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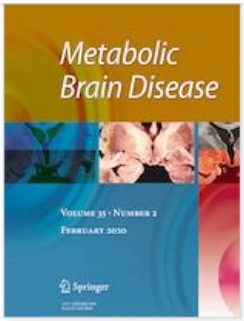

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REVIEW ARTICLE

Preclinical and clinical research on the toxic and neurological effects of cassava (*Manihot esculenta* Crantz) consumption

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Abstract

Cassava (*Manihot esculenta* Crantz) is a tropical plant that is used as fresh food, processed food, or raw material for the preparation of flours with high nutritional value. However, cassava contains cyanogenic glycosides, such as linamarin and lotaustralin, that can trigger severe toxic effects and some neurological disorders, including motor impairment, cognitive deterioration, and symptoms that characterize tropical ataxic neuropathy and spastic epidemic paraparesis (Konzo). These alterations that are associated with the consumption of cassava or its derivatives have been reported in both humans and experimental animals. The present review discusses and integrates preclinical and clinical evidence that indicates the toxic and neurological effects of cassava and its derivatives by affecting metabolic processes and the central nervous system. An exhaustive review of the literature was performed using specialized databases that focused on the toxic and neurological effects of the consumption of cassava and its derivatives. We sought to provide structured information that will contribute to understanding the undesirable effects of some foods and preventing health problems in vulnerable populations who consume these vegetables. Cassava contains cyanogenic glycosides that contribute to the development of neurological disorders when they are ingested inappropriately or for prolonged periods of time. Such high consumption can affect neurochemical and neurophysiological processes in particular brain structures and affect peripheral metabolic processes that impact wellness. Although some vegetables have high nutritional value and ameliorate food deficits in vulnerable populations, they can also predispose individuals to the development of neurological diseases.

Keywords Cassava · Linamarin · Acetone cyanohydrin · Neurotoxic · Motor disorder

Introduction

Manihot esculenta Crantz, known as cassava, tapioca, or yuca, is an edible vegetable in tropical and subtropical regions. Its use has spread to diverse parts of the world because of its high content of carbohydrates and some essential micronutrients for human nutrition. However, this plant also contains a high percentage of cyanogenic glycosides, such as linamarin (90%) and lotaustralin (10%; Soler-Martín et al. 2010). The consumption of this plant or its derivatives has been associated with the development of neurological disorders that principally produce motor impairment and cognitive deficits (Adamolekun 2011).

Clinically, chronic cassava consumption is associated with the development of such neuropathies as spastic epidemic paraparesis (Konzo) and tropical ataxic neuropathy (TAN; Tylleskär et al. 1992; Rivadeneyra-Domínguez et al. 2012; Netto et al. 2016; Kashala-Abotnes et al. 2019) that are attributable to its linamarin content, the hydrolysis of which forms hydrocyanic acid (Adamolekun 2010) that produces neuronal damage. Neurotoxic effects occur when high plasma concentrations of cyanide are reached in the form of thiocyanate, mainly in the liver (Ernesto et al. 2000). Preclinical studies showed that cassava consumption in albino goats induced liver and kidney damage, alterations of thyroid function and neuronal vacuolization, and the cellular infiltration of leukocytes (Soto-Blanco and Górniak 2010). In rats, a positive correlation was found between

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the consumption of cassava juice and the development of motor alterations (Rivadeneyra-Dominguez et al. 2013, 2019), neuronal damage in the CA1 area of the hippocampus (Rivadeneyra-Dominguez et al. 2013), medulla oblongata, and mesencephalon, axonal dystrophy, the degeneration of Purkinje cells, spongiosis, and gliosis (Soler-Martin et al. 2010; Soto-Blanco and Górniak 2010). Considering these findings, the present review focuses on findings from preclinical and clinical research on the neurotoxic effects of cassava and its derivatives to raise awareness of its potential health risks in vulnerable individuals who consume this vegetable as a principal component of their diet.

