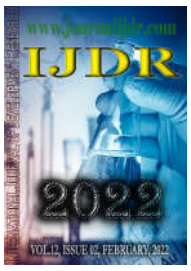
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 12, Issue, 02, pp. 53690-53694, February, 2022
https://doi.org/10.37118/ijdr.23840.02.2022



RESEARCH ARTICLE OPEN ACCESS

PRODUCTION OF BIOMOLECULES OF PHARMACOLOGICAL INTEREST BY TRICHODERMA SPECIES

Wesley Cristian Ferreira[1], Gabriela Silva Batista[2], Laura Gomes Lima[3], Rosa Elena Cardoza[4], Santiago Gutiérrez[5], Eriston Vieira Gomes[2,5,*]

[1]UniEvangelica College Medical School, Anápolis, GO, 75083-515, Brazil; [2]Morgana Potrich College, FAMP Medical School, Mineiros, GO, 75832-007, Brazil; [3]University of Rio Verde (UniRV) Medical School, Rio Verde, GO, 75901-970, Brazil; [4]Department of Microbiology, School of Agricultural and Forestry Engineering, University of León, Campus de Ponferrada, Avda. Astorga s/n 2, Ponferrada 24400, Spain; [5]Ribeirão Preto Medical School, FMRP, University of São Paulo, USP, Ribeirão Preto, SP, Brazil

ARTICLE INFO

Article History:
Received 10th November, 2021
Received in revised form
14th December, 2021
Accepted 06th January, 2022
Published online 20th February, 2022

Key Words:

Trichoderma, biomolecules, Antibacterial, Antitumor activity, Biotechnology, Pharmacology.

Corresponding author:
Eriston Vieira Gomes

ABSTRACT

The genus *Trichoderma* comprises more than 400 species of fungi distributed across all ecosystems worldwide. Fungi of this genus have been widely reported to produce metabolites with various activities, which have been used in diverse areas such as in pest biocontrol, resistance induction in plants, and production of biomolecules of biotechnological interest. This review aims to provide an overview of the main species of *Trichoderma* that produce biomolecules with activities that are useful in the biotechnological field, emphasizing metabolites with antibacterial and antitumor activity. We have provided an overview of 21 different species of *Trichoderma* and 59 metabolites that display activity of interest. In addition, more than 500 other metabolites have been reported in the scientific literature, which have not yet been tested or have not been demonstrated to show activity of interest with respect to the scope of this review, providing ample possibility for many other biotechnological applications of *Trichoderma* biomolecules.

Citation: ***Wesley Cristian Ferreira, Gabriela Silva Batista, Laura Gomes Lima, Rosa Elena Cardoza, Santiago Gutiérrez, Eriston Vieira Gomes.*** "Production of biomolecules of pharmacological interest by trichoderma species*", International Journal of Development Research*, 12, (02), 53690-53694.

INTRODUCTION

Historically, plants have been used to treat various diseases. However, the discovery and production of diverse fungal bioactive metabolites have changed this trend. Some fungi have the potential to produce toxins such as antibiotics, which can destroy other microbes even at low concentrations. Owing to the diversity of these toxins, they have been shown to be effective against prokaryotes and eukaryotes, the major producers of secondary bioactive metabolites, which can be useful for bio-competition, proliferation, search for nutrients, and other biological processes. These metabolites include flavonoids, alkaloids, and terpenoids with antibacterial, antifungal, antiviral, anti-inflammatory, and antitumor properties [1]. The genus *Trichoderma* is of particular interest, mainly with respect to the processes of environment colonization and host interactions (e.g., symbiosis with plants and mycoparasitism). Species of this genus have been widely used as biocontrol agents in agriculture owing to their suppressive effects on plant diseases and antibiosis activity. Thus, *Trichoderma* spp. have great potential for the development of drugs and compounds of biotechnological interest (Fig. 1) [2].

Here, this review aims to provide an overview of the main species of *Trichoderma* that produce biomolecules with activities that are useful in the biotechnological field, emphasizing metabolites with antibacterial and antitumor activity.

