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Ricinus communis intoxication in humans- An ancient and present story of plant toxin

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ABSTRACT:
Ricinus communis is found around the world and it contains protein which consists of A and B subunits. These subunits are produced inside the seeds of the plant. Ricin is one of the most potent poisons. Toxicity by ricin is caused because of its ability to inhibit protein synthesis. Toxicity also depends upon the dose and route of administration. Generally, there are three routes i.e ingestion, injectable, and inhalation. The toxic effect includes gastrointestinal hemorrhages, hypoglycemia, renal tubular necrosis, inflammation, etc. However, regardless of its lethal effect, it has the potential for therapeutic use. Ricinus communis is produced on a commercial level for the production of castor oil. During the production of castor oil, the by-product ricin is produced over 1 million tons per year. The compounds of Ricinus communis show therapeutic effects like anticonceptive, antidiabetic, antifertility, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, insecticidal, and wound-healing activities. Ricin A chain toxin coupled to monoclonal antibodies against cell surface proteins is used to treat various cancers. In this article, we will discuss the intended and non-intended poisoning caused by castor seeds and ricin.
Keywords: Castor bean, plant toxin, dual nature of plant, human intoxication, mechanism of toxicity, folk medicine.

I. INTRODUCTION:

Growing mindfulness and concern about ricin, a potent biological poison, as a possible terrorist armament has needed a comprehensivereview of this bane. In recent years, there has been heightened concern regarding the potential of various chemical and biological weapons as agents for urban terrorism.[1] A number of cultivated and wild-growing plants produce toxins. These may be alkaloids, glycosides, toxalbumins volatile oils, photosensitizing substances resins, and allergens. The best known of these are Colophony, produced from the distillation of pine resin and used as a solder flux or an additive to glue, poison ivy (Toxicodendron radicans), Gelsemium sempervirens, tulips, Euphorbia, Laportia, Dieffenbachia, vanilla, chrysanthemum, buttercups, hyacinth, common rue, Scilla and castor beans. These concerns have been reinforced by the recently attempted uses of ricin by various groups in the United States and the United Kingdom.[2,3] Ricin is a potent plant poison or toxin which is found in the seeds of Ricinus communis (castor plant). Ricin works by blocking cell protein synthesis, which causes cell death and multiple organ failure[4]. Furthermore, it is readily accessible, and its relative ease of extraction from the castor bean plant, as well as its stability in both hot and cold conditions[5], It has been regarded as one of the most potent poisons in the plant kingdom[6] and has been described as a toxin that can cause death. Ricin is toxic by several routes, including inhalation, ingestion, and injection. Bioterrorists might poison water or foodstuffs, inoculate persons directly via ricin-laced projectiles, or aerosolize liquid ricin or lyophilized powder. Ricin has been used as a biological weapon for assassinations but has never been used to harm groups of people. A very large quantity of ricin would be needed for a large-scale attack. Ricin poisoning is not contagious.[7] However, the plant and seeds have been used historically for the tratment of infection, inflammation and as a laxative. These seeds are a rich source of castor oil which is produced by milling, boiling, pressing or solvent extraction. Apart from its medicinal properties it has certain uses in paints, fuel for lamps, coats, cosmetic products and many more.[8,9] During the oil extraction from the plant, the leftover is a rich source of protein and it is detoxified first, then it is used as supplement feed for sheep, cattle and fish. [10–17] The residual can also be used the organic manure. [18–21]

Figure 1. Ricinus communis: The castor oil plant Ricinus communis with characteristic seedpods

History of ricin:

Ricin, a plant toxin has played interesting and important roles in the history of clinical medicine and biomedical research. The usage of these proteins for the treatment since ancient times is reviewed. Later the proteins played a vital role in the early days of immunological study and some of the basic principles of immunology were discovered with toxic proteins of this group. During the last three decades, the mechanism of action of the toxins was illustrated. Ricin has been used in bioterrorism. Recently, toxins have played important roles as experimental models to elucidate the intracellular trafficking of endocytosed proteins.[22]