Chemical compounds in cassava

Cyanogenic glycosides that are contained in the roots and leaves of cassava are the main active constituents that are related to neurotoxic and neurological effects (Jansz and Uluwaduge 1997). L-valine and L-isoleucine are precursors of linamarin and lotaustralin, respectively. The biosynthetic pathway (Fig. 1) of these compounds was identified using techniques with radioactive markers. Recent studies isolated microsomal enzymes (i.e., a multienzyme complex) from cassava phellodermis that convert valine-14C into acetone cyanohydrin (Jansz and Uluwaduge 1997). The initial step of the sequence (i.e., the synthesis of isobutyraldoxime) is catalyzed by cytochrome p450.

The identification of linamarin in cassava was achieved with the enzyme linamarase and sulfuric acid. In the last 25 years, analytical methods have been developed for such determinations (Yeoh et al. 1998). One such technique uses the hydrolysis of linamarin to detect hydrogen cyanide or glucose release. This semiquantitative procedure involves direct trituration of the roots and the addition of organic solvents that cause the release of linamarase to hydrolyze linamarin. The alkaline picrate test is then performed, which can detect hydrogen cyanide that is released in the reaction (Yeoh et al. 1998; Egan et al. 1998). The quantitative method of analysis involves the extraction of linamarin from the roots, which is then hydrolyzed by the action of exogenous linamarase. This is followed by the determination of hydrogen cyanide by amperometry, potentiometry, or spectrophotometry (Cooke 1978; Bradbury et al. 1991). Linamarin (2-[−D-glucopyranosyloxy]-2-methylpropanonitrile) is also called phaseolunatin. Its empirical formula is $C_{10}H_{17}NO_6$, with a molecular weight of 247.24 g/mol. It has an elemental composition of 48.58% C, 6.93% H, 5.6% N, and 38.83% O. It is soluble in water and appears as a white solid. Linamarin can be found in plants of the Compositae, Leguminosae, Euphorbiaceae, Linaceae, and Papaveraceae families (Seigler 1975), which usually exert toxic and neurological effects at high concentrations or at low doses with long-term consumption.

General neurotoxins in cassava

Cassava is usually classified as "sweet" or "bitter," based on the content of cyanogenic glucosanate (i.e., a promoter of hydrocyanic acid formation) in the roots of this plant (Nweke and Bokanga 1994). The sweet variety of cassava has a thin white skin. It is usually consumed raw, steamed, or roasted. Bitter cassava is characterized by a thicker pink skin. Cyanogenic compounds need to be removed by peeling the skin, boiling, slicing, soaking, fermenting, roasting, drying, or grinding, which apparently inactivate or eliminate the toxic components (Schaumburg et al. 1983). The differentiation between bitter and sweet varieties is not always accurate because the content of cyanogenic glycosides is not necessarily constant within a variety and also depends on the edaphoclimatic conditions of the crop. Bitter cassava is more common in the Amazonian and Caribbean regions, whereas the sweet variety is found more frequently in northern South America (Cock 1984).

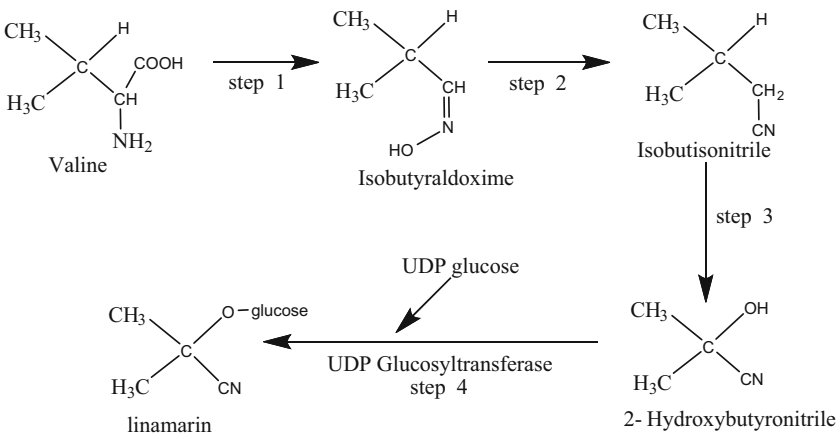

Fig. 1 Linamarin Biosynthesis. Based on Jansz y Uluwaduge, 1997

Cassava produces a sage or milky juice that contains the cyanogenic glucoside linamarin. Boiling, steaming, frying, or baking cassava causes the loss of 30–70% of cyanogenic glycosides, demonstrating remnant toxicity even after processing (Jansz and Uluwaduge 1997). The production of hydrocyanic acid (cyanide) depends on the biosynthesis of cyanogenic glycosides and the presence or absence of enzymes that degrade them (Hernández et al. 1995).

