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CHEMISTRY, ECONOMIC, AND BIOLOGICAL ASPECTS OF *RICINUS COMMUNIS* PLANT

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ABSTRACT

Castor oil plant (Ricinus communis L.) is a fast-growing plant with valuable economic, pharmaceutical, and environmental values. It was reported to be used in traditional medicine by different nations and to have a lot of pharmacological and biological activity. The economic importance of *R. communis* is attributed to the production of castor oil from its seeds to be used in various industries including biodiesel production. Ricin which is a deadly toxic protein isolated from the castor seeds. However, there are some known toxic allergens as well as ricinine alkaloid. This widely distributed plant may have a valuble role in pharmaceuticals and renewable energy industries as well as very interesting uses in environmental fields.

KEYWORDS

Ricinus communis, Castor oil, Ricin, Ricinine.

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INTRODUCTION

Ricinus communis (Castor oil plant, Figure No.1) is adicot plant that belongs to the spurge family, Euphorbiaceae[1,2]. However there is a debate about the origin of *R. communis* to Egypt, its use by the ancient Egyptians was confirmed by its presence around their mummies thousands of years ago[3]. It is an invasive fast growing plant cultivated in many tropical and subtropical areas all over the world especially in India, China and Brazil[2]. Todays, in Egypt, *R. communis*is mostly growing as a weed in Delta, Nile valley, and Sinai[4]. It is classified according to United States Department of Agriculture(https://plants.usda.gov/core/profile?symbol=RICO3).

Phytochemical composition

Phytochemical constituents of different parts of *R. communis* plant were examined in multiple researches that were reviewed by Ribeiro *et al*[5]. They have reported that *R. communis* leaves are the most extensively studied part of the plant followed by the seeds. Furthermore, they reported the isolation and identification of 83 compounds from different parts of *R. communis* plant[5]. Ricinine was found to be the major alkaloid in *R. communis* plant and lower amounts of other natural ricinine analogues were also isolated from different parts of *R. communis* as shown in Table No.1. In addition to alkaloids *R. communis was* found tocontain a wide variety of chemical constituents including flavonoids, coumarins, tocopherols, benzoic acid derivatives, glycosides, fatty acids and terpenoids (Figure No.2).

***R. communis* seeds**

R. communis seeds are characterized by the presence of high percentage of fixed oil and proteins. Castor oil represents about 46-55% of the total seed weight[6]. It is a non-edible oil that is mainly composed of ricinoleic acid (12-hydroxy oleic acid) which represents about 85-89% of its fatty acid content. In addition to other minor fatty acids as linoleic, oleic, palmitic, and stearic acids[6,7], (Figure No.3). Defatted seeds (castor meal or castor cake) that is obtained after the production of oil contains several toxic components including a highly toxic protein (ricin), other toxic allergens and a moderately toxic alkaloid (ricinine)[8]. Large scale production of castor meal represents an environmental hazard because of the presence of these toxins. However, castor meal have about 34-36% protein content, it is used with caution as organic fertilizer and cannot be used as an animal feed because of the presence of these toxins[8,9]. Castor meal contains about 0.77% w/w of the alkaloid ricinine and it represents a good source for isolation of this alkaloid[10-12]. Using castor meal for isolation of ricinine alkaloid on large scale may reduce its environmental hazards and may provide additional medical and economic benefits for *R. communis* plant[11].

Environmental and economic importance of *R. communis* plant

R. communis was described to be a magical plant because of its vast environmental applications in phytoremediation[2]. It was reported to be efficiently used for remediation of contaminated soil with different types of pollutants such as various toxic metals and organochlorine pesticides[2, 13-15]. In addition to its environmental value, *R. communis* has great economic importance. The economic importance of *R. communis* plant is attributed to the production of castor oil from its seeds. It also has multiple uses in industry and energy production[2]. The presence of a hydroxyl group in the major component of the castor oil, ricinoleic acid imparts unique physical and chemical properties to the castor oil and makes it a very important raw material for various pharmaceutical and industrial applications[16,17]. *R. communis* plant can also be considered as a renewable source of energy because of the use of its oil for biodiesel production[18-21]. In addition, *R. communis* leaves are used as a source of food for *Eri*-silk worms[22,23].

