Fungal Secondary Metabolites Through The Lens Of Climate Change

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The 1st African Fungus Day
25.05.2022

Fungi: Key element to the functioning of the planet's ecosystems

Fow of energy and carbon through ecosystems,
Mineral nutrient cycling and soil.

Fungi as Earth's natural internet

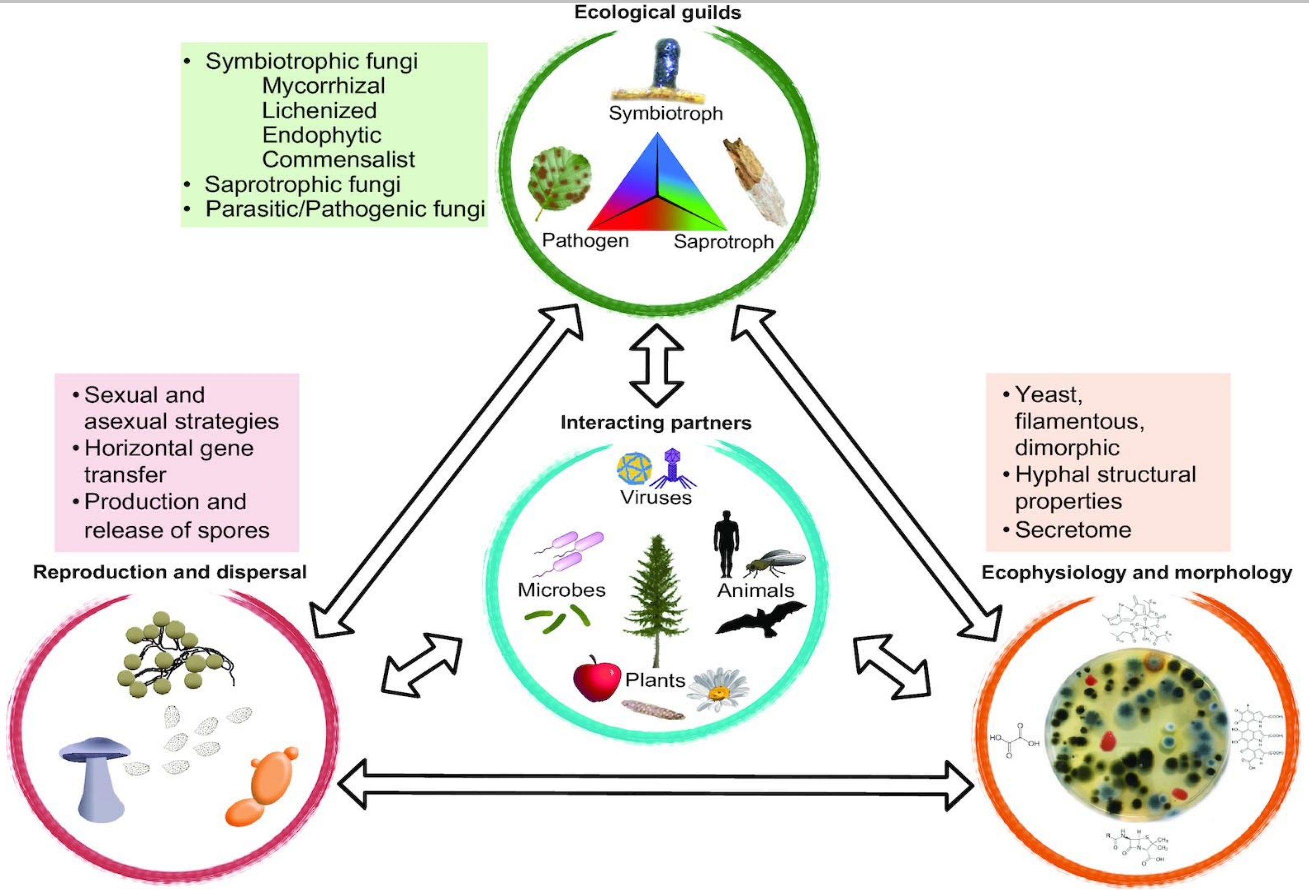


Fig. Proposed triangle of fungal traits that are integral to their success as organisms and as links between organisms and across ecosystems.

Bahram and Netherway (2022) Fungi as mediators linking organisms and ecosystems. FEMS Microbiol Rev, 46 (2). 1-16

Climate change

Atmosphéric CO_2 ↗ → Rise of Earth's temperature
Global warming

Affects the evolution of species
and their ability to adapt to, migrate between, and reside within ecosystems. x

Climate change effects and fungal response

Physiology

Change in Life cycle and sporulation

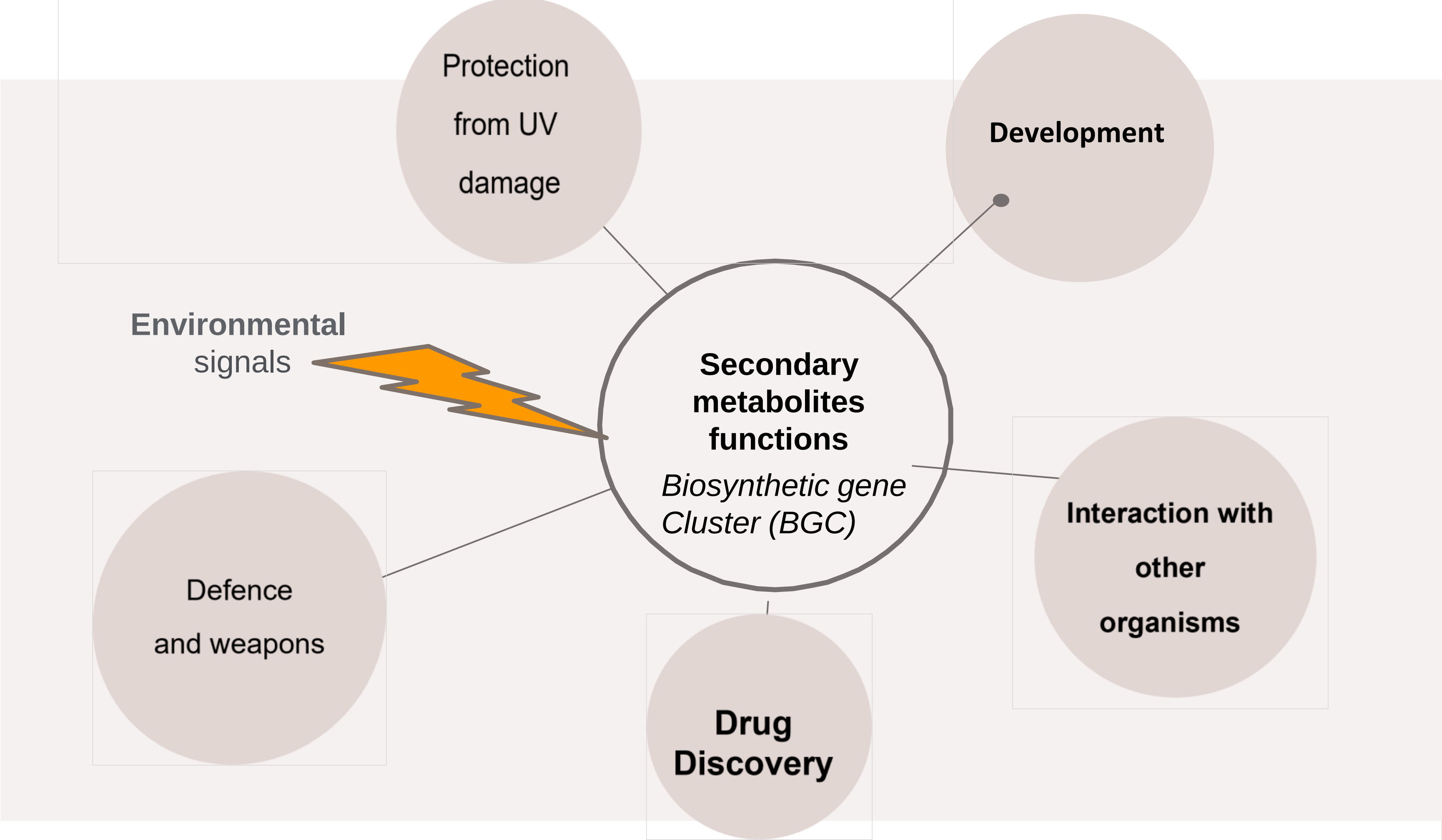
Fungal response

Direct effect

Organisms responses

Direct effect

FUNGI


Protection from UV damage
Development
Environmental signals
Secondary metabolites functions
Biosynthetic gene Cluster (BGC)
Defence and weapons
Interaction with other organisms
Drug Discovery

