



Pattern of bioterrorism in ancient times: lessons to be learned from the microbial and toxicological aspects

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Summary The current research aimed to analyze the history of bioterrorism in antiquity and to adapt the data to modern medical knowledge. To this end, a thorough evaluation of the literature related to the ancient history of bioterrorism and modern data was done using the Web of Sciences, Science Direct, Scopus, PubMed, and Google Scholar. Results showed that knowledge of bioterrorism has existed since antiquity in different civilizations. Biological and toxicological agents were used as an instrument of legal execution, as a warfare tool in battles, or to eliminate political rivals across nations. Ancient people researched bioterrorism to apply it against en-

emies and at the same time provide countermeasures in favor of themselves and allies. Despite the existence of the principles of bioterrorism since ancient times, adaptation of the data to modern research can assist in planning countermeasure efforts, preventive actions, and treatments in the framework of modern counterterrorism medicine.

Keywords Bioterrorism · Biology · Counterterrorism medicine · Toxicology · Medical history

Introduction

Bioterrorism means the use of biological agents, including microorganisms or their toxins, to scare or destroy animals, humans, and plants. It is a sinister tool used to deliberately scatter detrimental agents through food, water, vectors, or vapors [1–4]. Bioterrorism is now recognized as a significant biological threat that poses a risk to people's health and lives because of the rising trends in biological threats and the recent emergence and re-emergence of infectious diseases like HIV, Ebola, anthrax, swine flu, Zika virus, and COVID-19 just to name a few [5–8]. Another important component of bioterrorism involves toxic agents [9, 10]. Bioterrorism has become a top priority for societies that need medical preparedness [11, 12]. The importance of research in this field is so noteworthy that a new area of counterterrorism medicine has appeared to deal with its consequences by planning medical and healthcare frameworks for quick response [13]. This research aimed to elucidate the historical usage of bioterrorism in ancient civilizations of Asia, Europe, Africa, and America; the motives, methods, agents, and countermeasures; and to assess in this light of modern knowledge.

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Materials and methods

This research is a library study using the library method and content analysis, which was done by focusing on works and writings related to ancient times and based on data collected from various sources and books related to the ancient history of medicine. First, according to the topic of the research and preliminary investigation, the keywords of poison, poisons, poisonous plants, venomous animals, weapons, warfare, toxicology, antiquity, and ancient history were searched. Then, the sources were carefully studied, and the findings of each source were extracted. Also, the databases of Scopus, Science Direct, Web of Sciences, PubMed, and Google Scholar were searched using the mentioned keywords. Thereafter, the related literature was studied, and the obtained data were analyzed.

Results

Background of toxicology and bioterrorism knowledge in ancient times

Toxicology is derived from the word *toxicon*, which means a poisonous substance that was rubbed on the heads of spears to poison them [14]. The first toxicological information is related to early humans, in such a way that they used animal poisons and plant extracts in their weapons for hunting, murder, and assassination. These poisons include poisonous plants such as hemlock (*Conium maculatum*), monkshood (*Aconitum* species, known as a Chinese arrow or spearhead poison), opium (which was used as both poison and antidote), and some metals such as arsenic, mercury, and copper (Fig. 1). Poisoning was common among ancient people and the study of poisons and finding antidotes was of special importance [15]. The history of studying poisons probably dates back to reports from the ancient Sumerian tablets of Mesopotamia in 4500 BC indicating that they used poisons (Table 1; [16]). The Sumerian, Assyrian, Akkadian, and Babylonian civilizations are some of Mesopotamia's most important ones. They used not only venomous animals such as snakes, scorpions, and spiders, but also toxic plants such as spurge (*Euphorbia helioscopia*) and black nightshade (*Solanum nigrum*; Table 1). They also made an effort to treat the resulting poisonings [17]. Archaic civilizations including the Sumerian, Assyrian, Babylonian, and Egypt were acquainted with poisons and benefited from their toxic properties [18–21]. One of the first medical reports written on papyri conveys instructions about poisons. There is information about some of the known poisons in the Ebers Papyrus (approximately 1550 BC) [22]. The Leyden Papyrus tells us the basic recipe for preparing a syrup that puts a person to sleep without suspecting it, containing mandrake and henbane in wine [23]. The ancient Egyptians



