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REVIEW ARTICLE

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Neurotoxic and neuromotor implications of cyanate, an oxidative byproduct of cyanide derived from linamarin in cassava: A systematic review

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ABSTRACT

Background Linamarin-induced neurotoxicity manifests as either polyneuropathy, ataxia, and sensorineural deafness or as isolated symmetric spastic paraparesis of bilateral limbs, which are frequently observed in populations subsisting on a monotonous cassava-based diet. Attributable to the potential protein deficiency resulting from this dietary regimen, cyanide derived from linamarin may undergo oxidation to cyanate, a neurotoxin known to carbamoylate proteins and induce oxidative stress.

Aim: To synthesize preclinical and clinical evidence concerning cyanate-induced neurotoxicity, thereby identifying the predominant neurological adverse events following sodium cyanate exposure.

Methods: This study employed a systematic review methodology, utilizing four electronic databases (PubMed, Scopus, Cochrane Library, Google Scholar) to identify for publications on the neurotoxicity of cyanate from 1936 to 2024. A total of 1,089 articles were screened. Studies investigating non-neurotoxic effects and those lacking full-text availability were excluded, resulting in the selection of 10 for quality assessment and review. Preclinical studies were evaluated using the SYRCLE risk-of-bias tool, while non-randomized clinical studies were assessed using the Newcastle-Ottawa scale.

Results: The majority of studies were preclinical. One case-control study investigated the association between spastic paraparesis and protein carbamoylation. Rodents exposed to high-dose sodium cyanate (NaOCN) developed hindlimb spastic weakness or paralysis in 42.86% of animal studies, and ataxia, dysmetria, and cognitive impairment in 14.26%. Peptide carbamoylation was reported in 42.86%, while one study (14.26%) reported demyelination of the spinal cord. The sole case-control study reported a statistically significant (p = 0.01) association between severe konzo and carbamoylation of serum peptides.

Conclusion: Sodium cyanate administration at doses ranging from 60 to 200 mg/kg resulted in hindlimb weakness or spastic paralysis in rodents and spinal cord demyelination in primates, findings strikingly identical to the spastic paraparesis observed in konzo. Further investigations are required to determine the association between cyanate exposure and the development of spastic paraparesis resulting from monotonous cassava consumption.

Keywords: Cyanate, Neurotoxicity, Linamarin, Paralysis, Konzo, Cassava.

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1 INTRODUCTION

In certain regions of Sub-Saharan Africa, populations continue to subsist on a monotonous cassava-based diet, attributable to the crop's widespread availability, resilience to drought and poor soil conditions, and the cultural significance of fufu, a staple prepared from cassava flour (Chijioke *et al.*, 2021). Food processing typically involves fermentation through methods such as wetting, fresh pulp fermentation with air exclusion, or direct sun-drying, all of which differentially reduce the concentration of toxins, particularly the glycoside linamarin, within cassava (Chen *et al.*, 2021; National Research Council, 1992; Precoppe *et al.*, 2020).

Linamarin is hydrolyzed by β-glucosidase, found in cassava peel or intestinal bacteria, into cyanide precursors, ultimately yielding hydrogen cyanide (HCN) in the gastrointestinal tract (Paul *et al.*, 2020; Siritunga *et al.*, 2003). This mechanism, referred to as the cyanide hypothesis, is implicated in the pathogenesis of cassava-induced neurological diseases such as tropical ataxic neuropathy (TAN) and konzo (Osuntokun,

1981; Otubogun *et al.*, 2019; Tylleskär *et al.*, 1994). These conditions manifest as various neuromotor deficits and polyneuropathies. TAN is characterized by sensory polyneuropathy, ataxia, bilateral optic atrophy and sensorineural deafness, distinguishing it from the characteristic bilateral spastic paraparesis observed in konzo (Adamolekun, 2010; Baguma *et al.*, 2021).

