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Review Article

Antileishmanial derivates of natural products from Ricinus communis

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Abstract:

Continuous and advanced studies are necessary to explore and meet the continuous need of safe plant compounds necessary for pharmaceutical, therapeutic, food and other industries, especially special phytochemicals to be used as herbal and complementary medicine to combat various diseases and disorders. In this review, we highlight the uses of Ricinus communis in traditional medicine for treatment and others since ancient civilizations and its content of chemical compounds with multiple biological and therapeutic effects, including phenolic compounds, alkaloids, saponins, flavonoids, terpenes and oils and their uses as anti-cancer, antioxidant, anti-diabetic, anti-microbial, insecticide and anti-asthma Anti-ulcers, antimalarials, anti-inflammatories, hepatoprotective, bone regeneration, analgesics and anticonvulsants. It is worth noting that *Ricinus communis* grows in tropical and subtropical regions widely distributed throughout the world and the active substances are found in various parts of the plant, which necessitated that we focus the light on the plant and its multiple benefits and its rich effective compounds to further clinical, experimental and advanced studies to explore more and verify safety prospects.

Keywords: *Ricinus communis*, castor oilseed, *Leishmania*, pharmacology, bioactive compounds, fatty acids, essential oil.

1. An overview of castor (*Ricinus communis*)

There are many sources of treatment in nature, as many medicines depend on natural resources, including plants that are used as a basic source in folk medicine due to plant compounds are of great importance due to their diversity of pharmacological activities (Moreira et al., 2014; Said-Al Ahl et al., 2017; Hikal et al., 2021). Besides, plants are a source of food, fodder and fuel, etc (Fokou et al., 2016; Thomford et al., 2016; Hikal et al., 2017).

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Herbal medicines derived from plants and their use in treatment as an alternative to chemical medicines are easy to obtain and affordable, while being safe to use (Adaramola et al., 2016; Hamid et al., 2016; Hikal et al., 2020), plant-based bioactive compounds do not have any side effects compared to synthetic drugs and have a wide range of therapeutic applications (Samad et al., 2016; Hikal and Said-Al Ahl, 2019 a and b).

Ricinus communis is an annual oilseed crop, which grows in tropical and subtropical regions widely distributed throughout the world (Junior et al., 2011; Anjani, 2014). Also, Perdomo et al., 2013 showed that oil production seed oil content ranges from 40 to 60% and annual oil production is about 1.8 million tons worldwide. Castor oil is used in agricultural, pharmaceutical and industrial applications. Various castor oil products exist such as ointments, nylon, varnishes, airplane engine lubricants, hydraulic fluids, dyes, detergents, plastics, paints, synthetic leather, cosmetics, and perfumes (Yeboah et al., 2020; Ying et al., 2017) and biofuel/biodiesel production (Worbs et al., 2011; Berman et al., 2011). Residues after oil extraction from castor seeds are a rich source of protein and after detoxification have been used as a food supplement for cattle, sheep, chicken and fish (Gowda et al., 2009; Diniz et al., 2011; Ani et al., 2007), and the use of seed residues as manure or manure (Lima et al., 2011).

Traditionally, various plant parts such as roots, bark, leaves, flowers, stem, seed and seed oil were used for medicinal purposes as a laxative or to treat infections and inflammations, as a remedy for toothache and as a flavoring in ancient civilizations (Abdul et al., 2018; Parkouda et al., 2009). The leaves were also used against jaundice and to relieve stomach pain and flatulence, anti-fungal activity against *Mycobacterium tuberculosis* and yeast and in controlling mosquitoes and repelling aphids, rust mites and whiteflies (Abdul et al., 2018). The seeds were also used for resistance against *Tribolium castaneum* (Adekunle, 2011). In recent years, it has been reported numerous biological activities of *R. communis* plants are antimicrobial, antifungal, anticancer, antidiabetic, anti-inflammatory, antimalarial, antioxidant, central analgesic, anti-implantation, antiasthmatic, bone regeneration, molluscicidal, antiulcer, antihistamine, wound-healing, cytotoxic, insecticidal, anti-arthritic, antidandruff and hepatoprotective (Berman et al., 2011). Figure 1 shows the different stages of *Ricinus communis* plant.