Fungal climate change response

Melanization

Photoprotection

Fungal cell-wall Strength (Deep penetration into soil to access to water

Factor of Fungal Pathogenesis

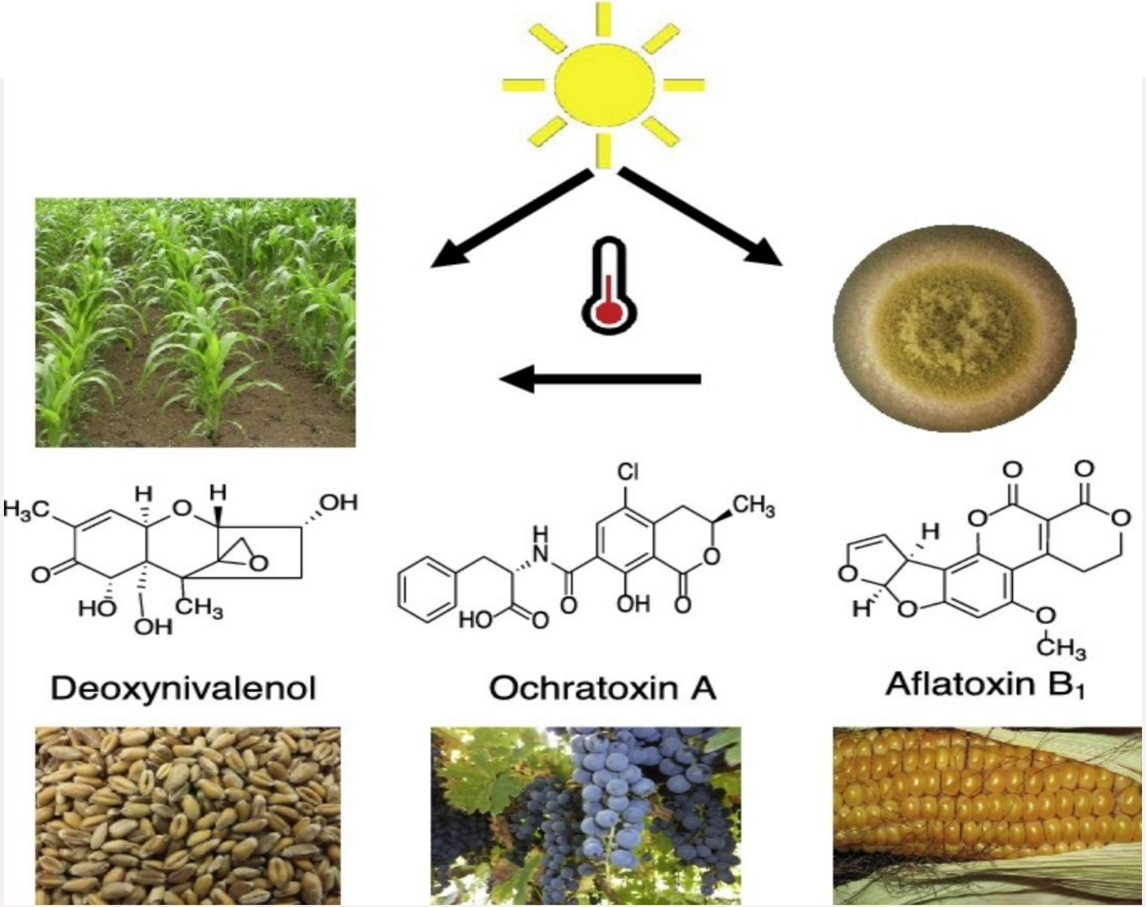
Protection from UV damage

- **Melanin (secondary metabolites =fungal cell wall or or secreted into the environment)**
- Polymerization of phenolic or indolic monomers (Dark color).
- Synthesized during spore formation for deposition in the cell wall.

Fungal climate change response

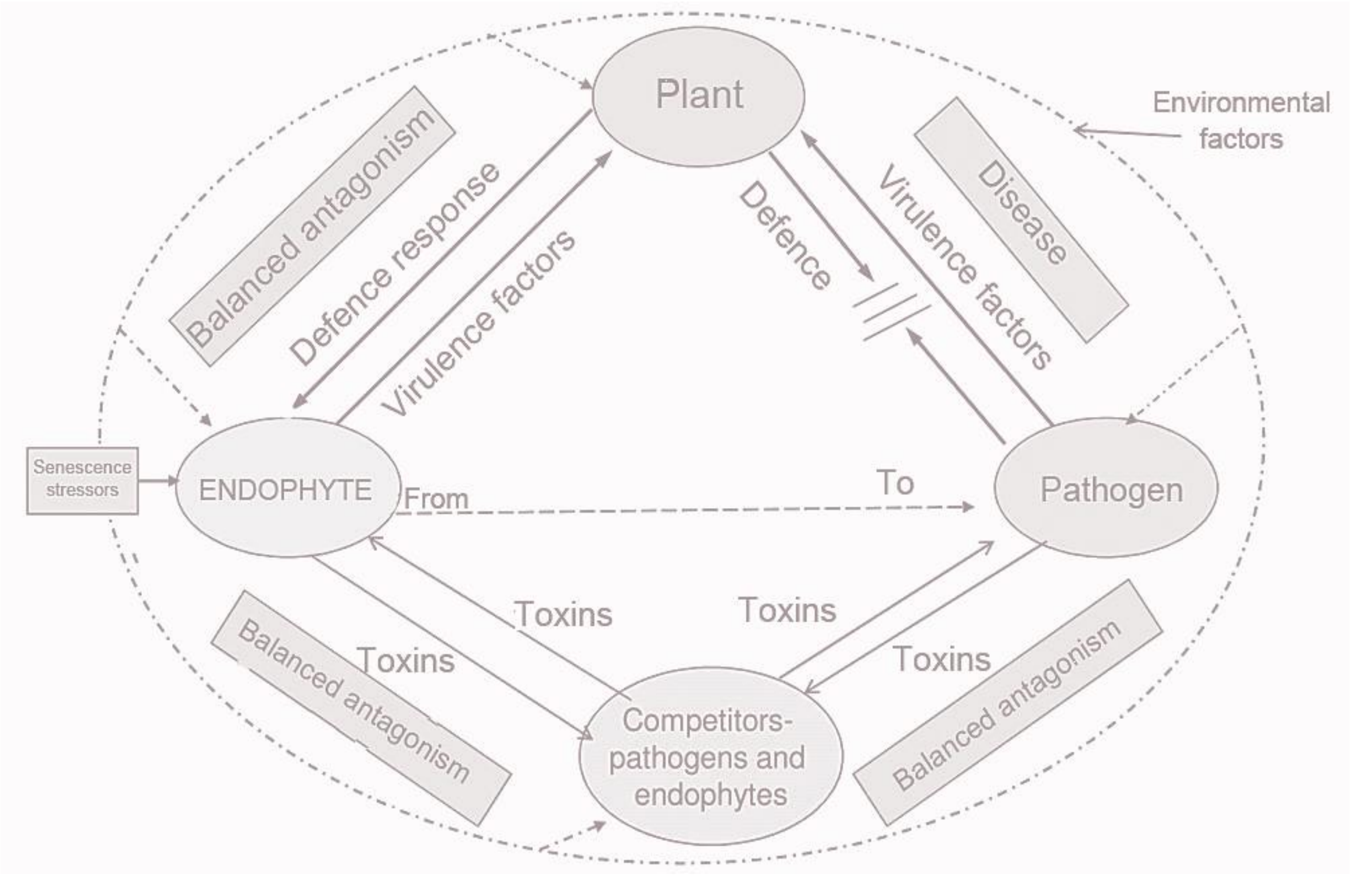
Mycotoxins

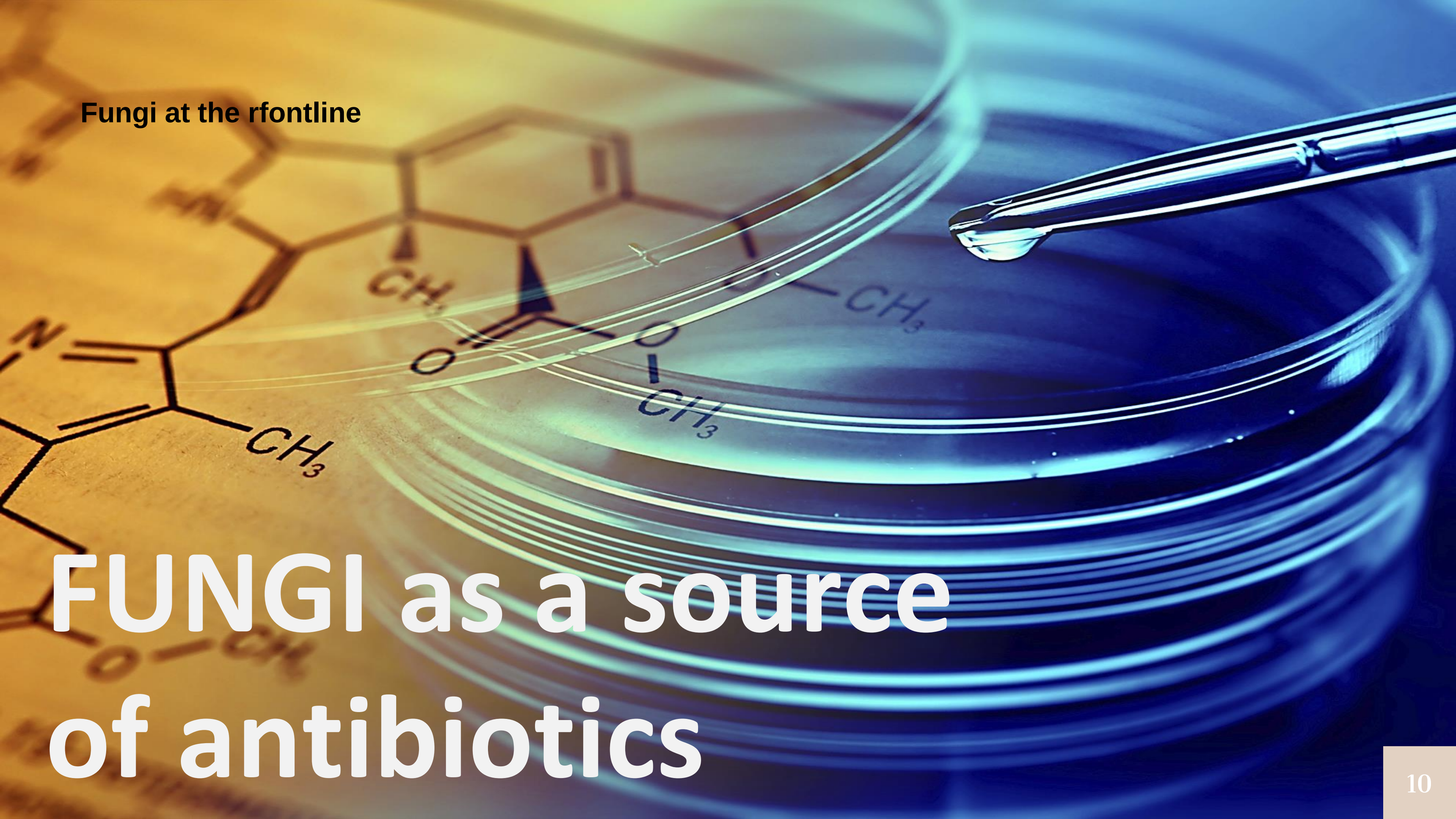
Defence and weapons



Medina et al., 2017. Impact of global warming on mycotoxins. *Current Opinion in Food Science* 18: Pages 76-81