However, the development of animal models for cassava-related neuromotor disease remains challenging, partly due to gaps in the current understanding of konzo and TAN pathophysiology. Firstly, acute cyanide poisoning elicits systemic signs and symptoms in affected patients, many of which are absent in patients with TAN or konzo, who primarily present with acute neurologic deficits that stabilize over time. Secondly, studies examining urinary thiocyanate levels in konzo patients and healthy controls within the same geographic region suggest the presence of cyanide detoxification pathways beyond trans-sulphuration in these populations. This inference stems from the fact that rhodanese detoxification requires the sulfur amino acids cysteine and methionine, which are frequently deficient in a monotonous cassava-based diet (Baguma *et al.*, 2021; Kambale *et al.*, 2017; Tylleskär *et al.*, 1992). Consequently, Tor-Agbidye *et al.*, (1999a) postulated that the activation of non-rhodanese detoxification pathways, independent of sulfur amino acids, represents a plausible adaptive mechanism to chronic cyanide exposure. One such mechanism involves the oxidation of cyanide to cyanate (OCN-), which has been demonstrated to increase exponentially in protein-deficient animal models exposed to cyanide and in individuals exposed to cyanide from cigarette smoke (Delporte *et al.*, 2018; Tor-Agbidye *et al.*, 1999b; Wang *et al.*, 2007).

Interestingly, sodium cyanate was historically utilized in the treatment of sickle cell anemia, owing to its capacity to inhibit erythrocyte sickling through selective binding to the NH_2 terminus of hemoglobin, thereby enhancing oxygen affinity in preclinical models (Manning & Acharya, 1984). However, accumulating evidence of neurologic adverse events, including seizures, hallucinations, and polyneuropathies in patients, along with hindlimb paralysis, spastic quadriplegia and death occurring in various animal models exposed to sodium cyanate, precluded its use as an oral treatment for sickle cell disease (Charache *et al.*, 1975; Harkness, 1976; Haut *et al.*, 1975; Manning & Acharya, 1984). This striking similarity between the neurological sequelae of sodium cyanate toxicity and the clinical manifestations of TAN and konzo suggests a potential contributory role for cyanate in these diseases.

To this end, this study aims to synthesize preclinical and clinical evidence pertaining to cyanate-induced neurotoxicity, thereby identifying determine predominant neurological adverse events following sodium cyanate exposure. Should these events exhibit similarities to the manifestations of TAN or konzo, the information garnered from this systematic review may inform the development of future animal models for foodborne neuromotor diseases.

2 METHODS

2.1 Study selection

In this systematic review, a comprehensive literature search was conducted utilizing four major electronic databases (PubMed NCBI, Scopus, Cochrane Library, and Google Scholar), adhering to the PRISMA guidelines, to collate all available evidence on the neurotoxic or neuromotor sequelae of sodium cyanate exposure. The search encompassed the period from the initial description of konzo in the literature (1936) to 2024 (Howlett, 1994; Liberati, 2009). The search strategy employed the following Boolean query: '((sodium cyanate) OR (NaOCN)) AND ((paralysis) OR (neurotoxicity) OR (toxicity) OR (neurologic) OR (motor deficit))' – which yielded 1,089 results. All study types, including journal articles, unpublished online manuscripts, and conference proceedings, published in both English and non-English languages, irrespective of country of origin, were assessed for eligibility. Abstracts were screened, resulting in the exclusion of 1,053 articles, including 14 duplicates. Subsequently, 22 articles underwent full-text review. Articles lacking full-text access via university subscriptions, thereby precluding adequate appraisal, were also excluded after attempts to request access from the corresponding authors (n=6). Meanwhile, articles with no control group and those discussing solely the non-neurotoxic effects of cyanate were also excluded. A final cohort of 10 full-text articles was selected for quality assessment and review (Figure 1).

2.2 Inclusion and exclusion criteria

Given the paucity of literature investigating the neurotoxic effects of cyanate, with the exception of recent studies elucidating the mechanism of cassava-induced toxicity in konzo, all controlled studies published between 1936 to 2024 were included to ensure sufficient data extraction for analysis. Articles were selected based on their relevance to the neurotoxic effects of sodium cyanate. Only controlled experimental studies involving sodium cyanate were screened, encompassing preclinical (*in vitro* and *in vivo*) and controlled clinical (case-control studies and randomized controlled trials) studies reporting neurotoxic outcomes following sodium cyanate exposure. Exclusion criteria included studies reporting solely non-neurotoxic effects of cyanide, uncontrolled studies such as case reports and case series, review articles, and articles lacking full-text access.