The destruction of cassava cells releases linamarin (97%) and lotaustralin (3%). The roots of cassava are consumed because of their high content of carbohydrates, but all cassava varieties contain linamarin. Linamarin is hydrolyzed in the gastrointestinal tract in humans by β-glycosidase. The cyanide that is generated is rapidly absorbed by the gastrointestinal tract and transported to the central nervous system (CNS). The liver also contains enzymes that are able to hydrolyze the absorbed linamarin, generating metabolites from which cyanide ions are generated (Maduagwu 1989).

The neurotoxic potential of such substances may depend on the nutritional status of the individual. Because cassava is the main dietary component of many people who are in a state of malnutrition, the toxic threshold can easily be exceeded and trigger acute or chronic diseases. The causal factors that contribute to cassava toxicity are associated with malnutrition (Mathangi et al. 2000). Linamarin is not toxic per se, but it contributes to the formation of cyanide in humans (Mlingi et al. 1992). The amount of linamarin that is ingested from cassava does not change intestinally within the first 24 h, which is maintained until it is excreted in urine (Brimer and Roseling 1993; Carlsson et al. 1995).

The linamarase enzyme acts on linamarin when cassava tissue is destroyed by cell membrane rupture, where by the hydrolytic action of the glucosidases acetone cyanohydrin is obtained, same that by enzymatic activity of the hydroxynitrile lyase decomposes in acetone and HCN. Cyanohydrin decomposes in an alkaline medium and also when it is exposes to more than 60 °C, whereas HCN remains the free toxic form or “free cyanide” (McMahon et al. 1995). The product of the action of linamarase on cyanide-containing compounds is hydroxynitrile, which is unstable in response to heat and an alkaline medium. Therefore, analytical proposals have considered that hydroxynitrile lyase is not required for this process of biotransformation. The cassava plant contains hydroxynitrile lyase that releases HCN from acetone cyanohydrin. Because of lability of the substrate, this enzyme has not been the subject of extensive investigations. Hydroxynitrile lyase in cassava increases the rate of cyanide release 20-fold (Conn 2009). This results in the addition of HCN to several aliphatic carboxyls with a molecular weight of 30 kDa and serine residues in the active site. Hydroxynitrile lyase in cassava has been shown to not be related to other acetone cyanohydrin lyases (Wajant and Forester 1995), in contrast to linamarase that is present in greater amounts in the leaf of the plant (Pancon and Hughes 1992).

Metabolic alterations associated with the consumption of cassava and its derivatives

Preclinical studies

In Wistar rats, the oral consumption of cassava for 21 days at a dose of 15 g/day increased serum thiocyanate concentrations (Kittirachra 2006). This increase occurred because cyanogenic glycosides (linamarin and a small amount of lotaustralin) are absorbed by the body and converted to thiocyanate, which is excreted in urine. Thiocyanate is widely accepted to reduce iodine that is captured by the thyroid gland, but other factors affect serum thiocyanate levels, including ingestion, detoxification, and excretion. Interestingly, the thyroid gland in rats that were fed cassava did not increase in size. Additionally, the increase in serum thiocyanate concentrations did not produce anatomical changes in the thyroid. One possible explanation for these findings could be that thiocyanate that is produced by ingesting cassava is insufficient to inhibit the transport of iodine.