Ricinus communis (Family: Euphorbiaceae)



Fig.1. Vegetative, flowering and fruiting stages of Ricinus communis.

2. Leishmaniases

Leishmaniasis is caused by the Leishmania parasite and is transmitted by more than 20 species of Leishmaniasis known to be infectious to humans by infected female phlebotomine sandflies. There are three main types of leishmaniasis: i) visceral, often known as kala-azar and

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the most serious form of the disease (VL); ii) cutaneous, the most common (CL); and iii) mucocutaneous. Leishmaniasis, classified as a neglected tropical disease, is a parasitic disease found in parts of tropical, subtropical and southern Europe as a result of infection with Leishmania parasites, which are spread by the bite of infected phlebotomine sand flies. There are several different forms of leishmaniasis in humans. The most common forms are cutaneous leishmaniasis, which causes skin sores, and visceral leishmaniasis, which affects several internal organs (usually spleen, liver, and bone marrow) (CDC, 2020). It is not found in Australia or the Pacific Islands. Also, leishmaniasis is found in some parts of Mexico, Central America, and South America. While, Some people have a silent infection, without any symptoms or signs, but the symptoms of cutaneous leishmaniasis can be clarified in the following; one or more sores on their skin. The sores can change in size and appearance over time and may be covered by scab or crust. While, the symptoms of visceral leishmaniasis are fever, weight loss, enlargement (swelling) of the spleen and liver, and abnormal blood tests. People may have low blood counts, including a low red blood cell count (anemia), a low white blood cell count (leukopenia), and a low platelet count (thrombocytopenia). Sand flies become infected by sucking blood from an infected animal or person. Some types (species) of Leishmania parasites also may be spread via contaminated needles (needle sharing) or blood transfusions. Congenital transmission (spread from a pregnant woman to her baby) has been reported. The number of new cases may vary or change over time and are difficult to estimate (CDC, 2020; Hikal and Said-Al Ahl, 2017; WHO, 2021). Tables 1-3 show the reported cases for the year 2020 according to the World Health Organization. However, table 4. Show the number of cases of cutaneous leishmaniasis and visceral leishmaniasis reported in Arab Countries (2008 – 2020).

1	Pakistan	16.770
2	Peru	4.178
3	Egypt	2.239
4	Sri Lanka	2.217
5	Honduras	1.467
6	Saudi Arabia	1.035
7	Ecuador	1.025
8	Panama	938
9	Costa Rica	528
10	Burkina Faso	416
11	Mexico	324
12	Guatemala	121
13	Turkmenistan	107
14	Israel	86
15	Kazakhstan	79
16	Senegal	64
17	Suriname	42
18	El Salvador	38
19	Jordan	23
20	Guyana	12
21	Kuwait	6
22	Bulgaria	1
23	Cyprus	1
24	Montenegro	1
25	Namibia	1
26	Nigeria	1
27	Slovenia	1

	Table 2. Number of cases of visceral leishman	niasis globally in 2020.
1	Sudan	2.563
2	India	2.033
3	Eritrea	1.034
4	South Sudan	827
5	Somalia	471
6	China	215
7	Uganda	55
8	Bangladesh	47
9	Georgia	42
10	Greece	34
11	Djibouti	9
12	Albania	6
13	Uruguay	2