Fig. 1 Monkshood (*Aconitum napellus*). This figure was originally published Open Access in the Wellcome Collection, JSTOR, <https://jstor.org/stable/community.24890573>

were aware of cyanide in plants. Indian physicians knew about poisons like arsenic, aconite, and opium (approximately 900 BC). As a result, the evidence suggests that humans have known about bioterrorism, including the use of toxicological agents, since ancient times [14, 24, 25]. According to archaeologists, primitive and nomadic tribal communities used poisons and infectious agents for fishing, hunting, or fighting. They obtained these toxins and biological agents from animals or plants and contaminated the arrows with them (e.g., the Melanesian tribe, Table 1; [26]). The Scythian tribe's members in ancient Greece used more sophisticated methods to create arrows that contained pathogenic agents in addition to poisons. In addition to taking human blood and pouring it into a container to spoil it, they also killed a specific species of young snakes and left them to spoil. The arrow tips were then coated with a mixture of the two [27].

Applications of toxicology and bioterrorism in ancient times

One of the punishments for sins such as treason, dishonor, and murder in ancient legal systems was that the sinner was forced to drink poison. In fact, in ancient Greece, the death penalty by eating hemlock (government poison) was usually applied to outlaw persons, because it was decided that the execution of these people should be done in the shortest possible time and with the least amount of suffering and pain. For this reason, when hemlock was fed to a person sentenced to death, his body gradually became numb and numb, and this numbness started from the feet and when it reached the heart, it caused the death of the person. According to the Greek laws, whoever committed asebeia or ungratefulness toward the Athens pantheon, his act was considered a great sin [28, 29]. Socrates was executed in 469–399 BC by being forced to drink a cup of hemlock-laced poison, which is a famous example. Accordingly, the Greek government executed people using this poisoned chal-

Table 1 Pattern of bioterrorism in different ancient civilizations in the light of modern medical knowledge

Civilizations	Bioterrorism agents
Mesopotamian (Sumerian, Assyrian, Akkadian, Babylonian)	Venomous animals (e.g., snakes, scorpions, spiders), poisonous plants; spurge (<i>Euphorbia helioscopia</i>), black nightshade (<i>Solanum nigrum</i>) Assyrian: ergot fungus (<i>Claviceps purpurea</i>) Babylonians: (microbes e.g., infected corpses), white hellebore (<i>Veratrum album</i> ; Babylonian used against the Alexander the Great)
Egyptians	Cyanide, arsenic, monkshood (<i>Aconitum</i>), opium, mandrake (<i>Mandragora officinarum</i>), henbane (<i>Hyoscyamus niger</i>), ricin (<i>Ricinus communis</i>)
Romans and Greeks	Microbes (infected corpses, <i>Clostridium tetani</i>), cyanide, deadly nightshade (<i>Atropa belladonna</i>), white hellebore (<i>Veratrum album</i> ; Atheian used to poison water in Kirrha surrendering), poison hemlock (<i>Conium maculatum</i>), monkshood (<i>Aconitum</i> spp.), poisonous mushrooms (e.g., <i>Amanita muscaria</i>), venomous animals (snakes, scorpions, insects), minerals and vapors (sulfur fumes)
Indians	Arsenic, monkshood (<i>Aconitum</i>), opium, strychnine (<i>Strychnos nux-vomica</i>), venomous animals (e.g., snake's venom)
Chinese	Monkshood (<i>Aconitum</i> spp.; Chinese arrow poison), poisonous frog (batrachotoxin), poisonous smokes (mercury, arsenic, copper, iron)
Japanese	Venomous animals, microbes (e.g., <i>Clostridium tetani</i>), minerals and vapors (burning mercury, arsenic, copper and iron ores to make poisonous objects), venomous and poisons animals (e.g., puffer fish)
Africans	<i>Strophanthus</i> plant
American Indians	Monkshood (<i>Aconitum</i> spp.), curare (<i>Strychnos toxifera</i>), poisonous frog (batrachotoxin)
Hittites	Tularemia (<i>Francisella tularensis</i>), plague (<i>Yersinia pestis</i>)
Melanesians	<i>Clostridium tetani</i>
Scythians	Microbes (decaying corpses, spoiled blood), and snake's venom (mixture of venoms and microbes such as <i>Clostridium perfringens</i> , <i>Clostridium tetani</i>)
Miscellaneous civilization agents	<i>Datura stramonium</i> , toxic honey (grayanotoxins)
Main delivery methods	Food Water Smoke Object
Motives	Execution Warfare Assassination
Agent categories	Microbial: bacteria, fungus Toxic: plant, animal, mineral, and smoke Mix: microbial and toxic
Countermeasures	Oligodynamic effects of metals (e.g., silver coin in water source) Poison detection methods (poison cups, food-tasters, avoidance of suspect foods and beverages in deployment) Avoidance of noxious smells in the environment R & D infrastructures for obtaining bioterrorism knowledge: – Menes, pharaoh of Egypt (cultivation and research on toxic plants) – Attalus III of Pergamon (research on various poisons) – Nero, Roman Emperor (establishment of a toxicology research center to conduct basic and clinical toxicology studies on the animals and convicted criminals thanks to the Lucasta's expertise)

