ISSN: 2616-8634 (Print) & Open Access

Scholars International Journal of Traditional and Complementary Medicine
Abbreviated key title: Sch. Int. J. Tradit. Complement. Med.
A Publication by "Scholars Middle East Publishers"
Dubai, United Arab Emirates

Controlling Dose May Be an Alternative and Effective Way in Citrinin Safety: A Review Emphasized on Neuropharmacological Effects

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Original Research Article

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Article History
Received: 12.06.2018
Accepted: 21.06.2018
Published: 30.06.2018

Abstract: Citrinin (CIT), a toxin first isolated from *Penicillium citrinum*, is known for its cytotoxic and nephrotoxic properties. To date, CIT has been identified in various species of *Penicillium* and several species of *Aspergillus* Toxic and protective effects of citrinin may be due to its dose relevant. More experimental setup is required to understand the fact clearly.

Keywords: citrinin; neurological effects; safety.

INTRODUCTION

Mycotoxins are the toxic secondary metabolites produced by organisms of the fungus kingdom [1]. Generally, one mold species may produce several different kind of mycotoxins [2], and most of them are toxic in nature and capable to cause diseases and death in both humans and animals [3].

Citrinin (CIT), a toxin first isolated from *Penicillium citrinum*, is known for its cytotoxic and nephrotoxic properties. To date, CIT has been identified in various species of *Penicillium* and several species of *Aspergillus* [3]. Moreover, CIT is evident for its antimicrobial (antibacterial, antifungal) activity. It also exerts toxic effects on cardiac and reproductive systems, liver, and kidney. Although, the carcinogenicity, genotoxic, and mutagenic effects of CIT are still controversial, but low dose may reduce oxidative stress, inflammatory reactions, suggesting its protective role in test systems [4]. This writing aims to feature and offer hopes in selecting doses for the evaluation of pharmacological activities of CIT.

Sense inspects of neurological tests

Glutamate excitotoxicity is responsible for neuronal death in acute neurological disorders, including stroke, trauma and other neurodegenerative diseases. CIT at high dose can result in apoptosis, but at low doses it can protect the nervous system. High dose mediated toxic effects of CIT may be used for the alteration of biochemicals in animals. For an example, mice treated with 15, 25 and 35 mg/kg (intra-peritoneally) of CIT for six weeks were found to decrease the levels of adenosine triphosphatase (ATP), hexokinase, lactate dehydrogenase (LDH), lactic acid and pyruvic acid, and an increase in glucose levels in blood and major organs, including brain of citrinin-treated mice[5,6]. In a recent study, in glutamate-induced cell death in cultured rat cortical neurons, CIT was found to show a significant neuroptotective effect at 0.1 to 1,000 nM [7].

ATP is the main sources of chemical energy in living matters, as it is involved in many cellular processes. It is evident that, in glycolysis, hexokinase is directly inhibited by glucose-6-phosphate, while pyruvate kinase by ATP [8]. LDH catalyzes the interconversion of pyruvate and lactate with concomitant interconversion of NADH and NAD^+. In the final product of glycolysis, LDH converts pyruvate to lactate when oxygen is absent or in short supply. However, at high concentrations of lactate, LDH exhibits a feedback inhibition, where the rate of conversion of pyruvate to lactate is decreased.

On the other hand, glucose is usually assumed to be the main energy source for living cells, including neurons [9]. Lactate-shuttle hypothesis suggests that glial cells are responsible for transforming glucose into lactate, and for providing lactate to the neurons [10], essential for main brain functions.

An inhibition of glycolysis may relate to the decrease in the levels of ATP, hexokinase, LDH, lactic acid and pyruvic acid, rather than glucose levels in the high CIT dose administered animals' brain. In short, dose-mediated effects of CIT are shown in the Fig.

