Programa de Pós-Graduação Interunidades em Biotecnologia

BTC5827 - Fungos e Biotecnologia

Docente:
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Link**: https://sites.usp.br/lbbp/**

Créditos: 4 (Aulas Teóricas: 4 h, Prática/Seminários: 2 h., Horas Estudo: 4 h)
Duração em Semanas: 6. Total: 60 h
Período: terça-feira (8:00 - 12:00 h)
Local: ICB IV – sala 03

2024

Metabolismo secundário.

Fungi produce a multitude of low-molecular-mass compounds known as secondary metabolites, which have roles in a range of cellular processes such as transcription, development and intercellular communication. In addition, many of these compounds now have important applications, for instance, as antibiotics or immunosuppressants.

Immunosuppressants

Compounds that reduce the activity of the immune system by inhibiting essential processes.

Cholesterol-lowering compound

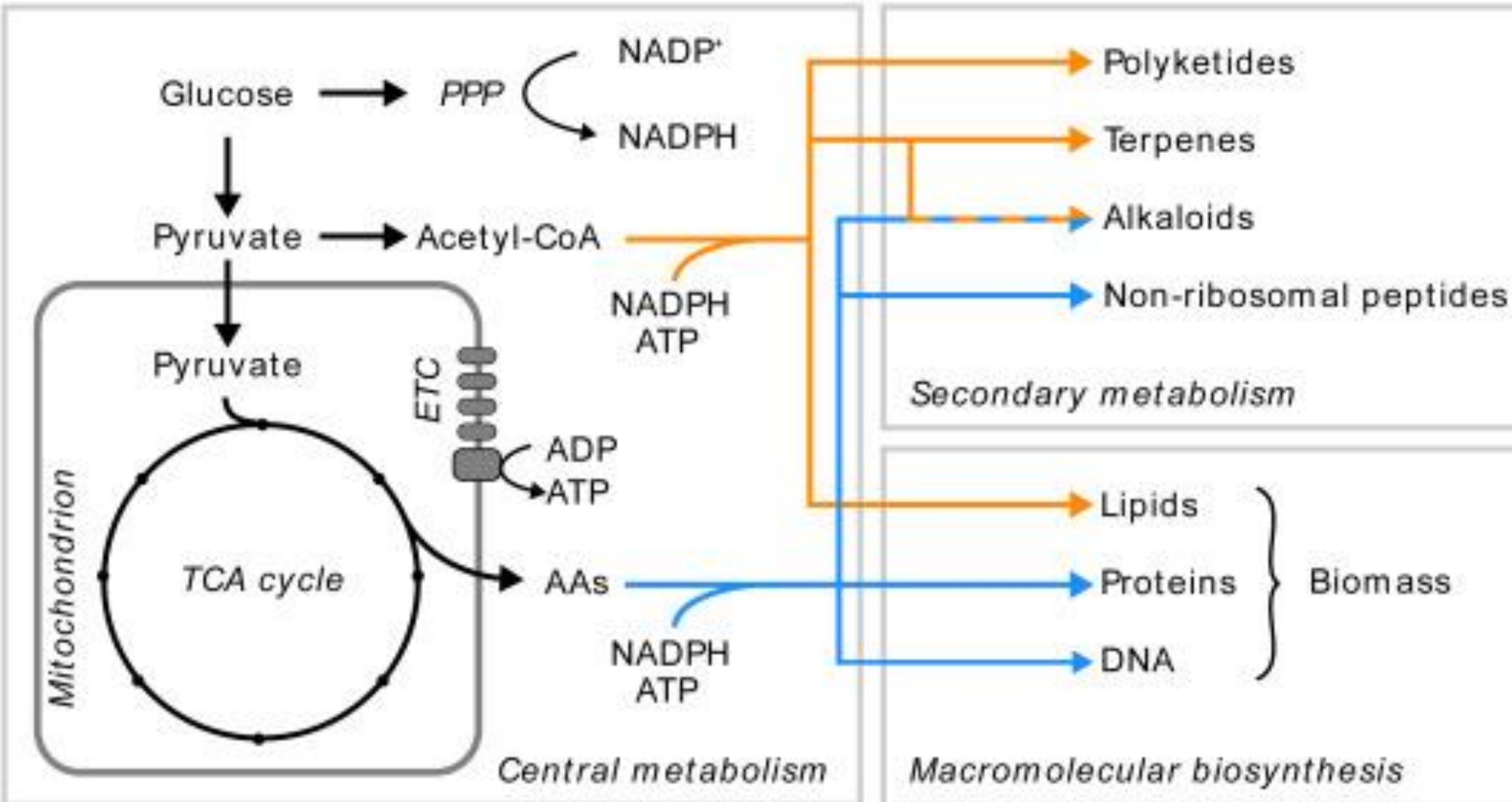
A compound that leads to a reduction of the cholesterol level in human blood (for example, by inhibition of the 3-hydroxy-3′-methyl glutaryl coenzyme A reductase activity involved in cholesterol biosynthesis).

Terpenes

Organic molecules formed of an isoprene ($C5H8$) unit backbone to give, for example, C10 (monoterpene), C15 (sesquiterpene) and C20 (diterpene) compounds.

Antibiotic compounds

Antibiotics are low-molecular weight organic natural products (secondary metabolites) made by microorganisms at low concentration.



https://doi.org/10.1016/j.synbio.2017.02.002

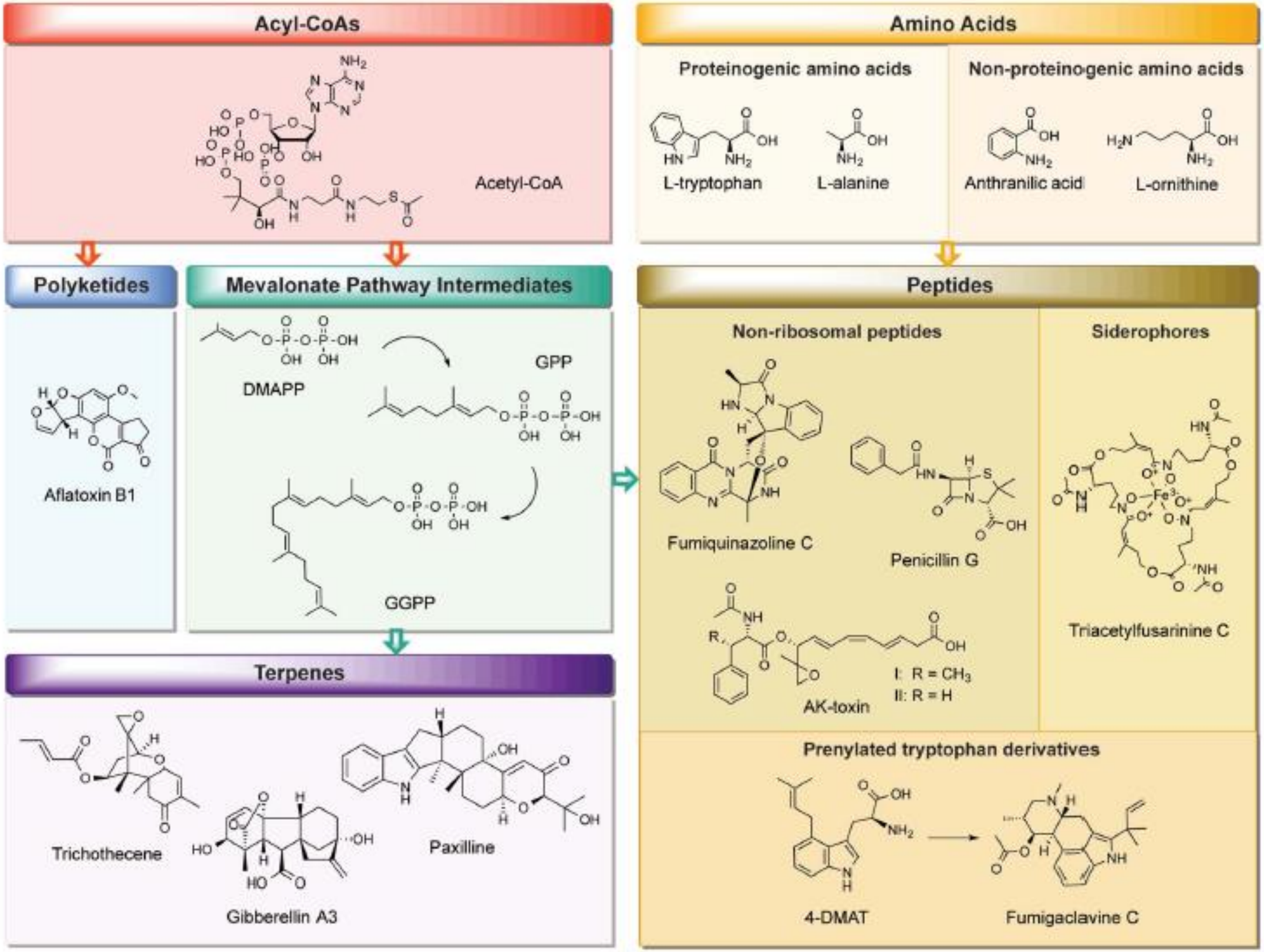


Fig. 1 Generating structures of increasing complexity. Depicts the biosynthetic flow of basic building blocks (acyl-CoA, amino acids) to generate highly complex chemical structures of select natural products discussed in this review. Formation of polyketide–peptide and polyketide–terpene

Polyketide synthases

Multidomain enzymes that produce polyketides from acyl-CoA precursors.

Non-ribosomal peptide synthetase

A large, multifunctional enzyme that synthesizes peptides or derivatives thereof via a thiotemplate mechanism, in which precursors are activated and bound as thioesters to the synthetase enzymes.

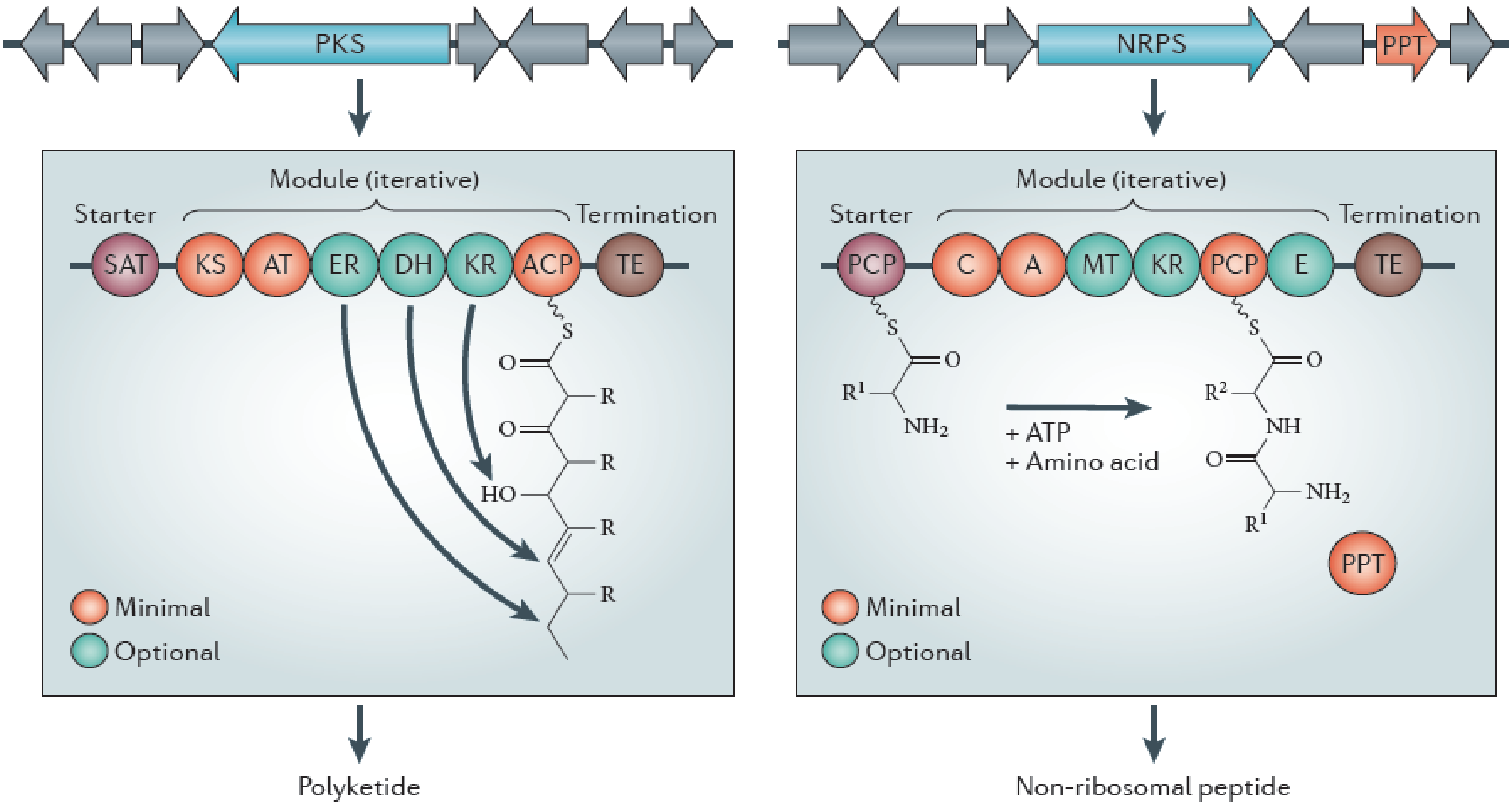


Figure 2 | **Gene clusters and enzymes for fungal secondary metabolism.** Gene clusters with a central non-ribosomal peptide synthetase (NRPS) gene (left) and polyketide synthase (PKS) gene (right). The domains of the encoded enzymes

Figure 1. An overview of the relative distribution of the 32 putative polyketide synthases (PKS) open reading frames (ORFs) on the eight chromosomes of *A. nidulans*. Green and red AN numbers represent assigned and unassigned PKS genes, respectively. Dark grey circles and ends symbolize centromeric and telomeric regions, respectively, and should not be considered to scale.

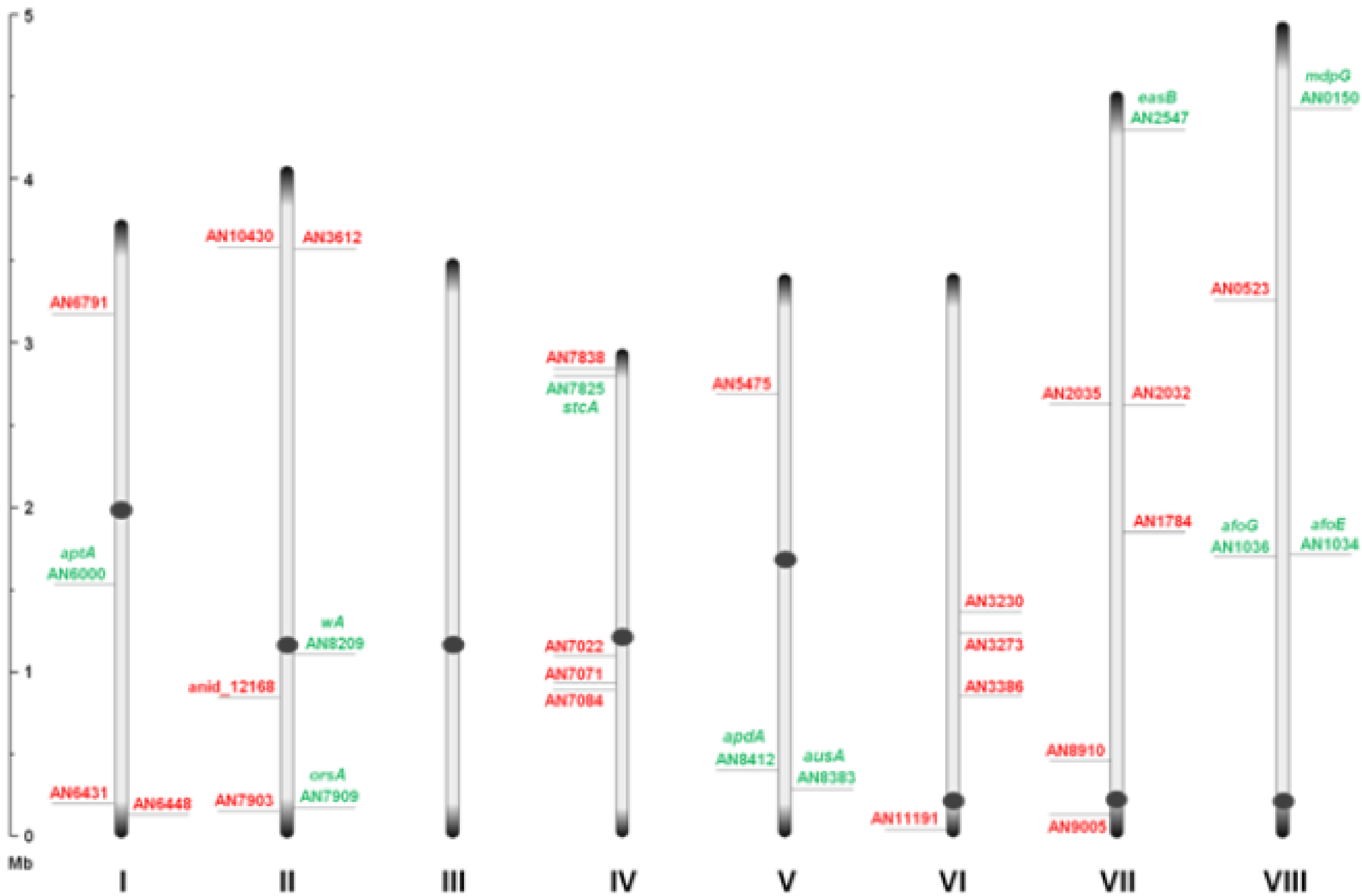


Table 1 | **Summary of secondary-metabolite gene classes in *Aspergillus***

Protein	***Aspergillus oryzae***	***Aspergillus fumigatus***	***Aspergillus nidulans***
PKS	30	14	27
NRPS	18	14	14
FAS	5	1	6
Sesquiterpene cyclase	1	Not detected	1
DMATS	2	7	2

PKS, polyketide synthase; NRPS, non-ribosomal peptide synthetase; FAS, fatty-acid synthase; DMATS, dimethylallyl tryptophan synthetase.

