Fungal infections

An increasing health problem

✓ Between 1979 and 2000 sepsis caused by fungi increased a 207% in USA.

✓ Deaths due to mycoses in USA increased from 1557 (1980) to 6534 (1997).

✓ Deaths were mainly related to infections by Candida, Aspergillus and Cryptococcus sp.

Fungal infections: Mycoses

**Classification**

- **Superficial**
  - Cutaneous
  - Subcutaneous

- **Systemic**
  - Internal organs

**Main pathogenic fungi**

- **Filamentous fungi**
  - Aspergillus sp.
  - Fusarium sp.
  - Penicillium sp.

- **Dermatophytes:**
  - Tricophyton sp.
  - Microsporum sp.
  - Epidermophyton sp.

- **Yeast**
  - Candida sp.
  - Cryptococcus sp.
Fungal infections

An increasing health problem

Higher incidence related to:

✓ ↑ Immunocompromised population
✓ ↑ Population mobility, with higher exposure to endemic fungal pathogens

Effectiveness of antifungal drug limited by:

✓ Delayed diagnosis
✓ ↑ Antifungal drug resistance
✓ Drug toxicity
✓ Lack of oral and i.v. preparations


Research of antifungal drugs

There is a need for new antifungal agents

✓ New mechanisms of action
✓ Broad spectrum antifungal activity
✓ Fewer dose-limiting side effects
✓ Economic
Research of antifungal drugs

There is a need for new antifungal agents

Why plants?

- Biodiversity ➔ Chemodiversity
- Traditional use
- Field partially explored

How to select the plant?

- Ethnopharmacological selection
- Chemotaxonomic selection
- At random

Drug discovery from plants

Why an ethnopharmacological approach?

- 80% of the people living in developing countries (64% of world population) are almost completely dependent on traditional medical practices.
- Higher plants are the main source of drug therapy in traditional medical systems.
- Ca. 74% of the drugs originated from higher plants were discovered in an ethnopharmacological context.
- Most of these plant-derived drugs are prototypes.
Ethnopharmacology in the development of new medicines

- Used as drug in unmodified state
- New analogues
- Chemical or pharmaceutical leads
- Bioactive molecules
- Scientific basis for the use of the herbal drug or its preparations
- Traditional use validation
- Ethnomedical preparations
- Herbal medicinal products

Ethnopharmacology and the discovery of new biologically active molecules

1. Data collection from indigenous population and data analysis
2. Collection of plant material and botanical identification
3. Literature search
4. Extraction
5. Biological / pharmacological testing
6. Bioguided isolation of active principles
7. Structure identification
Preparation of the extracts

With solvents of increasing polarity
- Dichloromethane
- MeOH 95%

Aqueous decoction

Distillation
- Essential oil

Screening of the antifungal activity

Assessment of the antifungal activity

Antifungigram
Growth inhibition diameters (mm)

Reference drugs:
- Nystatin
- Amphotericin B
Fungal strains

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Af</td>
<td>Aspergillus fumigatus</td>
</tr>
<tr>
<td>An</td>
<td>Aspergillus niger</td>
</tr>
<tr>
<td>Ca</td>
<td>Candida albicans</td>
</tr>
<tr>
<td>Cc</td>
<td>Cladosporium cladosporioides</td>
</tr>
<tr>
<td>Cn</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Fo</td>
<td>Fusarium oxysporum var. pinaster</td>
</tr>
<tr>
<td>Mg</td>
<td>Microsporum gypseum</td>
</tr>
<tr>
<td>Nc</td>
<td>Neurospora crassa</td>
</tr>
<tr>
<td>Pp</td>
<td>Penicillium purpurogenum</td>
</tr>
<tr>
<td>Sc</td>
<td>Saccharomyces cerevisiae</td>
</tr>
<tr>
<td>Tm</td>
<td>Tricophyton mentagrophytes</td>
</tr>
</tbody>
</table>

Ethnopharmacological selection

Paraguay

- Acanthospermum australe
- Acanthospermum hispidum
- Baccharis articulata
- Borreria valens
- Calycophyllum spruceanum var. multiflorum
- Croton gracilipes
- Croton urucurana
- Equisetum giganteum
- Erythrina crista-galli
- Geophila repens
- Maytenus ilicifolia
- Senecio grisebachii
- Tabebuia avellanedae
- Vernonanthura tweedieana

