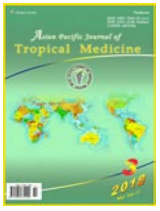

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Therapeutic role of *Ricinus communis* L. and its bioactive compounds in disease prevention and treatment

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ABSTRACT

Ricinus communis L. (*R. communis*), commonly known as castor oil plant, is used as a traditional natural remedy or folkloric herb for the control and treatment of a wide range of diseases around the globe. Various studies have revealed the presence of diverse phytochemicals such as alkaloids, flavonoids, terpenes, saponins, phenolic compounds such as kaempferol, gallic acid, ricin, rutin, lupeol, ricinoleic acid, pinene, thujone and gentisic acid. These phytochemicals have been responsible for pharmacological and therapeutic effects, including anticancer, antimicrobial, insecticidal, antioxidant, anti-diabetic, antinociceptive, anti-inflammatory, bone regenerative, analgesic, and anticonvulsant activity. *R. communis* harbours phytochemicals which have been shown to target peroxisome proliferator activated receptor (PPAR), nuclear factor NF-κ-B, cytochrome p450, P38 mitogen-activated protein kinases kinase (p38 MAPK), tumor protein P53, B-cell lymphoma-extra-large (Bcl-xL) and vascular endothelial growth factor receptor-2 (VEGFR-2). Considering its wide variety of phytochemicals, its pharmacological activity and the subsequent clinical trials, *R. communis* could be a good candidate for discovering novel complementary drugs. Further experimental and advanced clinical studies are required to explore the pharmaceutical, beneficial therapeutic and safety prospects of *R. communis* with its phytochemicals as a herbal and complementary medicine for combating various diseases and disorders.

1. Introduction

Nature has been an excellent source of therapeutic agents since the immemorial time[1]. Traditional and conventional medicines are mostly based on numerous natural resources, including plants which are being used as a primary source in folkloric medicine[2]. Before the discovery of chemical and synthetic compounds, these plants played a significant role as a traditional medicine for curing various diseases throughout the world[3]. However, with the emergence of modern techniques and equipment, synthesis of new classes of synthetic compounds has attracted attention among researchers during recent years. Some of these compounds were first isolated from the natural sources but further modified to improve their efficacy[4]. However, synthetic drugs have several limitations such as poor absorption, low bio-availability and adverse side effects. Thus, there is an urgent need to substitute these synthetic compounds with some excellent alternative sources of therapeutic

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agents which can be used for curing diseases around the globe. Plant-based biologically active compounds have gained momentum on a large scale in last 3 decades[5]. So, the idea of combining the old and conventional concept of using herbal plants as a primary source of folkloric medicine with the modern and latest technology based application can lead to tremendous development in the field of new drug discovery[6].

Plant-based compounds are of great interest for discovering a drug for the particular disease. Due to varied pharmacological activities of plants as tested by using the plant crude extracts, the screening and selection of lead candidates for drug development from medicinal plants have come into effect. The number of higher plant species estimated is 300 000–400 000. One of the most extensive programs of plant screening was conducted by Smith Kline & French in which about 19 000 plants species were screened using a simple colour test for alkaloid content detection in the 1960s[7].

Out of the 1 073 new chemical entities, that had been approved as drug between 1981 and 2010, the purely synthetic compounds amounts for only 36%, while most of the new drugs were derived from medicinal plants[1]. Many of the lead chemical structures used as a template for synthesis of drugs are derived from natural products which help in designing novel compounds with all the enhanced biological properties against some diseases. The WHO has predicted natural products as an essential resource for emerging therapeutics and future medicines. Based on the statistical estimation, nearly 83 billion USD worth of herbal medicine was used globally in 2008[8].

Development of resistance to various antibiotics is also a reason for the pharmaceutical industry to look for the discovery of novel molecules which can fight against various antibiotic-resistant microbes. Moreover, there is an urgent need to combat the menace of resistance developed towards anti-cancer drugs[9]. By deciphering the mechanism of action of various crude extracts and plant-based compounds, there is a excellent possibility for obtaining novel compounds[10]. Biological effects of the plants are determined and represented by various bioactive constituents present in it, which act as a ligand and bind to the protein targets of a particular pathogen, virus or tumour cell and exert their action[11].

Ricinus communis L. (*R. communis*) is a medicinal plant which grows to a height of about 6 m and is distributed around various continents including Arabian Peninsula. Castor plant has been cultivated as far back as 6 000 years ago[12]. The botanical name of *R. communis* was coined by Swedish naturalist Carlos Linnaeus in the 18th century[13]. Some scholars believe its origin to be from Tropical Africa. In Saudi Arabia, it is commonly known as Kherwa[12]. It is an angiosperm shrub which is commonly known as castor oil plant. Castor bean is an oilseed crop which is fast-growing, suckering perennial herb belonging to spurge (Euphorbiaceae) family, comprising of about 6 300 species[14]. *R. communis* has been a therapeutic agent for 4 000 years, used as a herbal medicine for treating many different diseases, disorders and also many infections. Leaves, root, bark and various parts of the *R. communis* have been used for medicinal purposes. It has been used as a laxative for 2 500 years in Greece and Rome[12]. Due to the large quantity of oil extracted from *R. communis* seeds, it has been known as castor oil plant[15]. This oil is of great application in various perspectives[12]. The various phytochemicals which are found in *R. communis* are steroids, terpenoids, saponins, alkaloids, flavonoids, and glycosides[19,22,30]. Lectins of *R. communis* are also used prominently in the treatment of some diseases, especially tumour[16]. In the present review, the primary focus is on the pharmacological activities and bioactive compounds of *R. communis*, and their applications in targeting of various microbes, infectious diseases and disorders.