ice [30, 31]. In referring to the punishments of ancient times, Will Durant, the famous American historian, mentioned the matter of execution and said that one of the methods of execution was that the sinner was forced to drink poison [32]. For instance, in Mesopotamian civilizations such as Assyrians, poisoning the lawbreaker was one of the punishments listed in the laws (Sargon II, reigned 721–705 BC), in addition to other penalties [32].

Archaeological findings confirm that while ancient humans used the conventional physical weapons of that time to fight and hunt, at the same time, they were looking for more effective and destructive means of death, and this is what probably motivated them to discover poisons. The grooves and rifling of ancient weapons have been discovered, which indicate that they were used to store or keep poisonous agents such as curare. At the same time, these findings proved that early humans discovered different poisons that had different properties and levels of toxicity and used

them in their weapons. Some researchers believe that the use of such mysterious substances was kept secret among the more important members and elders of the tribes or clans [33]. In the rituals around 246 BC, Chinese tribes produced smoke from the burning of poisons such as cinnabar (a mercury compound), realgar (an arsenic compound), green vitriol (copper sulfate), and iron ore, and in the conflict with the enemy, they used them at the appropriate times [34]. Germanicus Julius Caesar (15–19 BC) was a well-known ancient Roman general who was poisoned to death by Gnaeus Calpurnius Piso because of the directive of Tiberius [35, 36].

Types of methods and tactics used in ancient times for bioterrorism

Ancient examples of the use of bioterrorism include poisoning war soldiers with animal or plant poisons, using plague-related animal carcasses to break

down defenses inside city fortifications, introducing deadly fungi into the interior of pharaohs' tombs, and contaminating water supplies in an urban area [37]. In antiquity, various bioterrorism agents were used to contaminate food and water supplies, infect weapons with deadly toxins or microscopic organisms, and contaminate fomites [38, 39]. Additionally, different weapons such as daggers, swords, and arrows were smeared with various poisons to create a fatal weapon [40, 41]. Poisonous agents were delivered to the enemies through tainted food, drink, medicines, dishes, clothes, jewelry, and rings. Using different kinds of plant and animal poisons especially prevailed in the court of kings to eliminate rivals and enemies [42]. In ancient Rome, poisons were used not only orally, but also in the form of enemas, poisoned needles, and even poisoned feathers [43], the latter of which was used to kill the Roman emperor Tiberius Claudius Caesar Augustus Germanicus (10 BC–54 AD). He was initially poisoned with *Amanita muscaria* mushroom which caused muscarinic toxidrome. The poisoners were Agrippina and her accomplice Locusta. Agrippina planned to get rid of Claudius to put his son, Nero, on the throne. When Claudius solicited a feather to induce emesis for suspicious poisoning, a poisonous feather (possibly *Aconitum*) gave him to die [44]. Poison rings were another ancient way of storing poisons safely until the right moment to apply them as lethal weapons [45]. According to Sinuhe, the Pharaoh's physician, it was customary for the Egyptian priests to poison the tomb's door, wall, and all of its inanimate objects, including the pharaoh's coffin, after the pharaoh was buried. This poison was particularly potent and did not wear off over time. They did it so that if someone entered the tomb and wanted to steal, he would be killed by the poison [46]. According to Sinuhe, many pharaohs were also assassinated by poisons in their palaces [47, 48]. Also, Sinuhe revealed the terror of young Hittite's leader by him as an order of the Egyptian pharaoh, Horemheb (reigned 1319–1292 BC). He plotted to assassinate by attending a party that the Hittite king had hosted while carrying a jar containing his purported special drink and only drinking from that. This attracted the attention of the young leader of the Hittites, and he asked Sinuhe to give him some of his drink. Sinuhe reluctantly accepted and gave the young man a drink from the jar he had drunk from. In reality, the jar was contaminated with poison earlier, but because Sinuhe had consumed a lot of castor oil before coming to the feast it delayed the absorption of the poison and did not work on him. On the other hand, when the condition of the young Hittite king worsened and he finally died in great pain and suffering, no one doubted Sinuhe, because he had imbibed from the contents of the jar in front of everyone and his condition had not changed. However, no one knew that after the celebration, Sinuhe put his finger down his throat and brought up the

