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Fatal Outbreaks of *Burkholderia gladioli* Pathovar *cocovenenans* Bongkrekic Acid Food Poisoning: A Mitochondrial Toxin and Potential Biological Weapon

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Abstract: *Burkholderia mallei* and *Burkholderia pseudomallei*, two well-known members of the genus *Burkholderia*, are considered by the CDC of the USA as potential biological weapons. *Burkholderia gladioli* pv. *cocovenenans*, though less well-known than *B. mallei* and *B. pseudomallei*, is able to produce a highly fatal mitochondrial toxin, bongkrekic acid (BKA). At least around 10,000 cases of BKA poisoning have been recorded in Indonesia, with more than 1000 deaths, most of which related to consumption of fermented coconut-based tempe. Additional outbreaks/cases have also been reported from China, Bhutan, Mozambique, the USA, and recently in Taiwan. We hypothesize that *B. gladioli* pv. *cocovenenans* and BKA is a potential biological weapon due to a number of reasons. First, *B. gladioli* pv. *cocovenenans* is not uncommonly found; and therefore, when added to food items well-reported to be associated with BKA poisoning, could mimic natural contamination. Second, *B. gladioli* pv. *cocovenenans* replicates and synthesizes the BKA readily under natural conditions. Third, BKA is heat stable and will not be inactivated through cooking. Fourth, BKA is odorless and not associated with a strong taste. Fifth, there is no known antidote for BKA poisoning. Sixth, BKA poisoning is highly fatal. Seventh, when fatal BKA poisoning is reported in an area, particularly if repeatedly, widespread terror would be formed, achieving the purpose of a terrorist attack. Although most of us start to focus our attention on future crimes and future terrorist attacks on cybercrime and cyberterrorism, the more traditional and tangible forms of bioterrorism should not be overlooked.

Keywords: outbreak; *Burkholderia gladioli*; bongkrekic acid; food poisoning; biological weapon

1. Introduction

The genus *Burkholderia* comprises of more than 60 bacterial species of highly diverse pathogenic potential, geographical distribution, and host preference [1,2]. For the spectrum of pathogenicity, on the one extreme are *B. mallei* and *B. pseudomallei*, which are considered by the Centers for Disease Control and Prevention of the USA

as potential agents of biological warfare [3]; whereas on the other are bacteria with minimal pathogenicity (e.g., *B. thailandensis*) and are rarely associated with clinical diseases [4,5]. In terms of geographical distribution, *B. cenocepacia* is the most well-known one of global importance. In the western world, it is associated with chronic pulmonary infections in patients with cystic fibrosis [6,7]; whereas in our locality and other Asian countries where cystic fibrosis is not prevalent but tuberculosis is common, it is often found in individuals with acute exacerbation of bronchiectasis, which occurs frequently as a complication of old tuberculosis [8]. In contrast to *B. cenocepacia* which is more ubiquitous, *B. pseudomallei* is an important cause of melioidosis, a serious and potentially fatal disease characterized by pneumonia and sepsis that occurred mainly in Southeast Asia and Northern Australia, with high case-fatality rates of around 20% [1,9,10]. As for host preference, *B. mallei* is the causative agent of glanders in horses, donkeys and mules, and occasionally other mammals through consumption of meat from sick animals; whereas *B. pseudomallei* is mainly a human pathogen [11–13].

Burkholderia gladioli, which could be a less well-known member of the *Burkholderia* genus to some clinicians as compared to *B. cenocepacia*, *B. pseudomallei* and *B. mallei*, is in fact a highly versatile bacterium. Similar to *B. cenocepacia*, *B. gladioli* is most commonly found as a cause of chronic pulmonary infection in patients with cystic fibrosis or other chronic respiratory disorders [14,15]. As for bloodstream infections, *B. gladioli* bacteremia has only been reported in around a dozen patients [16]. Although it is relatively less prominent compared with some other *Burkholderia* species in causing invasive infections, around 15% of *B. gladioli* strains, named *B. gladioli* pathological variant *cocovenenans* (*B. gladioli* pathovar *cocovenenans* or *B. gladioli* pv. *cocovenenans*), produces a distinct toxin, called bongkrekic acid (BKA), which has been reported to be associated with a highly fatal condition due to consumption of specific fermented food items contaminated with the bacterium with the toxin [17–19]. Patients with BKA poisoning presented with malaise, drowsiness, dizziness, vomiting and abdominal pain. For the severe cases, patients can rapidly deteriorate to multiple organ failure and die [20,21].

