CHAPTER 19

Toxicity and Therapeutics: Antidotes and Treatments for Poisoning

URWA YOUNAS[1], TOOBA MEHAR[1], YASMEEN RASHEED[1], ANEES UR REHMAN[1], AISHA KHATOON[2], ALI AKBAR[1*], MUHAMMAD FAISAL HAYAT[1], AQSA ASLAM[1]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[2]Department of Pathology, University of Agriculture, Faisalabad, Pakistan
[*]Corresponding author: alo0703593@gmail.com

SUMMARY

The chapter provides an in-depth analysis of antidotes and their role in mitigating the effects of various poisons. Antidotes, which are substances that alter the kinetics or receptor interactions of toxins, have been a cornerstone of medical treatments since ancient times. They function to neutralize or eliminate poisons from the body. Acute poisoning, a significant global health issue, can occur intentionally or unintentionally. Antidotes play a crucial role in reducing morbidity and mortality. The chapter highlights the importance of appropriate antidote administration and the role of healthcare professionals in managing poisoning cases. The text details the impact of specific poisons, including cypermethrin, aflatoxins, ochratoxins, uremic toxins, cyanotoxins, and heavy metals, on the human body. Cypermethrin, a widely used pesticide, disrupts nerve cell function, leading to prolonged sodium channel opening and repetitive neural impulses. Aflatoxins and ochratoxins, produced by certain fungi, are potent carcinogens and hepatotoxins, with aflatoxin B1 and ochratoxin A being particularly harmful to the liver and kidneys. The chapter also discusses the accumulation of uremic toxins in chronic kidney disease (CKD), which contributes to cardiovascular damage and inflammation. Cyanotoxins from harmful algal blooms pose risks such as liver damage, gastrointestinal distress, and potential carcinogenic effects. Heavy metals, including lead, mercury, arsenic, cadmium, and chromium, cause severe health issues ranging from acute poisoning to chronic conditions like cancer and neurodevelopmental disorders. Overall, the chapter underscores the complexity of toxic exposures and the critical need for effective antidotal therapies.

INTRODUCTION

Since the start of medicine history, antidotes have been utilized due to their supernatural properties. Antidotes are defined as substances that modify the kinetics of the toxic substance or interfere with its effect at receptor sites. Antidotes work by altering the way of action of harmful drug in the body either by improving its removal or by affecting its mobility. As a result, the antidote can alter the poison action mechanism by changing its receptors. Antidote is used to control kinetics which can enhance the body detoxification process. Both antidotes and antivenoms can precisely target dangerous compounds and are used as crucial tools in the treatment of poisoning (De Garbino et al., 2009).

The intentional, unintentional or homicidal intake of toxic chemicals into the body can cause acute poisoning. Poisoning is a silent weapon because it is utilized without using violence. It is a serious problem everywhere in the globe (Dash et al., 2005). This can act by blocking the poison's ability to enter the body, attaching to it and neutralizing it directly. As a result, counteracting its effects on organs or preventing the conversion of the poison into more harmful metabolites (Salyer, 2007). It is important to emphasize that the antidote predicted benefit must be assessed and balanced against any possible negative effects and toxicity. When antidotes are delivered appropriately, they may minimize morbidity and mortality as demonstrated in paracetamol and digitalis overdose (Wang & Kazzi, 2012).

Furthermore, it is critical that the appropriate antidotes must be given in the appropriate doses and at the appropriate times. Pharmacists are among the multi-health professionals and medical support personnel who must be properly equipped to manage poisoning cases. Mithridate was the first global antidote which caused an ever-stronger dosage response against poison (Taghizadieh et al., 2020). Andromachus the Elder, Nero's physician, altered the recipe of mithridate in the first century AD. He included dozens of additional components such as viper meat which was widely believed to be an antidote to snake venom.

By assisting in the early detection of toxic exposure, the use of antidotes against poison or toxicant can lower poisoning and fatalities. Pharmacists can significantly benefit public

How to Cite: Younas U, T Mehar, Y Rasheed, AU Rehman, A Khatoon, A Akbar, MF Hayat & A Aslam, 2024. Toxicity and therapeutics: Antidotes and treatments for poisoning. In: Zoology: Advancements and Research Trends (Ijaz MU, N Ehsan, M Imran & S Yousaf, eds): FahumSci, Lahore, Pakistan, pp: 148-156. ISBN: 978-627-7745-02-8. https://doi.org/10.61748/Zool.2024/19

health by choosing, storing, and using antidotal medications appropriately.

IMPORTANT POISONS AND THEIR EFFECTS ON BODY

Cypermethrin is a synthetic pyrethroid pesticide that is widely utilized in cereals, cotton, vegetables, fruits and in fruit storage for the aim of insect control (Lin et al., 2011). Humans are indirectly affected by cypermethrin when they eat food contaminated with the toxin. In living organisms, this toxin has the potential to be cytotoxic and genotoxic. Cypermethrin can interfere with the usual process of nerve cell Na channel receptors, which allows Na+ ions to enter the cell. This substance causes the Na+ channel to stay open for up to a second longer than normal. So, Repetitive impulses in sense organs are caused by this change (Abbassy et al., 1983).

Aspergillus (which produces OTs and AFs) and Penicillium (which produces OTs) are the primary producers of ochratoxins (OTs) and aflatoxins (AFs) which are secondary metabolites (Bayman & Baker, 2006). Aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), and aflatoxin G2 (AFG2) are the most important among the more than 20 different types of chemicals found in AFs (Pickova et al., 2021). OTA and AFB1 are the most poisonous and have dangerous effects on humans and animals by ingestion, inhalation, and skin contact (Marin et al., 2013; Kos et al., 2012). There have been several reports worldwide of OTA and AFB1 contamination of a broad variety of agricultural goods, including cereals, legumes, nuts, spices, beers, wines, milk, and meats.

The primary hepatic metabolism of AFB1 results in the production of AFB1-8, 9-exo- and 8,9-endo-epoxides, which bind to DNA and induce toxicity (Marin et al., 2013). AFB1 exposure has been associated to liver toxicity (Caceres et al., 2020), while the target organs of OTA are regarded as the kidney and liver (Tao et al., 2018). The kidney was the organ most susceptible to the toxicity of combined OTA and AFB1 (Huff & Doerr, 1981). It indicated that OTA could generate nephrotoxicity, hepatotoxicity, immunotoxicity, teratogenicity, genotoxicity, and carcinogenicity (Imaoka et al., 2020; Le et al., 2020). AFB1 cause immunological suppression, hepatocellular carcinoma, teratogenicity, endocrine issues, infertility, and malabsorption of nutrients (Liu et al., 2016)

When the kidneys lose the ability to filter dangerous compounds from the bloodstream potentially toxic substances accumulate in the body. As a result, these accumulated compounds are known as uremic retention solutes or uremic toxins depending on whether they are physiologically or biochemically active. The accumulation of these chemicals is harmful to several body systems Liu et al. (2016)

Cardiovascular damage is a major source of concern among toxic consequences even in the early stages of chronic kidney disease (CKD). It dramatically increases morbidity and death. Patients with chronic kidney disease (CKD) have greater angiotensin A levels than those with normal renal function. Angiotensin A is distinguished by the decarbonization of the asparagine molecule in the peptide. More angiotensin variants persist in renal illness patients, contributing to the pathophysiology of vascular dysfunction (Vanholder et al., 2008; Herget et al., 2009).