**Extracts selected**

- **Acanthospermum australe**
  - Aerial parts
  - Dichloromethane extract

- **Calycopephyllum spruceanum**
  - Bark
  - Dichloromethane extract

- **Geophila repens**
  - Aerial parts
  - Dichloromethane extract
  - Methanolic extract

- **Vernonanthura tweedieana**
  - Root
  - Dichloromethane extract


---

**Antifungals from plants**

- **33 Species:**
  - Argentina
  - Mexico
  - Peru
  - Paraguay
  - Ecuador

**Screening for antifungal activity**

- Acalypha arvensis
- Acanthospermum
- Croton urucurana
- Croton zehtneri
- Mansoa alliacea
- Andira inermis
- Andira surinamensis
- Baccharis articulata
- Bixa orellana
- Blepharocalyx
- Borneri valens
- Calycophyllum
- Croton gracilipes
- Equisetum giganteum
- Erythrina crista-galli
- Maytenus ilicifolia
- Ocimum micranthum
- Persea laevigata
- Senecio grisebachii
- Tabebuia avellanedae
- Vernonanthura tweedieana

---

**Latin-American species studied**
Antifungals from plants

Bioguided isolation

Preparative Chromatography
CC, CTLC, HSCCC

Extract

Bioautography

Active compounds

Preparative chromatography

Techniques

Solid stationary phase

✓ Column chromatography:
  • Classical column chromatography
  • Flash chromatography
  • Medium pressure liquid chromatography

✓ Planar Chromatography:
  • Thin-layer chromatography
  • Centrifugal thin-layer chromatography

Liquid stationary phase

✓ High-speed counter current chromatography
Bioguided isolation

Bioautography

Active compound
Active compound

1 2 3

Derivatized Reference TLC

Bioautography

Antifungals from plants

Bioguided isolation

Preparative Chromatography
CC, CTLC, HSCCC

Structure elucidation
Spectroscopic techniques:
MS, $^1$H-NMR, $^{13}$C-NMR, UV-Vis

Extract

Bioautography

Analysis of the composition
GC-FID, GC-MS, $^{13}$C-NMR

Active compounds

Minimum inhibitory concentration (MIC)
Microdilution

Minimum fungicidal concentration (MFC)
Extension of the microdilution
Antifungals from plants

Classes of active compounds

- Fatty acids
- Peptides (defensins)
- Alkaloids
- Simple phenols and phenolic acids
- Coumarins
- Flavonoids
- Triterpenes
- Diterpenes
- Sesquiterpenes
- Monoterpines
- Simple phenols and phenolic acids
- Xanthenes
- Quinones
- Lignans

Antifungal fatty acids

Undecylenic acid

A semisynthetic compound

Seeds ➔ Castor oil

Ricinus communis

\[
\text{Triricinoleine}
\]

\[
\text{Ricinoleic acid}
\]

\[
\text{Undecylenic acid}
\]
Antifungal fatty acids

**Calycophyllum spruceanum var. multiflorum** (bark) Paraguay

Mixture of fatty acids

\[
\text{CH}_2\text{O} (\text{CH}_2)_{n} \text{COOH}
\]

Dichloromethane extract (13.80 g) Paraguay

MPLC/Si60; Hexane:EtOAc:MeOH (1:0:0)-(0:1:0)-(0:0:1)

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM-I</td>
<td>0.94</td>
</tr>
<tr>
<td>CM-II</td>
<td>2.44</td>
</tr>
<tr>
<td>CM-III</td>
<td>3.28</td>
</tr>
<tr>
<td>CM-IV</td>
<td></td>
</tr>
<tr>
<td>CM-V</td>
<td></td>
</tr>
<tr>
<td>CM-VI</td>
<td></td>
</tr>
<tr>
<td>CM-VII</td>
<td></td>
</tr>
<tr>
<td>CM-VIII</td>
<td></td>
</tr>
</tbody>
</table>

CC/LH-20; CH₂Cl₂:MeOH (50:50)

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM-VI1…CM-VI3</td>
<td>640</td>
</tr>
<tr>
<td>CM-VI-4</td>
<td>27</td>
</tr>
<tr>
<td>CM-VI-5</td>
<td>27</td>
</tr>
<tr>
<td>CM-VI-6</td>
<td>27</td>
</tr>
</tbody>
</table>
Antifungal fatty acids