Forensic medicine of *R. communis*

R. communis seeds have a long history of being used for intended and accidental intoxication in animals and humans. The poisonous effect of *R. communis* seeds is attributed to ricin protein which is classified as schedule 1 chemical weapon according to CWC. The cases of *R. communis* seeds or ricin poisoning were reviewed by Worbs *et al.*[24]. The most famous case for ricin intoxication was the historical assassination of the Bulgarian journalist Georgi Markov which took place in London, 1978. He was injected by a pellet impregnated with ricin fixed to an umbrella[25]. The presence of *R. communis* seeds and means for ricin isolation in criminal and terroristic locations worldwide was also reported[24]. Furthermore, threat letters containing ricin were reported to be sent to the White house members[24]. It is worth noting that however ricinine alkaloid has moderate toxicity, there is no reported cases for intoxication by ricinine alone. In addition, ricinine is used as a biomarker for tracing ricin toxicity[25].

Folk uses of *R. communis*

The traditional medicinal uses of *R. communis* worldwide were reviewed by Scarpa and Guerci[3]. They have mentioned that different parts of *R. communis* plant and its oil were used by different nations for treatment of respiratory, cardiovascular, digestive, venereal, and urogenital problems. They have also reported their uses for infectious diseases, oncology, paediatrics, dermatology, ophthalmology and gynaecology[3].

Pharmacological and biological activities of *R. communis*

The recent researches that were done on the pharmacological uses of *R. communis* plant extracts and the compounds isolated from them were reviewed by Jena and Gupta[26]. *R. communis* plant was reported to have the following activities:

Antimicrobial activity

It was reported that the antimicrobial activity of *R. communis* extracts, especially its leaf extract, is the most studied activity; however, the pure compounds responsible for this activity are not identified. The antibacterial and antifungal activities of extracts obtained from different tissues of *R. communis* using different solvents and its essential oil are tested against 33 microorganism. These different extracts showed various activities against different microorganisms, but it can be concluded that *R. communis* represents a good source for antimicrobial compounds and further studies are required for identification of these compounds[26].

Antioxidant activity

Several studies were done on the antioxidant activity of *R. communis* extracts and its essential oil using different test methods as summarized in Table No.2 and showed that *R. communis*has an efficient antioxidant activity. It was found that the antioxidant activity of the leaves extract is higher than that of the root extract and there were significant differences in the antioxidant activity of Tunisian samples that were collected from different places[27]. Singh and Chauhan[22] attributed the antioxidant activity of the leaves extract to the presence of phenolic and flavonoid compounds such as gallic acid, gentisic acid, quercetin, rutin, and epicatechin. While Oloyede[28] attributed the antioxidant activity of the methanolic extracts of the seeds toricinoleic acid, 12-octadecadienoic acid and their methyl esters. The essential oil obtained from *R. communis* aerial parts also showed a moderate antioxidant activity that was attributed to α-thujone, 1,8-cineole and other monoterpenes, but this activity was reported to be much lower than that of the positive control (BHT)[29].

Insecticidal activity

Ricinus communis is one of the most studied plants with insecticidal activity[30]. *R. communis* extracts showed insecticidal activity against various insects that cause loss for several important crops. *R. communis* seeds extract showed higher insecticidal activity than the leaves extract against *Culex pipiens* larvae[27] and *Spodoptera frugiperda* larvae[30]. It was also found that the methanolic extracts of the seeds had higher insecticidal activity than other solvent extracts[30]. Ramos-López *et al.*[30] attributed the insecticidal activity of *R. communis* against *S. frugiperda* to the castor oil and the alkaloid ricinine. While Wachira *et al.*[31] concluded that the alkaloid ricinine and its carboxylic acid derivative that were isolated from *R. communis* leaves extract contribute to its larvicidal activity against *Anopheles gambiae* vector and they showed slightly lower activity than the crude extract[31].

