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The natural history of the concept of antidote

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ABSTRACT

Over the centuries, the development of knowledge about poisons and antidotes depended on their conceptualization, however, a range of poisons and the concept of antidote evolved. With the passing of time, different substances of plant, animal, and mineral origin, moreover, man-made ones, were used deliberatively, accidentally, or unintentionally as poisons. The concept of antidote was changing in line with the progress of medicine and understanding of the mechanism of how poison works. From this perspective, the history of antidotes may be considered as the quintessence of changes within toxicology. Among the theories of antidote, the most interesting is the concept of a universal one, because it has never become obsolete. This review article focuses on the changing conceptualization of antidotes. It contains an analysis of historical toxicological treatises on antidotes and PubMed articles on the same topic.

1. Introduction

The term 'antidote' comes from the Greek word *ἀντίδοτον* (antídoton), derived from *ἀντί* (antí, 'against') and *δίδωμι* (dídōmi, 'I give'). Tradition attributes its invention to Mithridates VI (135–63 BC), the king of Pontus, but this is a simplification [1]. Among the territories he conquered, the most important was Colchis (a region of today's Georgia), providing the Kingdom of Pontus with human resources and raw materials. Its inhabitants were able to produce plant extracts and thicken them into a concentrate called 'the poison' and used in high dilutions as a medicine. Some light is shed on its composition by the myth of the Argonauts' expedition to the land of Aja (identical to Colchis), where an enchantress Medea lived. She produced poisons and medicines from local plants. They still grow in Georgia, such as: autumn crocus (*Colchicum autumnale*), hemlock (*Conium maculatum*), cowbane (*Cicuta vulgaris vel virosa*), belladonna (*Atropa belladonna*), black henbane (*Hyoscyamus niger*) and white veratrum (*Veratrum album*) [2]. In the 1st century AD, Galen (129–200) confirmed that the ingredients of the antidote, which Mithridates VI took in less and less diluted doses to become resistant to poisons, was a preparation mix produced by Medea in Colchis [3].

2. The concept of a universal antidote

The first universal antidote was mithridate, in which after taking it an increasingly strong dose response was induced [4]. In the 1st century AD, its composition was modified by Andromachus the Elder, Nero's physician, who added dozens of new ingredients to mithridate, including viper meat, which was commonly considered as an antidote to snake venom [5]. This is how Theriac Andromachi was made, the first anti-venom antidote, used for people bitten by snakes and other wild animals (Greek *θηριακός*, *thēriakós*, means 'concerning venomous beasts') living in the vast territory of the Roman Empire [6].

Galen's observations of the victims of venomous animals shaped the paradigm of poison, a substance that can cause a deterioration of health or even death when absorbed or introduced into the human body [7]. In the treatise entitled 'De antidotes', he noticed the dual nature of plants. Some of them, such as cowbane and hellebore, were food for animals, but were harmful to humans, thus endangering their lives. Theriac, the 'cleansing fire' produced from cowbane, aconite and black henbane, among others, was a remedy for the most dangerous poisonous plants and animal venoms. Due to the similarities between the violent reaction of the human body to animal venoms and symptoms of the plague, Galen treated contagion victims with theriac. He argued that as poison entered the body through the mouth, the evil entered from the air with the breath, therefore the administration of a universal antidote was justified. Theriac had to be taken constantly to ensure resistance to various diseases [8]. Arab doctors practising in medieval Europe did not bring new content to the knowledge of antidotes, limiting themselves to copying Galen's thoughts, including those about theriac as a means of preventing a plague [9]. Even in the 17th century, diseases caused by poisons and contagions were combined into one category and treated with theriac [10]. Until the mid-18th century, recipes for theriac, and also for mithridate, were in all official dispensatories and

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pharmacopoeias [1,10].