*Calycophyllum spruceanum var. multiflorum* (bark) Paraguay

- **CM-VI-4**
  - 640 mg
- 2 x CC-Si60/LH20
- CLC/Si60
  - Mixture of compounds
- Methylated (BF₃/CH₃OH)
- GC-FID / GC-MS

8 Fatty acids

Structure of the fatty acids

**Acetylenic fatty acids**

- \((\text{CH}_2)_n\)
- \(n = 7\) → 6-Hexadecinoic
- \(n = 8\) → 6-Heptadecinoic
- \(n = 9\) → 6-Octadecinoic
- \(n = 10\) → 6-Nonadecinoic
- \(n = 11\) → 6-Eicosinoic

**Saturated fatty acids**

- \((\text{CH}_2)_n\)
- \(n = 7\) → Palmitic
- \(n = 8\) → Heptadecanoic
- \(n = 9\) → Estearic
**Antifungal fatty acids**

*Calycophyllum spruceanum var. multiflorum* (bark) *Paraguay*

**MIC and MFC of the fatty acid mixture (CM-AG) (μg/ml)**

<table>
<thead>
<tr>
<th>Fungi strains</th>
<th>CM-AG</th>
<th>Amphotericin B</th>
<th>Nystatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC</td>
<td>MFC</td>
<td>MIC</td>
</tr>
<tr>
<td>Ca</td>
<td>-</td>
<td>-</td>
<td>0.16</td>
</tr>
<tr>
<td>Cn</td>
<td>-</td>
<td>-</td>
<td>0.16</td>
</tr>
<tr>
<td>Mg</td>
<td>0.25</td>
<td>0.25</td>
<td>0.31</td>
</tr>
<tr>
<td>Sc</td>
<td>-</td>
<td>-</td>
<td>0.16</td>
</tr>
<tr>
<td>Tm</td>
<td>0.25</td>
<td>0.25</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**Antifungal isoflavones**

*Andira surinamensis* (bark) *Ecuador*

Biochanin A

Genistein
Antifungal caffeic acid derivative

**Geophila repens** (aerial parts) Paraguay

Antifungal lignans

**Piper fulvescens** (leaf) Paraguay

---

Portillo et al. (2004) 2nd Int. IOCD-CYTED, Sao Pedro (Brasil)


---

### MIC (µg/mL)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ca</th>
<th>Cn</th>
<th>Mg</th>
<th>Sc</th>
<th>Tm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 256</td>
<td>&gt; 256</td>
<td>&gt; 256</td>
<td>&gt; 256</td>
<td>&gt; 256</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 256</td>
<td>&gt; 256</td>
<td>0,5</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>16</td>
<td>16</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fungi strains</th>
<th>A</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0,0625</td>
<td>0,125</td>
</tr>
<tr>
<td></td>
<td>0,05</td>
<td>0,5</td>
</tr>
</tbody>
</table>
**Antifungal triterpenes**

**Saponins from Solanum chrysotrichym**

![Image of Solanum chrysotrichym](image)

Leaves ➔ MeOH extract ➔


---

**Antifungal triterpenes**

**Saponins from Solanum chrysotrichym**

**Double blind RCT on Tinea pedis**

External application, 4 weeks, n= 101

**Verum**: Standardised extract of S. chrysotrichym

**Control**: ketoconazole (2%)

**Clinical efficacy**: 96.1% (S. chrysotrichym)
91.7% (Ketoconazole)

**Mycological efficacy**: 78.4% (S. chrysotrichym)
77.8% (Ketoconazole)

**Tolerability**: Both treatments were well tolerated in 100% of the patients

Antifungal triterpenes

Saponins from *Solanum chrysotrichym*

**Other clinical studies**

Double blind RCT on *Pityriasis capitis* (dandruff)
Efficacy: 92.2%
No differences to ketoconazole group

**Exploratory study on Candida sp.-associated vaginal infection**

Efficacy:
- Extract (125 mg/suppository): 57.1%
- Ketoconazole (400 mg/suppository): 72.5%


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Antifungal triterpenes

*Bixa orellana* (leaf)