Production of nanoparticles (NPs) with antibacterial activity: Nanotechnology is a rapidly growing field that deals with the synthesis and development of various nanomaterials with a wide range of applications. Copper, zinc, titanium, magnesium, gold, alginate, and silver can be used to create different types of metallic nanomaterials. Among the noble metals, gold NPs (AuNPs) and silver NPs (AgNPs) have received substantial attention in recent years given their wide range of potential applications such as in drug delivery and as therapeutics for various types of diseases, including microbial infections and cancer [3]. The cytotoxicity of NPs depends on their size, shape, coating/covering agent, and the type of pathogens against which their toxicity is investigated, as some pathogens are more susceptible to NPs than others. NPs slowly envelop microbes and enter the cell, thereby inhibiting vital cellular functions [4]. The possible mechanism underlying the antibacterial activity of AgNPs

may involve NPs penetrating the cell wall and entering the cells, where they compress the DNA, which simultaneously inactivates cellular proteins [5]. *Trichoderma* metabolites were shown to play a critical role in the production and dispersion of NPs. Guilger *et al*. [6] reported the synthesis of AgNPs from *T. harzianum*, and further demonstrated that a marine strain of *T. hamatum* (JX308232) is useful for the rapid and efficient synthesis of AgNPs and AuNPs. Saravanakumar [7] also synthesized AgNPs with antibacterial activity using a *Trichoderma atroviride* strain.

Trichoderma hamatum SU 136: AuNPs were shown to have antimicrobial activity against four pathogenic bacteria, namely *Bacillus subtilis* ACCB 133, *Staphylococcus aureus* ACCB 136, *Pseudomonas aeruginosa* ACCB 156, and *Serratia* sp. ACCB 178. Interestingly, AuNPs exhibited antimicrobial activity against the four pathogenic bacterial strains in the presence of the standard antibiotic streptomycin [3].

Trichoderma viride: AgNPs synthesized using *T. viride* were shown to have antibacterial activity against methicillin-resistant *S. aureus* (MRSA), *Shigella boydii*, *Acinetobacter baumannii*, *Shigella sonnei*, and *Salmonella typhimurium*. Gram-negative bacteria also exhibited greater zones of inhibition in the presence of *T. viride* AgNPs when compared with those produced by gram-positive bacteria and those produced in response to the antibiotic control [8]. Chitra and Annadurai [5] reported that AgNPs exhibited antibacterial activity against *B. subtilis* and *Klebsiella planticola* with a maximum zone of inhibition occurring after treatment with 50 µL of AgNPs. Moreover, depending on their shape and concentration, AgNPs were shown to have different antibacterial activities against other human pathogens. Spherical AgNPs of 2–5 nm led to a maximum inhibition of 40%, 32%, 51%, 43%, 53.9%, and 55.8% against *S. sonnei*, *Escherichia coli*, *Serratia marcescens*, *S. aureus*, and *P. aeruginosa*, respectively, whereas AgNPs with a size of 50–100 nm and a hexagonal shape showed 32%, 41%, 31%, 42.84%, and 42.80% inhibition against these species, respectively. Notably, the association of AgNPs with antimicrobials demonstrated greater bactericidal activity, even against multidrug-resistant microorganisms [9].

Trichoderma koningii: AgNPs produced using *T. koningii* showed antibacterial activity against *Salmonella typhimurium* at a concentration of 45 µg/mL [10]. A summary of the *Trichoderma* species, type of NPs, and their respective references is provided in Table 1.

Table 1. Nanoparticles (NPs) production from *Trichoderma* spp. with antibacterial activity

Species	Metabolite	References
T. hamatum SU 136	AuNPs (gold nanoparticles)	[3]
T. viride	AgNPs (silver nanoparticles)	[5,8,9]
T. koningii	AgNPs (silver nanoparticles)	[10]

Metabolites with antibacterial activity

Trichoderma harzianum: Crude extracts from different strains of *T. harzianum* have been used successfully in antibacterial assays. Anwar and Iqbal [1] reported the compounds extracted using ethyl acetate and acetonitrile. The ethyl acetate extracts showed a minimum inhibitory concentration (MIC) of 10.41 ± 4.50 µg/mL against *E. coli*, whereas the acetonitrile extracts showed a MIC of 6.50 ± 2.25 µg/mL against *S. aureus* [1]. Similarly, secondary metabolites obtained from *T. harzianum* crude extracts showed antibacterial activity against *S. aureus*, *E. coli, Klebsiella pneumoniae*, *Streptococcus pyogenes*, *P. aeruginosa*, *and Enterococcus faecalis* [11]. The T9 compound was isolated and tested for antibacterial activity against *S. aureus* ATCC25923, *Salmonella typhi* ATCC5784, *B. subtilis* TISTR008, *B. subtilis* ATCC6633, *Bacillus cereus* ATCC11778, *Bacillus amyloliquefaciens* TISTR1014, *Bacillus lichenisformis* TISTR1010, *S. aureus* E.15:H7, and *Vibrio cholerae* (clinical) [12]. Moreover, chitosan-oligosaccharides (COSs) were isolated from *T. harzianum* and evaluated for their antitumor and antibacterial activities. COSs were shown to have antibacterial activity at concentrations of 2.5–10 mg/mL, with the most sensitive bacterium being *E. coli* at a concentration of 2.5 mg/mL, whereas MRSA was the most resistant, being inhibited only at concentrations higher than 10 mg/mL [13].