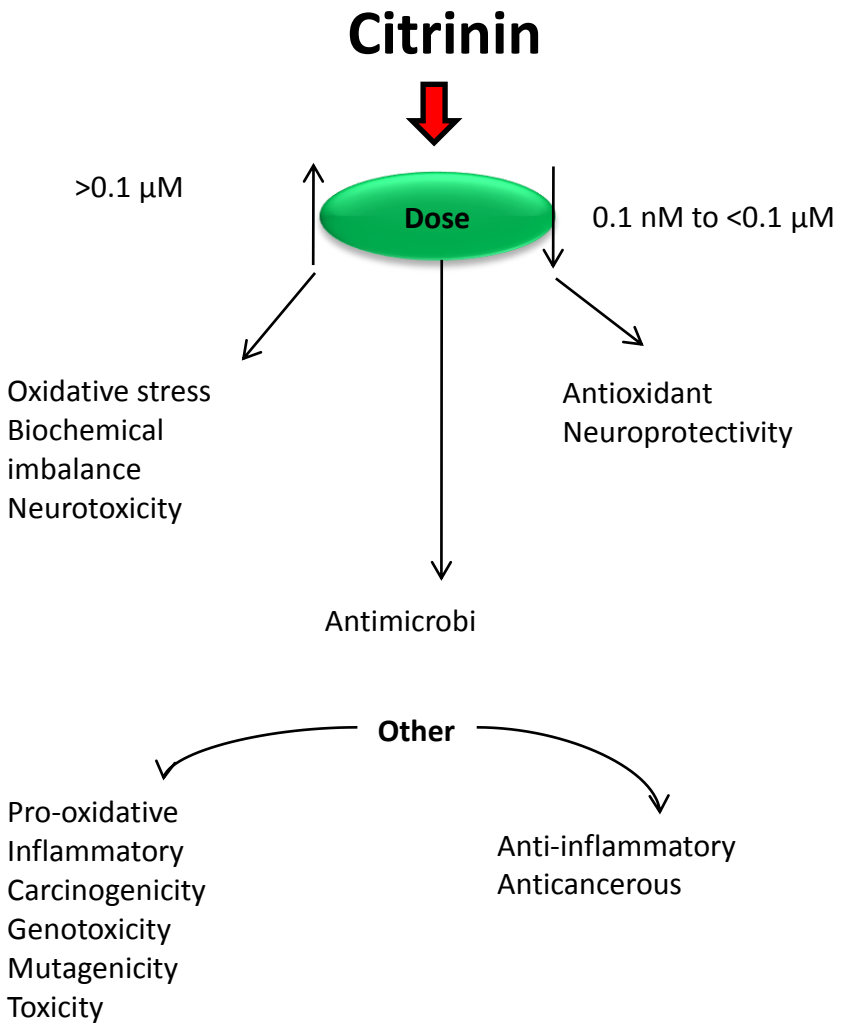

Fig-1: Pharmacological activities of citrinin, empashized on dose

Final considerations

According to a current review done by de Oliveira Filho *et al.* [4] CIT's pharmacological activities along with the dose ranges observed is summarized in Table 1.

Table-1: Dose/concentration-linked to the biological activities of CIT in different test systems [4]

Major effects observed in experimental system		Dose/concentration
Alterations (including biochemicals) in organs	Brain	15 to 35 mg/kg
	Lung	0.2 to 50 µg/mL
	Heart	20 to 50 µM
	Liver	15 to 87 mg/kg
	Kidney	0.1 mM to 77 mg/kg
	Reproductive system	2.5 µM to 6.25 mg/kg
Hematological alterations		0.65 mg/kg
Inflammatory		0.1 µg/mL to 30 µM
Cytotoxicity		0.1 µM to 40 mg/kg
Genotoxicity		25 µM to 25 mg/kg
Mutagenicity		10 to 100 µM
Protective effects		0.1 nM to 100 µM
Antioxidant		3 to 40 µM
Antimicrobial		3 to 200 µg/mL

According to the Table 1, it is possible to say that 0.1 nM to <0.1 μM of CIT may be the protective concentration. However, the safety and protectivity also depends on the test system and exposure time used to screen any substance.

CIT at high dose not only can raise oxidative stress and inflammatory reactions, but also can alter physiological biochemicals. Therefore, the toxic effects may occur directly or indirectly. Thus, selecting dose during its pharmacological assessment in experimental animals or other test system may bring some hopes, especially in microbial infection, organ protectivity and even treatment and prevention of cancers.

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