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# *Aspergillus oryzae* Compared to *A. flavus* - Genetic Analysis *in Silico*

**Gyulai G[1], Rubaj MG[2], Gyulai ZsG[1], Malone RP[3], and Tischner ZsB[4]***

[1]Institute of GBI, MATE University, 2100 Gödöllő, Hungary

[2]Language Department, MATE University, 2100 Gödöllő, Hungary

[3]College of Science and Health, Technological University, Grangegorman, Dublin 7, Ireland

[4]Department of Environmental Safety, IAES, MATE University, 2100 Gödöllő, Hungary

**ABSTRACT**

Two genetically close filamentous *Aspergillus species*, the non-toxic *A. oryzae* used for food fermentation for thousands of years (e.g., *koji mold, sake, soy sauce*) playing huge role in food industry, and the main *aflatoxin* producer of A. flavus are studied here based on genetic analysis *in silico*. The evolutionary *TimeLine* computer program of *Ascomycota* fungi showed 520 MYA origins. Phylogenetic tree of genome sequences of *Ascomycota* fungi was found to group in three main clades. The genome size of A. flavus (37.7 x10$^6$ bpDNA) but not A. sojae (41.1 x10$^6$ bpDNA) showed smaller size than the descendent (90-100 MYA) A. oryzae (37.9 x10$^6$ bpDNA). In phylogeny of mitogenomes (mtDNA) *A. terreus* showed a distinct clade, and the toxic *A. parasiticus* grouped to the non-toxic A. sojae. Fungal production of *aflatoxins, cellulases*, and the ribosomal post-translationally modified peptides (RiPPs) of *nisin, asperigimycin*, *gliotoxin*; the fungal *n*on-*r*ibosomal peptide (NRPs) *fusahexin*; the polyketide taxane and *mycolactone* are reviewed and discussed.

***Corresponding author**

Tischner ZsB, Department of Environmental Safety, IAES, MATE University, 2100 Gödöllő, Hungary.

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## Order of Ascomycota Fungi

Ascomycota fungi (Figure 1 and 2, Table 1) of plant and human pathogens, e.g., bronchopulmonary aspergillosis BPA, and IPA invasive pulmonary aspergillosis caused mainly by *A. fumigatus*, and *A. flavus*, *A. Niger*, *A. Tereus*, and *A. nidulans* comprise great number (>#82.000) of species [1]. [from Latin: flavus – *yellow*, fumigatus – *smoky*; niger – *black*, nidulans – *nesting*; terreus – terra – *soil*; [2]. *Aspergillus flavus* is a common soil saprophyte, and pathogen fungus of crops [3].

*A.oryzae* is a non-toxic food fermenter for thousands of years (e.g., *koji mold, sake, soy sauce*). Other *Ascomycota* species include *Aspergillus niger* ('black mold'), *Monilia* and *Monilinia* ('brown rot'), *Botrytis* ('grey mold'), Sclerotinia ('white mold'), *Taphrina* ('leaf curls'), and *Fusarium* (Figure 2) are plant pathogens [4-14].

The main fungus fermenters digest sugars to ethanol, e.g., *budding yeasts / bakers' yeast* (*Saccharomyces cerevisiae*), *fission yeast* (*Schizosaccharomyces pombe*). Aspergillus fermenters of *A. oryzae*, *A. sojae* and *A. kawachii* release sugars from the seed starch and cellulose of rice, barley and soybean (Figure 2) [15].

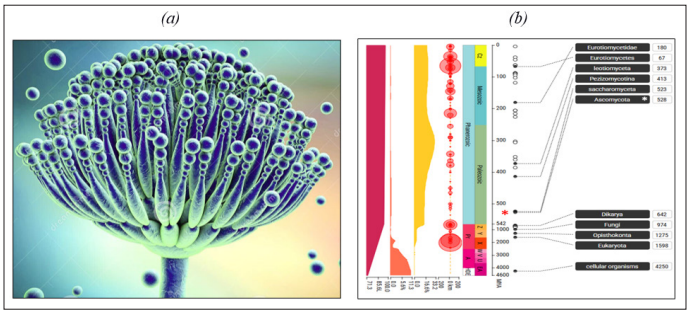


**Figure 1:** Chains of conidia on conidiophore of *Aspergillus species* (a) (*dreamstime.com*; ID #76296075, © Katerina Kon). Evolutionary *TimeTree of Life* for Ascomycota fungi (b) (indicated with [*]), and related organisms analyzed with Divergence Times (MYA) and global climate conditions edited by TTLO5 *timetree.org* [16].

