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Review Article

Pulicaria crispa (Forssk) Oliv: A Review of Ethnopharmacology, Phytochemistry and Biological Activities

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Abstract

Since early history, medicinal and aromatic plants had extensively been used in treatment of various diseases. Now days, the high evolution and development in phytochemical technology cause the phytotherapy as a science to be dramatically noticed. It exploited the rich information available in traditional medicines and then translated it into proved scientifical discipline.

Pulicaria crispa **(Forssk) Oliv** is one of medicinal and aromatic plant which is widely distributed around the world, especially in arid and sub- tropical regions. This review is an attempt to collect some information about this valuable plant, which is still widely used traditionally in treatment of many diseases. In this review, we tried to mention all of the proved scientific information according to pharmacognostical point of view, which consists of taxonomical classification, botanical description, traditional uses, phytochemical constituents, pharmacological and phyto-therapeutic uses.

Keywords: *Pulicaria crispa*, *Francoeuria crispa*, *Aster crispa*, *Inula crispa*, Asteraceae, Compositae.

Introduction

Medicinal and aromatic plants represent important natural sources for treatment of many diseases, traditional medicines- especially in developing countries- are directly dependent on medicinal and aromatic plants [1]. Recently, there is a paradigm shift in developed countries to medicinal and aromatic plants, being a source of plenty of phytochemical compounds, which promote their valuable role in the drug discovery [2].

Pulicaria species have been used in folk medicine as insect repellents, galactagogues, anti-epileptics and tonics; it is also used in treatment of colds, cough, dysentery, excessive sweating and as carminative. Chemical investigations of the genus *Pulicaria*, revealed basically the presence of terpenoids, sesquiterpene lactones, flavonoids and caryophyllene derivatives [3].

Sudan is rich with medicinal and aromatic plants, which emphasis its importance. *Pulicaria crispa* plant is widely distributed in Sudan, more commonly found in Northern and Central regions; it is one of the seven species of the genera *Pulicaria* which is present in Sudan [4]. In Africa, *Pulicaria crispa* was reported in Egypt, Ethiopia, and tonics; it is also used in treatment of colds, cough, dysentery, excessive sweating and as

carminative. Chemical investigations of the genus *Pulicaria*, revealed basically the presence of terpenoids, sesquiterpene lactones, flavonoids and caryophyllene derivatives [3].

Sudan is rich with medicinal and aromatic plants, which emphasis its importance. *Pulicaria crispa* plant is widely distributed in Sudan, more commonly found in Northern and Central regions; it is one of the seven species of the genera *Pulicaria* which is present in Sudan [4]. In Africa, *Pulicaria crispa* was reported in Egypt, Ethiopia, Cameroon, Niger, Mali, Senegal and Ghana. Other locations include Middle east, tropical and sub-tropical regions, so the plant is scattered around the World [5].

Pulicaria crispa have many folkloric uses in Africa, Europe, Middle East and Asia. It is used as a tonic, tea substitute, anti-spasmodic, hypoglycemic and for the preparation of perfumes. The essential oil obtained from its aerial parts exhibited insecticidal and antibacterial activities [5].

Taxonomical classification:

The family Asteraceae (Compositae) is one of the largest family among flowering plants, it includes about 1,620 genera and 23,600 species [5]. The genus *Pulicaria* belong to the tribe Inuleae, it consists of about 80 species. *Pulicaria* is an annual herb which is famous with its small bright yellow flowers [6 and 7].

Pulicaria crispa **(Forssk.) Oliv. - or (Forssk.) Benth. or (Forssk.) Benth.& Hook. or (Forssk.) Benth. ex Oliv.** - is classified according to Cronquist *et al.* (1972), as follows:-

Division: Tracheophyta
Class: Angiospermopsida
Sub- class: Dicotyledonidae
Order: Asterales
Family: Asteraceae
Genus: *Pulicaria*
Specie: *crispa*

Other synonyms for *Pulicaria crispa* **(Forsk) Oliv.**, Trans. Linn. Soc., Bot. 29 (1873) is the followings: *Aster crispa* **Forsk.**, Fl. Aegypt- Arab: 150 (1775); *Francoeuria crispa* **(Forsk.)** Cass, Dict. Sci. Nat. 38: 374 (1825); *Inula crispa* **(Forssk.) (Figure 1)**.