A study evaluated the effect of oral administration of the aqueous and methanolic extracts of cassava (*Manihot esculenta*) in Wistar rats (Adam Shama and Ahmed Wasma 2011). Increases were observed in the concentrations of glutamic pyruvic transaminases (alanine aminotransaminase [ALT]), glutamic oxaloacetic transaminases (aspartate aminotransaminase [AST]), alkaline phosphatase (ALP), urea, cholesterol, total proteins, and albumin. Additionally, hematological parameters, such as white blood cells, lymphocytes, neutrophils, and hemoglobin, decreased. Changes were observed in organs, including necrosis and the shrinkage of glomeruli and aggregates of lymphocytes in the renal cortex, accompanied by the cytoplasmic vacuolization of hepatocytes and neurons (Adam Shama and Ahmed Wasma 2011). These findings indicate that the toxic effects of cassava are associated with various biochemical and hematological alterations (Table 1).

The chronic administration of different concentrations of acetone cyanohydrin and subchronic treatment with linamarin increased various biochemical parameters in Wistar rats, indicating inadequate renal and hepatic function that can contribute to the formation of cyanide through metabolic processes and consequently impact the CNS. Cyanide is a potent inhibitor of electron chains and promotes oxidative stress, which can then damage neurons and cause significant motor disturbances. These preclinical findings may help explain neurological effects that have been found in clinical research.

Clinical studies

A clinical study included 39 subjects (30 men and 9 women, 4–46 years old) with a diet that was primarily based on

Table 1 Metabolic effects of cassava and its derivatives in animal models

Substance and treatment regimen	Subject	Effects	References
Oral 15 g/day and diet ad libitum with cassava for 9 months	Rats	↑ Serum thiocyanate	Howlett et al. 1990; Kittirachra 2006
Aqueous and methanolic extract of cassava tubers 75–300 mg/kg orally 14 days	Rats	↓ White blood cells ↓ Lymphocytes and neutrophils ↓ Hemoglobin ↑ Alkaline phosphatase ↑ Alanine aminotransferase ↑Aspartate amino transferase (AST) ↓ Total protein, albumin, and globulins ↑ Urea and cholesterol	Adam Shama and Ahmed Wasma 2011
Acetone cyanohydrin 10, 15, and 20 mM (0.3 ml/rat), i.p., for 28 consecutive days	Rats	Renal function: ↑ Urea, creatinine, uric acid, and BUN Hepatic function: ↑ Aspartate amino transferase, alanine aminotransferase, and alkaline phosphatase ↑ Total bilirubin, direct and indirect bilirubin ↓ Total protein and albumin	Rivadeneyra-Domínguez et al. 2017b
Linamarin 20 mM linamarin (0.4 ml), i.p., 24, 5, and 1 h before obtaining the sample	Rats	Renal function: ↑ Urea, creatinine, uric acid, and BUN Hepatic function: ↑ Aspartate amino transferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct and indirect bilirubin ↓ Total protein and albumin	Rivadeneyra-Domínguez et al. 2017a
Cassava ad libitum in diet No treatment time was specified	Rats	↑ Uric thiocyanate and serum creatinine ↓ Serum albumin	Tshala-Katumbay et al. 2001
Cassava ad ibitum in diet No treatment time was specified	Rats	↓ Serum albumin	Bumoko et al. 2014

↑, Increase concentration; ↓, Decrease concentration

cassava products. Serum thiocyanate concentrations were up to eight-times higher than the reference population in Mozambique (Howlett et al. 1990). This demonstrates an inability by the organism to detoxify cyanide through the enzyme rhodamine, thus increasing the formation of thiocyanate that is eliminated in urine. When constant exposure to cassava cyanogens occurs, the higher synthesis of kinase imposes an additional demand for amino acids from the body's reserves (Aristizábal and Sánchez 2007). To detoxify 1 mg hydrogen cyanide, the body needs a daily supply of approximately 1.2 mg sulfur from amino acids. If cassava is consumed regularly, then rhodamine and sulfur-containing amino acid resources are depleted. If the diet is insufficient for restoring these resources, then the synthesis of other proteins that are vital for CNS function can be impaired. Such metabolic alterations predispose the individual to the development of protein deficiency-related diseases. Over time, the loss of sulfur can trigger sudden and irreversible paralysis in the CNS (Padmaja 1995).

