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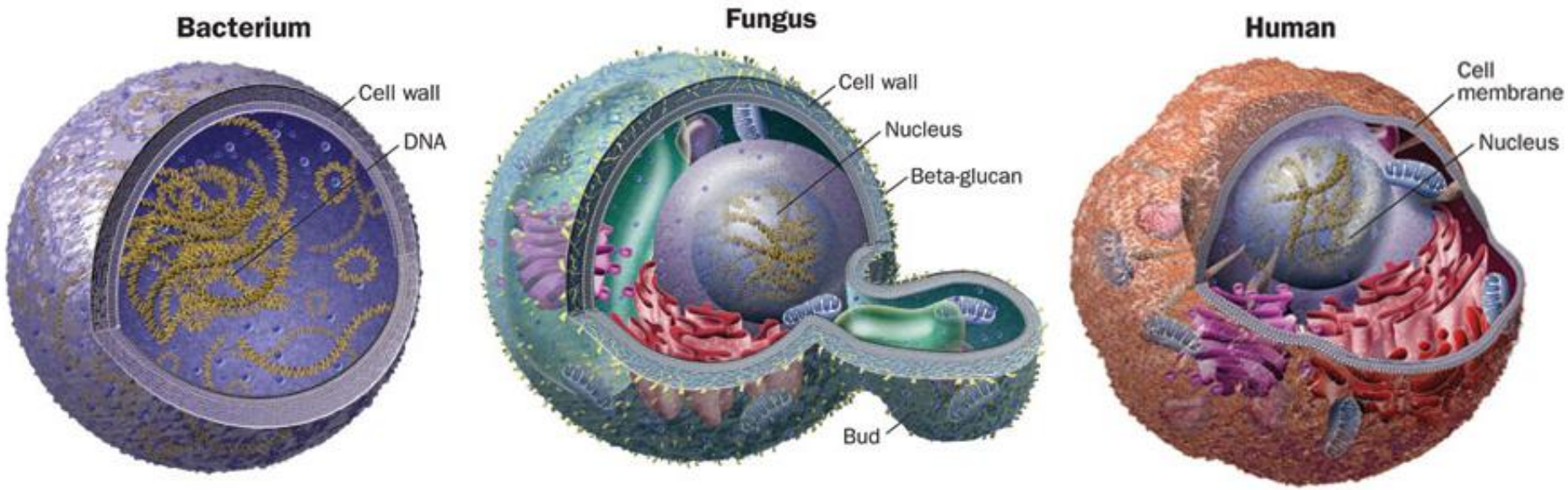
MED

ANTIMYCOTICS


Bacterium
Cell wall
DNA
Fungus
Cell wall
Nucleus
Beta-glucan
Bud
Human
Cell membrane
Nucleus

M U N I
M E D

MYCOSES

↑ Incidence: immunodeficiency, HIV, ...
DM
radiotherapy, chemotherapy, neutropaenic patients

Classification:

pathogen:
- candidosis
- aspergillosis
- cryptococcosis
- zygomycosis

localization:
- systemic
- organ
- mucosal
- skin

Monitoring of disease progression - determination of serum

- Panfungal (1 → 3) - β-D-Glucan
- Galactomannan (aspergillus inf.)

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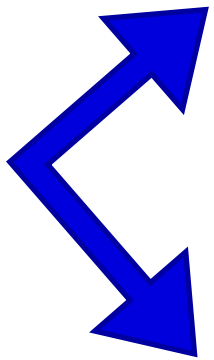
Specific