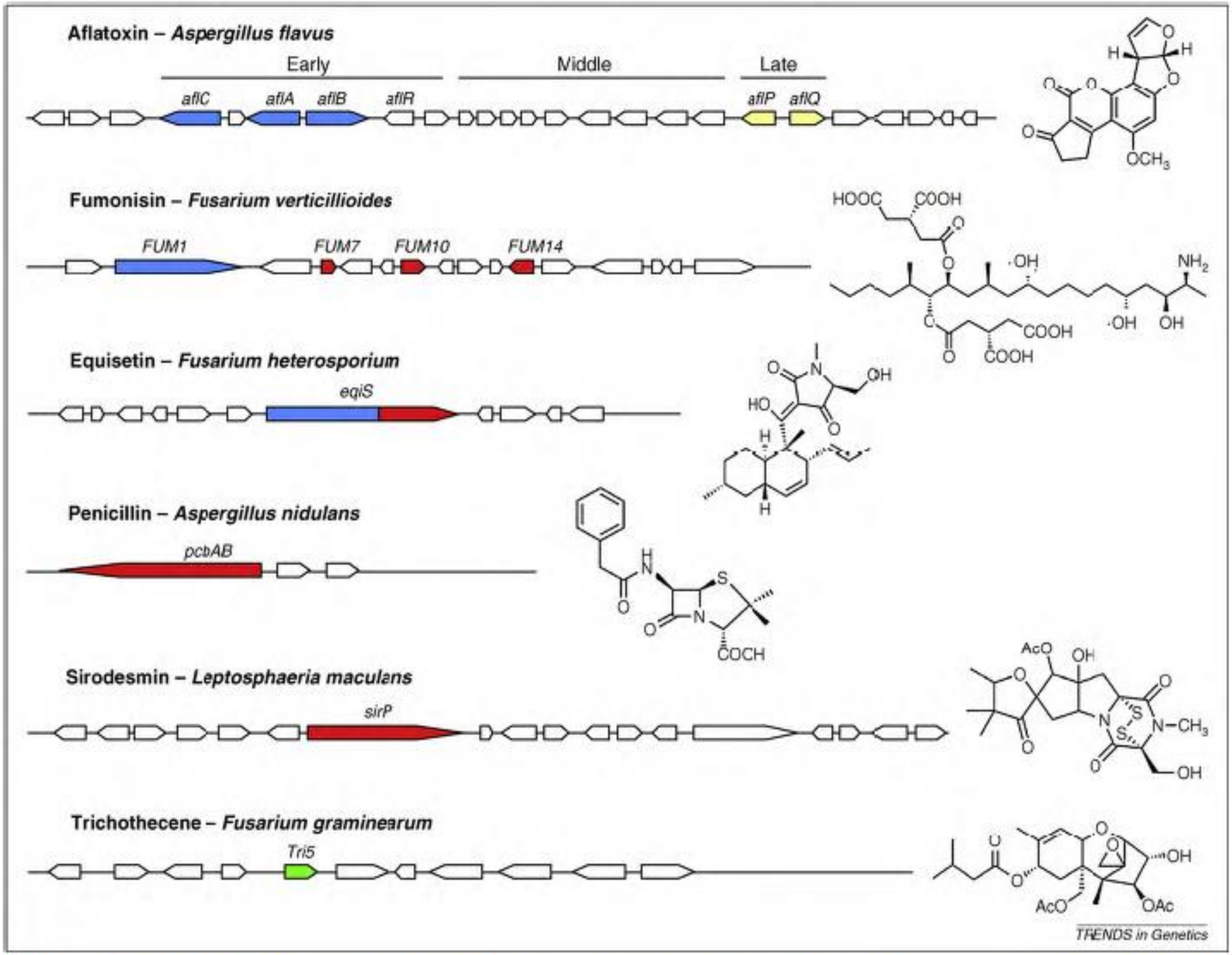


Figure 3. Secondary metabolic gene clusters from filamentous fungi. Examples of biosynthetic clusters for fungal polyketides, non-ribosomally synthesised peptides and terpenes are shown, with the respective signature genes coloured as follows: PKS (blue), NRPS (red), NRPS-PKS hybrid (blue/red); terpene synthase (green). The three red genes in the fumonisin cluster (*FUM7*, *10* and *14*) encode separate domains of an NRPS-like multimodular enzyme. The two genes in the aflatoxin cluster that enable conversion of sterigmatocystin into aflatoxins (*aflP* and *aflQ*) are in yellow. Adapted with permission from Refs [7,44]. Figure not to scale.

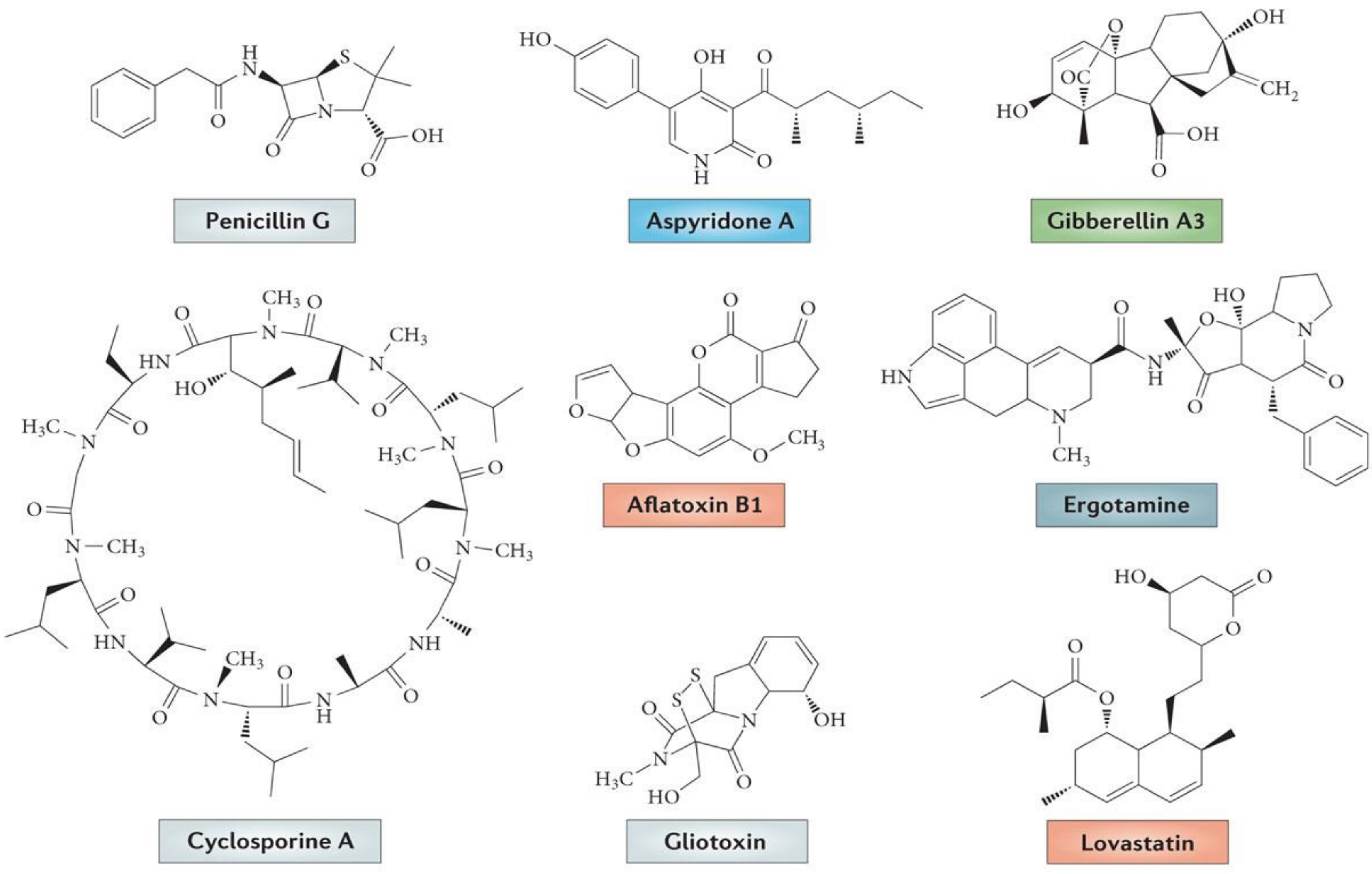
Osbourn, 2010

Why clusters?

Two main selective advantages can be invoked to account for the clustering of functionally related genes: the need to coregulate a set of genes controlling successive steps in a biosynthetic or developmental pathway; and the need for such a gene set to be coinherited, either by HGT from another organism or vertically, from generation to generation.

Osbourn, 2010

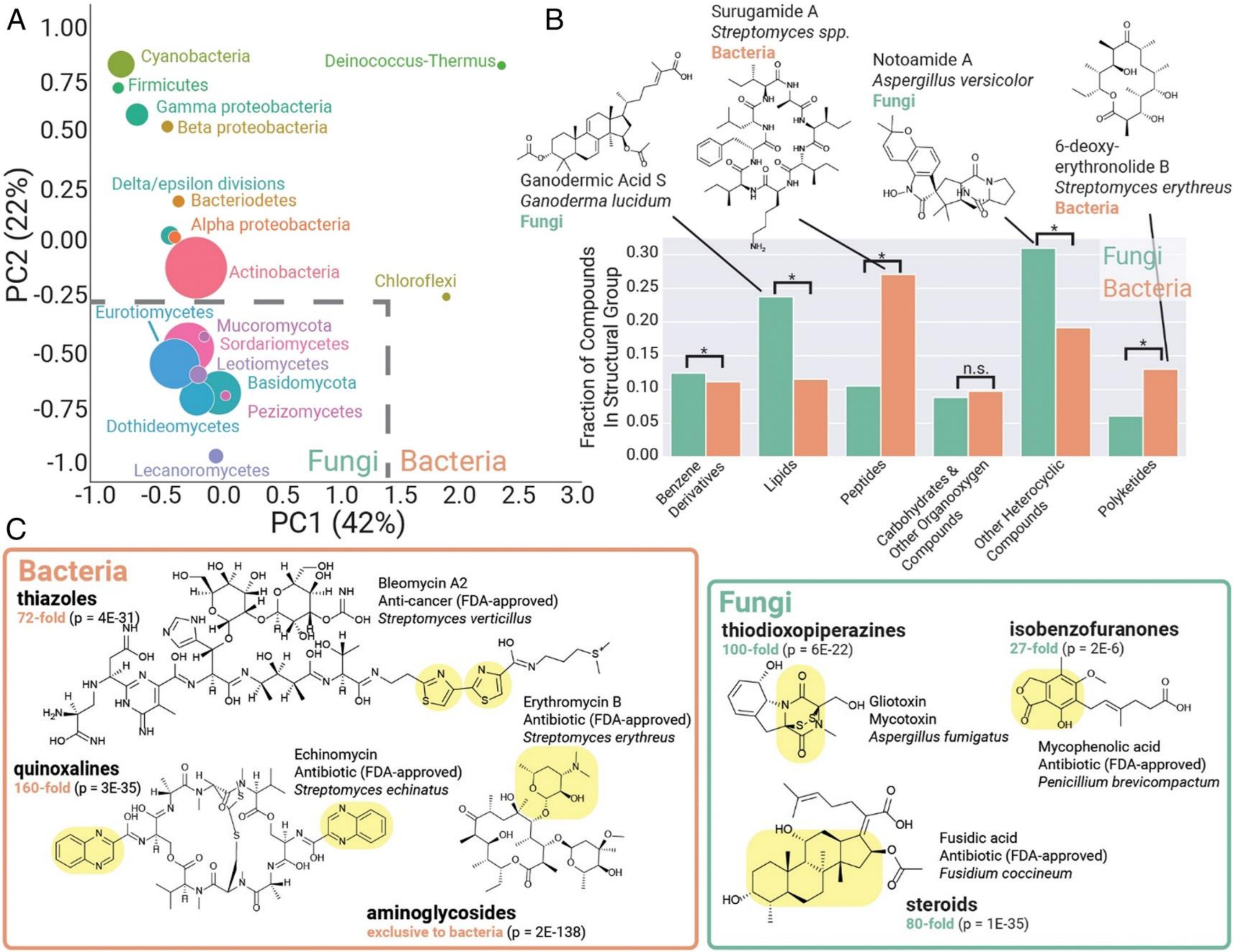
Metabolismo secundário.



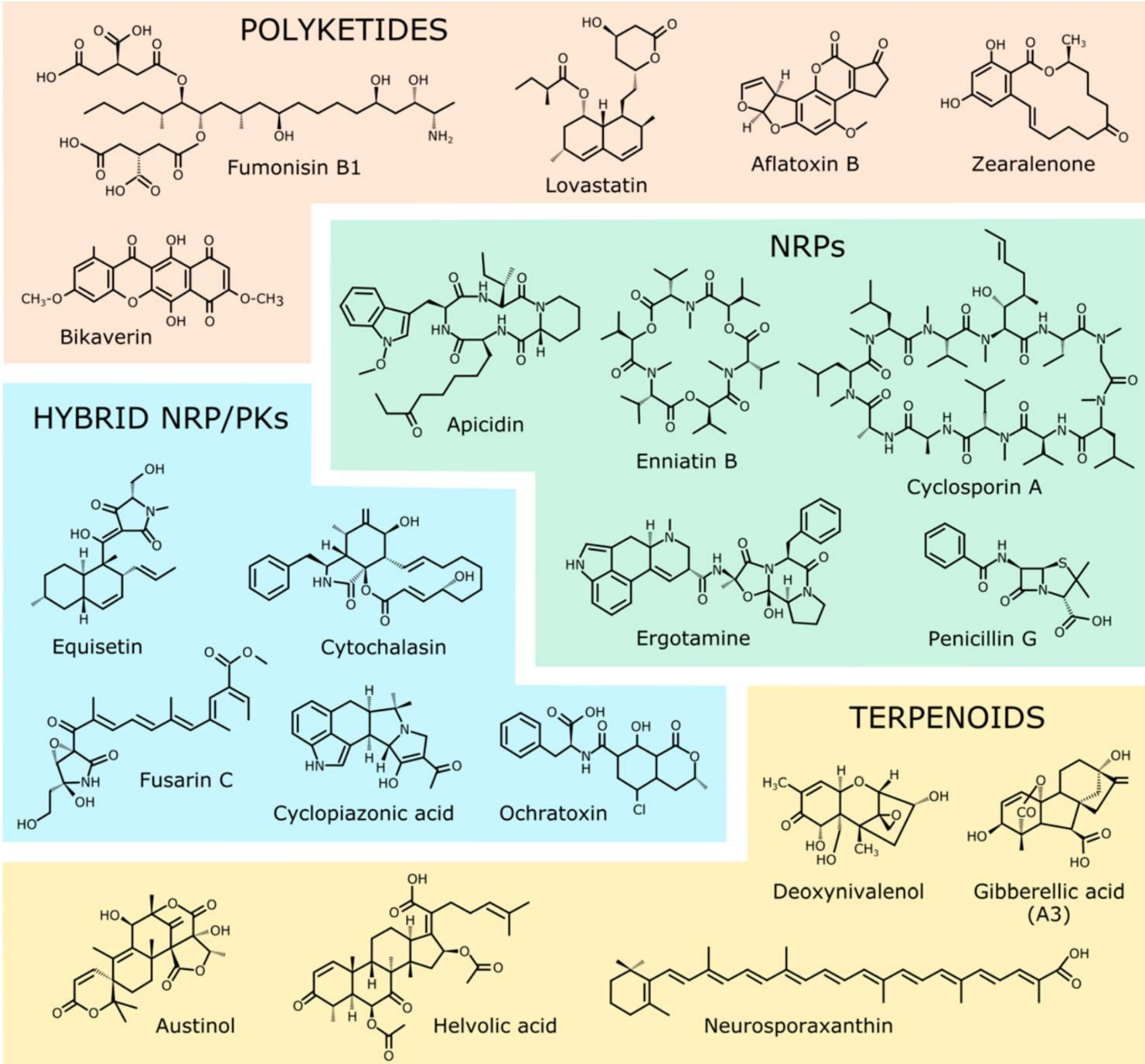
Nature Reviews | Microbiology

Light grey indicates non-ribosomal peptide derivatives; dark grey represents a non-ribosomal peptide derivative that requires a tryptophan dimethylallyltransferase for synthesis; red represents polyketide derivatives; blue represents a mixed polyketide–non-ribosomal peptide compound; green represents a gibberellin, for which synthesis involves terpene cyclase but no non-ribosomal peptide synthetase or polyketide synthase.

