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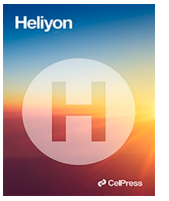

Research article

Acute rotenone poisoning: A scoping review

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ABSTRACT

Context: Rotenone is a toxic chemical found in various plants, including some used as food. Rotenone poisoning can be fatal and there is no antidote. Mechanistically, rotenone inhibits mitochondrial complex I, leading to reduced ATP production, compensatory glycolytic upregulation and secondary lactate production, and oxidative stress. Our literature review examined acute rotenone poisoning in humans, including exposure scenarios, clinical presentations, and treatments.

Methods: We searched five databases for relevant literature from database inception through the search date: July 12, 2022, pairing controlled vocabulary and keywords for "rotenone" with terms relating to human exposures and outcomes, such as "ingestion," "exposure," and "poisoning." We included all peer-reviewed reports found using the search terms where the full English text was available. Data abstracted included the number, age, weight, and sex of the exposed person(s), country where exposure happened, exposure scenario, ingestion context, estimated dose, clinical features, whether hospitalization occurred, treatments, and outcomes.

Results: After removing non-qualifying sources from 2,631 publications, we identified 11 case reports describing 18 victims, 15 of whom were hospitalized and five died. Most cases occurred in private quarters where victims unknowingly consumed rotenone-containing plants. Vomiting and metabolic acidosis occurred most commonly. Some patients exhibited impaired cardiopulmonary function. Supportive treatment addressed symptoms and included gastric lavage and/or activated charcoal to remove rotenone from the stomach, vasopressors for hypotension, mechanical ventilation for respiratory insufficiency, and sodium bicarbonate for acidosis. Some patients received N-acetylcysteine to counter oxidative stress.

Conclusions: Rotenone poisoning, though rare, can be fatal. Exposure prevention is impractical since rotenone is found in some plants used as food or pesticides. Cases may be under-diagnosed because symptoms are non-specific and under-reported in English-language journals since most cases occurred in non-English speaking countries. Treatments are supportive. Exploring antioxidant therapy in animal models of rotenone poisoning may be indicated considering rotenone's mechanism of toxicity.

1. Introduction

Rotenone is a colorless, odorless toxic isoflavone that occurs naturally in several plant species including the roots and leaves of the tuba plant (*Derris elliptica*), the stems and leaves of "Karanjvel" (*Derris trifoliata*), the fruits and seeds of *Millettia pachycarpa*, and the

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seeds of yam bean/jícama (*Pachyrhizus erosus*). Whereas *D. elliptica*, *D. trifoliata*, and *M. pachycarpa* belong to the genus of leguminous plants, *P. erosus* belongs to a genus of flowering plants.

In Asia and South America where some of these plants are commonly used as food (for succinctness, we referred to vegetables as "plants" in this manuscript), familiarity with the plants allows people to separate poisonous from edible plant or plant parts. For instance, yam bean roots are safe for human consumption but its fruits and seeds are poisonous [1–4]; *M. pachycarpa* is wholly poisonous and accidental poisoning has occurred after eating its fruits, which can be misidentified as other edible fruits, such as tamarind [5]. On the other hand, intentional ingestion of mixtures made from plants known to contain rotenone, such as "nivrée" vines and *D. trifoliata* leaves, to facilitate suicide has been reported [6,7]. Thus, food-borne poisoning can occur intentionally or mistakenly by ingesting rotenone-containing plant or plant parts.

Plants containing rotenone are also used as a non-selective piscicide to harvest fish for human consumption, and in the United States, rotenone is used in fishery management to remove invasive species. It is thought that rotenone's lipophilicity facilitates its absorption across fish gills where it then enters the animal's bloodstream. Rotenone is degraded by high heat. Therefore, cooking rotenone-containing plants or fish prior to consumption reduces the risk of human poisoning. Rotenone is also present in several commercially available pesticides, including Galicide, Bio Liquid Derris Plus™, and ONSAMI™. Galicide is an insecticide approved for external use on animals; a 100-mL bottle contains 6.1 g of rotenone [8]. Bio Liquid Derris Plus™ was used to eliminate various leaf pests until it was banned in the United Kingdom in 2009. Thus, humans can be exposed to rotenone by a variety of means.