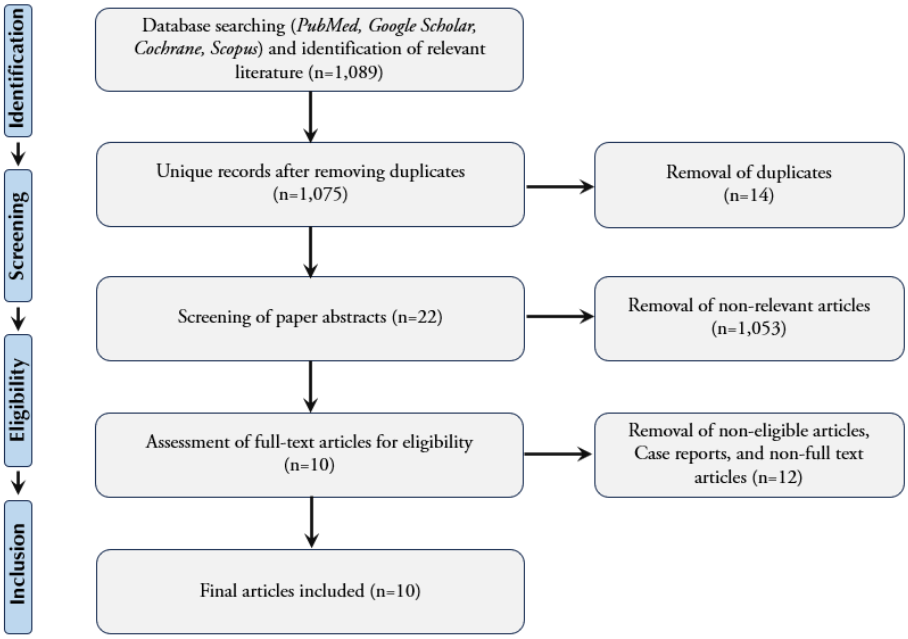

Figure 1. Diagrammatic workflow based on PRISMA guidelines

Additionally, only articles accessible through university subscriptions were included in this study.

2.3 Data extraction

Each full-text article was independently analyzed for eligibility and quality by two independent reviewers. Discrepancies in assessments were resolved through consensus with a third reviewer in case of conflicting assessments, such as those related to the quality and extent of bias of the papers included. In this study, a total of 10 articles were deemed eligible for the systematic review, comprising 9 preclinical studies and 1 controlled clinical study involving human participants. For each study, the following data were extracted: first author, year of publication, experimental model/population, sample size, concentration or dose of sodium cyanate as well as route of administration, and neurotoxic or neurological outcomes.

2.4 Quality assessment tools for selected studies

Following screening and data extraction, each study underwent a qualitative assessment tailored to its respective study design. *In vitro* cell culture and preclinical animal studies were assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool, adopting the methodology previously described by Cai & Li, (2020) for assessing animal experimental models and cell studies. Briefly, the SYRCLE risk of bias tool includes 10 domains that evaluate articles for the presence of five types of biases (selection, performance, detection, attrition, and reporting biases), modeled after the Cochrane risk-of-bias tool (Hooijmans *et al.*, 2014). The sole case-control study included was assessed using the Newcastle-Ottawa Scale for non-randomized studies, a validated instrument comprising eight questions across three principal domains: selection, comparability, and outcome. This scale determines whether participant selection, outcome recording and assessment, and adequacy of follow-up were conducted with minimal risk of bias (Wells *et al.*, 2024). Each of the ten articles included in this study were assessed on these domains individually by the investigators to determine the overall quality of their data prior to collation and analysis of results.

3 RESULTS

3.1 Study characteristics

In this systematic review, we assessed 10 journal articles investigating the toxicity of sodium cyanate. Of these nine (9) were preclinical comprising two *in vitro* neural cell line studies, seven *in vivo* rodent studies, and one non-human primate study. Notably, primates were utilized concurrently with rodents in one of the *in vivo* studies. Only one clinical study, employing a case-control design, explored the role of cyanate in the neurotoxicity of konzo. However, this investigation was indirect, as retrospective ascertainment of cyanate exposure is challenging, and only carbamoylation correlates, indirect markers of cyanate toxicity, were determined (Rwatambuga *et al.*, 2021) (Table 1). Due to the

