Chapter 6
6. Fungal Diseases and Toxins

Dr. Ariyah Terasawat

From an estimated 1.5 million species of fungi

- ✓8000 species cause plant diseases
- ✓200 species cause human diseases

•There are beneficial and harmful effects of fungi

•Some harmful effects of fungi includes

- ➢Destruction of food, lumber, paper and clothes
- ➢Cause animal and human diseases including allergies
- ➢Produce toxins which can be lethal
- ➢Cause plant diseases
- ➢Spoil agricultural products
- ➢Damage products such as magnetic tapes, disks, glass lenses, marble statues, bones, etc

- Most fungi are saprophytic and some are symbiotic
- Infection by fungi occurs when conditions are favourable
- These conditions includes three factors
    1. Fungal pathogenecity
    2. Host defence factors
    3. Environmental factors
- Fungus produce disease when conditions of these three factors are right
- Some of health effects due to fungal toxins include
    - ❑ death
    - ❑ health problems
    - ❑ weaken immune systems
    - ❑ allergies
    - ❑ harms normal microflora

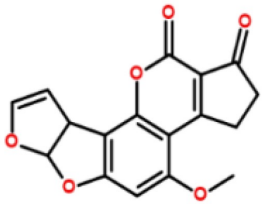
6.1. Mycotoxin and Their Impact on Health

- Mycotoxin – toxin produced by toxinogenic molds
- Appear in food chain as a result of
  - fungal infection of crops
  - consumption of fungus by humans
  - during livestock feed
- Mycotoxin remain in food chain and dairy products because
  - resist decomposition or being broken down during digestion
  - can not be destroyed by cooking and freezing
- Exert adverse health effects in human and animals
- Toxic effects varies depending on chemical structure of toxin
- Degree of adverse effects is determined by
  - toxin concentration in foods and feeds
  - duration of exposure to toxin

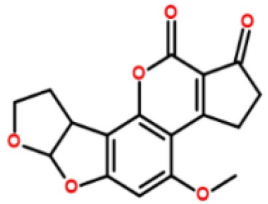
- Impact includes
  - losses in productivity
  - reducing weight gain
  - immunosuppression
  - genotoxic effects
  - causes human cancers
- Types of mycotoxins includes
  - Aflatoxins
  - Ochratoxins
  - Citrinins
  - Ergot Alkaloids
  - Patulins
  - Fusariums

a) Aflatoxin

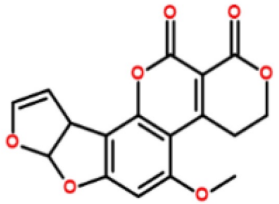
- produced by *Aspergillus* species such as *A. flavus* and *A. parasiticus*
- Aflatoxin refers to four different types of mycotoxins
  - Aflatoxin B_1
  - Aflatoxin B_2
  - Aflatoxin G_1
  - Aflatoxin G_2
- Among them Aflatoxin B_1 is
  - the most toxic
  - potent carcinogen
  - causes adverse health effects like liver cancer in many animals species
- Aflatoxins largely associated with commodities produced in tropics and subtropics such as cotton, peanut, spices and maize



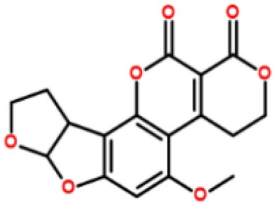
Aflatoxin B_1 (AFB_1)



Aflatoxin B_2 (AFB_2)



Aflatoxin G_1 (AFG_1)



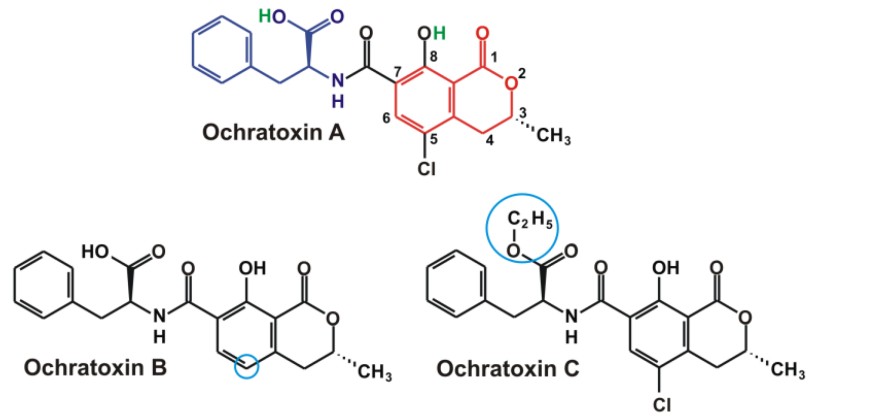
Aflatoxin G_2 (AFG_2)

b) Ochratoxin

- has three secondary metabolite forms, A, B and C
- produced by *Penicillium* and *Aspergillus* species
- Ochratoxin B is non chlorinated form of Ochratoxin A and Ochratoxin C is ethyl ester form of Ochratoxin A
- *Aspergillus ochraceus* contaminate wide range of commodities including beverages
- *A. carbonarius* found on vine fruit and releases toxin during juice making process
- *Ochratoxin A* is labeled as

  -Carcinogen and nephrotoxin

  - cause tumors in human urinary tract



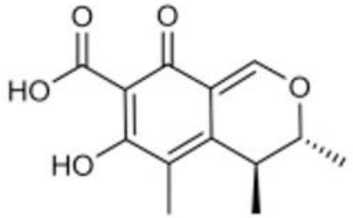
c) Citrinin

- Isolated from *Penicillium citrinum*
- Later isolated from dozen species of *Penicillium* and several species of *Aspergillus*
- Some species used to produce cheese (*P. camemberti*) and soy sauce (*A. oryzae*)
- Citrinin cause nephrotoxin in animal tested
- Full significance for human health is unknown
- Act synergistically with ochratoxin A to depress RNA synthesis in murine kidneys