Accumulation of toxic substances can reduce renal clearance of substances with antioxidant, anti-inflammatory, and vasodilation characteristics, including proinflammatory cytokines, α1-acid glycoprotein, neopterin, and calcitonin. Declining renal function may impact several acute-phase proteins, including myeloperoxidase, fibrinogen, α2-macroglobulin, and CRP, which are associated with inflammation.

Anemia, protein-energy deficit, and increased atherogenesis may all be linked to inflammation in patients with CKD. When it comes to CKD progression in response to both viral and noninfectious kidney damage, inflammation plays a significant role. Elevated levels of inflammatory markers in patients with end-stage renal disease (ESRD) and chronic renal failure indicate a bad prognosis (Aronov et al., 2011; Meyer et al., 2012).

The frequency of cyanotoxin pollution and deadly cyanobacterial blooms in freshwater during the summer months in the United States and many other parts of the world has increased during the last two decades. When vertebrates are exposed to cyanotoxins, they may experience several general health effects, including rhinitis, diarrhea, vomiting, fever, lassitude, paralysis, allergic reactions, gastrointestinal difficulties, organ damage, and cancer promotion (Aronov et al., 2011; Meyer et al., 2012). Cyanotoxin produces the following types of toxins: (a) neurotoxins; (b) hepatotoxins cylindrospermopsin, microcystins, and nodularin; (c) hepatotoxins; (d) cytotoxins; and (e) irritating toxins (Backer et al., 2013). Liver damage is the predominant symptom of microcystin exposure (Fischer et al., 2005).

Microcystis are actively transported by organic anion transporters in the liver, intestines, lungs, and kidneys (Carmichael, 2001). Microcystin treatment caused human liver cells to bleb, fragment, and separate from one another (Batista et al., 2003). They show symptoms as weakness, vomiting, diarrhea, stomach discomfort, and death. After extended exposure to microcystin, mitochondrial DNA loses stability and function (Li et al., 2016). Furthermore, evidence of reproductive harm and tumor promotion linked to endocrine disruption has been revealed (Chen et al., 2012).

Heavy metals have an acute and long-term negative influence on several human organs. Heavy metals' negative effects can cause birth deformities, cancer, vascular damage, nervous system abnormalities, skin lesions, immune system dysfunction, and digestive and kidney malfunctions. Exposure to multiple metals at the same time may have cumulative effects (Costa, 2019; Gazwi et al., 2020).

High levels of heavy metals, particularly lead and mercury, can induce serious adverse effects such as kidney failure, bloody diarrhea, and abdominal pain (Tsai et al., 2017).

However, low-dose exposure may result in neuropsychiatric illnesses such as anxiety and exhaustion, as well as deleterious impacts on children's IQ and intellectual function (Mazumdar et al., 2011). The fact that many metals have been identified as human carcinogens is another important aspect of chronic exposure. Arsenic, cadmium, and chromium are carcinogenic metals that can disrupt DNA synthesis and repair (Clancy et al., 2012; Koedrith et al., 2013).

ABCDE approaches for Poisoning management

Airway patency should be assessed in all cases unless a conscious-oriented patient without signs of upper airway obstruction. In case of altered sensorium or patient with stridor, hoarseness and other signs of upper airway obstruction should always be secured with maneuver such as headtilt-chinlift or may need airway adjuncts. Endotracheal intubation maybe required in these patients for airway protection and patency (Erickson et al., 2007).

If breathing or respiratory efforts are inadequate, besides the endotracheal intubation respiratory support is also required. Endotracheal incubation besides the altered level of consciousness to protect airway is indicated an acute respiratory failure. Supplement oxygen in case of poisoning is an additional indication (Erickson et al., 2007). The patient oxygen saturation SpO2 with standard bedside pulse oximetry can misleading in the poisoning with dyhemoglobinemias (carbon monoxide), where co-oximeter should be used to identify abnormal hemoglobin's and true SpO_2. The target SpO2 is 94-99% for most of the poisoning except in some poisoning where high SpO2 is associated with oxygen-mediated toxicity e.g. chlorine gas. In these patients, the lowest possible SpO2 should be targeted essential to prevent tissue hypoxia and in order to avoid oxygen-mediated toxicity (Erickson et al., 2007).

The patient with poisoning may present with hypotension or hypertension. The continuous monitoring of electrocardiogram along with blood pressure and heart is vital for all these patients. The initial resuscitation must include peripheral venous access using two large bore cannulas with targeted fluid resuscitation and vasopressor or inotropes if required for correction of hypertension. Further, treatment may depend on factors like inciting agents, severity and associated complications (Mokhlesi et al., 2003).

There are simple bedside scores such as Glassglow coma score or alert/verbal/Painful unresponsive (AVPU) score which can be used to access consciousness and to protect airway. However, neither has been validated and found to predict prognosis of poisoned patients (Erickson et al., 2007). Seizure is a common neurological finding along with pupillary abnormalities. The assessment of pupils may help to suspect some poison along with other systemic findings. The coma cocktail traditionally included dextrose, flumazenil, naloxone and thiamine were advocated in unknown poisoning with unconsciousness and coma. This is helpful in prehospital to avoid intubation and to treat common causes of altered level of consciousness. Examine the entire body for hidden injuries, rashes, bites or other lesions. Rashes such as hives can indicate the allergic reaction and other reactions indicate serious infections.

CONSIDERATIONS FOR ACTIVATED CHARCOAL AND GASTRIC LAVAGE

Gastric lavage (GL) is a method of stomach emptying that allows for direct irrigation and removal of unabsorbed material. The patient should be positioned in the head-down, left-lateral decubitus position for GL (Burke, 1972). The size of the GL tube should be as big as the patient can tolerate safely. A fully developed child could fit a 36 F tube with ease. It is recommended to use continuous pulse oximetry while washing newborns. Tap water or 0.9% saline can be used for gastric lavage, with 15 mL/kg cycles until the lavage fluid is clear (Comstock et al., 1981). To prevent fluid or electrolyte problems, the lavage return should be close to the volume of fluid administered. A technique that is now being employed by several researchers is the administration of activated charcoal by the oral gastric tube before to GL, as a result, poisons may be adsorbed to AC and prevented from passing through the pylorus and into the duodenum during the GL process.

Wood, coconut, petroleum, or other organic material is burned to about 900 degrees Celsius using steam and carbon dioxide during the "activation process" to make charcoal. This decreases the size of the particles, eliminates materials that have already been adsorbed, and enhances the surface area of the charcoal. And the net result is huge total adsorptive surface. Data from the American Association of Poison Control Centers indicates that throughout the past eight years, there has been an increase in the usage of activated charcoal (AC) (Litovitz et al., 1991) .In order to stop the majority of medications and poisons from being absorbed, activated charcoal ought to be the cornerstone of poison treatment. If toxins or medications are in dissolved or disassociated form, adsorption is more likely to occur. The overall surface area of AC that can be adsorbed varies according to the product, but most offer about 1000 m2 of surface area per gram. Large surface area products can bind more toxin and making it unlikely to be a limiting issue because of the massive adsorptive surface area of AC (Chung et al., 1982; Graff et al., 1982). The capacity of chemicals to bind to AC varies greatly. Therefore, the phenomena of compounds adhering to AC is not exclusive.