poisoned drink [49]. This murder was undoubtedly planned and executed intelligently, making it one of the most primitive examples of biological terror in ancient history. The assassination of the Egyptian pharaoh (reigned 1353–1336 BC) was done also by Sinuhe with a poisoned drink [48, 50]. The murder of Ramesses III (reigned 1186–1155 BC) was carried out through a secret plot in her court, probably with a slow-acting poison such as ricin, which is found in the seeds of the castor plant (*Ricinus communis*) [51].

Types of agents used in ancient times for bioterrorism

Microbial agents

The Hittites were an ancient Anatolian people who established an empire between 1600 and 1180 BC in modern-day Turkey. The Hittites are credited with using bioterrorism for the first time according to historical documents. The first people to use lethal bacteria against their enemies were the Hittites, who inhabited a region that is now part of modern-day Turkey. Tularemia agent, *Francisella tularensis*, was spread among their foes as a result of the patients and animals they sent to the enemy forces [52, 53]. Also, there are reports that Hittites used plague cadavers in their launching systems against their enemies [54]. Some literature speculated that the first known use of biological weapons occurred in 1346 AD, when the Mongols catapulted plague cadavers (*Yersinia pestis*) over the city walls of Kaffa on the Black Sea [54, 55]. Nevertheless, it is controversial since the plague is a widespread word in ancient texts which may indicate other agents and it is also unclear whether the intention of Mongols was intentional bioterrorism and there is doubt about the efficacy of this weapon concerning its contagiousness [27].

In the fourth century BC, the Greek historian Herodotus reports that Scythian archers contaminated their arrows by dipping them in mixtures of decaying human and animal corpses and rotten blood. According to our modern medicine, this mixture may contain *Clostridium perfringens* and *Clostridium tetani*, as well as snake venom [53, 56]. The Romans also spread this disease among the enemy forces by smearing their swords and arrows with the blood of tetanus victims [40, 57].

Another primitive form of bioterrorism was reported in the sixth century BC by the Assyrians. They contaminated and poisoned the enemy's water wells using rye ergot fungus. If consumed, *Claviceps purpurea*, a mold that grows on wheat and rye, can cause neurotoxic symptoms including convulsions. Contamination of water wells of forts, castles, and cities was one of the effective ways to kill the enemy in ancient times. Also, in the war with the Phoenicians, the Babylonians used to throw the intestines of the soldiers who died from fever and chills and digestive tract infections into the river that was flowing toward

the Phoenicians. In 300 BC, the Greeks used to pollute the drinking water wells of their enemies with the corpses of animals that died of disease [58, 59]. Later, Romans used the same tactic [60].