Cytotoxic activity

The cytotoxic activity of leaf extracts of *R. communis* against human Caucasian skin fibroblast was evaluated by Nemudzivhadi and Masoko[32]. This study showed that the crude leaf extracts are only toxic at high concentrations and they also affected the morphology of the cells by altering their shape[32]. The essential oil obtained from *R. communis* leaves showed quite strong cytotoxic activity on cervical cancer (HeLa cell lines) that was attributed to the synergistic effect between α-pinene and other components in the oil[33].

Hepatoprotective activity

The hepatoprotective activity of the ethanol extract of *R. communis* leaves was evaluated using galactosamine, paracetamol and carbon tetrachloride induced liver damage in rats by Visen

et al.[34] and Princea *et al.*[35]. In both studies the leaves extract showed comparable hepatoprotective activity to silymarine. The ethanol extract of the leaves also showed choleretic and anticholestatic activities[36]. They attributed these activities of the extract to the isolated compound, *N*-demethyl ricinine, which showed higher activities than the standard compound, silymarin[34,36]. While the alkaloid ricinine only showed mildcholeretic activity and no hepatoprotective activity[34,36]. Babu *et al.*[37] also studied the hepatoprotective activity of the methanolic leaves extract of *R. communis* against D-galactosamine induced liver damage in rats; However, they attributed this activity to the presence of the predominant compound, rutin[37].

Antidiabetic activity

Ricinus communis leaves extract obtained using 90% ethanol showed significant antidiabetic activity in streptozotocin-induced diabetes in rats[38]. *R. communis* root extract obtained using 50% ethanol has also showed hypoglycemic effects in both normal and diabetic rats[39]. In addition to its potent antihyperglycemic activity, the root extract also protected the animals' liver and kidneys from their damage by alloxan that was used for induction of diabetes. After fractionation of the root extract, only one fraction showed hypoglycemic activity; however the pure compound(s) responsible for this activity were not determined in this study[39].

Other activities

Ricinus communis is one of the most studied plants with insecticidal activity[30]. The cytotoxic activity of leaf extracts of *R. communis* against human Caucasian skin fi The hepatoprotective activity of the ethanol extract of *R. communis* leaves was evaluated using galactosamine, paracetamol and carbon tetrachloride induced liver damage in rats *Ricinus communis* leaves extract obtained using 90% ethanol showed significant antidiabetic activity in streptozotocin-induced diabetes in rats[38]. Anti-inflammatory anti-ulcer[39-43], antiulcer[44], analgesic[45], antiasthmatic[46], Immunomodulatory[47], antinociceptive[48], Contraceptive[49-50], antifertility[51,52] acaricidal[53-54] and anthelmintic[55] activities.

Ricinine is a simple, neutral, 2-pyridone alkaloid that is biosynthesised from nicotinic acid (Robinson and Fowell, 1959[56]; Waller and Henderson, 1961[57]; Waller and Nakazawa, 1963[58]. It was isolated for the first time from the castor-oil plant by Tuson in 1864 and the identification of its structure was accomplished in 1904 (Bogert, 1906; Jessen and Gademann, 2010). Ricinine is the predominant alkaloid in this plant, and it can be found in the extraction residue of the castor seeds, as well as other parts of the plant[57]. It is found in *R. Communis* leaves in combination with lower concentration of its *N*-demethylated derivative, *N*-demethy ricinine[59-61]. Although *R. communis* is the main source of ricinine, it can be also found in other plants as *Aparisthmium cordatum*[62], *Jatropha gossypifolia*, *Piper nigrum*, and some other solanaceous plants as *Nicotiana tabacum*[63].