Ricin toxin was discovered in 1888 by Hermann Stillmark, a student at the Dorpat University in Estonia.[23] During Stillmark's extensive research, he also observed that ricin caused agglutination of erythrocytes and precipitation of serum proteins.[22] Ricin inhibited protein synthesis and suggested that the effects resulted from restricted elongation of the nascent polypeptide chain.[24] Subsequent studies revealed that the molecular target of the toxin was the 60S ribosomal subunit.[25] In the last decade, immunotoxins using the ricin A-chain chemically linked to monoclonal antibodies have been used as an alternative in therapies against cancer, AIDS, and other illnesses.[26] Ricin-based immunotoxins, some of which contained deglycosylated ricin A chain conjugated to either the anti-CD22 antibody RFB4 [27] or its Fab fragment[28] have also been shown to provide enhanced therapeutic efficacy and resulted in improved antitumor activity [29]. However, the U.S. Food and Drug Administration (FDA) has put hault on clinical testing of RTA-based immunotoxins, as they cause vascular leak syndrome (VLS) in human beings. The US War Department considered ricin for chemical warfare as early as 1918.[30] Ricin was tested as an inhalational agent in the 1940s.[31] Although never laboratory-confirmed, it was most likely the etiologic agent used in the 1978 assassination of Bulgarian journalist Georgi Markov in Great Britain[32,33] In the 1940s in the United States and in the late 1980s in Iraq, weapons-grade ricin (ie, purified and inhalable particles that can be aerosolized for a mass attack) was manufactured and tested in animal experiments and in artillery shells in-field testing.[34,35] In 2003 and 2004, ricin was discovered in a South Carolina mail sorting facility, a mailroom serving US Senator Bill Frist's office, and inside a letter addressed to the White House.[36]

Ricin has given contribution to early stage of immunology, the treatment of cancer, and the better understanding of cell biology. During the World War I, the U.S. Bureau of Mines studied the obnoxious eventuality of ricin at the American University Experimental Station. Two weapon concepts were considered: the simplest approach was coating shrapnel and bullets with ricin to create a skin effect; the more challenging concept was a "dust cloud" that produced a lung effect. At the time, limited experimental work on animals demonstrated that it was possible to weaponize ricin. Interestingly, the average time it took for an animal to die was somewhat longer than is reported in contemporary studies. This early work also identified the main technical difficulty in weaponizing ricin: its thermal sensitivity. It was found that the heat generated while firing the coated bullets destroyed a significant amount of the agent.[37]

Early in World War II, England and Canada began work on ricin for use in 4-pound bursting bomblets. The French also had an interest in ricin but, like early U.S. researchers, felt that it was too dangerous to study without first having an antitoxin.[38] The U.S. military's interest in ricin resurfaced around 1942 as a project of the National Defense Research Committee[30] and led to chamber and field trials at Dugway Proving Ground, Utah, in 1944.[34] These efforts differed from those of the previous war in that only a lung effect was being considered, and considerable advances had been made in the science of aerosols. However, the thermal sensitivity of ricin remained the major technical issue.

Origin and geographical distribution:

It is believed that Ricin was originated in Africa but now it is widely spread in the tropical as well as sub-tropical regions.[35] This plant is native to North-Eastern Africa. Now a days its population can be seen in African continents, Tunisia to South Africa, Atlantic Coast to the Red Sea, and even on the Islands of the Indian Ocean. It can grow in different temperatures of Europe and in tropical and subtropical areas of America and Asia. It grows easily in many areas.[36]

Ricin, a Toxic Lectin from Ricinuscommunis:

Ricin toxin or ricin, as it is more commonly known, was discovered in 1888 as the first plant lectin, is a protein that consists of A and B subunits that can be extracted from the seeds of the castor plant, Ricinus communis L.[23] It has been cultivated primarily for castor oil.[22] Its seeds are extremely viable and germinate easily in any soil so that the plant has adapted to tropical as well as sub-tropical regions all over the world. Reports on the ricin content of castor beans vary but probably are in the range of 1% to 5 %.[42,43]Purified ricin is a white powder that is soluble in water and stable over a wide pH range.[30,34] It is inactivated by heat, 80°C in an aqueous solution for 1 hour[34] and requires higher temperatures or longer periods for inactivation when in powder or crude forms and has a molecular weight of 60 to 65 kDa.[40]