With a projectile system, bioterrorist agents could be launched at the adversary. Long before modern armies did, biological weapons were also used by ancient armies, who used catapults to launch diseased corpses into enemy defenses. For example, during the cities' siege, Alexander the Great used a catapult to launch the bodies of plague victims into the cities. As a result, the cities' defenses crumbled under the impact of the plague [61, 62]. In ancient Japan, ninjas used their special weapons, throwing stars or shurikens laced with animal saliva and other bodily fluids, infecting them with bacteria and other microorganisms so that when they injured an enemy, the bacteria eventually led to infection and death. One of these agents that were used by ninjas was the tetanus bacteria, *Clostridium tetani* [63].

Botanical agents

Plant poisons were another kind of poison that was employed. The first pharaoh of Egypt, Menes, commanded the planting of the first poisonous plants, and he started documenting their effects in 3000 BC [64, 65]. Using knowledge of plants to make lethal potions, many people were poisoned to death during the Roman Empire [43, 66]. The deadly poison cyanide which they used to harm their enemies was obtained by the ancient Egyptians from peach kernels. Ancient Greece used this substance for this purpose over 2000 years ago [67, 68].

Monkshood or *Aconitum* is one of the plants that has been applied frequently. The name of the plant comes from the Greek or Latin word meaning spearhead or arrow and alludes to the time when the ancient Chinese used it to poison their arrows. Wolfsbane means wolf killer or wolf hunter that are among other names for this plant. By soaking arrows in plant water or soaking traps in it in the distant past, this plant was used to kill wolves by ancient nations. *Aconitum* was also utilized by the ancient Egyptians and Romans [69, 70]. Claudius is alleged to have died from this poison [68, 71]. According to sources from the fourth century BC, monkshood was allegedly used for murder in Indian palaces. After coating their lips with a special substance and applying monkshood in the form of lipstick, they would give the intended victim one or more kisses or bites that would ultimately cause death [72]. With a history of a civilization spanning several thousand years, American Indians have always used the technique of dipping their arrows in battle, and it is still used today [40]. Deadly nightshade, or *Atropa belladonna*, was another plant that was used in antiquity (Fig. 2). According to historical evidence, the plant's name derives from the Latin word *dorycnion*, which means *spear drug* and was used in ancient Rome to smear arrows [54]. In vari-



Fig. 2 Deadly nightshade (*Atropa belladonna*). This figure was originally published Open Access in the Wellcome Collection, JSTOR, <https://jstor.org/stable/community.28356806>



Fig. 3 Henbane (*Hyoscyamus niger*). This figure was originally published Open Access in the Wellcome Collection, JSTOR, <https://jstor.org/stable/community.24738348>

ous ancient civilizations, the plant known as henbane or *Hyoscyamus niger* was used as a psychoactive drug, anesthetic, and narcotic poison (Fig. 3). Due to its potent narcotic compounds, such as hyoscyamine and scopolamine, this plant was among the arrow poisons of ancient times [54]. *Mandragora officinarum* was another plant belonging to the nightshade family similar to deadly nightshade, henbane, and *Datura* with respect to the active ingredients and narcotic effects that were applied as arrow poison in antiquity (Figs. 4 and 5; [54]). In ancient civilizations such as Egypt, these narcotic plants were used alone or in wine to kill or anesthetize guards, soldiers, and enemies. Imbibing with wine the highly intoxicating root of the mandrake, it is claimed that the two Carthaginian generals by the names of Himilco and Maharbal defeated enemies in ancient times [73, 74]. *Datura stramonium* is known by the common names thorn apple and jimsonweed. This plant is poisonous and similar to *Atropa belladonna* contains tropane alkaloids, which cause neurotoxicity, narcotic effects, and eventually death [75]. Thorn apple is one of the poisonous plants cultivated and researched by Attalus III of Pergamon (reigned 138–133 BC), along with other poisonous and therapeutic plants such as henbane, hellebore, hemlock, and aconite [76]. The priest of the temple of Apollo in Delphi tried to convey the prophecies to followers breathing in the smoke of *Datura* [77]. Additionally, the native Indians of South-



Fig. 4 Mandrake (*Mandragora Officinarum*). This figure was originally published Open Access in the Wellcome Collection, JSTOR, <https://jstor.org/stable/community.24888786>