Figure 1: A photo showing *Pulicaria crispa* aerial parts

Botanical description

Pulicaria crispa **(Forssk.) Oliv**, - with synonym *Francoeuria crispa* **(Forssk.)** Cass - is an annual herb or a perennial sub- shrub belonging to the family Asteraceae (Compositae). The general botanical description is as follow **(Figure 2)**:-

Perennial herb, ascending and often with hemispherical appearance, 12- 75 cm high, densely branched from the base with stems white wooly tomentose or occassionally nearly glabrous.

Leaves: Simple, sessile, somewhat amplexicaul, narrowly linear, acute to obtuse, denticulate, obovate- oblong to linear lanceolate, 0.5 – 1.5 × 0.5 - 0.6 cm in tomentose to nearly solitary, terminal, 0.3- 0.6 in across.

Flowers: Yellow disc floret (inflorescence), radiate, 0.5- 1 cm across, aromatic, achenes glabrous, pappus uniseriate, with a few short bristles.

Odor: Characteristic aroma.

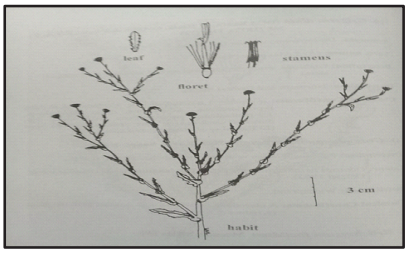

Figure 2: *Pulicaria crispa* **(Forssk) Oliv.** (El-Ghazali *et. al.*, 2004) [8]

Traditional uses

P. crispa is widely used traditionally for the treatment of various diseases. The plant has been used for the cure of many heart diseases and as gastro protective herb, all is due to their anti-oxidative property. The plant is used in the Arab and Middle East region, for the treatment of inflammations, as insects repellent and is taken as herbal tea form as tonic [5].

The plant is also used in traditional medicine in alleviating symptoms of colds, coughs, excessive sweating and as carminative [9].

Phytochemistry and isolated chemical constituents

Phytochemical screening

The methanolic percolated extract of *P. crispa* aerial parts showed the presence of alkaloids (Mayer's, Wagner's and Dragendorff's tests), carbohydrates (Molisch's, Benedict's and Fehling's tests), proteins (Ninhydrin and Biuret's tests),

fats and oils (Stain test), steroids (Liebermann-Burchard's and Salkowski's tests), flavonoids (Lead acetate test), saponins (Foams test), tannins and phenolic compounds (Ferric chloride test) [5].

Phytochemical screening of some medicinal plants belonging to Compositae growing in Saudi Arabia showed that *P. crispa* aerial part, which was collected at flowering stage and percolated by 96% ethanol, contains volatile oils, alkaloids, anthraquinones, flavonoids, coumarins and sterols [10].

The petroleum ether extract of *P. crispa* whole plant extracted by Soxhlet apparatus also revealed the presence of alkaloids, coumarins, triterpenoids and fatty acids [9].

P. crispa aerial parts powder form was screened for the presence of different phytochemical groups; it discovered the presence of flavonoids (NaOH test), alkaloids (Mayer's, Wagner's and Dragendorff's tests), saponins (froth test), triterpenoids (Liebermann-Burchard's test), tannins (FeCl3) and coumarins (NaOH and fluorescence test) [11].

Other more phyto- chemical studies on *P. crispa* stated that it contains alkaloids, flavonoids, tannins, reducing compounds, saponins and triterpenoids [12- 16].

Sesquiterpene lactones

Many previous studies had proved that the genus *Pulicaria* (including *P.* crispa) is characterized by the presence of sesquiterpene lactones [11 & 17].

One of the earliest studies conducted on *P. crispa*, had resulted in identification of five sesquiterpene lactone compounds, the first compound **(Figure 3)**, was belonging to a pseudo- guaianolide epoxide type (pulicariolide), and the second compound was belonging to a seco-sesquiterpene lactone type (secocrispolide), while the other compounds were belong to xantholide compounds [18].

Another study had shown the presence of three guaianolide sesquiterpene lactones, and they were:-

1- 2-alpha,4-alpha-dihydroxy-7-alpha H,8-alpha H,10-alpha H-guaia-1(5),11(13)-dien-8-beta,12-olide (**Figure 4)**.
2- 1-alpha,2-alpha-epoxy-4-beta-hydroxy-5-alpha H,7-alpha H, 8- alpha H,10-alpha H-guaia -11(13)-en-8 beta,12-olide.
3- 5,10-epi-2,3-dihydroaromatin.

The chemical structures of the three guaianolide sesquiterpene lactones were assigned on the basis of extensive 1D and 2D NMR experiments [19].