The ricin family has two major members, both, lectins, inclusively known as Ricinus communis agglutinin ll (ricin) and Ricinus communis agglutinin l (RCA). Stillmark, a Ph.D. student at the University of Dorpat in Estonia, did a study to know the toxicity of Ricinus seed extracts. He mixed seed extract with blood and noticed that the red blood cells(RBCs) began to agglutinate. He established that the active seed component was a protein that he termed ricin. The agglutination which was found during the study was due to the presence of the RCA, which is a strong haemagglutinin but a weak cytotoxin, whereas ricin is a weak haemagglutinin but potently cytotoxic in nature [44,45] This results from ricin having a single B chain, enabling it to bind to and enter target cells, whereas Ricinus communis agglutinin l (RCA) has two B chains allowing it to bind to, and thus agglutinate two target cells. Ricin is a heterodimer where catalytically-active A chain (ricin toxin A or RTA) is joined by a single disulfide bond to a B chain (RTB) i.e a galactose- and N-acetylgalactosamine-specific lectin. The action of A chain enzyme is to remove a specific adenine residue from the 28S ribosomal RNA (28SrRNA) of the large subunit of eukaryotic ribosomes [46] The adenine residue which is removed by RTA, adenine 4324 in the case of rat liver 28SrRNA, is located in the area of the rRNA that contains one of the most preserved of rRNA sequences. This region functions in the ribosomal elongation cycle, and the adenine removed as a result of RTA-catalysed depurination is the binding site for elongation factors 1 and 2.[47] Since RTA-modified ribosomes are not able to bind these translation factors they are no longer capable of continuing protein synthesis. This ultimately leads to cell death and accounts for the extreme cytotoxicity of ricin [22,48,49] RCA is a tetramer of two ricin-like heterodimers, each of which consists of an A and a B chain. The primary sequence of the A chains of ricin and RCA are identical in all but 18 positions (from a total of 267 amino acids) and are thus 93% homologous. The corresponding B chains differ at 41 residues (from a total of 262 residues) and are 84% homologous.[50,51] Two of the 18 residue differences between RTA and RCA A chain involve the substitution of cysteine residues, one of which (Cys156) forms a disulfide bond with an adjacent molecule to generate the mature ~128 kDa tetrameric RCA with the subunit arrangement B-A-A-B [52,53]

Ricin communis, a Dual use plant:

It shows the properties of regulating bowel movement and reducing flatulence. Its leaves are used for headaches and for wounds in the form of poultices. A decoction of leaves is basically used for sore throat, bile problems, bladder aches, and pain. After detoxification, their oil is used in oral medications. After detoxification of seeds, they are applied in the form of paste on scorpion stings. They are also useful to strengthen the hair.[54] It also shows some beneficial properties like antimicrobial, anthelmintic, insecticidal, anti-inflammatory, antioxidant, and laxative.[55] In certain diseases, it is used for the treatment like hypoglycemia, edema, rheumatism, asthma, ringworm, warts, dandruff, dermatitis, asthma. Applying it externally on the breast increase the milk flow and its oil reduces the labor pain.[56-62]

On the otherhand, as the castor plant is readily available in the market and has lethal effects, ricin has long been used as a weapon. During both world wars Britain, the United States, and other countries did experiment on artillery shells and bombs which can disperse clouds of finely ground ricin powder. Then authorities extrapolated that ricin which is also known as compound W would make a poor military weapon as the compound gets degraded under the heat of firing and to affect a massed troops a large quantity is required.

The research was continued during the Cold War, but under the terms of the Biological Weapons Convention of 1972 stockpiles were destroyed. Still, ricin is considered a possible weapon of terror and assassination. Some scenarios of terrorists might be the inoculation of ricin into a water supply or food or the spraying of a ricin aerosol in a confined indoor space. Such attacks would cause limited casualties but may trigger major emergency responses. There is no attempted use of ricin as a weapon for mass destruction has occurred till now.[63]

Phyto pharmacology:

Antioxidants

From seed extract it is concluded that antioxidant activity was determined by three methods i.e Lipid peroxidation by ferric thiocyanate, free radical scavenging method showed an effect on 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) and the third method is hydroxyl radical which is generated from the hydrogen peroxide. The diseases which are caused by oxidative stress can be treated with the help of seed extract of Ricinus communis at low concentration because it contains a high amount of antioxidative properties. Four chemical constituents were obtained that have the desired results of antioxidative properties; Methyl ricinoleate, methyl ester, 12 octadecadienoic acid, and ricinoleic acid.[64] Due to the presence of flavanoids in stems and leaves, they also show good oxidative properties.[65,6]

Antiasthmatic activity

The root extract (ethanolic) of Ricinus communis is very effective against asthma. It has mast cell stabilizing potential and an antiallergic effect. As extract is having the presence of saponins which shows mast cell stabilizing effect and flavonoids have smooth muscle relaxant and bronchodilator activity. Flavanoids like apigenin and luteolin work by inhibiting basophil histamine release as well as neutrophils beta-glucuronidase release thus showing antiallergic activity in-vivo. It also inhibited passive cutaneous anaphylaxis in vivo.[67]

Antinociceptive activity

Antinociceptive activity was evaluated from the methanolic extract of leaves of Ricinus communis. It was considered by using three classical pain models i.e acetic acid-induced writhing test, tail immersion method, and induced paw licking. Due to the presence of phytochemicals like saponins, flavonoids, steroids, and alkaloids antinociceptive activity is produced.[68]