The first lectures on poisons and their effects in the human body were given by Girolamo Mercuriale (1530–1606) at the University of Padua, based on the treatises of Galen, Aetius, Scribonius the Elder, Pliny, Avezoar and Avicenna. The systematizing of knowledge on poisons was such pioneering work, that Mercuriale asked Wojciech Szeliga (in Latin: Albert Scheliga, died 1585), a medicine student from Warsaw, to write down and compile the lectures, and in accordance with the then customs published them under his own name. This is how the textbook 'De venenis et morbis venenosis tractatus locupletissimi' was created in 1584 by Szeliga. He described the effects of poisons patterned on Mercurialis, i.e., in terms of the humoral pathology as systemic diseases caused by poisoning one of the humours, usually blood. The methods of the chemical identification of poisons were not known yet and they were recognized on the basis of a heart rate test. Unlike the plague, the effect of a poison manifested itself in an uneven pulse that gradually weakened until blood circulation finally ceased. Among less characteristic symptoms were vomiting, tremors, hiccups, and abdominal pain. At first, a doctor would remove a poisoned humour by administering emetic, diaphoretic, laxative, and diuretic agents. Additionally, a doctor could recommend mithridate or theriac, viper scorpion, toad or lizard oil, simple medicines with absorbing properties, such as Armenian clay, deer horn (Cornu Cervi) and bezoar, or emerald, topaz and hyacinth, or magic stones to protect against the hidden poison [9].

In the 17th century, poisoning was described from the perspective of iatromechanics. According to Sebastian Śleszkowski (1576–1648), in Latin called Slescovicus, the author of the book entitled 'Incomparabilis thesaurus alexitericus', the characteristic features of poisons were disorganisation and a change in body composition and nerve irritability, often with fatal consequences. He used the criterion of the toxic action strength to classify, one of the strongest which was ethanol. He emphasised that the same pharmaceutical agent can be a medicine, poison or antidote, such examples were: mugwort (*Artemisia*), agaric (Agaricus) or periwinkle (*Vinca pervinca*). However, he was uncritical of medical superstitions. Among effective antidotes, he mentioned lamb's blood, diamond, emerald and a picture of a snake that allegedly gave protection against a viper bite [11].

The problem of poisons and counteracting their harmful effects was also taken up by John Jonston (1603–1675), a Scottish physician who settled in Poland [12]. In the treatise 'Syntagma universae medicinae practicae', he described in detail eight mineral poisons (including copper, considered an antidote by Mercuriale and Szeliga), eight animal poisons (including leeches commonly used to let blood) and thirteen plant poisons, including monkshood (*Aconitum napellus*), henbane (*Hyoscyamus niger*), black hellebore (*Helleborus niger*), overseas strychnine tree (*Strychnos nux vomica*) and mandrake (*Mandragora officinarum*). Almost all poisonous plants have been known since antiquity [8].

In the 18th century, it was discovered that animal venoms reach the brain through the bloodstream. Instead of administering antidotes, it was necessary to limit the spread of the poison by burning or cauterising the wound after the bite, applying ligatures, cupping without scarification, applying cold compresses of diluted hydrochloric acid, amber oil mixed with musk, or scorpion oil with rue, chamomile and Peruvian balm. From then on, theriac became only an additive in camphoric vinegar or vesicants (patches causing irritation) when applied to the puncture wound [13]. William Heberden (1710–1801) contributed to the complete rejection of theriac by proving that behind the traditional name there were medicines produced by pharmacists according to various recipes, having incomparable effects and containing a multitude of ingredients inhibiting each other's biological activity [14].

3. The concepts of a universal poison

For Paracelsus (1493–1541), a Swiss physician, philosopher and alchemist, the concept of a universal antidote was the starting point for the theory of the ubiquity of poisons, including potent poisons [15,16]. During his turbulent life, he found time to travel in search of the roots of European medicine, that is, to the territory of the legendary Colchis. He probably learned the local medical traditions because his famous sentence: 'All things are poison and nothing is without poison, only the dose permits something not to be poison', matched the dual nature of the Colchis concentrate [2]. Paracelsus believed that no substance is devoid of poisonous properties, and some have more of them than others, constituting a potent poison. The goal of medical alchemy should therefore be to experimentally determine the therapeutic and lethal doses of potent substances of plant origin [17].