Ricinine occurs as colorless prisms or needles with melting point 201.5°C. Despite being an alkaloid, it does not form salts with acids due to lacking of basic characters nor reacts with routinely used alkaloidal reagents[64]. It was thought to be the only natural cyano-substituted pyridine alkaloid till the isolation of the ricinidine alkaloid, nudiflorine from *Trewia nudiflora* plant[65,66].

Biological activities of ricinine

Insecticidal activity

Ricinine was reported to be the main component responsible for the insecticidal activity of *R. communis*[67,30,31]. Ricinine was reported to have insecticidal activity against *Atta sexdens rubropilosa*ants[67], *Spodoptera frugiperda* larva[30], and *Anopheles gambiae* vector[31]. The insecticidal activity of the carboxylic acid derivative of ricinine against *Anopheles gambiae* vector was also tested by Wachira *et al.*[31]. They concluded that the substitution of the nitrile group at the position 3 of ricinine does not affect its larvicidal activity as it has close activity to its 3-carboxylic acid derivative[31].

Ricinine effects on CNS

Ricinine was reported to have a memory enhancing activity and it did not show neuroleptic activity like *R. communis* extract. However, like other memory

enhancing drugs, it showed CNS stimulation and convulsion inducing activity at large doses[68]. Ferraz *et al.*[68] also estimated the LD_{50} of ricinine in mice to be 25 mg/kg. They concluded that ricinine-like drugs may be useful for treatment of amnesia accompanied with neurodegenerative diseases like Alzheimer's disease. Ferraz *et al.*[69] also proposed the use of ricinine as a model for epilepsy. Tripathi *et al.*[70] reported that ricinine has anticonvulsant activity using the maximal electroshock model in mice at a dose of 60 mg/kg. They also supported its use for treatment of epilepsy[71].

Other activities of ricinine

Wnt signalling, which plays a major rule in neuronal circuits in the brain, was activated by ricinine through inhibition of casein kinase 1α[71]. Therefore, ricinine may be suggested for treatment of several diseases associated with Wnt signalling hypoactivity as osteoporosis and Alzheimer's disease because of its involvement in proliferation, differentiation, and cell aging[71]. Ricinine was reported to have anti-inflammatory activity in hind paw edema induced by carrageenan in wistar rats[22]. It also showed a significant goitrogenic effect in rats in a study made by Pahuja *et al.*[72].

Ricinine toxicity

It was thought that ricinine is the component responsible for the poisonous effect of the castor beans till the identification of the main toxic component, ricin[73]. Ricinine is reported to have mild toxicity leading to toxic reactions as vomiting, hypotension, convulsions, nephrotoxicity, hepatotoxicity, and it may cause death[74,75]. The hepatotoxicity of ricinine was indicated by metabolic disorders in amino acids like phenylalanine and phospholipids[74]. Farah *et al.*[76] attributed the toxicity of ricinine to the presence of the cyanide group in its structure. They estimated the LD_{50} of ricinine in mice to be 10 mg/kg after subcutaneous injection. Ricinine toxicity was represented by inhibition of respiratory enzymes, stimulation of the intestine and the uterus, and reduction of the coronary and renal blood flow[76].

Ricinine analogues

Ricinine belongs to alkaloids containing cyano-α-pyridone nucleus. This nucleus is represented by limited number of natural compounds belonging to family Euphorbiaceae (Table No.1). While, cyano free α-pyridone nucleus is represented by large number of natural compounds isolated mostly from fungi.. There are also large number of synthetic compounds containing α-pyridone group, some of them shows the presence of cyanide group too. They can be exampled by the commercially known phosphodiesterase inhibitors, milirinone and olprinone, whose structures are closely related to that of ricinine (Figure No.4), (Fleming *et al.*,[77]. The α-pyridone ring and its natural and synthetic derivatives, were reported to have broad spectrum of pharmacological activities, including the CNS activity, antibacterial, antiviral, antitumor, and anti-inflammatory activities[78-83]. Despite the importance of the α-pyridone ring of ricinine and the availability of *R.communis* plant as a source for it, there are very small number of ricinine-derived compounds (Table No.3). It is also worth noting that the biological studies done on ricinine and its derivatives are limited and further studies are required for evaluation of their biological activities.