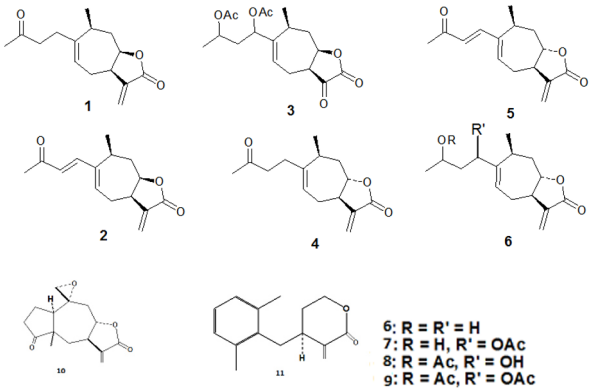

Figure 3: Chemical structures of sesquiterpene lactones isolated from *P. crispa*; **1-9:** Xantholides compounds, **10:** Pulicariolide; **11:** Secocrispolide (Bohlmann *et.al.*, 1979) [18].

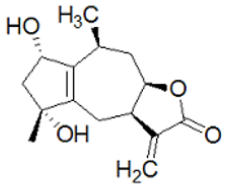

Figure 4: Chemical structure of 2-alpha,4-alpha-dihydroxy-7-alpha H,8-alpha H,10-alpha H-guaia-1(5),11(13)-dien-8-beta,12-olide (Stavri *et.al.*, 2008) [19].

Further study was also conducted by Abdel-Mogib and colleagues (1990), this study has showed the identification of two new sesquiterpene lactones [20].

An alternative study was carried out to determine the chemical structures of some isolated sesquiterpene lactones **(Figure 5)**, in which the plant was extracted by methanol 80%, and the extract was eluted with CHCl3 and increasing amounts of acetone using column

chromatography , two xantholides and four guaianolides were isolated and further purified by PTLC, the compounds **3, 5** and **6** were described for the first time in *P. crispa* [21].

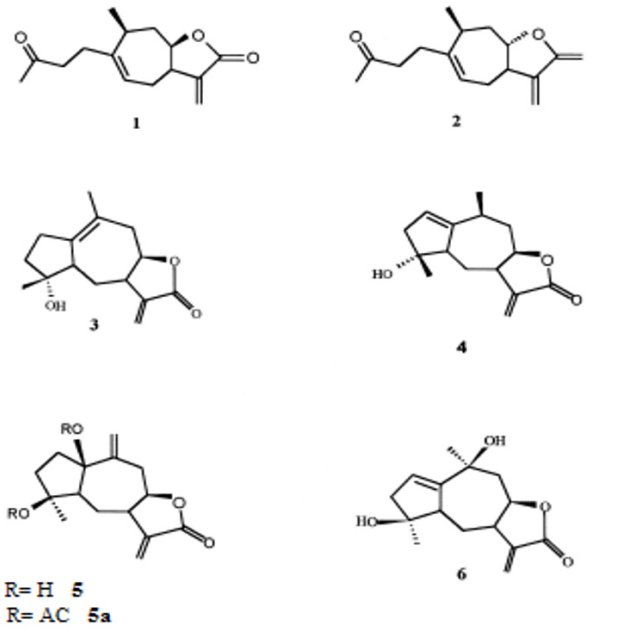

Figure 5: Chemical structures of some sesquiterpene lactones isolated from *P. crispa* (Dendougui *et. al.*, 2000) [21].

Al-Yahya and colleagues (1984) had isolated an eudesmanolide compound from petroleum ether extract of *P. crispa* aerial part, the compound was isolated by elution of petroleum ether extract (benzene/ ethanol mixture) and purified by recrystallization **(Figure 6)**, the compound was known as 2- α- hydroxy alantolactone [47]. The 5, 6 epoxy derivatives (sesquiterpene epoxide) was isolated from ethanol 95 % extract of the same plant **(Figure 6)** [22].

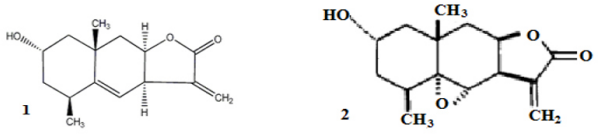

Figure 6: Chemical structure of 2 compounds isolated from *P. crispa*, **1:** 2- α- hydroxyl alantoalactone, a eudesmanolide compound; **2:** its 5,6 epoxy derivative [22].

Also Michael Stavri and colleagues (2008) had isolated a new sesquiterpene lactone; it was named as pulicrispiolide **(Figure 7)**. The compound was identified by using 1D and 2DNMR after the aerial parts of *P. crispa* was extracted by n-hexane via Soxhlet apparatus, further fractionated through vacuum liquid chromatography and eluted with n-hexane containing 10% increments of ethyl acetate [23].