Ecuador

![Chemical structure of 2α,3β-alphytolic acid](image)

Antifungal diterpenes

*Acanthospermum australe* (leaf) Paraguay

![Acanthoastralide](image)


### MIC and MFC (μg/mL) of acanthoastralide (AA-B)

<table>
<thead>
<tr>
<th>Fungi strains</th>
<th>AA-B</th>
<th>Amphotericin B</th>
<th>Nystatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC</td>
<td>MFC</td>
<td>MIC</td>
</tr>
<tr>
<td><em>Ca</em></td>
<td>8</td>
<td>16</td>
<td>0.16</td>
</tr>
<tr>
<td><em>Cn</em></td>
<td>2</td>
<td>4</td>
<td>0.16</td>
</tr>
<tr>
<td><em>Mg</em></td>
<td>8</td>
<td>8</td>
<td>0.31</td>
</tr>
<tr>
<td><em>Sc</em></td>
<td>4</td>
<td>8</td>
<td>0.16</td>
</tr>
<tr>
<td><em>Tm</em></td>
<td>2</td>
<td>2</td>
<td>0.63</td>
</tr>
</tbody>
</table>

### Antifungal sesquiterpene derivatives

**Vernonanthura tweedieana** (leaf) Paraguay

![Image of the plant](image)

**Chemical Structure:**

![Chemical structure image](image)

6-Cinnamoyl-1-hidroxy-eudesm-4-en-3-one


### MIC and MFC (µg/mL) of 6-cinnamoyl-1-hydroxy-eudesm-4-en-3-one (VT-E)

<table>
<thead>
<tr>
<th>Fungi strains</th>
<th>VT-E</th>
<th>Amphoterin B</th>
<th>Nystatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC</td>
<td>MFC</td>
<td>MIC</td>
</tr>
<tr>
<td>Ca</td>
<td>16</td>
<td>32</td>
<td>0.16</td>
</tr>
<tr>
<td>Cn</td>
<td>8</td>
<td>8</td>
<td>0.16</td>
</tr>
<tr>
<td>Mg</td>
<td>8</td>
<td>8</td>
<td>0.31</td>
</tr>
<tr>
<td>Sc</td>
<td>8</td>
<td>16</td>
<td>0.16</td>
</tr>
<tr>
<td><em>Tm</em></td>
<td>4</td>
<td>4</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Essential oils

Chemodiverse mixtures

- (Hemiterpenes)
- Monoterpenes
- Sesquiterpenes
- (Diterpenes)
- Fenilpropanoids
- C6-C1 aromatic compounds
- Aliphatic compounds
- Etc...

- Saturated
- Unsaturated
- Aromatic
- Monocyclic
- Bicyclic
- Tricyclic
- Alcohols
- Phenols
- Esters
- Etc...

Essential oil analysis

Plant material

Essential oil

GC
GC-MS
GC-FTIR
13C-NMR
CC

Retention indices
Mass spectra
IR spectra
NMR spectrum of the mixture
Isolation MS, NMR, IR

Identification of compounds
Essential oil analysis by $^{13}$C-NMR

- Library of $^{13}$C-NMR spectra
- Essential oil
- $^{13}$C-NMR spectrum of the essential oil
- Identification of compounds
  - Number of signals observed
  - $\Delta\delta$ between signal in oil and reference
  - Number of overlapped signals
- Computer processing

Antifungal essential oils

*Piper amalago* (spike, leaf, stem) Panama

 Identified: > 95%
40 Constituents

Vila et al. (2002) 50th GA Congress, Barcelona (Spain).
Antifungal essential oils

Piper amalago (spike, leaf, stem) Panama

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Fungi strains</th>
<th>MIC (µg/ml) of compounds 1, 2, 3 and 4.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ca</td>
<td>Cl</td>
</tr>
<tr>
<td>1</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>256</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>&gt;256</td>
<td>128</td>
</tr>
<tr>
<td>4</td>
<td>&gt;256</td>
<td>&gt;256</td>
</tr>
<tr>
<td>A</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>N</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Ca: Candida albicans
Cl: Candida lactis-condensi
Sc: Saccharomyces cerevisiae
A: Amphotericin B
N: Nystatin

2-Hexanoyl-3-hydroxycyclohex-2-enone (1)
2-Octanoyl-3-hydroxycyclohex-2-enone (2)
2-Decanoyl-3-hydroxycyclohex-2-enone (3)
2-Dodecanoyl-3-hydroxycyclohex-2-enone (4)

Freixa et al. (2005) 53th GA Congress, Florence (Italy).