Table No.1: Natural ricinine analogues isolated from *R. communis* plant

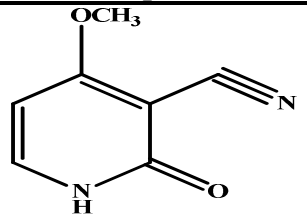
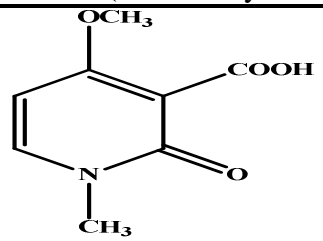
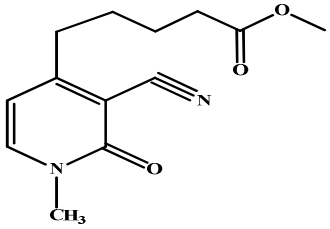
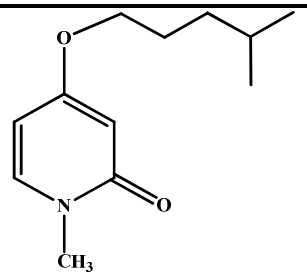
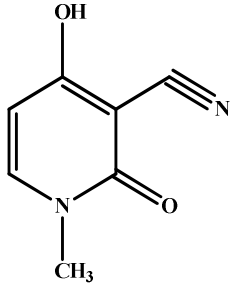
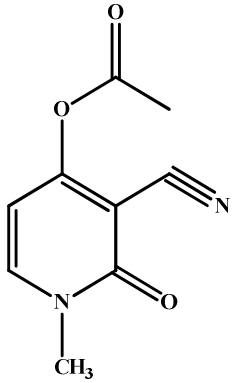
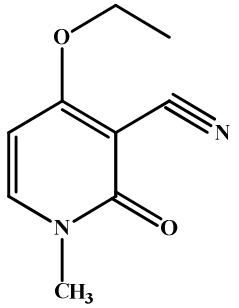
S.No	Compound	Source	Activity	References
1	 Norricinine (*N*-demethy ricinine)	*R. communis* leaves	Hepatoprotective activity	(61)
2	 4-Methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	*R. communis* leaves. It can also be obtained by biotransformation of ricinine with ricinine nitrilase.	Insecticidal activity against *Anopheles gambiae* vector.	(56)
3	 Methyl 5-(3-cyano-1-methyl-2-oxo-1,2-dihydropyridin-4-yl) pentanoate	*R. communis* seeds	Antifeedant activity against *Epilachna varivestis* larvae	(88)
4	 1-Methyl-4-((4-methylpentyl)oxy) pyridin-2(1*H*)-one	*R. communis* seeds	Antifeedant activity against *Epilachna varivestis* larvae	(88)

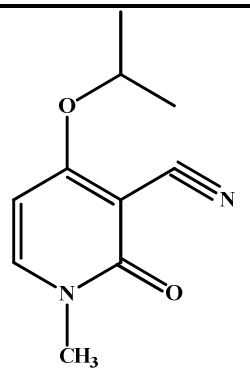
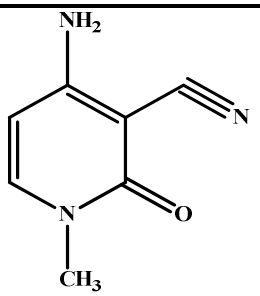
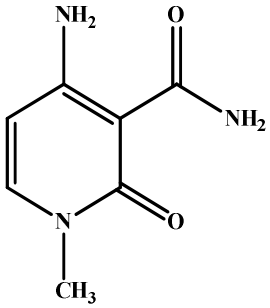
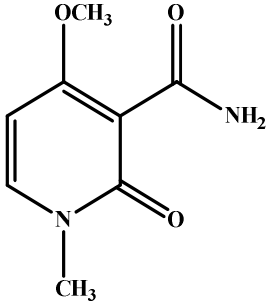
Table No.2: Summary of the reported antioxidant activity of *R. communis* extracts