Antihistaminic Activity

The ethanolic root extract of Ricinus communis shows antihistaminic activity at the dose range of 100, 125, and 150 mg/kg given intraperitoneally by using clonidine-induced catalepsy in mice.[69]

In vitro immunomodulatory activity

Our immune system is our defensive system, it protects our body against invading pathogens. Immunomodulatory agents from plant and animal origin help in enhancing the response against the pathogen by activating the nonspecific immune system. Studies showed the immunostimulant effect from the leaves of Ricinus communis by increasing the phagocytic function of human neutrophils. The process of engulfment of microorganisms by leucocytes is known as phagocytosis. The process of phagocytosis is the intracellular killing of the microorganism depending on metabolic thrust. Tannins are present in leaves which show anti-inflammatory and immunomodulatory properties.[70]

Anti-fertility activity

The ethanolic 50% extract of Ricinus communis showed anti-fertility effects. In epididymal sperm counts were reduced drastically. There was an alteration in the mode of movement, the morphology of the sperms, and motility. It is suggested that a reduction in the levels of fructose and testosterone decreases reproductive performance. Once the drug is withdrawn the anti-fertility effect reduces and functions normally, so this is a reversible process.[71]

Antiulcer activity

The anti-ulcer effect was studied by administration of ethanol or aspirin or pyloric ligation in rats. The dose of castor oil was given to the rat was 500mg/kg and 1000mg/kg orally 30 min. Prior to the induction of ulcer. This study showed that antiulcer activity of the castor oil of R. communis seed is because of the cytoprotective action of the drug as well as strengthening of gastric mucosa hence enhancing the mucosal defense.[72]

Molluscicidal, Insecticidal and Larvicidal activity

Molluscicidal activity against Lymnaea acuminata is possessed by the leaf extract of R.communis and the seed extracts of R.communis showed better action of insecticidal and insectistatic activity as compared to the leaf extracts against S. Frugiperda. It happens due to the active ingredients like castor oil and ricinine.[73,74,75] The aqueous leaves extracts of Ricinus communis showed Larvicidal activity against Culex Quinquefasciatus mosquitoes, Anopheles arabiensis, and Callosobruchus chinensis.[76]

Anti-inflammatory activity

Acute and chronic anti-inflammatory activities were studied on Wistar albino rats by using leaves and root extract. Inflammatory models were used on Wistar albino rats. It showed the formation of paw edema because of the sub plantar administration of carrageenan, characterizing the events (cellular) of acute inflammation. Dose of 250 and 500mg/kg of methanolic leaves extract of Ricinus communis possessed the protective effect in preventing cellular events which are formed during edema as well as in all stages of acute inflammation. It possesses anti-inflammatory activity due to the presence of flavonoids in it. Flavanoids have a protective effect against paw edema in rats.[77,78,79]

Ricin intoxication in Humans:

Ricin occurs in three major forms i.e. injection, ingestion, and inhalation.

In a case report, a 49 years old man committed suicide by injecting castor bean extract. He was then hospitalized after 24 hours of administration of the extract. When the person was admitted into the hospital he was conscious and had a history of nausea, diarrhea, vomiting, dyspnoea, muscle pain, and vertigo. Despite of intensive care and support were given by the hospital to the patient he died after 9 hours due to the multiorgan failure.[80]

In 2002 a man injected subcutaneously Castor bean extract and was admitted 36 hours later. The person was suffering from chest pain, back pain, severe weakness, dizziness, hematochezia, anuria, nausea, and metabolic acidosis. Then his condition became severe and he suffered from hepatic and renal failure.[81]

Among the cases reported about the parenteral administration of ricin, one case was reported in Bulgaria. A journalist named Georgi Markov was assassinated with the umbrella covered with ricin blown on the right thigh. He got about 500 µg of ricin toxin. He felt localized pain and had an angry red spot like a pimple on the backside of his right thigh. On the same day at night, he was hospitalized and had a high temperature, fast pulse, vomitings, and normal blood pressure. Regional lymph nodes were swollen. On the next day, his pulse rate was 160/ min and he was cold, sweating, and dizzy. His leukocyte count was 26,300/cm. On next day, he stopped passing out urine and blood was coming out with vomitings. He started pulling out intravenous lines in confusion and ultimately he died because of cardiac arrest.[30,82]

Phase 1 study was conducted with ricin on cancer patients by inhibiting protein synthesis. Ricin was given by parenteral route every two weeks and the dose range was 4.5 to 23 µg/sq m. Ricin development as an antitumor agent, at the dose range of 18 to 20 µg/sq m was well tolerated by the patients and was eliminated from blood. Prevalent side effects which were seen were flu-like symptoms with fatigue, pain in the muscle, and nausea.[83]

