoparasites including ticks, It can also be used to treat microfilariasis and heartworms and Ivermectin has no effect on cestodes, trematodes, or protozoa since these parasites do not utilize GABA as a neurotransmitter.

Toxicity: The main concern is neurotoxicity. It may induce local irritation at injection site and certain breeds of dogs are more sensitive to the toxicity of ivermectin.

5) Organophosphate anthelmintics: A number of organophosphates have been used as anthelmintics, which is effective against the major gastrointestinal nematodes. However, their use is declining due to their: 1) Relative toxicity, 2) Limited efficacy against immature stages,3) Narrow margin of safety and contamination of the environment through fecal excretions.

Clinical use**:** Dichlorvos is used as an anthelmintic in horses, pigs, dogs, and cats, Trichlorfon in horses and dogs and coumaphos, crufomate, haloxon, and naftalofos in ruminants.

**2) Antiprotozoal Agents**

Antiprotozoal Agents are drugs used to treat infections caused by protozoan parasites: Protozoa are eukaryotic, unicellular organism. Important drug targets for protozoa are: 1) Enzymes, 2) Membrane transporters, 3) Microtubules, 4) Synaptic transmission and unknown targets.

Protozoan parasites include: 1) Coccidia, 2) Babesia, 3) Trypanosome, 4) Toxoplasma, 5) Trichomonia and Leishmania**.** They can be water food or vector born. There are a large collection of antiprotozoal drugs

with variety of chemical structure and mechanisms of actions [9].

Drugs for Coccidiosis: Coccidiosis is severe disease and important from an economic point of view in poultry industry. Anticoccidial drugs are coccidiostatic or coccidiocidal based on their action on the parasite. They can act on extracellular stages (sporozoite, merozoite) to prevent penetration of cells or on the intracellular stages to prevent developments. They are grouped as: 1) Hydroxyquinolones and naphthoquinones, 2) Clopidol, 3) Robenidine, 4) Amprolium, 5) Nitrobenzamides, 6) Nicarbazin and Sulphonamides.

1) Hydroxyquinolones and Naphthoquinones: These include compounds like: Buquinolate, Decoquinate, Nequinate, Buparvaquone, Parvaquone and Atovaquone. They are coccidiostatic. Act by inhibiting DNA replication. Sporozoites may start growing after removal of the agent.

2) Clopidol is effective against all species of coccidia at sporozoite stage. Used as a prophylaxis in poultry coccidiosis. It has coccidiostatic activity. Sporozoites may start growing after cessation of treatment. The mechanism of action is similar to quinolones. Fed at 0.0125-0.025% for prevention of coccidiosis. It can pass to the egg if it is given for layers and no adverse effect if used as directed but overdose may cause inappetence [9].

Is a synthetic anticoccidial derivative of guanidine. Active against the first generation schizont and prevent the formation of merozoite. Changes the taste of meat and egg if the chicken is slaughtered or if the egg is consumed before the end of withdrawal period (5 days) and doesn't have effect on egg production.

A structural analogue of thiamine (vitamin $B_1$). It doesn't have intrinsic activity of thiamine but prevents coccidia from utilizing thiamine by blocking thiamine receptors (competitive antagonist). The parasite dies due to thiamine deficiency. It is poorly absorbed after oral administration. Act on the first generation schizont, has so effect on sexual stages and sporulating oocysts.

Therapeutic use: it can be used to prevent or treat coccidia outbreaks. Some species of coccidia are resistant to amprolium so combination with sulpha or other anticoccidial drugs is needed to increase the efficacy

Adverse effect: -It is safe when used as directed, no withdrawal period. Thiamine deficiency may occur following overdose or prolonged use especially in young animal so treatment should be limited for 2wks.

NB: administration of high dose of thiamine will reverse or reduce the effect of amprolium.

5) Nitrobenzamides**:** Aklomide and dinitolamide are nitrobenzamide anticoccidial agents. Act on the first generation schizont, dinitolamide also inhibits sporulation of oocysts. Dinitolamide is coccidiostat if it is given for 6 days but coccidiocidal if it is given for longer period of time.Their mode of action is not known. Fed at 0.0125% to prevent coccidiosis and nitrobenzamides resistant strains are quite common so combination therapy is needed.