Table 1. Summary of study characteristics and neurotoxic outcomes

Study	Type	Population	Sample size (n)	Dosing (NaOCN)	Outcomes
Alter *et al.*, 1974	Preclinical	Sprague-Dawley rats	n=12	60 – 85 mg/kg	Carbamoylation of Hgb Lethargy, decreased activity Spasticity of hindlimbs Hindlimb weakness No spinal cord pathologies
Tellez *et al.*, 1979	Preclinical	Pig-tailed macaque	n=11	15, 25, or 35 mg/kg	Demyelination of pyramidal tracts in the spinal cord No brain changes observed
Tor-Agbidye *et al.*, 1999a	Preclinical	CD-1 mice and Sprague-Dawley rats	n=10	100, 200, or 300 m/kg	Hindlimb weakness, arched back, dyspnea, sedation at 200 mg/kg Seizures at 300 mg/kg
Huang *et al.*, 2005	Preclinical	H19-7 cell line	n/a	0.3 mM	Increased opening probability of Ca^{2+}-activated big potassium (BK) channels
Kassa *et al.*, 2011	Preclinical	Heterozygous nude rats	n=5	200 mg/kg	Arched back Hindlimb weakness/paralysis Loss of extension reflex Decreased latency to fall Carbamoylation of serum peptides
Kimani *et al.*, 2013	Preclinical	Heterozygous nude rats	n=7–10	50 mg/kg	Decreased latency to fall Carbamoylation of albumin Carbamoylation of spinal cord proteins
Kimani *et al.*, 2014a	Preclinical	Sprague-Dawley rats	n=7–8	50 mg/kg	Fewer correct arm entries Working memory errors Longer navigation times
Kimani *et al.*, 2014b	Preclinical	Heterozygous nude rats and crab-eating macaques	n=7–10 n=12	50 mg/kg	Decreased latency to fall No observed changes in macaques fed cassava
Choi & Lee, 2017	Preclinical	C6 glioma cell line	n/a	0 – 40 mM	Caspase-8 and caspase-3-mediated apoptosis
Rwatambuga *et al.*, 2021	Case-control	Children with konzo	n=19–21	n/a	Inability to walk pep1 206–219 carbamoylation Lower serum albumin Lower neuropsychological testing performance

paucity of clinical data, significant heterogeneity among the included studies, and the presence of biases identified during the review process, a meta-analysis was not conducted at this time.

3.2 Methodological quality of included studies

The preclinical studies included for quality assessment exhibited sample sizes ranging from 5 to 12 animals, yielding an approximate average sample size of N=9-10 (Table 1). Exceptions to this were observed in the studies by Huang *et al.* (2005) and Choi & Lee (2017), which utilized H19-7 and C6 glioma cell lines, respectively (Table 1). The primary outcome measures for each study included motor deficits and alterations in neuronal function, with secondary outcomes including protein carbamoylation, changes in reflex responses, and variations in cognitive function. All preclinical studies incorporated a control group, thereby facilitating a robust assessment of sodium cyanate neurotoxicity. The majority of preclinical studies exhibited minimal risk of attrition and reporting biases, attributable to appropriate data handling for incomplete outcomes and the avoidance of selective reporting. In addition, all studies were able to establish the baseline characteristics of the sample size (100%). However, unclear risks of selection bias were identified, as sequence generation (22.2%) and allocation concealment (100%) were not explicitly addressed in some or all of the studies. Furthermore, all studies were assessed as having high risks of performance and detection biases (100%), owing to non-blinded outcome assessment, a limitation inherent in several preclinical studies (Figure 2). Detailed information on the quality assessment of each preclinical study, as evaluated using the SYRCLE risk-of-bias tool, is available in the *Supplementary Data* files. The single case-control study included in this systematic review was assessed by the reviewers as possessing high methodological quality. While concerns were noted regarding the representativeness of the cases, due to non-random selection