Table 2. Number of cases of visceral leishmaniasis glob	ballv in	2020.
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Table 3. Total number of cases of cutaneous and visceral leishmaniasis globally in 2020.
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		cutaneous leishmaniasis	visceral leishmaniasis	Total
1	Syria	61.559	22	61.581
2	Afghanistan	44.167	١٢	44.179
3	Brazil	16.056	1.954	18.010
4	Algeria	11.566	٣٣	11.599
5	Iraq	8.691	61	8.752
6	Colombia	6.124	8	6.132
7	Tunisia	4.872	28	4.900
8	Yemen	3.605	450	4.055
9	Libya	4.000	24	4.024
10	Morocco	3.774	67	3.841
11	Nepal	3.443	215	3.658
12	Ethiopia	1.402	1.077	2.479
13	Bolivia	2.059	2	2.061
14	Venezuela	1.597	6	1.603
15	Kenya	398	1.178	1.576
16	Uzbekistan	761	47	808
17	Argentina	176	11	187
18	Chad	38	74	112
19	Paraguay	54	26	80
20	France	34	26	60
21	Cameroon	4	٣٣	37
22	Italy	6	29	35
23	Armenia	1	15	16
24	Malta	1)	2

2.1. Antileishmanial property of *Ricinus communis*

Treatment of leishmaniasis takes a long time and needs frequent and painful injections with high cost, and besides the increasing resistance to common drugs, all of them have increased the complications of treatment of the disease (Sadeghian et al., 2008). Which led to the evaluation of therapeutic methods in the field of herbal products as a result of their benefits and the discovery of their chemical compounds against Leishmania infection (Accioly et al., 2012; Date et al., 2007; Corral et al., 2016). Ricinus communis have been reported as future alternatives to sand fly control (Sadeghian et al., 2008; Schlein et al., 2001) where, feeding on R. communis increases sandfly mortality and causes stomach abnormalities of the parasite (Dinesh et al., 2014). In vivo study on Ricinus communis ethyl acetate extract revealed the high effectiveness against amastigotes and promastigotes of Leishmania infantum and the low cytotoxicity towards murine monocytic cells (Rondon et al., 2011). Also, Bahmani et al. (2015) explained the antagonistic effect of *Ricinus communis* on cutaneous leishmaniasis.

Number of cases of cutaneous leishmaniasis reported [2008 - 2020]													
	2020	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008
Algeria	11.566	10.293	10.847	13.106	10.678	7.523	5.423	6.428	7.418	11.742	10.173	10.666	8.442
Egypt	2.239	1.811	1.161	566	643	2.243	1.444	464	1.260	864	318	174	471
Iraq	8.691	7.056	11.426	18.854	17.566	17.525	2.691	1.648	2.486	2.978	3.113	2.086	1.250
Libya	4.000	6.744	2.977	2.815	2.662	1.632	516	505	1500	1.327	2.273	1.691	1.800
Morocco	3.774	5.455	11.834	6.802	4.903	2.809	2.555	2.592	2.877	4.319	8.707	6.013	5.128
Saudi Arabia	1.035	1.096	921	1.007	1.337	1.490	2.190	1.988	1.464	1.951	4.129	2.549	2.321
Syria	61.559	71.704	80.215	53.232	47.377	50.972	53.876	71.996	55.894	58.156	42.172	46.348	29.140
Tunisia	4.872	7.085	7.467	4.902	6.095	6.611	3.368	4.113	5.376	5.114	3.811	1.737	2.750
Yemen	3.605	4.440	4.763	4.525	9.120	4.063	5.000	3.823	3.629	2.124	3.234	1.801	1.090
Jordan	23	69	150	155	126	70	182	146	103	136	155	148	244
Kuwait	6	-	4	1	7	0	2	14	4	7	12	8	_
Oman	0	0	0	1	1	0	0	-	2	0	3	4	7
Sudan	-	3.299	4.107	3.011	3.503	1.053	336	206	111	752	-	-	-
Lebanon	-	2	0	0	0	3	2	0	2	5	6	1	0
						al leishm		_					
	2020							2013	2012	2011	201		2008
Algeria	33	46	40	34	74	38	30	54	53	89	87	84	84
Egypt	0	0	00		0	0	0	0	0	0	-	-	1
Iraq	61	170	259	172	183	427	362	575	1.045	1.167	1.84		1.041
Libya	24	28	34	18	10	0	1	12	-	-	-	3	3
Morocco	67	91	106	106	92	81	85	111	113	107	139		163
Saudi Ara		0	1	4	4	3	10	5	8	7	8	17	32
Syria	22	47	38	55	25	20	36	30	17	18	19	16	17
Tunisia	28	27	23	23	17	30	44	38	37	55	36	55	63
Yemen	450	132	56	44	0	5	15	-	-	0	-	0	-
Jordan	-	2	1	0	0	0	0	0	0	0		-	-
Oman	0	0	0	2	-	1	0	-	1	0	1	1	0
Sudan	2.563							2.389	5.153	7.418	6.95		3.310
South Sud		1.01					7.472	2.364	4.353	10.468	9.16		582
Lebanon	0	0	0	0	0	0	0	2	0	0	F	0	-