In a recent declaration, the International Association for the Study of Pain (IASP) issued a statement on opioids. The statement is as follows: "During acute painful events and towards the end of life, opioids are essential for the treatment of severe and short-lasting pain." Currently not another oral drug that relieves severe pain quickly and effectively. Despite insufficient evidence supporting their effectiveness, opioids are increasingly being recommended for chronic non-cancer pain (CNCP). Predictive factors of excessive opioid usage and dose include doses of opioids, mental health, and drug addiction. Long term opioid therapy (LtOT) poses major hazards, including tolerance, physical dependence, addiction, and hyperalgesia. According to German guidelines, patients should not be treated with opioids if their chronic pain is the

primary symptom of either a functional condition (fibromyalgia, irritable bowel syndrome) or a mental disorder (somatoform pain disorder), or if their pain is predominantly caused by a headache (Hauser, 2016; Hauser, 2015; Hauser, 2014). According to certain American recommendations, opioids are an option for treating fibromyalgia. Many patients in the USA and, to a lesser extent in Australia receive treatment with opioids, often at excessive doses and without the proper precautions or indications (Hauser, 2017). The USA's opioid epidemic is illustrated by doctors' aggressive prescribing methods, widespread opioid abuse, and rising rates of overdose deaths from both prescription and illicit opioids (Clark, 2017). It is now evident that the primary cause of this phenomenon and the epidemic of opioid addiction is aggressive prescription practices (Lamvu, 2018). Nonetheless, there are notable regional variations in the rise of opioid prescriptions (Hauser 2016) as described in Table 1.

Table 1. Waves of opioid epidemic

Names	Description	References
Prescription opioids	From the late 1990s, when the first wave of the opioid epidemic began, until 2011, the number of opioid overdose deaths attributable to prescription opioids increased steadily. However, since 2011, it has significantly dropped (43%).	Paulozzi et al., 2011
Heroin	During this wave, the number of overdose deaths involving heroin increased; in 2010, 3036 deaths were linked to the drug; by 2016, that number upsurged to 15,469 deaths. Overdose deaths related to heroin have decreased slightly since 2016.	Rudd et al., 2014
Fentanyl and its analogs	Moreover, the fastest rise in opioid overdose deaths has occurred during the third wave. Since 2013, the number of opioid overdose deaths attributed to high-potency opioids, such as fentanyl and fentanyl analogs (F/FAs) has increased by more than tenfold.	Hedegaard et al., 2020

USE OF NALOXONE AS AN ANTIDOTE

The opioid receptor antagonists such as levallorphan and nalorphine were employed in the 1950s to treat opioid-induced respiratory depression; however, these medications alone have the potential to produce respiratory depression (Thomas & Tenney, 1955; Foldes et al., 1969).

Case studies of naloxone

For more than 50 years, naloxone has been recognized to be effective in reversing opioid-induced respiratory depression. A randomized experiment involving 172 patients suspected of having overdosed on opioids revealed that 72.3 and 77.5% of patients showed improvement within 10 minutes after receiving pre-hospital intranasal (IN) and intramuscular (IM) naloxone (Kerr et al., 2009). According to one study, 66% of patients who got naloxone before going to the hospital had a Glasgow Coma Score of more than 14, and these patients were also less likely to need further medical attention (Fidacaro et al., 2019).

CYANIDE POISONING

Cyanide is a toxin with several uses, including industrial and occupational hazards, poison in fire smoke, and an agent of suicide, murder, and terrorism. It is a gas, liquid, or solid that can be harmful to humans by a variety of methods, such as ingestion, inhalation, parenteral administration, or contact with the skin or conjunctiva (Kerns et al., 2006). Cyanide might have multiple toxic mechanisms. The most well-known and likely most significant harmful action of cyanide is the inability of the cell to use oxygen results in chemical asphyxiation**.** Mitochondrial cytochrome oxidase is an essential enzyme in the electron transport chain that produces aerobic energy for cellular function. Cyanide inhibits its oxidative function, preventing cells from utilizing oxygen (Kerns et al., 2006). Oxygen is often converted to water by cytochrome oxidase at the end of the electron transport chain. Large amounts of adenosine triphosphate (ATP) are produced by this oxidative metabolism through the electron transport chain from reducing equivalents (such as nicotine adenine dinucleotide, or NADH), which are obtained from intermediate metabolism. ATP is the primary source of cellular energy (Megarbane et al., 2003).

Because every tissue's cell depends on oxygen and ATP, acute cyanide poisoning affects every function of the body. Most susceptible organs are the heart and brain, which depend on a substantial, steady supply of ATP and oxygen to function normally (Kerns et al., 2006). Sodium thiosulfate removes cyanide from the blood through the action of the enzyme rhodanese (Hall & Rumack, 1986). Sodium thiosulfate has limited distribution into the brain, an organ highly susceptible to the effects of cyanide-induced histotoxic anoxia, and has limited penetration into the mitochondria, where the endogenous cyanide-detoxifying enzyme rhodanese is located (Baskin et al., 1992).

The effectiveness of hydroxocobalamin as a cyanide antidote was first demonstrated in 1952 (Mushett et al., 1952). The mechanism of action is direct binding to cyanide to form nontoxic cyanocobalamin (vitamin B12) that is excreted in the urine (Bowden & Krenzelok, 1997). Hydroxocobalamin was added to human fibroblasts cultured in a cyanide solution in an in vitro study. This led to a 75% reduction in intracellular cyanide concentrations and the formation of intracellular cyanocobalamin, suggesting that hydroxocobalamin can act intracellularly and penetrates cells (Astier & Baud, 1996).

TOXIC EFFECTS OF ORGANOPHOSPHATE AND NERVE AGENTS

Organophosphates (OPs) and nerve agents are highly toxic chemical compounds that primarily exert their effects by inhibiting acetylcholinesterase (AChE) a crucial enzyme involved in neurotransmission. Organophosphates are commonly used as pesticides while nerve agents such as sarin and VX are potent chemical weapons. Organophosphates and nerve agents exhibit highly toxic effects primarily targeting the

nervous system. These compounds often used in pesticides and chemical warfare agents inhibit acetylcholinesterase, an enzyme crucial for neurotransmitter regulation (Mukherjee & Gupta, 2020). Acute exposure results in an accumulation of acetylcholine leading to overstimulation of the nervous system. Symptoms include muscle twitching, convulsions, respiratory distress and, in severe cases respiratory failure and death. Long-term exposure to organophosphates has been associated with neurological disorders. Nerve agents, a subclass of organophosphates, such as sarin and VX are potent and rapidly acting causing rapid onset of symptoms and posing a significant threat in warfare scenarios (Kumar, 2016).

Atropine and pralidoxime are crucial antidotes used in the treatment of poisonings caused by organophosphates and nerve agents. Atropine, the primary anticholinergic drug used in the treatment of organophosphate and nerve agent poisoning by blocking the overstimulating effects of acetylcholine at muscarinic sites. Atropine is effective in reversing central apnea, relieving bronchoconstriction and reducing secretions addressing peripheral muscarinic symptoms and arresting early convulsions if administered promptly (Reddy, 2023).