Rotenone is commercially available for research purposes. Poisoning can occur via inhalation or transdermal absorption of the chemical if it is mishandled [9]. However, accidental or intentional ingestion of rotenone-containing plants or pesticides is the most common mode of exposure (Fig. 1A). Mechanistically, rotenone toxicity occurs primarily through inhibition of mitochondrial complex I (NADH:ubiquinone oxidoreductase), thereby reducing oxidative phosphorylation and ATP production [10] (Fig. 1B). Decreased mitochondrial ATP production increases cellular glycolysis, leading to increased lactate production and subsequent metabolic acidosis. In addition, mitochondria are a major source of reactive oxygen species (ROS) [11]: inhibiting mitochondrial respiration increases electron leakage, leading to increased reduction of molecular oxygen to superoxide (O_2^-). Superoxide dismutase may further catalyze O_2^- to hydrogen peroxide (H_2O_2). Oxidative stress and apoptosis are key outcomes of the inhibition of complex I [12].

The acute toxic effects of rotenone include nausea, vomiting, diarrhea, impaired cardiopulmonary function, and loss of locomotor function [13]. Impaired cardiopulmonary function can lead to hypoxemia, hypercapnia, and profound hypotension, and ultimately to death [14]. The lethal oral dose of rotenone is not known. Gupta approximated the oral LD_{50} value for rats to be 60–135 mg/kg [14]. In humans, Gleason et al. estimated it as 300–500 mg/kg, i.e., between 21 and 35 g for a 70-kg person [15]. In contrast, Lehman estimated humans can consume up to 200 g of rotenone, or 2,857 mg/kg [16]. A specific rotenone antidote does not exist and treatment for rotenone poisoning is purely supportive.

The incidence of rotenone poisoning is unknown, but it is generally considered an infrequent event. Thus, most physicians will not have encountered a patient. Moreover, a rapid method to detect rotenone poisoning is not available. Current methods to measure rotenone in biological samples require gel filtration followed by high performance liquid chromatography (HPLC) [8,17]. Although HLPC is specific and sensitive, it requires cumbersome equipment and is time-consuming. Thus, it is not suitable for emergency situations. This lack of a rapid detection method may cause misdiagnosis, such as a presumptive diagnosis of cyanide poisoning, which presents with similar signs and symptoms due to cyanide also inhibiting mitochondrial electron transport. The infrequency of rotenone

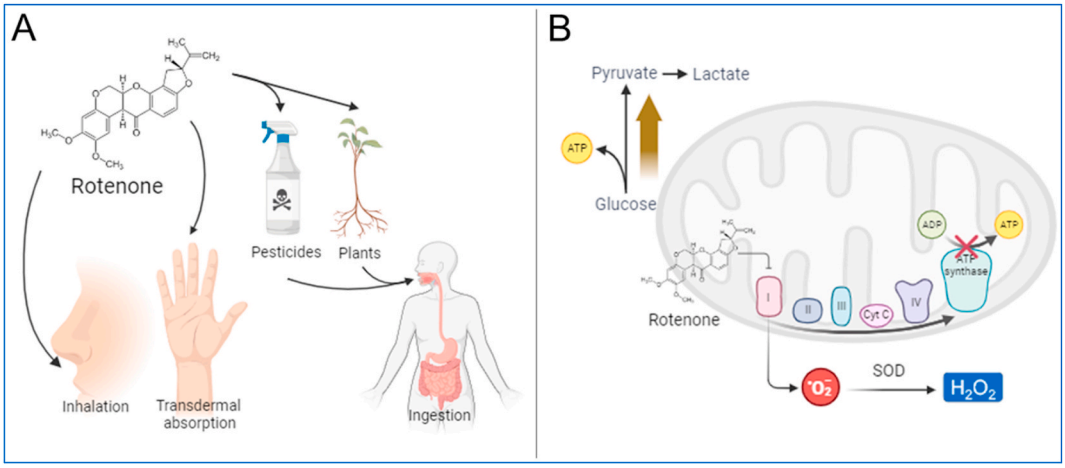

Fig. 1. Rotenone's routes of exposure and mechanisms of toxicity. A. Rotenone poisoning can occur via inhalation and transdermal absorption of the chemical, but ingestion of rotenone-containing plants or pesticides is the most common mode of exposure. **B.** Rotenone inhibits mitochondrial complex I. This inhibition leads to decreased mitochondrial ATP production, which in turn increases cellular glycolysis, resulting in elevated lactate production and subsequent metabolic acidosis. Inhibiting mitochondrial respiration also increases electron leakage, causing augmented reduction of molecular oxygen to superoxide (O_2^-), which may be catalyzed further to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). Both O_2^- and H_2O_2 are reactive oxygen species (ROS).