Fig. 5 Jimsonweed (*Datura stramonium*). This figure was originally published Open Access in the Wellcome Collection, JSTOR, <https://www.jstor.org/stable/community.24890602>

west America, with the guidance of the tribe's leaders, used the thorn apple in their religious ceremonies and special ceremonies [78]. White hellebore (*Veratrum album*) was another plant. One theory surrounding the death of Alexander the Great (reigned 336–323 BC) is that he was killed by *Veratrum album*. He was probably poisoned at a large banquet in Babylon (modern-day Iraq) by having his wine cup poisoned. As a result, he died [79]. Additionally, around 590 BC, Athens and its allies were besieging Kirrha, the location of the revered Oracle of Apollo. To end the siege, the commander gave his men orders to poison the city's water supply with hellebore [54]. Curare was a plant poison that was used as arrow poison both for hunting and combating enemies in incident times. Historical evidence stated that the American Indians extracted curare from *Strychnos toxifera* and would impregnate their swords and spears with this plant-based poison. In today's surgery and anesthesia, curare derivatives may be used as a drug [44, 45, 80]. Strychnine is a poison that extracts from a similar plant *Strychnos nux-vomica* (Fig. 6). This poison has been used since ancient times in different civilizations including Indian tribes for different poison arrows for killing prey and enemies [44, 81]. The *Strophanthus* plant was a deadly plant known as the Kombe plant



Fig. 6 Glass jar of *Strychnos nux-vomica* seeds. This figure was originally published Open Access in the Wellcome Collection, JSTOR, <https://jstor.org/stable/community.24786496>

and was applied to arrows by African natives for both hunting and combat purposes thousands of years ago [81]. This plant contains cardiac glycosides, used as a drug in the past, which causes toxicity and death in high doses [82].

Venomous animals

Poisonous animals and insects have been used in battle since ancient times [83]. According to historical records, ancient Indian archers dipped their arrows into snake venom in the fourth century BC [84, 85]. The ancient practice of using projectiles to deliver poisonous creatures to the enemy is an intriguing example of the use of animal poisons [40, 86]. One of history's most illustrious generals and politicians, Hannibal of Carthage, gave the order to his soldiers to throw clay jars filled with deadly snakes onto the decks of Greek ships in 184 BC [87]. The Chinese also behaved similarly during wartime; they trained these animals with the assistance of specialized trainers, and, during sieges of cities and castles, they placed the animals in brittle containers and threw them into the areas under attack. The animals were released in these areas as part of a siege, and by attacking the defending military forces and spreading panic among them, they easily succeeded in capturing these areas through a surprise attack [40, 88]. It has been reported that the Tatars also once threw clay jars filled with poisonous snakes at the large ships [85, 89].

Documents dating back to the second century BC refer to the use of frog poison (batrachotoxin) in China and South America [81, 90]. In addition to poisonous plants, ninjas in ancient Japan could add deadly animal poisons from a variety of sources to their shurikens. The venomous glands of snakes, the venomous secretions from the skin of amphibians, the scorpion venom, and arthropod venom were some of these sources [91, 92]. Poison-filled entrails of a particular type of puffer fish were also one of them. The

ninja dispatches the enemy in a matter of seconds by injecting shuriken with lethal poisons, the composition of which was known only to ninjas [93]. By burying shurikens in dirt or animal waste, it was also possible to infect the victims with *Clostridium tetani* [94]. When Hatra (current-day Iraq) was under siege by Lucius Septimius Severus Pertinax, the Roman emperor (reigned 193–211 AD), the city's defenders retaliated by hurling down containers filled with live scorpions and other venomous insects [83]. One of the most excruciating stings one can experience is from a member of the bee family (honeybee, wasp, or hornet). Bees were used as a weapon in ancient Rome to inflict physical harm on enemy soldiers. For instance, they would approach enemy warships in their boats and hurl specially made clay jars containing killer bees into the ship [95]. The bees were released when the jars were broken, which caused panic on the ship's deck and led to many people trying to save their lives by jumping into the water. Catapults were used by Roman legions in antiquity to launch honey beehives at foes and onto the castle walls of adversaries [96].