Systemic

\+

Topical

- polyenes
- azoles
- allylamines
- antimetabolites
- others

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ANTIMYCOTICS

Syntesis of cell wall components

squalene

ALLYLAMINES

squalenepoxidase

oxidosqualene

AZOLES

lanosterol-14α -demethylase

lanosterol

POLYENES

Ergosterol

ECHINOCANDINS

1-3 glukan

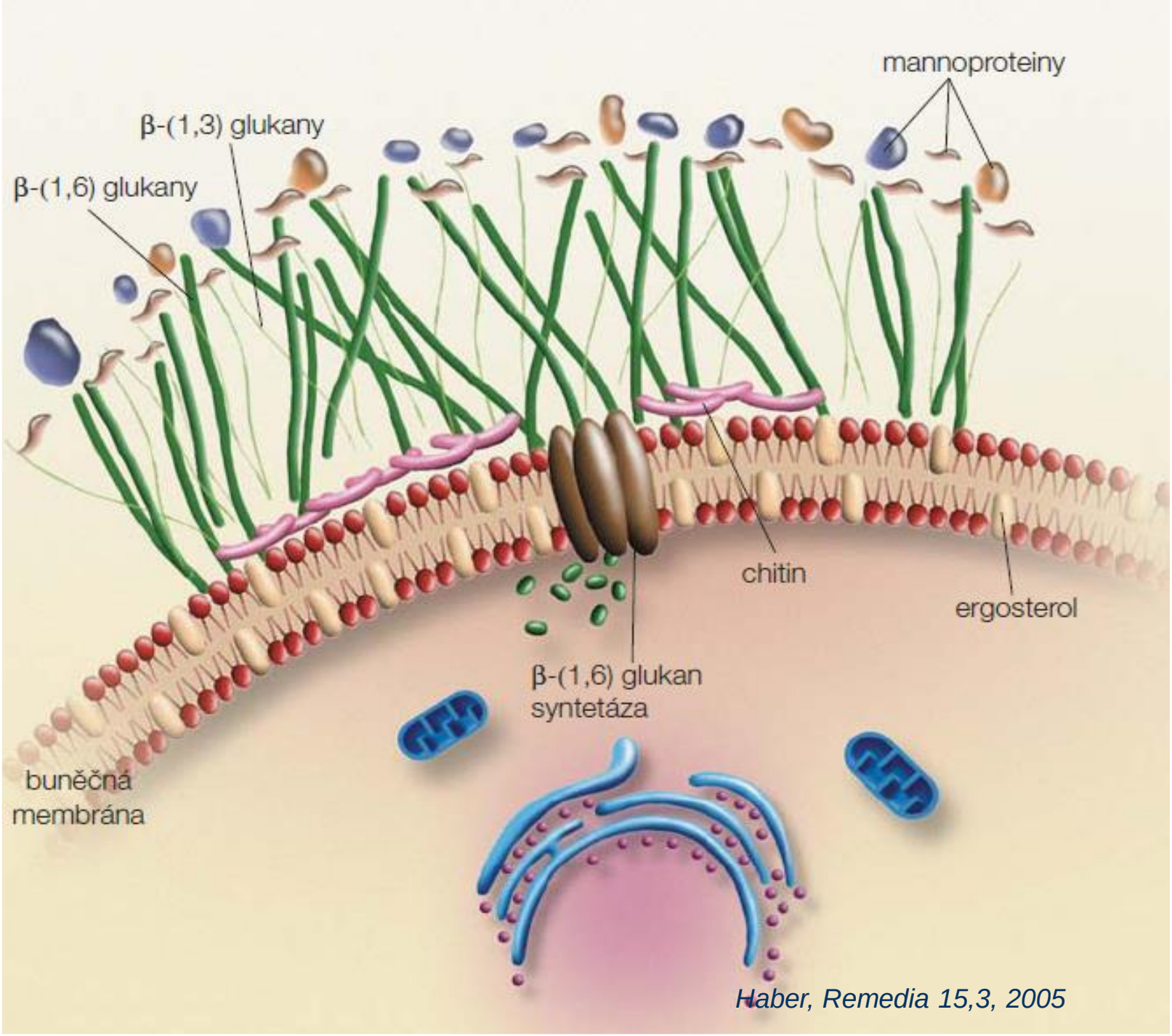
IMPAIRMENT OF MYCOTIC CELLT METABOLISM

HYDROXYPYRIDONE

DERRIVATIVE

ENZYME ACTIVITY
REDOX STABILITY
GENETIC INFORMATION

Ciclopirox



Haber, Remedia 15,3, 2005

Overview of antimycotics

Polyenes	systemic	***amphotericin B***
	topical	***nystatin*** ***natamycin***
Antimetabolites		***flucytosin***
Azoles	systemic	***ketoconazole, miconazole, fluconazole, itraconazole***
	topical	***econazole, clotrimazole, terconazole***
Allylamines	systemic	***terbinafin, naftifin***
others	systemic	***griseofulvin, caspofungin***
	topical	***ciclopiroxolamin, tolnaftate***