Fungal endophytes- plant relashionship = Balanced antagonism





FUNGI as a source of antibiotics

Definition of antibiotic

“

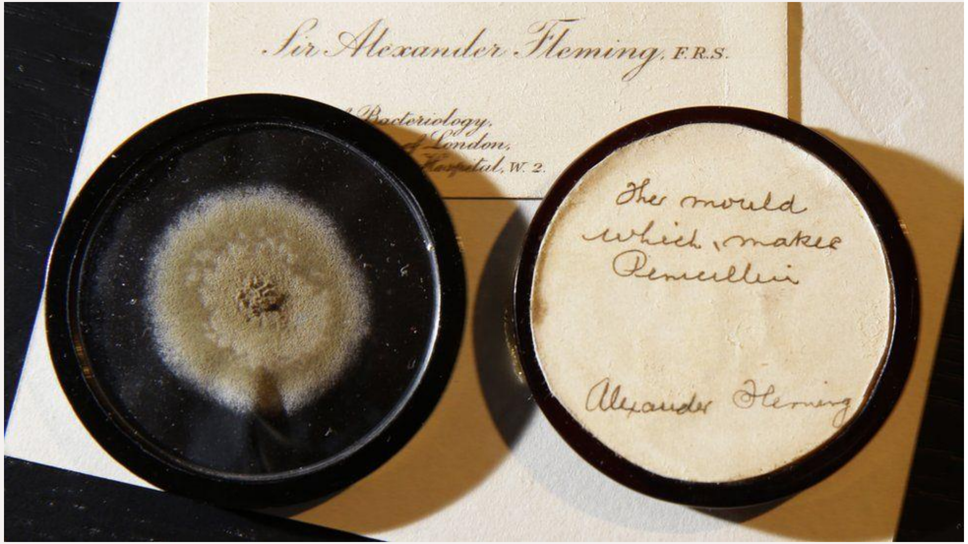
a chemical substance, produced by micro-organisms (including fungi), which has the capacity to inhibit the growth of and even to destroy bacteria and other micro-organisms

Waksman, 1947

Stating point of the era of antibiotic chemotherapy

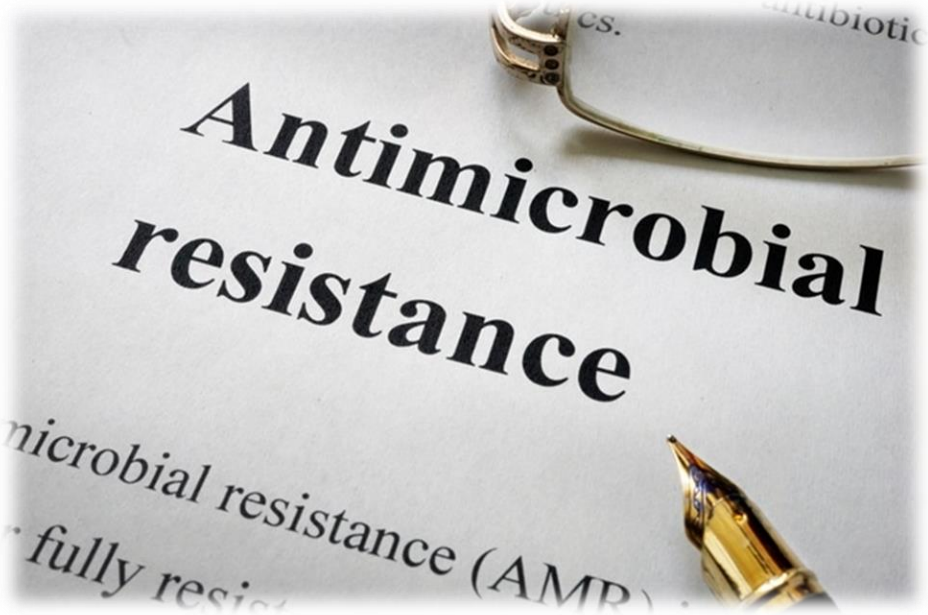
Discovery of Penicillin by Alexander Fleming (1928)

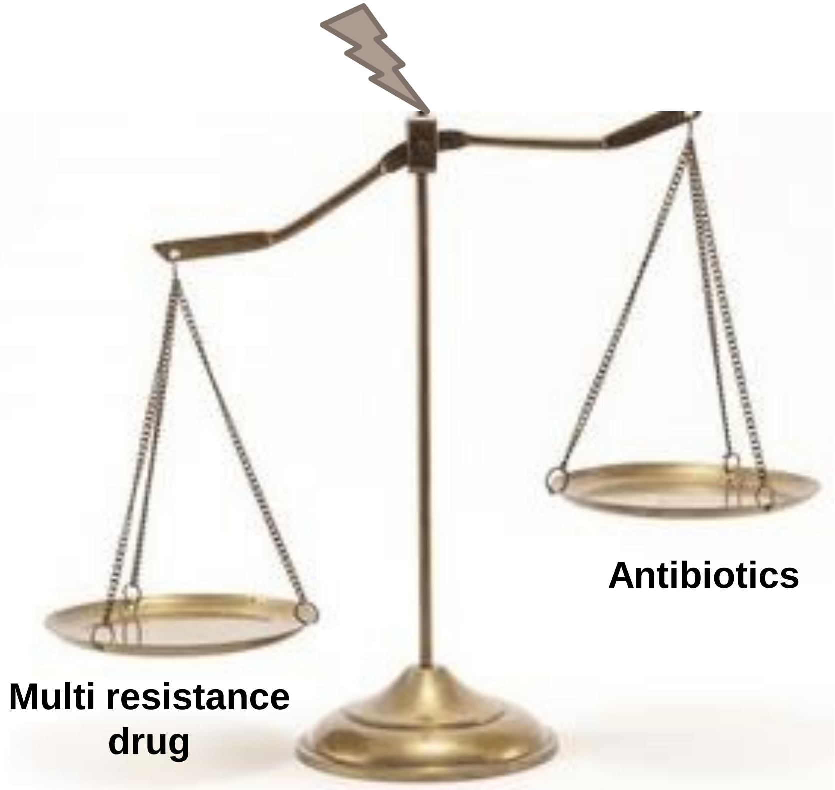
Penicillium notatum



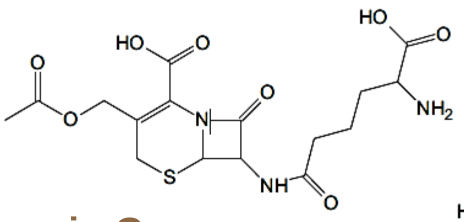
« Golden ages » of antibiotics (1950s to the 1970s)

“Post-antibiotic” era

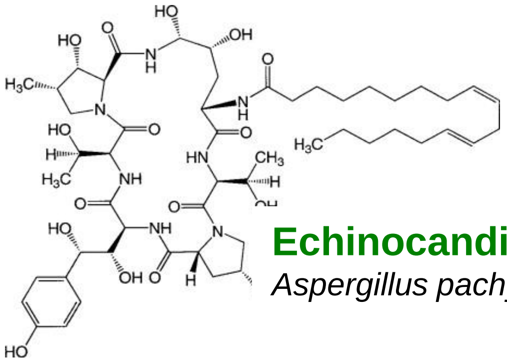




Antibiotics produced by Fungi

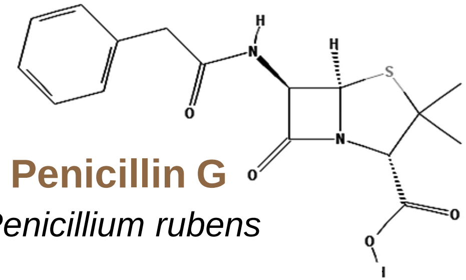


Cephalosporin C
Acremonium chrysogenum

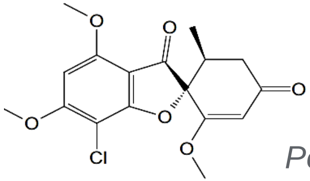


Echinocandin B
Aspergillus pachycristatus

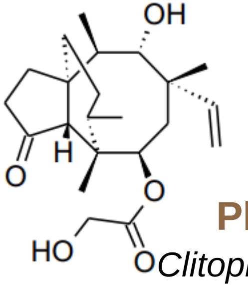
FUNGI



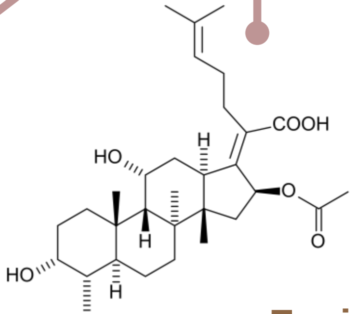
Penicillin G
Penicillium rubens



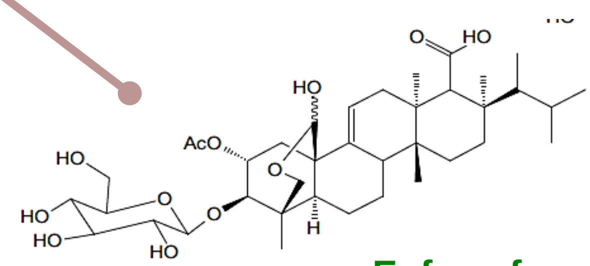
Griseofulvin
Penicillium griseofulvum



Pleuromutilin
Clitopilus passeckerianus
(Formely named *Pleurotus mutilus*)