His follower was Jan Baptist van Helmont (1579–1644), a Flemish physician who also insisted on chemical research into potent plants. Initially, van Helmont was concerned about how to reconcile the omnipresence of poisons with the message of the Book of Genesis that the world is inherently good. He discovered the positive power of poisons during experiments with aconite (*Aconitum napellus*), when he accidentally touched the solution with his tongue and then fell into a numbness combined with clarity of thought. He then stated that thanks to alchemy, all natural poisons, even the toxic mercury minerals, could one day be used in medicine [18].

The research postulates of Paracelsus and van Helmont were only implemented in the second half of the 18th century by Jacob Christian Schäffer (1719–1790), a pastor and dean of the Protestant parish in Regensburg, who published a botany manual for doctors and pharmacists, entitled 'Erleichterte Artzney-Kräuterwissenschaft'. The characteristics of the properties of strongly acting plants included in it inspired Anton von Störck (1731–1803), a professor of medicine at the University of Vienna, to conduct experiments on dogs, and then on himself, healthy volunteers and patients, in order to determine the effects of administering extracts from autumn crocus, hemlock, cowbane, belladonna, black henbane and white veratrum, as well as their therapeutic doses [19]. Based on the research conducted by Störck and other doctors working in Vienna, the dissertation was of great clinical importance because it justified the use of plants considered dangerous to health and life in medicine. Störck recalled that, inter alia, hemlock juice was once an ingredient of many ointments and patches. He proved that small amounts of the root of this plant reduces the pain of cancer patients and causes the regression of neoplastic lesions known as scirrhous carcinoma of the liver, spleen and pancreas. He personally found out that compresses made of hemlock extract obtained by brief boiling in a retort inhibit the progress of gangrene, contribute to the separation of necrotic tissues and eliminate tophi and arthritic nodules. Such compresses were also effective in the treatment of goitre and breast cancer. Störck gave the hemlock extract he made himself to a starving dog to eat, and then he himself took it without experiencing any side effects, which prompted him to increase the dose [20]. For over a year, he gave pills with an increased dose of hemlock extract to healthy people, including children, without noticing any side effects. In another study, he described the results of experiments with pills containing extracts of datura, black henbane and aconite [21].

After Störck's death, his achievements on the border of toxicology and pharmacology were popularised by Joseph Quarin (1733–1814), a professor at the University of Vienna, known for testing the effects of cowbane [22]. Thanks to the reputation of this university, its representatives were appointed chairs of various European universities. For example, Ferdinand Spitznagel (1757–1826) taught pharmacotherapy at the University of Vilnius from 1804 to 1822. He also promoted plant poisons to the role of medicines. He pointed out that small amounts of parts of poisonous plants stimulate the human life force, thus healing people from serious diseases. These parts included: the fruit of the strychnine tree (*Baccae Occuli Indici*), the seeds of Strychnos ignatii (*Ignatia amara – Faba Santi Ignati*), the dried leaves and the root of belladonna (*Herba et Radix Belladonnae*), the dried leaves of datura used in diseases of the nervous system, also known as a hallucinogen and aphrodisiac (*Herba Stramonii*), the dried leaves of aconite (*Herba Aconiti*) once used for skin diseases and chronic rheumatism, the dried leaves of

cowbane (*Herba Cicutae*) administered internally to 'eliminate tumours', the root of hellebore (*Radix Hellebori albi*), the seeds of sabadilla (*Semina Sabadillae*), the seeds of saxifrage (*Semina Saxifragae*) and laurel water (*Aqua Lauro-Cerasi*) [23]. These ingredients were also used in the medical practice of Jędrzej Śniadecki (1768–1838), a Polish doctor who, after studying medicine in Cracow, Padua, Edinburgh, and Vienna, took over the therapeutic clinic of Vilnius University. He treated patients primarily with potent plant preparations, which he administered as a universal antidote in increased doses, until side effects appeared. For example, he gave a woman suffering from polyarthritis a tincture of autumn crocus seeds at a dose of fifty to seventy drops until diarrhoea occurred [24]. He treated chronic gastritis and gastric cancer with black henbane extract. He administered hemlock extract to a woman who had a uterine prolapse due to excessively hard physical work. Moreover, he treated tuberculosis, syphilis, herpes and osteonecrosis with extracts of hemlock, cowbane and periwinkle [25].

