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RICIN TOXICITY : A REVIEW

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A B S T R A C T

Ricinus communis Linn. commonly called castors belonging to the family Euphorbiaceae. Ricin is a natural toxin contained in castor seeds. The glycosylated protein comprising two round polypeptide chain A, and chain B is connected by a disulphide bond. Its ability toxicity by inhibiting protein synthesis. Termination of protein synthesis is not the only cause of cell death caused by ricin but some reports indicate the induction of cell apoptosis as well. The ricin chains of A and the most commonly used modifications to make immunotoxin by incorporation with monoclonal antibody therapy (moAbs), form Ricin immunotoxin (R-immunotoxin). Therefore the target of ricin conjugated antibodies is cancer cells and has been studied as an immunotherapy agent.

INTRODUCTION

A castor plant (Ricinus communis Linn.) is an African tropical oleaginous plant that has been adapted to various climates(Meneguelli de Souza *et al.*, 2018). The castor plant is very common along rivers, river beds, lower soil and almost any hot and humid areas sufficient to maintain strong growth. Castor seeds are the source of many economically important products and are one of the commercial products, though highly toxic. Castor seeds are toxic to humans, animals, and insects(Ladda and Kamthane, 2014).

Ricin is a natural toxin contained in castor seeds, cultivated globally and processed in large quantities (Bozza *et al.*, 2015). Ricin is proteins consisting of subunits A and B. Ricin is a by product of castor oil production, when the crushed cast grain will form a slurry of castor oil extraction and the remaining ricin (Worbs *et al.*, 2011). The toxic effects are of ricin caused by inhibition of protein synthesis. Ricin can enter the body through inhalation of aerosols, or through food, injections, or infusions. Although ricin may be lethal, it has the potential for therapeutic use because it inhibits tumor growth (Worbs *et al.*, 2011).

History

Castor seeds are known for their high toxicity for centuries. In ancient times, breeders kept their cattle away from plants or would lose their livestock due to poisoning. Castor seeds have also been used in traditional medicine for various diseases (Poli *et al.*, 1997).

Castor seeds are originally from Asia and Africa, but the seeds can be found also in Europe and America (Olsnes and A Pihl, 1976). Castor seeds are usually used as ornamental beans, beads, bracelets, or necklaces. Castor seed has an outer shell that must be solved to cause poisoning (Hostetler, 2003). Castor oil is obtained from castor seed extract that has been used for a number of purposes in ancient Egypt.

By the end of the 19th century, it has been shown that the toxicity of castor seeds refers to a toxic protein called ricin. Ricin toxin cause erythrocyte agglutination and the deposition of serum proteins (Olsnes and A Pihl, 1976).

Ricin was first developed as a weapon by Canada, the United States, and Britain during and between two world wars. The US Army named it "compound W." Ricin and saxitoxin, are the only toxins that development, production, and storage are also prohibited in accordance with the 1993 Chemical Weapons Convention. However, ricin has been a favorite tool of radical and individual groups that have been linked to several events over the last few decades. The murder of Georgi Markov is the most famous incident by using weapons disguised as umbrellas (Maman and Yehezkelli, 2005).

In 1995 and 1997, several people were arrested in the United States for having their own self-made ricin. In addition, extremist groups in Minnesota were found and

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arrested for planning to kill US marshal using a ricin mixture with dimethyl sulfoxide (DMSO) solvents (Poli *et al.*, 1997; Maman and Yehezkelli, 2005).

The latest incident was in early 2003 when British police found a domestic laboratory that had succeeded in producing small quantities of ricin for use as armaments(Susan, 2003).

Structure

Ricin is a glycosylated protein consisting of two round polypeptide chain A and chain B containing 267 and 262 amino acid residues, respectively, linked by disulfide bonds, and where various glycoside chains (sugars) are attached (Lord, Roberts and Robertus, 1994).

Ricin is a 64 kDa type II ribosome-inactivating protein (type II RIP) consisting of two nonidentical polypeptide chains connected by a single disulfide bond. Chain B (RTB, ~ 34 kDa) is a lectin and is responsible for binding cells that interact with cell surface galactosides, internalizing RTA across cell membranes. The enzymatic activity (RNA N-glycosidase) from chain A (RTA, ~ 32 kDa) removes the adenine residue from the 28S ribosomal RNA loop(Meneguelli de Souza *et al.*, 2018).