S.No	Extract	Activity	Method	Reference
1	-Leaves extract -Root extract	IC_{50}: 0.65–3.91 µg/mL IC_{50}: 1.03–5.78 µg/mL	DPPH radical scavenging assay	(27))
2	-(MeOH-H_2O, 8:2) Leaves extract	IC_{50}: 2.70 µg/mL	DPPH radical scavenging assay	(22)

	-Methanolic leaves extract	IC_{50}: 4.66 µg/mL		
3	-Methanolic leaves extract	95% activity at 2.5 mg/mL	$ABTS^{+}$ scavenging assay	(32))
4	Essential oil of aerial parts	It exhibited half the antioxidant capacity of the +ve control at 300 µg/mL	DPPH radical scavenging assay, and α-carotene bleaching test.	(29)

Table No.3: Semisynthetic ricinine-derived analogues

S.No	Compound	Activity	Reference
1	 Ricininic acid (4-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile)	Not tested	(84)
2	 3-Cyano-1-methyl-2-oxo-1,2-dihydropyridin-4-yl acetate.	Not tested	(91)
3	 4-Ethoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile	Not tested	(56)

4	 4-Isopropoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile	Not tested	(56)
5	 4-Amino-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile	Not tested	(84)
6	 4-Amino-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	Not tested	(84)
7	 4-Methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	Antimicrobial activity against *Staphylococcus aureus*	(56)

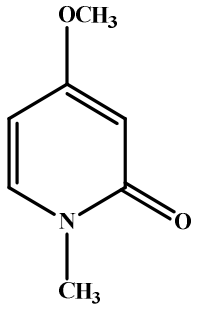
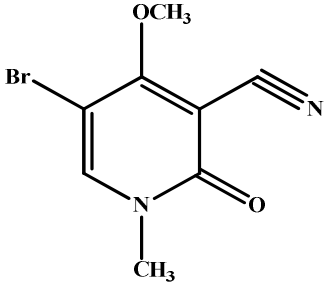
8	 4-Methoxy-1-methylpyridin-2(1*H*)-one	Not tested	(56)
9	 5-Bromoricinine (5-bromo-4-methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile)	Anti-tumor activity	(92)