poisoning coupled with delayed laboratory diagnosis could be especially problematic in a mass casualty event, such as where a group of patients may become poisoned after eating or drinking from communal food and beverage sources [2,18].

To address the gaps in knowledge, we sought to learn more about the circumstances underlying acute poisoning events and treatment options, and how they would relate to survival outcomes. We, therefore, methodically reviewed the literature focusing on exposure scenarios, clinical presentations, and treatment modalities.

2. Materials and methods

2.1. Search strategy

The study was conducted following the Cochrane Handbook for Systematic Reviews and is reported according to Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. On July 12, 2022, we searched PubMed (pubmed.gov), Embase (embase.com), CINAHL (Ebscohost.com), and Web of Science Core Collection (webofscience.com) with no date or language limits. Controlled vocabulary terms (where possible) were paired with keyword terms for rotenone, e.g., "yam bean," and combined with the controlled vocabulary and keyword terms for ingestion or poisoning along with a focus on humans and excluding non-human studies. Full search strategies for all databases are included in Supplemental Table 1. Supplemental Google searches were conducted using the same search strategy. Results were imported into EndNote and de-duplicated following the Wichor-Bramer process and then exported to Excel [20].

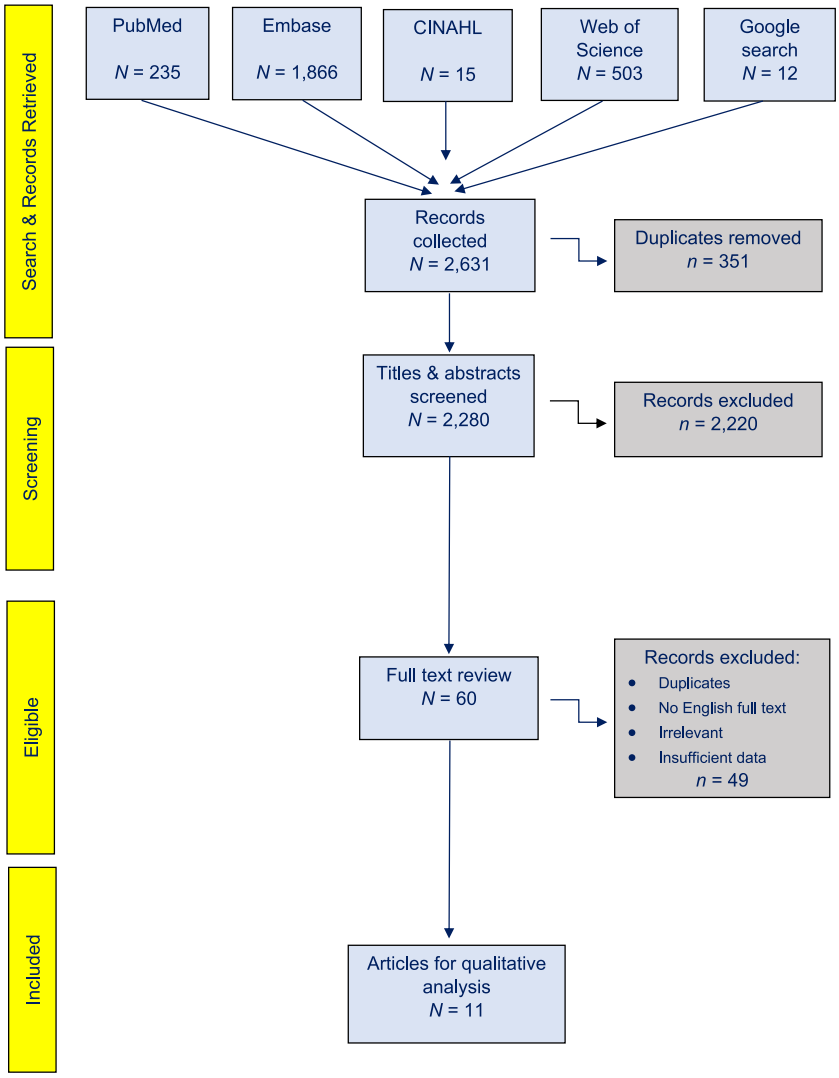

Fig. 2. Peer-reviewed articles concerning human cases of acute rotenone exposure.