In March 2024, an outbreak of six cases of fatal BKA poisoning occurred in Taiwan, the first of its kind in this locality. Further investigations revealed that all six patients who succumbed had consumed stir-fried rice noodles in a Malaysian vegetarian restaurant in Taipei, and BKA was detected from clinical samples collected from the patients as well as a Vietnamese chef of the restaurant. In this article, we reconstructed the sequence of events for the outbreak using publicly available information from the internet and reviewed other outbreaks of BKA poisoning in the English literature as well as its biosynthesis and mechanism of action. The hypothesis of using *B. gladioli* pv. *cocovenenans* as a biological weapon is also discussed.

2. March 2024, Fatal Food Poisoning Outbreak, Taiwan

From 19 to 22 March 2024, more than 30 patients developed nausea, vomiting and diarrhea shortly after dining at a Malaysian vegetarian restaurant in Taipei, Taiwan [22]. These patients were admitted to different hospitals in Taipei [23]. Some of the patients deteriorated rapidly to the stage of multiorgan failure and six patients died [22]. As an example, a 66-year-old male patient with good past health developed generalized discomfort after consuming rice noodles in the Malaysian restaurant on 19 March [24]. Although his condition improved transiently after seeking medical attention, he developed nausea, diarrhea and vomiting shortly afterwards [24]. In the morning of 21 March, he went to the emergency room of hospital Y and was immediately admitted and transferred to the intensive care unit due to acute hepatic failure [24]. On 25 March, extracorporeal membrane oxygenation was used but he passed away on 27 March due to multiorgan failure [24]. Similarly, another patient was also transferred to hospital Y on 23 March from a smaller hospital X, but deteriorated rapidly and passed away on 24 March [25].

Outbreak investigations revealed that most of the patients, including all the six patients who died, had consumed stir-fried rice noodles or “kway teow” (Figure 1A) in the Malaysian vegetarian restaurant [23]. Environmental inspection showed that there was violation of hygienic protocols [23]. Unfortunately, no left-over rice noodles from the meals of the patients could be collected [26]. All branches of the Malaysian vegetarian restaurant in Taiwan were closed on 27 March [27]. Subsequently, blood samples collected from the patients and deceased revealed the presence of BKA [28]. Moreover, the handprint and stool sample of a Vietnamese chef of the Malaysian restaurant were also positive, but his blood sample was negative, for BKA [29]. This suggested that he might have ingested a trace amount of BKA through his contaminated hands, but the amount in the intestine was too small so that it was not absorbed to a detectable level in the blood [26]. Rice noodles from batches that were different from the one used for cooking the stirred-fried rice noodles the victims in the outbreak consumed were tested negative for BKA [28]. By 11 June 2024, a total of 33 confirmed cases of BKA poisoning with six deaths were confirmed [26].

Figure 1. Food items implicated to be the sources of BKA poisoning. Panel **A**, stir-fried rice noodles or "kway teow" prepared by a local restaurant in Taiwan. Panel **B**, fermented coconut-based tempe or tempeh (*tempe bongkrek*) from a street vender in Java, Indonesia. Panel **C**, snow fungus (*Tremella fuciformis*) prepared by a local restaurant in Taiwan. Panel **D**, black wood ear (*Auricularia heimuer*) from a local market in Taiwan.

3. BKA Poisoning Outbreaks

3.1. BKA Poisoning Outbreaks in Asia

The first records of BKA poisoning and outbreaks were related to fermented coconut-based tempe or tempeh (*tempe bongkrek*) (Figure 1B) in Java, Indonesia around a century ago [30]. Tempe is a group of traditional Indonesian food made from the fermentation of variety of natural products, of which a mold (e.g., *Rhizopus oligosporus*, *Rhizopus oryzae*) is used for the fermentation process. These fermented foods are key sources of protein in Indonesia, and are frequently found in the markets and food vendors on the street. Among this group of fermented food, one of them, known as *tempe bongkrek*, was made from coconut meat. The product is a coconut compact cake covered and penetrated by the mold used for fermentation. However, the traditional fermentation process is usually carried out without sufficient hygienic precautions; and if the coconut meat is contaminated by *B. gladioli* pv. *cocovenenans*, BKA poisoning may occur. This problem was particularly evident during the years of economic depression, when homemade *tempe bongkrek* was common. Throughout the years, at least 10,000 cases of BKA poisoning have been recorded in Indonesia, with more than 1,000 deaths [31]. Almost all the cases were from Java Island.