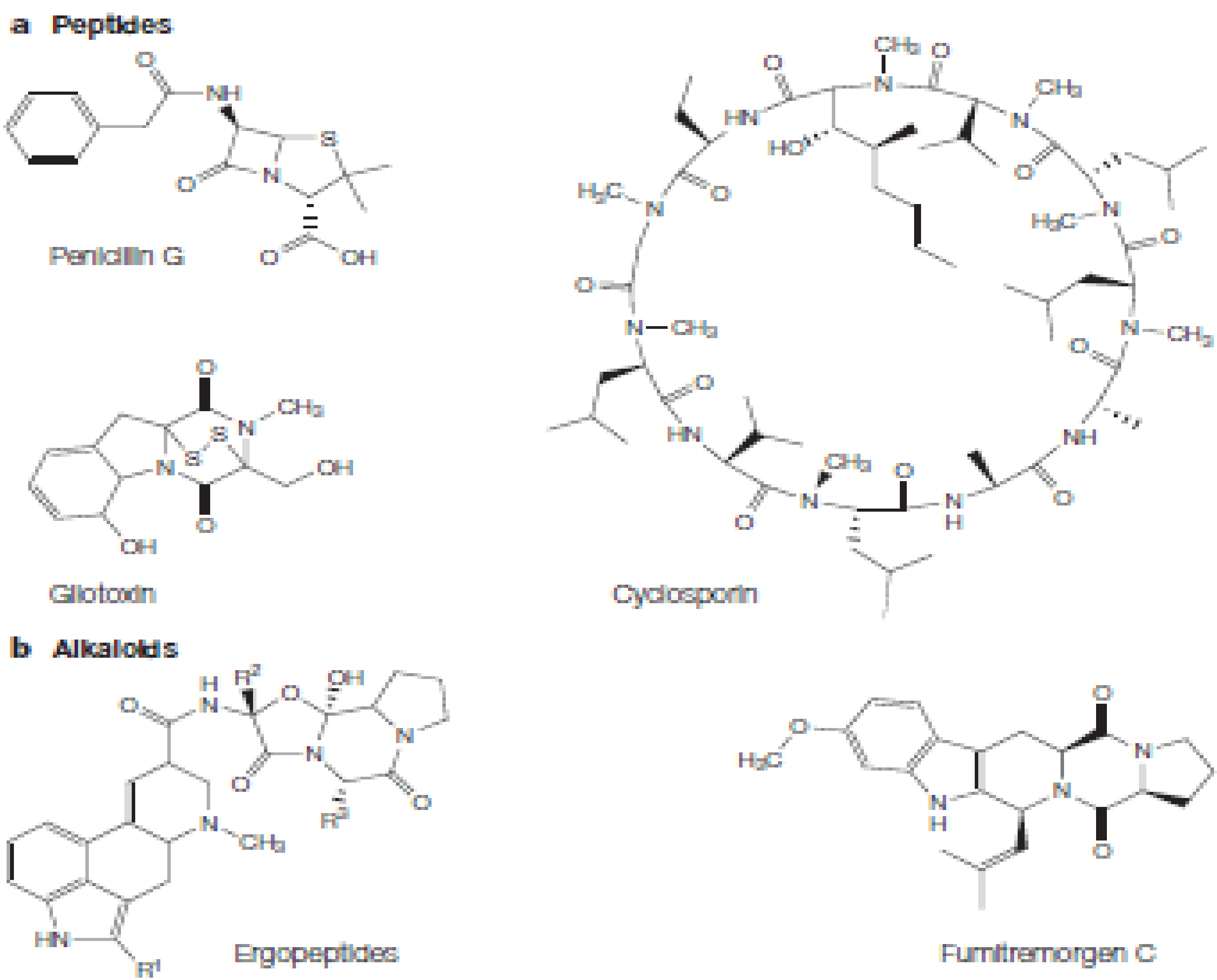
Brakhage, A. Nature Reviews/Microbiology. 2013, (11):21



An interpreted atlas of biosynthetic gene clusters from 1,000 fungal genomes
2021 118 (19) e2020230118
https://doi.org/10.1073/pnas.2020230118

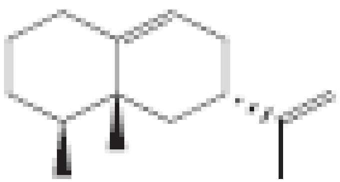


Encyclopedia **2022**, *2*(1), 1-13; https://doi.org/10.3390/encyclopedia2010001

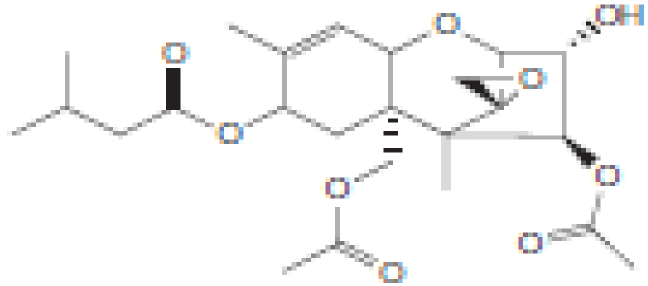


a Peptides
Penicillin G
Gliotoxin
Cyclosporin
b Alkaloids
Ergopeptides
Fumitremorgen C

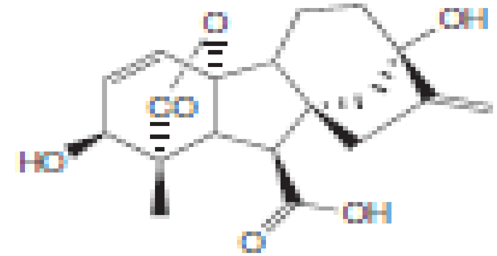
c Terpenes



Aristolochene



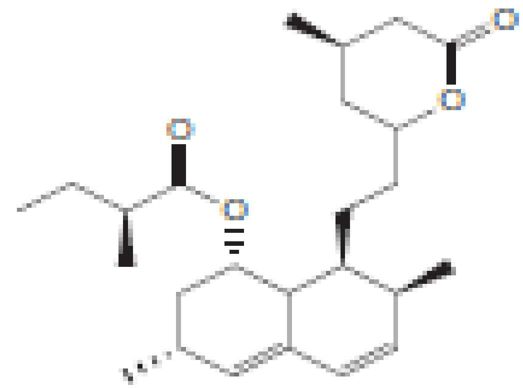
Trichothecene T2 toxin



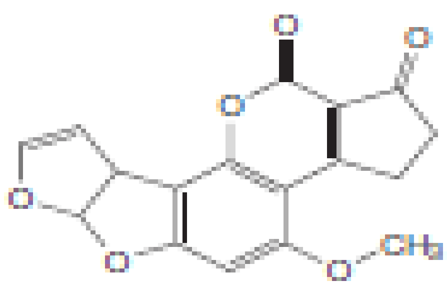
Gibberellin GA3

d Polyketides

Fusarin C



Lovastatin



Aflatoxin B1

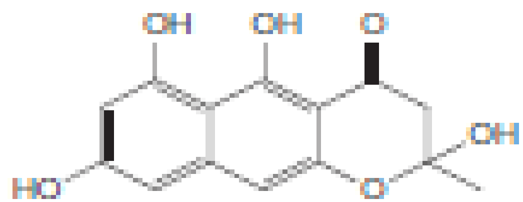


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Table 1. A selection of fungal secondary metabolites. Five representative examples are indicated for each SM family.

Chemical Family	Metabolite	Function/Activity	Representative Producing Genera	Reference
Polyketides (PKs)	Fumonisin B1	Mycotoxin	*Fusarium*	[11]
	Lovastatin	HMG-CoA reductase inhibitor	*Aspergillus*	[12]
	Aflatoxin	Mycotoxin	*Aspergillus*	[13]
	Bikaverin	Antibiotic (protozoa)	*Fusarium*	[14]
	Zearalenone	Mycotoxin (estrogenic)	*Fusarium*	[10]
Non ribosomal peptides (NRPs)	Enniatin B	Mycotoxin (cytotoxic)	*Fusarium*	[15]
	Cyclosporine A	Immunosuppressant	*Tolypocladium*	[16]
	Ergotamine	Ergot alkaloid	*Claviceps*	[17]
	Penicillin G	Antibiotic (bacteria)	*Penicillium*	[18]
	Apicidin	Histone deacetylase inhibitor	*Fusarium*	[19]
Hybrid NRP/PKs	Equisetin	Antibiotic (bacteria)	*Fusarium*	[20,21]
	Fusarin C	Mycotoxin	*Fusarium*	[22]
	Cytochalasin	Actin inhibitor	*Penicillium, Chaetomium*	[23]
	Cyclopiazonic acid	Mycotoxin	*Aspergillus, Penicillium*	[24]
	Ochratoxin A	Mycotoxin	*Aspergillus, Penicillium*	[25,26]
Terpenoids	Gibberellic acid (GA3)	Plant hormone	*Fusarium*	[27,28]
	Deoxynivalenol	Mycotoxin	*Fusarium*	[29]
	Neurosporaxanthin	Carotenoid pigment	*Neurospora, Fusarium*	[30,31]
	Austinol	Unknown	*Aspergillus*	[32]
	Helvolic acid	Antibiotic (bacteria)	*Aspergillus*	[33]

Encyclopedia **2022, *2*(1), 1-13; https://doi.org/10.3390/encyclopedia2010001**

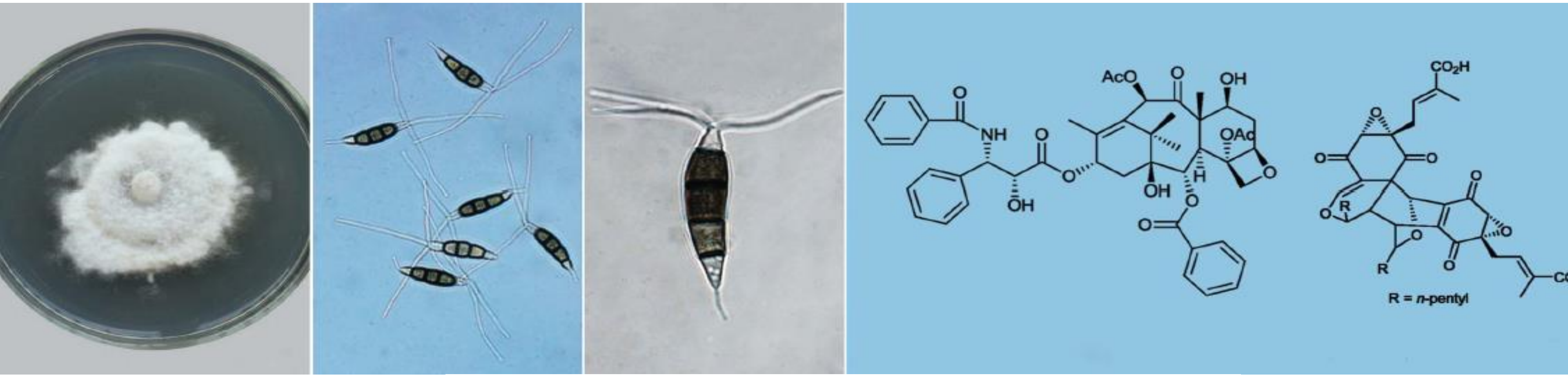
Cite this: *Nat. Prod. Rep.*, 2012, **29**, 622

www.rsc.org/npr

REVIEW

The taxonomy, biology and chemistry of the fungal *Pestalotiopsis* genus

Xiao-Long Yang,[ab] Jing-Ze Zhang[c] and Du-Qiang Luo*[a]



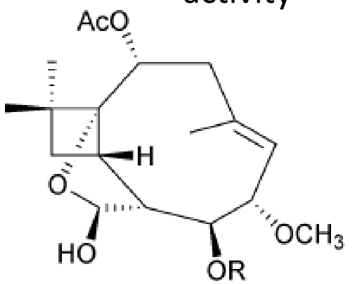
196 metabolitos

Secondary metabolites of the Pestalotiopsis genus

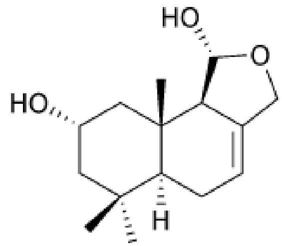
4.1 Terpenoids

4.1.1 Sesquiterpenes (22 compostos)

cytotoxicity and immunosuppressive activity



1 R = H, (+)-pestalotiopsin A
3 R = CH_3, (+)- pestalotiopsin C



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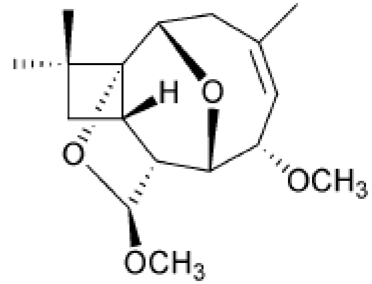
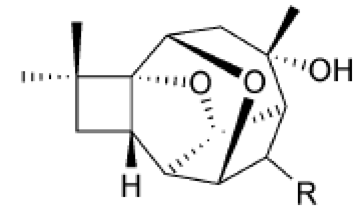
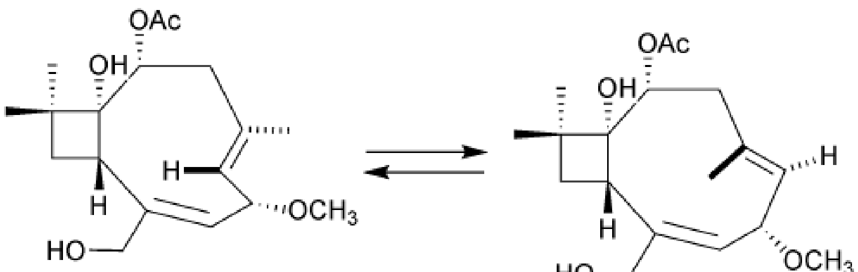


6 pestalodiopsolide A

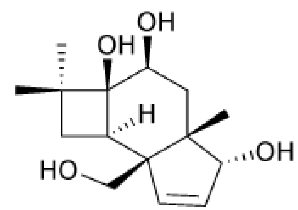


7 R = β-OCH_3, taedolidol
8 R = α-OCH_3, 6-epitaedolidol



minor (β,β) major (β, α)

2 (-)-pestalotiopsin B



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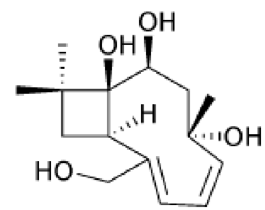

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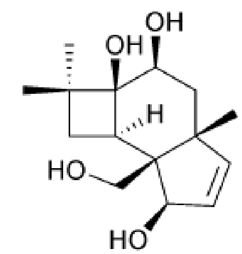
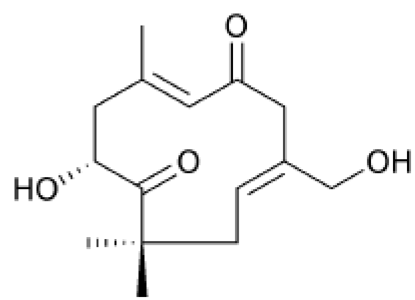


