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# Medicinal significance, pharmacological activities, and analytical aspects of ricinine: A concise report

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ABSTRACT

Ricinine (3-cyano-4-methoxy-N-methyl-2-pyridone) is an alkaloid present in leaves and seeds of castor plant *i.e. Ricinus communis*. It can cause vomiting, convulsions, hypotension, liver and kidney damage and several other complications in human. Ricinine presents mainly in young plant and it is the only cyano-substituted pyridine compounds occurred naturally. Ricinine also found in some other plants such as *Piper nigrum, Discocleidion rufescens, Aparisthmium cordatum* and *Nicotiana tabacum*. Accidental and intended *Ricinus communis* intoxications in humans and animals have been known for centuries. In the present review, we summarize the information regarding its medicinal uses, pharmacological activities, analytical techniques and intended and unintended poisoning cases in humans and animals. This review will be beneficial for the researcher in the field of herbal medicine and other allied sciences.

## 1. Introduction

Natural plant material is mainly used as raw material for the growth and development of human being and other species. Our ancestors used herbal materials as a source of drugs for the treatment of different disorders on believes of its less side effect and economic values. In the present scenario, the drugs used for the treatment of different disorders is either expensive or not freely available in the market. So for better therapeutic approach it is necessary to innovate and access low-cost materials with reasonable safety. Bio-based materials with combination of modern chemistry could be used for the better approach in the pharmaceutical industries. A large number of the drugs recommended for the treatment of various disorders by the physicians in the world are mainly derived from the natural sources such as plants and animals. A large number of communities of African and Asian population used traditional medicines for their primary health aspects[1,2].

Development of food science and technology is one of the major platforms in the modern scientific trends which cover the various health aspects offered by food ingredients from plants. Herbal medicines are popular for treatment of various ailments in the world due to belief in its fewer side effects. Many synthetic and other compounds have been derived from different natural sources such as plants, minerals and organic matter[3,4]. World Health Organization also listed many plant materials for its medicinal property in the world. Plant contains enormous number of phytoconstituent which is responsible for the different pharmacological activities. Dietary anthocyanins have been well known for their health-promoting benefits like reducing the risk of coronary heart disease and preventing several chronic diseases[5].

## 2. An overview of alkaloids

Alkaloids are natural products mainly distributed in the plants, food materials, beverages and even in the tobacco smoke. Alkaloids are one of the important phytoconstituents mainly derived from natural sources, play a major role in the plants and animals. Alkaloids is important for the plant defences systems against various pathogens and animals. The applications of alkaloids are not limited

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to only animal or plants but it also showed various pharmacological activities in human. Alkaloidal compounds possess many activities, *e.g.* antimicrobial, anti-HIV and antiparasitic activities[6]. Alkaloids have been known for its toxicological property and it may cause severe illness, injury or even death in human and other animal species. Alkaloidal poisoning mainly occurs because of either unintentional ingestion of plant material or intentional ingestion of abused plant material[7].

## 3. An overview of ricinine

Pyridine nucleotides are one of the most distributed and substituted pyridine compounds in the nature. Ricinine (3-cyano-4-methoxy-N-methyl-2-pyridone) (Figure 1) is one of the important phytochemicals which obtained from the castor plant *Ricinus communis* L. (*R. communis*). Ricinine presents in all parts of the plants but specially in young plants and is the only cyano-substituted pyridine compound occurred naturally[8]. Ricinine can be also found in several plant species including *Piper nigrum*, *Nicotiana tabacum* and plant species belonging to the family Solanaceae. Ricinine has been demonstrated to have an insecticide effect and showed high alkaloid toxicity[9]. Accidental and intended *R. communis* intoxications in humans and animals have been known for centuries. *R. communis* is grown worldwide on an industrial scale for the production of castor oil. The seeds contain various phytoconstituents including highly homologous agglutinin and the alkaloid ricinine[10]. Ricinine is an alkaloid mainly obtained from the different parts of castor plant such as leaves and seeds. Ricinine can cause vomiting and other toxic reactions such as liver and kidney damage, convulsions and hypotension[11].