Table 1
Organized by publication year.

Article	Number of cases	Country where exposure happened	Sex	Age	Weight (kg)	Exposure scenario	Accidental or suicidal ingestion (mode)	Estimated ingestion (gram)	Clinical features	Admitted? (Time to admission since ingestion)	Treatments	Survival
de Wilde et al., 1986 [8]	1	Belgium	Female	3.5	15	Home	Accidental (pesticide)	0.60	Vomiting Arrhythmia Asystole Respiratory depression Metabolic acidosis	Yes (3.5 h)	Intubation Ventilation Gastric lavage	No
Narongchai et al., 2005 [3]	1	Thailand	Male	59	N/A	N/A	Accidental (food)	0.20	Asystole Fixed pupils Coma Respiratory depression	Yes (2 h)	N/A	No
Wood et al., 2005 [23]	1	The United Kingdom	Female	47	64	Home	Suicidal (pesticide)	1.60	Vomiting Asystole Hypotension Hepatoxicity Metabolic acidosis	Yes (N/A)	Hemodialysis Sodium bicarbonate Antioxidants N-acetylcysteine Multi-vitamins Zinc sulfate Intravenous iron	No
Hung et al., 2007 [2], [a]	5	Taiwan	Female	54 46 41 35 35	N/A	N/A	Accidental (all; food)	0.12	Vomiting (all five) Abdominal cramping Diarrhea Coma Hypertension Metabolic acidosis	Yes (all patients admitted; 3 h)	Cyanide kit Sodium nitrite Sodium thiosulfate Gastric lavage with activated charcoal Right heart catheterization Intravenous fluid and pressor therapy	Yes (all patients)
Chesneau et al., 2009 [6]	1	French Guiana	Female	86	55	Home	Suicidal (plant extract)	N/A	Vomiting Coma Hypotonia and hyporeflexia Respiratory depression Hypertension	Yes (2 h)	Supplemental oxygen Metoclopramide	Yes
Faber et al., 2014 [24]	1	India	Male	49	N/A	Home	Suicidal (pesticide)	3.12	Vomiting Coma Respiratory depression Hypotension Hypokalemia Bradycardia Metabolic acidosis	Yes (1 h)	Activated charcoal Intravenous hydration Ephedrine Dobutamine Norepinephrine	No
Fu and Wang. 2012 [1]	1	Taiwan	Female	54	N/A	Home	Accidental (food)	0.08	Vomiting Abdominal cramping Diarrhea Hypotension	Yes (4 h)	Atropine Intubation Ventilation	Yes

(*continued on next page*)

Table 1 (*continued*)

Article	Number of cases	Country where exposure happened	Sex	Age	Weight (kg)	Exposure scenario	Accidental or suicidal ingestion (mode)	Estimated ingestion (gram)	Clinical features	Admitted? (Time to admission since ingestion)	Treatments	Survival
									Bradycardia Likely respiratory depression Metabolic acidosis			
Rhee et al., 2016 [17]	1	South Korea	Male	33	70	Home	Suicidal (pesticide)	3.00	N/A	No (Found dead)	N/A	No
Torrents et al., 2017 [7]	1	French Polynesia	Male	63	N/A	Home	Suicidal (plant extract)	N/A	Hepatoxicity Likely respiratory depression	Yes (14 h)	Intubation Ventilation Benzodiazepine N-acetylcysteine	Yes
Yu et al., 2020 [4], [b]	2	Taiwan	Female Male	64 N/A	72 N/A	Home	Accident (all; food)	0.16 0.06	Vomiting Nausea Diarrhea Hypertension Metabolic acidosis	Yes (3 h) N/A	Supportive care N-acetylcysteine N/A	Yes (all)
He et al., 2021 [18], [c]	3	China	Male	N/A N/A 32	N/A	Work	Accident (all; food)	N/A	Vomiting Dizziness Diarrhea Two workers had transient nausea and dizziness Limb weakness Dizziness Coma Central nervous system depression Respiratory depression Metabolic acidosis	N/A Yes (1 h)	N/A Intubation Ventilation Gastric lavage Hemoperfusion Sodium bicarbonate	Yes (all)

"N/A" means not available.