Apart from Indonesia, BKA poisoning and outbreaks have also been reported from at least nine provinces in China. Most of these BKA poisoning outbreaks in China occurred in provinces from the south, including Guangdong, Guangxi, Guizhou, Sichuan, and Yunnan provinces [32]. This was probably because the contaminated bacterium, *B. gladioli* pv. *cocovenenans*, multiplied much faster at higher environmental temperature in the southern than northern provinces; or alternatively, the food involved were more popular in the southern provinces. In contrast to the outbreaks in Indonesia of which coconut-based *tempe bongkrek* was the main food involved, fermented corn flour has been pinpointed as a major source of the early reported outbreaks [33]. In order to reduce the risk of BKA poisoning, homemade fermented corn flour was banned by the Chinese government in 2000. In a subsequent article that summarized the BKA poisoning outbreaks in China from 2010–2020, it was observed that

the major types of food implicated were fermented corn flour products, wet rice noodles, edible fungi (e.g., snow fungus, black wood ear), and sweet potato flour products (Figure 1C,D); and more than three quarters of the outbreaks occurred in households, whereas the remaining minority were restaurant-based [34]. It is of note that since 2011, all food poisoning cases in China that involved two or more patients or one fatal case have to be reported systematically to the government using a web-based surveillance system, which may explain why a relatively large number of BKA poisoning outbreaks have been reported in China [34]. Moreover, most of the outbreaks occurred in the warmer months, also in line with the fact that the bacterium's rapid multiplication rate at higher temperatures. Horrifyingly, one of the recent outbreaks that took place in Heilongjiang Province has resulted in a fatality of 100% [35]. The culprit of this residential outbreak, which occurred in October 2020, was traced to a homemade fermented corn flour sour soup. All nine members of the family died and the BKA doses consumed by the victims were more than 20 times the lethal dose in humans [36]. It was believed that the contaminated *B. gladioli* pv. *cocovenenans* had probably multiplied to high levels because there were some irregularities during the food handling process due to a lack of refrigerator space [36].

In addition to those from Indonesia and China and that from Taiwan in 2024, an outbreak of BKA poisoning occurred in Dagana, a town in southwestern Bhutan, in August 2020 [32]. In this outbreak, four patients died and the source was traced to a locally brewed corn alcohol *Bangchang*. These cases from Bhutan and Taiwan have expanded our understanding of the geographical distribution and epidemiology of BKA poisoning.

3.2. BKA Poisoning Outbreaks Outside Asia

In 2015, the first BKA poisoning outbreak outside Asia was reported [37]. This outbreak that took place in Chitima, a rural town in northwestern Mozambique in Africa, has involved more than 230 patients with 75 deaths. The median interval between consumption of pombe and symptom onset was 16 h (range 0–148 h). Outbreak investigation revealed that all patients had attended a funeral ceremony and the culprit was a locally brewed traditional alcoholic beverage called pombe, which was made from fermented corn flour. *B. gladioli* pv. *cocovenenans* was isolated from the corn flour for preparing the pombe.

In 2024, the first case of BKA poisoning in the USA was reported [38]. The patient was a 67-year-old man who presented with non-specific symptoms of nausea and malaise two days after consuming home-fermented corn ogi, a Nigerian fermented cornmeal-based pudding. The patient succumbed eight days after hospitalization. In fact, the patient's wife has also consumed the pudding but in a smaller amount; and therefore, has only developed self-limited gastrointestinal symptoms.

4. The BKA Toxin

4.1. BKA as a Secondary Metabolite

Secondary metabolites are bioactive compounds produced by bacteria, fungi, etc. that are not related to their basic growth and development [39]. Although unlike primary metabolites that are crucial for survival, secondary metabolites provide survival advantages to the microbes. Some of the most well-known secondary metabolites include pigments, antibiotics and mycotoxins [39–43]. For example, antibiotics produced by a particular bacterium or fungus will suppress the growth of other bacteria in the vicinity, giving it a survival advantage over the neighbors [44,45].