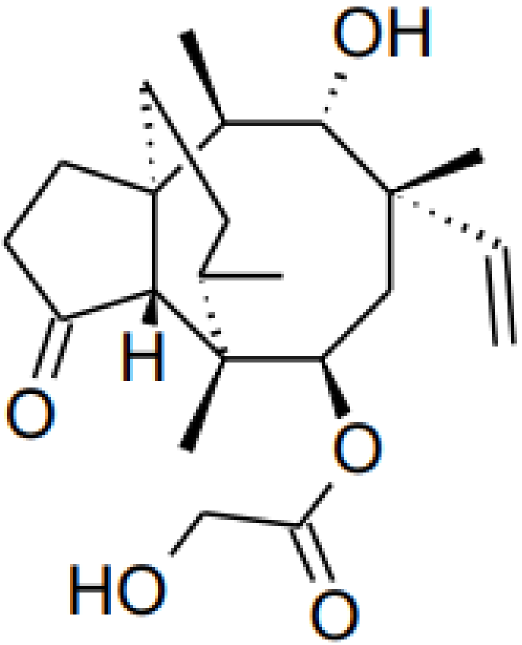
Fusidic acid
Acremonium fusidioides



Enfumafungin
Hormonema carpetanum

Pleuromutilin

Tricyclic diterpene



570 BOTANY: KAVANAGH, ET AL. PROC. ... S.

ANTIBIOTIC SUBSTANCES FROM BASIDIOMYCETES. VIII. PLEUROTUS MULTILUS (FR.) SACC. AND PLEUROTUS PASSECKERIANUS PILAT*

By FREDERICK KAVANAGH, ANNETTE HERVEY AND WILLIAM J. ROBBINS

DEPARTMENT OF BOTANY, COLUMBIA UNIVERSITY AND THE NEW YORK BOTANICAL GARDEN

Communicated July 18, 1951

Fig. Basidiomata of *Clitopilus passeckerianus* (Formely named *Pleurotus mutilus*) (Entolomataceae, Agaricales – basidiomycota)

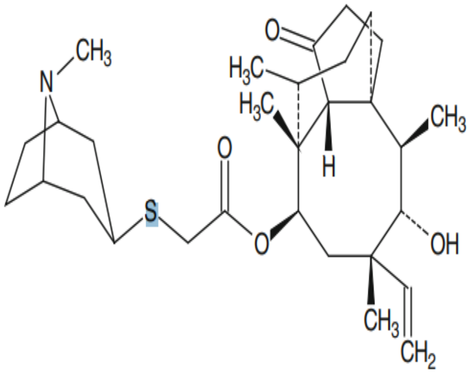
Antibacterial activity

Mode of action: inhibit bacterial protein synthesis by binding the peptidyl transferase center (PTC) of the ribosome

First Pleuromutilin synthetic derivatives approved as antibacterial drug for use in human therapeutics.

Retapamulin

(Clinical agent)



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SCIENTIFIC REPORTS

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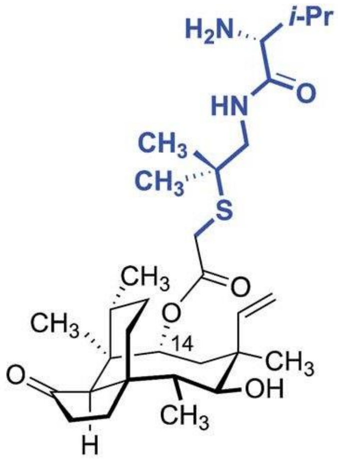
Identification and manipulation of the pleuromutilin gene cluster from *Clitopilus passeckerianus* for increased rapid antibiotic production

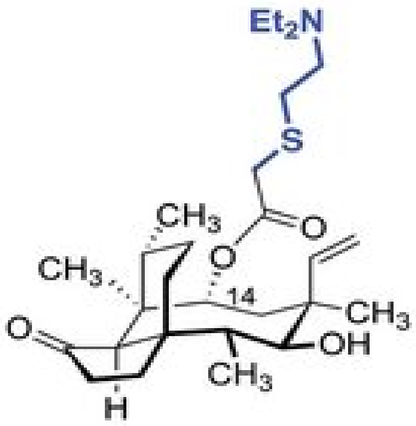
Received: 18 February 2016
Accepted: 11 April 2016
Published: 04 May 2016

Andy M. Bailey[1], Fabrizio Alberti[1], Sreedhar Kilaru[1], Catherine M. Collins[1], Kate de Mattos-Shipley[1], Amanda J. Hartley[1], Patrick Hayes[1], Alison Griffin[2], Colin M. Lazarus[1], Russell J. Cox[3], Christine L. Willis[3], Karen O'Dwyer[4], David W. Spence[3] & Gary D. Foster[1]

Tiamulin and Valnemulin (other synthetic derivatives of pleuromutilin)



Valnemulin

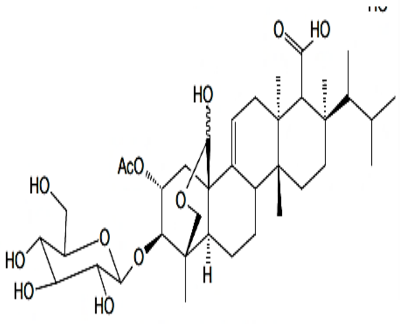


Tiamulin

Treatment of infections in poultry and swine

Antifungal activity

Enfumafungin



Fungal endophyte

Hormonema carpetanum
isolated from leaves
of *Juniperus communis.*

environmental microbiology

sfam society for applied microbiology

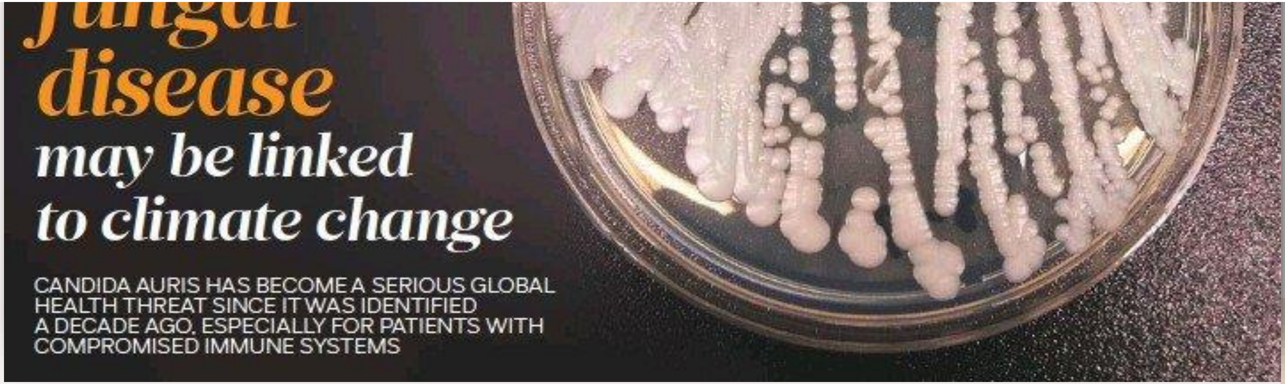
Research article

Enfumafungin synthase represents a novel lineage of fungal triterpene cyclases

Eric Kuhnert, Yan Li, Nan Lan, Qun Yue, Li Chen, Russell J. Cox, Zhiqiang An, Kenichi Yokoyama, Gerald F. Bills

First published: 26 July 2018 | https://doi.org/10.1111/1462-2920.14333 | Citations: 8

Kuhnert et al., 2018. Enfumafungin synthase represents a novel lineage of fungal triterpene cyclases *Environmental Microbiology* 20 (9): 3325-3342



Bioactive compounds isolated from fungal endophytes

Department of Microbial Drugs, Helmholtz Centre for Infection Research (**HZI**), Braunschweig , Germany.

Under the supervision of:

Prof. Dr. Marc Stadler

HELMHOLTZ CENTRE FOR INFECTION RESEARCH

Globularia alypum (Plantaginaceae, Scrophulariales) (Host plant)

1.1. *Preussia similis .strain* DSM 104666

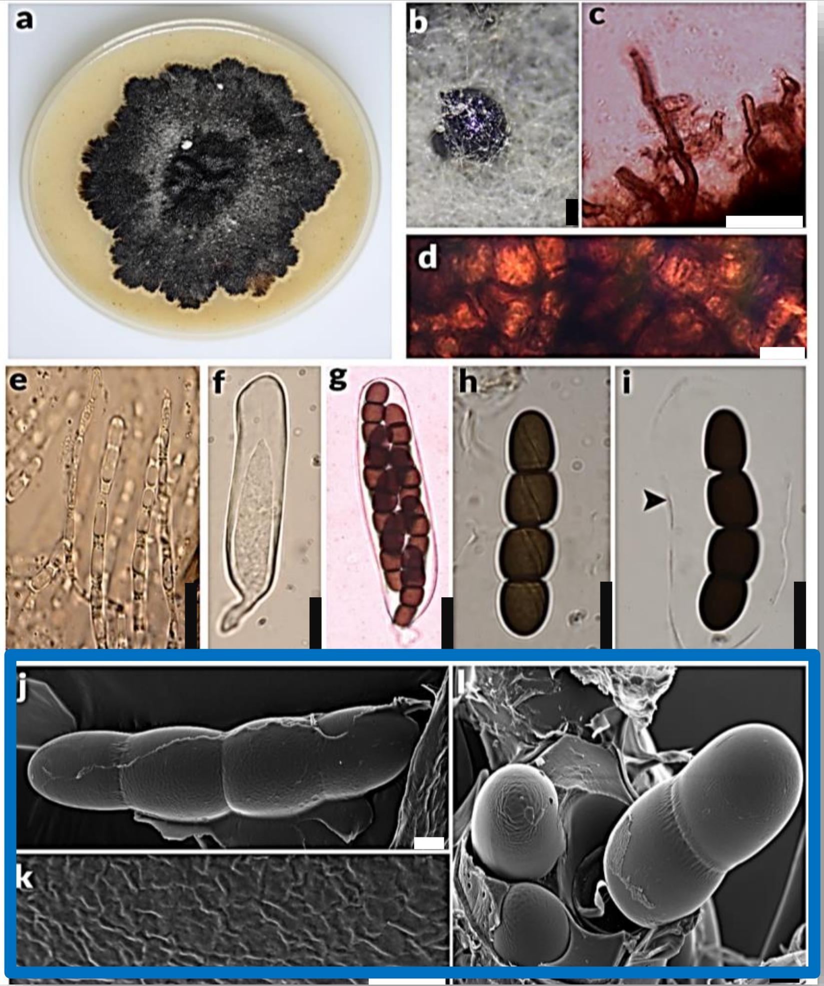


Fig. Teleomorph features of *Preussia similis* DSM 104666.