*Aspergillus* fungus was isolated first from soil and named after the similarity to *holy water sprinkler* [Aspergillum] used in the Catholic sermons (*MycoBank* MB #7248, *www.mycobank.org*). *Aspergillus* fungi developed in the evolution 200-520 MYA (Figure 1) [17]. Species of genus *Aspergillus* were found to show divers morphology however with monophyletic evolution lineage [4,18].

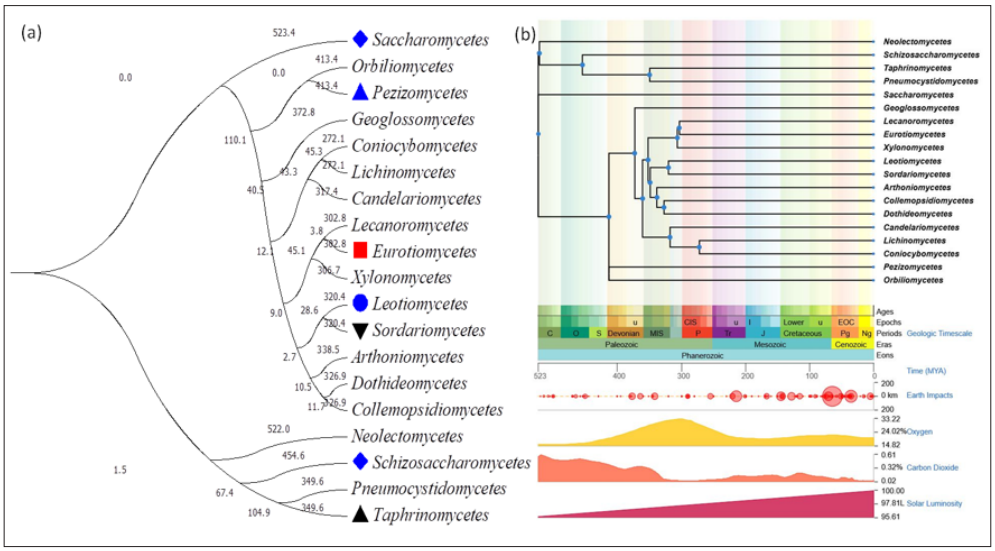


**Figure 2:** Three clades (a) of Ascomycota genomes edited by NJ Phylogram analysis (Neighbor Joining tree) by MEGA7 computer program based on data minded by *TToL5* server [16,19]. (b) Important *Ascomycota* orders are labeled with different symbols. Species numbers (#) were collected from *www.indexfungorum.org* (with total of #618.592 records)

[♦] *Saccharomyces's, e.g., S. cerevisiae - 'budding yeasts'/ bakers' yeast (#489), and Candida (#902) including C. albicans* - a regular member of the human flora, and *C. krusei* used for cacao beans fermentation. [♦] *Schizosaccharomycetes* -'*fission yeasts*' (#42), *e.g., S. pombe*, named after 'pombe' meaning millet beer in African *Swahili* language (Lindner, P., 1893) (*www.gbif.org/species/2586935*). [■] Eurothiomycetes (#3,810), e.g., *Aspergillus* (#1137) and *Penicillium* (#1550). [●] *Leotiomycetes*, e.g., *Botrytis* (#436), *Monilia* (#335), *Monilinia* (#51), and *Sclerotinia* (#259). [▲] *Pezizomycetes* (#2,000), e.g., *Tuber* (#772) ('truffles'), *Morchella* (#368) ('*morels*'). [▼] Sordariomycetes, e.g., *Fusarium* (#1897), *Trichoderma* (#590), *Claviceps* (#120), and *Verticillium* (#50). [▲] *Taphrinomycetes*, e.g., *Taphrina* (#189) ('leaf cirl'). (b) TimeTree phylograms of fungi genome sequences which were edited by TToL5 server (www.timetree.org) with depiction of geological *Timescale* and *Divergence times* (MYA) with indications of environmental indicators of O2 and CO2 levels and solar energy levels [16,20].