11

activity against Bacillus subtilis, Staphylococcus aureus



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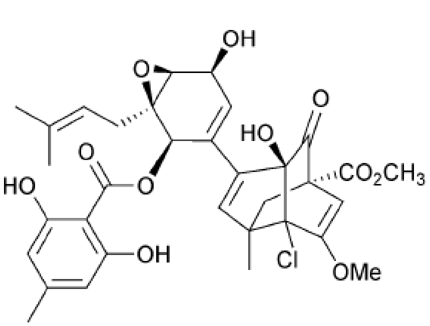
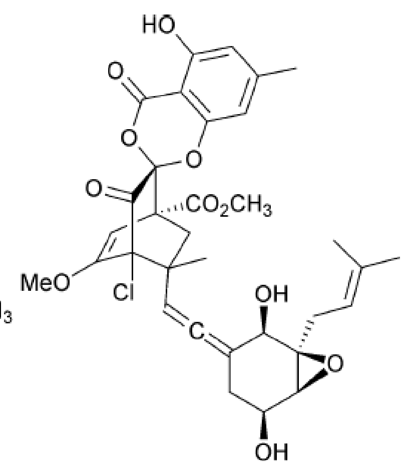
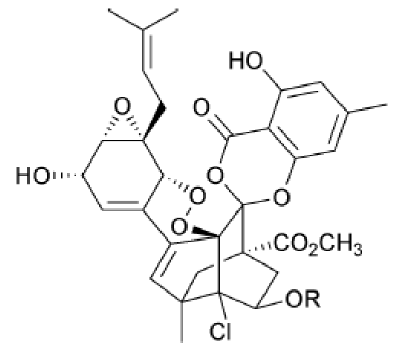


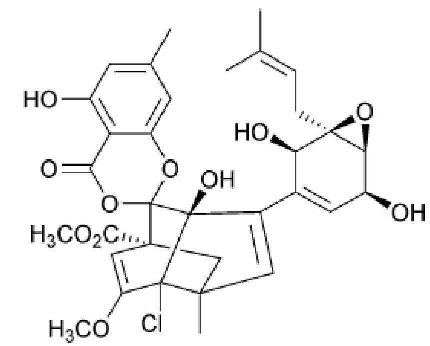
12 chloropupukeananin



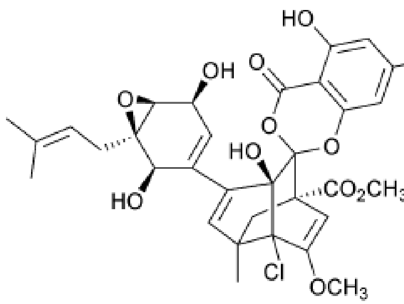
13 chloropestolide A



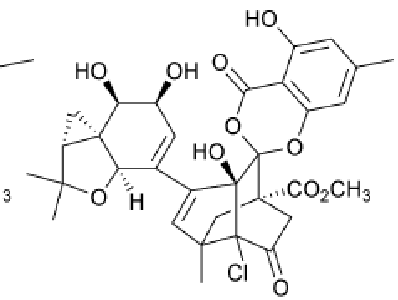
14 R = Me, chloropupukeanolide A
15 R = H, chloropupukeanolide B



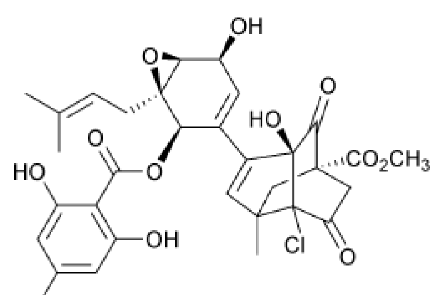
16 chloropupukeanolide C



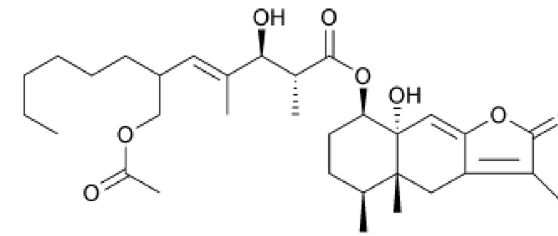
17 chloropupukeanolide D



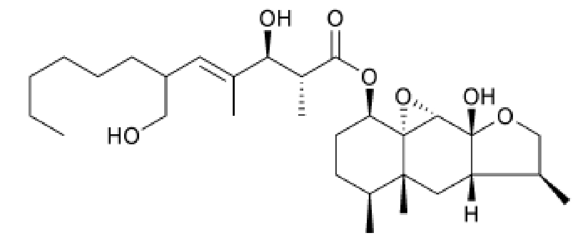
18 chloropupukeanolide E



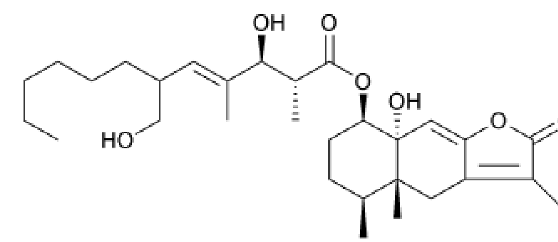
19 chloropupukeanone A



20 pestalotiopins C



21 dihydroberkleasmin



22 berkleasmin C

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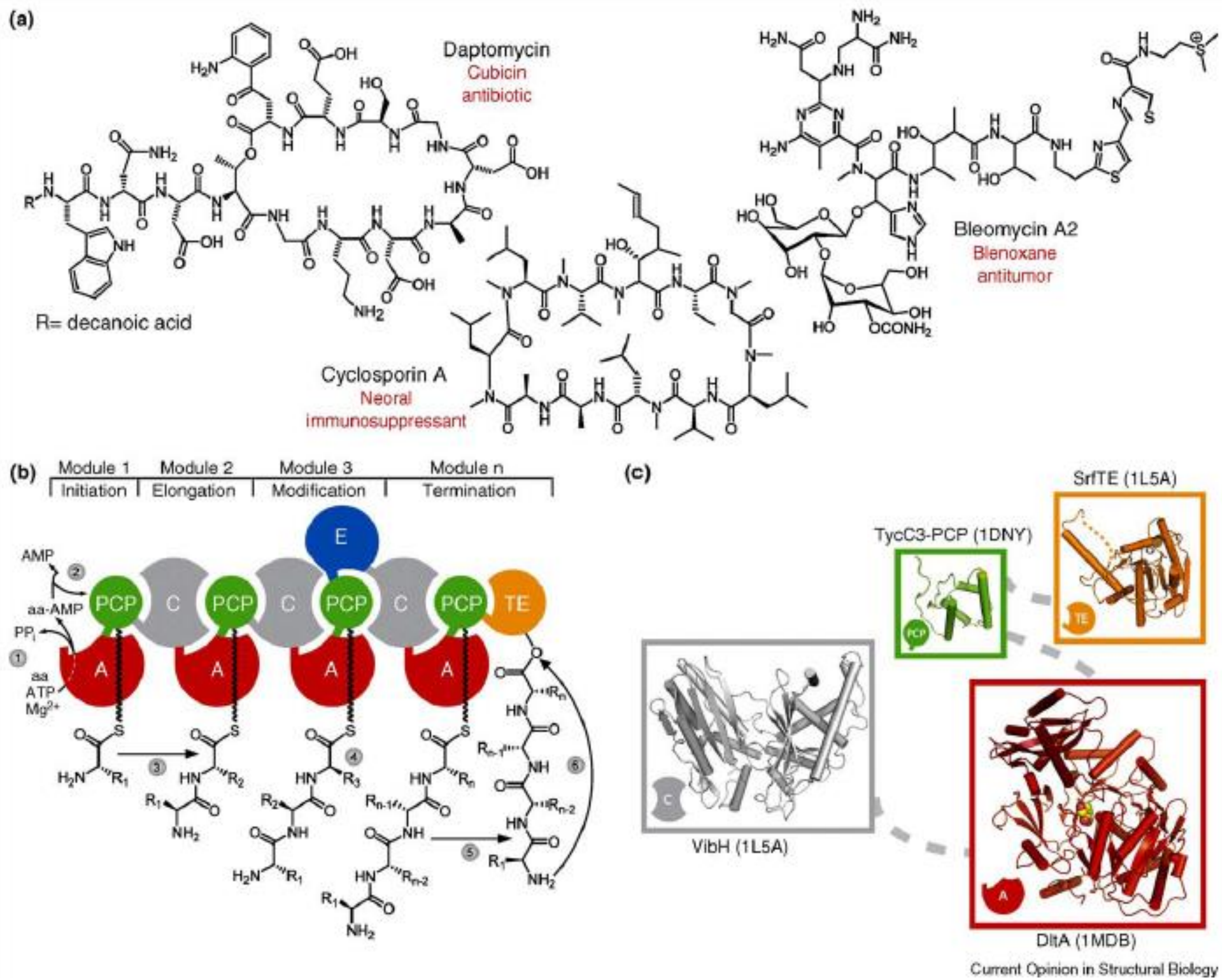
Current Opinion in Structural Biology

Nonribosomal peptide synthetases: structures and dynamics

Matthias Strieker, Alan Tanović and Mohamed A Marahiel



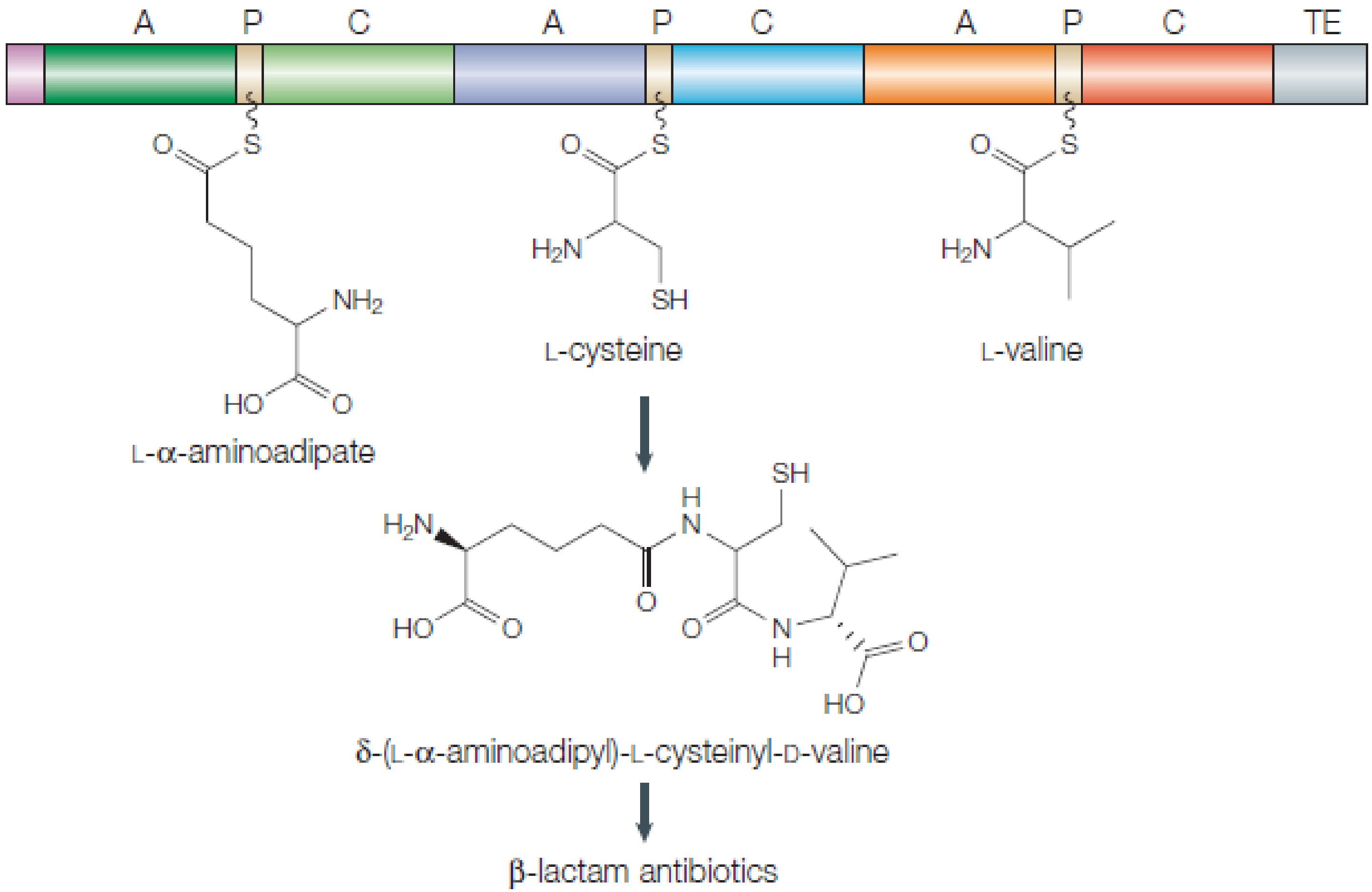


Figure 3 | **ACV synthetase, a trimodular non-ribosomal peptide synthetase.**
δ-(L-α-aminoadipyl) L-cysteinyl-D-valine (ACV) synthetase catalyses the first committed step in penicillin and cephalosporin biosynthesis. Each amino acid is recognized and activated by the cognate adenylation domain (A), and attached as a thioester to 4′-phosphopantetheine at the peptidyl carrier domain (P). Peptide bonds are formed with the involvement of the condensation domain (C). The final tripeptide, attached to the peptidyl carrier domain of the C-terminal module, is released by the integrated thioesterase domain (TE), with the L-valine isomerized to D-valine. The tripeptide is subsequently cyclized to isopenicillin N.

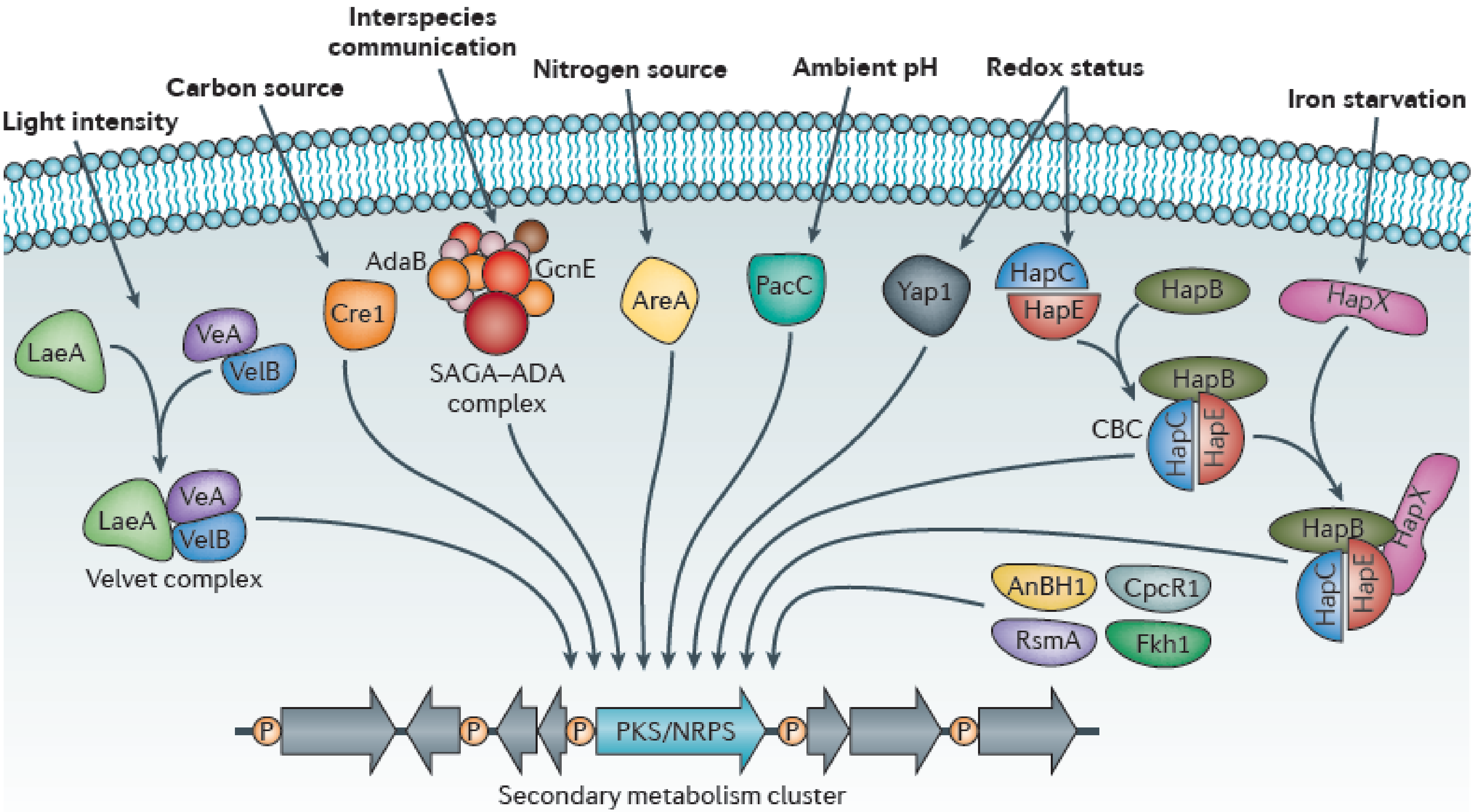


Figure 3 | **Global regulatory proteins involved in the regulation of secondary metabolism gene clusters in various fungi.** Environmental signals can influence the regulation of various secondary metabolism gene clusters through regulatory proteins that respond to these environmental stimuli and, in turn, modulate the expression of the clusters. Shown is a model secondary metabolism gene cluster containing a gene encoding a central non-ribosomal peptide synthetase (NRPS), a polyketide synthase (PKS) or a hybrid PKS–NRPS enzyme. CBC, CCAAT-binding complex; CpcR1, cephalosporin C regulator 1; LaeA, loss of *aflR* expression A; RsmA, restorer of secondary metabolism A; SAGA–ADA, Spt–Ada–Gcn5–acetyltransferase–ADA.