Trichoderma gamsii SP4 and Trichoderma flavus SP5: *T. gamsii* SP4 crude extracts were shown to have antibacterial properties. Moreover, *T. flavus* SP5 extracts were found to be effective against various human pathogens such as *P. aeruginosa* ATCC 27853, *E. coli* ATCC52922, and *Candida tropicalis* ATCC 750 [14].

Trichoderma asperellum: The ethyl acetate extract from *T. asperellum* was shown to have antibacterial activity, with an 80% inhibitory concentration (IC_{80}) between 15.6 and 62.5 µg/mL, whereas methanol extracts showed antibacterial activity with an IC_{80} of 31.2–62.5 µg/mL against *S. aureus* and *E. coli* [15]. In addition, four *T. asperellum* metabolites, namely bisabolane sesquiterpene, norbisabolane, sesquiterpene, and trichodenone, were revealed to have antibacterial activity. The compounds displayed weak antibacterial activity against *Vibrio parahaemolyticus*, *Vibrio anguillarum*, *Vibrio harveyi*, and *Vibrio splendidus* for which the compounds showed the highest antibacterial activity [16].

Trichoderma brevicompactum: The ethyl acetate extract exhibited antibacterial activity with an IC_{80} between 15.6 and 62.5 µg/mL, whereas methanol extracts exhibited antibacterial activity with an IC_{80} of 31.2–62.5 µg/mL against *S. aureus* and *E. coli* [15]. Degenkolb *et al*. [17,18] isolated 75 metabolites from *T. brevicompactum* by producing alamethicins similar to those produced by *T. viride* with known antibacterial activity, as well as chrysospermins, which can form non-elongated membrane channels, thus exhibiting strong antibacterial activity against gram-positive bacteria, yeasts, and fungi. *Trichothecene*-produced harzianum A (HA) was also identified, suggesting effective antibacterial activity.

Trichoderma koningiopsis: Ethyl acetate and methanol extracts showed antibacterial activity with an IC_{80} of 15.6–62.5 µg/mL and 31.2–62.5 µg/mL against *S. aureus* and *E. coli,* respectively [15]. Similarly, five isolated compounds showed antibacterial and antitumor activities: (1) Koninginol A, (2) Koninginol B, (3) Koninginol C, (4) 11-hydroxy-15-drimeneoic acid, and (5) Koninginol D. Compounds 1 and 2 showed significant antibacterial activity against *B. subtilis* with MIC values of 10 and 2 µg/mL, respectively [19].

Trichoderma longibrachiatum: Ethyl acetate and methanol extracts showed antibacterial activity with an IC_{80} of 15.6–62.5 µg/mL and 31.2–62.5 µg/mL against *S. aureus* and *E. coli,* respectively [15].

Trichoderma atroviride: *The* T. atroviride *metabolites TM1 (1,3-dione-5,5-dimethylcyclohexane) and TM2 (4H-1,3-dioxin-4-one-2,3,6-trimethyl) showed significant inhibitory activity against* Helicobacter pylori *and Shiga toxin-producing* E. coli *(STEC). TM1 was shown to have a MIC of 8.92 ± 1.80 µg/mL for* E. coli *and 17.18 ± 1.25 µg/mL for STEC. However, TM2 showed greater antibacterial activity at low concentrations, with a MIC of 14.5 ± 0.4 µg/mL and 14.67 ± 0.15 against* E. coli *and STEC, respectively [7]. The compounds isolated from the* T. atroviride *extract also demonstrated antibacterial activity against* S. aureus *and* Staphylococcus epidermidis*, with inhibition of 40% and 10%, respectively. This extract was also shown to exhibit an inhibitory effect of more than 10% for* Candida *species [20].*

Trichoderma asperelloides: Santos *et al*. [21] demonstrated that *T. asperelloides* extracts have more efficient antibacterial activity than gentamicin for *S. aureus*, while also inhibiting the formation of biofilms produced by the bacterium.

Trichoderma saturnisporum: Saturnispols F was extracted from *T. saturnisporum* DI-IA after fermentation. This species lives in marine environments and excretes metabolites based on sorbicillin

(secondary metabolites classified as sorbicillinoids, which are a diverse group of yellow pigments produced by several fungal groups). The isolated compound showed significant antibacterial activity against vancomycin-resistant enterococci. In addition, antibacterial activity was found against the gram-negative bacteria *K. pneumoniae* and *P. aeruginosa*, with MIC values ranging from 1.63 to 12.9 µg/mL [22].