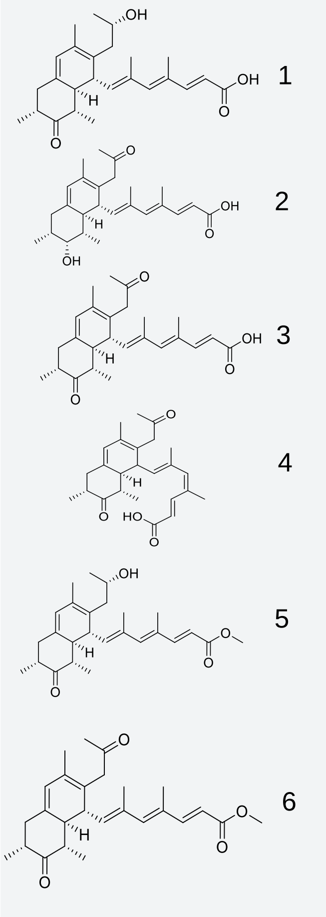
a Culture on OMA after 4 weeks on 9 cm Petri dish with sporulating regions as black spots in the centre and periphery, **b** Pseudoperithecium without ostiole, **c** Ascomata hyphae ornamentations, **d** Details of exoperidium, **e** Pseudoparaphyses, **f** Immature ascus, **g** Mature ascus, **h** Ascospore showing germ slit, **i** Ascospore surrounded by hyaline gelatinous sheath indicated by arrow, **j** Gelatinous sheath showed in SEM microphotography, **k** SEM microphotography showing perispore details, **l** SEM microphotography showing ascospores arrangements within bitunicate ascus, apical view, part of ascospore cleaved out of ascus, Scale bars: **b**=100 μm, **c, h, i, e** = 20μm, **j, l** =2 μm, **k** =1 μm, **f, g** =50 μm, **d** =10 μm.

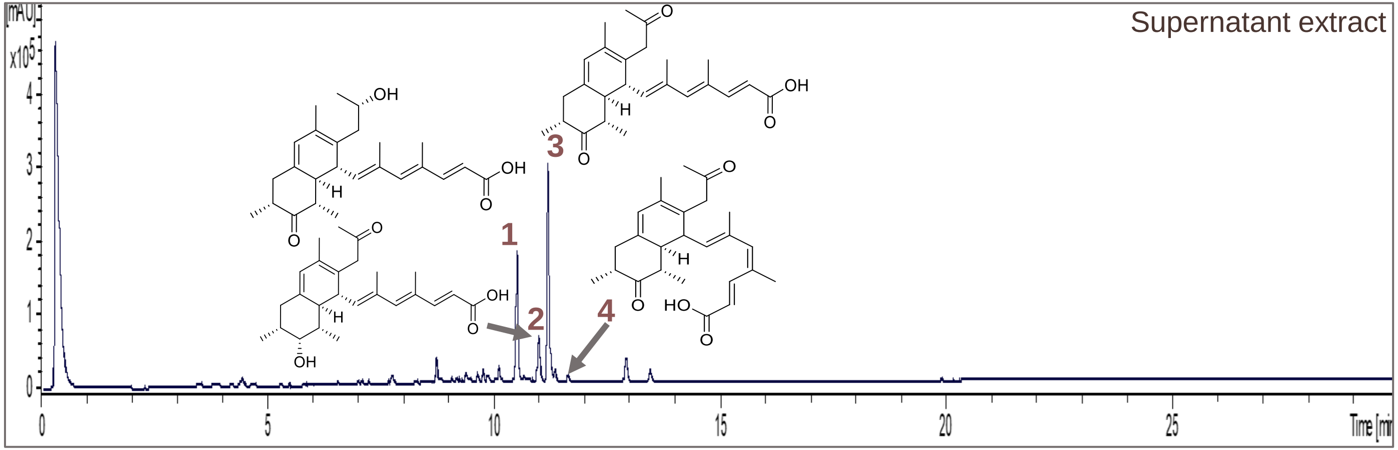
For the first time, the ultrastructure of ascospores was further investigated by Scanning Eletron Microscopy (SEM).

New bicyclic polyketides

Preussilides A-F « 1-6 »

Preussia similis **Strain DSM 104666**





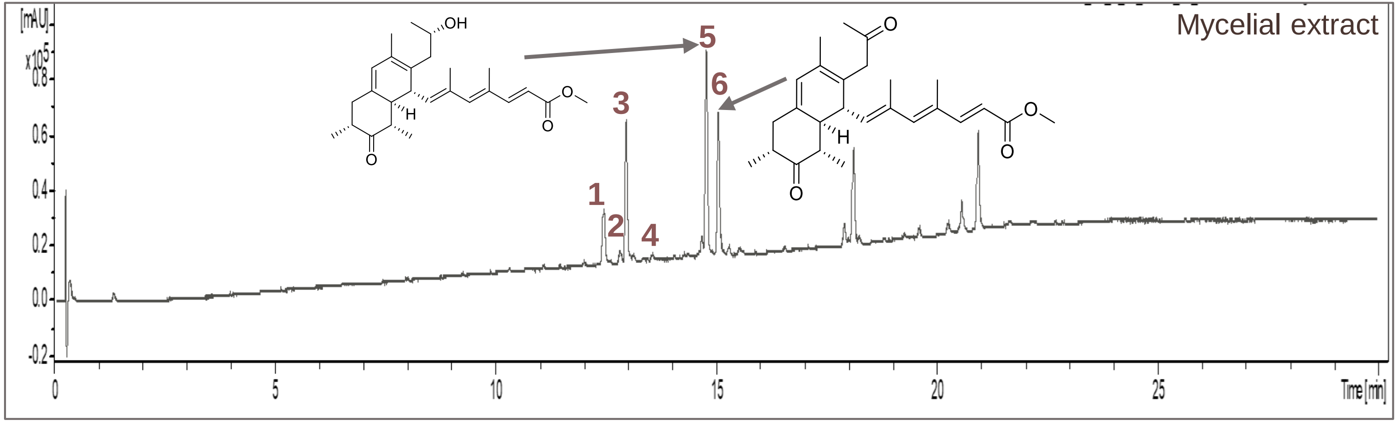
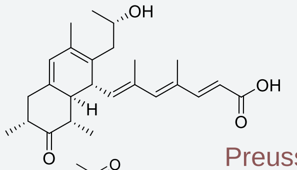
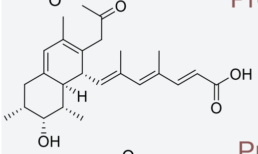


Fig. HPLC Chromatograms of supernatant and mycelial crude extracts from *Preussia similis* strain **DSM 104666**

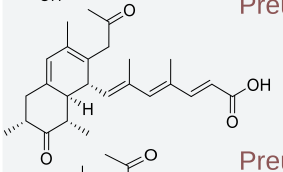
Preussilides A-F (1-6) : Selective activity against Eukaryotes



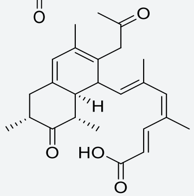
Preussilide A (1)



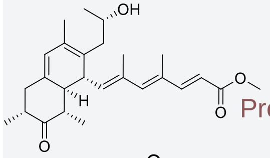
Preussilide B (2)



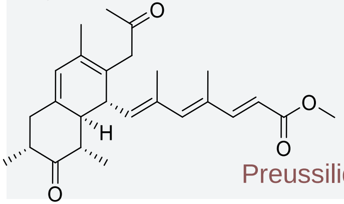
Preussilide C (3)



Preussilide D (4)



Preussilide E (5)

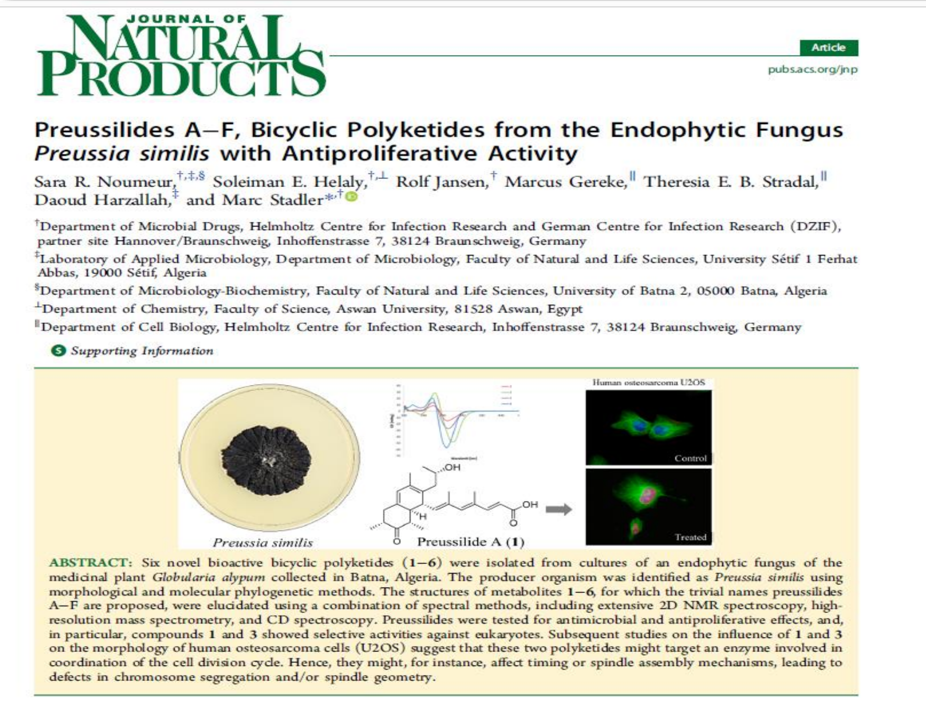


Preussilide F (6)

Table. Antifungal activity MIC values (µg/ml) of the

Filamentous fungi	1	2	3	4	5	6	Cycloheximide
Aspergillus fumigatus DSM 819	66.67	n.a.	8.33	n.a	n.a	n.a	33.33[e]
Mucor hiemalis DSM 2656	n.a	n.a	n.a	n.a	n.a	n.a	16.67[d]
Mucor plumbeus MUCL 49355	150	n.a	37.5	n.a	n.a	n.a	3.12[d]

Noumeur et al., 2017. *Journal of natural products* **80** (5): 1531–40.