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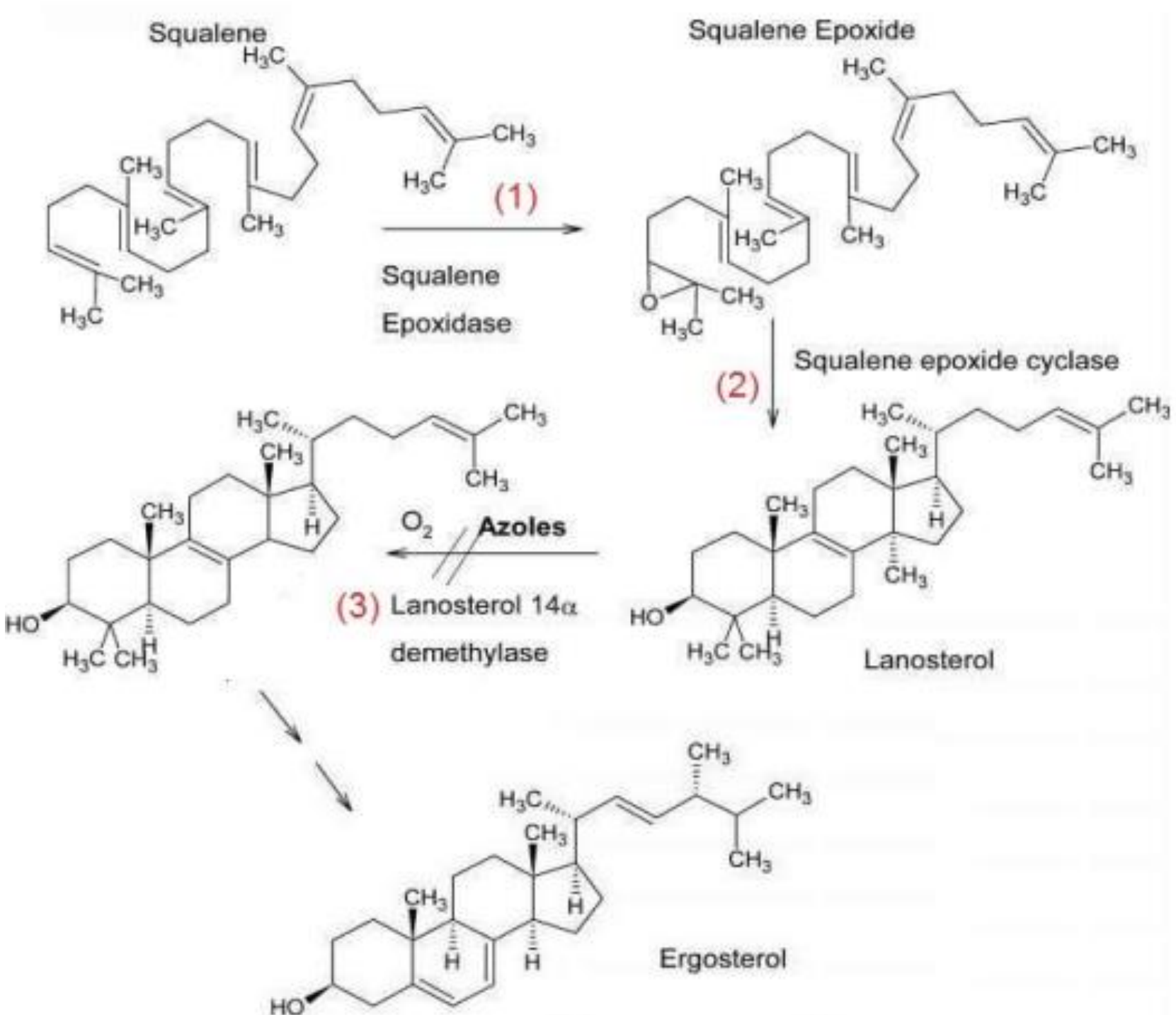
Squalene
Squalene Epoxide
(1)
Squalene
Epoxidase
(2)
Squalene epoxide cyclase
Lanosterol
O_2
Azoles
(3) Lanosterol 14α
demethylase
Ergosterol