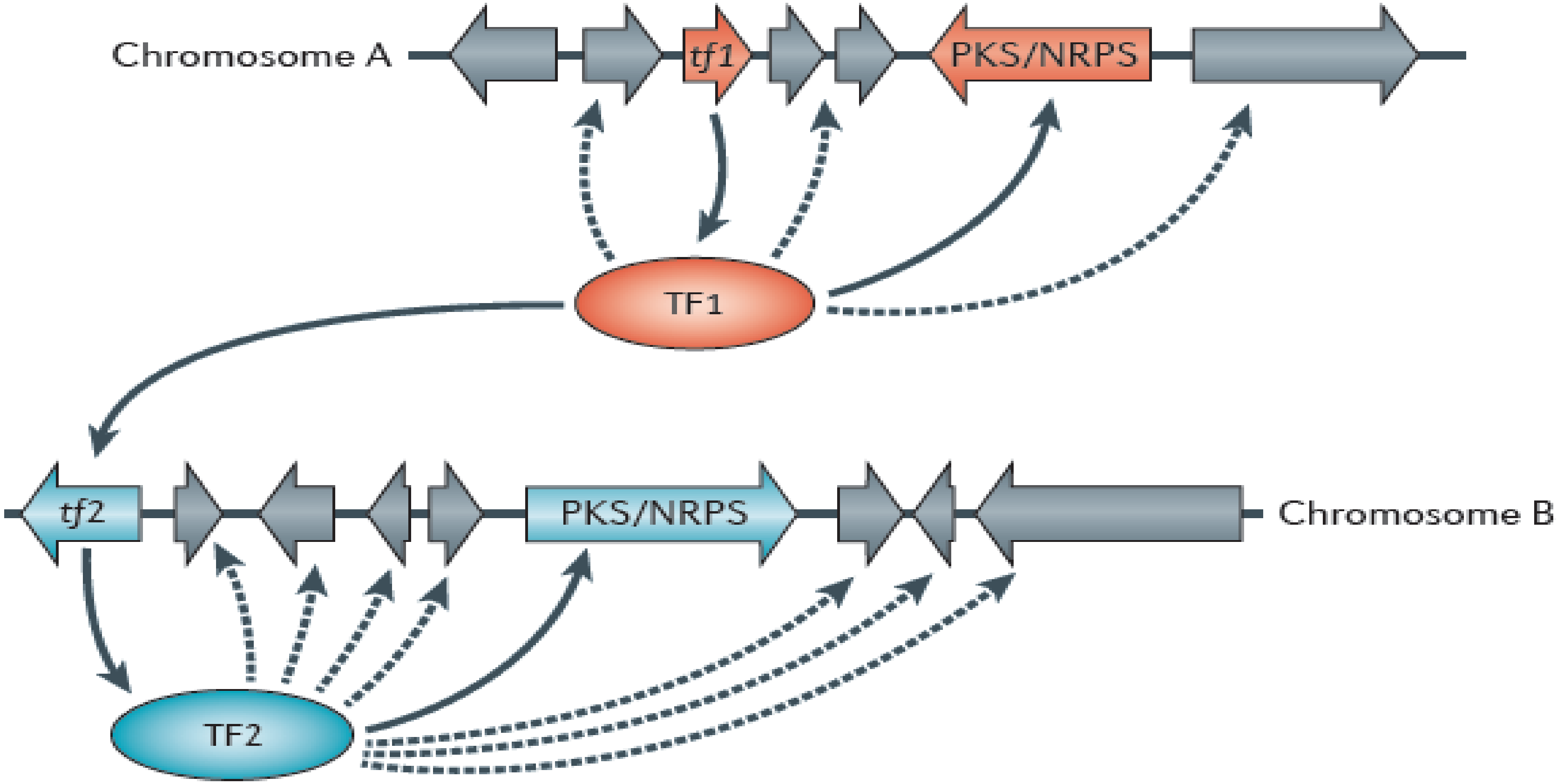


Figure 4 | **Pathway-specific regulatory genes and proteins, and crosstalk between secondary metabolism gene clusters.** Secondary metabolism gene clusters encode polyketide synthase (PKS), non-ribosomal peptide synthetase (NRPS) or hybrid PKS–NRPS enzymes. Many of these clusters also contain genes encoding transcription factors (TFs) that are required for expression of the cluster genes. Dashed arrows indicate possible activation by these TFs, in addition to the required activation of PKS/NRPS genes. Moreover, crosstalk between clusters has been reported[34]. In this illustrative example, a pathway-specific *tf1* gene on chromosome A encodes a TF that activates not only its own cluster, but also the pathway-specific *tf2* gene of another gene cluster on a different chromosome, leading to activation of this second gene cluster.

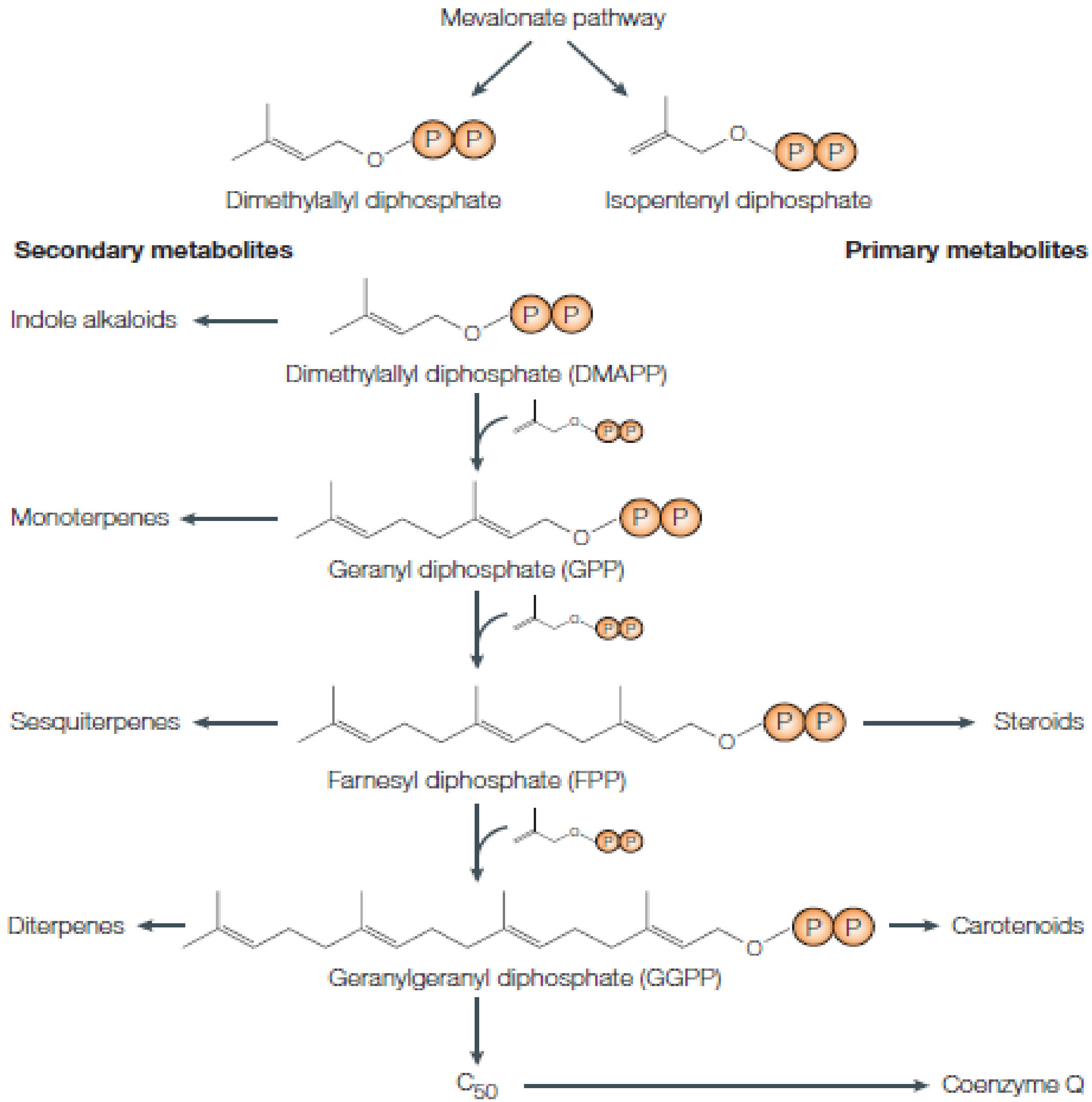


Figure 4 | **Terpene biosynthetic pathway.** Isopentenyl diphosphate and its isomer dimethylallyl diphosphate (DMAPP), products of the mevalonate pathway, are the building blocks (5C isoprene units) for the linear polyprenyl diphosphates, which are precursors of steroids, carotenoids and coenzyme Q in many species. A family of isoprenyl diphosphate synthases is responsible for chain elongation. DMAPP and the isoprenoid intermediates are also the starting points for a wide range of secondary metabolites, including indole alkaloids, monoterpenes, sesquiterpenes and

Metabolite(s)	Fungus	Application(s)
Thysanone	*Thysanophora penicilloides*	Human rhinovirus 3C-protease inhibitor
Variculanol	*Emericella variecolor*	Toxicity to *Eimeria tenella*
Ophioblin K and 6-epiophiobolin K	*Aspergillus ustus*	Toxicity to *Caenorhabditis elegans*
L-696,474 (18-dehydroxy cytochalasin H)	*Hypoxylon fragiforme*	HIV-1 protease inhibitor
3-(Dimethylaminomethyl)-1-(1,1-dimethyl-2-propenyl)indole	*Penicillium daleae*	5-HT$_{1D}$ receptor agonists
Calbistrin A	*Aspergillus versicoIor*	Broad spectrum antifungal, increased human LDL receptors
Maxikdiol	Unidentified coelomycete MF5717	Agonist of maxi-K (large-conductance calcium-activated potassium) channels
Apicidins	*Fusarium* spp.	Broad spectrum antiparasitic agents, histone deacetylase inhibitors
Ascosteroside	*Mycoleptodiscus atromaculans*	Antifungal, β-1,3-glucan synthase inhibitor
Sporandol	*Chrysosporium merdarium*	Insecticide and antiparasitic agent
Equisetin	*Fusarium heterosporum*	HIV-1 integrase inhibitor
Phomasetin	*Phoma* sp.	HIV-1 integrase inhibitor
Cytosporic acid	*Cytospora* sp.	HIV-1 integrase inhibitor
Nodulisporic acids	*Nodulisporium* sp.	Insecticide, invertebrate-specific glutamate-gated chloride ion channels
Hyalodendrosides A and B	*Hyalodendron* sp.	Antifungal, β-1,3-glucan synthase inhibitor

Metabolite(s)	Fungus	Application(s)
Nalanthalide	*Chaunopycnis pustulata*	Blockage of voltage-gated potassium (Kv1.3) channels and L-type Ca^{2+} channels
Candelalides	*Sesquicillium candelabrum*	Blockage of voltage-gated potassium (Kv1.3) channels
Dihydrotubingensin A, B	*Aspergillus tubingensis*	No activity
Sordarins	*Rosellinia subiculata*	Antifungal, elongation factor 2 inhibitor
Integramides A and B	*Dendrodochium* sp.	HIV-1 integrase inhibitors
Xylarenal A and B	*Xylaria liquidambar*	Selective binding to neuropeptide Y receptor Y5
Xanthonol	Non-sporulating fungus MF6460	Insecticidal activities against larvae of *Lucilia sericata*, *Aedes aegypti*, and anthelmintic against *Haemonchus contortus*
Coccidiostatin A	*Penicillium rugulosum*	Antiparasitic activity against *Besnoitia jellisoni*, *Eimeria tenella*, and *E. mitis*
Mellamide	*Aspergillus melleus*	Insecticidal activity in bioassays against larvae of *Lucilia sericata* and *Aedes aegypti*

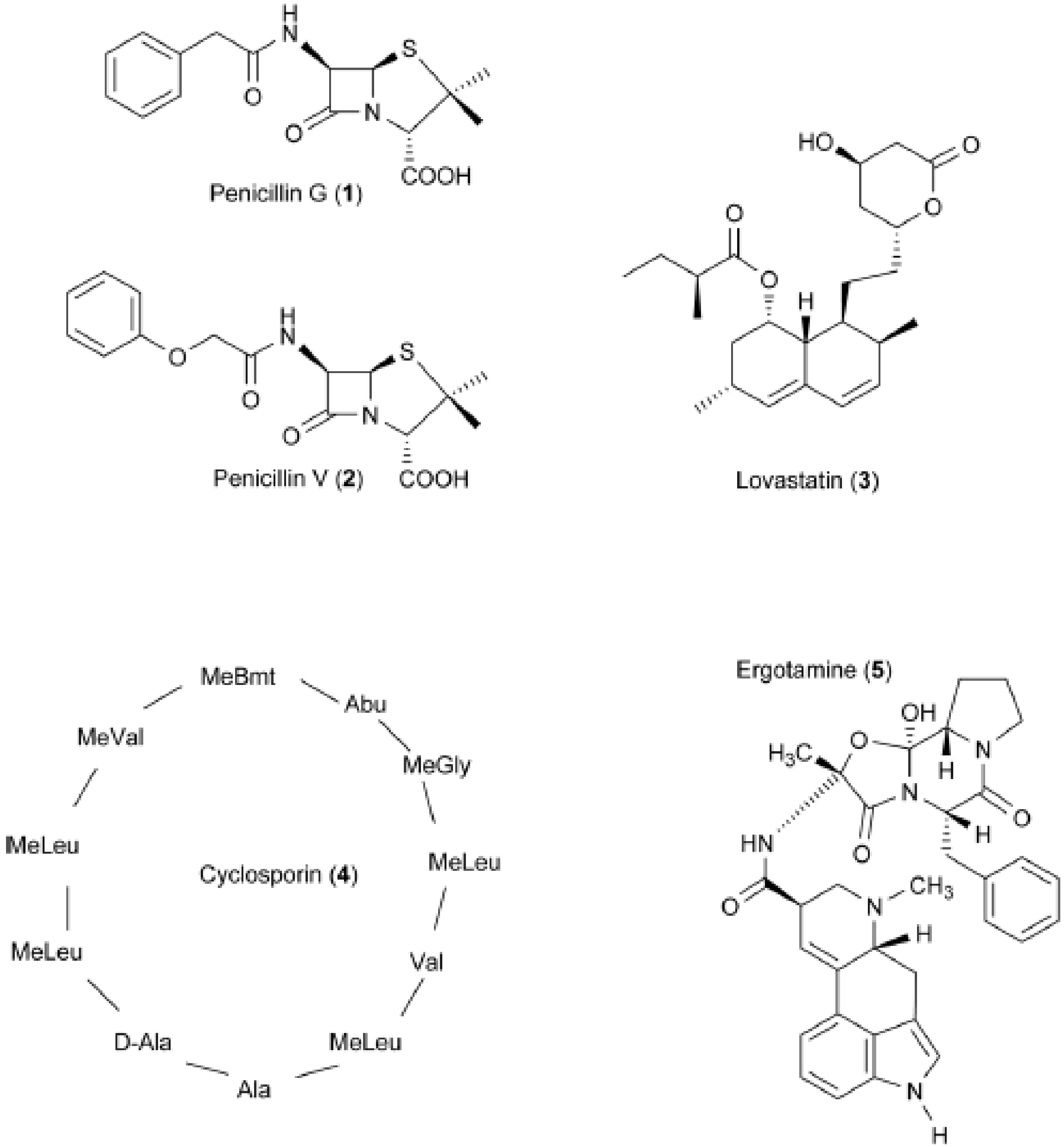
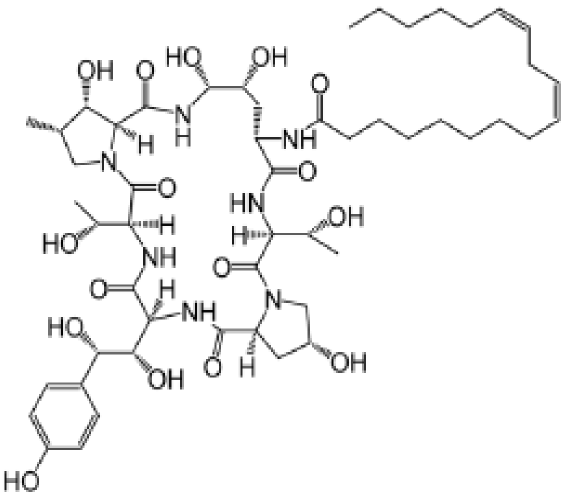
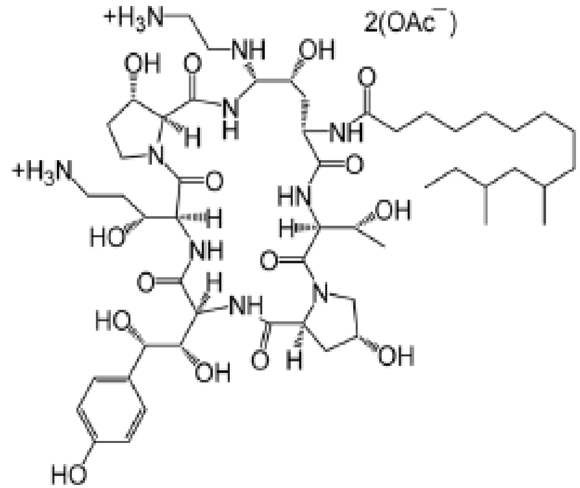