JOURNAL OF NATURAL PRODUCTS

Article

pubs.acs.org/jnp

Preussilides A–F, Bicyclic Polyketides from the Endophytic Fungus *Preussia similis* with Antiproliferative Activity

Sara R. Noumeur,[†,‡,§] Soleiman E. Helaly,[†,⊥] Rolf Jansen,[†] Marcus Gereke,[‖] Theresia E. B. Stradal,[‖] Daoud Harzallah,[‡] and Marc Stadler[*,†]

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[⊥]Department of Chemistry, Faculty of Science, Aswan University, 81528 Aswan, Egypt

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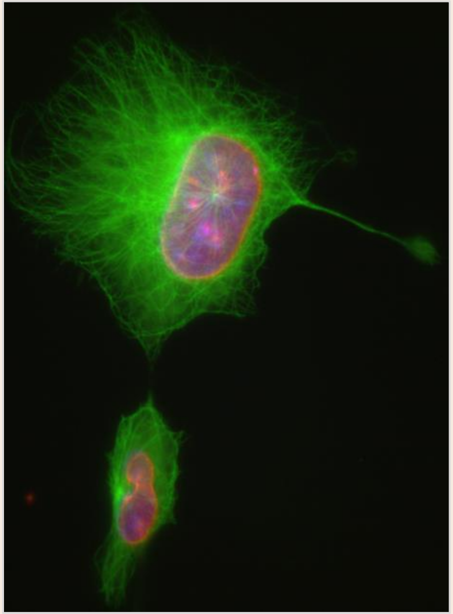
S Supporting Information

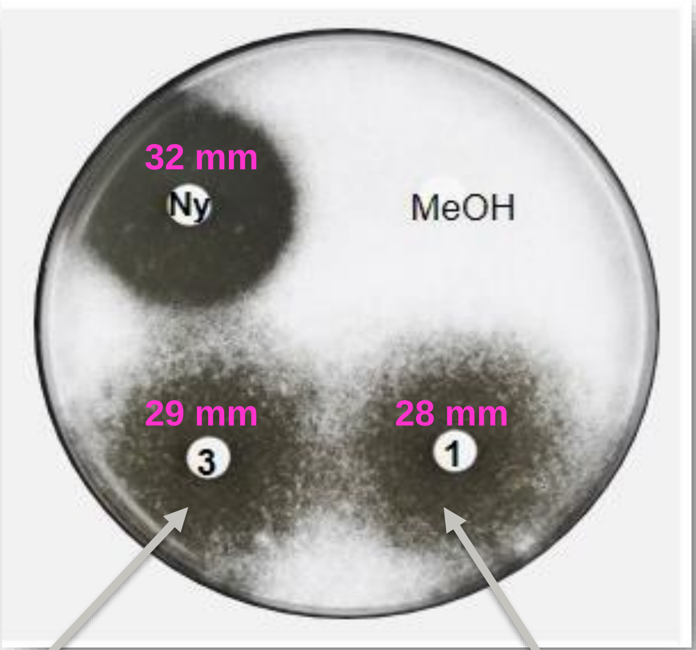
ABSTRACT: Six novel bioactive bicyclic polyketides (1–6) were isolated from cultures of an endophytic fungus of the medicinal plant *Globularia alypum* collected in Batna, Algeria. The producer organism was identified as *Preussia similis* using morphological and molecular phylogenetic methods. The structures of metabolites 1–6, for which the trivial names preussilides A–F are proposed, were elucidated using a combination of spectral methods, including extensive 2D NMR spectroscopy, high-resolution mass spectrometry, and CD spectroscopy. Preussilides were tested for antimicrobial and antiproliferative effects, and, in particular, compounds 1 and 3 showed selective activities against eukaryotes. Subsequent studies on the influence of 1 and 3 on the morphology of human osteosarcoma cells (U2OS) suggest that these two polyketides might target an enzyme involved in coordination of the cell division cycle. Hence, they might, for instance, affect timing or spindle assembly mechanisms, leading to defects in chromosome segregation and/or spindle geometry.



Unfair division of Human osteosarcoma cells (Defects in chromosome segregation and/or spindle geometry)

Antifungal activity of preussilides A (**1**) and C (**3**) against phytopathogen *Sclerotinia sclerotiorum* determined by Agar diffusion at 100µg/disk (positive control nystatin 20 µg/paper disk)

White mold caused by *Sclerotinia sclerotiorum*



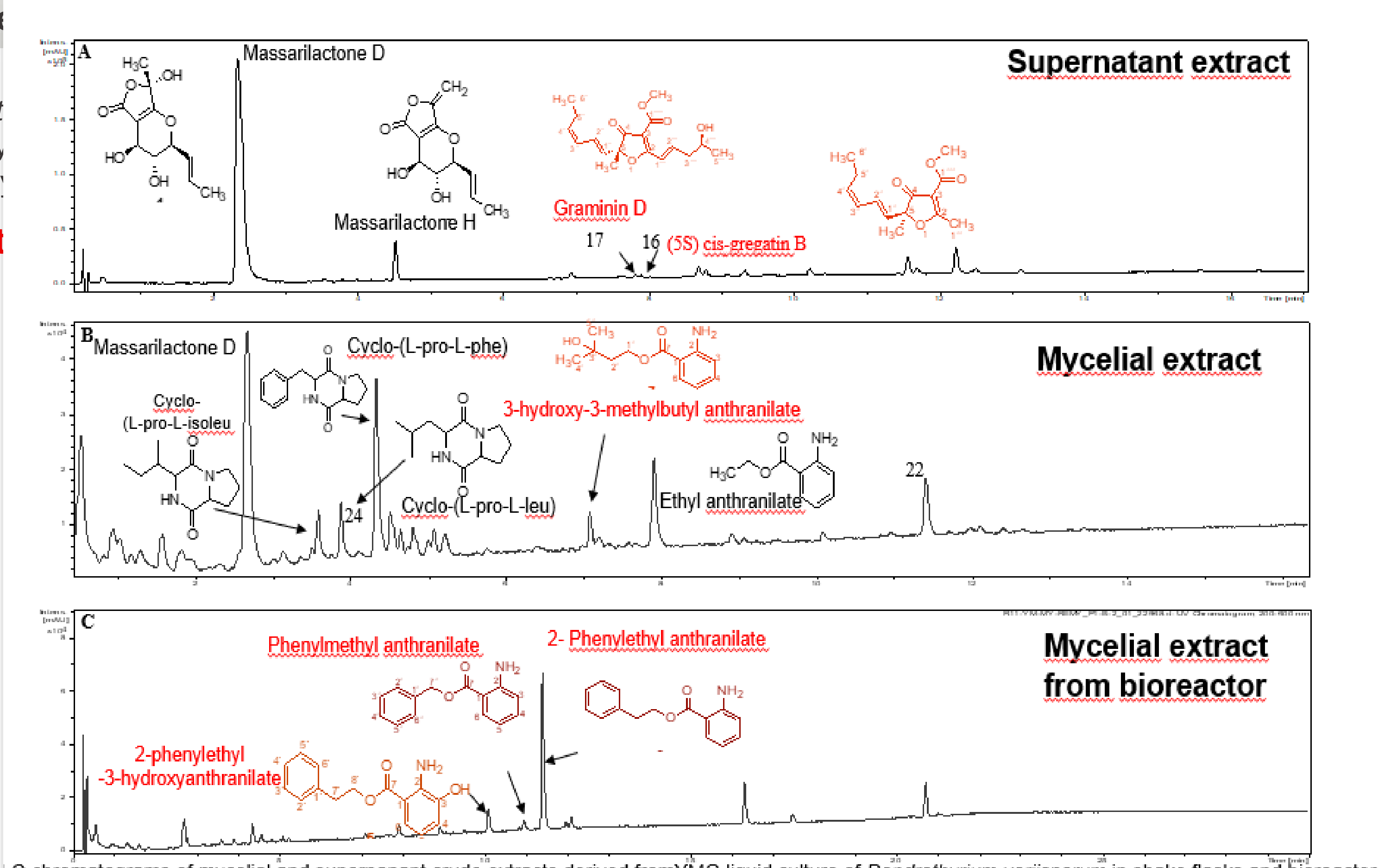
Preussilide C

Preussilide A

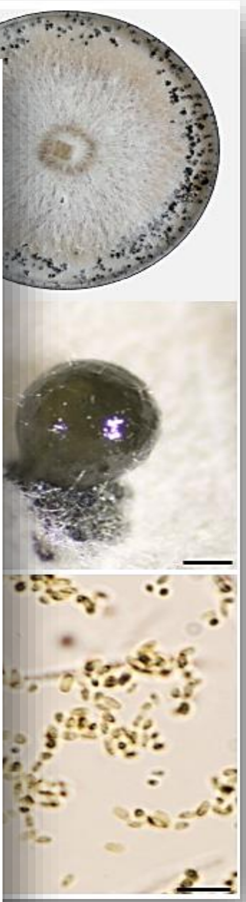
Five New anthranilic acid derivatives isolated from the fungal e

Dendrot
coelomy
(Verkle

First st



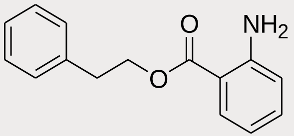
LC chromatograms of mycelial and supernanant crude extracts derived fromYMG liquid culture of *Dendrothyrium variisporum* in shake flasks and bioreactor



ium variisporum
sh, b. Culture on OMA
orming on the edge of
culture on OMA medium, d. Conidiomata, e. Conidiogenous cells, f. Conidia, Scale bar: e, f =10 μm, d=100 μm.