Among the results of Jacobson and Schlein (1999) *in vitro*, it was found that *R. communis* extract led to promastigote agglutination and death. Upon infection, the sandfly fed on *R. communis* extract resulting in maximum parasite mortality. The carbohydrates present in the extracts inhibit the agglutination. As well as, Soosaraei et al. [2017] showed that *R. communis* has anti-leishmanial activity. Zarandi et al (2021) explained that the aqueous-alcoholic extract of *R. communis* is effective in killing promastigotes of *L. major*. The extract can exert lethal effects on the flagellate for the content of alkaloids. Jumba et al. (2015) reported the antileishmanial activity of *R. communis* extracts against *L. major in vivo* and *in vitro*. The results obtained showed that, *R. communis* was showed potency against *Leishmania major*, where *R. communis* methanolic extract reduced *L. major* infection. These findings agree with earlier studies against parasitic organisms of trypanosomatidae (Carneiro et al., 2012; Anthony et al., 2005) and *L. donovani* (Dayakar et al., 2015). Zahir et al., (2012) studied the effect of *R. communis* seeds extract against promastigotes form of *Leishmania donovani*. The results showed that, *R. communis* seeds

communis seeds has antileishmanial activity against visceral leishmaniasis. Okech et al., (2006) found that aqueous and ethanol extracts of *R. communis* have antileishmanial activity on *Leishmania* promastigotes. Figure 2 shows the major *R. communis* phytochemicals.



Fig. 2. The major components of Ricinus communis.

2.2. *Ricinus communis* chemistry

Previous studies on *Ricinus communis* have indicated the presence of diverse phytochemicals such as flavonoids, terpenes, alkaloids, saponins, tannins, lectins, steroids, glycosides, phenolic compounds such as gallic acid, ricin, kaempferol, rutin, ricinoleic acid, and gentisic acid (Berman et al., 2011; Alugah and Ibraheem, 2014; Zahir et al., 2010; Oyeewole et al., 2010). other studies have also reported on these compounds, kaempferol-3-O-beta-drutinoside, kaempferol-3-O-beta-d-xylopyranoside, and kaempferol-3-O-β-D-glucopyranoside (Khafagy et al., 1979), diterpene (ingenol mebutate) (Rinner, 2015) triterpenoids (lupeol, β- and α -amyrin) (Vermeer et al., 2003), gallic acid and quercetin (Ghosh et al., 2013), monoterpene (α thujone, camphor and β -thujone) chiefly contribute to the anti-inflammatory (Zarai et al., 2012), ricin (Ngo et al., 2016), epicatechin (Zahir et al., 2011), gentisic acid (Singh et al., 2009), catechin (Rondon et al., 2011), ricinoleic acid and linoleic acid (Houbairi et al., 2015), and quercetin-3-O-β-monoterpenoids (Jeyam et al., 2014), indole-3-acetic acid, ricin A, B & C, ricinus agglutinin, and an alkaloid ricinine are the compounds found in castor as mentioned by (Junior et al., 2011; Kang et al., 1985; Darmanin et al., 2009; Singh et al., 2009; Khogali et al., 1992). Aqil et al., (1997) isolated ricinitin, rutin and quercetin-3-o-glucoside from root. This, Berman et al. (2011) attributed the pharmacological and therapeutic effects of castor to those chemical compounds and their anti-cancer, antioxidant, anti-diabetic, and anti-microbial effects in addition to their anti-inflammatory effects, insecticidal, antinociceptive, analgesic, bone regenerative, and anticonvulsant activity. Figures 3 and 4 show the chemical structures of some components in Ricinus communis.