Pralidoxime, a vital antidote in the treatment of organophosphate and nerve agent poisonings functions as an acetylcholinesterase reactivator. Its mechanism involves the reactivation of the inhibited acetylcholinesterase enzyme which has been rendered inactive by exposure to toxic agents. By restoring the activity of acetylcholinesterase pralidoxime enables the breakdown of excess acetylcholine, counteracting the overstimulation of cholinergic receptors (Sungur & Guven, 2001). When used in conjunction with atropine, which addresses muscarinic symptoms pralidoxime contributes to a comprehensive treatment approach for organophosphate and nerve agent poisonings (Worek et al., 2002).

HEAVY METAL POISONINGS AND THEIR HEALTH EFFECTS

Mercury (Hg) is a naturally occurring metallic element liquid at room temperature symbolized by Hg originating from the Greek word "hydrargyrum," meaning liquid silver (Tangahu et al., 2011). As a persistent, bio-accumulative and toxic pollutant mercury exists in metallic, inorganic and organic states released into the atmosphere via either natural occurring sources like volcanic eruptions or man-made sources like mining and fossil fuel extraction. Anthropogenic activities have significantly elevated atmospheric mercury levels nearly tripling its presence contributing to environmental concerns (Vianna et al., 2019; Rice et al., 2014). Mercury poisoning presents significant health risks with diverse consequences. Mercury exposure, whether acute or chronic can lead to diverse health impacts, including lung damage, respiratory distress and adverse effects on the cardiovascular and renal systems such as hypertension and kidney damage. Exposure to mercury often through contaminated fish consumption or industrial processes can lead to detrimental effects on the nervous system resulting in symptoms such as tremors, memory loss and cognitive impairments (Zhang et al., 2011). Methylmercury, a highly toxic form of mercury accumulates in aquatic life and can magnify through the food chain posing a serious risk to those consuming contaminated fish. It can also affect the gastrointestinal system leading to symptoms such as nausea, vomiting and abdominal pain (Alina et al., 2012).

Lead is a bright silvery metal slightly bluish in a dry atmosphere. Exposure to lead typically through contaminated air, water or products like lead-based paint can result in a range of adverse health effects. It also disrupts a wide range of biological functions including the heart, bones, intestines, kidneys, reproductive and neurological systems. Once absorbed into the bloodstream lead accumulates in bones and soft tissues yielding long-term health implications (Kumar et al., 2020). Lead poisoning is a serious health concern with widespread implications for human well-being. Children are particularly vulnerable and even low levels of lead exposure can impair cognitive development leading to learning disabilities and behavioral problems. In adults lead poisoning can cause hypertension, kidney damage and fertility issues. Chronic exposure to lead can have severe consequences impacting multiple organ systems (Martin & Griswold, 2009).

CHELATING AGENTS LIKE EDTA AND DIMERCAPROL USED FOR HEAVY METAL DETOXIFICATION

Chelating agents are substances that have several electron-donating groups in them which allows them to combine with metal ions to form solid coordination complexes. Chelating agents such as EDTA and dimercaprol play crucial roles in heavy metal detoxification by forming stable complexes with toxic metals. EDTA is a synthetic compound known for its ability to bind with a variety of metal ions preventing their harmful effects in the body. It forms water-soluble complexes with metals like lead, mercury and cadmium facilitating their excretion from the body (Risher & Amler, 2005). Dimercaprol, also known as BAL (British Anti-Lewisite) is effective against arsenic, mercury and lead poisoning. It contains thiol groups that form complexes with metal ions leading to the formation of compounds that are easily eliminated through urine.

Venomous snake bites and their effects

Snakes are distributed throughout the earth's surface with some exceptions such as the Arctic, Antarctic and various small islands. The mortality associated with snake bites is much greater than that of other neglected tropical diseases (Williams et al., 2010). Venomous snakes are widely distributed in almost all countries between latitudes 50°N and 50°S. Venomous snake bites can have diverse and potentially life-threatening effects on humans. The severity of symptoms depends on factors such as the snake species, the amount of venom injected and the victim's health. Common symptoms include intense pain, swelling and bruising at the bite site accompanied by nausea, dizziness and difficulty breathing. Some venomous snakes, like cobras and vipers can cause systemic effects such as organ failure, paralysis and even death if not treated promptly (Sasaki et al., 2009).

Venomous spider bites and their effects

The Araneae order of arachnids includes the huge group of creatures known as spiders. There are currently about 40,000 known species of spiders across the entire world. All spiders with the exception of two tiny arachnid families have poison glands and secrete their contents into venom sacs located close to their chelicerae (Hickman et al., 2006). Other spiders typically become violent when they are frightened, imprisoned or agitated. The degree of response is dependent upon several variables, including the quantity, site and duration of the bite in addition to the victim's age and overall health. Various peptides and chemicals that impact glutamate and acetylcholine receptors as well as sodium, calcium and potassium channels in neurons are found in spider venom. The black widow and brown recluse are extremely poisonous (Fusto et al., 2020).

Venomous spider bites can lead to a range of effects varying from mild discomfort to severe medical complications. Species such as the black widow and brown recluse are notorious for their potent venom. Black widow bites typically result in localized pain, muscle cramps and nausea with severe cases causing difficulty in breathing and elevated blood pressure. Brown recluse bites can lead to necrotic skin lesions and in rare systemic circumstances symptoms such as fever and organ failure (Gopalakrishnakone et al., 2016).

ANTIVENOM AND SPECIFIC TREATMENTS FOR ENVENOMATION

Envenomation is the process of being injected with venom typically through a bite or sting leading to toxic effects from venomous animals. The treatment for snake and spider bites involves immediate supportive measures like elastic bandages, limb immobilization and prompt hospital transportation with analgesics, opioids, muscle relaxants and injectable calcium and anti-venom administered especially in specific populations. Pre-treatment with corticosteroids or epinephrine may mitigate hypersensitivity reactions but individualized usage is crucial. Antivenom, also known as antivenin, derived from snake venom-immunized animal serum has been crucial in reducing snakebite mortality for over a century (Sakai, 2013).

THE DANGERS OF CARBON MONOXIDE POISONING

Carbon monoxide is one of most common contaminants of our environment. In fact, carbon monoxide (CO) contributes almost half of all dangerous poisonings that are reported worldwide each year. CO poisoning causes a serious threat to human health due to its colorless, odorless nature. When inhaled carbon monoxide displaces oxygen in the bloodstream leading to oxygen deprivation in vital organs such as the brain and heart. Symptoms range from mild such as headaches and dizziness to severe including confusion, unconsciousness and death. Pulmonary edema is rare in carbon monoxide (CO) poisoning unless accompanied by smoke inhalation; additional potential consequences encompass hepatocellular damage, pancreatitis, kidney damage and skeletal muscle necrosis (Bleecker, 2015).

Carbon monoxide (CO) poisoning induces neuropathological consequences characterized by neuronal death in diverse brain areas that may include substantia nigra, globus pallidus and cortex. The most severe consequence is the emergence of delayed neurological condition also referred as delayed neuropsychiatric syndrome that affect 3–40% of patients within 2–28 days post-poisoning. This delayed impact manifests as cognitive difficulties such as poor judgement, inability to focus, memory loss and a general lack of awareness of obvious neurological deficiencies (Hampson et al., 2012).