Polyketides are a diverse group of secondary metabolites produced by microbes. These compounds are synthesized by complex enzymatic systems known as polyketide synthases. The neighborhood of the polyketide synthase genes also include additional genes that encode various modifying enzymes, forming biosynthetic clusters. Bacterial polyketide synthases are classified into type I and type II. Type I polyketide synthases are huge multifunctional proteins with many modules containing domains and perform the enzymatic reaction in a non-iterative way, whereas type II polyketide synthases have mono-functional polypeptides that work iteratively to produce the polyketides [46]. BKA is a secondary metabolite and polyunsaturated methoxy tricarboxylic acid polyketide produced by *B. gladioli* pv. *cocovenenans* (Figure 2); and so far, *B. gladioli* pv. *cocovenenans* is the only known bacterial species that produces BKA [32,47].

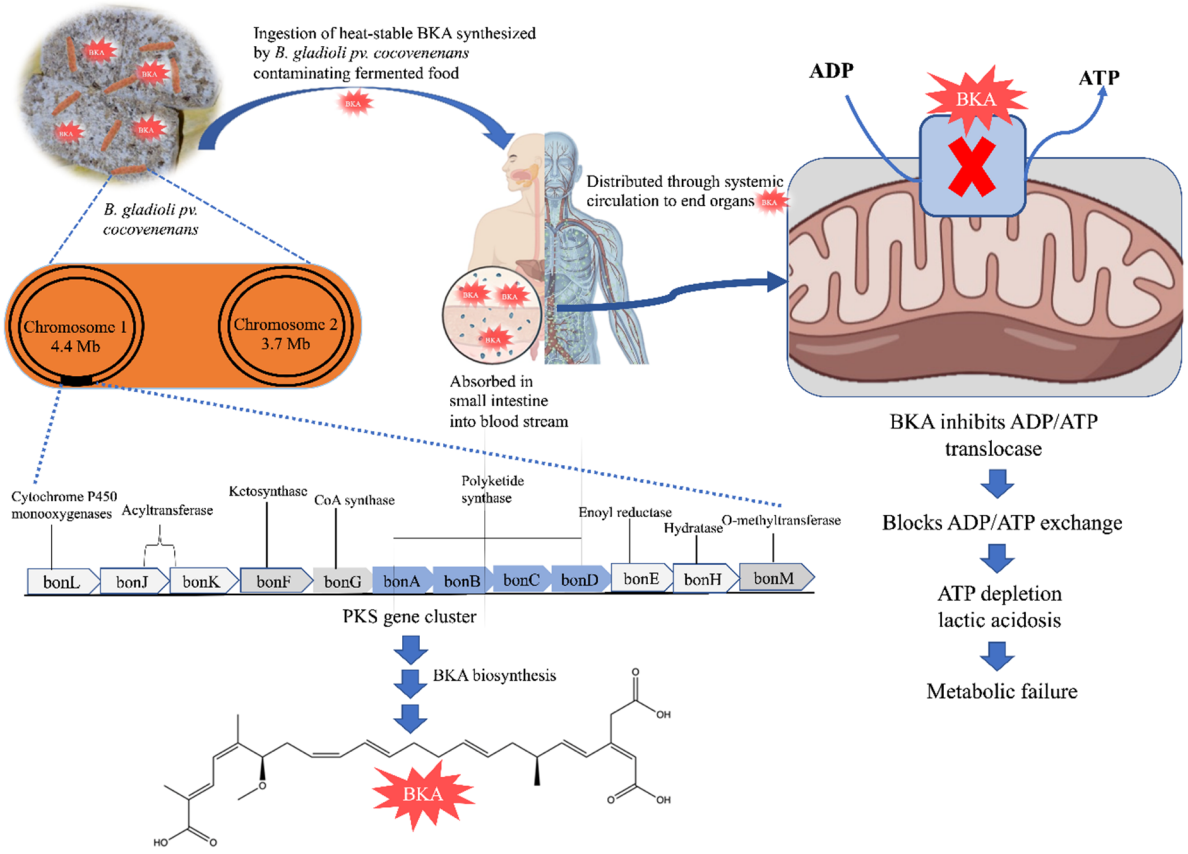

Figure 2. Pathogenesis of BKA poisoning.