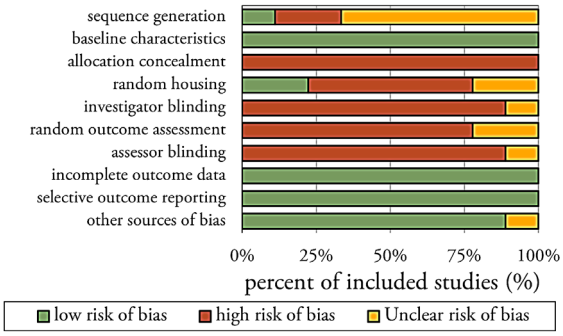

Figure 2. Summary of methodological quality using the SYRCLE risk of bias tool

of konzo cases, predominantly of the severe type, and the inherent limitation of a case-control study design wherein the outcome of interest (neuromotor disease) is present at study inception, the execution of other parameters, such as the selection of unaffected controls, ascertainment of exposure, comparability of cases and controls, outcome assessment, and the length and adequacy of follow-up, was deemed appropriate, based on supplementary information extracted from the cohort study conducted concurrently with this project (Boivin *et al.*, 2017) (Figure 3).

Rwatambuga *et al.*, 2021

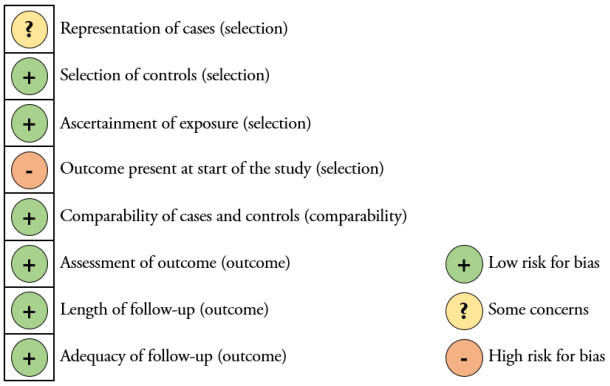

Figure 3. Methodological quality of the case-control study using the Newcastle-Ottawa scale

3.3 Neurotoxic outcomes in preclinical studies

The neurotoxic effects of sodium cyanate in animal models and cell lines are summarized in Table 2. The studies employed rodents of varying strains (CD-1, Sprague-Dawley, and heterozygous nude rats) as well as primates (pig-tailed and crab-eating macaques), to assess motor and cognitive deficits induced by sodium cyanate. Consistent with all preclinical studies, outcomes were compared with a control group, utilizing NaOCN doses ranging from 15 to 300 mg/kg. For the two studies employing neuronal cell lines, the NaOCN concentrations ranged from 0 to 40 mM (Table 1). As this study aims to elucidate the potential neurotoxic and neuromotor effects of sodium cyanate, the neurological adverse events observed in these animal studies were aggregated and presented as percentages, as detailed in Table 2. Briefly, rodents exposed to high-dose NaOCN exhibited pronounced deficits in neural and motor functions, characterized by hindlimb spastic weakness or paralysis in 42.86% of studies, ataxia or dysmetria in 14.26% and cognitive impairment in 14.26%. Three of the seven animal studies reported peptide carbamoylation (42.86%), while one study (14.26%) reported demyelination of the spinal cord. In the two cell line studies, exposure to 5 – 40 mM NaOCN induced apoptosis of C6 glioma cells, with an observed increase in the opening of BK Ca^{2+} channels at 0.3 mM in H19-7 cells, suggesting that NaOCN is directly neurotoxic and may attenuate neuronal excitability within the central nervous system (CNS) (Alter *et al.*, 1974; Kimani *et al.*, 2014b). It is imperative to acknowledge that significant heterogeneity existed among the animal species and strains utilized, as well as the administered dosages of sodium cyanate, thereby precluding the feasibility of a meta-analysis.

3.4 Neurological outcomes in clinical studies

The single case-control study included within this systematic review examined the relationship between cassava-induced neurotoxicity (konzo) and genetic polymorphisms or protein carbamoylation patterns in children with a mean age of 9.2