[a] Unless specified, publication only reviewed the 54-year-old female patient in depth.

[b] Unless specified, publication only reviewed the 72-year-old female patient in depth.

[c] Unless specified, publication only reviewed the 32-year-old male patient in depth.

2.2. Selection and data extraction

Inclusion criteria were any peer-reviewed articles focusing on acute human exposure to rotenone and presenting information regarding the context of poisoning, e.g., accidental or suicidal, symptoms, treatments, and outcomes. Exclusion criteria were articles on chronic exposure to rotenone, editorials or commentaries, articles with insufficient data or irrelevant accounts, e.g., those lacking discussion of human rotenone poisoning, animal or cell line only studies, or articles without an English language translation of the full text, i.e., only the article's title and abstract were available in English. The level of evidence for each article was determined using the hierarchy of evidence [5]. If a case was reported in both a peer-reviewed paper and a conference abstract, we included data only from the peer-reviewed paper.

2.3. Estimating rotenone exposure dose

The ingested rotenone amount was either reported in the publications, or was estimated by us, assuming that each 1-g yam bean seed contains 2 mg/g of rotenone before processing [21]. Since patient weight was not always reported, we standardized the estimated mass to mass concentration (mg/kg) of rotenone ingested by dividing the reported (or estimated) amount ingested by the 70-kg standard person reference.

2.4. Statistical analysis

All of the case reports that were reviewed met level VII evidence—opinions of authorities and/or reports of expert committees [5]. We could not perform quantitative bias analysis on these reports, because no quantitative data were available that would allow us to correlate gender, age, weight, ingestion amount, or treatment modalities with outcomes.

2.5. Graphic art

Fig. 1 was created using BioRender.com [22], a free scientific image and illustration software.

3. Results

We collected 2,631 publications and removed 351 duplications. Of the remaining 2,280 papers, we excluded 2,220 papers after screening the titles and abstracts and finding that the same case was published in multiple journals, or that the report consisted of cell- or animal-based studies or had no reference to human exposure. We then performed a full-text review of the remaining 60 eligible publications, excluding an additional 49 articles due to duplication where two different authors (or groups) published the same case, lack of the full text in English, non-relevance to acute rotenone poisoning in humans, and/or insufficient data. Altogether, 11 publications met our inclusion criteria and were reviewed (Fig. 2).

All of the exposures were via oral ingestion, either accidental or suicidal; when available, we noted the form of rotenone ingested, i.e., pesticide, plant extract, or food. Some publications described poisoning events involving several people, but only presented detailed data for one patient [2,4,18]. In these cases, we included only patients for whom relatively complete information was available, unless otherwise indicated in Table 1. We have included in Table 1 whether a patient was hospitalized, and how much time was estimated to have elapsed between initial exposure and admission.

Of 18 acute poisonings, two occurred in European countries [8,23], 15 happened in Asian and Pacific Island nations [1–4,7,17,18,24], and one was in South America [6]. Only one case came from a country where English is the main language [23]. Eight (44%) cases were males and ten (56%) were females. The median age was 47 years old with a range from 3.5 to 86 years old. In 13 cases (72%), exposure was accidental through food while in five cases (28%) rotenone was ingested with suicidal intentions. The amount of rotenone ingested varied from 0.06 g to 3.12 g. Nine victims (50%) were exposed to rotenone at home [1,4,6–8,17,23,24], and three (17%) were at work [18], with the location of exposure unclear for the remaining six (33%) victims, but most likely in private quarters [2,3].