Fig. 1 Chemical structures of clinically used fungal secondary metabolites. Abbreviations for amino acids: MeBmt = (4*R*)-4-[(*E*)-2-butenyl]-4-methyl-l-threonine, Abu = 2-aminobutyric acid, MeGly = *N*-methylglycine, MeLeu = *N*-methylleucine, MeVal = *N*-methylvaline.

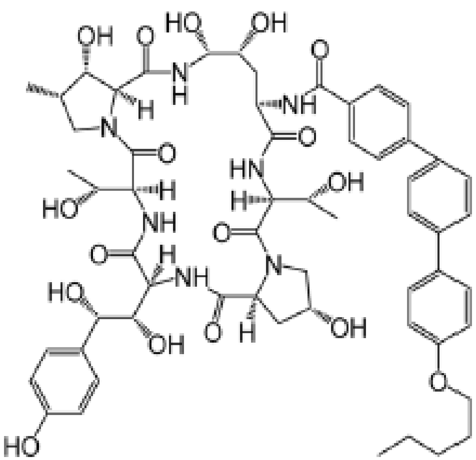
Fig. 2 Selected natural compounds from fungi with antifungal activity.



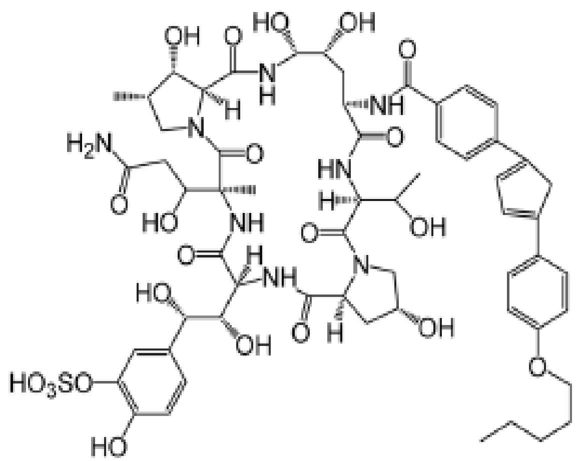
Echinocandin B (**6**)



Caspofungin (**7**)



Anidulafungin (**8**)



Micafungin (**9**)

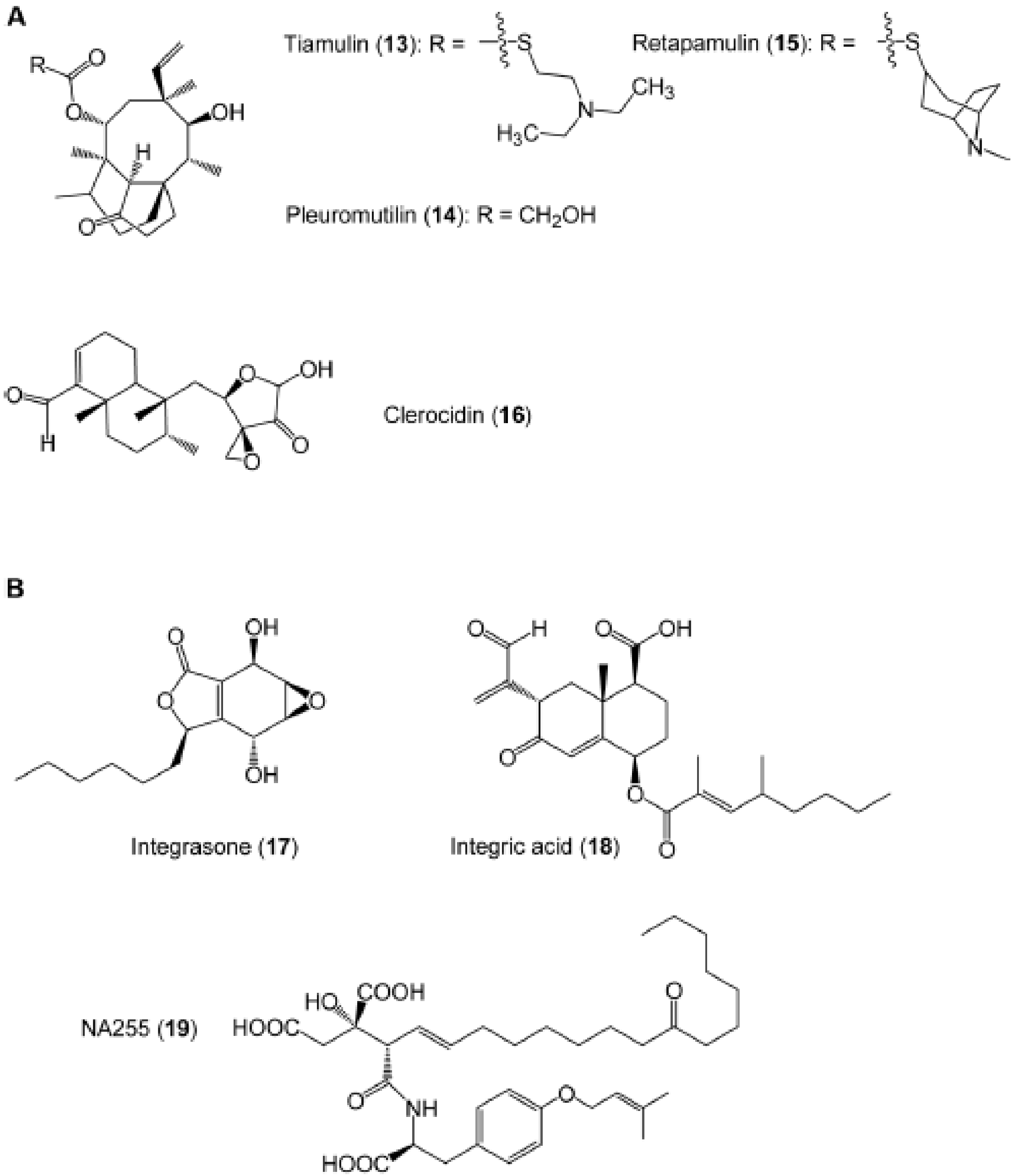


Fig. 3 Highlighted fungal secondary metabolites with **A**) antibacterial and **B**) antiviral activity.

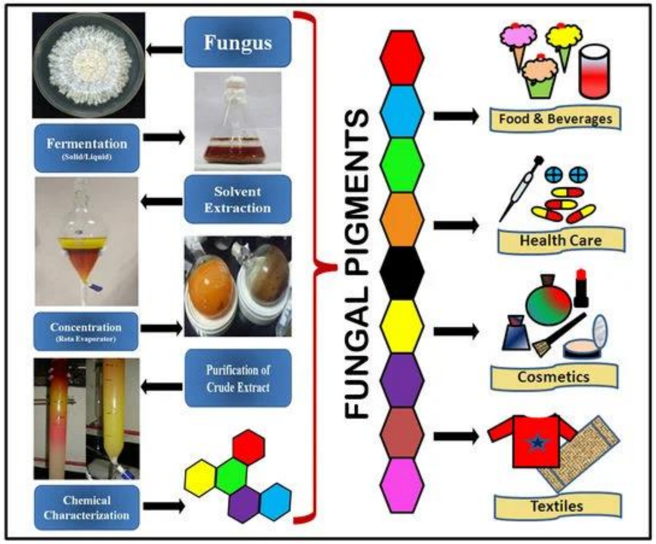
Fungal Pigments and Their Prospects in Different Industries

by Ajay C. Lagashetti [1], Laurent Dufossé [2,*], Sanjay K. Singh [1,*] and Paras N. Singh [1]

Abstract

The public's demand for natural, eco-friendly, and safe pigments is significantly increasing in the current era. Natural pigments, especially fungal pigments, are receiving more attention and seem to be in high demand worldwide. The immense advantages of fungal pigments over other natural or synthetic pigments have opened new avenues in the market for a wide range of applications in different industries. In addition to coloring properties, other beneficial attributes of fungal pigments, such as antimicrobial, anticancer, antioxidant, and cytotoxic activity, have expanded their use in different sectors. This review deals with the study of fungal pigments and their applications and sheds light on future prospects and challenges in the field of fungal pigments. Furthermore, the possible application of fungal pigments in the textile industry is also addressed.

Keywords: color; natural pigments; fungal pigments; dyeing; textile fabrics



Microorganisms 2019, *7*(12), 604; https://doi.org/10.3390/microorganisms7120604

ELSEVIER

Current Opinion in Biotechnology
Volume 26, April 2014, Pages 56-61

Filamentous fungi are large-scale producers of pigments and colorants for the food industry

Laurent Dufossé [1], Mireille Fouillaud [1], Yanis Caro [1], Sameer AS Mapari [2 4], Nuthathai Sutthiwong [1 3]

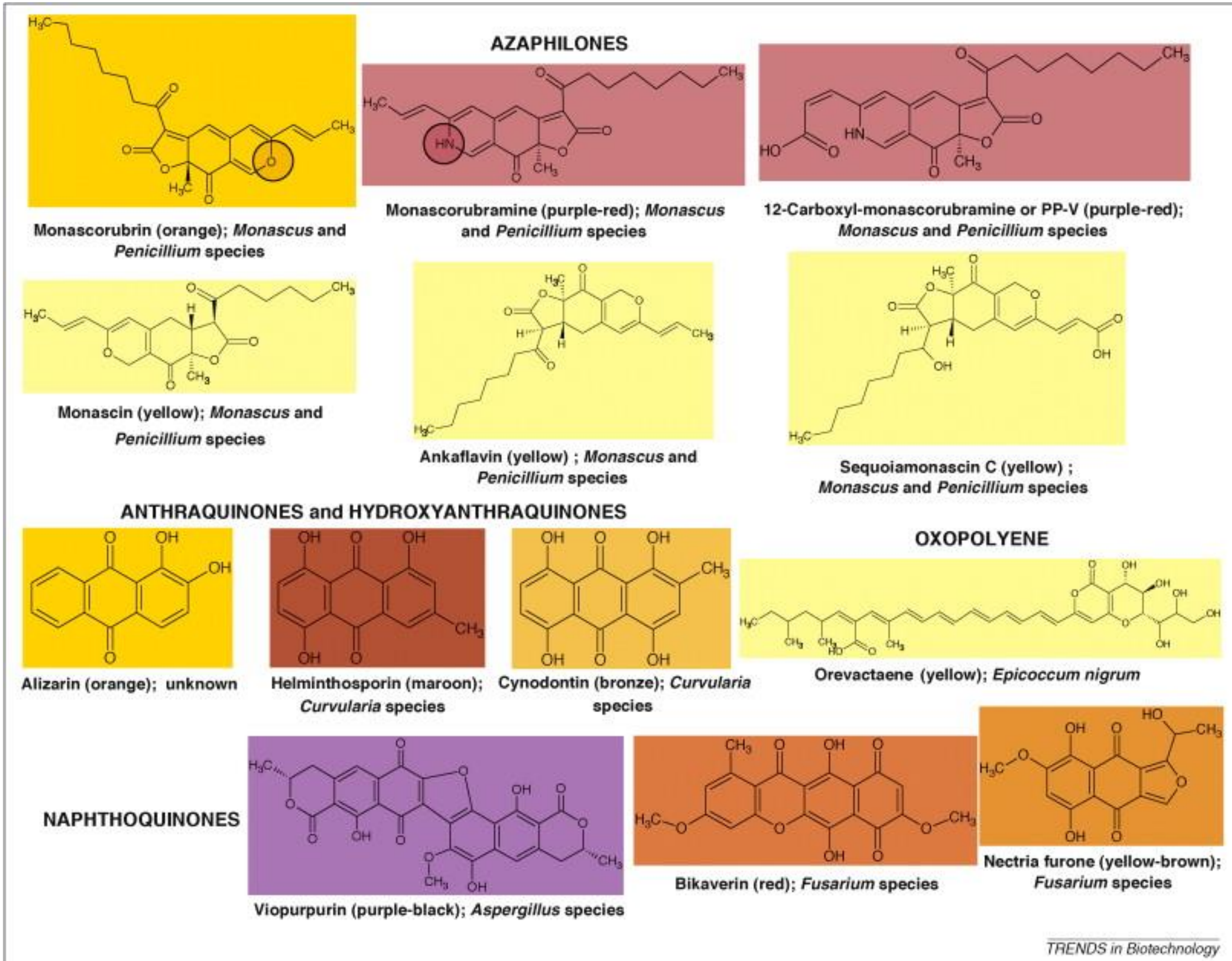
Pigmented filamentous fungi

Pigments and colorants produced and extracted

Food formulation and processing

Highlights

- Fungi can efficiently produce pigments and colorants for the food industry.
- Growing world awareness on the necessity of replacing the synthetic coloring agents.
- Pigments of chemical origin substituted by natural healthier alternatives.
- Mycotoxin risk could be managed.