Trichoderma sp. strain MF106: *Wu* et al. *[23] isolated two compounds that showed antibacterial activity: (1) trichodin A and (2) pyridoxatin. Trichodin A showed moderate antimicrobial activity against gram-positive* B. subtilis *(50% inhibitory concentration [IC_{50}] = 27.05 ± 0.53 µM),* S. epidermidis *(IC_{50} = 24.28 ± 3.90 µM), MRSA (IC_{50} = 80 µM), and the yeast* Candida albicans *(IC_{50} = 25.38 ± 0.41 µM). Pyridoxatin was shown to be active against* B. subtilis*,* S. epidermidis*, MRSA,* C. albicans*, and* Trichophyton rubrum*, with IC_{50} values of 5.28 ± 0.42 µM, 4.25 ± 0.81 µM, 4.40 ± 0.14 µM, 26.25 ± 0.14 µM, and 4.05 ± 1.28 µM, respectively [23].*

Trichoderma sp. strain Ym311505: *Trichoderma* sp. YM 311505, which was isolated from *Azadirachta indica* fruit, was found to produce three metabolites with antibacterial activity. The compound 7-methoxy-4,6-dimethyl phthalide was shown to have antibacterial activity for *E. coli*, *B. subtilis*, and *Pyricularia oryzae* with a MIC of 64 pg/mL. However, 7-hydroxy-4,6-dimethyl phtalide and daidzein showed antibacterial activity only against *E. coli*, with a MIC of 64 pg/mL [24].

Trichoderma sp. strain Jing-8: The compound 1-hydroxy-9-methyl ether was obtained from *Trichoderma* sp. Jing-8 isolated from the *Panax notoginseng* stem, and was shown to have antibacterial activity against *B. subtilis* and *S. aureus* with a MIC of 64 µg/mL [25].

Trichoderma arundinaceum: The trichothecene pathway is used in the synthesis of trichodiene, in which, after consecutive oxygenations and hydroxylations, HA and trichodermin, two mycotoxins with antibiotic and antitumor activities, are produced. HA, which was isolated from *T. arundinaceum* and *T. brevicompactum* cultures, was previously confirmed to exhibit antifungal activity against *Kluyveromyces marxianus* [26]. Cardoza *et al*. [27] also identified the gene involved in the production of HA and demonstrated that only *Trichoderma* species have this gene, indicating that other fungal species cannot produce HA. The species of *Trichoderma* and the types of antibacterial metabolites produced with their respective references are summarized in Table 2.

Antitumor activity

T. harzianum: In addition to their antimicrobial activity, COSs isolated from *T. harzianum* showed antitumor activity against HeLa cells, a cervical cancer cell line, by altering cell proliferation and causing deformations in the cell structure. The most effective concentration was 8 mg/mL, with a decrease in cell proliferation of approximately 40% ($p < 0.05$), whereas at concentrations of 4 and 6 mg/mL, cell proliferation decreased by 23% and 32%, respectively [13]. In addition, L-methioninase, which was also isolated from *T. harzianum*, displayed high antitumor potential. However, further analyses are necessary [29].

Hypocracea (Trichoderma) sp. strain F000527: HA was shown to have antitumor activity against HT1080 fibrosarcoma cells (IC_{50} = 0–65 µg/mL), HeLa cells (IC_{50} = 5–07 µg/mL), and the human breast cancer cell line MCF-7 (IC_{50} = 10–13 µg/mL) [30].

***Trichoderma gamsii* SP4:** The crude extract of *T. gamsii* SP4 was shown to have antitumor activity against Hep2 liver cancer cells, with an IC_{50} of 25.7 µg/mL [14].

Trichoderma koningiopsis: Chen *et al*. [19] reported three isolated metabolites, named 2, 15, and 16, which showed antitumor activity by inhibiting cell growth in the human lung cancer cell line A549, with IC_{50} values of 46.6, 31.3, and 22.2 µM, respectively.

Table 2. Metabolites with antibacterial activity

Species	Metabolite	Reference
T. harzianum	Ethyl acetate	[1]
	Secondary metabolites	[11]
	T9	[12]
	Chitosan-oligosaccharides (COS)	[13]
T. gansii SP4	Secondary metabolites	[14]
T. flavus SP5	Secondary metabolites	[14]
T. asperellum	Ethyl acetate	[15]
	Bisabolane sesquiterpene	[16]
	Norbisabolane Sesquiterpene	[16]
	Trichodenone	[16]
T. brevicompactum	Ethyl acetate	[15]
	Alamethicins	[18]
	Chrysospermins	[17]
	Harzianum A	[17]
T. koningiopsis	Ethyl acetate	[15]
	Methanol extracts	[15]
	Koninginol A	[19]
	Koninginol B	[19]
T. longibrachiatum	Ethyl acetate	[15]
	Methanol extracts	[15]
T. atroviride	TM1	[7,26]
	TM2	[7,26]
	Secondary metabolites	[24]
T. asperelloides	Secondary metabolites	[21]
T. saturnisporum	Saturnispols F	[22]
T. sp. Strain MF106	Trichodin A	[23]
	Pyridoxatin	[23]
T. sp. Strain *Ym311505*	7-Methoxy-4,6-dimethyl Phthalide	[24]
	7-Hydroxy-4,6-dimethyl Phthalide	[24]
	Daidzein	[24]
T. sp. Strain Jing-8	1′-Hydroxy-9-methyl ether	[25]
T. arundinaceum	Harzianum A	[26,27]
	Trichodermin	[26]