Ricinine, belongs to the group of piperidine alkaloids, was first discovered in the seeds of *R. communis*. Chemical structure, biosynthesis and metabolism of ricinine have been also investigated. Ricinine can be found in all parts of the plant but mainly in castor seeds (*R. communis*) which contain approximately 0.2% of the alkaloidal compounds. Ricinine causes hyperactivity, seizures and subsequent death due to respiratory arrest in the experimental mouse models. Smaller doses of ricinine could induce central nervous system effects like seizures in different animal model. Ricinine is high temperature resistance and cannot be inactivated by conventional heat treatment. After elimination of ricinine by a suitable extraction procedure, castor oil could be used for animal feeding[10]. A reduction of sperms number and increase of malformation of sperm was found to be in the male albino mice treated with ricinine. These effects may result by strongly inhibiting protein synthesis in the nucleus of sperm. Ricinine inhibits protein synthesis by irreversibly in activating eukaryotic ribosome, which could reduce sperm concentration. Ricinine considered as a promising cognition enhancing drug that may be used for treatment of the human amnesias[12]. Ricinine has been reported to cause stimulation of the central nervous system and it is also a potent goitrogen. Because it is an endogenous feed toxin, ricinine could be useful as a marker for indirectly evaluating the toxicological diagnosis[13].

## 4. Pharmacological aspects of ricinine

The alkaloid ricinine isolated from the plant *R. communis*, when administered to mice at high doses, induces clonic seizures accompanied by electroencephalographic alterations in the cerebral cortex and hippocampus. The lethal nature of ricinine-induced seizures is considered to be a good model for the study of the events that cause death during clonic seizures, particularly those related to respiratory spasms[14]. The anticonvulsant activity of the ricinine was evaluated in mice using the maximal electroshock model. The isolated compound ricinine at a dose of 60 mg/kg body weight, orally, significantly reduced the extensor tonus phase of convulsion in albino mice when compared with the standard drug diazepam[15]. Ricinine elicited seizures could be used as a novel chemical model of convulsive seizure. When more than 20 mg/kg dose level of ricinine administered to the mice, animals showed seizures including marked preconvulsive phase followed by short duration hind limb myoclonus, respiratory spasms and death[16]. The extract of the pericarp of castor bean showed central nervous system stimulant effects in the mice. The memory-improving effect and the seizure-eliciting properties of the extract were also observed with the administration of ricinine. Ricinine can be considered as a promising cognition-enhancing drug that may be used for the treatment of human amnesias in different animal model[17].

Hepatoprotective activity of 3-bromo-6-(4-chlorophenyl)-4-methylthio-2H-pyran-2-one, an isostere of dimethyl ricinine, was evaluated in adult male albino rats intoxicated with carbon