2. Traditional uses of *R. communis*

There are numerous uses of *R. communis* plant which utilizes every part of the plant including roots, seeds, bark, leaves, flower, fruit and stem[12]. The leaves are made up of 5–12 deep lobes, which are coarsely toothed segmental, that are palmate and alternate. The powdered leaves are found to be effective in combating mosquitoes, repelling aphids, rust mites and whiteflies. Apart from this, the leaves are found to be responsible for the increase in the yield of milk in cattle which is fed with these leaves. The oil derived from these leaves is used in relieving flatulence in infants. An infusion of leaves is used as an eye lubricant and also for relieving stomach ache. The leaves as such are used as a decoction or poultice and applied to breasts of females for an increase in milk secretion (lactation). Fresh juice obtained from leaves has been reported for its use as an emetic in the poisoning of narcotics like opium. Some have reported that leaves can be useful against jaundice too[18]. Extracts from leaves of the plant are being marketed under the trade name 'Spra Kast' in the United States. Antifungal activity of aqueous and alkaline extracts against *Mycobacterium tuberculosis* and yeast was also reported[17].

Roots are used for various purposes such as a powerful purgative, for a toothache, and this can be possible when the roots are administered in the form of decoction and paste respectively. Roots contain Indole-3-acetic acid. Seeds of *R. communis* vary in size, shape, and color, and they are compressed and oval with a diameter of 8–18 mm. Castor seeds have a wart appendage called the caruncle. Seeds are the primary source of oil which is in use both as a herbal medicine and as a conventional therapy for various ailments[18].

3. Phytochemical composition of *R. communis*

R. communis is rich in a diverse variety of phytochemicals, Alugah

and Ibraheem have reported the flavonoids and tannins content in the castor plant[19]. Following are the individual studies reporting the isolation of compounds from R.communis plant. *R. communis* contain various bioactive phytochemicals such as kaempferol-3-*O* and kaempferol-3-*O*- β -*D*-glucopyranoside[20], ingenol[21] triterpenoids (lupeol, β - and α -amyrin)[22], quercetin and gallic acid[23], αthujone, camphor and beta thujone[24], ricin[25], epicatechin[26], gentisic acid[27], catechin[28], linoleic acid and ricinoleic acid[29], kaempferol-3-*O*- β -*D*-glucopyranoside and quercetin-3-*O*- β -monoterpenoids[30].

4. Pharmacological applications of *R. communis*

R. communis is a multipurpose folkloric medicinal plant with some medicinal properties; these properties are associated with either direct application of crude plant extract as a therapeutic agent in various diseases or by inhibition of harmful pathogens, which are known to cause various infections and diseases. Among the various reported activities of *R. communis*, a large number of them are attributed to its extract in crude form followed by various fractions which could be ethanolic, methanolic or chloroform, ethyl acetate, toluene, benzene, and butanol solvents.

Numerous studies have been carried out and published on the biological activities of *R. communis* plants. These activities are both due to the crude extract and its phytochemical compounds which can be of great interest in future for the development of plant-based complementary medicine. Presently, the properties of *R. communis* mentioned in this review include antimicrobial, antifungal, anti-cancer, antidiabetic, anti-inflammatory, antimalarial, antioxidant, central analgesic, anticonvulsant, antinociceptive, anthelminthic, antifertility, laxative, uterine contracting, anti-implantation, anti-asthmatic, bone regeneration, molluscicidal, antiulcer, antihistamine, wound-healing, cytotoxic, insecticidal, anti-arthritic, antidandruff and hepatoprotective (Figure 1). Diverse phytochemicals bind to specific molecular targets and hence exhibit several pharmacological activities as shown in Table 1.

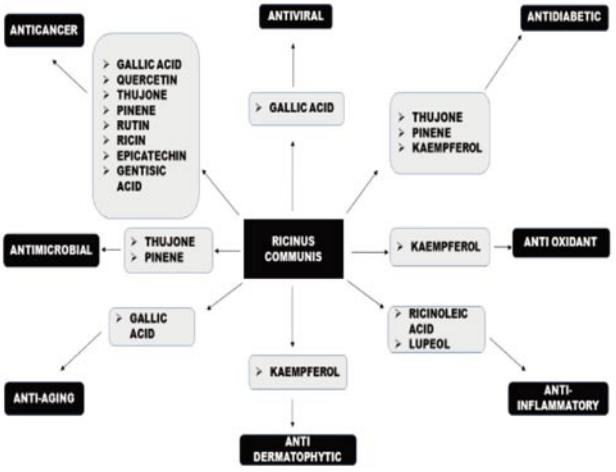

Figure 1. Phytochemicals of *R. communis* and their pharmacological activity.

4.1. Antibacterial activity

Due to the increase in the incidence of infections in human beings with various clinical strains of bacteria and adoption of resistance against the antibiotics, there is a great need to find the reliable alternative sources to combat this so-called life-threatening issue of antibiotic resistance[43]. *R. communis* and its phytochemicals have been found to have antimicrobial properties against various microorganisms. Some of the reported antimicrobial activity of the crude extract includes inhibition of various bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mutans*, *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus*[44].

The activity of the *R. communis* has been tested using various aqueous and solvent-based extracts. The different solvents systems used are ethanolic extract (hot and cold), methanolic extract, ethyl acetate extract, butanolic extract and so forth. The ethanolic extract was found to be most effective in a large number of the cases, and the highest activity was shown against *Staphylococcus aureus* with a MIC of 5 mg/mL[45]. In one study, methanolic extract

Table 1

Biological activity of phytochemicals from *R. communis* against different potential molecular targets.