POLYENE ANTIMICOTICS

Amphotericin B

- Broadest spectrum, lowest resistance
- Quite highly toxic, most of patients percieve some grade of toxicity/AE
- Durg of choice in aspergiloses

MA: binding to ergosterol in cell wall

Pharmacokinetics: poor GIT bioabailability, administered i.v.- lipidic complex (ABLC)

Toxicity

Acute manifestations: fever, chills, rigor, nausea, vomiting, headache, muscle pain, joint pain, allergies, thrombophlebitis

Chronic manifestations: nephrotoxicity (total dose reversibility) followed by electrolyte imbalance, normocytic normochromic anemia (therapy: erythropoietin)

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TOPICAL POLYENE

Nystatin (*Streptomyces noursei*)

- again yeasts
- p.o. candidiosis in GIT

Natamycine (*Streptomyces natalensis*)

- against candidoses and *Trichomonas* infections

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ANTIMETABOLITES

Flucytosine (5-fluorocytosine)

MA: inhibition of nucleic acid synthesis

- narrow spectrum – cadida, cryptococcus
- amphotericine combined treatment = spectrum widening

AE: granulocytopenia, GIT intolerance

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AZOLES

MA: inhibition of C-14-α-demethylase (CYP450)

IT: CYP and Pgp inhibition !!!

Classification:

topical / systemic

imidazoles / triazoles

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AZOLES

Systemic

Imidazoles:

Miconazole - block of tromboxansynthetase

Ketoconazole - steroidogenesis inhibition

Triazols:

Itraconazole – imunomodulative

Fluconazole

Voriconazole

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AZOLES

topical

Econazol
- also efficient against some bacterias

Clotrimazol
- depo in *stratum corneum*
- hepatic metabolism after absorption

Fenticonazol
Tioconazol

	CYP1A2	CYP2C9	CYP2C8	CYP2C19	CYP2D6	CYP3A4	PgP
Fluconazole	0/?	↓	0/?	↓	0/?	S/↓	0
Itraconazole	0/↑CYP1A1	↓	0	0	0	S/↓	↓
Voriconazole	0	S/↓	0	S/↓	0	S/↓	?
Posaconazole	0	0	0	0	0	↓	S
Ketoconazole	0/?	↓	0/?	↓	0/?	S/↓	S/↓

ECHINOCANDINS

= lipopetides

Caspofungin

MA: inhibition of β-1,3-D-glucan synthesis
(cell wall component of many fungi and yeasts)

- parenteral administration
- synergism when combined with azoles or polyenes
- not metabolized via CYP

I: alternative therapies for severe mycoses (aspergillosis)

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Allylamines

Systemic – **Terbinafine**

MofA: block of squalenepoxidase

- administered orally
- cummulation in the adipose tissue and skin
- synergistic effect with ketoconazole

AE: dyspepsia, loss of apetite

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Griseofulvin

Narrow spectrum, fungistatic
MA: interaction with microtubules – mitotic poison

- administered orally
- cummulation in stratum corneum, hair, nails
- local effect on skin
- I: dermatomycoses

AE: GIT irritation, alergy, leucopenia, hepatotoxicity, nerologic disorders

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Ciclopirox-olamine

topical fungicidal antimycotic agent
+ G+/G- bacteria, mycoplasms, trichomonades
MA: chelates Fe3+ (➡ metaloproteins function abruption)
➡ cytochrom – blocks energy metabolism of the mycotic cell
➡ catalase, peroxidase – block antioxidative protection

Cytoplasmatic membrane – block of transporters
- deplete essent. AA (Leu), nukleotides, ..
antioxidant - scavenger ROS (OH•)
inhibitor AA ➡ inh. Synthesis a LT in human PMN cells
antiinflammatory aktivity in vivo - 2,5 % hydrokortison