## Genome sizes of Aspergillus Fungi

Genome sizes of fungi genus *Aspergillus* were found to vary from 27.8 to 40.2 x$10^6$ bpDNA (Table 1). The genome size of *A. flavus* (37.7 x$10^6$ bpDNA) shows smaller size than the descendent (90-100 MYA) species of *A. oryzae* (37.9 x$10^6$ bpDNA) (Figure 3) [21,22] which may indicate gene-gain or genome variation taking place during *genome reductive evolution* of parasites and decomposers [23-25]. [To compare, plant genome of *A. thaliana* is 0.1191 x$10^9$ bpDNA, NCBI# GCA_000001735.2; and the *human* genome is 3.1 x$10^9$ bpDNA, NCBI# GCA_000001405.29].

**Table 1: Genome sizes of some *Aspergillus* species/isolates of >#1,515 entries to date at NCBI/Genome (*www.ncbi.nlm.nih.gov*) in increasing sizes. The mtDNA mitome sizes of *A. flavus*♦ (29.205 bpDNA), and *A. oryzae*■ strain RIB40 (29.202 bpDNA) (NCBI# AP007176.1) are indicated [26]**

| *Aspergillus* species | Genomes (n) (x$10^6$ bpDNA) | Chr. # | NCBI entry # | Submitting dates | Submitters |
|---|---|---|---|---|---|
| *A. glaucus* | 27.8 | n.a. | GCF_001890805.1 | 2016 | DOE Joint Genome Inst. USA |
| *A. cristatus* | 28.3 | 14 | GCA_054825215.1 | 2026 | Shenzhen University, China |
| *A. terreus* | 29.3 | n.a. | AAJN00000000.1 | 2005 | Broad Institute, USA |
| *A. niger* | 33.9 | 8 | GCF_000002855.4 | 2007 | DSM, The Netherlands |
| *A. flavus** | 37.7 | 8(+mt♦) | GCA_009017415.1 | 2019 | Univ. of California, Berkeley |
| *A. oryzae** | 37.9 | 8(+mt■) | GCF_000184455.2 | 2011 | NITE, Japan |
| *A. sojae* | 40.1 | 8 | GCA_008274985.1 | 2019 | South Korea, Chungbuk |
| *A. alliaceus* | 40.2 | n.a. | GCF_009176365.1 | 2019 | DOE Joint Genome Inst. USA |

*A. oryzae* genome entries at *Mycobank.org* database comprises from *A. oryzae var. oryzae*, 1884 [MB #418420] to *A. oryzae var. globosus*, 1944 [MB #351901]. The entry numbers of *A. flavus* (#23 isolates/species) includes *A. flavus*, 1809 [MB #209842] and *A. flavus var. parvisclerotigenus*, 1993, 2005 [MB #500166]. Two new *aflatoxin* producer *Aspergillus* species were identified recently the *A* [27]. *pseudocaelatus sp. nov*., and *A. pseudonomius sp. nov*., both from the section *A. Flavi*, which section includes *A. flavus and A. parasiticus*. A *sterigmatocystin* hyperproducer A. *creber* was also isolated recently [28].