Phytochemical	Molecular targets	Therapeutic effect	Reference
Rutin	Peroxisome proliferator activated receptor	Anti-diabetic	[31]
	NFK-*p*	Anti-cancer	[32]
Gentistic acid	Cytochrome p450	Anti-cancer	[33]
Quercetin	P38mitogen-activated protein kinases kinase	Anti-cancer	[34]
	P53 B-cell lymphoma-extra-large	Anti-cancer	[35]
Gallic acid	Epidermal growth factor	Delay in cellular aging	[36]
Kaempferol-3-*O*- β -*D*-rutinoside	THR15	Anti-dermatophytics	[30]
Ricin-A	Cyclooxygenase-2 and nuclear factor- κ B/p65	Anti-cancer	[37]
Ricin	Caspase 3	Anti-cancer	[38]
Ricinus agglutinin	Vascular endothelial growth factor receptor-2	Anti-tumor	[39]
α-pinene	Cyclin dependent kinase	Anti-cancer	[40]
	Campylobacter jejuni 1687	Anti-bacterial	[41]
α-thujone	5-hydroxy-3-methylglutaryl-coenzyme A	Anti-diabetic	[42]

exhibited maximum activity against *Escherichia coli* and lowest activity against *Bacillus subtilis*[46]. A study, conducted for testing the antibacterial activity indicated that *Ricinus* aqueous extract had shown the highest activity against *Staphylococcus aureus* and lowest activity was shown towards *Klebsiella pneumonia*[47]. A randomised clinical study, against bacterial pathogens, has shown the *R. communis* activity as a complete cleanser solution. Inhibition of biofilm formation is due to the presence of sodium ricinoleate in *R. communis* oil, which damages cell wall and leads to cell death by loss of cytoplasmic components[48]. By the above results, it can be concluded that *R. communis* can be a good source for an antibacterial drug against various bacterial pathogens.

4.2. Antifungal activity

Various parts of *R. communis* including root, leaf and stems are known to have antifungal activity. Both methanolic and aqueous extracts of *R. communis* are found to be active against many fungal species. A study was carried out for testing the antifungal activity of *R. communis* extract against various fungal species, the maximum antifungal activity was shown against *Candida albicans*, and lowest activity was detected against *Alternaria solani*[17]. One of the studies, showed that the methanolic extract has prominent inhibitory activity against *Aspergillus niger* and *Aspergillus fumigatus* and less activity against *Aspergillus flavus*[45]. Another study, carried out with aqueous *R. communis* leaf extract have shown lowest activity against *Aspergillus fumigatus* and *Aspergillus flavus*[46]. The above-mentioned studies confirm the antifungal activity of *R. communis* extract, and it may be a good source for identifying a new drug candidate for inhibiting the fungi.

4.3. Anti-diabetic activity

Diabetes is a chronic disease that occurs either when the pancreas does not produce insulin required by the body or due to development of insulin resistance. The number of people who have diabetes has risen steeply from 108 million cases to 422 million in 2014 (WHO). In 2012 diabetes was the sole cause of 1.5 million deaths (WHO 2015). A study was conducted to test the antidiabetic activity of ethanolic extract of *R. communis* roots and have been found to be effective against hypoglycemic rats. After treating alloxan diabetic rats for 20 d with a single dose of 500 mg/kg body weight (effective dose), lipid profile was observed by collecting blood on day 0, day 10 and day 20 of the experiment. This study demonstrated the significant lowering of fasting blood sugar to almost normal level and an increase in insulin levels, thereby causing improvement in lipid profile and body weight as well. The decrease in blood glucose levels was from (379±72) mg/dL (Diabetic rat) to (149±11) mg/dL (control)[49]. Another *in vivo* study, on alloxan-induced diabetic rats, had reported that blood glucose levels decreased from 390.0 to 148.5 mg/dL after treatment with *Ricinus* extract, approximately 61.97% reduction in blood glucose for over a period of 7 d[50]. These studies suggest the potential of *R. communis* as a therapeutic agent for diabetic control.

4.4. Anti-cancer activity

Some studies have been carried out using fractions with 100% ethanol, methanol and an aqueous phase which have shown activity against specific cancer cell lines such as melanoma, MCF7 (Breast cancer), HepG2 (Hepatic cancer), PC3 (Pancreatic cancer), and cervical cancer[51]. Both *in vitro* and *in vivo* studies have confirmed the anti-cancer activity of *R. communis* using various plant parts and ricin lectins[52,53].

Anti-cancer activity of *R. communis* was studied and reported by several researchers. Initial studies revealed the cytotoxic effect of lectins from *R. communis* on three different cell lines HeLa cells, sarcoma 180 and human erythrocytes[54]. Lin and Liu observed the increase in lifespan of the mice which is treated with ricin A[55]. In one study, the aqueous extracts of *R. communis* was found to exhibit cytotoxic effects on A375 cell lines (human melanoma cancer cell lines) with IC_{50} value of 48 μg/mL[56]. According to You and colleagues, the agglutinin 1 from *Ricinus*, resulted in rapid down-regulation of vascular endothelial growth factor-2 (VEGFR-2) and also caused apoptosis of endothelial cells in tumour blood vessels[39]. Ohishi *et al*. have analyzed an alkaloid pyridine which was found to be effective against the β-catenin (WNT) signalling pathway, having an essential role in proliferation, differentiation and development of cells leading to cancer[16].

Some other *in vitro* studies were carried out to test the cytotoxic effects of *R. communis* on various cell lines such as colon cancer, liver cancer, breast cancer, cervix cancer, ovarian cancer (OVCAR-5), skin melanoma (B16F10) and prostate cancer. At lower concentrations of about 100 μg/mL, the *R. communis* extract was tested against these cancer cell lines and was shown to be effective[51]. The anti-cancer activity of *R. communis*, as revealed by several studies, clearly suggests that *R. communis* may be a good source for anti-cancer therapeutic compounds.

4.5. Anti-inflammatory activity

R. communis has been shown to possess potent anti-inflammatory activity. Various fractions like ethanolic, methanolic or hexane have been utilised for assessing the anti-inflammatory potential of *R. communis*. In one of the studies, the anti-inflammatory action of *R. communis* extract was tested by using the hexane, acetone, and

methanol fractions. The methanolic extract showed significant anti-inflammatory activity which may be due to flavonoids present in it. In this study, Raw 264.7 macrophage cell lines were used to test the anti-inflammatory activity which resulted in 95% scavenging activity at 2.5 g/mL with methanolic extract [57].