Additionally, historical accounts demonstrate that some Turkish villages were guarded against Greek and Roman attacks using poisonous honey. The villagers deftly dumped honey hives in the village streets despite being aware that honey produced during specific months of the year was naturally poisonous. According to one report, Greek soldiers once discovered several beehives stocked with honey while pillaging Turkish villages close to Trabzon. They happily consumed the honey, and as a result, they were severely poisoned—many even passed out. As a result, thousands of them were quickly killed because they were unable to fight [97]. Mad honey, also known as toxic honey poisoning, is made from the nectar of *Rhododendron* species that grow on the mountains in Turkey's eastern Black Sea region and other poisonous plants that contain grayanotoxins [98]. The inscriptions on the tombs of the pharaohs, who were regarded as the keepers of the coffin, often included images or statues of snakes and scorpions, demonstrating their familiarity with animal poisons [99].

Toxic minerals and fumes

In ancient Rome and China, arsenic, which is the Persian name derived from Zarnikh, was used to poison the tips of spears and arrows [15, 100]. Another mineral poison was sulfur fumes. It appears that the ancient Greeks produced a lethal smoke containing sulfur fumes around 1000 BC [83, 101]. In the Peloponnesian War (431–404 BC) that occurred in ancient Greece between Sparta and Athens, the Spartans used sulfur vapor (containing sulfur dioxide) against their enemy, the Athenian [102]. Around 246 BC, the Chinese burned mineral poisons including mercury, arsenic, copper, and iron ores, and put the smoke on a bunch of objects (feathers) so that these poisonous

objects could be used at the right time against the enemy [34, 103].

Countermeasures used in ancient times against bioterrorism

Since ancient times, humans have sought security measures and improved health and tried to avoid harmful agents including toxins. Ancient humans took advantage of the oligodynamic effects of some common metals to kill pathogens and diminish contaminations. In the Edwin Smith Papyrus, the use of silver and copper as disinfectants is recommended [104, 105]. Indigenous Americans used to put copper and silver coins into their water tanks and other drinks to keep them cold and, if there were any toxins present, to neutralize them [106, 107]. Ancient kings and their armies were well aware of the threat posed by bioterrorism, which prompted them to study and create both poisons and antidotes. Due to the threat of being poisoned, it was necessary to conduct this research to both defeat the adversaries and protect oneself. For instance, the Roman emperor Nero Claudius Caesar Augustus Germanicus appointed the creator of death potions, Lucasta, as his consultant on the science of poisons and founded a school of toxicology where she could research different poisonings. Animals and convicted criminals were used in Lucasta's toxicology experiments [26]. In ancient times, emperors took great care to avoid being poisoned. Also, to protect themselves and their friends from all poisons, they conducted scientific studies on poisons [54]. Additionally, "poison cups" which were vessels made of metal alloys, were used in ancient times to test whether there was poison in food and drinks or not [108]. It is noteworthy that in ancient times, the kings' courts had individuals referred to as *praegustators*, or food tasters, who tested the food to determine whether it was poisonous [44, 109]. Before the Battle of Actium (31 BC), Mark Antony reportedly refused to eat any food sent to him by Cleopatra unless his bodyguard first tasted it. Because of loving Antony, Queen Cleopatra intervened at the last second to stop him from giving her the poison and instead gave the cup to a prisoner who died instantly after consuming it [70, 110]. Since ancient times time, people have recognized the connection between illness and unpleasant smells. To reduce their chances of getting sick and dying in ancient times, military forces made an effort not to consume food or water that smelled bad while they were at war [111].

Discussion

Health and medical aspects related to bioterrorism are issues of internal medicine as well as an emergent field of counterterrorism medicine [112–114]. Moreover, recent military research recommendations for enlarging this field of study suggest that bioterror-

ism is one of the subjects that should be prioritized in military medical research directions [115, 116]. The present study revealed that since antiquity, toxicology and bioterrorism have been studied, and early civilized nations including the Romans, Greek, Mesopotamian (e.g., Sumerian, Assyrian, Akkadian, and Babylonian), Egyptians, Hittites, Indians, Chinese, Japanese, Africans, and American Indians knew about them. The knowledge of bioterrorism and poisons could be used in weapons, to eliminate political adversaries, or as a method of execution. Ancient people were familiar with poisons, and they conducted extensive research on them for both defensive and offensive purposes. In the past, different biological agents were used to infect victims in a variety of ways, including enemas, needles, and feathers, as well as water and food sources, objects like dishes, clothes, and jewelry, and weapons like daggers, swords, and arrows. Moreover, bioterrorism agents were harvested from human and animal remains, excrement, soil, and other polluted environments by various civilizations. Toxic substances were extracted from different plants, animals, and minerals. Concerning the type of biological agents, the present study revealed that microbial and toxic agents would be used, or in some cases a mixture of the two (Table 1).