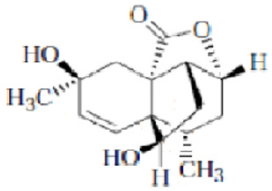

Figure 7: Chemical structure of pulicrisiolide [23].

P. crispa is characterized by the presence of volatile oil (mono and sesquiterpenes). Many authors had studied the chemical constituents of these volatile oils; the volatile oils have many uses and applications, especially in food and beverages flavors, cosmetics and perfumes industries, insecticidal and bacteriostatic agents [24- 28].

Elegami 1989 investigated the volatile oil content of *Pulicaria crispa* using gas chromatography; the study identified the presence of linalool, limonene, carvolanactone, nerol and eugenol **(Figure 8)** [24].

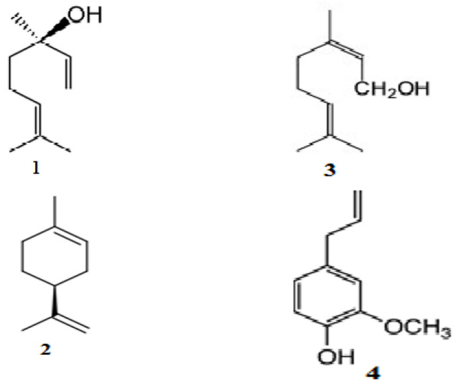

Figure 8: Chemical structures of some volatile oil compounds isolated from *P. crispa*; **1:** linalool; **2:** limonene; **3:** nerol; **4:** eugenol [24].

Williams and Fliming (1980) reported that the volatile oils of *P. crispa* are mostly chemical compounds which contain hydroxyl group [29].

Adam 1989 had also investigated the essential oil of *P. crispa* by Iron Trap Mass Spectroscopy in USA, the study stated that linalool has insecticidal action, which agreed and matched with the traditional uses of *P. crispa* as insecticidal herb; also he stated that β- caryophyllene has anti-inflammatory property [30].

Rizk and Ismail (1981) phyto chemical study showed the presence of volatile oils, in addition to tannins, coumarins and alkaloids [31].

Diterpenes

Abdel- Mogib and colleagues (1990) isolated two diterpenes from the aerial parts of *Francoeuria crispa*; they were two diterpene glycosides derived from ent-kauren-19-oic acid **(Figure 9)** [20].

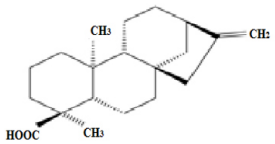

Figure 9: Ent-kauren-19-oic acid derivative of diterpene glycoside in *P. crispa* [20].

Triterpenes and phytosterols

A study was conducted in Saudi Arabia on *P. crispa* that resulted in the isolation and identification of several compounds that belongs to triterpenes and phytosterols, these constituents were β-amyrin, unidentified triterpene and β-sitosterol **(Figure 10)** [32].

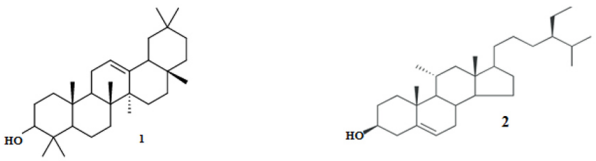

Figure 10: Chemical structures of some triterpenes and phytosterols isolated from *P. crispa*; **1:** β-amyrin; **2:** β- sitosterol [32].

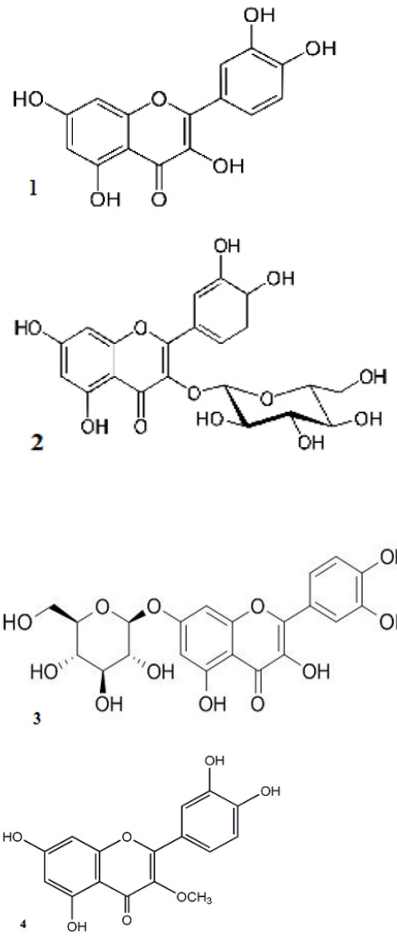

Figure 11: Chemical structures of some flavonoids compounds isolated from *P. crispa*; **1:** Quercetin; **2:** Quercetin-3-O-glucoside; **3:** Quercetin-7-O-glucoside; **4:** Quercetin-3-methyl ether [33].