In the Democratic Republic of Congo, 2723 inhabitants were invited to answer a questionnaire to detect the prevalence of Konzo cases (Tshala-Katumbay et al. 2001). Of the total participants, 152 had difficulty walking, and 55 had Konzo. Decreases in albumin concentrations and increases in creatinine concentrations were observed, indicating alterations of renal function. Additionally, high concentrations of thiocyanate were found in urine, which is consistent with other studies (Howlett et al. 1990). Another study that included 40 children from the Democratic Republic of Congo whose diet was basically based on cassava also reported lower albumin concentrations, possibly attributable to malnutrition that was caused by a low-protein diet.

These changes in renal and hepatic function indicate that the peripheral effects of cassava and its derivatives might have deleterious effects on the brain, resulting in the development of neurological disorders that are associated with cassava consumption.

Chemical compounds in cassava and the development of neuropathies

Chronic cyanide poisoning from the metabolism of cassava components has been suggested for decades to be the main etiological factor that is involved in developing TAN (Osuntokun 1968) because elevated serum levels of thiocyanate are detected in these patients (Osuntokun 1968). The administration of hydroxocobalamin, a potent antagonist of cyanide recognition sites, prevented the toxic effects of cyanide (Adamolekun 2011). Similarly, the specific neurotoxic effects of the cyanogenic glucoside linamarin were proposed to be the cause of Konzo because linamarin can be transported to the cytoplasm of neurons where it causes

neurodegeneration (Sreeja et al. 2003). Individuals with Konzo do not present the known clinical effects of cyanide. Therefore, another hypothesis was proposed that involved another chemical compound of cassava, the acetone cyanohydrin (linamarin aglycone), in the development of Konzo (Soler-Martín et al. 2010). However, a preclinical study in rats that were exposed to acetone cyanohydrin reported no motor alterations that are typically seen in Konzo cases (Adamolekun 2011). Oral acetone cyanohydrin administration in rats (Fig. 2) caused selective neuronal degeneration in different areas of the brain, including non-cortical areas (Nzwalo and Cliff 2011). Cyanogenesis is initiated in cassava when the plant tissue is damaged. Acetone cyanohydrin in cassava flour is unstable and can decompose spontaneously in acetone and hydrogen cyanide at pH > 5 or temperatures >37 °C or enzymatically through the reaction of hydroxynitrile lyase (Nzwalo and Cliff 2011). Consequently, people who consume these products regularly can potentially develop neuronal damage and suffer neurological disorders in the long-term.

Neurological disorders associated with cassava consumption

Several clinical and preclinical studies have shown that the long-term consumption of cassava and its derivatives is associated with the development of behavioral, motor, and cognitive alterations (Table 2), which could explain some neurological disorders that are reported in people who consume this vegetable or its derivatives (Madhusudanan et al. 2008; Kashala-Abotnes et al. 2018). Tropical ataxic neuropathy and spastic epidemic paraparesis (Konzo) occur with high frequency in communities where cassava is the basis of their diet (Tylleskär et al. 1993; Tshala-Katumbay et al. 2016; Boivin et al. 2017). Preclinical studies have shown that some active ingredients of cassava, such as linamarin and lotaustrastalin, can cross the blood-brain barrier and cause neuronal damage in such brain structures as the hippocampus, cerebral cortex, and cerebellum, among others. These findings have contributed to the formulation of hypotheses that attempt to establish the neurobiological substrates of the behavioral, motor, and cognitive alterations that are associated with neurological disorders in humans who consume cassava and its derivatives.