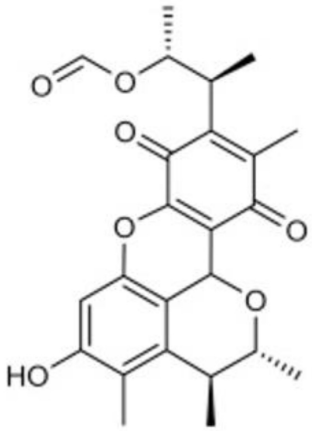
Penicillium digitatum
green mold

Softening of demage tissue

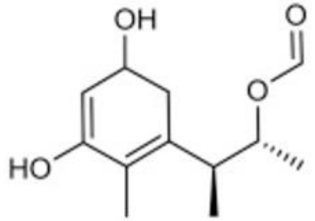
White fungal growth progressively becomes green



Citrinin



Citrinin H1

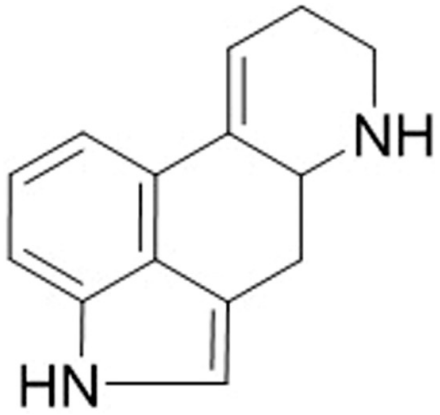


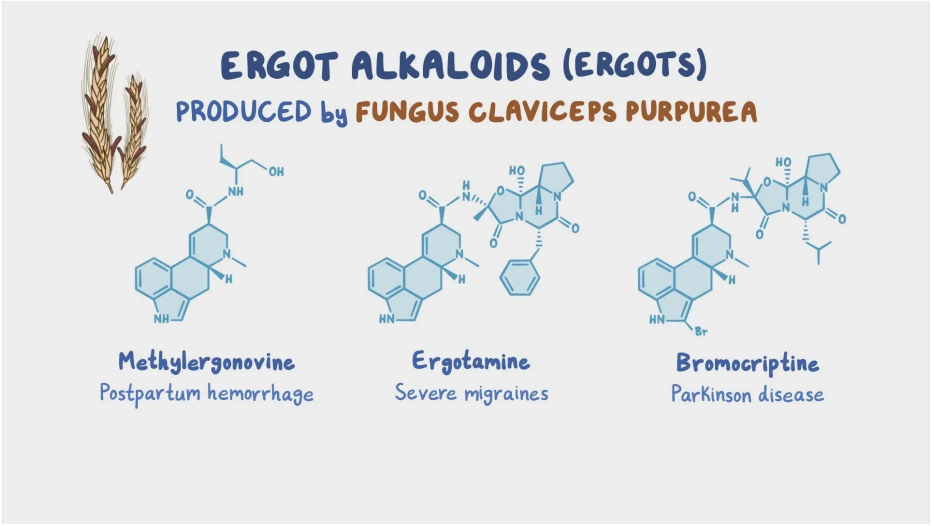
Citrinin H2

d) Ergot Alkaloids

- toxic mixture of alkaloids produced by *Claviceps purpurea* species (phylum *Ascomycota*)
- pathogens of various grass species
- ingestion causes ergotism (St. Anthony's fire)
- two forms of ergotism
  - gangrenous – affect blood supply to extremities
  - convulsive – affect central nervous system

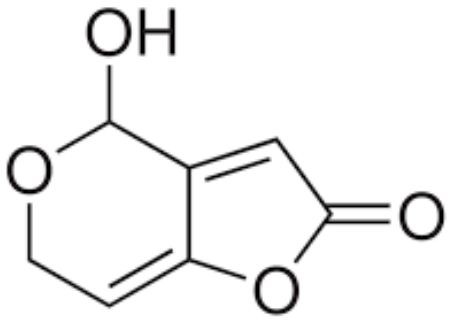
- modern method of grain collecting reduced ergotism
- still an important veterinary problem
- ergot alkaloids also used pharmaceutically





e) Patulin

- Produced by some species of *Penicillium* and *Aspergillus*
- associated with moldy fruits and vegetables
- can destroyed by fermentation in beverages
- not carcinogenic
- damage immune systems in animals



f) Fusarium

- produced by over 50 species of Fusarium
- infect grain of developing cereals (wheat and maize)
- three types of fusarium toxin
  - fumonins – affect nervous system of horses, causes cancer to rodents
  - trichothecenes – chronic and fatal toxic effects in humans and animals
  - zearalenone – no fatal toxic effects

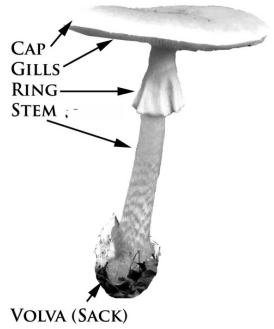
6.2. Amatoxins

• toxin produced by toxic mushrooms

• found in several genera of poisonous mushrooms

- *Amanita phalloides* and several other members of genus *Amanita*

- Some species of mushroom like *Conocybe, Galerina* and *Lepiota*



• Amatoxins are potent and selective inhibitors of RNA polymerase II

• when amatoxins inhibits RNA polymerase II

-synthesis of mRNA stops

-Cell metabolism stops

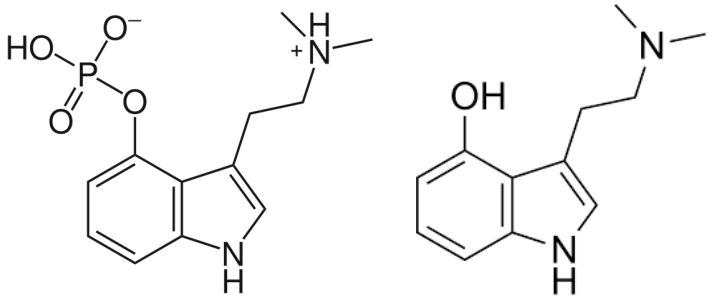
- cell lysis ensues

- primary mode of exposure to amatoxins is by ingestion
- can be absorbed through inhalation and skin contact
- upon exposure to amatoxins
    - -Gastrointestinal tract absorbs it
    - - liver is affected
    - - kidney is affected
    - - heart is affected
    - - cause headache
    - - cause diarrhea
    - - cause back pain
    - - cause coughing
    - - result in death