Table 2. Summary of adverse events recorded in the included animal studies

Adverse events	Percent of animal studies (%)
Hindlimb weakness or paralysis	42.86
Decreased latency to fall	42.86
Carbamoylation of peptides	42.86
Arched back	28.57
Working memory errors	14.26
Ataxia/Dysmetria	14.26
Sedation	14.26
seizures	14.26
Brain glutathione depletion	14.26
Demyelination of spinal cord	14.26

years in the Democratic Republic of Congo (Rwatambuga *et al.*, 2021). Employing genomic exon sequencing and liquid chromatography with tandem mass spectrometry (LC-MS/MS), the researchers identified potentially deleterious genetic variants in enzymes involved in cyanide detoxification, specifically thiosulfate sulfurtransferase and mercaptopyruvate sulfurtransferase. Furthermore, they reported a statistically significant association between the presence of carbamoylated peptides 206–219 (pep1) and konzo (0.03, 95% CI 0.2–0.5, p = 0.01). Similarly, the same carbamoylated peptides exhibited a negative correlation with motor proficiency, as assessed by the Buininks/Oseretsky Test, which evaluates fine and gross motor function, stability, and coordination in children and young adults (Rwatambuga *et al.*, 2021). Given that the majority of case patients (81%) presented with the severe form of the disease, the observed strength of association may be accentuated by disease severity. Consequently, caution is warranted during interpretation. Nonetheless, these findings suggest that the presence of circulating cyanate, which results in peptide carbamoylation, may serve as a marker of disease status. However, the determination of whether it represents a causative factor or a consequence of konzo necessitates longitudinal investigations.

4 Discussion

Cyanate is recognized to induce cellular damage and stress through a variety of mechanisms, the most prominent of which is the carbamoylation of amino acid residues within proteins, leading to alterations in their structure and function. Concurrently, another mechanism for cyanate-induced stress is lipid peroxidation, which can compromise cellular and tissue membrane integrity, culminating in senescence and apoptosis (Hu *et al.*, 2019). In a seminal investigation by Tor-Agbidye *et al.*, (1999a), administration of sodium cyanate via intracerebral injection in rats resulted in glutathione depletion within critical brain regions, attributed to secondary inhibition of glutathione reductase (GRx), the enzyme responsible for recycling glutathione disulfide (GS-SG) to reduced glutathione. In a related study, Delporte *et al.*, (2018), demonstrated that cyanide undergoes a two-step oxidative conversion to cyanate, mediated by myeloperoxidase or its reactive oxygen species (ROS) by-products, resulting in the carbamoylation of taurine and lysine residues as well as low-density lipoproteins. Consequently, it is plausible to posit that cyanate, through a synergistic combination of protein carbamoylation, lipid peroxidation, and depletion of brain glutathione, may significantly contribute to the pathogenesis of konzo, for which cyanide is currently considered the primary etiological agent.

To date, no animal models have successfully replicated the non-progressive, irreversible spastic paraparesis of the lower limbs observed in konzo. However, the finding of hindlimb paralysis following high-dose sodium cyanate administration is a serendipitous observation, given its striking similarity to the bilateral lower extremity spastic paralysis of konzo. Indeed, initial reports of hindlimb paralysis in rodents were incidental, arising from studies primarily investigating the hepatotoxic and hematologic effects of sodium cyanate as a potential treatment for sickle cell anemia (Alter *et al.*, 1974; Haut *et al.*, 1975). Although this systematic review identified hindlimb weakness or paralysis in 42.86% of animal studies, this proportion is likely underestimated due to the heterogeneous primary outcomes of the included studies. For instance, not all animal studies included hindlimb paralysis or weakness in their primary outcomes and instead focused on either cognitive function (Kimani *et al.*, 2014a), carbamoylation correlates with plasma/serum proteins (Kimani *et al.*, 2013), or histopathological effects of sodium cyanate exposure (Tellez *et al.*, 1979). Conversely, not all studies included cognitive function assessment in their animal models, focusing instead on the evaluation of motor function exclusively. Consequently, the reported percentages of certain adverse events may underestimate the true prevalence had both cognitive and motor functions been assessed comprehensively. In the singular case-control study included herein, patients with severe konzo exhibited a statistically significant association between disease status and plasma peptides carbamoylation, indicating substantial cyanate exposure in these individuals (Rwatambuga *et al.*, 2021). Collectively, these findings implicate sodium cyanate as a potential neurotoxin in konzo. The association with tropical ataxic neuropathy (TAN), however, remains less clear. Unlike konzo, TAN is characterized by sensory polyneuropathy, encompassing ocular and auditory involvement, leading to optic atrophy, sensorineural deafness and ataxia, and is predominantly observed among populations in Nigeria and Tanzania (Oluwole *et al.*, 2000; Adamolekun, 2010). Prior investigations have established a strong correlation with cassava consumption; nevertheless, the underlying mechanisms also implicate vitamin B_1 (thiamine) deficiency in addition to cyanide exposure from linamarin in cassava, which may account for the distinct clinical manifestations and spinal involvement observed in this disease (Monekosso *et al.*, 1964; Adamolekun, 2010). Given that cyanate was demonstrated to affect the spinal cord in various animal models included in this review (Table 1), a potential role for cyanate in the pathogenesis of TAN exists, particularly through the carbamoylation of spinal cord proteins, which may ultimately lead to degeneration, polyneuropathy and ataxia. However, the manifestation of spastic paraparesis of bilateral lower limbs, a hallmark of konzo, is absent in TAN, suggesting the involvement of distinct mechanism.