Volume 28, Issue 6, June 2010, Pages 300-307; https://doi.org/10.1016/j.tibtech.2010.03.004

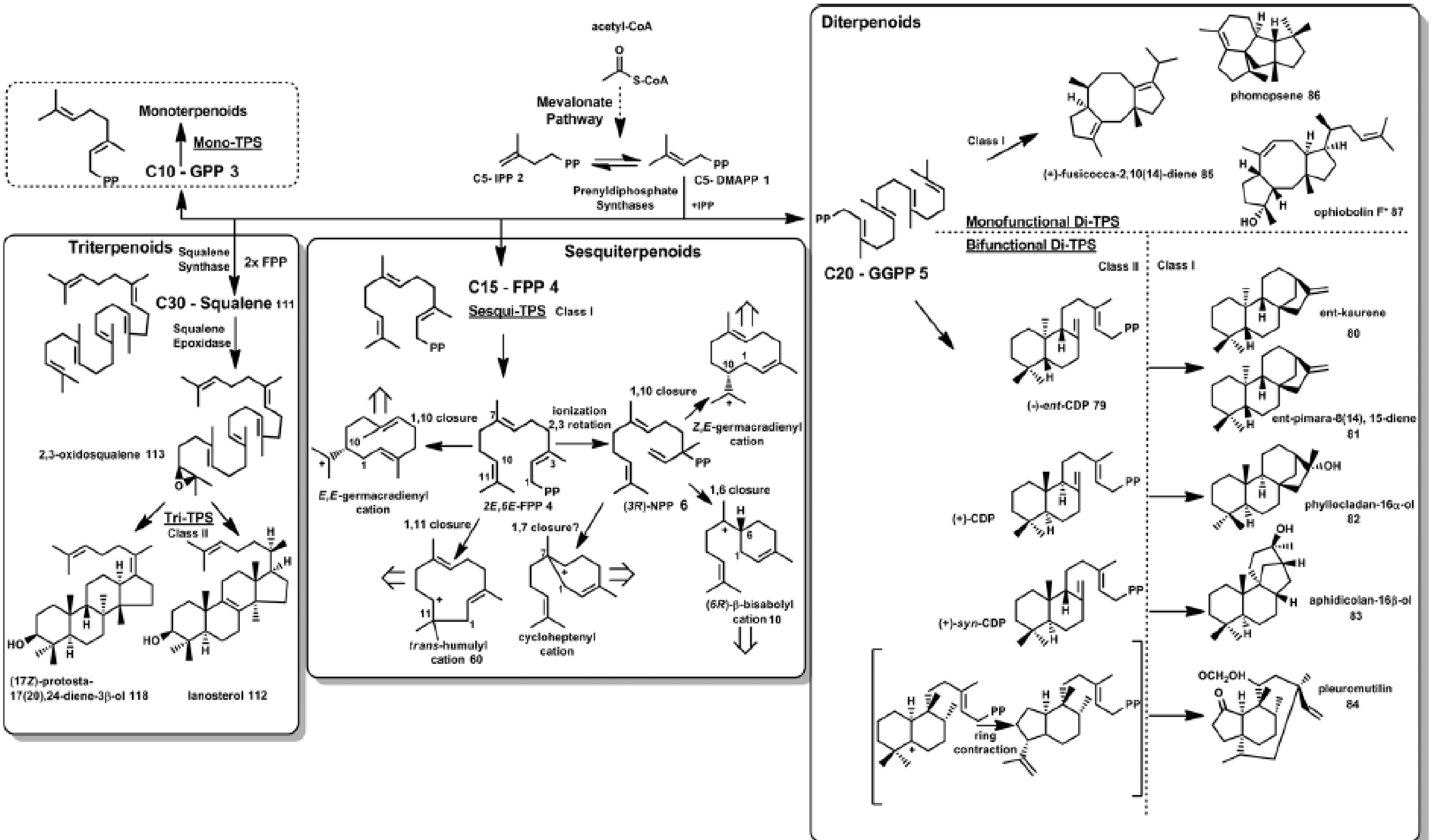
Fungi	Pigment	Color	Fabrics	References
Penicillium oxalicum	Anthraquinones	Arpink Red	Wool	Sardaryan et al. [97]
Trichoderma virens	Anthraquinones	Yellow	Silk, Wool	Sharma et al. [77]
Alternaria alternata	Anthraquinones	Reddish-Brown		
Curvularia lunata	Anthraquinones	Black		
Alternaria alternata	Anthraquinones	Reddish-Brown	Cotton	Devi and Karuppan [95]
Thermomyces sp.	Anthraquinones	Yellow	Cotton, Silk, Wool	Poorniammal et al. [94]
Trichoderma sp.	Anthraquinones	Yellow	Cotton, Silk, Silk cotton	Devi [98]
Trichoderma sp.	Anthraquinones	Yellow	Silk, Wool	Gupta et al. [93]
Penicillium oxalicum (NRC M25)	Anthraquinones	Faint Reddish-Brown	Wool	Mabrouk et al. [24]
Sclerotinia sp.	Anthraquinones	Pinkish-Red	Cotton	Perumal et al. [84]
Aspergillus sp. AN01	Asperyellone	Yellow	Silk, Cotton, Synthetic and Wool fabrics	Iswarya et al. [99]
Monascus purpureus	Azaphilones	Red	Cotton	Velmurugan et al. [96]
Penicillium purpurogenum		Yellow		
Isaria farinosa		Pink		
Fusarium verticillioides		Reddish-Brown		
Emericella nidulans		Red		
Penicillium murcianum	Carotenoids	Yellow	Wool	Hernandez et al. [100]
Talaromyces australis		Red		
Talaromyces australis	2, 4-Di-tert-butylphenol	Red	Cotton fabric	Shibila and Nanthini [101]
Phoma herbarum	Magenta pigment	Magenta	Nylon	Chiba et al. [102]
Monascus purpureus	Monascorubramine	Red	Wool	De santis et al. [103]
Talaromyces verruculosus	Polyketide	Red	Cotton fabric	Chadni et al. [89]
Monascus purpureus	Rubropunctamine	Red	Wool	De santis et al. [103]
Chlorociboria aeruginosa	Quinones	Green	Bleached cotton, Spun polyamide,	Weber et al. [48]; Hinsch et al. [91]
Scytalidium cuboideum		Red		

May 2020
Journal of Fungi 6(2):68
DOI:10.3390/jof6020068

Traversing the fungal terpenome

Maureen B. Quin,† Christopher M. Flynn† and Claudia Schmidt-Dannert*

Cite this: *Nat. Prod. Rep.*, 2014, 31,



Scheme 1 Overview of fungal terpene biosynthesis. The mevalonate pathway yields the C5 isoprene precursors dimethylallyl diphosphate (DMAPP) 1 and its isomer isopentenyl diphosphate (IPP) 2. Head-to-tail condensation of DMAPP 1 with one, two or three IPP 2 units catalyzed by

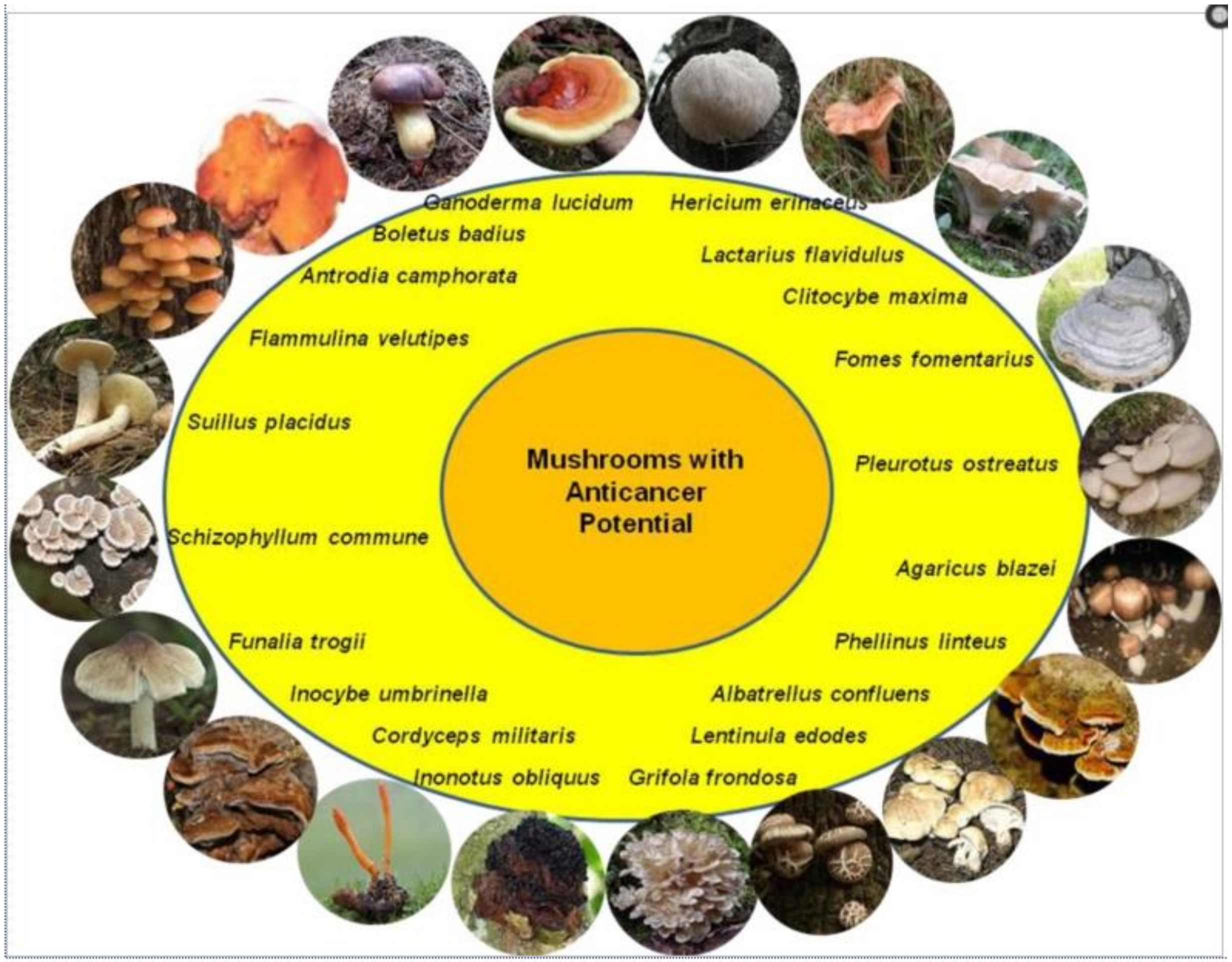
In conclusion, our relationship with fungi is arguably described best as light *and* shade, as friend *and* foe. Given their biochemical ingenuity and overwhelming metabolic wealth, however, fungi will not let the drug lead pipeline run dry. Moreover, the major portion of the fungal organismic diversity still remains to be discovered. Consequently, a huge untapped reservoir of new natural products and intriguing enzymes as tools for chemoenzymatic syntheses appeals to pharmaceutical biologists and chemists as an open road ahead. With respect to the pharmaceutical sciences, the bright and friendly side of fungal biology prevails.

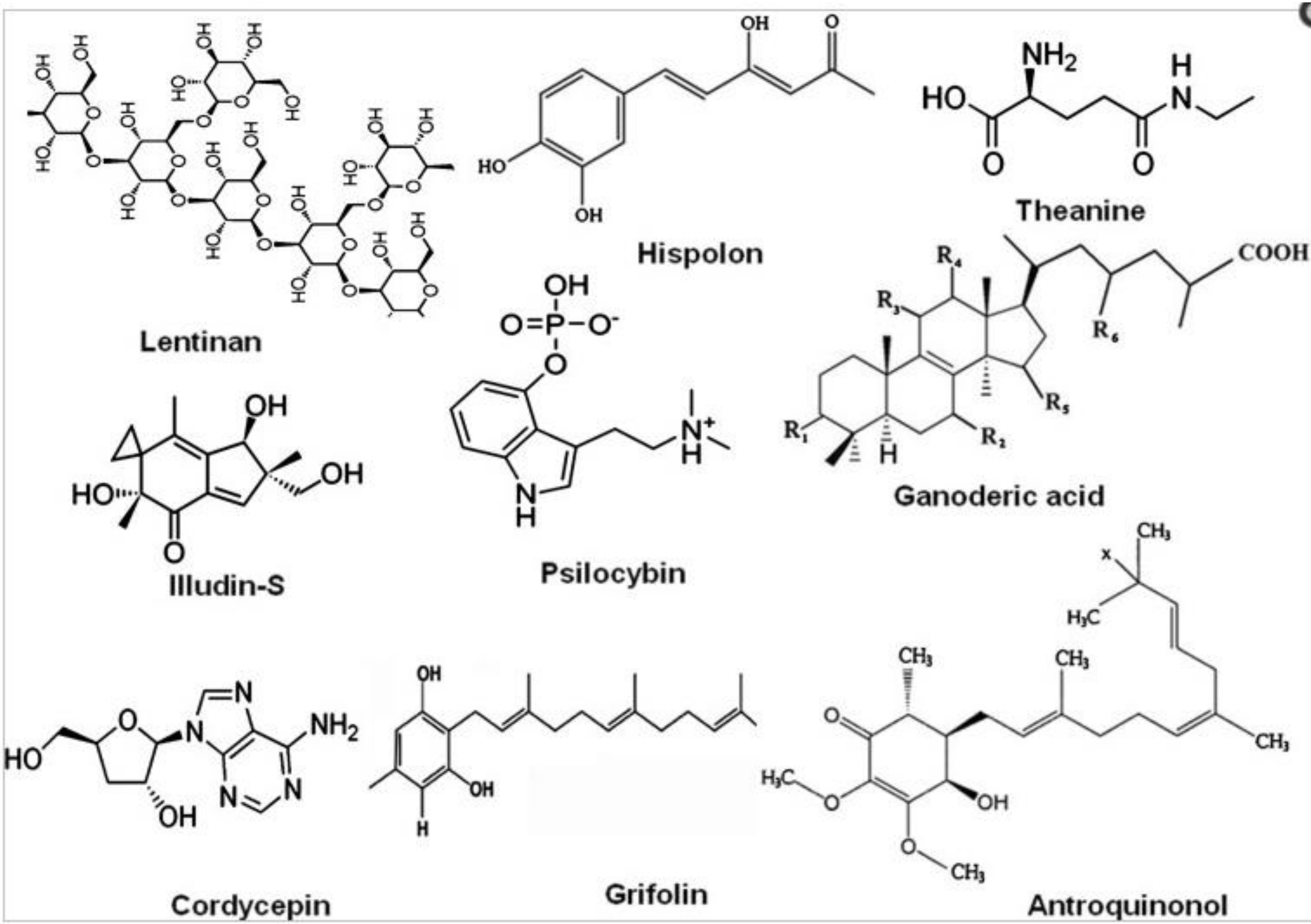
3 Biotech (2012) 2:1–15
DOI 10.1007/s13205-011-0036-2

REVIEW ARTICLE

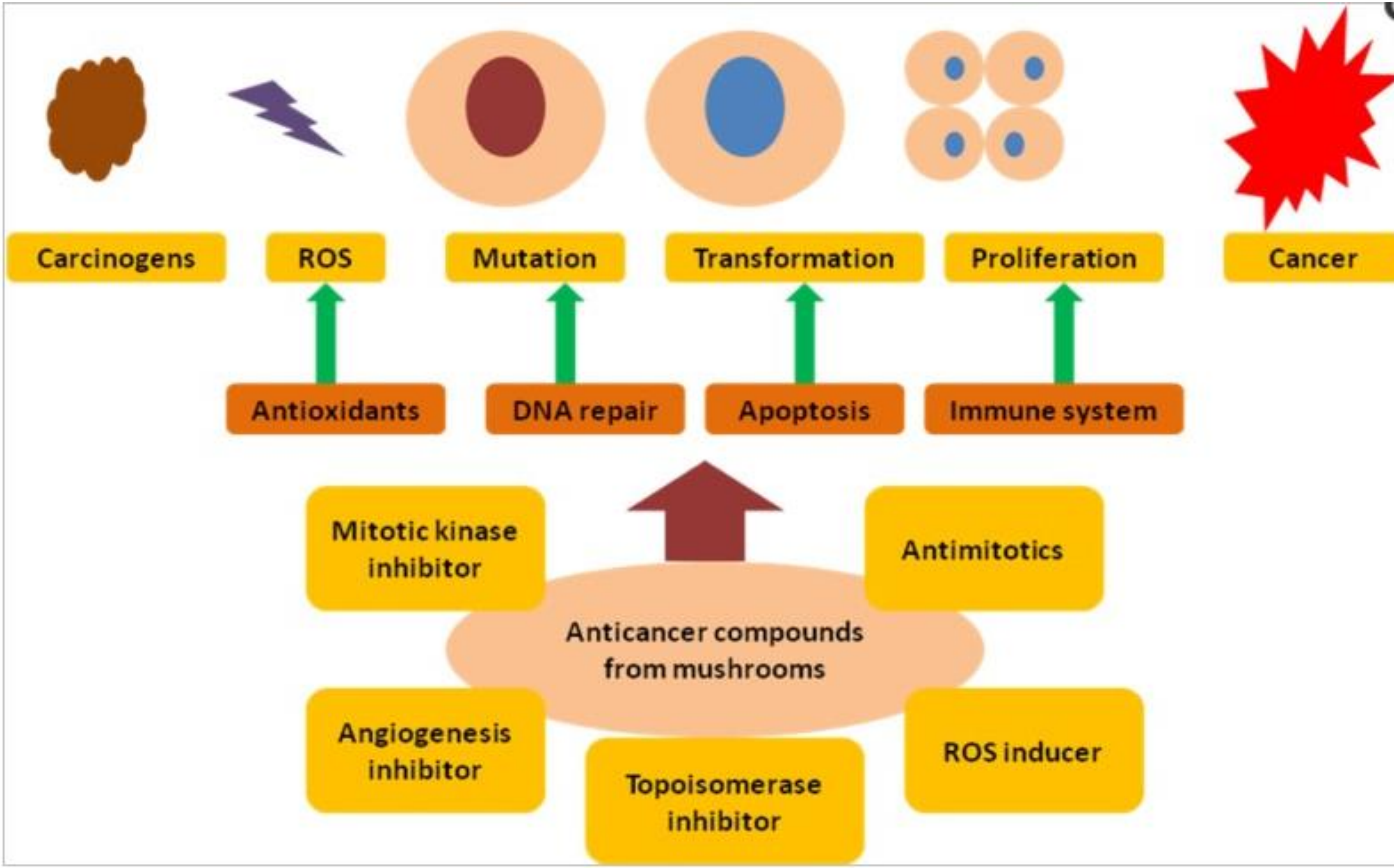
Recent developments in mushrooms as anti-cancer therapeutics: a review