4. The concept of a specific antidote

Still in the 19th century, venom remained the archetype of a poison, and toxicology was called the science of venoms and anti-venoms [26]. Belladonna, datura and strychnine [27] extracts were used for the bites of poisonous snakes and rabid dogs [28]. The threat posed by venomous animals on all continents, except Antarctica, prompted scientists to undertake research on the chemical properties and biological activity of venoms. Original research methodology was implemented by Felice Fontana (1730–1805). In 1765, he studied the influence of cobra venom on various species of animals, including leeches and tree-vipers. After a series of ingenious experiments, he proved that the venom of the viper is not a poison to this animal itself. He also showed that viper venom changes the composition of the blood, and thus affects the entire body, particularly the nerve fibres, changing their sensibility. He achieved similar results by experimenting with curare [29].

Subsequent studies of viper venom were only carried out in 1861 at the Smithsonian Institute in Washington. Silas Weir Mitchell investigated the mode in which the venom influenced the metabolism of animals. He used the method of vivisection, torturing many birds, dogs and rabbits for the sake of humanity because the use of chloroform was out of the question. Snakes were supplied by bark pickers from Virginia. In captivity, they did not want to eat but drank, which allowed him to keep them alive and obtain venom. Mitchell tested the effects of the venom on the blood and other tissues of pigeons, and also determined its lethal dose. He demonstrated that snakes were not harmed by venom administered to their stomachs. He proved that the venom penetrated the membranes surrounding the brain, pericardium and peritoneum. However, he was unable to determine how the venom affected plasma and how it damages the coagulating power of the blood [30].

It was no coincidence that snake venom tests were carried out in British India as many snakebite victims died there. Thus, L. A. Wadell, a physician who practised there, raised the question of whether snake venom could kill other snakes. It turned out that it only works on warm-blooded animals. In turn, Joseph Fayrer (1824–1907), the chief surgeon of British India, studied the effects of cobra venom on leukocytes and germinating seeds and a man named Reichert Mitchell determined the effect of rattlesnake venom on the ciliary motion of sperm [31]. Fayrer shared samples of cobra and viper venoms with Charles Darwin, which allowed him to study their effects on insectivorous sundew (*Drosera rotundifolia*) [32]. Despite a lot having been learned about animal venoms, it is still difficult to recognise the species of snake that has bitten and unfortunately misclassification leads to incorrect treatment. The World Health Organization recommends that a monospecific anti-venom should be administered instead of a polyvalent anti-venom [33].

Nevertheless, in the 19th century, toxicological theories and concepts changed slowly. Even in the first half of the century, Joseph Frank (1771–1842), a German professor of the universities in Pavia and Vilnius, reasoned like Galen and combined diseases caused by poisons and contagions into one group. He compared the effects of poisons on the heart and gastrointestinal tract with the symptoms of violent passions and plague, proving the need to differentiate them by giving vomit or food left by patients to hungry dogs. He recommended theriac for the bites of animals including spiders, bees, flies, mosquitoes and toads, although he was aware that only opium was active in it. In other cases of poisoning, it was necessary to remove the poison from the body by provoking vomiting with zinc sulphate or a decoction of the ipecacuanha root, or neutralise it by drinking warm water, oil or melted butter. Frank rejected bloodletting, laxatives and cupping with scarification, and recommended rubbing with spirit vinegar, tobacco smoke enemas, warm baths and vesicants. He described the poisonous properties of potent plants and darnel (*Lolium temulentum*), not knowing that it was a harmless plant. Only the fungus that parasitises it has poisonous properties [34].

Matthieu Orfila (1787–1853), a physician of King Louis XVIII and a pioneer of forensic toxicology, contributed to the end of treatment by a universal antidote. He searched for a chemical compound that could be the specific antidote to the sublimate and replace the egg white used for this purpose [35]. In turn, the aforementioned Frank pointed out that the specific antidotes for lead poisoning are mercury compounds, alum, quinine and camphor. He was also the first to focus on the toxicity of gas fumes in chemical laboratories [34].