- 0.1 mg/kg is estimated minimum lethal dose (child , old people)
- 7 mg/kg is estimated maximum lethal dose (adults)
- susceptibility to effects of amatoxins increase due to persons
  - pre-existing skin disorders
  - central nervous system disorders
  - impaired kidney, liver and pulmonary functions
- amatoxins effects develops rapidly due to their
  - swift intestinal absorption
  - thermostability
- toxic hepatitis is most effective amatoxin and cause hepatorenal syndrome

6.3. Hallucinating mushrooms

- name given to psychoactive fungi
- affects mind
- experience real perception of something not actually present
- contain hallucinogenic compounds like psilocybin and psilocin
- at low doses their primary effects are
  - perceptual distortions
  - alteration of thought or mood
  - lucid awareness (dream like thought)
  - minimal effects on memory and orientation
- chemically diverse class due to their chemical structures
- use of hallucinogenic drugs rarely results in true hallucinations



6.4. Introduction to mycosis

- Mycosis – fungal infection of animals including humans

- Variety of environmental and physiological conditions contribute to development of fungal diseases

-spread generally from the environment to people (animals) with limited person-to-person spread

- Skin and lungs are predominant entry site for many fungi

- persistent infections initiated by :-

  - inhalation of fungal spores
  - localized colonization of skin by fungus

-Mycoses often start in lungs or on skin

- Fungal infection of skin was 4th most common disease in 2010

- people at risk of fungal infections due to
  - taking antibiotics for long periods of time
  - •Weakened immune system
  - •Diabetes
  - • Age

Types of Mycoses

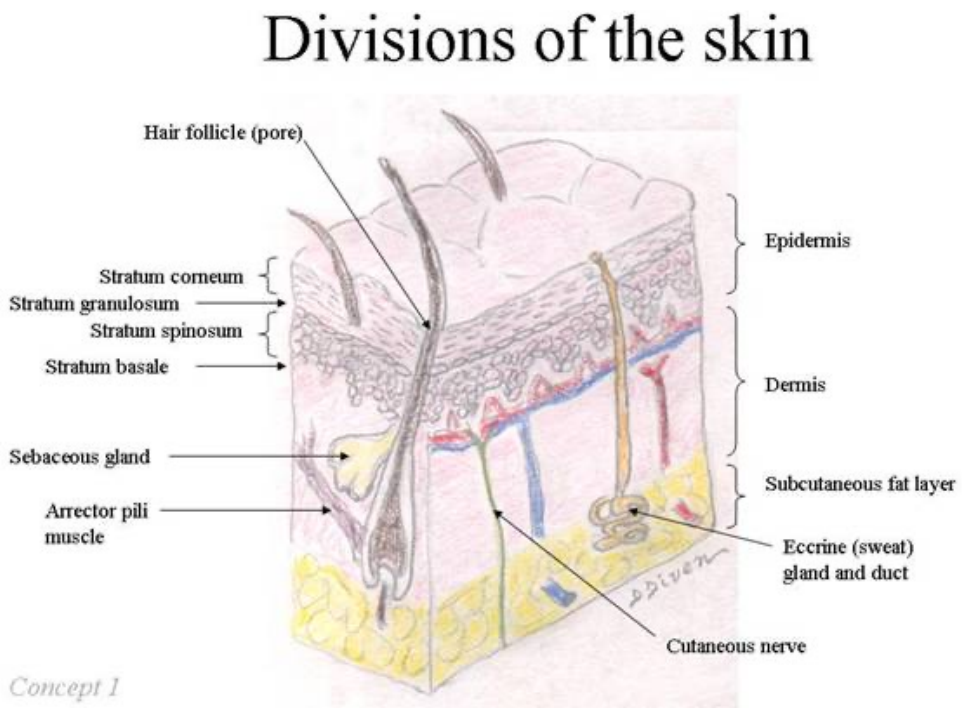
A) Superficial mycoses

B) Cutaneous mycoses

C) Subcutaneous mycoses

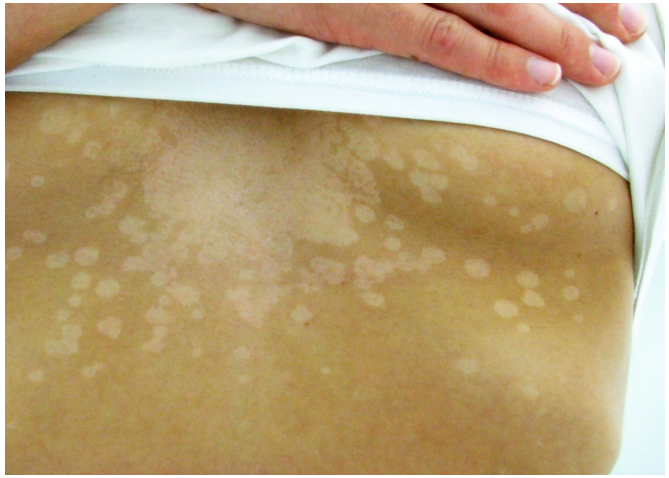
D) Systematic mycoses due to primary pathogens