4.2. The B. gladioli Genome and Biosynthesis of BKA

Similar to many other *Burkholderia* species, such as *B. pseudomallei* and *B. mallei*, the genome of *B. gladioli* consists of two circular chromosomes [48]. The genome size of *B. gladioli* is around 8.1 Mb, with chromosome 1 around 4.4 Mb and chromosome 2 around 3.7 Mb respectively (Figure 2). Around 15% of B. gladioli strains, named *B. gladioli* pv. *cocovenenans*, are capable of synthesizing BKA through enzymes encoded by a *bon* polyketide synthase gene cluster on chromosome 1, the presence of which distinguishes these toxin-producing strains from the non-toxin-producing ones.

The *bon* polyketide synthase gene cluster of *B. gladioli* pv. *cocovenenans* comprises 13 open reading frames (*bon L*, *bon J*, *bon K*, *bon F*, *bon G*, *bon A*, *bon B*, *bon C*, *bon D*, *bon E*, *bon H*, *bon I*, and *bon M*) (Figure 2). The core of the *bon* polyketide synthase gene cluster is occupied by *bon A*, *bon B*, *bon C*, and *bon D*, which encode the modules of the polyketide synthase, a type I polyketide synthase, responsible for the cycles of polyketide chain elongation [30,32,47]. As for the other nine open reading frames, they encode various enzymes that facilitate BKA biosynthesis. These enzymes include acyltransferase (BonJ and BonK), enoyl reductase (BonE), ketosynthase (BonF), 3-hydroxy-3-methylglutaryl-CoA synthase (Bon G), and enoyl-CoA hydratase (BonH and BonI), O-methyltransferase (BonM), and cytochrome P450 monooxygenase (BonL) respectively [30,32].

4.3. Pathogenesis of BKA Poisoning

After being synthesized in the bacterial cell, BKA is secreted extracellularly via standard bacterial metabolite transport mechanisms. Since it is heat-stable, BKA survives the standard cooking methods. When the contaminated food item is consumed, BKA is absorbed in the small intestine and distributed throughout the various vital organs through the cardiovascular system (Figure 2). After entering the mammalian cell, BKA penetrates the inner membrane of the mitochondria. In contrast to cyanide, another well-known mitochondrial toxin that interfere directly with the electron transport chain, BKA binds, from the matrix side, tightly to the ADP/ATP translocase, also known as the adenine nucleotide translocator (ANT), which is located on the inner mitochondrial membrane and is an essential player responsible for transporting ADP into the mitochondria for ATP synthesis, and ATP out for cellular usage (Figure 2). BKA is highly specific and locks the translocase in a specific conformation [30,49]. As a result, cellular respiration stalls, ATP production collapses, and cells experience severe energy failure,

especially in high-demand tissues like the liver, brain and heart [30,32]. Therefore, patients with BKA often present with clinical features of rhabdomyolysis, hepatic and renal dysfunction, progressive neurological deterioration as a result of cerebral edema and increased intracranial pressure, and in severe cases multi-organ failure [30,50].

5. Potential of *B. gladioli* pv. *cocovenenans* as a Biological Weapon

Biological weapons are usually living organisms (e.g., plants, bacteria, viruses) or their toxins that are used to intentionally cause mass casualties, widespread fear and societal disruption. Some key characteristics of biological weapons are their abilities to spread through different methods (e.g., aerosol, food and water), high fatality or incapacitation rates that overwhelm the health care system, difficult to treat on a timely basis, and the creation of widespread panic and social and economic instability. Some of the well-recognized potential biological weapons are the highly pathogenic bacteria and their toxins, such as *Bacillus anthracis*, *B. mallei*, *B. pseudomallei*, *Clostridium botulinum*, *Coxiella burnetii*, *Francisella tularensis*, and *Rickettsia rickettsii*, which are the causes of anthrax, glanders, melioidosis, botulism, Q fever, tularemia, and Rocky Mountain spotted fever respectively [51–53]. Among these notorious candidates include two members of the genus *Burkholderia*, *B. mallei* and *B. pseudomallei* (Table 1). This could be partially explained by the fact that members of this genus of bacteria have relatively large genome size that ranges from around 6.3 to 9 Mb; and therefore, are able to encode many secondary metabolites of various functions.

