

# **University of Karbala**

## **College of veterinary medicine**

### **Pharmacology Lect. 2**

#### **Antifungal Drugs**

**Dr. Sattar K. Abdul-Hussain, PhD., DVM, DABT**

Dr. Sattar K. Abdul-Hussain

There are 200,000 known species of fungi, and estimates of the total size of Kingdom Fungi range to well over a million. Populations of the kingdom are quite diverse and include yeasts, molds, mushrooms, smuts, the pathogens *Aspergillus fumigatus* and *Candida albicans*, and the source of penicillin, *Penicillium chrysogenum*. Fortunately, only ~ 400 fungi caused disease in animals, and even fewer caused significant human disease. Fungi are eukaryotes with unique cell walls containing glucans and chitin, and their eradication requires different approaches different than those for treatment of bacterial infections.

Figure 1 provides information on the mechanism of action of available antifungal agents have effects on:

1. The synthesis of membrane and cell-wall components,
2. Membrane permeability,
3. The synthesis of nucleic acids, and
4. Microtubule/mitotic spindle function

#### **A. Griseofulvin:**

It is a cyclohexane benzofuran antibiotic derived from *Penicillium griseofulvin*. It is insoluble in water.

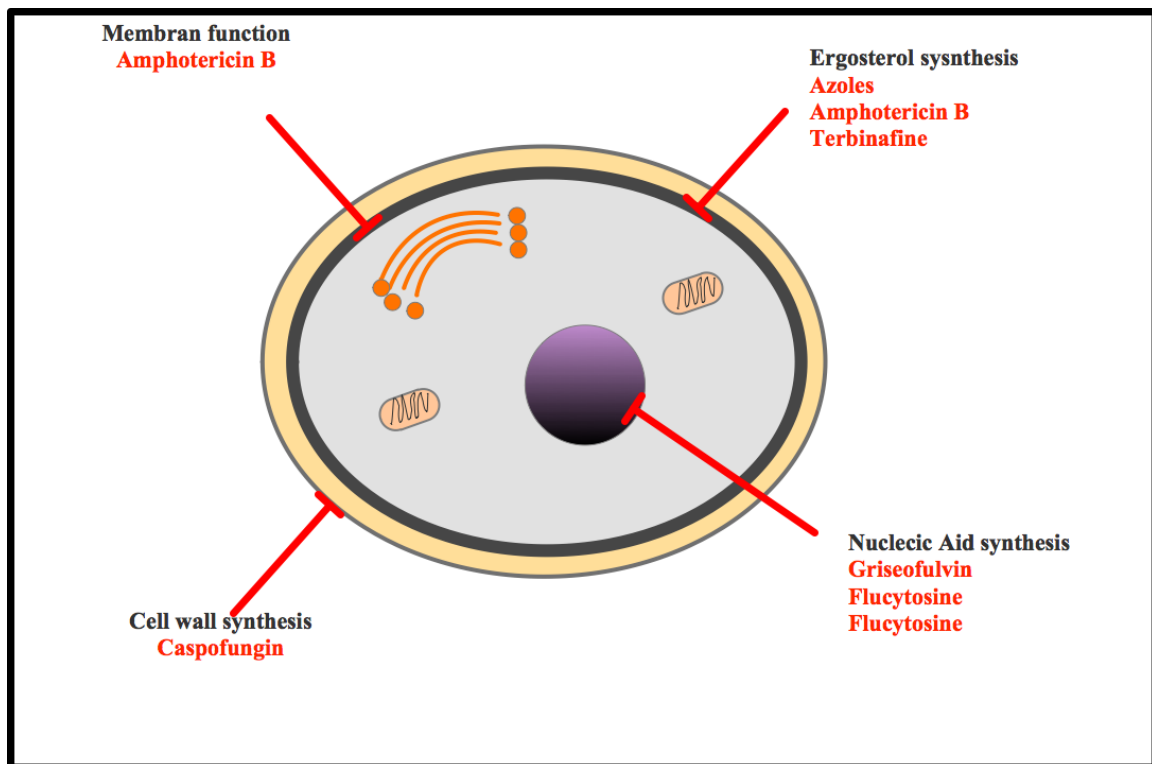
**Mechanism of action:** It inhibits microtubule function and thereby disrupts assembly of the mitotic spindle (Figure 1). It is actively taken up by growing dermatophytes (ringworm). It is fungistatic for dermatophytes such as *Microsporum* species and *Trichophyton* species.

**Therapeutic uses:** It used in dogs, cats, and horses for multifocal dermatophyte infections.

**Pharmacokinetics:** It is not absorbed well from GI tract. The absorption can be increased by high-fat diet and by preparation consisting of micronized particles. It distributes to keratin precursor cells of skin, hair shafts, and nails. It is metabolized by the liver by demethylation and glucuronide conjugation and excreted in urine.