Figure No.1: Photograph of *Ricinus communis* plant

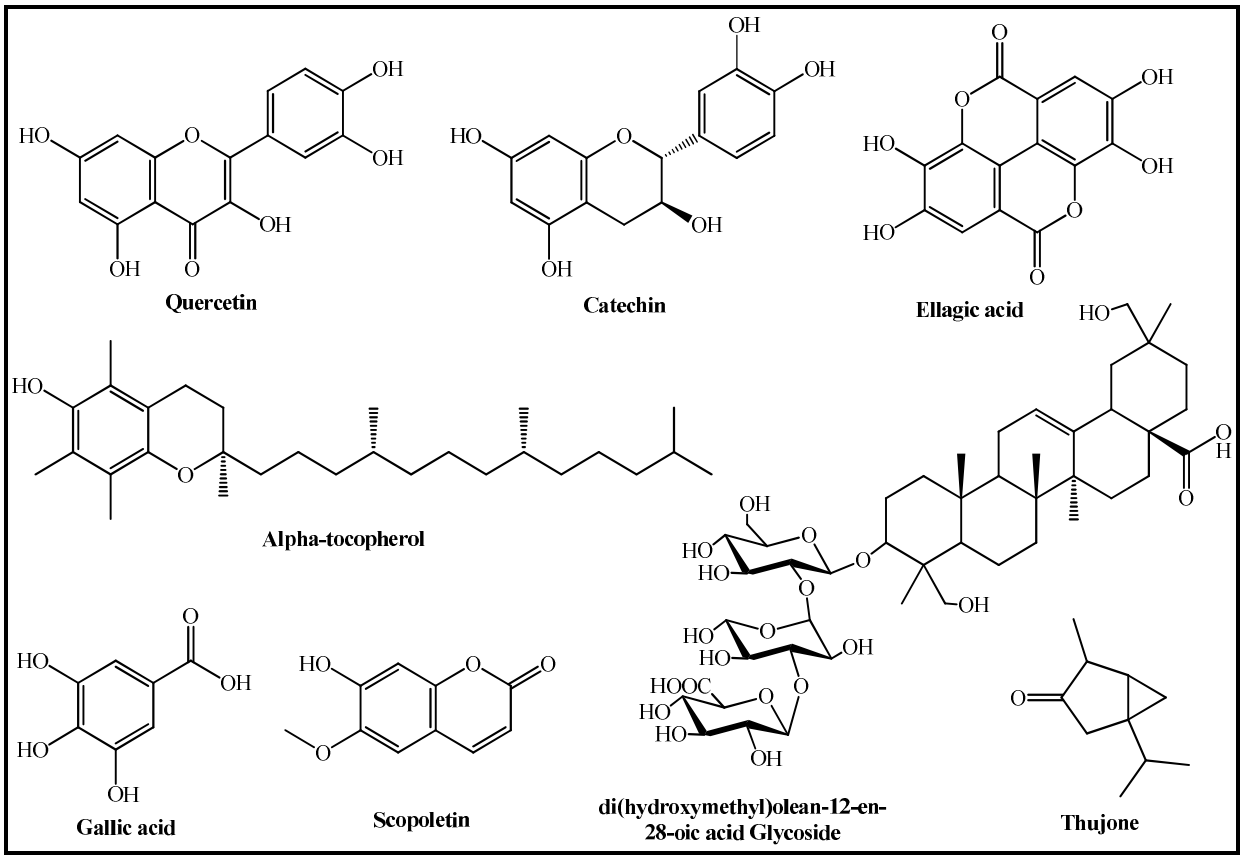


Figure No.2: Structures of other compounds representing different classes isolated from various parts of *R. communis* plant