The most common symptom was vomiting, observed in eleven patients (61%) [1,2,4,6,8,23,24]. Five patients presented with respiratory depression [3,6,8,18,24], and two likely had respiratory depression based on having received mechanical ventilation [1,7]. Among these seven patients (39%), four vomited before presenting with respiratory depression [1,6,8,24]. Three people (17%) presented with hypertension [2,4,6] and three (17%) with hypotension [1,23,24]. Three patients (17%) who developed cardiac asystole following hospital admission all died [3,8,23], and seven patients (39%) developed metabolic acidosis [1,2,4,8,18,23,24].

Five (28%) of the 18 patients died [3,8,17,23,24]. A 3.5-year-old child accidently consumed the pesticide Galicide; she appeared to have died in the Emergency Department from respiratory arrest [8]. Two male patients also died in the Emergency Department [3,24]. One of them received supportive treatment, but likely died from refractory hypotension and circulatory collapse [24]. Treatment modalities and cause of death were not specifically reported for the other patient, but he seems to have died from cardiac arrest [3]. A 47-year-old patient likely died in the Intensive Care Unit from cardiac arrest [23]. One patient was found dead at home likely by suicidal ingestion of the organic pesticide ONSAMI™ [17]. These five patients had ingested between 0.2 and 3.12 g of rotenone compared to between 0.08 and 0.16 g of rotenone for those who accidently ingested rotenone and survived [1,2,4]. Using a 70-kg standard reference, we estimate that those who died ingested 2.85–44.6 mg/kg of rotenone, whereas survivors ingested 1.14–2.28 mg/kg.

Fourteen patients (78%) were transported to the Emergency Department for treatment, with a median time of 3 h after ingestion prior to initiation of treatment. Care was purely supportive in response to symptoms with certain additional treatments worthy of highlighting. Gastric lavage was used in three patients (17%) [2,8,18], and two patients (11%) received activated charcoal, one with and one without gastric lavage [2,24]. Of the seven patients who (likely) had respiratory depression, mechanical ventilation was required in four patients [1,7,8,18], three of whom survived. Sodium bicarbonate was administered to one patient for metabolic acidosis [23]. N-acetylcysteine was given to three patients (17%) to counteract oxidative stress [4,7,23], two of whom survived. One patient received sodium nitrite, a treatment normally reserved for cyanide poisoning because her symptoms mirrored cyanide poisoning; but this was before toxicology reports could confirm cyanide poisoning [2]. Her blood pressure upon Emergency Department admission was 133/84 mm Hg. Following nitrite exposure, she exhibited hypotension (63/41 mm Hg) and methemoglobinemia (8.8%).

4. Discussion

Rotenone is a naturally occurring isoflavone found in several plant species and is used in pesticides and piscicides. Acute rotenone exposure has varying effects, from mild illness to death. Patients were most frequently exposed to rotenone at home, consistent with rotenone's presence in commercial pesticides and in several plant species used as food or that could be mistaken as food.

Accidental ingestion cases highlight the ease of food-borne exposure. Except for one patient who had coronary artery disease [3], accidental ingestion did not result in death. This is likely due to four reasons. First, high heat destroys rotenone, and thus cooking rotenone-containing foods will mitigate toxicity. Second, rotenone is insoluble in aqueous solutions, which may limit its intestinal absorption. Third, vomiting was a common symptom [1,2,4,6,8,23,24], which could have expelled at least some of the poison from the stomach. And fourth, many victims sought medical attention, thereby mitigating rotenone's toxic effects. Travelers to countries where rotenone-containing plants are common should exercise caution when trying unfamiliar food and seek immediate medical attention if a food-borne illness is suspected. Because rotenone intoxication can have non-specific signs and symptoms, such as nausea, abdominal pain, and vomiting, it is possible that rotenone poisoning cases are under-reported.

Suicidal victims ingested rotenone either through drinking extracts prepared from rotenone-containing plants, or commercial pesticides containing rotenone, e.g., Galicide, Bio Liquid Derris Plus™, and ONSAMI™ [8,17,23]. The highest survivable dose we reviewed was estimated to be 2.28 mg/kg. This is significantly less than what was previously estimated by Gleeson et al. and Lehman (300–500 mg/kg and 2857 mg/kg, respectively), highlighting the need to be aware of rotenone's potential danger. Other than providing mental health care for victims contemplating suicide, preventing access to rotenone is not feasible due to its widespread use.