6. Nicarbazin is the mixture of two compounds. The mechanism of action is unknown. Recommended to control coccidia outbreaks in poultry (125 ppm). Causes the reduction of egg production

7. Sulpha drugs are used both for treatment and control of outbreaks of coccidiosis in all species. Show most activity against asexual stages and lesser activity against the sexual stages of coccidian. They are more effective against the intestinal than caecal species and most active on schizont. They are most commonly used in combination with others due to the occurrence of resistant strains.

Drugs for trypanosomiasis: Animal trypanosomosis is a wide-spread, devastating disease in sub-Saharan Africa. It is caused by the protozoan organisms of the genus Trypanosoma . The parasite infects animals in approximately 10 million $km^2$, involving 37 countries in Africa. Trypanocidal drugs: Chemotherapy and chemoprophylaxis are essential for the control of trypanosomiasis.

There are problems associated with tryps control and prevention which include: **1)** There is no effective vaccine, 2) Vector control strategies are not implemented very well, 3) Development of drug resistance, 4) High toxicity and dermonecrosis associated with some drugs and Absence of new drug in the market.

The widely used compounds are quinapyramine, homidium, pyrithidium, isometamidium, diminazene and suramin. To overcome or reduce resistance these compounds are often used in sequence and in combination. Antitrypanosomal drugs are often divided as: Group I compounds (Act immediately after injection, Example diminazene). Group II compounds (Produce their trypanocidal effect in vivo only after a latent period of 24 hrs, Examples: Homidium, quinapyramine and suramin).

Antitrypanosomal drugs are also divided as: curative drugs, Example: (Diminazene aceturate , Quinapyramine sulfate), preventive drugs, Have long acting effect (Example: Quinapyramine dimethylsulfate). Both (Isometamidium chloride, Suramin, Homidium bromide). In general preventive treatments tend to select resistant strains because of their slow elimination. Therefore, it is very important

to respect the period of time between two treatments (to ensure that curative treatment is given using a trypanocide of a different chemical category).

Quinapyramine is a trypanocidal drug used in the treatment and prophylaxis of trypanosomiasis mostly in camels and cattle. It is not safe drug toxic signs especially after 2hrs of injection include salivation, tremor, dyspnea, incoordination, and tachycardia. Promote multiple drug resistant.

Ethidium bromide /Homidium/ It has been commonly used since the 1950s in veterinary medicine to treat Trypanosomosis in cattle Active against T. congolense, T. vivax, less active against T. brucei, not effective against T. evansi . Side effects: Local swelling at injection site and transient lameness and widely believed to be a carcinogen or teratogen. Pyrithidium is similar to ethidium bromide in its activity. Isometamidium : It is a trypanocidal agent. Used mostly for prevention (can prevent for 6 months).

Diminazene is a di-amidine. It binds DNA and RNA. It is the active component of diminazene aceturate. Commonly sold as Berenil. It may induce reaction at injection site. Suramin was introduced into the therapy of trypanosomiasis in 1920. Suramin contains 8 benzene rings, 4 of which are used in pairs (naphthalene), six amide and sulphonate groups. The drug binds firmly to host plasma proteins. The compound enters the trypanosome by endocytosis. It has a selective action on trypanosomal enzymes. It is used for treatment of diseases caused by trypanosomes. It has been also used in the treatment of onchocerciasis [9].

Side effects: Suramin is relatively toxic, particularly in a malnourished patient, the main toxic effect being in the kidney. Other slowly developing adverse effects reported include. Optic atrophy. Adrenal insufficiency and skin rashes. Haemolytic anaemia and agranulocytosis.

**3. Drugs for External Parasites /Ectoparasiticides/:**

These types of drugs are grouped as acaricide and insecticide. Acaricides are pesticides that kill members of the Acari group, which includes ticks (ixodicides) and mites (miticides). Insecticides are pesticides that kill insects. A drug can be both insecticide and acaricides. They continue to be the primary means of control for ectoparasites on livestock but should be integrated with other methods. Problems related with the use of acaricides and insecticides include **safety** (may not be safe for the host, environment, professional), **resistance** (ticks, tsetse and others) [7].