HYPERBARIC OXYGEN THERAPY AS A TREATMENT

Hyperbaric oxygen therapy (HBOT) is a treatment approach utilized in carbon monoxide (CO) poisoning to mitigate the toxic effects of this harmful gas. The therapy involves breathing pure oxygen in a pressurized room or chamber enabling the body to receive higher levels of oxygen under normal conditions. In the context of CO poisoning HBOT serves to rapidly eliminate carbon monoxide from the bloodstream facilitating the replacement of carboxyhemoglobin with oxygen-bound hemoglobin. This accelerated removal helps to avoid long-term neurological damage and reduces the risk of delayed complications. By promoting oxygen delivery to tissues and organs HBOT aids in reversing the hypoxic effects of CO poisoning (Huang et al., 2017).

IMPACT OF TOXIC MUSHROOMS ON HEALTH

Toxic mushrooms pose a severe threat to human health as many varieties contain potent toxins that can lead to a range of adverse effects from gastrointestinal distress to organ failure and death. Ingesting poisonous mushrooms such as the notorious Amanita species can result in symptoms like nausea, vomiting, abdominal pain, and diarrhea within hours. Certain toxic mushrooms contain compounds that can disrupt cellular function leading to organ failure and in extreme cases fatalities (Govorushko et al., 2019), details of which have been presented in Table 2.

SPECIFIC ANTIDOTES AND TREATMENTS FOR MUSHROOM POISONING

The specific antidotes and treatments for mushroom poisoning vary depending on the type of toxic mushroom ingested. However, a general method contains quick medical attention induced vomiting or gastric lavage if administered within the first hour of ingestion and the management of activated charcoal to limit absorption. In cases of known mushroom toxicity identifying the specific mushroom ingested is crucial for targeted treatment. Antidotes include binders, such as activated charcoal, phytomedicines (*Moringa oleifera* and curcumin) corticosteroids and vasodilators. Some mushrooms may require specific antidotes, such as atropine for certain types of muscarinic poisoning or silybin for amatoxin-containing mushrooms (Diaz, 2005).

Table 2. Poisonous Mushrooms: Species, Toxins and Affected Organs

Poisonous mushrooms	Mushroom species	Toxin	Affected organ	References
Death cap	Amanita phalloides	Amatin/Phalloidin	Liver and upper gastrointestinal	Garcia et al., 2015
	Amanita virosa	Amanitns	Liver	Tavassoli et al., 2019
	Amanita verna	Amanitins	Liver	Wu et al., 2021
False Morel	Gyromitra esculenta	Mono Methyl Hydrazine (MMH)	PLP	Arłukowicz-Grabowska et al., 2019
Sorrel web cap	Cortinariusorellanus tries	Orellanine	Kidney	Holmdahl, 2001
Inocybe or clitocybe	Inocybeerupescens	Muscarine	CNS	Dehariya et al., 2011
	Clitocyberivulosa	Muscarine	CNS	Dehariya et al., 2011
Fly Agaric	Amanita muscaria	Muscimol	CNS	Satora et al., 2005

RECENT ADVANCEMENTS IN ANTIDOTE DEVELOPMENT

Humans have long been captivated by poisons. Although poisons were once thought to be harmful or dangerous compounds, they are now used in cosmetics and medicine under strict regulation. At the same time, antidotes have emerged as essential reversal agents to neutralize a poison's effects and are now employed to reverse a poison's beneficial effects after consumption (Yin et al., 2021). In parallel, several antidotes have been found over time (such as mithridate, an antidote from antiquity with a complicated formula), and the majority of deadly poisons that are still in use today have an antidote. These include cyanide (antidote sodium nitrite or thiosulfate), opioids (antidote naloxone), lead (antidote the succimer chelator), heparin (antidote protamine sulfate) and the three drugs methotrexate, trimethoprim, and pyrimethamine that share the same antidote: leucovorin. To counteract the effects of venoms, modern methods involve the development of certain antibodies (Parreno et al., 2018). The majority of antidotes for venoms are tiny molecules, with the exception of antibodies. Recently, a novel class of supramolecular antidotes has emerged as a result of a breakthrough in the field of antidotes. Moreover, other compounds, such as cyclodextrins, pillararenes, cucurbiturils, and derivatives of acyclic cucurbituril, have the potential to be employed as antidotes in poisoning therapy. Meanwhile, scientists studying supramolecular chemistry have created a wide range of different host molecules with different topologies. Macrocycles and related host molecules are among the many supramolecular systems that have been extensively researched for biomedical applications because of their consistent physical and chemical characteristics, high biocompatibility, and batch-to-batch consistency (Zhou et al., 2017).

With the rapid growth of the number of reported host molecules (Yu et al., 2018 ; Yang et al., 2020) numerous macrocycles have demonstrated intriguing binding characteristics to bioactive substances, and several of them have good inhibitory and reversal actions against harmful substances and medications with unfavorable side effects, though the development of host compounds as clinically approved antidotes has yielded only one commercial success (Wang et al., 2009; Ma et al., 2012; Yin et al., 2018).

CONCLUSION

Antidotes are substances that neutralize the effects of a poison or toxin. Antidotes work by stopping the toxin from being absorbed, binding and neutralizing the poison, counteracting its end-organ impact, or inhibiting the toxin's conversion to more hazardous metabolites. Antidote administration works by reducing the level of free or active toxin, the toxin's end-organ effects through methods such as competitive inhibition, receptor blocking, or direct toxin antagonism. It can play its role against poison when given in an adequate dose and at an appropriate time. The Airway, Breathing, Circulation, Decontamination, and Exposure (ABCDE) strategy is a generally acknowledged, for assessing and managing critically sick patients of all age groups**.** Antidotes have been used successfully in the field of medicine for the treatment of poison or alter the effects of poison especially in emergency situation by rapid recognition of poison and its action mechanism. By altering the action of poison, antidote significantly reduced the rates of mortality and morbidity even in emergency situation. There are numbers of antidotes which are used as treatment of poisoning such as atropine and pralidoxime used against organophosphate poisoning. Several advanced techniques like use of antivenom and hyperbaric oxygen therapy, supramolecular antidotes and macrocycles systems are using in order to be reduced poisonous effects. The development of antidotes and its related techniques ae providing a good role in medicine field and gain commercial success.

REFERENCES

Abbassy MA, ME Eldefrawi & AT Eldefrawi, 1983. Pyrethroid action on the nicotinic acetylcholine receptor/channel. Pesticide Biochemistry and Physiology 19:299-308. https://doi.org/10.1016/0048-3575(83)90058-5

Alina M, A Azrina, AS Mohd Yunus et al., 2012. Heavy metals (mercury, arsenic, cadmium, plumbum) in selected marine fish and shellfish along the Straits of Malacca. International Food Research Journal 19:135-40.