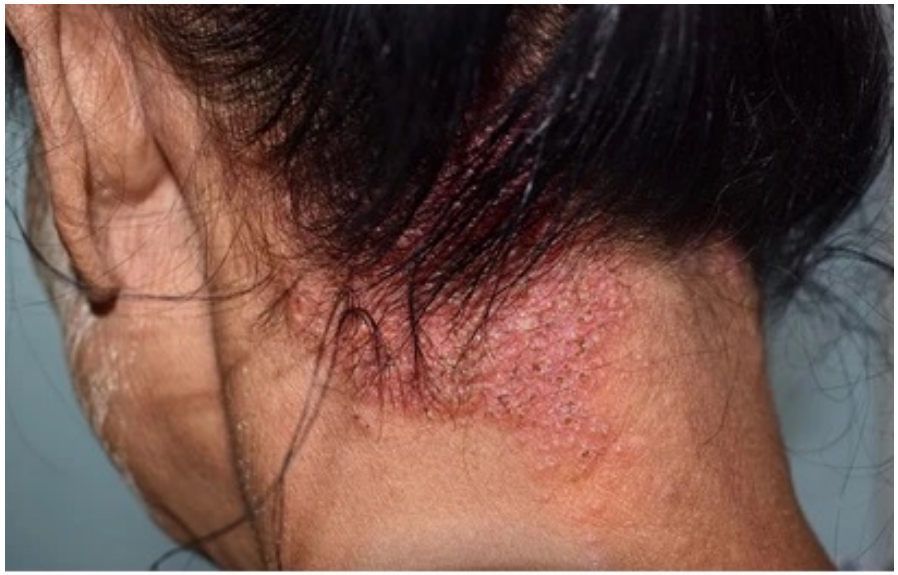
E) Systematic mycoses due to opportunistic pathogens



A. Superficial mycosis:

- occur on outer skin layer
- no immune response
- caused mostly by yeasts
- example of such fungal infection is *Tinea versicolor* and dandruff
- affects skin of young people esp. chest, back, upper arms and legs
- caused by fungus that lives in skin of some adults
- produces spots that are lighter than skin or reddish brown
- become more visible due to
    - high humidity
    - immune and hormone abnormalities
- Almost all people with this very common condition are healthy





B. Cutenous mycoses:

• infect epidermal layers including invasive hair and nail diseases

• may evoke immune response

• restricted to keratinized layers of skin, hair and nails

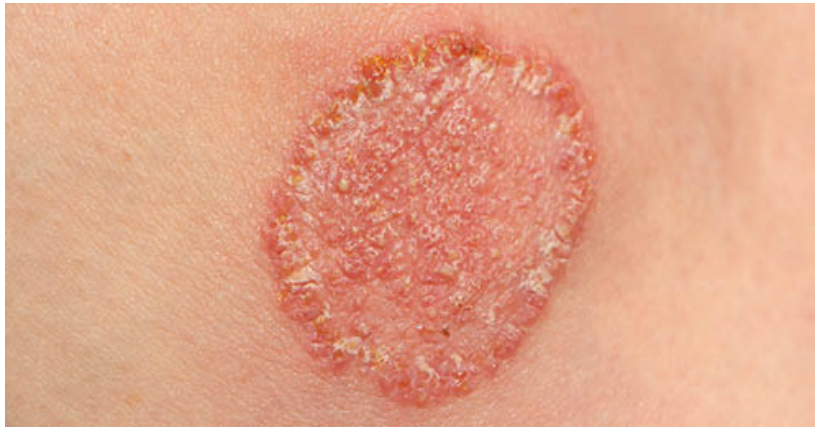
• caused by dermatophytes molds

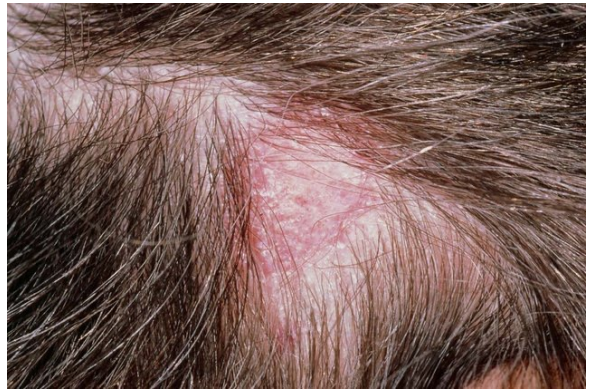
•Tinea (Ringworm, Athlete's foot, jock itch)

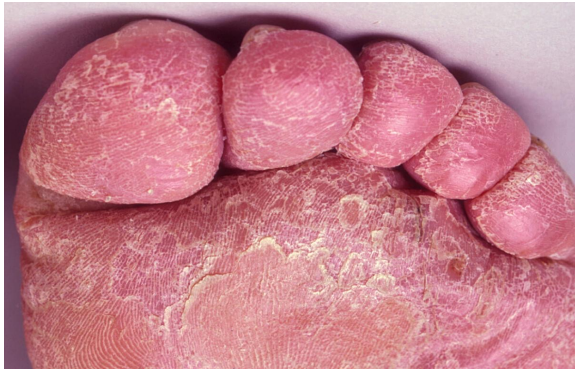
-caused by Dermatophytes (*Trychophytum, Microsporum, Epidermophyton)*

- cutaneous mycoses often called ringworm (but no worm involved)