Rizk and Ismail (1982) studied and characterized a flavonoidal compound isolated from *P. crispa* **(Figure 12)**; the compound was known as rhamnetin-3-galactoside; also they were able to isolate and identify apigenin-7-glucoside [34].

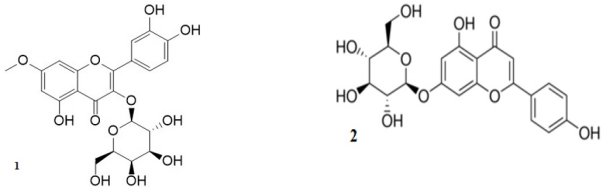

Figure 12: Chemical structures of **1:** Rhamnetin-3-galactoside; **2:** Apigenin-7-glucoside [34].

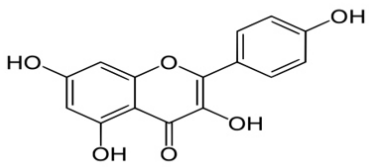

Figure 13: Chemical structure of kaempferol [35].

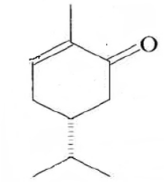

Figure 14: Chemical structure of *S*-carvotanacetone [36].

Gas chromatography and mass spectroscopy (GC- MS)

A study conducted by Ross *et.al.* (1997) in which the fresh *P. crispa* plant material was collected and steam distilled, the obtained oil was identified by GC- MS, and it showed the presence of 26 components, 16 components of which were identified and representing 97.9 % of the total components, also they characterize *S*-carvotanacetone (**Figure 14)** (93 %, t_R: 20.15 minutes, RI: 1,251) for the first time in *P. crispa* by applying 1D and 2D NMR. **(Table 1)** shows the compounds isolated by GC- MS [36].

Table 1: Composition of *Francoeuria crispa* essential oil (Ross *et.al.*, 1997) [36].

No.	Component	% yield
1	Hexenal<2->	< 0.001%
2	Tricycline	< 0.001%
3	α-Pinene	0.1%
4	Unknown	< 0.001%
5	Carene<2->	< 0.001%
6	*o*-Cymene	0.3%
7	Limonene	0.1%
8	1,8-Cineole	0.1%
9	Linalol oxide<cis->	0.2%
10	Linalol oxide<trans->	< 0.001%
11	Linalool	3.5%
12	Isomenthol	0.2%
13	α-Terpineol	0.2%
14	1,4-Cineole	< 0.001%
15	Menthol<$_L$->	< 0.001%
16	Unknown	0.2%
17	*S*-carvotanacetone	93%
18	Unknown	0.2%
19	Unknown	0.4%
20	Unknown	< 0.001%
21	*Cis*-Jasmone	0.3%
22	Unknown	0.6%
23	β-Caryophyllene	0.1%
24	Unknown	< 0.001%
25	Unknown	0.3%
26	Unknown	< 0.001%

Elshiekh *et.al.* (2015) subjected the whole plant petroleum ether extract of *P. crispa* that extracted by Soxhlet apparatus to GC- MS. The extract discovered the presence of complex constituents, 14 compounds identified shown by table (2). [9].

Table 2: Content of *P. crispa* petroleum ether extracted by Soxhlet apparatus (Elshiekh *et.al.*, 2015) [9].

No.	Component
1	Benzene, 1-ethyl-2,3,4,5,6-pentafluoro-
2	2-Propenamide.
3	Hexane,1-(hexyloxy)-3-methyl-
4	Heptacosane.
5	Heneicosane.
6	3-Ethyl-3-methylheptane.
7	Tetratriacontane.
8	Decane, 1-iodo-
9	Tetratriacontane.
10	Tetradecane.
11	7b-Phenyl-2a,7b-dihydro-3H-cyclobuta[a]indene.
12	Stannane, diethyldimethyl-
13	2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-, [4R-(4.alpha.,4a.alpha.,6.beta.)]-
14	Hop-22(29)-en-3.beta.-ol.