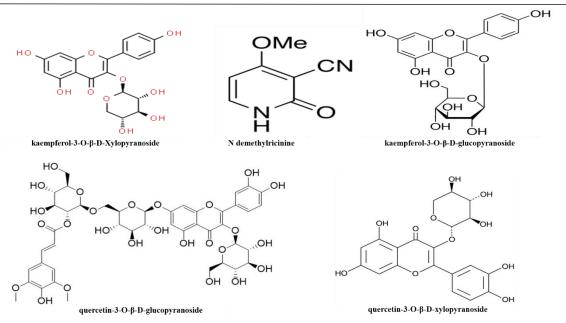


Fig. 3. Chemical structures of some bioactive components in Ricins communis.

Chouhan et al., 2021 attribute the medicinal properties of castor to the presence of alkaloids, saponins, steroids, flavonoids, glucosides, and phenolic compounds such as gallic acid, quercetin, rutin, epicatechin, and ellagic acid. In the same context, Rana et al., (2012) showed that the antioxidant_j anti-inflammatory properties antidiabetic, antitumour, larvicidal antinociceptive and antiasthmatic activity of the castor are due to its content of gallic acid,quercetin, gentistic acid, tannins and alkaloid. The same results were obtained by (Kang et al., 1985; Singh et al., 2009; Darmanin et al., 2009).

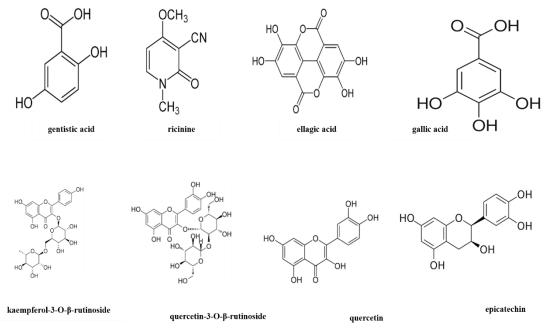


Fig. 4. Chemical structures of some bioactive components in Ricins communis.

It is worth that previous studies attributed the biological effects of castor as a result of the active compounds such as ellagic acid, gallic acid, quercetin, epicatechin, gentisic acid, rutin and

alkaloids; ricinine (0.55%) and N demethylricinine (0.016%)] and flavones; glycosides kaempferol-3-O- β -D-Xylopyranoside, kaempferol-3-O- β -D-glucopyranoside, quercetin-3-O- β -D-xylopyranoside, quercetin-3-O- β -D-glucopyranoside, kaempferol-3-O- β -rutinoside and quercetin-3-O- β -rutinoside (Kang et al., 1985; Singh et al., 2009 Nath et al., 2011; Rana et al., 2012), and tannins (Sibi et al., 2012). As well as, monoterpenoids (1, 8-cineole, camphor and α -pinene), sesquiterpenoid (β -caryophyllene), and phenolic compounds include, gallic acid, quercetin, gentisic acid, rutin, epicatechin and ellagic acid. Indole-3-acetic acid has been extracted from the roots (Darmanin et al., 2009 and Singh et al., 2009, 12). Figure 5. Shows the health benefits of *Ricinus communis*.

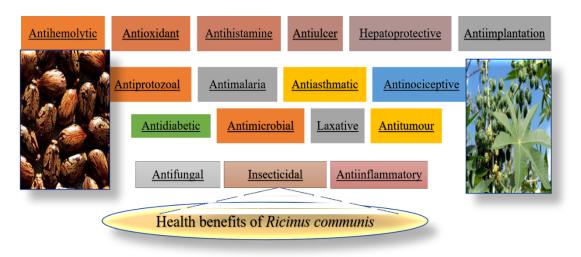


Figure 5. Health benefits of *Ricinus communis*.