- one common disease is athlete's foot, commonly affects children before puberty

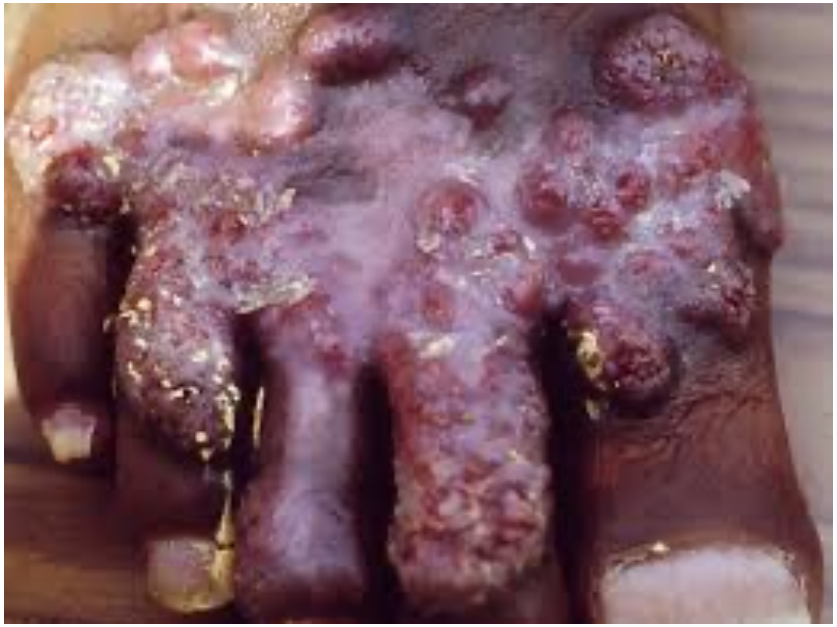






C. Subcutenous mycoses:

- Chronic infection of subdermal tissues including muscle and fascia
- can be initiated by piercing trauma to skin which allows fungi to enter
- may require surgical intervention

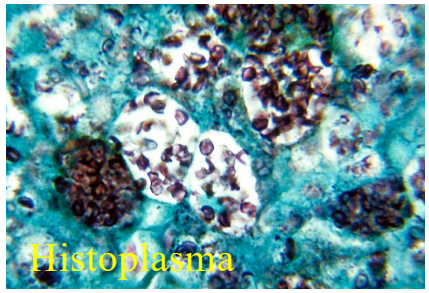


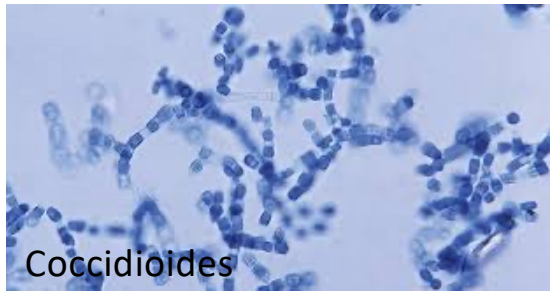
D. Systemic mycoses due to primary pathogens:

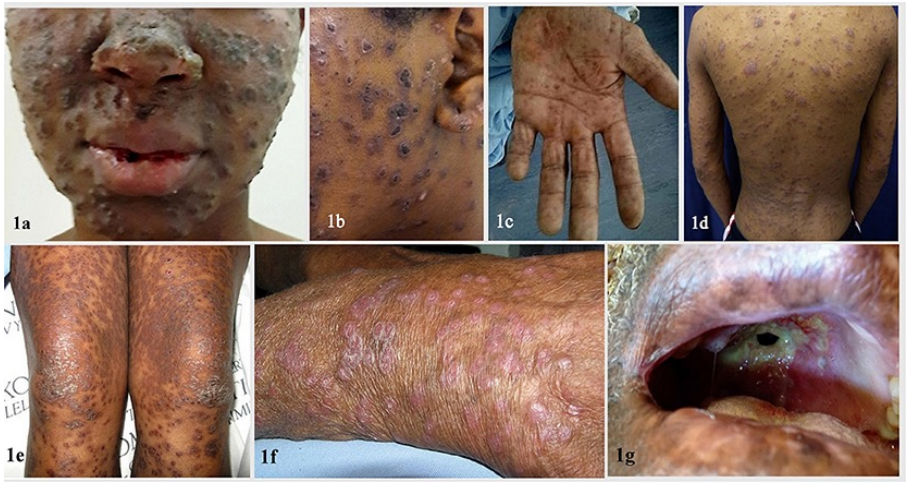
Mostly originating in the lung and may spread to many organ systems

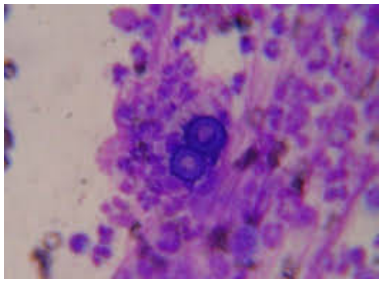
caused by virulent dimorphic fungi

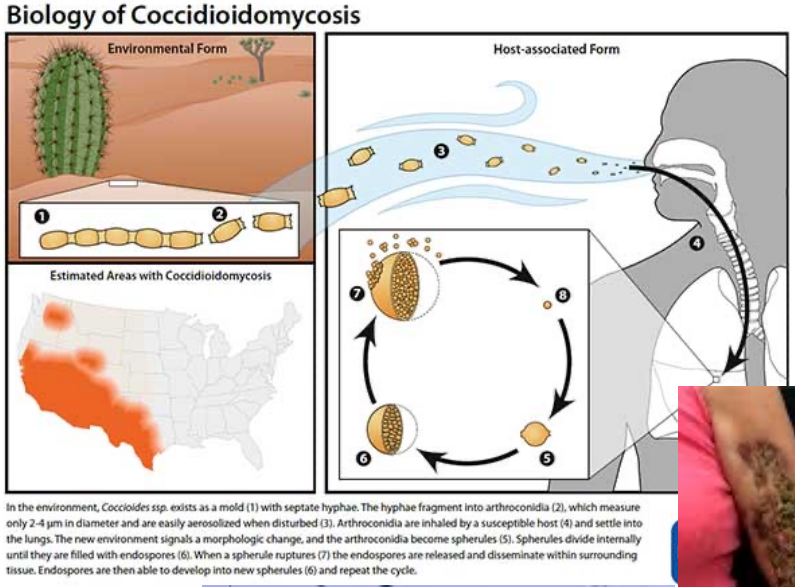
Blastomycosis, Histoplasmosis, Coccodiomycosis, Sporotrichosis