Trichoderma longibrachiatum: The Trichogin GA IV compound isolated from *T. longibrachiatum* was shown to have antitumor effects against HeLa cells, with an IC_{50} of 4–6 µM [31].

Trichoderma atroviride: Two *T. atroviride* metabolites, namely TM1 and TM2, with antitumor activity against human prostate cancer PC3 cells were isolated. TM2 was shown to be more effective at inducing cell death when compared to TM1, with IC_{50} values of 1250 µg/mL for TM1 and 187.2 µg/mL for TM2 [7,28].

Trichoderma viride: L-Lysine α-oxidase isolated from *T. viride* was shown to severely inhibit the growth of ovarian cancer cells while exhibiting relatively low cytotoxicity for normal cells. Furthermore, Kalra *et al*. [32] reported that lysyl-oxidase, which produces reactive oxygen species such as H_2O_2 that act on L-lysine, showed antitumor activity, reaching 250% inhibition in ovarian cancer cells depending on the dose.

Trichoderma kanganensis: A novel water-soluble polysaccharide metabolite designated as TPS was shown to inhibit the proliferation of mouse colon cancer cells (CT26) while exerting no toxicity on normal cells (LO2). The inhibition rate reached 34.28% at a concentration of 800 µg/mL. In addition to its cytotoxic activity, TPS demonstrated great antioxidant activity when compared to ascorbic acid, with an increase in activity from 13.29% to 58.11% in a dose-dependent manner [33].

Trichoderma (marine) Hypocrea lixii TSK8, Hypocrea rufa SKS2: Saravanakumar et al. [6] reported the identification of two compounds: 16-methylheptadecanoic acid methyl ester (HDA) and 9,12-octadecadienoic acid (ODA). Both compounds were found to have antitumor activity against oral cancer cells (KB) and skin carcinoma cells (A431). The IC50 against KB oral cancer cells was 18.75 ± 0.12 mg/mL for HDA and 75.50 ± 0.42 mg/mL for ODA, whereas the IC50 values of HDA and ODA against A431 cells were 37.5 ± 0.42 mg/mL and 72.89 ± 0.15 mg/mL, respectively. In vivo

testing was also performed using albino mice, with a 33.44% survival rate for mice with KB tumors [6].

Trichoderma pseudokoningii: Exopolysaccharides (EPS) derived from *T. pseudokoningii* were isolated and tested against MCF7 breast cancer cells at a concentration of 1.0 mg/mL for 72 h. The results showed that the viability of MCF-7 cells was reduced to 50.35% post-treatment, demonstrating that EPS exhibit significant antimoral activity [34].

Trichoderma arundinaceum: Rivera-Chávez *et al*. [35] tested several biological compounds against human cancer cells. Biocomposite 1, identified as Trichoverin BIII-D, showed moderate activity against HCT 116 and HT-29 cells, with IC_{50} values of 6.8 mM and 6.7 mM, respectively. Compound 3, identified as GLU (OME) in Alameticin F50, was shown to be the most active compound, with IC_{50} values ranging from 2.5 to 6.5 mM for HCT 116 cells (colorectal carcinoma); DLD-1, HT-29, and SW948 cells (colorectal adenocarcinoma); Hep-G2 and Huh-7 cells (liver cancer); and HeLa cells (adenocarcinoma) [35]. As previously mentioned, HA isolated from *T. arundinaceum* showed effective antitumor activity in addition to reasonable antifungal and antibacterial activity [30,36].

Trichoderma sp. strain MF106: Compounds produced by *Trichoderma* sp. strain 307 were evaluated to determine their cytotoxic activity, which were shown to have antitumor activity against GH3 cells (pituitary adenoma) and MMQ cells (prolactinoma). Compound (3R)-de-O-methylla siodiplodin (3.8 mg) exhibited greater toxicity against GH3 and MMQ cells, with an IC_{50} of 6.44 and 6.58 μM, respectively. Compound (3R)-nordinone showed moderate cytotoxicity, with IC_{50} values of 12.33 and 10.13 μM, respectively. Finally, compound 8 was shown to be the least active, with IC_{50} values of 21.42 and 13.59 μM, respectively [37]. The species of *Trichoderma* with the types of antitumor metabolites produced and their respective references are summarized in Table 3.