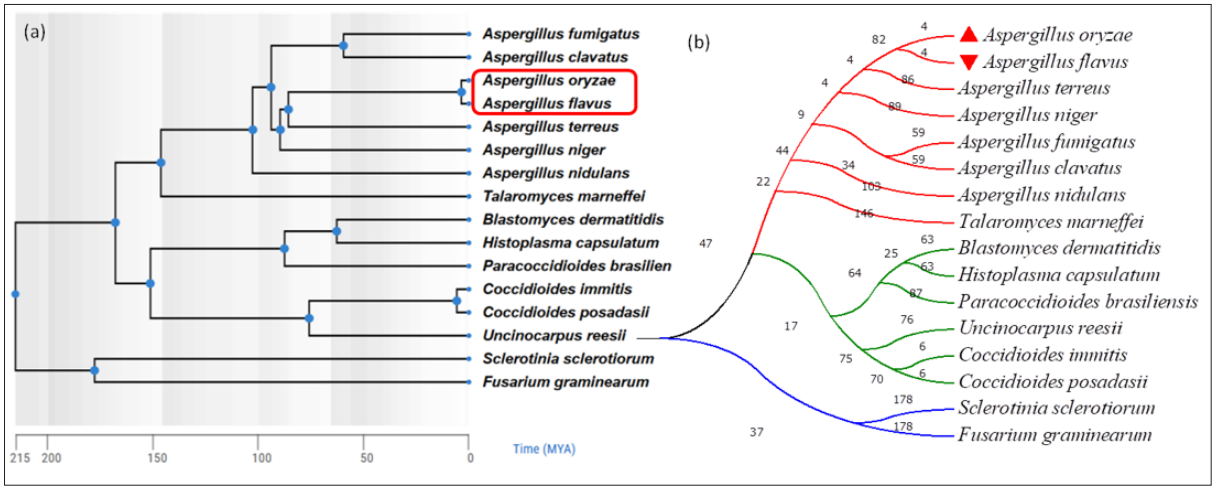


**Figure 3:** Phylogenetic tree (a) (ML, Maximum Likelihood) of *Aspergillus* genes with *TimeLine* (MYA) indication of *Aspergillus* and related fungi species based on #1148 genes were reedited from the data of *Sharpton et al., 2009, Genome Res, 10:1722-31, DOI: 10.1101/gr.087551.108*). The phylogram was data minded and edited by *TTOL5 server* [16] (*www.timetree.org*). (b) Reedition of phylograms (a) by *MEGA7* computer program [19]. Species of *A. flavus* and *A. oryzae*, and the branch lengths are indicated.

**Mitogenomes (mtDNA) of Aspergillus Fungi**

Sequences of the complete mitochondrial DNAs (mtDNA) studied here showed high level of DNA sequence similarity which reflects high level of conserved gene orders (Table 1, Figure 4) [26,29]. However, the mtDNA sequence variations of human pathogen *A. fumigatus* showed diagnostic levels [30].

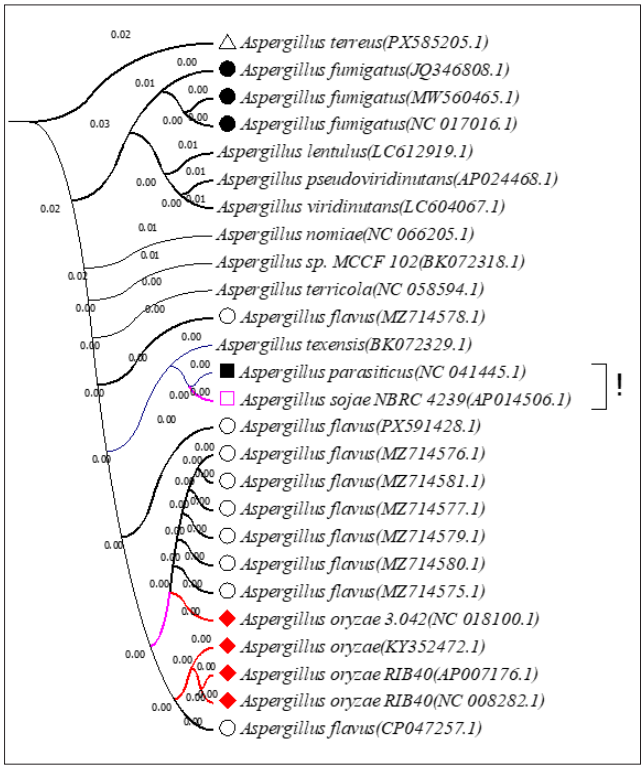


**Figure 4:** Phylogram (NJ), edited by NCBI/DistanceTree, of complete mitochondrial genomes (mtDNA) of *Aspergillus* species aligned to mitogenome of *A. oryzae* strain RIB40 (29,202 bpDNA, NCBI#AP007176.1) with the indication (!) of the poisonous *A. parasitivus* which grouped to *A. sojae* in the same a branch.

The guanine≡cytosine content (GC%) of *Aspergillus* mtDNAs were found to have low levels (>25%) compared to the 'theoretical' level (50%) [26,31,32]. In mtDNA analysis, *A. oryzae* showed the closest similarity to *A. terreus*, however, in our study the mtDNA of *A. terreus* was found in an independent clade (Figure 4) [32]. In general, the sizes (Table 1, Figure 4) of *Aspergillus* mtDNAs were found to be closer to the human (*Homo sapiens*) mtDNA (16.569 bpDNA, encoding 37 genes; NCBI# NC_012920.1) then to the huge plant mtDNAs (e.g., *Arabidopsis thaliana*, 367.808 bpDNA, encoding 58 genes; NCBI# BK010421.1).