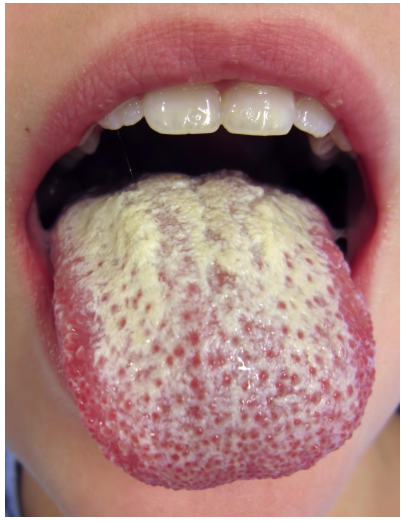


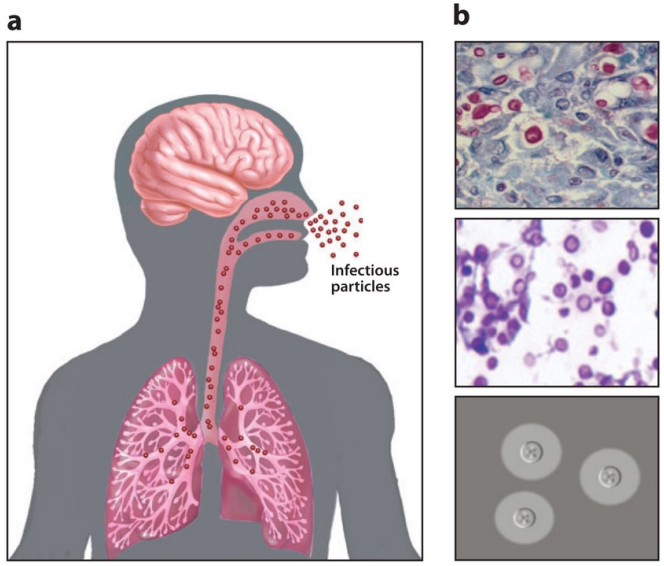


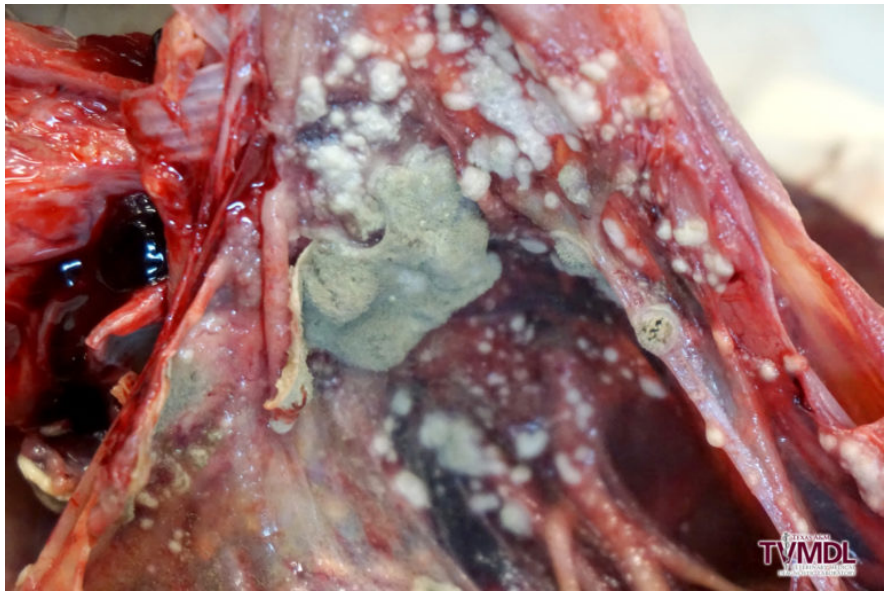


E) Systemic mycoses due to opportunistic pathogens

- infection of patient with immune deficiencies who would other wise not be infected
- conditions that allow to become infected by this mycoses include
  - AIDS
  - alteration of normal flora by antibiotics
  - immunosuppressive therapy
  - metastatic cancer
- eg:- Candidiasis, Cryptococcosis and Aspergillosis







6.5. Fungal disease of plants

- Of all types of plant pathogens, fungi constitute 90%.
- Parasitic fungi; 1-Obligate parasites/ necrotrophes.

  2-Facultative >> / biotrophes.

6.5.1. Fungal pathogens of economically important plants

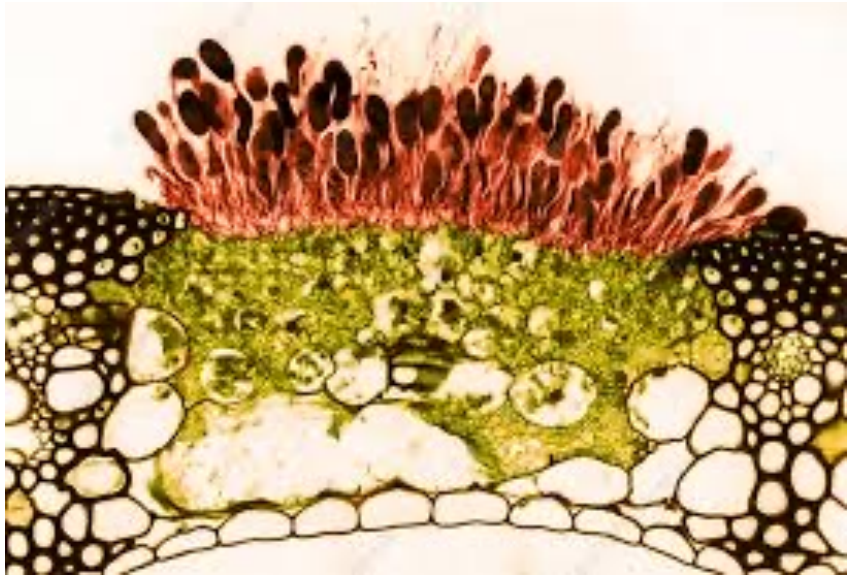
- The most common cereal crops pathogens are ergot, rust, smut,

  ("lebaklet, wage, aremamo")
- Ergot caused by *Claviceps purpurea,* ascomycota, affects grasses, cereals crops:-rye ~barley, oat.
  - Reduce yield and qualities of crops and hay.
  - produce mycotoxins which is toxic to animals & man.
  - Spore dispersal: insects, wind, rain splash,
- Prevention done by-crop rot., deep plough,
- Positive- medicinal aspects.