Invitro and invivo biological studies

The pharmacological parameters, which include the effect on the nervous system, cardio- vascular system, smooth and skeletal muscles, of *P. crispa* (with other Compositae medicinal plants) have been studied by Tariq *et.al.* (1987). *P. crispa* aerial part was percolated by 96% ethanol. It produced reduction in the force of contraction of isolated rabbit heart and caused transient fall in blood pressure of anaesthetized rabbit.; neuro pharmacological studies showed mild CNS depression; in addition the extract inhibit the contractions of isolated frog's rectus abdomens

muscle induced by acetyl choline. (neuro-muscular blocking effect) [10].

Adam and Elhag (2000) tested the toxic effects of *P. crispa* leaves on rats; leaves was fed to rats with t 2% and 10% of their diet weight for eight weeks. The results showed that rats fed on 10% *P. crispa* diet, there was a decrease in average body weight, decrease in feed efficiency, soft feaces, signs of entero hepato- nephrotoxicity (raised serum AST, GGT, urea and cholesterol concentrations and decrease of total protein and albumin levels). Moreover, there was leucopenia leucopenia and normocytic normochromic anemia. It was found that the growth of rats fed on 2% *P. crispa* diet was promoted compared with rats on a control diet [37].

Anti- inflammatory activity

Ageel and co- workers (1989) tested a large number of herbs; these herbs are used in Saudi Arabian traditional medicine in treatment of rheumatism, gout, arthritis and other forms of inflammation; *Francoeuria crispa* was one of these tested herbs; it was extracted by ethanol 96% and the dried extract was administered orally to carrageenan- induced inflammation rats, it was found that the inhibition percentage of inflammation after measuring the paw volume was significant (24%); this result comply with the traditional medicine in the treatment of inflammations [38].

Antioxidant activity

The antioxidant activity of methanolic percolated extract of *P. crispa* aerial parts was performed by DPPH radical scavenging and ferric- reducing power assays. Ascorbic acid was used as positive control. The results showed significant antioxidant potential in a concentration manner with both assays [5].

Elshiekh *et. al.* (2015) tested the antioxidant activity of petroleum ether extract of *P. crispa* whole plant by DPPH scavenging method, it was extracted by Soxhlet apparatus and the oil sample was showed 85% ± 0.06 DPPH scavenging activity, which was considered as potential antioxidant activity [9].

The antioxidant activity of *P. crispa* whole plant was also tested, the plant was dried and extracted with different extraction methods, they were continuous extraction, maceration and decoction, and the solvents used were petroleum ether, ethyl acetate, ethanol, 70% methanol and water. The results showed DPPH scavenging activity equal to 88±0.01, 87±0.01 and 84±0.02% for ethanol, water, 70% methanol respectively, while ethyl acetate extract showed only 39± 0.04% [12].

Abdelaaty and colleagues (2014) studied the antioxidant activity of some wild Saudi Arabian Asteraceae plants including (*P. crispa*). The plant material was extracted by methanol 80%, the results showed that the phenolic compounds content in *P. crispa* is 3.71 g/ 100g [39].

Another study was conducted in Oman, in which antioxidant activity of some wound healing plants growing in Oman was tested (includes *P. crispa*), *P. crispa* was extracted by aqueous ethanol and its antioxidant activity was studied by using *in vitro* DPPH and phosphomolybdenum assay. The results showed that the inhibition DPPH radical property of *P. crispa* ethanolic extract was within 19 other plants (89- 93%) at concentration 50 µg/ ml; regarding phosphomolybdenum assay, the antioxidant capacity of *P. crispa* extract was the highest as gallic acid equivalents of 1,790 mg/ g [40].

Anti- bacterial activity

Foudah *et.al.* (2015) tested the anti- bacterial activity of methanolic extract of *P. crispa* aerial parts, the extract was obtained by percolation, the bacteria strains selected for the test were *Staphylococcus aureas* and *Bacillus subtilis* as Gram-positive, while *Escherichia coli*, *Klebsiella pneumonaie* and *Proteus vulgaris* were selected as Gram negative bacteria, the anti- bacterial activity was investigated by agar disk diffusion method, the

results showed the inhibition zones were 28 mm, 22 mm and 21 mm with *K. pneumonaie*, *B. subtilis* and *E. coli* respectively, the results were considered as good anti- bacterial activity with respect to the three bacterial strains [5].