Another study by Lindauer *et al*. demonstrated the anti-inflammatory and pro-inflammatory activity upon repeated application, and this was found to be mediated by ricinolein[58]. *In vivo* studies for anti-inflammatory activity were carried out in two animal models, i.e., carrageenan-induced paw edema model and cotton pellet granuloma model. In carrageenan model, the dose of 100 mg/kg was found to inhibit edema by 26.47%[59]. *Ricinus* methanolic extract reduced edema by 43.28% in cotton pellet granuloma models at a dose of 250 and 500 μg/kg[60]. This activity was due to the activation of the nucleotide-binding domain and leucine-rich protein (NALP3) inflammasome. Another *in vivo* study, exhibiting the anti-inflammatory activity of *R. communis* was performed in carrageenan or histamine-induced edema in mice or guinea pigs respectively. Topical administration of ricinoleic acid from *R. communis* for 8 d (0.9 mg/mouse) reduced edema by 58%. This confirms that ricinoleic acid has the potential to be a new capsaicin-like substance representing a class of potent anti-inflammatory compound[61].

4.6. Antioxidant activity

Antioxidants are the first line of defence towards free radical damage and play a significant role in maintaining cell viability and optimum health. Many of the neurodegenerative diseases are related to free radicals exposure to the cell. The DPDH (1,1-diphenyl-2-picryohydrazyl) mediated *in vitro* study, reveals the antioxidant activity of *R. communis* due to the presence of compounds such as gallic acid, quercitin, gentisic acid, rutin, epicatechin and ellagic acid in leaves and methanolic extract[62]. In another study, the antioxidant activity of *R. communis* was confirmed in the methanolic extract; polar solvents seem to extract compounds responsible for antioxidant activity. This study, suggests *R. communis* as a source to scavenge both 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals[63]. Another study has shown the scavenging abilities of DPDH, NO, and superoxide radicals to prove *R. communis* as a novel antioxidant[62]. Highest antioxidant activity was shown by butanol fraction of *Ricinus*[64]. Ethyl acetate extract of *R. communis* was also found to be a potent antioxidant. The antioxidant activity of *R. communis* is attributed more to flavonoids as compared to tannins[63, 65].

4.7. Mosquitocidal activity

R. communis exhibited larvicidal effects against various mosquito larvae. Studies have been carried out on various species of mosquitoes such as *Anopheles gambiae*, *Anopheles stephens*, *Anopheles albopictus*, and *Culex quinquefasciatus*, with a mortality of nearly 100%. The lethal concentration of seed extract of *Communis* among various larval species is as follows: *Culex quinque fasciatus* (7.10 μg/mL)>*Anopheles stephensi* (11.64 μg/mL)>*Anopheles albopictus* (16.84 μg/mL)[66,67].

Malaria is a life-threatening disease which is caused by parasites that are transmitted by the bites of certain species of infected *Anopheles* mosquitoes to humans. Despite an increase and growth in research to a large extent over the past 2 decades, malaria has been a worldwide epidemic leading to hundreds of thousands of deaths every year. According to WHO global estimate documents, about 2.7 million cases of malaria were reported and an estimated 627 000 deaths were seen in 2012 (WHO 2012). *Plasmodium falciparum* is known to exhibit resistance to various available anti-malarial drugs. *R. communis* is found to have the highest activity against the *Anopheles gambiae* which is a vector for malaria. Both male and female larvae of *Anopheles gambiae* are susceptible to *R. communis* extracts. This activity was supposed to be due to the presence of two compounds ricinine and 3-carboxy-4methoxy-N-methyl-2-pyridone[67]. The larvicidal activity of the different extracts was found to be increasing with increase with the larval exposure. Extracts from *R. communis* have recorded highest mortality with a lethal concentration 50 (LC_{50}) of 0.18 mg/mL[67]. Apart from this, the extract from *Ricinus* was found to be effective against *Anopheles arabiensis* and *Culex quinque fasciatus*[68].

4.8. Analgesic activity

R. communis was found to possess potent central analgesic activity. Various studies have been conducted for demonstrating the analgesic activity of *R. communis* extract. It is studied and proved that *R. communis* extract has typical central nervous system stimulant and neuroleptic effects. The stimulant effects such as hyperreactivity, memory improvement and clonic seizures are due to the alkaloid ricinine in *R. communis*. Ricinine is non-anxiogenic as it does not reduce exploratory behaviour of the brain[69].

In another study, the analgesic activity of aqueous extract of *R. communis* root bark was evaluated against a standard drug diclofenac at a dose of 50 mg/kg. The doses of *R. communis* extract used are 100 and 200 mg/kg in Albino mice. Two methods were used for determining the analgesic activity, i.e., Eddy's hot plate method and tail immersion method[69,70]. In one of the studies, the effect of methanolic extract of *Ricinus* leaves has proved to be having high antinociceptive activity. A dose of 150 mg/kg showed a gradient increase in the tail flick of mice from (2.900±0.194) in control at 0 min to (6.30±0.110) with *Ricinus* treated mice indicating the analgesic activity of *R. communis*[71].

4.9. Anticonvulsant activity

Epilepsy is a pervasive disorder with seizure formation due to neuronal discharges of the brain. Some isolated compounds from *R. communis* have been tested for anticonvulsant activity and proved to be reliable epileptic. After electric shock treatment, all the animals exhibited convulsions. Animals receiving a dose of 60 mg/kg of a compound from *R. communis* seeds exhibited an inhibition of seizure to about 82% compared to a standard drug which exhibited an 8.89% seizure inhibition[72].

4.10. Anti-helminthic activity

R. communis was studied for its antihelmintic activity in inducing paralysis and time taken to cause the death of worm. Both ethanolic and aqueous extracts were used for evaluating the anthelmintic activity. Aqueous *Ricinus* extract showed high activity at 100 mg/mL in less time when compared to ethanolic extract, *i.e.*, 8.50±0.64 (paralysis) and 31.50±1.25 (death) at a concentration of 100 mg/mL was demonstrated for aqueous extract. Thus the aqueous extract of *R. communis* was found to be having more anti-helmintic activity[73].