**Aflatoxins (AFs) Produced by Aspergillus Fungi**

*Aflatoxins* produced by *Aspergillus* species [i.e., *Aspergillus* FL*Avus* TOXIN) back to the turkey poultry (*Meleagris gallopavo*) disease, UK, 1960s [MW: 328.27 g $mol^{-1}$; $C_{17}H_{12}O_7$, PubChem CID #14403, *Aflatoxin* B1] are the most poisonous *mycotoxins* compared to, e.g., ergot alkaloids of Claviseps, or *patulin* of *Penicillium patulum* (Figure 5) [33].

Toxicity mechanism of *aflatoxins* (-M1, -B1, -B2, -G1, -G2) (Figure 5) is suggested to inhibit the DNA and RNA polymerase enzymes (*https://pubchem.ncbi.nlm.nih.gov*).

Species of *Aspergillus* section *Flavi, e.g., A. flavus* and *A. parasiticus* produce *aflatoxins*, while species of *Aspergillus* section *Circumdati*, e.g., *A. ochraceus* and *A. sclerotiorum* produce *ochratoxin* [34,35].

Species of the non-toxic *A. oryzae* and *A. sojae* are postulated to be domesticated ecotypes developed from the toxic *A. flavus* by inactivation of *aflatoxin* genes [36-41]. The gene inactivations were resulted from a 257 bpDNA deletion from the *aflT* gene, a frameshift mutation in *norA* gene, and base pair substitutions in the verA gene of the cluster of 25 genes in the 70 kbpDNA region of genomic DNA of *A. flavus* [21,42].

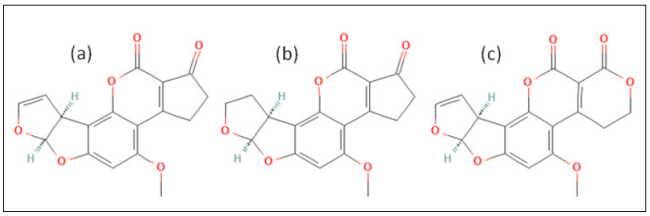


**Figure 5:** Molecular structures of aflatoxins -B1 (a), -B2 (b), and -G1 (c) [*https://pubchem.ncbi.nlm.nih.gov*]

**Cellulase Enzymes Produced by Aspergillus Fungi**

Gene clusters of extracellular production of *cellulase* enzymes complex comprises *endoglucanase*, *exoglucanase* and *β-glucosidase* which digest cellulose to glucose [43,44]. The whole enzymatic process was analyzed in *A. oryzae* and found 26 genes involved in the processes [44,45]. Cellulase enzyme activities provided possibility of cellulose industry, and the basis of Asian food industry for thousands of years [46,47].

**RiPPs, Ribosomally Synthesized and Post-Translationally Modified Bactericide Peptides Produced by Aspergillus Fungi**

The bactericide peptide *nisin* (Figure 6) ['*N* Inhibitory *Streptococcus substance*', the suffix '-in' indicate the antibacterial properties] of *A. oryzae* was identified in the same year 1928 of penicillin discovery from *P. rubens* by Flemming, A., Nobel Prize in Physiology or Medicine, 1945 [48,49].

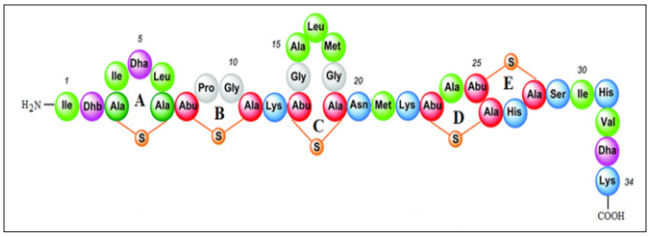


**Figure 6:** Molecular composition of the *nisin RiPPs* peptide. The numbers of amino acids with three letter codes (1 to 34), pentacyclic rings (A to E), disulphide bonds (S), and N- and C-terminals of the protein chain are indicated [50].

The thioether amino acids of *nisin* molecules (e.g., lanthionine, *Lan*; and methyllanthionine. *MeLan*) are synthesized through post-translational modifications (*i.e*., ribosomally synthesized and post-translationally modified peptides: RiPPs) [51-53].

Molecular structure of *nisin* peptides [E234, 34 amino acid, FW: 3354.07 g $mol^{-1}$, Nisin-A: $C_{143}H_{230}N_{42}O_{37}S_7$] shows pentacyclic rings (Figure 6). In the protein database *www.uniprot.org*, #3,904, mainly bacterial *nisin* entries are available coupled with >#30 *Aspergillus* entries.

