



REVIEW ARTICLE

Cycads and their association with certain neurodegenerative diseases[☆]

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Alternative food;
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Abstract

Introduction: Cycads are ornamental plants that in some parts of the world are used as fresh food or raw material for producing flour with a high nutritional value. However, they also contain active compounds, including methylazoxymethanol, β -methylamino-L-alanine, β -alanine-L-oxalylamino and cycasin, which may produce neurotoxic effects. Some studies have associated consuming cycads and their derivatives with neurodegenerative diseases such as amyotrophic lateral sclerosis/Parkinsonism dementia complex, and other diseases characterised by motor impairment. Therefore, we must not forget that any product, no matter how natural, may present health risks or benefits depending on the chemical compounds it contains and the susceptibility of those who consume it.

Development: We completed a literature analysis to evaluate the neurotoxic properties of cycads and their association with neurological diseases in order to provide structured scientific information that may contribute to preventing health problems in people who use these plants.

Conclusion: Cycads contain neurotoxic compounds that may contribute to the development of neurological diseases when ingested improperly. We must be mindful of the fact that while some plants have a high nutritional value and may fill the food gap for vulnerable populations, they can also be toxic and have a negative impact on health.

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PALABRAS CLAVE

Cícada;
Neurotóxico;
Enfermedad
neurodegenerativa;
Metilazoximetanol;

Las cícadas y su relación con algunas enfermedades neurodegenerativas

Resumen

Introducción: Las cícadas son plantas que en algunas partes del mundo son empleadas como alimento fresco o materia prima para la elaboración de harina con alto valor nutricional. Sin embargo, contienen principios activos como metilazoximetanol, β -metilamino-L-alanina, β -oxalilamino-L-alanina y cicasina, entre otros, que pueden producir efectos neurotóxicos. El

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Alimento alternativo;
Alteración motriz

consumo de cícadas y sus derivados se ha asociado con enfermedades neurodegenerativas, como el complejo demencia-parkinsonismo-esclerosis-lateral amiotrófica y otras enfermedades caracterizadas por alteraciones en la motricidad. Por lo tanto, no debemos perder de vista que todo producto, aunque sea de origen natural, puede ser benéfico o perjudicial para la salud, lo cual dependerá de sus componentes químicos y de la vulnerabilidad de quienes los consumen. *Desarrollo:* Se realizó un análisis de la literatura sobre las propiedades neurotóxicas de las cícadas y su asociación con enfermedades neurológicas, con el fin de proporcionar información estructurada a la población para contribuir a la prevención de problemas de salud en quienes interactúan con estas plantas.

Conclusión: Las cícadas contienen neurotóxicos que contribuyen al desarrollo de enfermedades neurológicas cuando son ingeridas inadecuadamente, por lo que debemos considerar que si bien algunos vegetales pueden tener un alto valor nutricional y subsanar el déficit alimentario en las poblaciones vulnerables, también pueden ser tóxicos e impactar negativamente sobre la salud. © 2013 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Cycads are gymnosperms that are considered living fossils because they have been present in different parts of the world ever since they emerged in the Mesozoic era. Researchers have described some 185 species of cycads, most of which are endemic. While these species are frequently cultivated as exotic ornamentals, they also provide food for humans. Due to poor management of these resources, and to the plants' complex reproductive cycles, many cycads are threatened or endangered. As such, international trade in cycads is regulated by the Convention on Trade in Endangered Species (CITES). While the seeds of some cycads are used as fresh food or as raw material used to make highly nutritious meal,¹ some contain significant amounts of highly toxic chemical compounds.² Scientists have found an association between consumption of cycad seeds/derivatives and motor and electroencephalographic changes in animal models (Table 1). In humans, cycad consumption has been linked to neurodegenerative diseases such as amyotrophic lateral sclerosis-Parkinsonism dementia complex (ALSPD) and other motor diseases.^{2,3} Neurotoxic active ingredients identified in cycad seeds include methylazoxymethanol acetate (MAM), β -methylamino-L-alanine (L-BMAA), β -oxalylamino-L-alanine (L-BOAA), and cycasin. These substances have also served as tools for exploring possible aetiologies of ALSPD, a complex presenting frequently on the island of Guam, where the native diet included certain cycad derivatives.³ This study therefore reviews the link between cycad toxins and the development of neurodegenerative disease in order to inform at-risk populations and warn about health problems in those who come into contact with these plants.

Development

Chemical compounds in cycads and their neurotoxic effects

Cycadales synthesise and store a number of neurotoxic and carcinogenic active ingredients (Table 2) including such

glucosides as MAM.⁴ The active ingredient is released by the main glucoside through enzymatic processes occurring in digestion. Cycasin, a β -D-glucoside of MAM, has also been identified in cycads.^{5,6} Cycasin is the most common glucoside in all types of cycads; others, present in smaller percentages, include macrozamin and neocycasin. The toxic part of cycasin is the methyl-azoxy group present in its structure; this is released as MAM when cycasin is metabolised in the digestive system by the β -glucosidase enzyme produced by normal bacterial flora of the small intestine. For this reason, cycasin only exerts a toxic effect when it is ingested.⁷ MAM is a product of macrozamin metabolism and the presence of the azoxy group in its chemical structure renders it highly toxic and carcinogenic. At the cellular level, this compound inhibits protein synthesis and affects the DNA of vulnerable neurons, in which it also induces apoptosis. Botanist Knut Norstog⁸ observed that cycads endemic to Guam produce abundant pollen, which contains high concentrations of cycasin and L-BMAA. When pollen comes into contact with nasal epithelium, cycasin and other toxins can be transported to brain tissue, where they induce neurotoxic effects.⁹ In mice, intranasal administration of MAM damages the olfactory epithelium¹⁰ and may affect brain tissue over the long term. These findings suggest that the respiratory system may be a route of entry for cycad toxins; therefore, long periods of environmental exposure to the pollen of these cycads may result in high concentrations of the toxin in the nasal epithelium. Cycasin has the most thoroughly studied toxicology of all of the azoxyglycosides; it paved the way for studies of mutagenicity and carcinogenicity of other azoxyglycosides, such as macrozamin and neocycasin.¹¹ Azoxyglycosides present risk of mutagenesis when they are ingested because intestinal flora is able to deglycosylate them and render them highly toxic. Human carcinogenicity of certain cycad compounds is supported by laboratory results that show that cycasin and MAM are carcinogenic to various organs, and also in numerous species.^{12,13} Other studies have not detected associations between consumption of cycad flour and cancer,¹⁴ but these studies do not rule out the possibility that other cycad flour samples or different cycad derivatives may contain this toxin and constitute a health risk for consumers.

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