Another case was seen of a 36-year-old quality control chemist, he injected ricin itself. He made this injection by cutting castor oil beans and soaked in tap water for one week. After 16 hours of administration, he was admitted to the hospital. Two intramuscular injections was containing 150 mg of ricin. During the examination, his pulse rate was 120/min. And blood pressure 140/80 mm/Hg. The site of injection was enlarged up to 3mm in diameter. To maintain alkaline urea sodium bicarbonate was given intravenously and to prevent renal tubular damage. His temperature was constant at 37.5-39.0^0 C for the following eight days. The injection site rose to 12 cm but without necrosis. No evidence was seen about hemolysis. The patient recovered and discharged after 10 days of administration.[84]

Around 1000+ RT cases have been reported in the literature showing poisoning effects after consumption. After 4-6 hours of ingestion of Castor Bean it shows signs and symptoms like oropharyngeal irritation, vomiting, pain in the abdomen, bleeding in the GI like melena, hematochezia, and hematemesis which is secondary to necrosis of GI.[81] Within 2 hours of Ricin absorption, it causes toxicity via lymphatic vessels and blood. Accumulation of toxin occurs in liver and spleen.[85] For Ricin toxicity it is essential to absorb the ricin from castor bean. If the castor bean is swallowed as it is, then it well pass out from the gastrointestinal tract without caution any reaction in the body as cator bean has a solid shell-like coating. If the castor bean is chewed and crushed while eating then ricin will be absorbed and will cause the toxicity. Hence, will lead to multiorgan failure and ultimetely death.[82,86]

A Hispanic 3 years old boy ate seeds of unknown plant. After one hour he had abdominal pain and vomiting. After eight hours he had mucoidal diarrhoea. After 20 hours he was admitted to the hospital, pulse rate was 120/ min., blood pressure was 100/60 mm/Hg, temperature was 37.8^0 C. IV fluids were administered and after eight hours he was discharged. Twelve hours later he was taken back to the hospital because of the regular vomitings and nausea. During this period of time seeds were identified as castor seeds. After 24 hours he stopped vomiting. On the fifth day he was discharged in good condition.[87]

Workers who are exposed to castor bean dust reported chest pain, itching eyes, nose and throat congestion and urticaria. Though cases of ricin inhalation are rare.[81] Adult 5 Rhesus monkeys inhaled dose of 20.95-41.8 micrograms/kg of aerosolized ricin. They developed an acute airway inflammation and fibrinopurulent necrotizing pneumonia. In thoracic cavity they had microscopic lesions. The main cause of death in monkeys was pulmonary alveolar flooding.[88]

Treatment and Vaccination:

Currently, there is no approved antidote or therapy against ricin exposure. Modern treatment focuses on some medicines and involves usage of intravenous fluids as well as suppression of hypertension. Electrolytes are given to maintain the balance of electrolytes and preventing dehydration from nausea and diarrhoea. To prevent further absorption of the toxin, oral activated charcoal (250 mL/30g) or gastric lavage can also be advocated depending on the time of administration after oral ingestion. Monitor hypotension, bone marrow suppression, hepatotoxicity for cardiac effects, liver damage, and multiple organ damage.[89]

In order to protect certain people like soldiers or emergency staff, there is an interest in developing a vaccine against the intoxication of ricin. However, there is no as such any evidene of availability of vaccine but one vaccine is in an advanced stage of legislative approval[90-93] i.eRiVax^{TM}, it is based on the recombinant catalytic inactive A- chain ricin. It was subjected to clinical trials in humans where it induced the functionally active antibodies.

II. CONCLUSION:

Ricin is a toxin which is found in the Castor beans, and it is commonly regarded as the one of the most toxic substance found in the plant. It basically causes toxicity by inhibiting protein synthesis within eukaryotic cells. During the oil extraction from the plant, the leftover is a rich source of protein and it is detoxified first, then it is used as supplement feed for sheep, cattle and fish.There are many cases where ricin killed many people. Common symptoms are vomiting, nausea, abdominal cramps, diarrhoea and dehydration. Toxicity by ricin can be detected by Enzyme Linked Immuno Sorbent Assay (ELISA). It has a potential to use it as a tumor reducing agent in cancer therapy. Ricinus communis contains saponins, flavanoids, ricinine, steroids and flavanoids which shows beneficial properties like antiasthmatic, antioxidants, antiulcer, antifertility. With respect to forensic analysis, ricin detection in clinical samples is difficult due to its rapid absorption and internalization within the tissue. As a surrogate marker, the alkaloid ricinine can be successfully monitored.

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