In addition to the fact that microbial agents create their pathogenicity and toxic agents also leave their effects and that the etiology of many microbial agents is their toxins, an interesting point lies in the combined use of these agents. For instance, Scythians smeared the arrows with a mixture of rotten snakes (venoms) and human blood (microbes) [27]. Importantly, the synergistic relationship between microbial and toxic agents has been suggested in the literature. For instance, the resistant microbial population in snake venoms has been suggested as a cause of cases in which the healing of bite sites lasted for an unusually long time [117]. Also, it has been suggested that there is a synergistic correlation between aflatoxin B and viral hepatitis (e.g., B, C) in hepatocellular injuries including carcinogenesis [15, 118]. Consequently, it is suggested that further research be conducted on the interaction between microorganisms and toxic chemicals to ascertain the extent of such a phenomenon and incorporate suitable countermeasures in counterterrorism medicine in the future.

Another finding from our research was that through research and development, ancient people attempted to find ways to avoid, treat, and deal with biological and toxic agents. Prevention was among the countermeasure strategies against biological threats. For instance, ancient people used the antimicrobial properties of metals like silver to prevent poisoning by contaminated food and water. Notably, this silver property is still utilized to the point where silver is one of the active ingredients in burn ointments that also contain sulfadiazine for the prevention of infections and rapid healing [119]. Additionally, using the max-

imum antimicrobial properties of silver has encouraged researchers to fabricate nanomaterials of silver for different health problems [120]. Also, an intriguing point is that modern research has suggested that silver ions may even have the capacity of environmental degradation of toxic material including pesticides [121].

Early detection of the biothreat was another countermeasure strategy. Using vessels made of metal alloys, food tasters, and bad smell avoidance were the repertoires of early detection methods in the hands of ancient civilizations [108]. Notably, the fact that poisons can be identified by reacting with some metals is also applicable in modern toxicology and is a basis of the Reinsch test, which was used in forensic toxicology laboratories until recently [122, 123]. However, due to the advancement of microbial and toxic screening techniques, biosensors can be mentioned as alternatives to food testers in terms of ethical issues and other matters [124, 125]. Regarding smell, which was considered in ancient times as one of the early warning signs of biological threats, research is currently being conducted to make use of this biological phenomenon for the benefit of mankind. An intriguing example is using smell to detect some volatile substances and cancer in its early stages [126].

Conclusion

The present study revealed that toxicology and biological terrorism, whether in the form of microbial agents or poisonous substances derived from plants, animals, minerals, or vapors, have been among the means used by ancient civilizations to subjugate others, both in wars and non-war circumstances. Toxicology and bioterrorism have always been considered and researched in ancient times. Menes, pharaoh of Egypt, Attalus III of Pergamon, and Nero, Roman emperor, were among the pioneers in bioterrorism and toxicology research. This fact demonstrates the importance of research in utilizing the traits of biological agents and developing defenses. In conclusion, it is important to note that bioterrorism's underlying principles have been studied since antiquity and are not a recent phenomenon. Additionally, research on countermeasures, prevention, and treatment dates back to antiquity and can be comparable to modern knowledge.

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EE, and HS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials The original contributions presented in the study are included in the article and further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest E. Eslami, H. Siamian, J. Rezaei Orimi, Z. Aghabeiglooei, E. Salimi-Sabour, and M. Amrollahi-Sharifabadi declare that they have no conflict of interest.

Ethical standards The present study was approved by the ethics code IR.MAZUMS.REC.95.1673 in the Medical Ethics Committee of Mazandaran University of Medical Sciences.

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