Table 3. Metabolites with antitumor activity

Species	Metabolite	Reference
T. harzianum	Chitosan-oligosaccharides (COS)	[13]
	L-methioninase	[29]
Hypocracea (T.) sp. strain F000527	Harzianum A	[30]
T. gansii SP4	Crude extract	[14]
T. koningiopsis	Koninginol D	[11]
	Koninginol C	[11]
	11-Hydroxy-15-drimeneoic acid	[11]
T. longibrachiatum	Trichogin GA IV	[31]
T. atroviridi	TM1	[7,28]
	TM2	[7,28]
T. viride	L-Lysine α oxidase (LysOX)	[32]
	Lysyl-oxidase	[32]
T. kanganensis	TPS metabolite	[33]
Trichoderma (marine) *Hypocrea lixii* TSK8, *Hypocrea rufa* SKS2	16-Methylheptadecanoic Acid methyl ester (HDA)	[6]
	9,12-Octadecadienoic acid (ODA)	[6]
T. pseudokoningii	Exopolysaccharide (EPS)	[34]
T. arundinaceum	Trichoverin BIII-D	[35]
	GLU (OME)	[35]
	Harzianum A	[30,35]
Trichoderma sp. strain MF106	(3R)-de-O-methylla Siodiplodin	[37]
	(3R)-nordinone	[37]

CONCLUSION

Trichoderma spp. are widely known for their bioactivity and abundance of secondary metabolites. In this review, we identified a broad spectrum of *Trichoderma*-derived metabolites that showed antibacterial and antitumor activity. In addition, several authors have reported on their antifungal, cytotoxic, anti-inflammatory, and enzymatic inhibitory effects, as well as their role as growth promoters and their ability to induce local and systemic resistance in plants. Therefore, owing to the growing demand for biomolecules with such properties, further research on metabolites of microbial origin, and particularly of fungal origin such as those from the genus *Trichoderma*, is necessary for the development of new drugs and biofertilizers, as well as cleaner, cheaper, and more environmentally friendly methods of biological pest control.

Acknowledgments: This work was developed with the support of FAMP, Faculdade Morgana Potrich (Morgana Potrich College) – Mineiros, Goiás, Brazil.

REFERENCES

1. Anwar J, Iqbal Z. Effect of Growth Conditions on antibacterial activity of *Trichoderma harzianum* against selected Pathogenic Bacteria. Sarhad J Agric. 2017;33:501–10. http://doi.org/10.17582/journal.sja/2017/33.4.501.510.
2. Guimarães GR, Ferreira DdS, Galvão CdS, Mello SCM, Carvalho DDC. Ação de metabólitos voláteis e não voláteis de *Trichoderma harzianum* sobre o crescimento de *Cladosporium herbarum*. Pesqui Agropec Pernambucana. 2016;21:7–11. https://doi.org/10.12661/pap.2016.002.
3. Abdel-Kareem MM, Zohri AA. Extracellular mycosynthesis of gold nanoparticles using *Trichoderma hamatum*: Optimization, characterization and antimicrobial activity. Lett Appl Microbiol. 2018;67:465–75. https://doi.org/10.1111/lam.13055.
4. Siddiqi KS, Husen A, Rao RAK. A review on biosynthesis of silver nanoparticles and their biocidal properties. J Nanobiotechnology. 2018;16:14. https://doi.org/10.1186/s12951-018-0334-5.
5. Chitra K, Annadurai G. Bioengineered silver nanobowls using *Trichoderma viride* and its antibacterial activity against gram-positive and gram-negative bacteria. J Nanostructure Chem. 2013;3. https://doi.org/10.1186/2193-8865-3-9.
6. Saravanakumar K, Vivek R, Boopathy NS, Yaqian L, Kathiresan K, Chen J. Anticancer potential of bioactive 16-methylheptadecanoic acid methyl ester derived from marine *Trichoderma*. J Appl Biomed. 2015;13:199–212. https://doi.org/10.1016/j.jab.2015.04.001.
7. Saravanakumar K, Mandava S, Chellia R, Jeevithan E, Babu Yelamanchi RS, Mandava D et al. Novel metabolites from *Trichoderma atroviride* against human prostate cancer cells and their inhibitory effect on *Helicobacter pylori* and Shigella toxin producing *Escherichia coli*. Microb Pathog. 2019;126:19–26. https://doi.org/10.1016/j.micpath.2018.10.011.
8. Elgorban AM, Al-Rahmah AN, Sayed SR, Hirad A, Mostafa AA, Bahkali AH. Antimicrobial activity and green synthesis of silver nanoparticles using *Trichoderma viride*. Biotechnology & Biotechnological Equipment. 2016;30:299–304. https://doi.org/10.1080/13102818.2015.1133255.
9. Kumari M, Pandey S, Giri VP, Bhattacharya A, Shukla R, Mishra A et al. Tailoring shape and size of biogenic silver nanoparticles to enhance antimicrobial efficacy against MDR bacteria. Microb Pathog. 2017;105:346–55. https://doi.org/10.1016/j.micpath. 2016.11.012.
10. Tripathi RM, Gupta RK, Shrivastav A, Singh MP, Shrivastav BR, Singh P. *Trichoderma koningii* assisted biogenic synthesis of silver nanoparticles and evaluation of their antibacterial activity. Adv Nat Sci Nanosci Nanotechnol. 2013;4. https://doi.org/ 10.1088/2043-6262/4/3/035005.
11. Reena P, Nagar K. Antimicrobial activity of *Trichoderma harzianum* against bacteria and fungi. Int J Curr Microbiol Appl Sci. 2014;3:96–103.
12. Phupiewkham W et al. Antibacterial agents from *Trichoderma harzianum* strain T9 against pathogenic bacteria. Chiang Mai J Sci. 2015;42:304–16.
13. Dario Rafael OH, Luis Fernándo ZG, Abraham PT, Pedro Alberto VL, Guadalupe GS, Pablo PJ. Production of chitosan-oligosaccharides by the chitin-hydrolytic system of *Trichoderma harzianum* and their antimicrobial and anticancer effects. Carbohydr Res. 2019;486:107836. https://doi.org/10.1016/j.carres.2019.107836.