*Nisins* (-A,-F,-G,-J,-H,-U, and -VP) inhibit food borne Gram-positive bacterium *Listeria monocytogenes* which causes food borne *illness listeriosis*, and was found to also inhibit *enterococci*, *staphylococci*, and *streptococci* [54].

Genes of the 30% of *Nisin* biosynthetic gene clusters (nBGCs) were predicted to be located on mobile genetic elements (plasmids, transposons, and mobile prophages), which indicate the nBGCs from bacteria to mammals [52].

*Nisin*-like peptides were identified recently in 5 phyla, 25 families, 59 genera, and 123 species of bacteria (e.g., the human pathogens *Streptococcus suis*, *S. agalactiae* and *S. aureus*) [52].

**Asperigimycin Produced by Aspergillus Fungi**

Fungal *RiPPs* of *asperigimycin* (Figure 7) with central molecule of *aspergicin* [$C_{20}H_{17}N_3O_4$; MW: 363.4 g $mol^{-1}$] was studied as a potential medicine for human cancer therapy in #12 *Aspergillus* species including *A. flavus* and *A. oryzae* through protein-protein interactions (SLC46A3; NM_181785.4) [21,53,55].

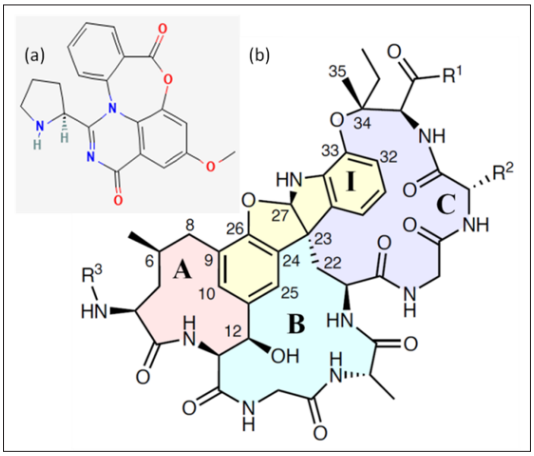


**Figure 7:** Molecular structure of *aspergicin* (a), and *asperigimycin* (b). Rings (A, B, and C, benzofuranoindoline I), and side chains ($R^1$ to $R^3$) are indicated [53].

**Gliotoxins Produced by Aspergillus Fungi**

Gliotoxin [$C_{13}H_{14}N_2O_4S_2$, MW: 326.39 g·$mol^{-1}$] is an immunosuppressive peptide (Figure 8) of epi-polythio-dioxo-piperazines (ETPs) [56]. It was named and isolated first from *Gliocladium fimbriatum* in 1936, and later was found in human patients infected by *Aspergillosis* (IPA, invasive pulmonary aspergillosis) caused by *A. fumigatus* [1]. The synthesis of *gliotoxin* starts from *phenylalanine* and *serine* amino acids (aa) (Figure 8) followed by regulating by 13 enzyme genes regulated by *gli* gene cluster [57,58].

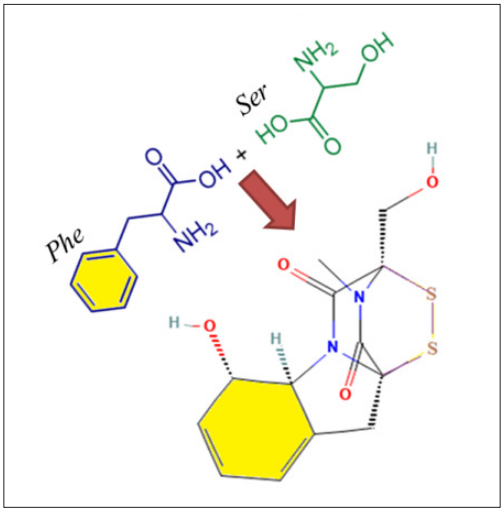


**Figure 8:** Molecular structure of *gliotoxin* (*https://pubchem.ncbi.nlm.nih.gov/compound*), an immunosuppressive protein-toxin produced by *Aspergillus fumigatus* (benzyl ring of *Phe* aa is labeled in yellow) [58].