El-Kamali and Mahjoub (2009) tested the anti-bacterial activity of some plants (includes *Francoeuria crispa*) against selected bacterial strains of *Staphylococus aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella para typhi* B and *Klebsiella pneumonaie* by using *in vitro* agar diffusion method; *Francoeuria crispa* was extracted by ethanol and was further fractionated by petroleum ether, ethyl acetate, methanol and water; the results showed that the ethanol extract of *F. crispa* aerial parts had significant anti- bacterial against all strains except *S. para typhi* B. The ethyl acetate fraction of the same plant showed high anti- bacterial activity against all tested Gram- positive and Gram-negative bacteria with inhibition zones (IZ) ranged between 17- 21 mm. Most of the bacteria species showed a fairly high degree of sensitivity to the methanolic fraction of *F. crispa* aerial parts; while the aqueous fraction showed no antibacterial activity against all bacterial species used in the test. [41].

Another study was conducted by Bogdadi *et.al.* (2007), in which some Libyan medicinal plants were selected (includes *P. crispa*), they were extracted successively by Soxhlet apparatus by n-hexane, chloroform and methanol; the crude drugs were also macerated by ethanol 80%. *P. crispa* aerial parts extract was tested against seven strains of bacteria by broth dilution method; the bacteria strains selected were *Bacillus cereus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. The result showed that the ethanol extract of *P. crispa* possessed a strong activity against Gram- positive bacteria with MIC ranged between 1- 4 mg/ml [42].

Anti- fungal activity

Bogdadi and his co- workers (2007) studied the anti- fungal properties of *P. crispa* and other Libyan medicinal plants. *In vitro* broth dilution method was applied, aerial parts of *P. crispa* was extracted by n-hexane, chloroform and methanol by Soxhlet apparatus, also the extraction was done by maceration using ethanol 80%, the organism selected for the test was *Candida albicans*. The results showed that ethanol and n-hexane extracts possessed the strongest anti- fungal activity with MIC not exceeding 1 mg/ml [42].

Foudah et.al. (2015) tested the anti- fungal activity of methanolic extract of *P. crispa* aerial parts, the extract was obtained by percolation, the selected strains were *Aspergillus niger* and *Candida albicans*, the fungus strains were sub cultured in potato dextrose agar media (at 25° C) by agar disk diffusion method, the results showed inhibition zones of 18 mm and about 24 mm with *A. niger* and *C. albicans* strains respectively, the results was considered as good anti- fungal activity [5].

Anti- Schistosomiasis activity

Abdelmageed and his colleagues (2017) investigated the effect of the aqueous extract of *P. crispa* leaves on survival and fecundity of *Bulinus truncates* adult snails, the molluscicidal potency was achieved in very low concentrations with LC50 and LC90 equal to 206.06 ppm and 237.19 ppm respectively, so *P. crispa* was considered as a promising molluscidal plant in the control of schistosomiasis [43].

In another study, *P. crispa* aerial part was extracted by continuous extraction method using methanol 90%. The extract was injected intra peritoneal in mice which were infected by *Schistosoma mansoni* cercariae; the objective of this study was to know the immune stimulatory effects of *P. crispa* extract before and after infection with *S. mansoni* in mice. The blood samples were collected after 10 days, and the results showed that sera from mice treated with the *P. crispa* extract showed

significantly higher levels of IL- 2 ($p< 0.05$) when compared with sera from untreated mice. Also, sera from treated mice showed significantly higher IgG reactivities ($p < 0.05$) against ECL when compared to sera of untreated mice, and sera from treated mice that received *S. mansoni* infection showed significantly higher IgG reactivities ($p< 0.05$) against crude *Escherichia coli* lysate (ECL) in comparison to sera from infected untreated mice. Also sera from mice treated with *P. crispa* extract followed by *S. mansoni* infection showed significantly higher IgG levels ($p< 0.05$) against crude soluble worm antigen preparation (SWAP) when compared to sera of untreated infected mice. In addition, sera from mice treated with *P. crispa* extract followed by *S. mansoni* infection showed significantly higher IgG levels ($p< 0.05$) against CBH when compared to infected untreated mice. Also, sera from infected mice that were previously treated with the plant extract showed significantly higher IgG levels ($p< 0.05$) against cancer bladder homogenate (CBH) when compared with sera from treated uninfected mice. In conclusion, treating mice with methanolic extract of *P. crispa* reduces the *S. mansoni* worm burden and stimulates significant IL- 2 production as well as significant IgG response that reacted in ELISA against bilharzia, *E. coli* and cancer bladder antigens, which might represent a new hopeful alternative approach for therapy of infection with such diseases and should need further detailed studies [44].