4.11. Anti-fertility activity

The anti-fertility effects of *R. communis* were studied in male rats which revealed a reduction of epididymal sperm counts. Main features observed after treatment with 50% ethanolic extracts of *R. communis* include alteration in motility and morphology of sperms was also affected[74]. In another study, semen parameters have been observed wherein the suppression of testicular function is reported in male Wistar rats treated with *R. communis* (10 mg/kg)[65]. Clinical study, carried out by Isichei and colleagues, for antifertility effects in females with a single dose have prevented pregnancy for 12 months[75].

4.12. Laxative and uterine contracting

Castor oil induces laxation and uterus contraction by involving ricinoleic acid activating prostaglandin receptors 2. Castor oil and ricinoleic acid induce contraction of the intestinal smooth muscle. Both gut and uterus motility is affected. Prostaglandin receptors 2 are proved to be potential targets for drugs to induce laxation[76].

4.13. Antiulcer activity

R. communis was found to possess significant antiulcer properties. A study, carried out with initial dose 500 mg/kg, has demonstrated the anti-ulcer property of *R. communis*. The mechanism underlying the anti-ulcer activity of *R. communis* is the cytoprotective action and strengthening of gastric mucosa which ultimately results in the enhancement of mucosal defence[77].

4.14. Antiasthmatic activity

In a study by Dnyaneshwar and Patil, *R. communis* had shown significant anti-asthmatic activity. *R. communis* exhibited the mast cell stabilising effect due to saponin content in its roots, whereas flavonoids are responsible for bronchodilation and smooth muscle relaxant activity. The anti-allergic activity was determined by *in vivo* studies which play a vital role in the treatment of asthma. The ethanolic extract was effective in reducing the milk induced leukocytosis and eosinophilia due to the presence of flavonoids and saponins[78].

4.15. Bone regeneration

Oil of *R. communis* was used in various bone-related diseases in ancient period as a herbal and folkloric medicine. The diseases which used to be treated by *R. communis* include bone deformities, acute osteomyelitis, articular pains, and afflicted limbs[12]. R.communis has the unique capacity of regeneration of bone without the formation of any scar following its damage. Formation of polyurethane resin promotes fibroblastic neoformation progressively replacing the bone from inside and around the porosities of the biomaterial in the absence of delayed inflammatory reaction without any signs of systematic toxic effects, as being observed both in rat alveolus and rabbit skulls[79]. Biological properties of *R. communis* polyurethane can be improved by subsequently incubating in the synthetic body fluids. *R. communis* polyurethane blended with calcium phosphate could promote matrix mineralisation and can be of immense interest in the preparation of biocompatible materials, when compared with demineralised bone. The *R. communis* polyurethane has the advantage of slower reabsorption process[79]. The animal study was performed for treatment of osteoarthritis by using *Lawsonia inermis* and *R. communis* in rats for 14 d and had shown a significant effect in treatment without any adverse effects A[80]. All the above data confirmed the bone reformation activity of *R. communis*, and it may be a novel bone reforming substance for treatment of arthritis and osteoarthritis.

5. Toxicological studies of *R. communis*

R. communis has shown some toxic effects accidentally due to the presence of toxic compounds such as ricin and ricinine. Some of the *in vivo* mouse model studies have shown the ricin toxicity which may vary from hyperactivity to seizure formation and maybe even lead to death at a dose of more than 340 mg/kg

intraperitoneally and 3 g/kg orally. However, independent of its uptake, ricin is found to be almost toxic, and there is an increase in the severity of symptoms with an increase in the dose. Symptoms include abdominal pain, emesis, muscular pains, cramps in the limbs, dyspnea, circulatory collapse, dehydration, dysfunction of kidney and liver. Autopsy results in fatal cases have shown the hemorrhagic necrosis in heart, intestine, and edema[43,81].

6. Conclusions and prospects

R. communis is one of the medicinal plants which have multiple pharmacological applications against various diseases and disorders. The anti-cancer, antidiabetic and antimicrobial activities of *R. communis* are the shaft of light in treating the death-causing diseases throughout the world. The various biological activities of *R. communis* is due to the presence of a varied degree of bio-active phytochemicals. Through this review, it can be justified that both crude form of plant extract and the isolated compounds are responsible for its pharmacological and therapeutic potential. Further studies and utilisation of these plant compounds in an isolated form can be performed to explore their mechanism of action and by deciphering the actual process by which these plant phytochemicals reach the target and exert their action. Novel drugs can be designed by performing various *in vitro* and animal studies of these phytoconstituents. *R. communis* was used for the synthesis of nanoparticles for testing its activity against both microbial pathogens and cancer cell lines; these nanoparticles will be of keen interest in target drug delivery.

Conflict of interest statement

The authors declare that they have no competing interests.

References

[1] Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* 2016; **79**(3): 629-661.

[2] Moreira DL, Teixeira SS, Monteiro MHD, De-Oliveira ACAX, Paumgartten FJR. Traditional use and safety of herbal medicines. *Rev Bras Farmacogn* 2014; **24**(2): 248-257.

[3] Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol Adv* 2015; **33**(8): 1582-1614.

[4] Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010; **74**(3): 417-433.

[5] Bérdy J. Thoughts and facts about antibiotics: Where we are now and where we are heading. *J Antibiot* 2012; **65**(8): 441.

[6] Haque MA, Louis VR, Phalkey R, Sauerborn R. Use of traditional medicines to cope with climate-sensitive diseases in a resource poor setting in Bangladesh. *BMC Public Health* 2014; **14**: 202.

[7] Koehn FE, Carter GT. The evolving role of natural products in drug discovery. *Nat Rev Drug Discov* 2005; **4**(3): 206-220.

[8] Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Front Neurol* 2014; **4**: 1-10.

[9] Levy SB. Factors impacting on the problem of antibiotic resistance. *J Antimicrob Chemother* 2002; **49**(1): 25-30.