In the last century, newly discovered medicines became significant achievements, but their side effects and toxic interactions caused the growing demand for specific antidotes. Other synthetic chemical compounds, such as combat gases, DDT, mercury compounds, non-metallic pesticides, and herbicides, also were toxic. Each case of chemical poisoning had to be treated individually; however, searching for their antidotes was cost productive. In the discovery of new antidotes and explanations of their antidotal activity, chemical theories became crucial. For example, in 1893, Alfred Werner introduced the theory of the ligand-metal complex. In 1945, dimercaprol (BAL) was used successfully to decrease the toxicity of arsenic, mercury, and lead. According to Werner's theory, BAL chelates metal ions into the ligand-metal complex [36].

The theory of two chemical compounds binding to each other to produce a less toxic product explains how hydroxocobalamin works as a specific antidote in cyanide toxicity. Cyanide binds with hydroxocobalamin rather than cytochrome oxidase and forms cyanocobalamin, which is renally excreted [37]. Another example is mercury in which the pathophysiological target is selenium. They bind to each other; hence, supplementation of selenium mitigates toxicity because they bind to each other [38].

The antidotal activity of oximes results from the enhancement of enzyme function, and is another mechanism of detoxification. Oximes are used to reactivate OP-inhibited acetylcholinesterase in organophosphorus pesticides poisoning [39]. Another mechanism is the competitive receptor blockade; an example of this is the use of naloxone in opioids intoxication. One more example of the mechanism of action concerns fomepizole; injected into a vein to counteract the effects of the methanol or ethanol poisoning, it blocks the enzyme that converts methanol to a more toxic metabolite [40].

5. Revival of the concept of a universal antidote

In the 21st century, the concept of a universal antidote is slowly returning. To this role is promoted activated charcoal, chemical reagent, because its aqueous suspension absorbs many medications, for example, vitamin K antagonists, alkaloids, and other chemicals [41]. Another non-specific antidote is sodium bicarbonate, effective in certain pharmacological toxicities, including sodium channel blockers overdose, and in a pulmonary injury after phosgene and chlorine gas exposure. It acts through a few distinct mechanisms, among them its adverse effects are used as antidotal [42].

Table 1
Articles concerning antidotes in the PubMed database in 1951–2020.

Decade	1951–1960	1961–1971	1971–1980	1981–1990	1991–2000	2001–2010	2011–2020
Number of articles	848	3,001	7,454	14,214	17,521	15,025	20,488

Source: the PubMed database, access: 15 March, 2021.

The multitude of toxic chemical compounds in every-day use makes it difficult to complete a kit of life-saving antidotes for emergency rooms. A new concept of a universal antidote is needed, and possibly concerning activity at the molecular level. Such a proposal just exists. There are the molecules capable to sequester oligonucleotides in an independent manner and thus have the potential to counteract the side effects of aptamers, i.e. oligonucleotide-based drugs [43]. However, if the cause of poisoning is not recognized, doctors only need to observe toxidromes to identify the toxins and initiate the appropriate symptomatic treatment [44]. It is like in antiquity, when poisons were identified by symptoms occurring in victims. Powerlessness in the face of the irreversible tendency to chemise everyday life and the economy causes that the direction of toxicology has to change from the study of poisons, intoxication, and antidotes to the science of ensuring the safety of food, medicines, pesticides and other industrially manufactured products [36].

A survey of the PubMed database proves that new antidotes are more and more in demand. Between 1789 and 2020, 78,604 articles on antidotes were published. In 1789–1950, i.e. for 161 years, 344 articles on antidotes were published, whereas in the following 70 years their number increased to 78,260 (see Table 1).

6. Conclusion

The conceptualisation of antidotes resulted from the fear of intentional poisoning and the bites of venomous animals in antiquity. For several centuries, the antidote paradigm was the same as the drug paradigm. As chemistry progressed, the concepts of a specific chemical antidote was assumed, while the achievements of molecular biology encourage the search for antidotes that act at the molecular level. Acute poisoning requiring clinical intervention are often caused by household cleaners, cosmetics, recreational drugs, pesticides, and other chemicals in daily use which are being absorbed intentionally or unintentionally by humans and animals. The evolution of human lifestyles necessitates a reorientation of the future of toxicology which needs to focus more on the prevention of poisoning than antidotes.

Conflict of interest

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