Preclinical studies

Laboratory rats that were orally fed cassava gradually developed motor incoordination and low dopamine concentrations in the striatum and cerebellum (Mathangi et al. 1999; Spencer and Palmer 2012). Both the striatum and cerebellum are involved in motor control. Rats that were treated with cassava juice for 28 consecutive days gradually developed motor incoordination, hyperactivity, a decrease in exploration, and a decrease in self-grooming (Rivadeneyra-Dominguez et al. 2013). When these rats were subjected to a swim test, they exhibited atypical swimming behavior that was characterized by swimming on one side and rotating on their own axis compared with animals that did not consume cassava juice. These neurological alterations were associated with the high content of linamarin (0.22–0.30 mg/ml) that is present in cassava juice (Rivadeneyra-Dominguez et al. 2013). Indeed, when linamarin was microinjected in the CA1 area of the hippocampus in rats, alterations of motor coordination were observed that were similar to when cassava juice was administered. This suggests neurological deterioration that is associated with toxic components of the plant (Rivadeneyra-Domínguez and Rodríguez-Landa 2016). Interestingly, microinjections of acetone cyanohydrin, another toxic component of cassava, in the CA1 area of the hippocampus produced the same neurological alterations (Rivadeneyra-Dominguez et al. 2019). Apparently, these effects derived from excitatory processes and oxidative stress, which in the long-term can cause

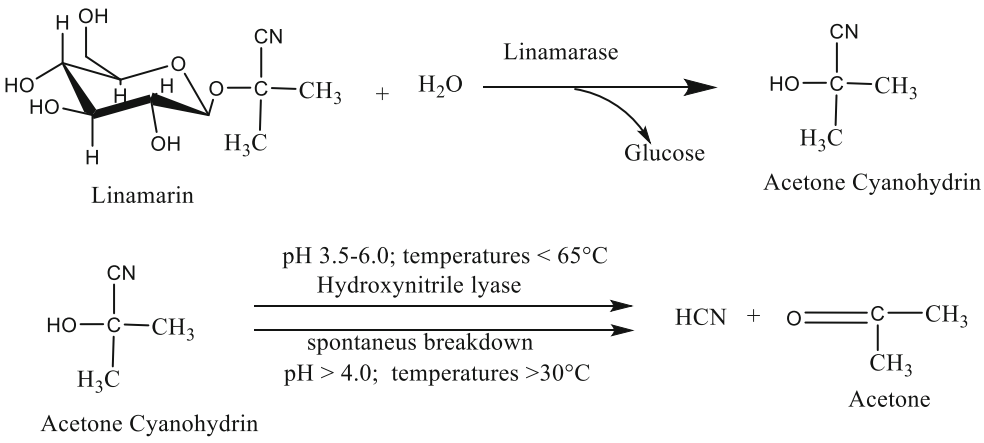

Fig. 2 Linamarin Hydrolysis. Based on McMahon et al. 1995

Table 2 Cassava toxicity in experimental animals

Neurotoxic	Effects on the central nervous system	Neurological alterations	Subjects	References
Cyanide contained in cassava leaves 30 consecutive days, orally, 6 mg/kg	Vacuolization and myelin degeneration in white matter	*	Goats	Soto-Blanco and Górniak 2010
Acetone cyanohydrin 14–42 consecutive days, orally, 50 μmol/kg	Neuronal degeneration in cortical areas	*	Rats	Soler-Martín et al. 2010
Cassava tubercle parts 60 consecutive days, orally, 2–60 g/rat	Neuronal degeneration and neuroinflammation in the visual cortex (V1), lateral geniculate body, and superior colliculus	*	Rats	Ogundele et al. 2010
Methanolic extract of cassava tuber 14 consecutive days, orally, 75 and 300 mg/kg	Neuronal vacuolization	*	Rats	Adam Shama and Ahmed Wasma 2011
Linamarin contained in cassava tuber juice 28 consecutive days, orally. 0.075–0.3 mg/kg	*	Hyperactivity and motor incoordination, lateral swimming, and spinning on own axis	Rats	Rivadeneyra-Dominguez et al. 2013
Linamarin 7 consecutive days, intrahippocampal administration, 1 μl, 10–20 mM	*	Motor incoordination, lateral swimming, and spinning on own axis	Rats	Rivadeneyra-Domínguez and Rodríguez-Landa 2016
Cassava tuber juice that contained 0.3 mg/kg linamarin 28 consecutive days, orally	Neuronal degeneration and neuroinflammation in the CA1 area of the hippocampus	Motor hyperactivity, motor incoordination, lateral swimming, and turning on own axis	Rats	Rivadeneyra-Domínguez et al. 2014, 2017b
Acetone cyanohydrin 7 consecutive days, intrahippocampal administration. 1 μl, 10–20 mM	*	Motor hyperactivity, motor incoordination, lateral swimming, turning on own axis	Rats	Rivadeneyra-Domínguez et al. 2017a