**NRPs, Non-Ribosomal Peptides Produced by Aspergillus Fungi**

The synthesis of NRPs peptides (*Non-Ribosomal Peptides*) differ from RiPPs as they are synthesized by *NRPs peptide synthetases* enzyme complexes. The NCBI/Protein databank shows, e.g, of *NRPs6* of *Aspergillus fumigatus*, KAH1618191, 1240 aa; and KAH3371766, 1083 aa. The *NRPs4* of *Penicillium rubens* is 2076 aa, KAJ5044881. For *Aspergillus* species 25 NRPs entries are available to date (Figure 9).

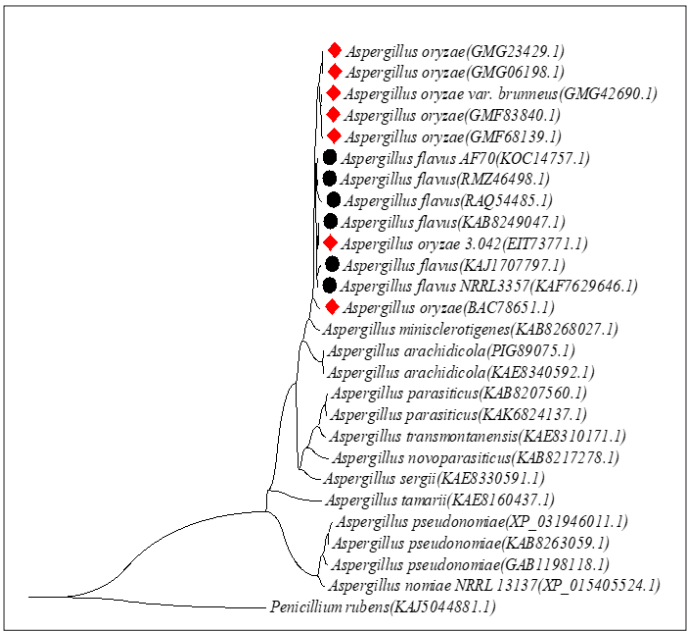


**Figure 9:** NJ cladogram (NCBI) of NRP peptide sequences of *Aspergillus* with *Penicillium rubens* outgroup and the genbank entry numbers. *A. oryzae* and *A. flavus* entries are labeled.

The NRPs-4 gene clusters for *fusahexin* (Figure 10), NRPs-5/9 for *fusaoctaxin* and *NRPs*-8 for *gramilin* were identified which escape the functions of mRNAs and ribosomes [35,59-62].

Key enzyme of the *NRPs* are the ACV synthetases [Amino-adipyl-Cysteinyl-*Valine*, *Syn*.: N-(5-amino-5-carboxypentanoyl)-L-cysteinyl-D-valine] (EC 6.3.2.26) encoded by *PcbAB* gene cluster, which also participates in the biosyntheses of *penicillin* and *cephalosporin*, and which has very likely been transferred horizontally from prokaryotic cyanobacterial blue-green algae (i.e., Cyanobacteria, e.g., of *Anabaena* sp., and *Microcystis* sp.) to *Ascomycota fungi* (e.g., *Aspergillus nidulans*, XM_655133.1) [63].

ACV synthetase of *Penicillium chrysogenum* (ABR12615) has 3791 aa; *Aspergillus oryzae* (EIT77324) has 3774 aa; *Aspergillus flavus* (RAQ52156) has 3753 aa; and Aspergillus parasiticus (KAK6829282) has 3774 aa.

Further NRPs sequences were identified, e.g., *fusaric acid* (FA, from *Fusarium* and *Penicillium* species), *fusahexin* (from *F. graminearum*) (Figure 10), *gramillin* (from *Fusarium graminearum*), *apicidin F* (APF, from *Fusarium fujikuroi*), *fusarochromene* (NRPs-like, from *Fusarium sacchari*), *fusaristatin A* (a lipopeptide) and *oxysporidinone* (from *Fusarium oxysporum*), *fusaridione* A (from *F. heterosporum*), and *chrysogine* (from *Penicillium chrysogenum*) (The Dictionary of Natural Products. *https://dnp.chemn etbase.com*., 2023) [59,64]. A hexa-cyclic *fusahexin* was isolated from *F. graminearum* [59].

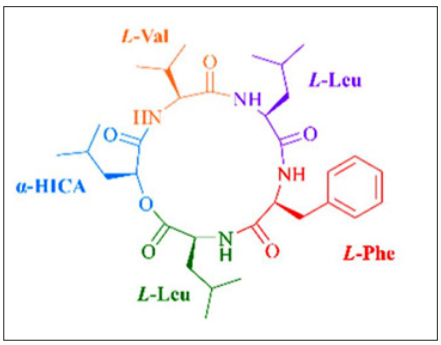


**Figure 10:** *Fusahexin*, a sample of cyclic NRPs, a penta-cyclic oligo peptide (isolated first from *F. graminearum*), three letter codes of aa are indicated [65].