Nonetheless, the precise mechanism facilitating the conversion of cyanide to cyanate remains incompletely understood, beyond its established occurrence *in vivo*. Under specific conditions, cyanide may react with hydrogen peroxide (H_2O_2) and other downstream ROS, such as hydroxyl or perhydroxyl radicals to undergo direct oxidation to cyanate (Tian *et al.*, 2016). A common denominator among these reactions is the presence of oxidative stress, which we hypothesize to be a critical factor in the pathogenesis of neuromotor diseases arising from linamarin ingestion in cassava. Clinically, this suggests that if cyanate is the principal pathogenic driver of disease, lipid- and protein-rich regions of the CNS would be susceptible to lipid peroxidation and protein carbamoylation, resulting in neuronal damage to myelin-rich motor neurons of the CNS and manifesting as spasticity. Based on the cell studies included in this review, sodium cyanate at low doses may activate Ca^{2+}-activated BK channels resulting in decreased excitability of neurons, as well as the activation of caspases at higher doses potentially inducing neuronal apoptosis (Huang *et al.*, 2005; Choi & Lee, 2017). These mechanisms may explain why cyanate toxicity manifests mainly as neuromotor deficits, due in part to its neurotoxic potential. This may account for the irreversible upper motor neuron disease observed in konzo, likely resulting from lesions in the corticospinal tract at the decussation of pyramids, and clinically presenting as symmetric paraparesis and hyperreflexia of the lower limbs. In TAN, this may result in neurodegeneration of the posterior horn of the spinal cord or of the peripheral nerves, resulting in characteristic ataxia and polyneuropathy.

Nevertheless, the interpretation of results in this systematic review is subject to certain limitations. For instance, the majority of preclinical studies exhibited a high-risk of bias due to non-blinding and non-randomization. Secondly, while sodium cyanate induces hindlimb weakness or paralysis, severe clinical illness and mortality were also observed at high doses, which are not typically observed in konzo. Future research directions should encompass the investigation of antioxidants, including glutathione, and the activity of enzymes involved in free radical reduction, such as glutathione peroxidase, superoxide dismutase, in both children at risk for and those afflicted with konzo or TAN. Furthermore, determining plasma cyanate levels in relation to daily cassava consumption will provide valuable insight into the likelihood of cyanate formation from linamarin-derived cyanide.

5 Conclusion

Cyanate is a recognized neurotoxin, documented to elicit adverse neurological effects in patients undergoing treatment for sickle cell anemia. A striking observation of similarity between the motor deficits induced by sodium cyanate and the clinical characteristics of konzo has implicated cyanate as a potential contributory factor in this disease. This systematic review demonstrates that the majority of animal studies reported hindlimb weakness and paralysis following exposure to 60–200 mg/kg NaOCN, accompanied by significant carbamoylation of serum peptides. Based on the current literature, it is plausible that cyanide interacts with free radicals in the circulation, in addition to being catalyzed by myeloperoxidase, to generate cyanate. Cyanate is known to promote protein carbamoylation, lipid peroxidation, and the depletion of brain antioxidants, such as glutathione, all of which may precipitate the clinical neuromotor deficits observed in konzo. Similarly, reduction in neuronal excitability and induction of apoptosis of neurons in the spinal cord or peripheral nerves may lead to polyneuropathy and ataxia seen in TAN. Further investigations are required to definitively establish the role of cyanate in foodborne neuromotor diseases.

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