Arłukowicz-Grabowska M, M Wójcicki & J Raszeja-Wyszomirska, 2019. Acute liver injury, acute liver failure and acute on chronic liver failure: A clinical spectrum of poisoning due to *Gyromitra esculenta*. Annals of Hepatology 18:514-6. https://doi.org/10.1016/j.aohep.2018.11.009

Aronov PA, FJG Luo, NS Plummer et al., 2011. Colonic contribution to uremic solutes. Journal of the American Society of Nephrology 22:1769-76. https://doi.org/10.1681/ASN.2010121220

Astier A & FJ Baud, 1996. Complexation of intracellular cyanide by hydroxocobalamin using a human cellular model. Human and Experimental Toxicology 15:19-25. https://doi.org/10.1177/096032719601500104

Backer LC, JH landsberg, M Miller et al., 2013.Canine cyanotoxin poisoning in the United States (1920s_2012). Review of suspected and conformed

cases from three data sources. Toxins 5:1597-628. https://doi.org/10.3390/toxins5091597
Baskin SI, AM Horowitz & EW Nealley, 1992. The antidotal action of sodium nitrite and sodium thiosulfate against cyanide poisoning. The Journal of Clinical Pharmacology 32:368-75. https://doi.org/10.1002/j.1552-4604.1992.tb03849.x
Batista T, G de Sousa, JS Suput et al., 2003. Microcystin-LR causes the collapse of actin, filaments in primary human hepatocytes. Aquatic Toxicology 65:85-91. https://doi.org/10.1016/S0166-445X(03)00108-5
Bayman P & JL Baker, 2006. Ochratoxins: A Global Perspective. Mycopathologia 162:215-23. https://doi.org/10.1007/s11046-006-0055-4
Bleecker ML, 2015. Carbon monoxide intoxication. Handbook of Clinical Neurology 131:191-203. https://doi.org/10.1016/B978-0-444-62627-1.00024-X
Bowden CA & EP Krenzelok, 1997. Clinical applications of commonly used contemporary antidotes: A US perspective. Drug Safety 16:9-47. https://doi.org/10.2165/00002018-199716010-00002
Burke M, 1972. Gastric lavage and emesis in the treatment of ingested poisons: A review and clinical study of lavage in 10 adults. Resuscitation 1:91-105. https://doi.org/10.1016/0300-9572(72)90013-5
Caceres I, A Al Khoury, R El Khoury et al., 2020. Aflatoxin Biosynthesis and Genetic Regulation: A Review. Toxins 12:150. https://doi.org/10.3390/toxins12030150
Carmichael W, 2001. Health efforts of toxin producing cyanobacteria: "The cyanoHABs". Human and ecological risk assessment 7:1393-407. https://doi.org/10.1080/20018091095087
Chen W, Y jia, E Li et al., 2012. Soil based treatments of mechanically collected cyanobacterial blooms from lake Taihu: Efficiencies and potential risks. Environmental Science and Tecbnology 46:13370-376. https://doi.org/10.1021/es3027902
Chung DC, JE Murphy & TW Taylor, 1982. In vivo comparison of the adsorption capacity of superactivated charcoal and fructose with activated charcoal and fructose. Clinical Toxicology 19:219-24. https://doi.org/10.3109/15563658208990384
Clancy H, AH Sun, L Passantino et al., 2012. Gene expression changes in human lung cells exposed to arsenic, chromium, nickel or vanadium indicate the first steps in cancer. Metallomics 4:784-93. https://doi.org/10.1039/c2mt20074k
Clark DJ & MA Schumacher, 2017. America's opioid epidemic: supply and demand considerations. Anesthesia and Analgesia 125: 1667-74. https://doi.org/10.1213/ANE.0000000000002388
Comstock EG, TP Faulkner, EV Boisaubin et al., 1981. Studies on the efficacy of gastric lavage as practiced in a large metropolitan hospital. Clinical Toxicology 18:581. https://doi.org/10.3109/15563658108990285
Costa M, 2019. Review of arsenic toxicity, speciation and polyadenylation of canonical histones. Toxicology and Applied Pharmacology. 375:1-4. https://doi.org/10.1016/j.taap.2019.05.006
Dash SK, AS Raju, MK Mohant et al., 2005. Sociodemographic profile poisoning cases. Journal of Indian Academy of Forensic Medicine 27:133-8.
De Garbino, JP Haines, JA Jacobsen et al., 1997. Evaluation of antidotes: Activities of the international programme on chemical safety. Journal of toxicology 35:333-43. https://doi.org/10.3109/15563659709043364
Dehariya P, A Kushwaha & K Dehariya, 2011. Effect of Poisnous Mushrooms on Humankind. An Overview of Toxicants.
Diaz JH, 2005. Syndromic diagnosis and management of confirmed mushroom poisonings. Critical Care Medicine 33:427-36. https://doi.org/10.1097/01.CCM.0000153531.69448.49
Erickson TB, TM Thompson & JJ Lu, 2007. The approach to the patient with an unknown overdose. Emergency Medicine Clinics of North America 25:249-81. https://doi.org/10.1016/j.emc.2007.02.004
Fidacaro GA, P Patel, G Carroll et al., 2019. Do patients require emergency department interventions after prehospital naloxone? Journal of Addiction Medicine 14:224-30. https://doi.org/10.1097/ADM.0000000000000563
Fisher WJ, S Altheimer, V cattori et al., 2005. Organic anion transporting polypeptides expressed in liver and brain mediate uptake of microcystin. Toxicology and Applied Pharmacology 203:257-63. https://doi.org/10.1016/j.taap.2004.08.012
Foldes F, FD Duncalf & S Kuwabara, 1969. The respiratory, circulatory, and narcotic antagonistic effects of nalorphine, levallorphan, and naloxone in anaesthetized subjects. Canadian Anaesthetists' Society Journal 16:151-61. https://doi.org/10.1007/BF03005795
Fusto G, L Bennardo & ED Duca, 2020. Spider bites of medical significance in the Mediterranean area: Misdiagnosis, clinical features and management. Journal of Venomous Animals and Toxins Including Tropical Diseases 26. https://doi.org/10.1590/1678-9199-jvatitd-2019-0100
Garcia J, VM Costa & A Carvalho, 2015. Amanita phalloides poisoning: Mechanisms of toxicity and treatment. Food and Chemical Toxicology 86:41-55. https://doi.org/10.1016/j.fct.2015.09.008
Gazwi HS, EE Yassien, HM Hassan et al., 2020. Mitigation of lead neurotoxicity by the ethanolic extract of Laurus leaf in rats. Ecotoxicology and Environmental Safety 192:110297. https://doi.org/10.1016/j.ecoenv.2020.110297
Gopalakrishnakone P, G Corzo, ME De Lima et al., 2016. Spider venoms. Springer, Netherlands. https://doi.org/10.1007/978-94-007-6389-0
Govorushko S, R Rezaee, J Dumanov et al., 2019. Poisoning associated with the use of mushrooms: A review of the global pattern and main characteristics. Food and Chemical Toxicology 128:267-79. https://doi.org/10.1016/j.fct.2019.04.016
Graff WBV, L Thompson, I Sunshine et al., 1982. Absorbent and cathartic inhibition of enteral drug absorption. Journel of Pharmacology and Experimental Therapeutics 221:656-63.
Hall AH & BH Rumack, 1986. Clinical toxicology of cyanide. Annals of Emergency Medicine 15:1067-74. https://doi.org/10.1016/S0196-0644(86)80131-7
Hampson NB, CA Piantadosi, SR Thom et al., 2012. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. American Journal of Respiratory and Critical Care Medicine 186:1095-1101. https://doi.org/10.1164/rccm.201207-1284CI
Hauser W, F Bock, P Engeser et al., 2015. Recommendations of the updated LONTS guidelines: Long-term opioid therapy for chronic noncancer pain. Der Schmerz 29:109-30. https://doi.org/10.1007/s00482-015-0009-1
Hauser W, F Petzke, L Radbruch et al., 2016. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: a transatlantic perspective. Pain Management 6:249-63. https://doi.org/10.2217/pmt.16.5
Hauser W, F Wolfe, P Henningsen et al., 2014. Untying chronic pain: Prevalence and societal burden of chronic pain stages in the general population-a cross-sectional survey. BMC Public Health 14:1-8. https://doi.org/10.1186/1471-2458-14-352
Hauser W, S Schug & AD Furlan, 2017. The opioid epidemic and national guidelines for opioid therapy for chronic noncancer pain: A perspective from different continents. Pain Reports 2:599. https://doi.org/10.1097/PR9.0000000000000599
Hedegaard H, AM Minino, M Warner, 2020. Drug overdose deaths in the United States, 1999-2018. NCHS Data Brief No. 394, USA.
Herget-Rosenthal S, G Glorieux, J Jankowski et al., 2009. Uremic toxins in acute kidney injury. Seminars in Dialysis 22:445-8. https://doi.org/10.1111/j.1525-139X.2009.00598.x
Hickman CP, LS Roberts, A Larson et al., 2006. Integrated principles of zoology (Vol. 15). McGraw-Hill, New York USA.
Holmdahl J, 2001. Mushroom poisoning: Cortinarius speciosissimus nephrotoxicity. PhD Thesis: University of Göteborg, Sweden.
Huang CC, YC Chen, HJ Lin et al., 2017. Hyperbaric oxygen therapy is associated with lower short-and long-term mortality in patients with carbon monoxide poisoning. Chest 152:943-53. https://doi.org/10.1016/j.chest.2017.03.049
Huff WE & JA Doerr, 1981. Synergism between aflatoxin and ochratoxin a in broiler chickens. Poultry Science Journal 60:550-5. https://doi.org/10.3382/ps.0600550
Imaoka T, J Yang, L Wang et al., 2020. Microphysiological system modeling of ochratoxin a-associated nephrotoxicity. Toxicology 444:152-582. https://doi.org/10.1016/j.tox.2020.152582
Kerns WP & MA Kirk, 2006. Cyanide and hydrogen sulfide. In: Goldfrank's Toxicologic Emergencies (Flomenbaum NE, LR Goldfrank, RS Hoffman et al., eds): McGraw-Hill, New York< USA, pp: 1498-514.
Kerr D, AM Kelly, P Dietze et al., 2009. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction 104:2067-74. https://doi.org/10.1111/j.1360-0443.2009.02724.x
Koedrith P, H Kim, JI Weon et al., 2013. Toxicogenomic approaches for understanding molecular mechanisms of heavy metal mutagenicity and carcinogenicity. International Journel of Hygiene and Environmental Health 216:587-98. https://doi.org/10.1016/j.ijheh.2013.02.010
Kos J, E Janić Hajnal, A Malachova et al., 2012. Mycotoxins in maize harvested in republic of Serbia in the period 2012-2015. Part 1: Regulated Mycotoxins and Its Derivatives. Food chemistry 312:126034. https://doi.org/10.1016/j.foodchem.2019.126034
Kumar A, CP Chaturvedi & AK Shabnam, 2020. Lead toxicity: Health hazards, influence on food chain, and sustainable remediation approaches. International journal of Environmental Research and Public Health 17:2179. https://doi.org/10.3390/ijerph17072179