Antimicrobial activity of the new anthranilic acid derivatives

2- Phenylethyl anthranilate



Gram positive bacteria

Micrococcus luteus: 16.66 µg/mL

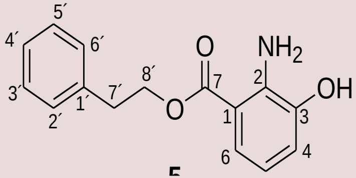
Bacillus subtilis : 8.33 µg/mL

Staphylococcus aureus: 66.67µg/mL

Yeast: *Rhodotorula glutinis* : 66.67µg/mL

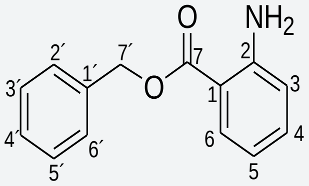
Filamenteus fungi: *Mucor hiemalis*: 33.33 µg/mL

2-phenylethyl-3-hydroxyanthranilate



Gram positive bacteria: *B. Subtilis* and *Staphylococcus aureus*: 66.67µg/mL

Phenylmethyl anthranilate



Inactive

molecules

MDPI

Article

Furanones and Anthranilic Acid Derivatives from the Endophytic Fungus *Dendrothyrium variisporum*

Rémy B. Teponno [1,2,†], Sara R. Noumeur [1,3,4,†], Soleiman E. Helaly [1,5], Stephan Hüttel [1], Daoud Harzallah [3] and Marc Stadler [1,*]

1 Department of Microbial Drugs, Helmholtz Centre for Infection Research and German Centre for Infection Research (DZIF), partner site Hannover/Braunschweig, Inhoffenstrasse 7, 38124 Braunschweig, Germany; remyteponno@gmail.com (R.B.T.); noumeur.sara@gmail.com (S.R.N.); soleiman.helaly@aswu.edu.eg (S.E.H.); Stephan.Huettel@helmholtz-hzi.de (S.H.)
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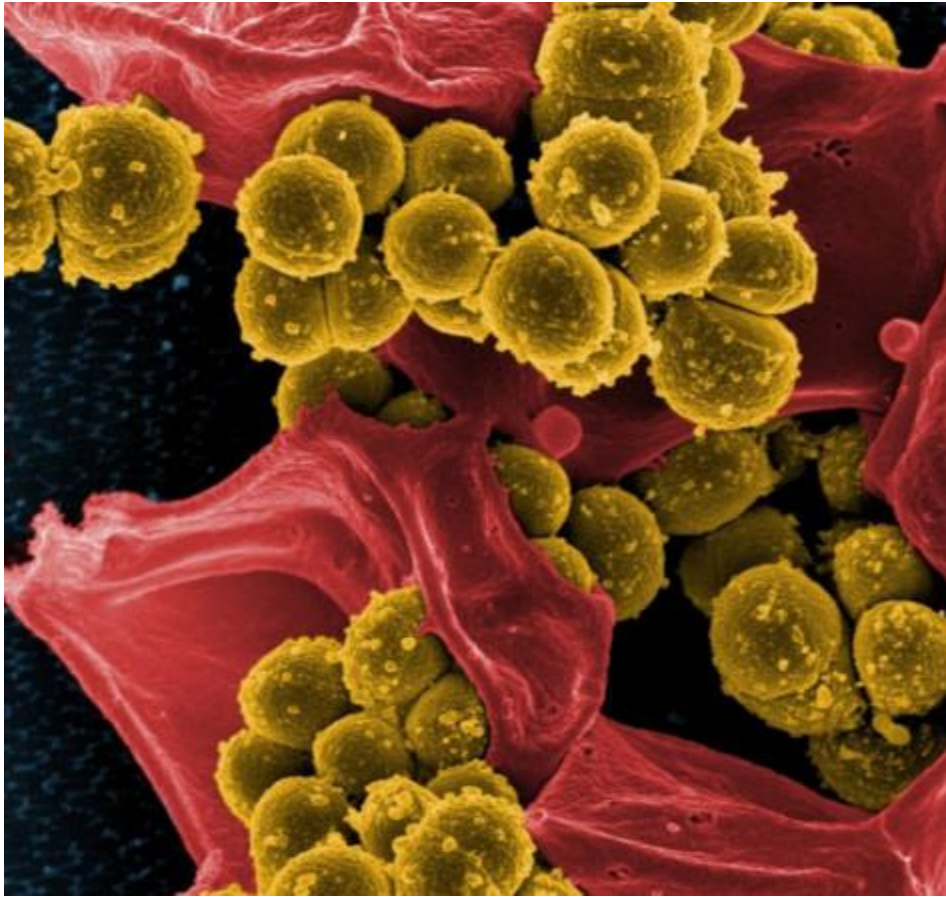
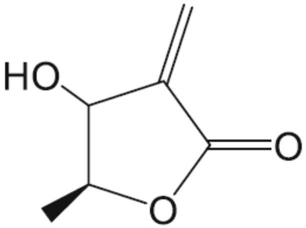
Fungi as source of Biofilm inhibitors



Biofilm Inhibitor

Coprinuslactone



Edible mushroom
Coprinus comatus

Dissolves preformed Biofilms of *Pseudomonas aeruginosa*

Carvalho et al.(2016) Coprinuslactone protects the edible mushroom Coprinus comatus against biofilm infections by blocking both quorum sensing and Mur A. Environmental Microbiology 18:4254–4264.

Coprinuslactone protects the edible mushroom *Coprinus comatus* against biofilm infections by blocking both quorum-sensing and MurA.

Author(s) : Carvalho, M. P. de ; Gulotta, G. ; Amaral, M. W. do ; Lünsdorf, H. ; Sasse, F. ; Abraham, W. R.
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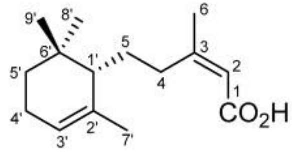
Journal article : Environmental Microbiology 2016 Vol.18 No.11 pp.4254-4264 ref.70

Abstract : Pathogens embedded in biofilms are involved in many infections and are very difficult to treat with antibiotics because of higher resistance compared with planktonic cells. Therefore, new approaches for their control are urgently needed. One way to search for biofilm dispersing compounds is to look at defense strategies of organisms exposed to wet environments, which makes them prone to biofilm infections. It is reasonable to assume that mushrooms have developed mechanisms to control biofilms on their sporocarps (fruiting bodies). A preliminary screening for biofilms on sporocarps revealed several species with few or no bacteria on their sporocarps. From the edible mushroom *Coprinus comatus* where no bacteria on the sporocarp could be detected (3R,4S)-2-

Biofilm Inhibitor

Roussoellenic acid



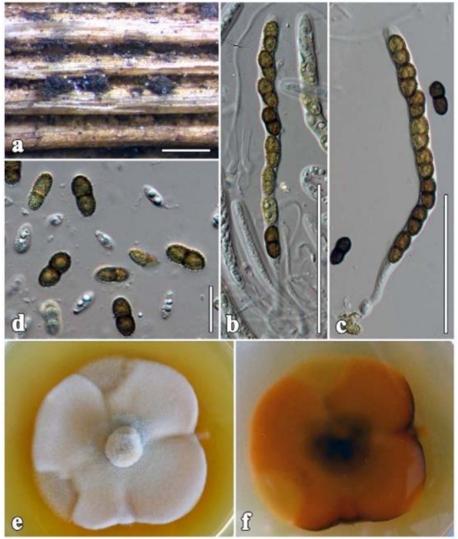
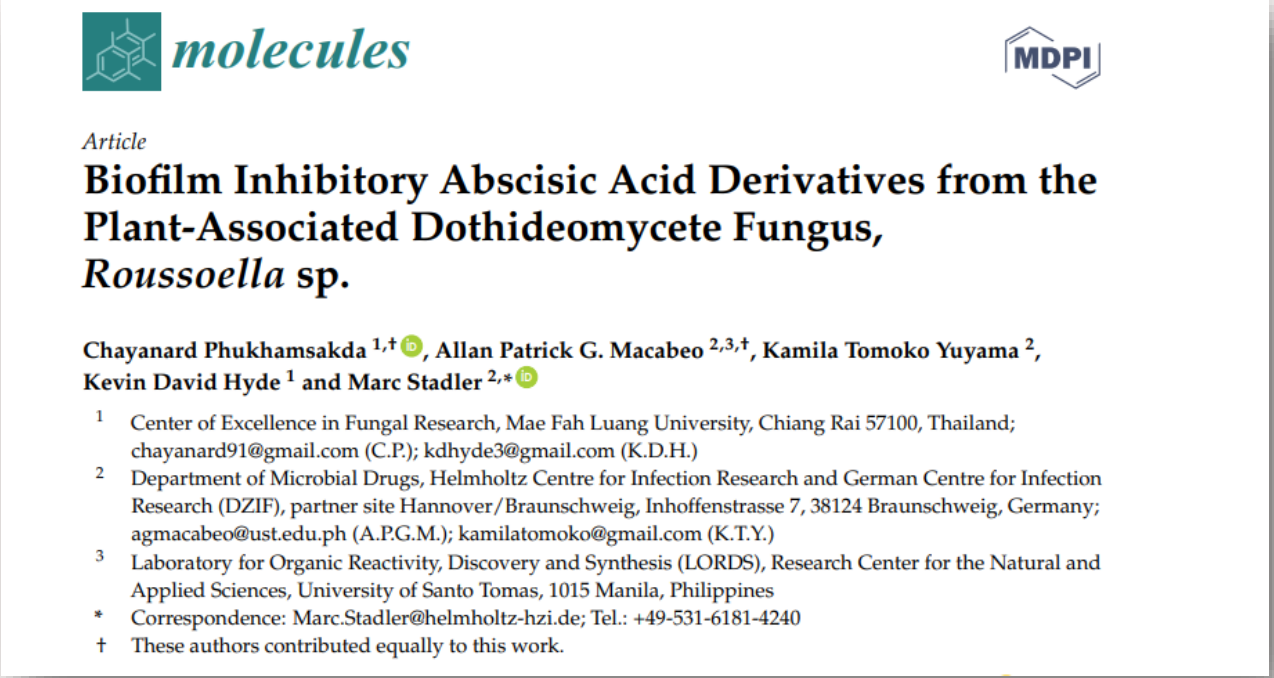


Fig. Roussoella sp. MFLUCC 17-2059 a Appearance of ascomata on host surface b-c Asci d Ascospores e-f Culture characters on YMG agar. Scale bars: a = 500 µm, b-c = 50 µm, d = 10 µm.