**Polyketides (PKs) Produced by Ascomycota Aspergillus Fumigatus and Basidiomycota Fungi**

Polyketides (PKs) are chemical compounds with multi ketene groups (RR'C=C=O) [66]. It was identified first in *Penicillium griseofulvum*, and later was found from bacteria to animals. Polyketide synthetases enzyme complexes (i.e., mPKs – modular PKs) contribute in synthesis of antibiotics (e.g., *tetracycline*) and anticancer drugs (e.g., *taxane*) [67,68].

Taxane [Mw 276.5 g $mol^{-1}$, PubChem CID 9548828, Budapest Treaty #CBS 279.92] (Figure 11) is produced by *Taxomyces andreanae*, (Basidiomycota) #ASM196922v1 which was isolated from yew tree (Taxus brevifolia) and used to treat human prostatitis [69].

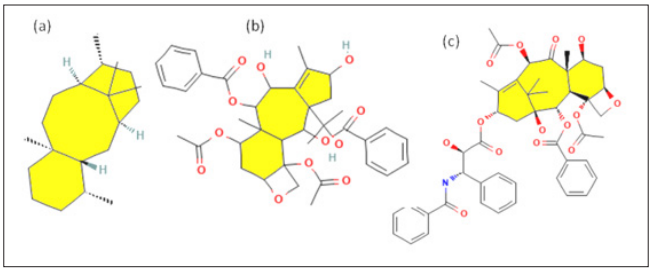


**Figure 11:** Molecular structures of taxane (a) [MW: 276.5 g mol-1, gene xanE (O-*methyltransferase*; NCBI #3505486) of *Aspergillus fumigatus* Af293]; and the chemically modified

taxanes of *deacethylTAXchinin* (b) [MW: 692.7 g mol$^{-1}$], and *paclitaxel* (taxol) (c) [MW: 853.9 g mol$^{-1}$, #33069-62-4] (*https://pubchem.ncbi.nlm.nih.gov; clinpgx.org/pathway*) [70,71].

*Mycolactone* with a huge mPK gene complex (51 Kbp DNA; *mlsA1*, *mlsA2*, and *mlsB*) encodes an 1800 kDa protein which was found to consists of nine functional enzymes identified in human pathogen *Mycobacterium ulcerans* (Figure 12) [68,72].

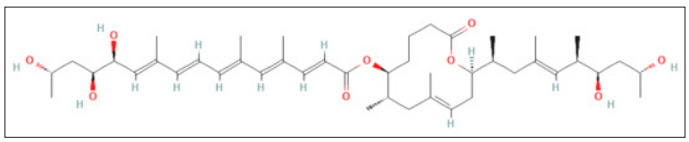

**Figure 12:** Molecular structure of *mycolactone* polyketide [Mw 743.0 g mol-1, PubChem CID #5282079] (*https://pubchem.ncbi.nlm.nih.gov*)

## Methodology

Gene sequences were downloaded from servers of NCBI and UNIPROT (*www.uniprot.org*) followed by alignments by ClustalW computer program inbuilt to NCBI and Bio Edit computer programs according to Kukolya et al, Heszky and Gyulai et al. [25,73-77]. Phylogenetic NJ and ML phylograms were edited by computer programs MEGA7-and-12 [19]. *TimeTree* of Life phylograms were edited by server of TToL5 timetree.org [16]. For analyze of numbers and melecular structures of groups and species of fungi six databank were used *www.speciesfungorum*.org, www.indexfungorum.org, *www.mycobank.org, www.ncbi.nlm.nih.gov / pubchem.ncbi.nlm.nih.gov, and www.gbif.org/species*.

## Conclusion

*Aspergillus oryzae* of *Ascomycota fungi* shows adaptive evolutionary and speciation event which indicates how a poisonous fungus turn to became a harmless new fungus species used in food industry for thousand years. Genes and poisonous metabolites of *Aspergillus* and related fungi became also the source of antibacterial and tumor therapy agents used in human medication. These fungal properties urge the research work to isolate and modify newer and newer fungal compounds.

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