The rust

- Attacks grains, leaf, mostly form rusty color,
- Basidio., wheat rust called *Puccinia graminis*.
- Two hosts required to complete its life cycle barberry & insects.

Life cycle:-



The smut

- Dirty fungus, basidio., most affect ovaries of cereals

- Significant fungal plant pathogens include:

Ascomycetes

- *Fusarium* spp. (causal agents of Fusarium wilt disease)
- *Thielaviopsis* spp. (causal agents of: canker rot, black root rot, *Thielaviopsis* root rot)
- *Verticillium* spp.
- *Magnaporthe grisea* (causal agent of blast of rice and gray leaf spot in turfgrasses)
- *Sclerotinia sclerotiorum* white mold

Basidiomycetes

- *Ustilago* spp.
- *Rhizoctonia* spp.
- *Phakospora pachyrhizi* (causal agent of soybean rust)
- *Puccinia* spp. (causal agents of severe rusts of virtually all cereal grains and cultivated grasses)
- *Armillaria* spp. (the so-called honey fungus species, which are virulent pathogens of trees and produce edible mushrooms)

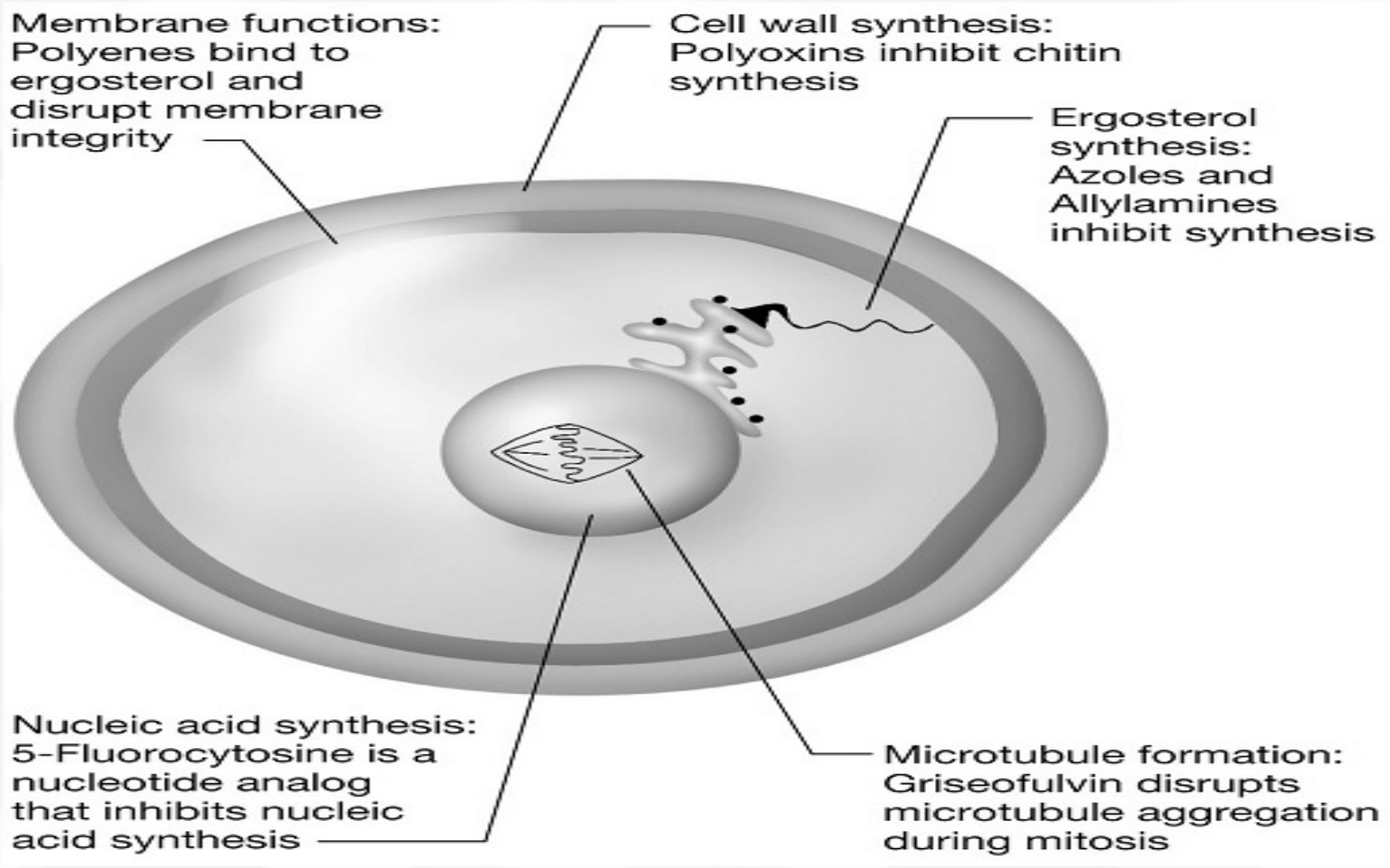
6.6. Antifungal Therapy

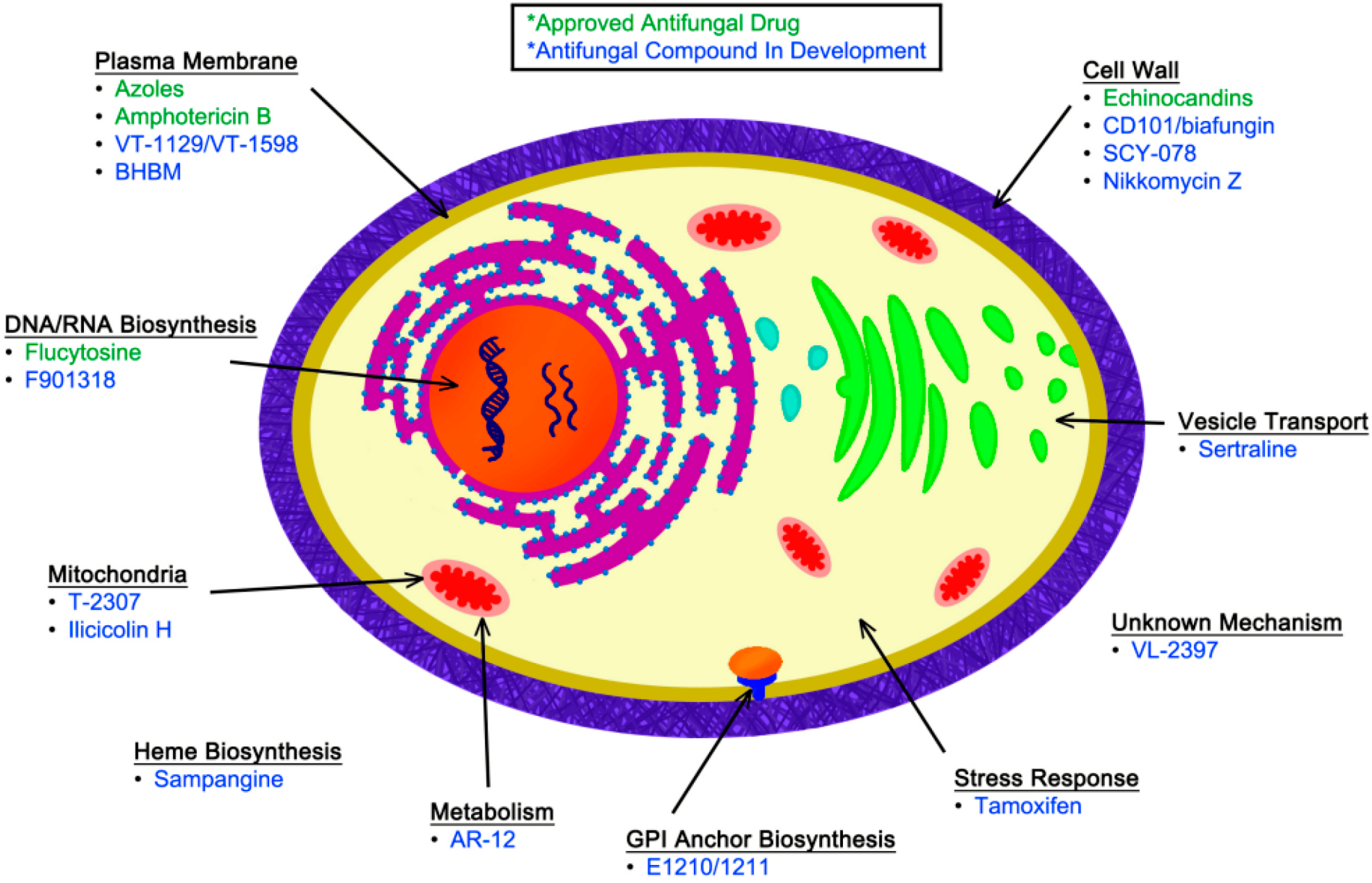
- Fungi, like mammalian cells, are eukaryotic. Therefore, antifungal agents can indiscriminately affect both fungal and host cells.
- Toxic side-effects is always a common during or following chemotherapy with antifungal drugs.
- Eg.Three major classes antifungal therapy : polyenes, azoles and 5-fluorocytosine.
- Based on the mechanism of action and kill cells (fungicidal) or reversibly inhibit their growth (fungistatic).
- Antifungal agents may be naturally derived (antibiotics) or chemically synthesized (synthetic) compounds.