Kumar S, G Kaushik & JF Villarreal-Chiu, 2016. Scenario of organophosphate pollution and toxicity in India: A review. Environmental Science and Pollution Research 23:9480-91. https://doi.org/10.1007/s11356-016-6294-0

Lamvu G, J Feranec & E Blanton, 2018. Perioperative pain management: An update for obstetrician-gynecologists. American Journal of Obstetrics and Gynecology 218:193-9. https://doi.org/10.1016/j.ajog.2017.06.021

Le G, X Yuan, L Hou et al., 2020. Ochratoxin a induces glomerular injury through activating the Erk/Nf-Kb signaling pathway. Food and Chemical Toxicology 143:111-516. https://doi.org/10.1016/j.fct.2020.111516

Li X, L Xu, W Zhou et al., 2016. Chronic exposure to microcystin-LR affected mitochondrial DNA maintenance and caused pathological changes of lung tissue in mise. Environmental Pollution 210:48-56. https://doi.org/10.1016/j.envpol.2015.12.001

Lin Q, S Chen, MT Hu et al., 2011. Biodegradation of Cypermethrin by a newly isolated actinomycetes HU-S-01 from wastewater sludge. International Journal of Environmental Science and Technology 8:45-56. https://doi.org/10.1007/BF03326194

Litovitz TL, KM Bailey, BF Schmitz et al., 1991. Annual report of the american association of poison control centers national data collection system. The American Journal of Emergency Medicine 9:461 -509. https://doi.org/10.1016/0735-6757(91)90216-7

Liu T, Ma Q, L Zhao et al., 2016. Protective effects of sporoderm-broken spores of *Ganderma lucidum* on growth performance, antioxidant capacity and immune function of broiler chickens exposed to low level of aflatoxin B1. Toxins 8:278. https://doi.org/10.3390/toxins8100278

Ma D, B Zhang, U Hoffmann et al., 2012. Acyclic Cucurbituril-Type molecular containers bind neuromuscular blocking agents in vitro and reverse neuromuscular block in vivo. Angewandte Chemie International Edition 51: 11358-62. https://doi.org/10.1002/anie.201206031

Marin S, AJ Ramos & G Cano-Sancho et al., 2013. Mycotoxins: occurrence, toxicology, and exposure assessment. Food and Chemical Toxicology 60:218-37. https://doi.org/10.1016/j.fct.2013.07.047

Martin S & W Griswold, 2009. Human health effects of heavy metals. Environmental Science and Technology Briefs for Citizens 15.

Mazumdar M, DC Bellinger, M Gregas et al., 2011. Low-level environmental lead exposure in childhood and adult intellectual function: a follow-up study. Environmental Health 10:24. https://doi.org/10.1186/1476-069X-10-24

Mégarbane B, A Delahaye, D Goldgran-Tolédano et al., 2003. Antidotal treatment of cyanide poisoning. Journal of the Chinese Medical Association 66:193-203.

Mégarbane B, A Delahaye, D Goldgran-Tolédano et al., 2003. Antidotal treatment of cyanide poisoning. Journal of the Chinese Medical Association 66:193-203.