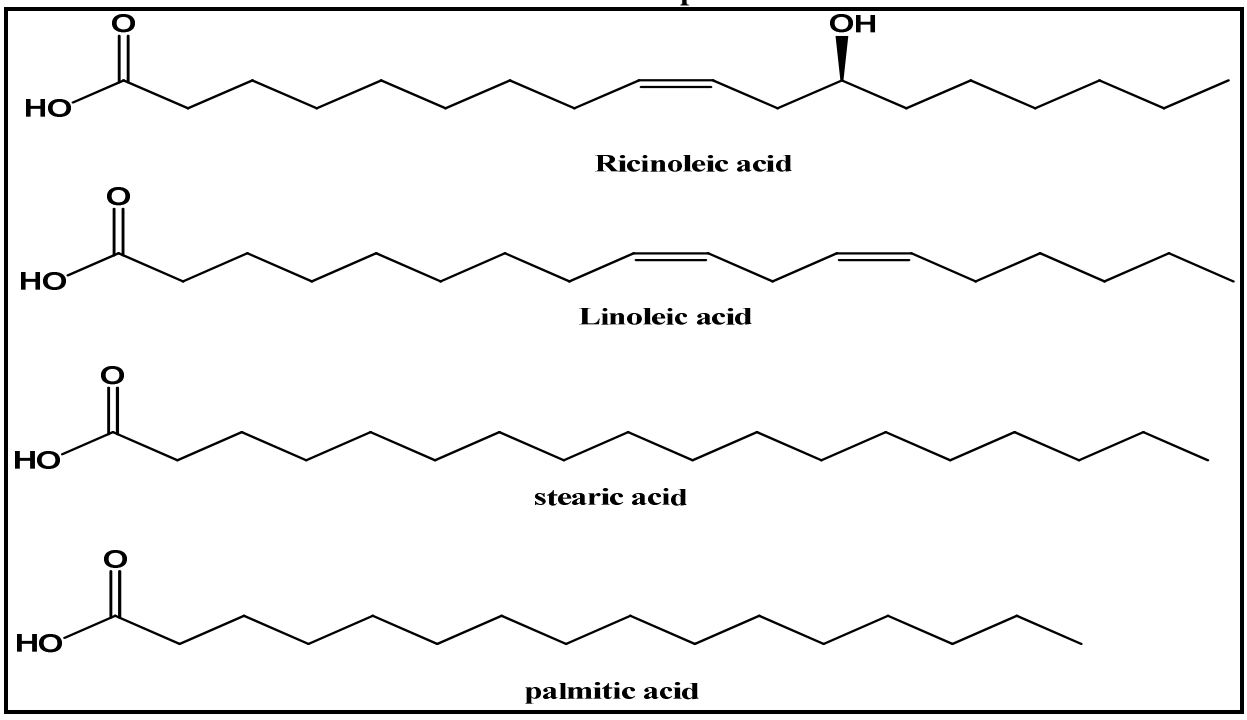


Figure No.3: Structures of some castor oil compo

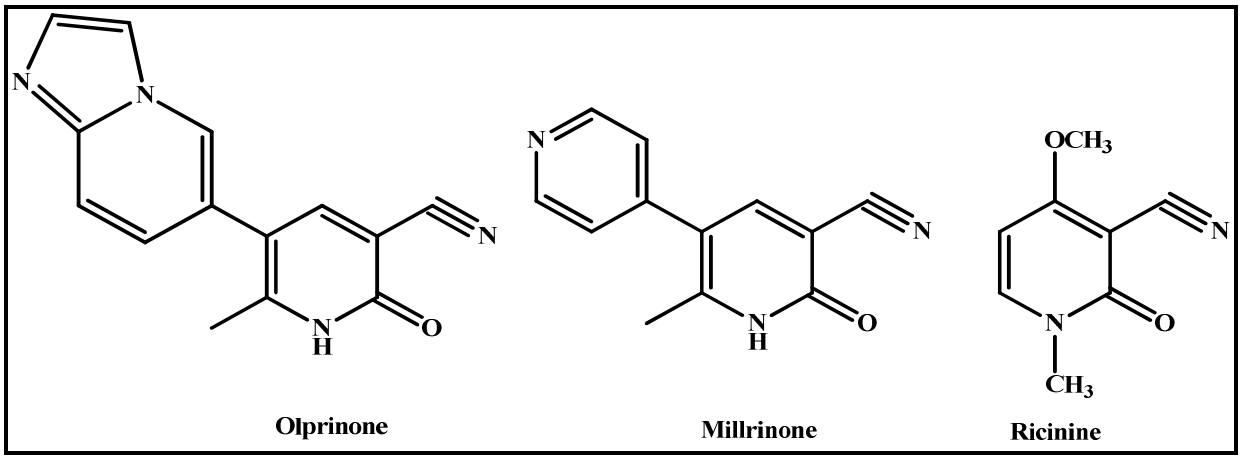


Figure No.4: Chemical structures of ricinine and the closely related phosphodiesterase inhibitors, milirinone and olprinone

CONCLUSION

R. communis could be a magical plant for its vast environmental applications in phytoremediation of contaminated soil with different types of pollutants such as various toxic metals and organochlorine pesticides. Moreover, it can also be considered as a renewable source of energy because of the use of its oil for biodiesel and as a source of food for *Eri*-silk worms. *Ricinus communis* is one of the most studied plants with insecticidal activity, cytotoxic activity of leaf extracts of *R. communis* against human Caucasian skin, hepatoprotective activity of the ethanol extract of *R. communis* leaves, and significant antidiabetic activity in streptozotocin-induced diabetes in rats. Also, showed Anti-inflammatory, analgesic, Immunomodulatory, antinociceptive, contraceptive, acaricidal, and anthelmintic activities.

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CONFLICT OF INTEREST

There is no conflict of interest.

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