14. Anand BG, Thomas CKN, Prakash S. *In vitro* cytotoxicity and antimicrobial activity of *Talaromyces flavus* SP5 inhabited in the marine sediment of Southern Coast of India. Chin J Nat Med. 2016;14:913–21. https://doi.org/10.1016/S1875-5364(17)30016-X.
15. Leylaie S, Zafari D. Antiproliferative and antimicrobial activities of secondary metabolites and phylogenetic study of endophytic *Trichoderma* species From Vinca Plants. Front Microbiol. 2018;9:1484. https://doi.org/10.3389/fmicb.2018.01484, Jul n, p. 1–16.
16. Song YP, Miao FP, Fang ST, Yin XL, Ji NY. Halogenated and nonhalogenated metabolites from the marine-alga-endophytic fungus *Trichoderma asperellum* CF44-2. Mar Drugs. 2018;16:4–12. https://doi.org/10.3390/md16080266.
17. Degenkolb T, Dieckmann R, Nielsen KF, Gräfenhan T, Theis C, Zafari D et al. The *Trichoderma brevicompactum* clade: A separate lineage with new species, new peptaibiotics, and mycotoxins. Mycol Progress. 2008;7:177–219. https://doi.org/10.1007/s11557-008-0563-3.
18. Degenkolb T, Gräfenhan T, Nirenberg HI, Gams W, Brückner H. *Trichoderma brevicompactum* complex: Rich source of novel and recurrent plant-protective polypeptide antibiotics (peptaibiotics). J Agric Food Chem. 2006;54:7047–61. https://doi.org/10.1021/jf060788q.
19. Chen S, Li H, Chen Y, Li S, Xu J, Guo H et al. Three new diterpenes and two new sesquiterpenoids from the endophytic fungus *Trichoderma koningiopsis* A729. Bioorg Chem. 2019;86:368–74. https://doi.org/10.1016/j.bioorg.2019.02.005.
20. Víglaš J, Olejníková P. *Trichoderma atroviride*: An isolate from forest environment with secondary metabolites with high antimicrobial potential. Acta Chimica Slovaca. 2019;12:46–55. https://doi.org/10.2478/acs-2019-0008.
21. Santos SS, Augusto DG, Alves PAC, Pereira JS, Duarte LMB, Melo PC et al. *Trichoderma asperelloides* ethanolic extracts efficiently inhibit *Staphylococcus* growth and biofilm formation. PLOS ONE. 2018;13:e0202828. https://doi.org/10.1371/ journal.pone.0202828.
22. Meng J, Cheng W, Heydari H, Wang B, Zhu K, Konuklugil B et al. Sorbicillinoid-based metabolites from a sponge-derived fungus *Trichoderma saturnisporum*. Mar Drugs. 2018;16:1–15. https://doi.org/10.3390/md16070226.
23. Wu B, Oesker V, Wiese J, Schmaljohann R, Imhoff JF. Two new antibiotic pyridones produced by a marine fungus, Trichoderma sp. strain MF106. Mar Drugs. 2014;12:1208–19. https://doi.org/ 10.3390/md12031208.
24. Xuan Q, Huang R, Miao CP, Chen YW, Zhai YZ, Song F et al. Secondary metabolites of endophytic fungus *Trichoderma* sp. YM 311505 of *Azadirachta indica*. Chem Nat Compd. 2014;50:139–41. https://doi.org/10.1007/s10600-014-0891-2.
25. Zhang JC, Chen GY, Li XZ, Hu M, Wang BY, Ruan BH et al. Phytotoxic, antibacterial, and antioxidant activities of mycotoxins and other metabolites from *Trichoderma* sp. Nat Prod Res. 2017;31:2745–52. https://doi.org/10.1080/ 14786419.2017.1295235.
26. Cardoza RE, Malmierca MG, Hermosa MR, Alexander NJ, McCormick SP, Proctor RH et al. Identification of loci and functional characterization of trichothecene biosynthesis genes in filamentous fungi of the genus *Trichoderma*. Appl Environ Microbiol. 2011;77:4867–77. https://doi.org/10.1128/ AEM. 00595-11.