Mechanism of Toxicity

The activity of ricin A chain N-glycosidase was first discovered by Endo and Tsurgi(Endo and Tsurugi, 1987). The chain of ricin A binds and specifically removes the adenine residue (A4324) from the GAGA sequence of the RNA ribosome 28S in a sarcin-ricin loop (SRL). Loop SRL is a very short structure and is located near 3 'end of rRNA (Rajamohan, Mao and Uckun, 2001). The Ricin A chain is attached to the ribosomal for the depuration of SRL and the displacement of the A chain to the ribosome is accelerated by conformational change into a pentameric (Li *et al.*, 2010). Thereafter, the A chain flanking a single adenine (A4324) between two tyrosine rings on the catalytic site and hydrolyzing the C-N glycosidic bond with N-glycosidase activity(Rajamohan, Mao and Uckun, 2001). The SRL is responsible for binding the eukaryotic elongation factor 1 (eEF-1) and eEF-2 and finally protein synthesis.

Depurinasi SRL prevents the binding of EF-1 and EF-2 elongation factors, resulting in the cessation of protein synthesis. Conformational changes in RTA are also important for efficient termination of mRNA translation. It has been shown that the α-helix (residue 99-106) of RTA may affect the orientation of the Glu-177 side chain due to its flexibility and modulate the chain-derived depuration activity of A (Tyagi *et al.*, 2015).

Termination of protein synthesis is not the only cause of cell death caused by ricin but some reports indicate the induction of cell apoptosis as well. Cell apoptosis involves two major pathways; One is the mediation or extrinsic pathway receptor involving caspase 8 or 10 as the initiator of caspases while the other is the mitochondrial or intrinsic pathway activated by cellular stress and involves caspase 9 as the caspase initiator. Next caspase begins to activate the caspase-3 and caspase-7 effects and leads to apoptosis. Ricin is involved in the initiation of apoptosis through intrinsic or mitochondrial pathways. Several studies have reported the role of ricin in loss of mitochondrial membrane potential, cytochrome c release, and activation of caspase 9 (Tyagi *et al.*, 2015). Ricin also cleaves DNA fragmentation factor (DEF) by activating caspase 3 which ultimately produces DNA fragmentation(Liu *et al.*, 1997).

Ricin increases the production of reactive oxygen species (ROS) and decreases free radical glutathione levels (Rao *et al.*, 2005). Most studies have reported the role of ricin in activating intrinsic or mitochondrial pathways but there have been several studies that identify the role of ricin in induction extrinsic pathway(Tyagi *et al.*, 2015).

Potential Medical Use

The discovery of ricin and its potential toxicity attracted the attention of scientists for a long time (Kaushal *et al.*, 2013). However, due to nonspecific toxicity, initial ricin control trials as therapeutic agents in leukemia patients were unsuccessful. But when used with proper targeting, this powerful toxin can specifically kill unwanted cells in the body that are now being explored for the development of immunotoxins in targeted cancer therapy (de Virgilio *et al.*, 2010).

Use of malignant cells is more susceptible to ricin toxicity because it expresses more on the surfaces where carbohydrate-containing lectins contained in non-malignant cells (Musshoff and Madea, 2009). The ricin chain of A and the modifications most commonly used to make immunotoxin by combining with monoclonal antibody therapy (moAbs) form Ricin immunotoxin (R-immunotoxin) (Becker and Benhar, 2012). Therefore the target of ricin conjugated antibodies is cancer cells and has been studied as an immunotherapy agent (Musshoff and Madea, 2009).

In combination with monoclonal antibodies directed at tumor cell surface receptors, the ricin meets Erlich's 'Magic Bullet' rule in the treatment of certain malignancies. Immunotoxin has recently been enhanced by pegylation (Musshoff and Madea, 2009). Ricin is also used in studies of neurologic degenerative disorders and neuropathy treatment by using 'suicide transport' in neurons(Wiley and Lappi, 2003).

R-immunotoxins still require further research, before being used as a successful therapy because of its high toxicity. Some studies use R-immunotoxins to treat cancer and clinical trials are terminated due to very high toxicity. In clinical trials, patients with fatal encephalopathy despite normal CT brain scans at the beginning of therapy, however, trials were discontinued. Patients with metastatic carcinoma are treated with anti-transferrin receptor antibodies combined with recombinant A-chain chips given intraperitoneally. Some researchers have proven that R-immunotoxins are quickly eliminated from circulation, with localization in the liver causing liver damage (Kaushal *et al.*, 2013).

It appears that the moAbs used for the synthesis of immunotoxins respond in the same way that the risin has relatively nonspecific toxicity. Drug design and clinical modification will allow scientists to develop newer R-immunotoxins with minimal side effects. Meanwhile,

changes in clinical protocols may be the main variable that will make immunotoxins a valuable therapy option (Kaushal *et al.*, 2013).

CONCLUSION

Castor plants *Ricinus communis* has toxic proteins contained in seeds. The toxic protein compound is ricin. Ricin has the ability to inhibit protein synthesis. Many studies on the use of ricin toxin one of them is the use of ricin as a cancer therapy agent

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