Anti- malarial activity

The aqueous extract of *P. crispa* aerial part was tested *in vitro* against Gambian isolate strain of *Plasmodium falciparum*, the extraction process was done by de- ionized water, which shaken in a water bath at 40 °C, with the plant at concentration of 100 mg/ ml. The extract was diluted with a dilution factor 1:200 with water before been used in the assay, and the anti-malarial activity was checked after 72 hours of incubation period, it was found that *P. crispa* possess strong plasmodial growth inhibitory effect equals to 100 % [45].

Anti- leishmanial activity

The aerial parts of *P. crispa* were extracted successively by Soxhlet apparatus using petroleum ether, chloroform and methanol. The extracts were tested on *Leishmania donovani* promastigotes. The petroleum ether and chloroform extracts had showed significant anti- leishmanial activity with IC_{50} equal to 4.9 and 3.75 µg/ ml respectively [11].

Anti- laraval effect

A study conducted by Al-Doghairi and Elhag (2003) investigated the effect of *Francoeuria crispa* and other plants on the larvae and eggs of *Culex pipiens*. The result showed that the aqueous extract of *F. crispa* leaves at concentration 0.25% caused 55.3% mortality after 10 days, leading to 34.3% and 21.2% of successful pupation and adult emergence respectively [46].

Cytotoxicity effect

The petroleum ether whole plant extract of *P. crispa* was tested *in vitro* on Brine Shrimps (*Artemia salina*), the Brine Shrimp lethality (IC_{50}) was found to be 37.9 µg/ ml. It was considered as significant cytotoxic [9].

Also Al-Yahya and colleagues (1988) isolated 5, 6 epoxy derivative of 2- α- hydroxy alantolactone from the ethanolic extract of *P. crispa* aerial part, its cytotoxicity as anti- cancer potential was tested, the result showed that its ED_{50} was 0.33 µg/ ml [22].

The aqueous extract of *P. crispa* aerial part was tested *in vitro* against two melanoma cell lines, one was sensitive to chemotherapy drug while the second was resistant, the extraction process was done by de- ionized water with shacking in water bath at 40 °C, and the concentration was 100 mg/ ml. The melanoma cytotoxicity assay was applied with final concentration of 1:20. The results showed that the cytotoxicity percentages were 92.9% and 98.1% with melanoma sensitive cell

lines and melanoma resistant cell lines respectively [45].

In another work, resazurin assay was used to assess the cytotoxicity of some selected plant extracts (including *P. crispa* extract) on a panel of human cancer cell line; the aerial part of *P. crispa* was macerated with 80% methanol. The results showed that at dose 40 µg/ ml, more than 50% growth inhibition of leukemia CCRF-CEM was recorded (76.17%), the IC_{50} was 1.81 µg/ ml. The extract was further tested on the cell cycle distribution of CCRF-CEM cells, it was found that *P. crispa* (and other extracts in addition to doxorubicin) considerably altered the distribution of the different cell cycle phases after 24 hours; it also significantly induced apoptosis after 24 hours of treatment at percentage equal to 66.9%. Also *P. crispa* extract (and vinblastine) were able to alter the mitochondrial membrane potential (MMP) in CCRF-CEM after 24 hours of treatment. The cytotoxicity of the methanolic extract was studied towards sensitive and drug- resistant solid cancer cell lines, its IC_{50}s were less than 10 µg/ ml with many tested cell lines; the study investigated the cytotoxic potential of *P. crispa* methanolic extract [47].

Al-Fatimi and his colleagues (2005) had tested twenty- five plants used in traditional medicine in Yemen, they were screened for cytotoxic activity against human ECV-304 cells, *P. crispa* was one of these plants which showed remarkable cytotoxic activity [48].

Al-Yahya and colleagues (1984) had isolated a eudesmanolide compound from petroleum ether extract of *P. crispa* aerial part, the compound was known as 2- α- hydroxy alantolactone, and its anti-leukemic cytotoxicity was tested on KB cells, the ED_{50} was 0.05 µg/ ml [49].

Conclusion

This review is an attempt to collect some information about *Pulicaria crispa* (Asteraceae) from different published researches, we tried to collect all studies published from different official web sites, like Hinary, Science direct, Hindawi, Google scholar, Google, Pub med and others; this plant is wildly distributed in many countries, and it is extensively used traditionally in treatment of many diseases. The abundance of studies and large amount of information we got regarding the isolated natural compounds and pharmacological uses of *P. crispa*, forces us to recommend it as a promising plant which needs more additional studies and efforts, still many natural compounds are not discovered or isolated, and indeed these natural compounds can be tried in many pharmacological models of studies, as it may highly contribute to the field of drug discovery and development.

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