*Data not reported

neuronal damage and the deterioration of motor coordination. Indeed, when rats were co-administered cassava juice and a standardized extract of *Ginkgo biloba* that contained a high percentage of flavonoids and antioxidants, motor impairments and hippocampal damage were not observed (Rivadeneyra-Domínguez et al. 2014, 2019).

The preclinical data show that neuronal damage in the brain and neurological symptoms that are produced by cassava consumption may be attributable to the presence of two cyanogenic glycosides, linamarin and acetone cyanohydrin, whose effects on the CNS likely have neurochemical and neurobiological bases that underlie such neurological disorders as TAN and Konzo in individuals who consume cassava and its derivatives. These preclinical findings support epidemiological studies, in which some neurological disorders in humans are associated with the consumption of cassava.

Clinical studies

The excessive or inappropriate consumption of cassava appears to be associated with TAN and Konzo. Tropical ataxic neuropathy is a syndrome of sensory polyneuropathy that includes sensory ataxia, bilateral optic atrophy, and bilateral deafness (Osuntokun 1968). This neurological disorder has been reported in communities in Tanzania, Sierra Leone (Rowland 1963), Nigeria (Monekosso and Annan 1964; Osuntokun 1968), and India (Madhusudanan et al. 2008), where cassava consumption is high relative to other communities. The syndrome progresses slowly over years and affects men and women equally. Patients are characterized by an ataxic gait and osteotendinous areflexia in 80% of cases and hyperreflexia in 20% of cases, which is attributable to the loss of myelin (Banea-Mayambu et al. 1997). The prolonged

intake of poorly processed cassava, low protein consumption, and other nutritional or metabolic factors produce the same symptomatology (Zaninovic 2003), accompanied by high concentrations of serum thiocyanate (Schulz et al. 2003; Llorens et al. 2011). However, such a wide variety of factors has not allowed identification of the latency of the appearance of symptoms after cassava consumption (Oluwole and Onabolu 2003).

Exposure to cyanide in TAN cases is measured by serum thiocyanate content, which is elevated in patients with cyanide poisoning. Nonetheless, serum thiocyanate content is low in patients with Konzo. This apparent contradiction between these two myelopathies appears to be related to the high exposure to cyanide in the diet in patients with TAN, which predominately consists of cassava (van Heijst et al. 1994). Although the hypothesis that metabolites of cassava contribute to the development of TAN has not been fully proven, clinical studies have shown that patients with this neuropathy have high plasma concentrations of cyanide and thiocyanate, contrary to observations in patients who had a diet that was free of cassava and its derivatives (Spencer et al. 1987). Therefore, dietary exposure to cyanogenic glycosides through the ingestion of cassava and its derivatives could be a factor that predisposes individuals to the development of some types of neuropathy (Spencer et al. 1987).

Konzo is a neurological disorder that is characterized by damage to upper motor neurons. It initially produces irreversible, non-progressive, and symmetric spastic paraparesis (Nzwalo and Cliff 2011). It is characterized by spasticity and progressive weakness of the lower extremities that consequently produces alterations of motor coordination. Additionally, abrupt symmetric spastic paraparesis appears in epidemic and endemic forms in tropical and subtropical countries (Tylleskär et al. 1993; Adamolekun 2011). It mainly affects children and young women who consume cassava and its derivatives that contain linamarin for prolonged periods of time (Sreeja et al. 2003). Interestingly, neurological alterations that are associated with Konzo have been related to cassava consumption (Tylleskär et al. 1993). The toxicity of cyanogenic glycosides that are contained in cassava mainly affects neurons in brain structures that are involved in neurological and cognitive processes (i.e., thalamus, piriform cortex, hypothalamus, hippocampus, and cerebellum), including the integration of memory, emotions, the control of visceral functions, olfaction, and motor skills, among others (Soler-Martín et al. 2010).