27. Cardoza RE, McCormick SP, Lindo L, Kim HS, Olivera ER, Nelson DR et al. A cytochrome P450 monooxygenase gene required for biosynthesis of the trichothecene toxin harzianum A in *Trichoderma*. Appl Microbiol Biotechnol. 2019;103:8087–103. https://doi.org/10.1007/s00253-019-10047-2.
28. Saravanakumar K, Shanmugam S, Varukattu NB, MubarakAli D, Kathiresan K, Wang MH. Biosynthesis and characterization of copper oxide nanoparticles from indigenous fungi and its effect of photothermolysis on human lung carcinoma. J Photochem Photobiol B. 2019b;190:103–9. https://doi.org/10.1016/ j.jphotobiol.2018.11.017.
29. Salim N, Santhiagu A, Joji K. Process modeling and optimization of high yielding L-methioninase from a newly isolated *Trichoderma harzianum* using response surface methodology and artificial neural network coupled genetic algorithm. Biocatal Agric Biotechnol. 2019;17:299–308. https://doi.org/ 10.1016/j.bcab.2018.11.032.
30. Lee HB, Kim Y, Jin HZ, Lee JJ, Kim CJ, Park JY et al. A new *Hypocrea* strain producing harzianum A cytotoxic to tumour cell lines. Lett Appl Microbiol. 2005;40:497–503. https://doi.org/ 10.1111/j.1472-765X.2005.01719.x.
31. Tavano R, Malachin G, De Zotti M, Peggion C, Biondi B, Fornaggio F et al. The peculiar N- and C-termini of trichogin GA IV are needed for membrane interaction and human cell death induction at doses lacking antibiotic activity. Biochim Biophys Acta. 2015;1848:134–44. https://doi.org/10.1016/ j.bbamem.2014.10.005.
32. Kalra S, Midha K, Monika -, Kaur M. Studies on anti-cancer activity of Lysil oxidase from *Trichoderma viride* MTCC 167. Int J Appl Sci Biotechnol. 2016;4:57–63. https://doi.org/10.3126/ ijasbt.v4i1.14378.
33. Lu Y, Xu L, Cong Y, Song G, Han J, Wang G et al. Structural characteristics and anticancer/antioxidant activities of a novel polysaccharide from *Trichoderma kanganensis*. Carbohydr Polym. 2019;205:63–71. https://doi.org/10.1016/ j.carbpol.2018.09.068.
34. Wang G, Liu C, Liu J, Liu B, Li P, Qin G et al. Exopolysaccharide from *Trichoderma pseudokoningii* induces the apoptosis of MCF-7 cells through an intrinsic mitochondrial pathway. Carbohydr Polym. 2016;136:1065–73. https://doi.org/ 10.1016/j.carbpol.2015.09.108.
35. Rivera-Chávez J, Raja HA, Graf TN, Gallagher JM, Metri P, Xue D et al. Prealamethicin F50 and related peptaibols from *Trichoderma arundinaceum*: Validation of their authenticity via in situ chemical analysis. RSC Adv. 2017;7:45733–51. https://doi.org/10.1039/c7ra09602j.
36. Sun J, Pei Y, Li E, Li W, Hyde KD, Yin WB et al. A new species of *Trichoderma hypoxylon* harbours abundant secondary metabolites. Sci. Rep.:2016:6:37369. https://doi.org/10.1038/ srep37369.
37. Zhang L, Niaz SI, Khan D, Wang Z, Zhu Y, Zhou H et al. Induction of diverse bioactive secondary metabolites from the mangrove endophytic fungus *Trichoderma* sp. (strain 307) by co-cultivation with *Acinetobacter johnsonii* (strain B2). Mar Drugs. 2017b;15:1–14. https://doi.org/10.3390/md15020035.

****