Overview of Antifungal Drugs

	MECHANISM OF ACTION
Polyenes (Amphotericin, Nystatin)	Selectively bind to ergosterol in fungal cell membrane, altering membrane fluidity and producing pores and osmotic cell death. Much less binding to cholesterol.
Azoles (Ketoconazole, Miconazole, Fluconazole, Itraconazole, Voriconazole, Posaconazole)	Selectively block ergosterol synthesis by inhibiting demethylation of lanosterol. Fungal P450 enzyme much more sensitive than mammalian counterpart.
5-Flucytosine	Converted by fungal cytosine deaminase into 5-fluorouracil; inhibits DNA synthesis. Mammalian cells lack cytosine deaminase.
Griseofulvin	Inhibit fungal growth by binding to microtubules, disrupting mitotic spindles. Mammalian microtubules less sensitive.
Echinocandins (Caspofungin, Micafungin, Anidulofungin)	Inhibit fungal Beta glucan synthesis, disrupting cell wall integrity. Mammalian cells have no cell walls.
Allylamines (Terbinafine)	Selectively blocks ergosterol synthesis by inhibiting squalene epoxidase (not found in animals)

Antifungals - Summary




*Approved Antifungal Drug
*Antifungal Compound In Development
Plasma Membrane
• Azoles
• Amphotericin B
• VT-1129/VT-1598
• BHBM
Cell Wall
• Echinocandins
• CD101/biafungin
• SCY-078
• Nikkomycin Z
DNA/RNA Biosynthesis
• Flucytosine
• F901318
Vesicle Transport
• Sertraline
Mitochondria
• T-2307
• Ilicicolin H
Unknown Mechanism
• VL-2397
Heme Biosynthesis
• Sampangine
Metabolism
• AR-12
GPI Anchor Biosynthesis
• E1210/1211
Stress Response
• Tamoxifen