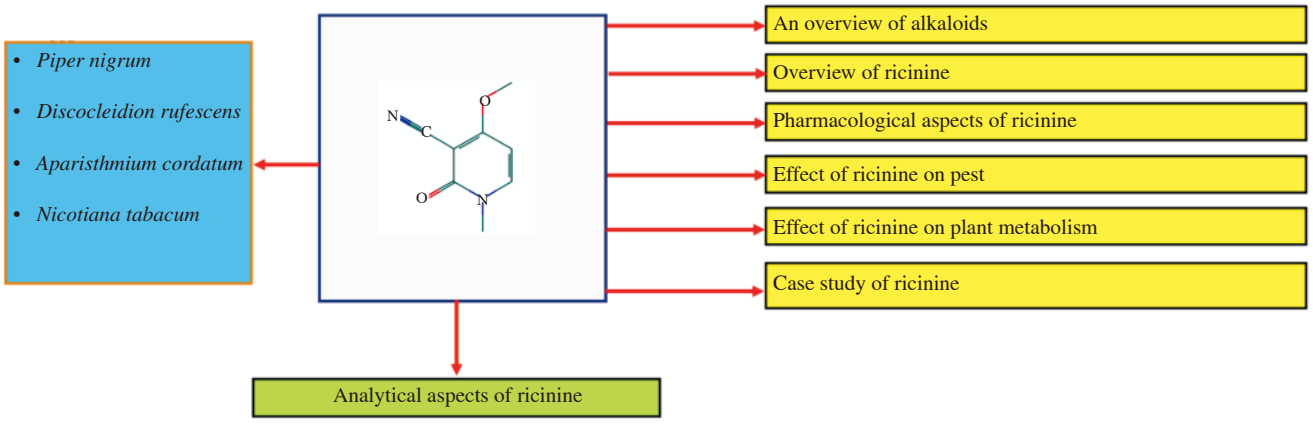


**Figure 1.** Overview of pharmacological and analytical aspects of ricinine.

tetrachloride, paracetamol or thioacetamide. The test compound showed significant hepatoprotection in the rats for seven consecutive days[18]. The toxic effects of ricinine on the metabolic profiles of rats were studied. Principal component analysis of the chromatographic data was used to identify the control and the tested rats. Biomarkers associated with the renal damage were determined in this investigation. Furthermore, histopathology and clinical chemistry studies were also used to confirm the success of hepatic injury[11]. Wnt signaling pathway plays important roles in proliferation, differentiation and development of cells. Cells treated with ricinine had higher β-catenin and lower of p-β-catenin protein levels, whereas glycogen synthase kinase 3β and casein kinase 1 protein levels remained unchanged. Results showed that ricinine activated the Wnt signaling pathway by inhibiting casein kinase 1[19].

## 5. Effect of ricinine on pest

Toxicity test and pot experiment were conducted to study the nematocidal activity of *R. communis* extracts and ricinine on *Meloidogyne incognita*. The results showed that both the ricinine and *R. communis* water extract had high nematocidal activity in which ricinine had shown the strongest nematocidal activity[20]. Toxic activity of isolated active compounds of leaf extracts of *R. communis* in the leaf-cutting ant *Atta sexdens rubropilosa* Forel and its symbiotic fungus *Leucoagaricus gongylophorus* Möller was studied. The main compounds responsible for activity against these fungus and ant were found to be ricinine[21]. In another toxicity study, ricinine was found to be active against *Spodoptera frugiperda* and *Myzus persicae*. Further a high dose of ricinine on mice showed effects on central nervous system, especially the cerebral cortex and hippocampus[9].

## 6. Effect of ricinine on plant metabolism

Ricinine-3,5-($^{14}$)C administered to senescent leaves of *R. communis* L. was translocated to all other tissues of the plant. Developing fruit and especially seeds were found to be labeled the most rapidly. Young growing leaves and other developing tissues of the plant imported ricinine from the senescent leaves much more quickly than mature leaves[22]. Chemically synthesized ricinine-3,5-($^{14}$)C was used to study the metabolism of alkaloid in the plant *R. communis* L. In a time course study, ricinine-3,5-($^{14}$)C was administered to a series of *R. communis* L. and the radioactivity recovered in the ricinine samples showed a decrease with increase in time. In a comparison of the ricinine content of the various tissues it was observed that in the yellow leaf only a trace amount of the alkaloid was present[23].

## 7. Case study of ricinine on human

Serial ricinine levels are reported in the serum and urine of a patient suffering from intentional ricin intoxication. The patient was brought to hospital 4 h after injection and oral intake of a castor bean extract, but died 38 h later. The creatinine values indicated a concentration-time profile with a maximum ricinine level in urine between 12 and 29 h after exposure[24]. A case presented the attempted suicide of a 58-year-old man using castor beans. Urine samples were taken throughout the hospital stay for analysis of ricinine. The samples were found to be positive for ricinine, with a maximum concentration of 674 μg/g-creatinine excreted approximately 23 h post-exposur[25]. A case report presented a 49-year-old man who committed suicide by intravenous and subcutaneous injection of a castor bean extract. The identification of ricinine in the blood was performed by solid phase extraction in combination with full-scan gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography with photodiode array detection and liquid chromatography-mass spectrometry (LC-MS) operated in the full-scan mode respectively[26]. A case of multisystem organ failure after subcutaneous injection of castor oil for cosmetic enhancement was reported. Castor oil absorption was inferred from recovery of ricinine, in the patient's urine[27].