3. Pharmacological applications

From the results of previous studies, which showed the use of *R. communis* in the treatment of hepatitis, skin and breast cancer (Rana et al., 2012; Gupta et al., 2004; Shukla et al., 1992; Visen et al., 1992), antidiabetic (Shokeen et al., 2008; Abbas et al., 2018) and antioxidant due to phenolic and flavonoid compounds (Iqbal et al., 2012; Surveswaran et al., 2007) as well as antifeedant and toxic effects i.e., abrin and ricin; leaf extracts of *R. communis* had effects against pest (Kodjo et al., 2011; Olsnes et al., 1975; Aslani et al., 2007; Devanand and Rani, 2008). Besides being insecticidal (Upasani et al., 2003), contraceptive (Okwuasaba et al., 1997) and antifertility activity (Sandhyakumary et al., 2003), antimalaria, insecticidal, antioxidant, anti-implantation, antiinflammatory, antidiabetic, antitumour, larvicidal, anti-microbial and antifungal, antinociceptive and antiasthmatic activity were biological activities as mentioned by (Berman et al., 2011; Junior et al., 2011; Kang et al., 1985; Darmanin et al., 2009; Singh et al., 2009; Khogali et al., 1992; Ochora et al., 2014; Basheer, 2014; Lomash et al., 2010).

El-Naggar (2019) showed that the ricinine alkaloid in *Ricinus communis* and its derivatives have antimicrobial activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeuroginosa, Staphylococcus aureus*, and *Candida albicans*. Antioxidant, antihemolytic and antibacterial activities of *Ricinus communis* was also endorsed by Alugah and Ibraheem (2014), due to its content of flavonoids and tannins in the various parts (leaves, stems, roots, capsules and seeds). Previous research supported the active role of *Ricinus communis* as antioxidant, antimicrobial, antihelmintic, laxative, diuretic, insecticidal, anti-inflammatory, hypoglycemia treatment, headache, edema, dermatitis, ringworm, rheumatism, asthma, warts,

dandruff (Jena et al., 2012; Obumselu et al., 2011; Nath et al., 2011; Rana et al., 2012; Sibi et al., 2012; Friedman et al., 2013).

Studies on *R. communis* seeds have confirmed its effectiveness an anti-fertility effect as decreasing testosterone, reproductive organs weight, sperm functions and disruption of seminiferous tubules and erosion of the germinal epithelium in male rats (Nath et al., 2011; Raji et al., 2006), and reduction of progesterone, altering the oestrogen/progesterone balance, and abortifacient effect on the uterus and fallopian tube (Nath et al., 2011; Okwuasaba et al., 1997). As appeared as in the study of Bhakta and Das (2015) being an antiimplantation, anticancer, antioxidant, antifertility, antinociceptive, in vitro immunomodulatory, hepatoprotective, antidiabetic, antiulcer, antimicrobial and antifungal, insecticidal, bone regeneration, central anagesic, antihistaminic, antiasthmatic, molluscicidal and larvicidal, lipolytic, antiinflammatory and wound healing, due to the steroids, saponins, alkaloids, flavonoids, and glycosides contents.

Haque et al., (2020) revealed that *Ricinus communis* (leaf, twig, bark, stem, root, precarp and seed) extracts have allelopathic properties. (Taur et al., 2011) said that, Ricinus communis leaves contains of alkaloids, saponin and steroids and have antinociceptive activity. Leaf, root and seed oil have been used for the treatment of inflammation and liver disorders (Kirtikar and Basu, 1985). It is reported that this plant possesses hepatoprotective (Yanfg et al., 1987; Visen et al., 1992), antidiabetic (Shokeen et al., 2008), laxative (Capasso et al., 1994), and antifertility activities (Sandhyakumary et al., 2003). Root extract shows anti-inflammatory and free radical scavenging activity (Ilavarasan et al., 2006). Moreover, quercetin, ellagic acid, gallic acid, gentisic acid, rutin and epicatechin are possessing antioxidant activity (Singh et al., 2009).