Mechanistically, rotenone inhibits complex I/NADH:ubiquinone oxidoreductasein the electron transport chain, thereby depleting the intracellular ATP supply. Compensatory upregulation of glycolysis generates lactate, which likely contributes to the metabolic acidosis observed in seven patients [1,2,4,8,18,23,24]. However, it is unclear why only one of these seven patients received sodium bicarbonate [23].

Several patients required mechanical ventilation [1,7,8,18]. This could be because *in silico* predictions indicate rotenone can bind surfactants, and thus, rotenone could potentially increase alveolar surface tension and the work of breathing [25]. It also seems plausible that decreased mitochondrial ATP production in muscles could compromise respiratory muscle function.

The effect of rotenone on blood pressure was varied; some patients presented with hypertension [2,4,6], while others had hypotension [1,23,24]. It is not known how rotenone regulates blood pressure. Celotto et al. reported that acute metabolic acidosis increased plasma nitric oxide levels, resulting in hypotension in rabbits [26]. Two patients were treated with activated charcoal; one of whom died [2,24]. Although the World Health Organization suggests the use of activated charcoal as a treatment for acute rotenone poisoning [27], whether rotenone binds to activated charcoal is not known. Gastric lavage was not performed until at least 1 h post exposure [2,8,18], which is later than the recommended time of 30–60 min post ingestion.

Due to mechanistic and symptomatic similarities to cyanide intoxication, one patient was given the cyanide antidotes sodium nitrite and sodium thiosulfate [2]. However, it seems unlikely that nitrite or thiosulfate would have a beneficial effect. Furthermore, nitrite might exacerbate the hypotension found in some patients, by virtue of its reduction to nitric oxide, a potent vasodilator; nitrite can also oxidize hemoglobin, leading to methemoglobinemia. Both hypotension and methemoglobinemia were observed in this patient.

Inhibiting mitochondrial electron transport leads to increased production of reactive oxygen species. This could be particularly harmful to the brain, which has a high oxygen requirement and a high concentration of polyunsaturated fatty acids that are susceptible to lipid peroxidation [4,28]. Neuronal injury could contribute to autonomic dysfunction, and thus, to the reported cardiopulmonary abnormalities. N-acetylcysteine was administered as an antioxidant in three cases [4,7,23]. However, N-acetylcysteine is only weakly antioxidative; it reacts slowly with superoxide and hydrogen peroxide, the two reactive oxygen species generated by mitochondria that are increased by rotenone exposure [29–31].

4.1. Limitations

While the reports we included were peer-reviewed, they were case studies, which are prone to publication bias. Publication bias is exacerbated because most cases occurred in countries where English is not the main language. They, therefore, may not have been discovered by our search strategy. An article would also have been missed if it was published but not included in the databases we used. Both issues, in addition to the small sample size, limit generalizability. Moreover, an inherent limitation of case reports is whether someone chooses to publish a case and whether the diagnosis was made correctly. In several cases, the victims' families brought in the

bottles of pesticide or the food that the victim had ingested. In the case of pesticides (e.g., Galicide or Bio Liquid Derris Plus™), rotenone is listed as an ingredient; in the case of food, familiarity of rotenone toxicity in certain plants led clinicians to suspect rotenone toxicity. The actual incidence of rotenone poisoning could be greater than that reported.

5. Conclusions

To our knowledge, this study is the first to comprehensively summarize acute rotenone poisoning in humans and to describe associated treatments and consequences. We found that rotenone poisoning is rare but can be fatal. As with most food-borne poisoning events, cases may be underreported. This issue is exacerbated by most poisoning events occurring in countries where English is not the primary scientific language, thus eliminating inclusion in our study. Until a specific rotenone antidote is identified, treatment will remain supportive, including intubation and mechanical ventilation.

5.1. Future research direction

Since rotenone can increase oxidative stress in cells (Fig. 1B), it seems possible that an agent which neutralizes reactive oxygen species could be useful in treating rotenone poisoning [4,7,32–34]. Testing of such agents in animal models would appear indicated.

Data availability statement

All data reviewed for the manuscript are provided in the main text and supplemental material and are thus readily available.

CRediT authorship contribution statement

John Tat: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Karen Heskett:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Gerry R. Boss:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28334.

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