[10] Pan SY, Zhou SH, Gao SH, Yu ZL, Zhang FS, Tang MK, et al. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. *Evid Based Complement Alternat Med* 2013; **2013**: 1-25.

[11] Sasidharan S, Chen Y, Saravanan D, Sundram KM, Yoga Latha L. Extraction, isolation and characterization of bioactive compounds from plants' extracts. *Afr J Tradit Complement Altern Med* 2011; **8**(1): 1-10.

[12] Scarpa A, Guerci A. Various uses of the castor oil plant (*Ricinus communis* L.) a review. *J Ethnopharmacol* 1982; **5**(2): 117-137.

[13] Ogunniyi DS. Castor oil: A vital industrial raw material. *Bioresour Technol* 2006; **97**(9): 1086-1091.

[14] Rivarola M, Foster JT, Chan AP, Williams AL, Rice DW, Xinyue L, et al. Castor bean organelle genome sequencing and worldwide genetic diversity analysis. *PLoS One* 2011; **6**(7): e21743.

[15] Chan AP, Crabtree J, Zhao Q, Lorenzi H, Orvis J, Puiu D, et al. Draft genome sequence of the oilseed species *Ricinus communis*. *Nat Biotechnol* 2010; **28**(9): 951-956.

[16] Ohishi K, Toume K, Arai MA, Sadhu SK, Ahmed F, Mizoguchi T, et al. Ricinine: A pyridone alkaloid from *Ricinus communis* that activates the Wnt signaling pathway through casein kinase 1. *Bioorg Med Chem* 2014; **22**(17): 4597-4601.

[17] Vandita P, Amin N, Khyati P, Monisha K. Effect of phytochemical constituents of *Ricinus communis*, *Pterocarpus santalinus*, *Terminalia belerica* on antibacterial, antifungal and cytotoxic activity. *Int J Toxicol Pharmacol Res* 2013; **5**(2): 47-54.

[18] Rana M, Dhamija M. *Ricinus communis* L. – A Review. *Int J Pharmacol Res* 2012; **4**(4): 1706-1711.

[19] Alugah CI, Ibraheem O. Whole plant screenings for flavonoids and tannins contents in castor plant (*Ricinus communis* L .) and evaluation of their biological activities. *Int J Herbal Med* 2014; **2**(2): 68-76.

[20] Khafagy SM, Mahmoud ZF, Salam NAE. Coumarins and flavanoids of *Ricinus communis* growing in Egypt. *Planta Medica* 1979; **37**: 191.

[21] Rinner U. Progress in the preparation of jatrophane diterpenes. *Eur J Org Chem* 2015; **15**: 3197-3219.

[22] Vermeer CP, Nastold P, Jetter R. Homologous very-long-chain 1,3-alkanediols and 3-hydroxyaldehydes in leaf cuticular waxes of *Ricinus communis* L. *Phytochem* 2003; **62**(3): 433-438.

[23] Ghosh S, Tiwari SS, Srivastava S, Sharma AK, Kumar S, Ray DD,

et al. Acaricidal properties of *Ricinus communis* leaf extracts against organophosphate and pyrethroids resistant Rhipicephalus (Boophilus) microplus. *Vet Parasitol* 2013; **192**(1-3): 259-267.

[24]Zarai Z, Chobba IB, Mansour RB, Békir A, Gharsallah N, Kadri A. Essential oil of the leaves of *Ricinus communis* L.: *In vitro* cytotoxicity and antimicrobial properties. *Lipids Health Dis* 2012; **11**: 102.

[25]Ngo T, Nguyen T, Bui D, Hoang N, Nguyen T. Effects of ricin extracted from seeds of the castor bean (*Ricinus communis*) on cytotoxicity and tumorigenesis of melanoma cells. *Biomed Res Ther* 2016; **3**(5): 633-644.

[26]Zahir AA, Rahuman AA, Bagavan A, Geetha K, Kamaraj C, Elango G. Evaluation of medicinal plant extracts and isolated compound epicatechin from *Ricinus communis* against Paramphistomum cervi. *Parasitol Res* 2011; **111**(4): 1629-1635.

[27]Singh PP, Ambika, Chauhan SMS. Activity guided isolation of antioxidants from the leaves of *Ricinus communis* L. *Food Chem* 2009; **114**(3): 1069-1072.

[28]Rondon FCM, Bevilaqua CML, Accioly MP, Morais SM, Andrade-Junior HF, Machado LK, et al. *In vitro* effect of *Aloe vera*, *Coriandrum sativum* and *Ricinus communis* fractions on *Leishmania infantum* and on murine monocytic cells. *Vet Parasitol* 2011; **178**(3-4): 235-240.

[29]Houbairi S, Elmiziani I, Lamiri A, Essahli M. Comparison of the antioxidant activity of aromatic medicinal plants of Moroccan origin. *Eur J Med Plants* 2015; **10**(4): 1-10.

[30]Jeyam M, Arangaraj M, Ravikumar P, Shalini G. Computational analysis of phytocompounds with 1,3- β -*D*-glucan synthase for antidermatophytic activity. *Sci Rep* 2014; **6**: 24027.

[31]Sharma S, Ali A, Ali J, Sahni JK, Baboota S. Rutin: Therapeutic potential and recent advances in drug delivery. *Expert Opin Investig Drugs* 2013; **22**(8): 1063-1079.

[32]Kyung TW, Lee JE, Shin HH, Choi HS. Rutin inhibits osteoclast formation by decreasing reactive oxygen species and TNF-alpha by inhibiting activation of NF-kappaB. *Exp Mol Med* 2008; **40**(1): 52-58.

[33]Nafees S, Ahmad ST, Arjumand W, Rashid S, Ali N, Sultana S. Modulatory effects of gentisic acid against genotoxicity and hepatotoxicity induced by cyclophosphamide in Swiss albino mice. *J Pharm Pharmacol* 2012; **64**(2): 259-267.