4. Essential oil

Kadri et al. (2011) showed that, α -thujone (31.71%), 1,8-cineole (30.98%), α -pinene (16.88%), camphor (12.98%) and camphene (7.48%) were the major compounds in *Ricinus communis* leaves essential oil, which has anticarcinogenic and antimicrobial properties as well as repellent potential and insecticidal effect against *Tribolium castaneum* and *Lasioderma serricorne* (Salem et al., 2017). They added that, 2,4-bis (dimethylbenzyl)-6-t-butylphenol was the main volatile compound of castor essential oil. *Ricinus communis* oil is also used as anticancer, insecticidal, antidiabetic, larvicidal, antiprotozoal, and adult emergence inhibition activities (Manpreet et al., 2012), and ricin is used in phytotherapy and traditional medicine (Bum et al., 2011). Figure 6. shows the chemical structures of some essential oil components identified from *Ricinus communis*.

5. Oil seed

Studies on R. communis seeds concluded that seeds are a source of protein and oil. The oil yield in the seeds is about 50%. The oil has medicinal activities and various applications such as coating materials, print ink, resin materials and cosmetics. However, presence of ricin and agglutinin is a major problem for using *R. communis* oil in nutritional applications (Ahmad, 2017). The fatty acid profiles of castor oil are oleic, stearic, palmitic, linoleic, linolenic acid, and ricinoleic acid is a monounsaturated fatty acid dominant acid represents about 75 to 90% of the total oil composition (Beruk et al., 2018; Panhwar et al., 2016; Yusuf et al., 2015). Also, the fatty acid profile of castor has low amount of saturated and polyunsaturated fatty acids and this enhance its stability (Yusuf et al., 2015), so castor oil shares a higher similarity with that of macadamia nut, palm kernel, olive, and sunflower oil (Nor Hayati et al., 2009; Sinanoglou et al., 2014), and those nutritional unsaturated acids play an important role in reducing individual risks associated with asthma, cardiovascular diseases, cancer, and diabetes (Ganesan et al., 2018).

Castor oil has high nutritional value owing to its rich amount of monounsaturated fatty acid and bioactive active antioxidants compounds such as vitamin E component (tocopherols or tocotrienols), phospholipids and phenolic compounds (Sedeek et al., 2012; Said et al., 2016). As the tocopherols are one of the natural antioxidants in castor oil with anti-proliferative and anti-inflammatory properties (Said et al., 2016; Sbihi et al., 2018).

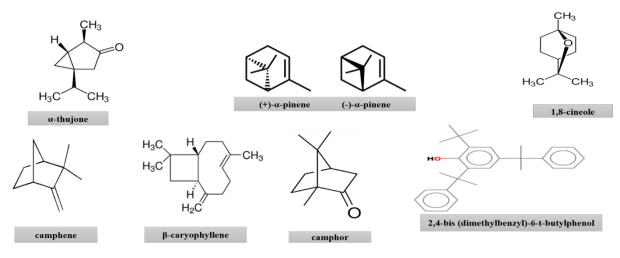


Fig 6. Chemical structures of some essential oil components

6. Conclusion

In this review, the medicinal properties of *Ricinus communis* were examined to confirm its therapeutic importance. *R. communis* is an important medicinal plant with potential effect on ulcers, microorganisms, bacteria, insects, and other parasites that affect health and immunity. Based on the above literature, it may conclude that the disease prevention and recurring characteristic of the *Ricinus communis* made this plant highly noticeable which provides many alternatives solutions in medical areas, and several fields such as agriculture, pharmacy, economic, industry and others. The pharmacological activities shown by the Ricinus communis have supported the traditional use of this herb as a medicinal plant and creating the source for sustainable synthetic drugs. As a result of its content of biologically active compounds that allow a good future in the medical world and have built opportunities for further investigation to find the new compounds of *Ricinus communis*.

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