Table 1. Clinical and microbiological characteristics of *B. mallei*, *B. pseudomallei* and *B. gladioli* pv. *cocovenenans.*

Characteristics	*B. mallei*	*B. pseudomallei*	*B. gladioli* pv. *cocovenenans*
Genome size	5.8 Mb	7.3–7.8 Mb	8.1 Mb
Number of chromosomes	2	2	2
Natural transmission	Inhalation or percutaneous inoculation of bacteria	Inhalation, percutaneous inoculation or ingestion of bacteria	Ingestion of BKA contaminated food
Pathogenesis	Direct invasion	Direct invasion	BKA binds and locks ADP/ATP translocase
Clinical syndrome	Pneumonia, sepsis	Pneumonia, sepsis	Rhabdomyolysis, hepatic and renal dysfunction, progressive neurological deterioration
Laboratory diagnosis	Bacterial culture, PCR, serology	Bacterial culture, PCR, serology	Bacterial culture, PCR, mass spectrometry
Treatment	Antibiotics	Antibiotics	Supportive

There are a number of factors that make *B. gladioli* pv. *cocovenenans* and BKA another potential biological weapon of the genus *Burkholderia* (Table 1). First, *B. gladioli* pv. *cocovenenans* is not uncommonly found; and therefore, when added to food items (e.g., rice noodle, corn flour, coconut, mushroom) that are well-reported to be associated with *B. gladioli* pv. *cocovenenans* BKA poisoning, could mimic natural contamination. Second, *B. gladioli* pv. *cocovenenans* replicates and synthesizes the BKA readily under natural conditions. It does not require highly specific incubation conditions, such as oxygen or carbon dioxide levels, temperature, sodium chloride concentration, etc. for reasonable growth. In fact, *B. gladioli* pv. *cocovenenans* multiplies readily at 22–30 °C, pH 6.5–8.0 and less than 2% sodium chloride concentration [54]. Third, since BKA is heat stable, the BKA that has already been synthesized by the *B. gladioli* pv. *cocovenenans* in contaminated food items will not be inactivated through cooking. Fourth, BKA is odorless and not associated with a strong taste; and therefore, will not be easily recognized by the person who consumes the contaminated food. Fifth, there is no known antidote for BKA poisoning and management is limited to supportive care. Sixth, BKA poisoning is highly fatal. From the outbreaks that have been reported, the mortality rate often ranged from 20% to 60%, but could be as high as 100% in one study [35]. In fact, the median lethal dose 50 by oral administration of BKA is only 1 to 3.16 mg/kg, comparable to that of ricin toxin by inhalation (5 to 10 μg/kg), another well-known biological weapon extracted from the castor oil plant *Ricinus communis* seeds. Seventh, when fatal BKA poisoning is reported in an area, particularly if repeatedly, widespread terror would be formed, achieving the purpose of a terrorist attack.

6. Concluding Remarks

B. gladioli pv. *cocovenenans* produces a highly fatal mitochondrial toxin BKA. Outbreaks resulting in high mortalities due to consumption of various food items contaminated with the bacterium and toxin have been recorded in Indonesia, China, Bhutan, Mozambique, the USA, and recently in Taiwan. Preventing BKA poisoning relies on safe preparation and storage of fermented or starch-rich food, including good hygiene, proper refrigeration and avoiding spoiled or improperly fermented products. Since BKA is heat-stable, reheating contaminated food does not make it safe. We hypothesize that *B. gladioli* pv. *cocovenenans* and BKA is a potential agent of biological warfare. Although most of us start to focus our attention on future crimes and future terrorist attacks on cybercrime and cyberterrorism, the more traditional and tangible forms of bioterrorism should not be overlooked.

Author Contributions

H.L.: visualization, literature review, investigation, validation, writing—original draft preparation, writing—review and editing; S.P.: literature review, investigation, visualization, validation, writing—review and editing; Y.-C.L.: literature review, investigation, validation; P.C.Y.W.: conceptualization, methodology, project administration, supervision, funding acquisition, writing—original draft preparation, writing—review and editing; All authors have read and agreed to the published version of the manuscript.

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No AI tools were utilized for this paper.

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