Meyer TW & TH Hosetter, 2012. Uremic solutes from colon microbes. Kidney International 81:949-54. https://doi.org/10.1038/ki.2011.504

Mokhlesi B, JB Leiken, Murray P et al., 2003. Adult toxicology in critical care: part I: General approach to the intoxicated patient. Chest 123:577-92. https://doi.org/10.1378/chest.123.2.577

Mukherjee S & RD Gupta, 2020. Organophosphorus nerve agents: Types, toxicity, and treatments. Journal of Toxicology 2020: 3007984. https://doi.org/10.1155/2020/3007984

Mushett CW, KL Kelley, GE Boxer et al., 1952. Antidotal efficacy of vitamin B12a (hydroxo-cobalamin) in experimental cyanide poisoning. Proceedings of The Society for Experimental Biology and Medicine 81: 234-7. https://doi.org/10.3181/00379727-81-19831

Parreno JMJ, E Huet, A Fernández-del-Carmen et al., 2018. A synthetic biology approach for consistent production of plant-made recombinant polyclonal antibodies against snake venom toxins. Plant Biotechnology Journal 16:727-36. https://doi.org/10.1111/pbi.12823

Pickova D, V Ostry, J Toman et al., 2021. Aflatoxins: History, significant milestones, recent data on their toxicity and ways to mitigation. Toxins 13:399. https://doi.org/10.3390/toxins13060399

Reddy DS, 2023. Advances in targeted therapy of organophosphate neurotoxicity and chemical warfare nerve agents. In Sensing of Deadly Toxic Chemical Warfare Agents, Nerve Agent Simulants, and their Toxicological Aspects (Das S, S Thomas & PP Das, eds): Elsevier, Amsterdam, Netherlands, pp: 489-500. https://doi.org/10.1016/B978-0-323-90553-4.00026-3

Rice KM, JR Walker, EM Wu et al., 2014. Environmental mercury and its toxic effects. Journal of Preventive Medicine and Public Health 47:74. https://doi.org/10.3961/jpmph.2014.47.2.74

Risher JF & SN Amler, 2005. Mercury exposure: Evaluation and intervention, the inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning. Neurotoxicology 26:691-9. https://doi.org/10.1016/j.neuro.2005.05.004

Sakai A, 2013. Diagnosis and treatment of snakebite by Mamushi and Yamakagashi. Chudoku Kenkyu: 26:193-9.

Salyer SW, 2007. Toxicology emergencies. In: Essential Emergency Medicine (Salyer SW, ed): W.B. Saunders, Philadelphia, USA, pp: 923-1049. https://doi.org/10.1016/B978-141602971-7.10017-0

Sasaki K, SF Fox, D Duvall et al., 2009. Rapid evolution in the wild: Changes in body size, life-history traits, and behavior in hunted populations of the Japanese mamushi snake. Conservation Biology 23:93-102. https://doi.org/10.1111/j.1523-1739.2008.01067.x

Satora L, D Pach & B Butryn, 2005. Fly agaric (*Amanita muscaria*) poisoning, case report and review. Toxicon 45:941-3. https://doi.org/10.1016/j.toxicon.2005.01.005

Sungur M & M Güven, 2001. Intensive care management of organophosphate insecticide poisoning. Critical Care 5:1-5. https://doi.org/10.1186/cc1025

Taghizadieh A, R Mohammadinasab, JG Sharbaf et al., 2020. Theriac in the persian traditional medicine. Erciyes Medical Journal 42: 235.

Tangahu BV, SRS Abdullah, H Basri et al., 2011. A review on heavy metals (As, Pb, and Hg) uptake by plants through phytoremediation. International Journal of Chemical Engineering 2011:939161. https://doi.org/10.1155/2011/939161

Tao Y, S Xie, F Xu et al., 2018. Ochratoxin A: Toxicity, oxidative stress and metabolism. Food and Chemical Toxicology 112:320-331. https://doi.org/10.1016/j.fct.2018.01.002

Tavassoli M, A Afshari & AL Arsene, 2019. Toxicological profile of Amanita virosa-A narrative review. Toxicology Reports 6:143-50. https://doi.org/10.1016/j.toxrep.2019.01.002

Thomas DV & SM Tenney, 1955. The effect of levorphan and levallorphan on the respiratory mechanism of normal man. Journal of Pharmacology and Experimental Therapeutics 113:250-5.

Tsai MT, SY Huang, SY Cheng et al., 2017. Lead poisoning can be easily misdiagnosed as acute porphyria and nonspecific abdominal pain. Case Report in Emergency Medicine 2017:9050713. https://doi.org/10.1155/2017/9050713

Vanholder R, N Meert, E Schepers et al., 2008.Uremic toxins: Do we know enough to explain uremia? Blood Purification 26:77-81. https://doi.org/10.1159/000110570

Vianna ADS, EPD Matos, IMD Jesus et al., 2019. Human exposure to mercury and its hematological effects: A systematic review. Cadernos de SAUDE PUBLICA 35:91618. https://doi.org/10.1590/0102-311x00091618

Wang K, DS Guo, HQ Zhang et al., 2009. Highly Effective binding of viologens by p-Sulfonatocalixarenes for the treatment of viologen poisoning. Journal of Medicinal Chemistry 52:6402-12. https://doi.org/10.1021/jm900811z

Wang RY & ZN Kazzi, 2012. Editorial: antidotes and rescue therapies. Current Pharmaceutical Biotechnology 13:1914-6. https://doi.org/10.2174/138920112802273164

Williams D, JM Gutiérrez, R Harrison et al., 2010. The Global Snake Bite Initiative: An antidote for snake bite. The Lancet 375:89-91. https://doi.org/10.1016/S0140-6736(09)61159-4

Worek F, G Reite, P Eyer et al., 2002. Reactivation kinetics of acetylcholinesterase from different species inhibited by highly toxic organophosphates. Archives of Toxicology 76:5. https://doi.org/10.1007/s00204-002-0375-1

Wu J, X Gong, Z Hu et al., 2021. Acute liver failure caused by Amanita verna: A case series and review of the literature. BMC Surgery 21:1-7. https://doi.org/10.1186/s12893-021-01434-6

Yang LP, X Wang, H Yao et al., 2020. Naphthotubes: Macrocyclic hosts with a biomimetic cavity feature. Accounts of Chemical Research 53: 198-208. https://doi.org/10.1021/acs.accounts.9b00415

Yin H & R Wang, 2018. Applications of Cucurbiturils (n=7 or 8) in pharmaceutical sciences and complexation of biomolecules. Israel Journal of Chemistry 58: 188-98. https://doi.org/10.1002/ijch.201700092

Yin H, X Zhang, J Wei et al., 2021. Recent advances in supramolecular antidotes. Theranostics 11:1513. https://doi.org/10.7150/thno.53459

Yu Y & J Rebek, 2018. Reactions of folded molecules in water. Accounts of Chemical Research 51:3031-40. https://doi.org/10.1021/acs.accounts.8b00269

Zhang Y, GH Zheng, GH Liu et al., 2011. Morphological and physiological responses of root tip cells to Fe 2+ toxicity in rice. Acta Physiologiae Plantarum 33:683-9. https://doi.org/10.1007/s11738-010-0590-y

Zhou J, G Yu & F Huang, 2017. Supramolecular chemotherapy based on host-guest molecular recognition: A novel strategy in the battle against cancer with a bright future. Chemical Society Reviews 46:7021-53. https://doi.org/10.1039/C6CS00898D