Essential oils with antimicrobial activity

Applications in the infections of skin and mucous membrane

✓ Acne
✓ Onychomycosis
✓ Vaginal infections
✓ Gingivitis
✓ Teeth and gums health care
Antifungal activity

Essential oil constituents

![Diagram of essential oil constituents]

Tea tree oil

*Melaleuca alternifolia* Cheel

leaf

Essential oil content in the fresh herbal drug: 1-2%

<table>
<thead>
<tr>
<th>Essential oil</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terpinen-4-ol</td>
<td>(30-48%)</td>
</tr>
<tr>
<td>1,8-Cineol</td>
<td>(≤ 15%)</td>
</tr>
<tr>
<td>Terpinen-4-ol</td>
<td>(30-48%)</td>
</tr>
</tbody>
</table>
# Tea tree oil

## Indications and preparations

<table>
<thead>
<tr>
<th>Topical use</th>
<th>Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infections of skin and mucous membranes:</td>
<td>✔ Unguents</td>
</tr>
<tr>
<td>✔ Acne</td>
<td>✔ Creams</td>
</tr>
<tr>
<td>✔ Onychomycosis</td>
<td>✔ Gels</td>
</tr>
<tr>
<td>✔ Furunculosis</td>
<td>✔ Shampoos</td>
</tr>
<tr>
<td>✔ Vulvovaginitis</td>
<td>✔ Liquid soap for intimae hygiene</td>
</tr>
<tr>
<td>• Wounds</td>
<td></td>
</tr>
<tr>
<td>• Burns</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical trial in candidiasic vaginitis**

**Topical treatment of women with candidiasic vulvovaginitis**

<table>
<thead>
<tr>
<th>Design</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>➞ Number of patients: 28</td>
<td>85% patients symptom free</td>
</tr>
<tr>
<td>➞ Duration: 90 days</td>
<td>77% patients free of <em>C. albicans</em></td>
</tr>
<tr>
<td>➞ 200 mg/day essential oil</td>
<td></td>
</tr>
</tbody>
</table>

Belaïche 1988
**Thymol and carvacrol**

**Antibacterial mechanism**

- Damage to the membrane integrity:
  - ↑ Permeability
  - ↑ pH alteration
  - Loss of inorganic ions
- ↓ Intracellular ATP

**Antifungal essential oils**

**Mechanisms**

- Degradation of cell wall
- Damage to the cytoplasmic membrane
- Inhibition of germ tube formation
- ↓ Ergosterol biosynthesis

*Candida albicans* untreated (a) and treated (b and c) with the essential oil of *Ocimum gratissimum* (main constituent: eugenol)

Antifungal essential oils

Synergism among constituents

Table 4  Checkerboard assay of combinations of the four major components of *Thymus* (thymol, 1,8-cineole, *p*-cymene and carvacrol)

<table>
<thead>
<tr>
<th></th>
<th>C. albicans M1</th>
<th>C. krusei H9</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymol/Cineole</td>
<td>0.125</td>
<td>0.125</td>
<td>Synergy</td>
</tr>
<tr>
<td>Thymol/<em>p</em>-Cymene</td>
<td>0.125</td>
<td>0.125</td>
<td>Synergy</td>
</tr>
<tr>
<td>Thymol/Carvacrol</td>
<td>0.500</td>
<td>0.500</td>
<td>Indifferent</td>
</tr>
<tr>
<td><em>p</em>-Cymene/Carvacrol</td>
<td>0.500</td>
<td>0.500</td>
<td>Indifferent</td>
</tr>
<tr>
<td>Carvacrol/Cineole</td>
<td>0.250</td>
<td>0.250</td>
<td>Synergy</td>
</tr>
<tr>
<td><em>p</em>-Cymene/Cineole</td>
<td>0.250</td>
<td>0.250</td>
<td>Synergy</td>
</tr>
</tbody>
</table>

MIC was determined by the macrodilution technique.