[34]Ranganathan S, Halagowder D, Sivasithambaram ND. Quercetin suppresses Twist to induce apoptosis in MCF-7 breast cancer cells. *PLoS One* 2015; **10**(10): e0141370.

[35]Wang G, Zhang J, Liu L, Sharma S, Dong Q. Quercetin potentiates doxorubicin mediated antitumor effects against liver cancer through p53 / Bcl-xl. *PLoS One* 2012; **7**(12): e51764.

[36]Buachan P, Chularojmontri L, Wattanapitayakul S. Selected activities of *Citrus maxima* Merr. fruits on human endothelial cells: Enhancing cell migration and delaying cellular aging. *Nutrients* 2014; **6**(4): 1618-1634.

[37]Zhou XX, Ji F, Zhao JL, Cheng LF, Xu CF. Anti-cancer activity of anti-p185HER-2 ricin A chain immunotoxin on gastric cancer cells. *J Gastroenterol Hepatol (Australia)* 2010; **25**(7): 1266-1275.

[38]Tyagi N, Rathore SS, Ghosh PC. Efficacy of liposomal monensin on the enhancement of the antitumour activity of liposomal ricin in human epidermoid carcinoma (KB) cells. *Indian J Pharm Sci* 2013; **75**: 16-22.

[39]You W, Kasman I, Hu-lowe DD, Mcdonald DM. *Ricinus communis* agglutinin I leads to rapid down-regulation of VEGFR-2 and endothelial cell apoptosis in tumor blood vessels. *Am J Pathol* 2010; **176**(4): 1927-1940.

[40]Chen W, Xu B, Mao J, Wei F, Li M, Liu T, et al. Inhibitory effects of α-pinene on hepatoma carcinoma cell proliferation. *Asian Pac J Cancer Prev* 2014; **15**: 3293-3297.

[41]Kovac J, Šimunovic K, Wu Z, Klancnik A, Bucar F, Zhang Q, et al. Antibiotic resistance modulation and modes of action of (-)-α-Pinene in Campylobacter jejuni. *PLoS One* 2015; **10**(4): e0122871.

[42]Baddar NW, Aburjai TA, Taha MO, Disi AM. Thujone corrects cholesterol and triglyceride profiles in diabetic rat model. *Nat Prod Res* 2011; **25**(12): 1180-1184.

[43]Friedman M, Rasooly R. Review of the inhibition of biological activities of food-related selected toxins by natural compounds. *Toxins* 2013; **5**(4): 743-775.

[44]Abew B, Sahile S, Moges F. *In vitro* antibacterial activity of leaf extracts of *Zehneria scabra* and *Ricinus communis* against *Escherichia coli* and methicillin resistance *Staphylococcus aureus*. *Asian Pac J Trop Biomed* 2014; **4**(10): 816-820.

[45]Jeyaseelan EC, Jashothan PTJ. *In vitro* control of *Staphylococcus aureus* (NCTC 6571) and *Escherichia coli* (ATCC 25922) by *Ricinus communis* L. *Asian Pac J Trop Biomed* 2012; **2**(9): 717-721.

[46]Abd-Ulgadir KS, Suliman SI, Zakria IA, Hassan NEA. Antimicrobial potential of methanolic extracts *Hibiscus sabdariffa* and *Ricinus communis*. *Adv Med Plant Res* 2015; **3**: 18-22.

[47]Naz R, Bano A. Antimicrobial potential of *Ricinus communis* leaf extracts in different solvents against pathogenic bacterial and fungal strains. *Asian Pac J Trop Biomed* 2012; **2**(12): 944-947.

[48]Salles MM, Badaró MM, Arruda CN, Leite VM, Silva CH, Watanabe E, et al. Antimicrobial activity of complete denture cleanser solutions based on sodium hypochlorite and *Ricinus communis* – a randomized clinical study. *J Appl Oral Sci* 2015; **23**(6): 637-642.

[49]Shokeen P, Anand P, Murali YK, Tandon V. Antidiabetic activity of 50% ethanolic extract of *Ricinus communis* and its purified fractions. *Food Chem Toxicol* 2008; **46**(11): 3458-3466.

[50]Matthew OO, Olusola L, Matthew OA. Preliminary study of hypoglycaemic and hypolipidemic activity of aqueous root extract of *Ricinus communis* in alloxan-induced diabetic rats. *J Phys Pharm Adv* 2012; **2**(10): 354-359.

[51]Prakash E, Gupta DK. *In vitro* study of extracts of *Ricinus communis* Linn on human cancer cell lines. *J Med Sci Pub Health* 2014; **2**(1): 15-20.

[52]Ravishankar K, Indira K, Vijay Bhaskar R. *In vivo* hepatoprotective activity of *Ricinus communis* Linn leaf extract against CCl_4 induced

hepatic damage in albino rats. *Int J Bio Pharma Res* 2012; **3**(3): 444-449.

[53]Saha S, Ghosh M, Dutta SK. Role of metabolic modulator Bet-CA in altering mitochondrial hyperpolarization to suppress cancer associated angiogenesis and metastasis. *Sci Rep* 2016; **6**: e23552.

[54]Endo Y, Tsurugi K. Mechanism of action of ricin and related toxic lectins on eukaryotic ribosomes. *Nucleic Acids Symp Ser* 1986; **17**: 187-190.

[55]Lin JY, Liu SY. Studies on the antitumor lectins isolated from the seeds of *Ricinus communis* (castor bean). *Toxicon* 1986; **24**(8): 757-765.

[56]Shah TI, Sharma E, Shah GA. Inhibitory property of aqueous extract of *Ricinus communis* leaves on proliferation of melanoma treated against A375 cell lines. *World J Pharma Sci* 2015; **3**(4): 758-761.

[57]Nemudzivhadi V, Masoko P. *In vitro* assessment of cytotoxicity, antioxidant and anti-inflammatory activities of *Ricinus communis* (Euphorbiaceae) leaf extracts. *J Evid Comple Altern Med* 2014; **2014**: e625961.