New abscisic acid derivative against biofilm formation in *Staphylococcus aureus*

Phukhamsakda et al.(2018) Biofilm inhibitory abscisic acid derivatives from the plant-associated Dothideomycete fungus, *Roussoella* sp. Molecules 23:2190.



molecules MDPI

Article

Biofilm Inhibitory Abscisic Acid Derivatives from the Plant-Associated Dothideomycete Fungus, *Roussoella* sp.

Chayanard Phukhamsakda [1,†], Allan Patrick G. Macabeo [2,3,†], Kamila Tomoko Yuyama [2], Kevin David Hyde [1] and Marc Stadler [2,*]

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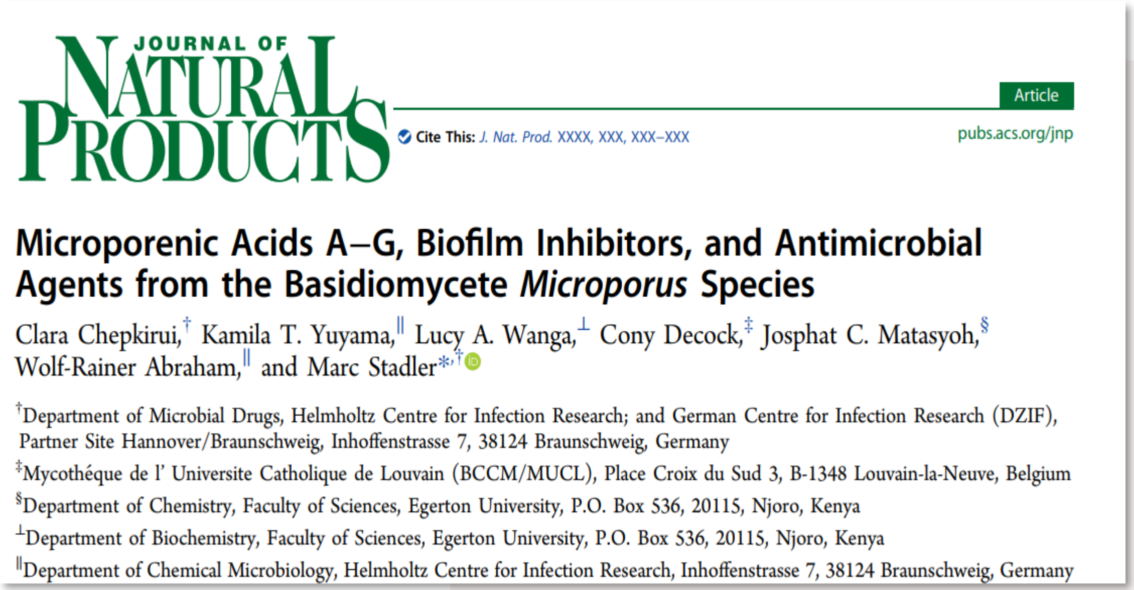
† These authors contributed equally to this work.

Biofilm inhibitor : compound from *Microporus* sp. (Polyporaceae, Basidiomycetes)

Chepkirui et al., 2018. *Journal of Natural Products*. 81(4):778-784


JOURNAL OF NATURAL PRODUCTS
Article
Cite This: J. Nat. Prod. XXXX, XXX, XXX−XXX
pubs.acs.org/jnp

Microporenic Acids A−G, Biofilm Inhibitors, and Antimicrobial Agents from the Basidiomycete *Microporus* Species

Clara Chepkirui,[†] Kamila T. Yuyama,[‖] Lucy A. Wanga,[⊥] Cony Decock,[‡] Josphat C. Matasyoh,[§] Wolf-Rainer Abraham,[‖] and Marc Stadler*,[†]

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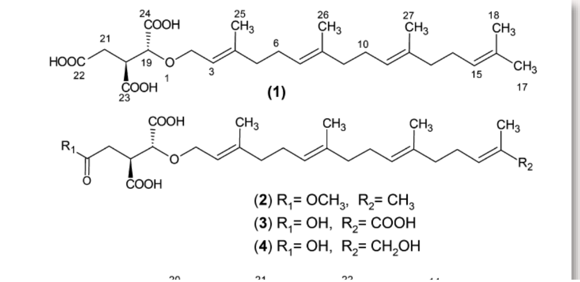
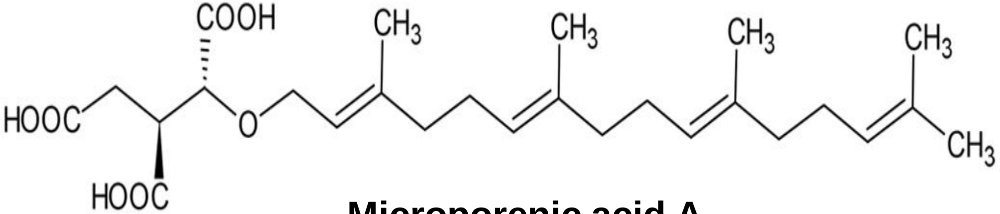
Microporenic acids A-G (1-7)



Staphylocoocus aureus
Inhibition of *Staphylococcus aureus* biofilm

MIC (256 µg/ml)	86%
MIC (64 µg/ml)	54%
MIC (16 µg/ml)	28 %



Microporenic acid A

Biofilm Inhibitor

Cytochalasans

Promising class of compounds as inhibitors of *Staphylococcus aureus* biofilm formation at subtoxic levels.

biomolecules

MDPI

Article

The Effect of Cytochalasans on t… Cytoskeleton of Eukaryotic Cell… Structure–Activity Relationship…

Robin Kretz [1,2], Lucile Wendt [1], Sarunyou Wongkanoun… Frank Surup [1], Soleiman E. Helaly [1,4], Sara R. Noumeu… and Theresia E.B. Stradal [6,*]

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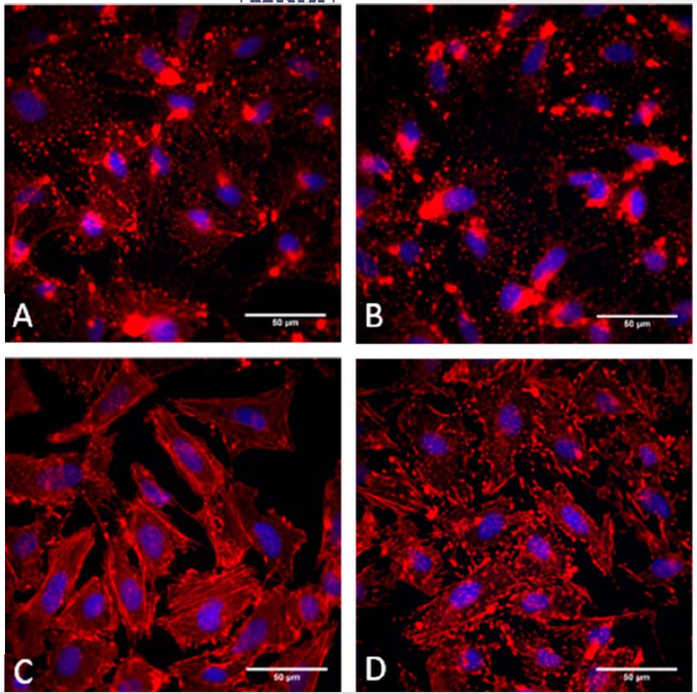
Cytochalasin H

Cytochalasin B



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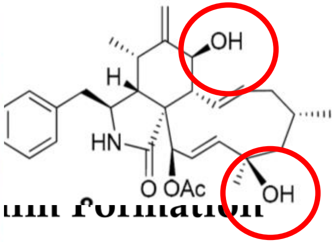
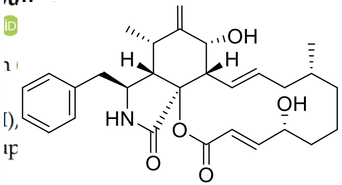


…Kretz [2], Clara Chepkirui [2],

…(M.S.)

…DA, 113 Thailand Science Park, …iland;



The presence of C–7 and C–18 hydroxylation is correlated with high potency to disrupt the actin cytoskeleton of eukaryotes,

Conclusion

Fungi : on the frontline of the climate crisis

- **Fungi have provided the world with penicillin and other globally significant medicines, and they remain an untapped resource with enormous industrial potential.**
- **Use of moderne techniques:**
  - **Use of Uncultured microorganisms**
  - **Screening microbes in non-conventional sources**
  - **Metagenomics approaches**
  - **Co-cultivation** can help either to encrypt silent fungal secondary metabolites gene clusters under standard laboratory growth conditions or can allow a


Imagine an organism
that feeds you, heals
you, reveals secrets of
the universe, and could
help save the planet...
today.

Thank you