---

Antifungal essential oils

Synergism between estragole and ketoconazole

Figure 1. Time-kill curves of ketoconazole (MIC) in combination with estragole in concentration of 1/2 MIC (a) and MIC (b) against *C. albicans*. The fungal suspensions were cultured with estragole alone (○), ketoconazole alone (□), and ketoconazole plus estragole (●) with 30 μl of Tween 80 in all cultures. Data were compared with control (○).

Antifungal essential oils

**Plinia cerrocampanensis** *Leaf*

**Zuccagnia punctata** *Aerial part*

**Ferula hermonis** *Root*
Al-Ja’fari *et al.* (2011) Phytochemistry, 72: 1406-1413

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Antifungal essential oils

**Ferula hermonis** *(root)*  
Lebanon/Syria

- Used in the Middle East to improve sexual behaviour in the treatment of frigidity and impotence.
- Several *Ferula* sp. are traditionally used for the treatment of skin infections.

Shirsh-el-Zallouh

Antifungal essential oils

Ferula hermonis (root)  Lebanon/Syria

Constituents of the essential oil

Identified: > 90% (79 constituents)

Major constituents:
α-Pinene (43.3 %)
α-Bisabolol (11.1 %)
3,5-Nonadiyne (4.4 %) (1)

Other constituents:
Jaeschkeanadiol derivatives:
Jaeschkeanadiol (1.9 %)
Jaeschkeanadiol benzoate (1.9 %) (2)
Jaeschkeanadiol angelate (0.1 %) (3)

Al-Ja’fari et al. (2011) Phytochemistry, 72: 1406–1413

Antifungal essential oils

Ferula hermonis (root)  Lebanon/Syria

MIC and MFC (µg/ml) of the active constituents and fractions

<table>
<thead>
<tr>
<th>Substance</th>
<th>M. gypseum</th>
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<th></th>
<th>T. mentagrophytes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MIC</td>
<td>MFC</td>
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<tr>
<td>α-Pinene</td>
<td>32</td>
<td>32</td>
<td>64</td>
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<tr>
<td>α-Bisabolol</td>
<td>16</td>
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<tr>
<td>Nonadiyne</td>
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<td>trans-Verbenol</td>
<td>32</td>
<td>32</td>
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<tr>
<td>α-Bisabolol oxide</td>
<td>64</td>
<td>128</td>
<td>64</td>
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<tr>
<td>Jaeschkeanadiol benzoate 73%</td>
<td>64</td>
<td>128</td>
<td>0.25</td>
<td>0.25</td>
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<tr>
<td>Jaeschkeanadiol angelate</td>
<td>32</td>
<td>64</td>
<td>32</td>
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<tr>
<td>Spathulenol 50%</td>
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<td>Amphotericin B</td>
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<td>Nystatin</td>
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<td>Ketokonazole</td>
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<td>Clotrimazol</td>
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Al-Ja’fari et al. (2011) Phytochemistry, 72: 1406–1413
Antifungal compounds from plants

Conclusions

• Fungal infections are still an unsolved health problem.
• There is a need of new antifungal agents.
• Plants offer a good opportunity for new developments.
• Unsaturated fatty acids, triterpene derivatives and essential oils have been shown as promising groups.
• There is a limited knowledge on mechanisms, pharmacokinetics and clinical profile.

International cooperation on antifungals

<table>
<thead>
<tr>
<th>Country</th>
<th>Institution</th>
<th>Researcher</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARGENTINA</td>
<td>Universidad de Rosario</td>
<td>S. Zacchino</td>
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<td>BRASIL</td>
<td>Universidade Bandeirante de São Paulo</td>
<td>S. Mendonca</td>
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<td>ECUADOR</td>
<td>Fundación Hábitat Siglo XXI</td>
<td>F. Chia</td>
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<td>FRANCE</td>
<td>Université de Corse/CNRS</td>
<td>J. Casanova, F. Tomi</td>
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<td>PANAMA</td>
<td>Universidad de Panamá</td>
<td>M.P. Gupta</td>
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<td>PARAGUAY</td>
<td>Universidad Nacional de Asunción</td>
<td>E. Ferro</td>
</tr>
<tr>
<td>PORTUGAL</td>
<td>Universidade de Coimbra</td>
<td>L. Salgueiro</td>
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</table>
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