**Administration:** Griseofulvin is administered orally twice a day to dogs and cats and once daily to horses for 4-6 weeks.

**Adverse effects:** Are very rare, however, leucopenia and anemia may occur as an idiosyncratic reaction in kittens



**Figure 1. Sites of action of antifungal drugs**

**B. Azoles:** This group of antifungal includes: ketoconazole, itraconazole, and fluconazole, which are imidazole antifungals for systemic use. Other imidazoles used topically for dermatophyte include miconazole and clotrimazole.

**Mechanism of action:** The azoles inhibit the synthesis of ergosterol in fungal cytoplasmic membranes by blocking cytochrome P450 enzymes and increasing cellular permeability. They are fungistatic for most pathogenic fungi causing systemic infections such as *Blastomyces*, *Coccidioides*, *Cryptococcus*, and *Histoplasma* species (Figure 1).

**Therapeutic uses:** Ketoconazole is used in dogs, cats, horses, and birds for systemic mycoses and for severe yeast infections. Fluconazole and itraconazole have replaced ketoconazole in most treatment regimens for the systemic mycoses because of their longer half-life time, greater activity, and lower toxicity.

Clotrimazole and miconazole are used topically in the treatment of *Candida*, *Aspergillus*, and *dermatophyte* infections.

**Pharmacokinetics:** Azoles are very well absorbed after oral administration in particular with presence of food that stimulates bile flow. They are metabolized by microsomal enzymes of the liver and excreted in the bile.

**Administration:** Ketoconazole is given orally twice a day for 3-6 months for systemic mycotic infections. Fluconazole and itraconazole are administered orally or IV once a day to dogs and cats for systemic mycoses. Clotrimazole and miconazole are applied topically for the treatment of yeast or dermatophyte infections.

**Adverse effects:** Anorexia, vomiting, and diarrhea may occur with ketoconazole.

**C. Amphotericin B:** Amphotericin B is a polyene macrolide with antifungal activity. It is a heptaene macrolide containing seven conjugated double bonds in the *trans* position and 3-amino-3-, 6-dideoxymannose connected to the main ring by a glycosidic bonds.

**Mechanism of action:** It binds to ergosterol of fungal cell membranes for form pores of channels, which result in leakage of cell contents (Figure 1).

**Therapeutic uses:** Amphotericin B is used to treat systemic fungal infection in dogs, cats, horses, and birds.

**Pharmacokinetics:** Amphotericin B is not well absorbed from GI tract. It is slowly distributed into all body tissues except CNS after IV administration. Approximately 65% of amphotericin B is excreted unchanged into urine into urine and feces.

**Administration:** Amphotericin B is usually diluted in 5% dextrose and given IV. Frequency of treatment varies with the type of infection.

**Adverse effects:** Renal toxicity is the major and serious side effect associated with the use of amphotericin B. It produces renal vasoconstriction, decreased GFR, and damage to tubular epithelium.

**D. Flucytosine:** It is also known as 5-FC. It is a fluorinated pyrimidine that is deaminated by fungi (not mammalian cells) to 5-fluorouracil, a potent antimetabolite.

**Mechanism of action:** It inhibits thymidylate synthase and DNA and RNA synthesis in susceptible fungi (Figure 1).

**Therapeutic uses:** It is combined with amphotericin B for synergistic effect in the treatment of cryptococcosis in dogs and cats. Flucytosine used alone in treating aspergillosis and candidiasis in birds.

**Pharmacokinetics:** Flucytosine is well absorbed orally and widely distributed in all body tissues including the CNS. It is excreted in unchanged in urine.

**Administration:** Flucytosine is administered orally 3-4 times a day for a minimum of 4 weeks.

**Adverse effects:** Flucytosine has low toxicity with mild GI disturbances.

E. **Terbinafine:** Terbinafine is a synthetic ally amine.

**Mechanism of action:** Terbinafine inhibits the synthesis of ergosterol, a component of fungal cell membranes. It inhibits the conversion of squalene to sterols by blocking the enzyme squalene monooxygenase and caused accumulation of squalene (Figure 1). Terbinafine does not block cytochrome P450 enzymes. It is fungicidal against dermatophytes and fungistatic against yeast.

**Therapeutic uses:** Orally or topically, terbinafine is useful for treating dermatophytic infections in dogs and cats. It is also useful in treatment of systemic mycotic infections in birds.

**Pharmacokinetics:** No information available for animals at this time

**Adverse effects:** It is well tolerated by most animals and adverse effects are not likely to occur.