Seema Patel · Arun Goyal



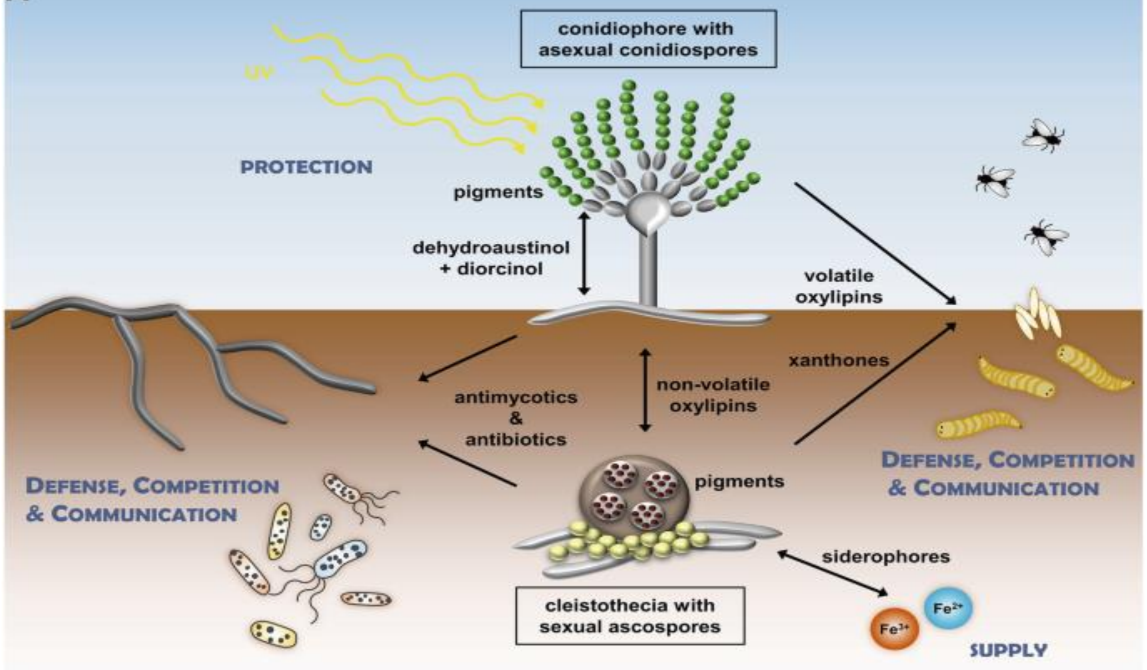


Structure of anti-cancer compounds isolated form mushrooms (collected from http://www.wikipedia.org)



Anti-cancer mechanism of mushroom bioactive compounds

A

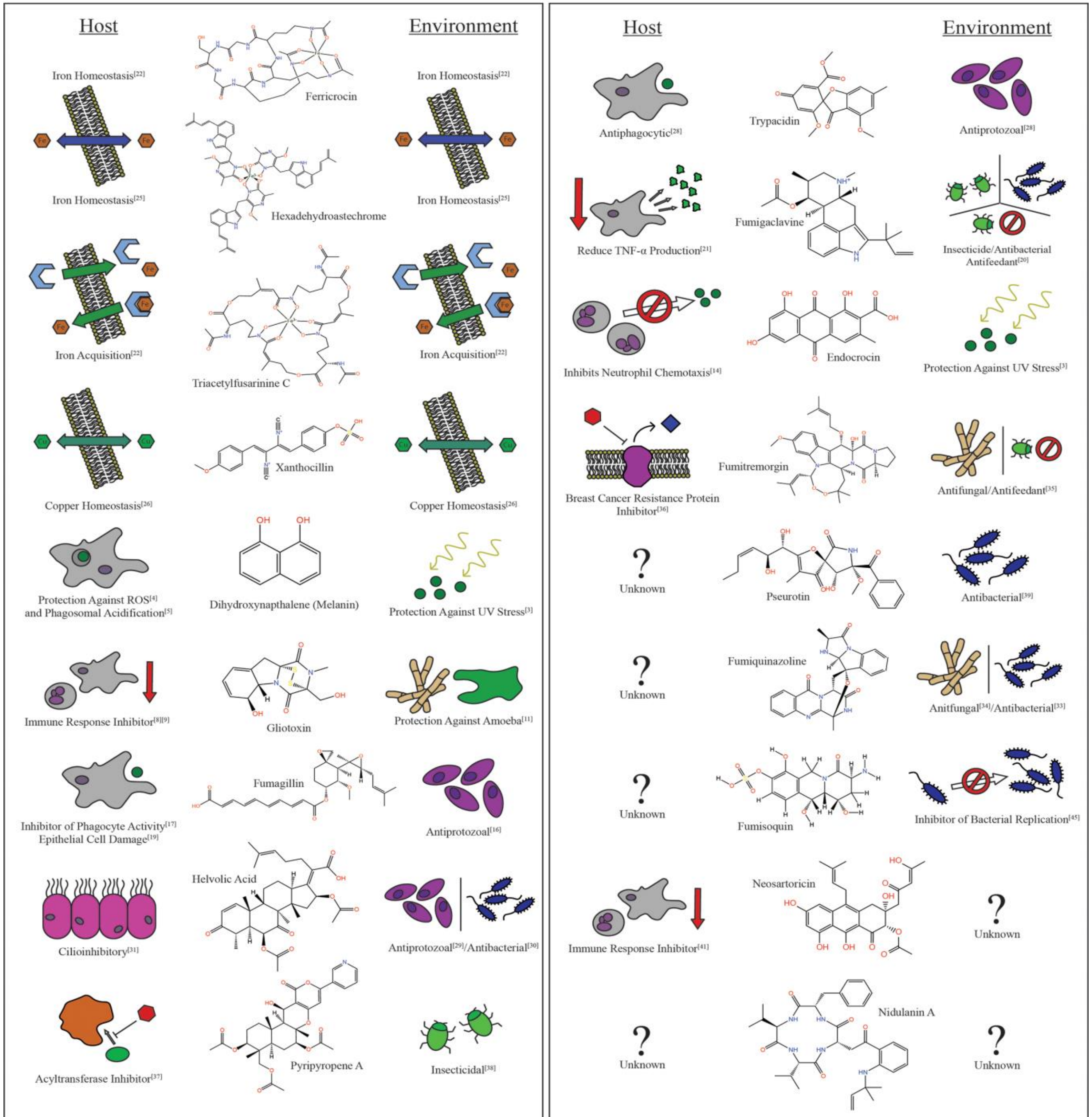


B

Main Classes	Precursors	Enzymes	Examples
Polyketides	malonyl-CoA, acetyl-CoA, propionyl-CoA, methylmalonyl-CoA	polyketide synthases (PKS)	aflatoxins, sterigmatocystin, lovastatin, orsellinic acid, F-9775A, F-9775B, xanthones, amphotericin B
Nonribosomal peptides	proteinogenic and non-proteinogenic amino acids	non-ribosomal peptide synthetases (NRPS)	penicillin, ciclosporin, gliotoxin
Terpenes	isoprene units	terpene synthases (terpene cyclases)	aristolochenes, carotenoids, gibberellins, trichothecenes, taxol
Indole alkaloids	tryptophan, indole-3-glycerol-phosphate, tryptamine	dimethylallyl tryptophan synthases (DMATS)	paxilline, communesin F, lysergic acid, psilocybin
Subclasses			
Peptide-polyketide hybrids	malonyl-CoA, acetyl-CoA, propionyl-CoA, methylmalonyl-CoA, proteinogenic and non-proteinogenic amino acids	PKS-NRPS hybrids	emericellamides, aspyridone, pseurotin A
Meroterpenoids	isoprene units, malonyl-CoA, acetyl-CoA, propionyl-CoA, methylmalonyl-CoA	terpene synthases (terpene cyclases) & PKS	austinol, dehydroaustinol, fumagillin
	isoprene units, proteinogenic and non-proteinogenic amino acids	terpene synthases (terpene cyclases) & NRPS	terpendole E
Isocyanides	proteinogenic and non-proteinogenic amino acids	isocyanide synthases, isocyanide synthase-NRPS hybrids	xanthocillin, xanthoascin
Oxylipins	polyunsaturated fatty acids	oxygenases	hydroxylated oleic (18:1) acid, hydroxylated linoleic (18:2) acid

Gerke, J., Köhler, A.M., Meister, C., Thieme, K.G., Amoedo, H., Braus, G.H. (2020). Coordination of Fungal Secondary Metabolism and Development. In: Benz, J.P., Schipper, K. (eds) Genetics and Biotechnology. The Mycota, vol 2. Springer, Cham. https://doi.org/10.1007/978-3-030-49924-2_8

Roles of *Aspergillus fumigatus* Secondary Metabolites



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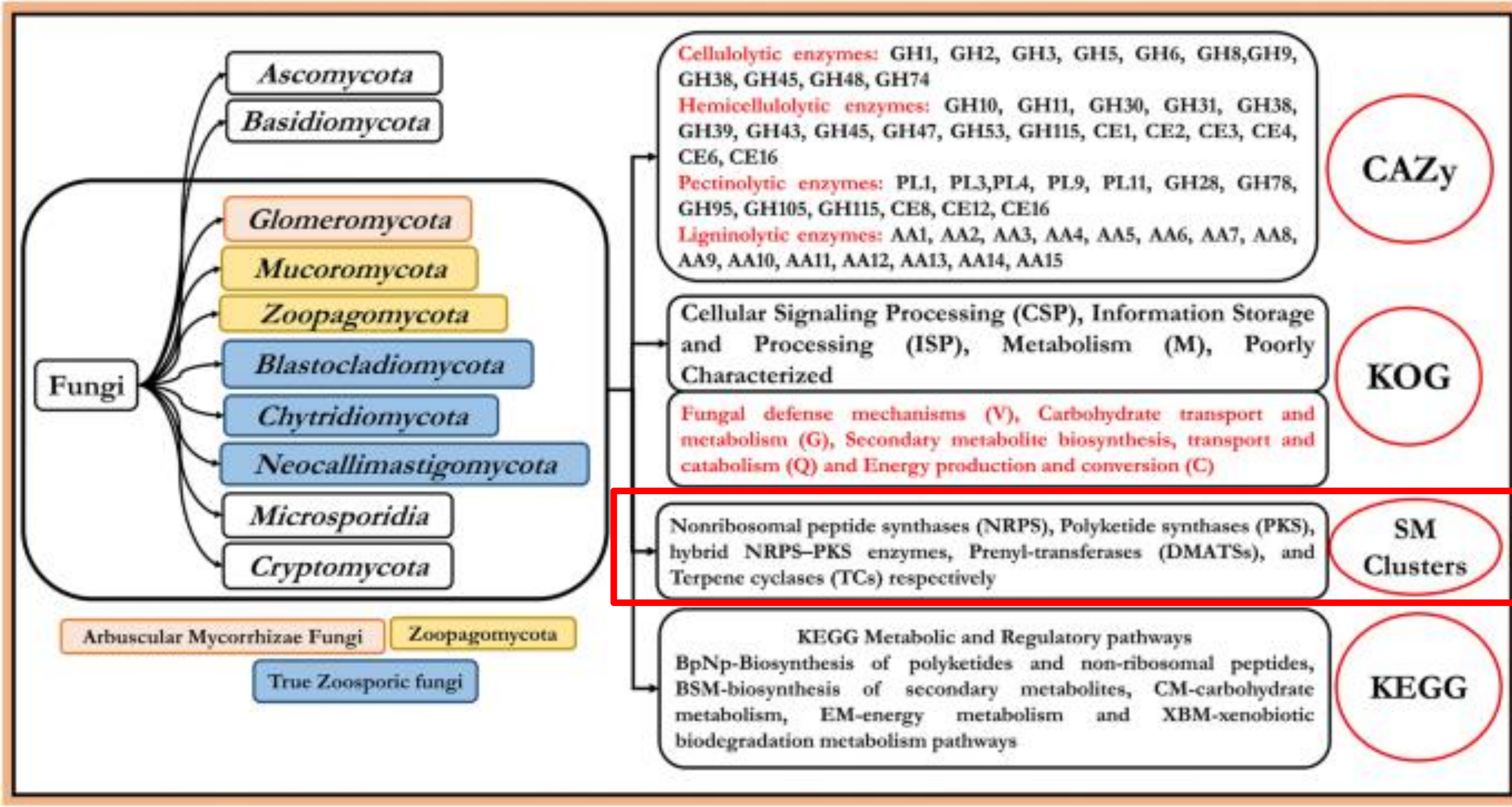

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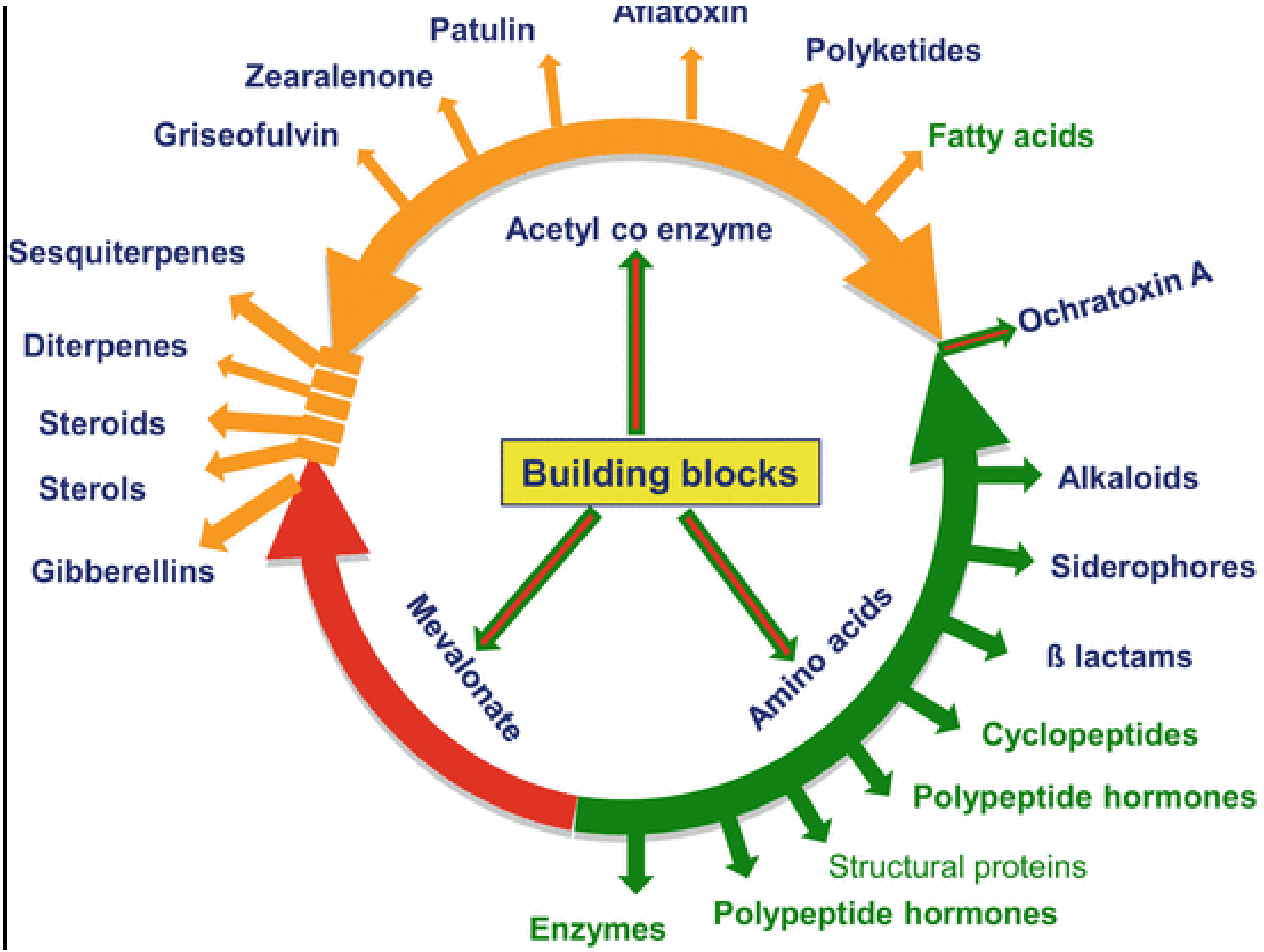

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