[58]Lindauer M, Wong J, Magun B. Ricin toxin activates the NALP3 Inflammasome. *Toxins* 2010; **2**(6): 1500-1514.

[59]Valderramas AC, Moura SHP, Couto M, Pasetto S, Chierice GO, Guimarães SAC, et al. Antiinflammatory activity of *Ricinus communis* derived polymer. *Brazil J Oral Sci* 2008; **7**(27): 1666-1672.

[60]Srivastava P, Jyotshna, Gupta N, Maurya AK, Shanker K. New anti-inflammatory triterpene from the root of *Ricinus communis*. *Nat Prod Res* 2014; **28**(5): 306-311.

[61]Vieira C, Evangelista S, Cirillo R, Lippi A, Maggi CA, Manzini S. Effect of ricinoleic acid in acute and subchronic experimental models of inflammation. *Mediators Inflamm* 2000; **9**: 223-228.

[62]Ahmed D, Khan M, Saeed R. Comparative analysis of phenolics, flavonoids, and antioxidant and antibacterial potential of methanolic, hexanic and aqueous extracts from *Adiantum caudatum* leaves. *Antioxidants* 2015; **4**(2): 394-409.

[63]Singh PP, Ambika, Chauhan SMS. Activity guided isolation of antioxidants from the leaves of *Ricinus communis* L. *Food Chem* 2009; **114**(3): 1069-1072.

[64]Iqbal J, Zaib S, Farooq U, Khan A, Bibi I, Suleman S. Antioxidant, antimicrobial, and free radical scavenging potential of aerial parts of *Periploca aphylla* and *Ricinus communis*. *ISRN Pharmacol* 2012; **2012**: 563267.

[65]Nath S, Kadasi A, Grossmann R, Sirotkin AV, Kolesarova A, Talukdar AD, et al. *Ricinus communis* L stem bark extracts regulate ovarian cell functions and secretory activity and their response to luteinising hormone. *Int J Impot Res* 2015; **27**(6): 215-220.

[66]Mandal S. Exploration of larvicidal and adult emergence inhibition activities of *Ricinus communis* seed extract against three potential mosquito vectors in Kolkata, India. *Asian Pac J Trop Med* 2010; **3**(8): 605-609.

[67]Wachira SW, Omar S, Jacob JW, Wahome M, Alborn HT, Spring DR, et al. Toxicity of six plant extracts and two pyridone alkaloids from *Ricinus communis* against the malaria vector *Anopheles gambiae*. *Parasit Vectors* 2014; **7**(1): 312.

[68]Elimam AM, Elmalik KH, Ali FS. Larvicidal, adult emergence inhibition and oviposition deterrent effects of foliage extract from *Ricinus communis* L against *Anopheles arabiensis* and *Culex quinquefasciatus* in Sudan. *Trop Biomed* 2009; **26**(2): 130-139.

[69]Ferraz AC, Angelucci MEM, Costa MLD, Batista IR, Oliveira BHDE, Cunha CDA. Pharmacological evaluation of ricinine, a central nervous system stimulant isolated from *Ricinus communis*. *Plant Physiol* 1999; **63**(3): 367-375.

[70]Almeida RN, Navarro DS, Barbosa-Filho JM. Plants with central analgesic activity. *Phytomedicine* 2001; **8**(4): 310-322.

[71]Taur DJ, Waghmare MG, Bandal RS, Patil RY. Antinociceptive activity of *Ricinus communis* L. leaves. *Asian Pac J Trop Biomed* 2011; **1**(2): 139-141.

[72]Tripathi AC, Gupta R, Saraf SK. Phytochemical investigation, characterisation and anticonvulsant activity of *Ricinus communis* seeds in mice. *Nat Prod Res* 2010; **25**: 1881-1884.

[73]Rana M, Kumar H, Parashar B. *In vitro* anthelmintic activity of bark of *Ricinus communis* Linn. *J Chem Pharma Res* 2013; **5**(6): 40-42.

[74]Sandhyakumary K, Bobby RG, Indira M. Antifertility effects of *Ricinus communis* (Linn) on rats. *Phytothera Res* 2003; **17**(5): 508-511.

[75]Isichei CO, Das SC, Ogunkeye OO, Okwuasaba FK, Uguru VE, Onoruvwe O, et al. Preliminary clinical investigation of the contraceptive efficacy and chemical pathological effects of RICOM-1013-J of *Ricinus communis* var minor on women volunteers. *Phytother Res* 2000; **42**(1): 40-42.

[76]Tunaru S, Althoff TF, Nusing RM, Diener M, Offermanns S. Castor oil induces laxation and uterus contraction via ricinoleic acid activating prostaglandin EP3 receptors. *Proc Natl Acad Sci USA* 2012; **109**(23): 9179-9184.

[77]Rachhadiya RM, Prasad KM, Shete RV. Evaluation of antiulcer activity of castor oil in rats. *Int J Res Ayur Pharm* 2011; **2**(4): 1349-1353.

[78]Dnyaneshwar JT, Patil RY. Antiasthmatic activity of *Ricinus communis* L. roots. *Asian Pac J Trop Biomed* 2011; **1**: S13-S16.

[79]Beloti MM, Oliveira PT, Tagliani MM, Rosa AL. Bone cell responses to the composite of *Ricinus communis* polyurethane and alkaline phosphatase. *J Biomed Mater Res A* 2007; **84**(2): 435-441.

[80]Ziaei A, Sahranavard S, Gharagozlou MJ, Faizi M. Preliminary investigation of the effects of topical mixture of *Lawsonia inermis* L. and *Ricinus communis* L. leaves extract in treatment of osteoarthritis using MIA model in rats. *DARU J Pharma Sci* 2016; **24**: 12.

[81]Bhaskaran M, Didier PJ, Sivasubramani SK, Doyle LA, Holley J, Roy CJ. Pathology of lethal and sublethal doses of aerosolized ricin in *Rhesus macaques*. *Toxicol Pathol* 2014; **42**(3): 573-581.