Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.44.007124

Chemistry of Gliotoxins and their Derivatives

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ARTICLE INFO

Received: June 21, 2022

Published: July 01, 2022

Citation: Bafana Radebe, Jeremiah Senabe, Amos Kekae, Nomusa Dlamini. Chemistry of Gliotoxins and their Derivatives. Biomed J Sci & Tech Res 44(5)-2022. BJSTR. MS.ID.007124.

ABSTRACT

Gliotoxin is a sulphur-containing fungal secondary metabolite of the class of epidithiodioxopiperazine which is characterized by an internal disulphide bridge. Gliotoxin is produced by various pathogenic fungi, including Aspergillus fumigatus, Eurotium chevalieri, Gliocladium fimbriatum, and several Trichoderma and Penicillium species. Gliotoxin possesses medicinal properties and biocontrol abilities but, unfortunately, has toxic properties in humans. Gliotoxin is found in compost piles, decaying vegetation, and water damaged buildings. Toxin exposure is known to occur either by accidental ingestion or by in situ generation in those with existing fungal infections. The greatest concern is the occurrence of opportunistic Aspergillus infections in immunocompromised patients, such as organ transplant recipients and those with cancer or AIDS. Gliotoxins have a range of effects on the immune system, including immunosuppression and disrupting the integrity of the epithelial and endothelial barriers to enhance systemic fungal invasion. Due to their immunosuppression properties, gliotoxins can cause systemic manifestations, ranging from eye irritation to respiratory arrest, in addition to more general and nonspecific symptoms, such as headaches, malaise, skin hypersensitivity, and alterations to olfactory and taste sensations. Research on gliotoxins at CSIR started in the 1960's, where the gliotoxins were produced as standards and making it available to the agricultural and pharmaceutical sectors. Research has also been done on the behaviour and chemistry of gliotoxins, and on methods of how to deactivate them and combine with fertilizer to enhance crop production. Gliotoxin are effective in inhibition of several phytopathogenic fungi such as Rhizoctonia solani, Botrytis cinerea, Colletotrichum spp., Pythium ultimum, Fusarium spp. and other fungal species.

Some of the other benefits of the deactivated gliotoxins are that they can be used as antibiotics. Gliotoxin research is ongoing and could contribute to improved food security by enhancing food crop production by preventing plant diseases.

Introduction

Research on gliotoxins at CSIR started in the 1960s when the gliotoxins were produced as standards and making it available to the agricultural and pharmaceutical sectors. Research has also been done on the behaviour and chemistry of gliotoxins, and on methods of how to deactivate them and combine them with fertilizer to enhance crop production. Gliotoxin is effective in the inhibition of several phytopathogenic fungi such as Rhizoctonia solani, Botrytis cinerea, Colletotrichum spp., Pythium ultimum, Fusarium spp. and other fungal species. Some of the other benefits of deactivated gliotoxins are that they can be used as antibiotics. Gliotoxin research is ongoing and could contribute to improved food security by enhancing food crop production by preventing plant diseases.

Experimental Methods

Growth conditions were optimised for growing the gliotoxin using isolates of Aspergillus Fumigatus culture from ATCC stored at -70°C using a bead cryopreservation system. The three A. fumigatus isolates were grown on Sabouraud glucose agar (SAB) plates for 2 days at 37 °C and the conidia were then extracted with sterile 0·5% Tween 20 and adjusted to a concentration of 107 conidia ml^{-1} in distilled water based on haemocytometer counts. One millilitre volume of this conidial suspension was used to inoculate 100 ml of liquid medium, Czapek-Dox broth (CDB; 30 g carbohydrate (glucose, lactose, maltose or sucrose), 3 g Na_2NO_3, 0·5 g $MgSO_4 \cdot 7H_2O$, 0·5 g KCl, 0·01 g FSO_4 in 1 l distilled water), in 250 ml flasks. The cultures were incubated at 37 °C in a shaking incubator at 1400 rpm for 2, 4, 6 or 10 days the broth was filtered and separately the broth and supernatant were extracted using chloroform and chloroform/ methanol 1:1 v;v respectively. Various experimental derivatives were obtained from gliotoxin. Reactions were monitored on Merck F254 silica gel plates and chromatography for both gliotoxin and derivatives purified using Merck 230-400 mesh silica gel. Solvents used in reactions were anhydrous solvents obtained from Merck chemical company as starting which were later screened for various therapeutic areas [1-3].

Results

Toxicity Data

All derivatives and their by-products are given orally to rats and did not show any evident sign of toxicity at the test concentrations of 3000-2000mg/kg except for gliotoxin which was toxic. ^{1}H NMR spectrum (DMSO-d_6, 400 MHz): 3.44 (1H, dd, J = 4.8, H-3a), 4.28 (^{1}H, dd, J = 9.9, H-3a), 4.39 (^{1}H, dd, J = 6.8, H-5), 4.842 (^{1}H, m, H-6), 5.78 (^{1}H, d, J = 9.9, H-7), 5.95 (^{1}H, m, H-8), 6.00 (1H, m, H-9), 2.96, 3,73 (^{1}H, d, J = 18.1, H-10), 3.20 (3H, s, H-11). $_{13}$C NMR spectrum (DMSO-d 6, 100 MHz): 166.0 (C-1), 77.2 (C-3), 60.5 (C-3), 165.2 (C-4), 69.8 (C-5), 75.6 (C-6), 129.9 (C-7), 123.4 (C-8), 120.2 (C-9), 130.7 (C-19a), 36.6 (C-10), 73.1 (C-10a), 27.5 (C-11). LREI-MS m/z: 349 [M]+ ($C_{21}H_{23}N_3O_2$). LREI-MS m/z: 326.38 [M]+ ($C_{13}H_{14}N_2O_4S_2$).

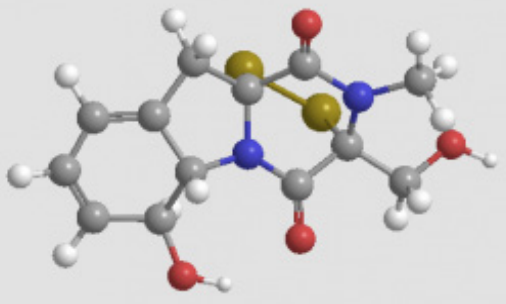

Figure 1.

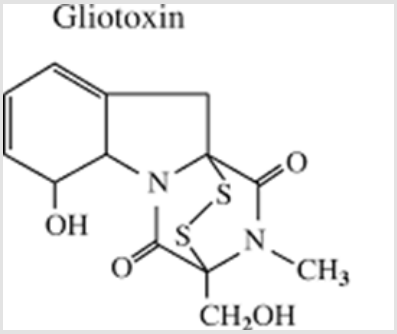

Figure 2.

Figure 3: Control land without treatment

Figure 4: Farmland treated with Activated Gliotoxin

Conclusion

Biological assays were conducted on the gliotoxin derivatives and the by-products *in vitro* and *in vivo* potent for anti-viral, antifungal, and antibacterial activities and growth stimulants.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.44.007124

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