## 8. Analytical aspects of ricinine

Initial analytical methods for evaluating ricinine in the plants were based on paper chromatography and UV detection. Further mass spectrometry (MS) analyses of ricinine have been reported using electron impact and electrospray ionization[28]. A rapid and accurate method by liquid chromatography/tandem MS using positive electrospray was established for the determination of ricinine in cooking oils. This developed method could be valuable for rapid quantification of ricinine in cooking oils[29]. A metabonomic approach based on ultra performance liquid chromatography coupled with MS was used to study the hepatotoxicity of ricinine in rats. Potential biomarkers of ricinine toxicity and toxicological mechanism were analyzed by serum metabonomic method. Significant changes of metabolite biomarkers like phenylalanine, tryptophan, cholic acid, lysophosphatidylcholines and phosphatidylcholines were detected in the serum by this method[11]. Column chromatography and spectral analysis were used to isolate and identify the constituents present in the *Discocleidion rufescens* plants. Ten compounds were obtained and identified from root bark of *Discocleidion rufescens* including ricinine[30]. Ricinine is a urinary biomarker that can be measured to confirm human exposure to castor bean products. Sample preparation included a 96-well polystyrene divinylbenzene high throughput extraction and preconcentration step. Purified samples were analyzed by an efficient dual column, reversed-phase liquid chromatography separation and $^{13}$C-isotope dilution tandem MS[31]. The chemical study of *Aparisthmium cordatum* led to the isolation of alkaloid ricinine and other common compounds[32]. A generic method based on LC with full-scan high-resolution MS was systematically investigated for the simultaneous detection of a wide range of plant toxins including ricinine in a variety of food and feed matrices[33]. The ethanol extract of the dried, powdered hull portion of *R. communis* seeds indicated the presence of alkaloids, steroids, flavonoids, glycosides and phenolics. Ricinine was isolated as an active constituent and further characterised by various chemical and spectroscopic techniques[15]. in another study, ricinine is extracted from the sample with methanol. The sample extract is directly

used for screening with LC-MS and is cleaned up using solid-phase extraction for quantification with high performance liquid chromatography and LC-MS. A 9-min isocratic elution with 10% acetonitrile (v/v) at a flow rate of 0.2 mL/min is performed on an Atlantis dC18 column (5 microm, 2.1 mm × 100 mm) at ambient temperature[14]. A two-phase solvent system was used for high-speed counter-current chromatographic isolation of ricinine. Further LC-MS and GC-MS was used for high yield and purity. Identification of ricinine was performed by comparison of $^{1}$H nuclear magnetic resonance (NMR), $^{13}$C NMR and LC-MS/MS data[34]. Analysis of L-abrine was added to an existing method for quantifying ricinine as a marker for ricin exposure in human urine and analytically validated. One-milliliter urine samples were processed using solid-phase extraction prior to a 6-min high-performance liquid chromatography separation. Protonated molecular ions were formed via electrospray ionization in a triple-quadrupole mass spectrometer and quantified via multiple reaction monitoring[35]. In another method, the alkaloid ricinine was detected in gastric content by using a newly developed LC-MS method[36]. A new quantification method for ricinine was developed by using solid-phase extraction, isocratic high performance liquid chromatography, followed by electrospray ionization tandem MS[29]. A new analytical method using GC-MS in the electron ionization- and negative chemical ionization- or positive chemical ionization-mode and MS(n)-measurements with a 30 m Rtx 5MS fused-silica capillary column is developed to identify and quantify mycotoxins. This developed method can also be used to determine free ricinine in terroristic attacks[37]. LC-MS and matrix assisted laser desorption/ionization time-of-flight MS methods were developed for the determination of ricinine in crude plant materials[38]. Activity-guided fractionation of the methanol extract of *R. communis* stem led to the isolation of four compounds including ricinine[19]. In another method, two compounds ricinine, and its carboxylic acid derivative 3-carboxy-4-methoxy-N-methyl-2-pyridone were identified in the *R. communis*[39]. Serial ricinine levels are reported in the serum and urine of a patient suffering from intentional ricin intoxication. Ricinine was isolated from the samples by solid-phase extraction and quantitatively determined by isotopic dilution LC-MS method[24]. Identification of ricinine in the extract was performed by solid phase extraction in combination with full-scan GC-MS, high-performance liquid chromatography with photodiode array detection and LC-MS operated in the full-scan mode[26]. Ricinine was isolated from methanolic extract of Riccinus communis leaves by column chromatography method and further analyzed by IR and $^{1}$H NMR, $^{13}$C NMR and MS techniques[40].

## 9. Conclusions

The use of ricinine has been investigated as a multi-purpose medicinal phytoconstituents in the world of pharmaceuticals. It has been used for the development of different commercial applications in the natural health, food product and research field. Ricinine has several traditional medicine as well as modern medical uses. It showed different pharmacological activities including antiparasitic activity. Scientific validations have been done for its different pharmacological activities and for determination in the living tissue as well as in the plant several modern analytical methods have been validated. On the basis of its pharmacological activities, medicinal uses and analytical techniques, we can conclude that this unique phytoconstituent could be useful for the medical professionals, scientists and research scholars in the field of medicine and therapeutics. So this natural phytoconstituents should be further investigated in order to prove its benificial properties. In recent years, attention has been drawn to the health promoting activity of plant foods and their active components[41-43].

## Conflict of interest statement

We declare that we have no conflict of interest.

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