Method of application ant arthropods includes the:1) Spray (manual, knap sac, automatic (motorized) ) on the animal or environment, 2) Dipping (dipping tank (concreted), plastic dipping tank), 3) Shampoo, 4) Spot on or pour on, 5) Collars or tags (put around the neck or attached to ears) and injection.

Drugs of ectoparasite can be grouped based on their chemical structure and modes of action as: 1) Organophosphates and carbamates, 2) Chlorinated hydrocarbons, 3) Botanical derivatives (Rotenone, pyrethrins and pyrethroids), 4) Formamides (Amitraz) and others like avermectins [7].

1) Organophosphates (OP) are the general name for esters of phosphoric acid with insecticidal, acaricidal, and helminthicidal properties.Grouped into two based on their chemical structure: Thio compounds include coumaphos, cythioate, fenthion, chlorpyrifos, diazinon, famphur and Oxy compounds include dichlorvous, trichlorfon.

Mechanism of Action: OP performs by inhibiting the action of acetylcholinesterase (AChE) in nerve cells. These compounds must be metabolized to oxy compound to inhibit AChE. Absorption: OPs are lipid soluble so well absorbed through the skin and GIT. ExcretionExcreted via urine. Ops have no residue problems. Adverse Effect: OPS acute toxicity induces SLUDDE which stand for; (Salivation, Lacrimation, Urination, Defecation, Dyspnoea and Emesis) and chronic toxicity induces nerve damage. Treatment of toxicity involves atropine or pralidoxime injection [7].

2) Carbamates is frequently used preparations include carbaryl, methiocarb and propoxur

Mechanism of action: Inhibits ACHE via carbamylation but more reversible than those of OP, Their pharmacokinetics are not well understood and Toxicity similar to organophosphates.

3) Chlorinated hydrocarbons: a) Chlorinated ethane derivatives. Include DDT (dichlorodiphenyltrichloroethane), but banned in some countries [7].

Mechanism of action: Increase the $Ca^{++}$ content of the cytosol of nerve tissue. They tend to accumulate in body fat, sign of toxicity may be protracted for several days

b) Hexachlorocyclohexanes (lindane): BHC (benzene hexachloride): Lindane has been used for longer period of time than other chlorinated hydrocarbon agents. It is the active ingredient in spray or dip for control of fleas, lice and mites on dogs. It can also be used as a spray to control ticks and screwworms in cattle, sheep, goats, swine and horses.

4) Botanical Derivatives: 1) Rotenone: Chemical that is used as a broad-spectrum insecticide and pesticide. Occurs in naturally in the roots and stems of several plants (derris plant). Act by blocking NADH (nicotine amine dinuclelotide hydrogen) related

oxidation hence affects ATP production. It is used to control fleas, ticks, lice and mites on dogs and cats.
Side effect: It is not as such safe Signs of toxicity include GIT upset, hyperpnoea, seizure, coma, death [8].

2) Pyrethroids is a synthetic chemical compound similar to the natural chemical pyrethrins produced by the flowers of pyrethrums (Chrysanthemum cinerariaefolium and C. coccineum). Pyrethroids are common in commercial products such as household insecticides and insect repellents. They are usually broken apart by sunlight and the atmosphere in one or two days, and do not significantly affect groundwater.

Mechanism of action:They affect the sodium channel of the arthropod; recent studies also indicated that pyrethroids suppress GABA and glutamate receptor of the insect. Pyrethrum may be absorbed after inhalation or ingestion and absorption from the skin is not significant
Toxicity: They are the safest ectoparasiticides.

5) Formamidines (Amitraz ) is the only formamidine used as insecticide. It acts by inhibiting monoamine oxidases of the parasites. Used to control ticks, lice and other animal pests and also used in treatment for demodectic mange, notoedres, and sarcoptid mites.

Side effects: Amitraz has wide safety of margin for mammalian species but it may induce sedation in high dose. Side effects of amitraz are associated with its ability to activate α2 adrenergic receptors. $\alpha_2$ antagonist like yohimbine can be used as an antidote and toxic for cats and rabbits, so should not be used in this species [8].

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