The mechanisms of action of the neurotoxic effects of chemical compounds in cassava have not been completely elucidated. Neurophysiological studies have related Konzo with alterations of cortico-motor neurons and descending motor pathways (Nzwalo and Cliff 2011). The initial symptoms are described as heaviness and tremor or weakness of the lower extremities. Over time, weakness of the upper extremities occurs, with difficulty speaking and blurred vision. Sensory symptoms include radicular pain of the lower back and paresthesia in the lower extremities (Cliff et al. 1985). Neurological alterations that are produced by high concentrations of cyanide are apparently attributable to a decrease in mitochondrial energy through competitive inhibition of the aerobic metabolism of complex IV when joining the hemobinuclear group of the enzyme cytochrome oxidase, which generates oxidative stress and apoptosis and leads to neuronal damage (Pearce et al. 2008; Leavesley et al. 2008). The exact mechanisms that are involved in the neurotoxicity of cassava metabolites and their relationship to Konzo are not yet fully known (Tor-Agbidye et al. 1999).

Final comments

Cassava (*Manihot esculenta* Crantz) is a plant that is the first source of caloric intake in the diet among populations in the tropics; in other regions, it places fourth, after rice, sugar, and corn. Although cassava and its derivatives are an important source of calories for more than 500 million people worldwide (Mederos 2006), its high content of cyanogenic glycosides that are synthesized in the leaves and transported to the roots must also be considered. They are biotransformed by the enzyme linamarase to produce hydrocyanic acid, a highly toxic substance that, at high concentrations, can cause death. The intake of improperly processed cassava products, combined with a diet that is deficient in sulfur-containing amino acids, can cause chronic cyanide poisoning (Jørgensen et al. 2011). Sulfur is utilized during the detoxification process (Cock 1984) to convert cyanide into thiocyanate, which is excreted in urine (Duarte and Sandoval-Castro 2002). Acute cyanide poisoning inactivates cytochrome-mitochondrial oxidase, thus blocking the electron chain and favoring the development of neuronal damage and neurological alterations, such as Konzo and TAN (Nzwalo and Cliff 2011; Kambale et al. 2017). As described in the present review, the substances that are responsible for these neurological alterations are the main cyanogenic glycosides in cassava, including linamarin, lotaustralin, and acetone cyanohydrin.

The conclusion is clear. Diverse populations around the world are experiencing a food and nutritional emergency that can lead to diseases that are a public health problem. This has led to the development of more easily grown crops to cover basic food needs, but some of these crops can have negative effects on health. This reveals the need for further epidemiological studies by neurologists and other specialists to identify

possible neurological manifestations among consumers of these products and their derivatives, such as cassava.

Some vegetables with high nutritional value can be used to correct food deficits in vulnerable populations. However, studies are needed to identify the presence or absence of potential toxic effects that can seriously impact human health. Such toxic effects have been identified with other vegetables, such as cycads (Rivadeneyra-Domínguez and Rodríguez-Landa 2013). Cassava is easily cultivated because of its adaptation to diverse climates, but its potential toxic effects must be considered in vulnerable populations. Therefore, every product, even if it has a natural origin, can be beneficial or toxic to the organism. Oftentimes, such effects depend on the type and quantity of its active ingredients and the vulnerability of the people who consume them.

Conclusions

Cassava contains cyanogenic glycosides with neurotoxic actions that predispose individuals to the development of neurological disorders that are characterized by alterations of motor skills, motor incoordination, and cognitive deterioration when it is consumed at high concentrations or for prolonged periods of time. Although cassava has high nutritional value and has been consumed to correct food deficits in vulnerable populations, it also has toxic potential that can negatively impact brain function and affect quality of life.

Compliance with ethical standards

Conflict of interest The authors report not conflict of interest.

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