Pharmacological Properties and Chemical Constituents of *Chiliadenus iphionoides* (syn. *Varthemia iphionoides*): a review

Abstract

Chiliadenus iphionoides (Boiss. & Blanche) Brullo has been used in traditional medicine for different medical issues including stomach ailments, diabetes, male and female fertility problems, eye infection, kidney stones, and as an anti-inflammatory~~antiinflammatory~~. Extracts of *C. iphionoides* *have* ~~has~~ shown to exhibit useful pharmacological activities. Phytochemical studies have shown the existence of many biologically active compounds, such as essential oils, flavonoids, and phenolic compounds. This review aims to collect the published research about the traditional uses, chemical constituents, and pharmacological properties of *C. iphionoides*. This review showed that different extracts and active ingredients of *C. iphionoides* had various pharmacological properties such as anticancer, antidiabetic, antimicrobial, antioxidant, antispasmodic, and antiplatelet activities which might be due to the excitant of flavonoids and phenolic compounds. *Chiliadenus iphionoides* and its constituents exhibit many pharmacological properties that play a crucial role in human health, therefore, clinical trials should be conducted to study the valuable effects of the active ingredients of *C. iphionoides* in humans models and develop new drugs.

Keywords: *Chiliadenus iphionoides*, chemical constituents, pharmacological activities, traditional medicine, *Varthemia iphionoides*

1. Introduction

Chiliadenus genus belongs to the Asteraceae family, is a small genus includes ten species mainly distributed throughout the southern edge of the Mediterranean Sea. Most of its species grow in rocky places and semidry land distinguished by pappus with double rows of hairs, the outer row is very short setae while the inner is equaling the corolla [1, 2]. *Chiliadenus iphionoides* (Boiss. & Blanche) Brullo (syn, *Varthemia iphionoides*) is a valuable medicinal species grown across the eastern Mediterranean region belonging to the genus *Chiliadenus* and classified as a rare species in some regions [3, 4]. It is a bushy perennial chamaephyte herb, 20-50 cm long, with small leaves, woody base with many branched aromatic, hairy and sticky stems, and has tubular yellow flowers with a flowering season extending from September to December [5, 6]. *C. iphionoide*s grows wild in rocky environment, deserts and extreme deserts of the ~~Irano~~-Turanian, ~~Saharo~~-Arabian, and the Mediterranean region [7-9]. It is distributed throughout Palestine, Jordan, Syria, Lebanon, and Sinai [2, 10-13]. *C. iphionoides* is commonly used in traditional medicine as a decoction or infusion for the treatment of different ailments. *C. iphionoides* has been reported to exhibit many pharmacological therapeutic properties such as anticancer, antidiabetic, antimicrobial, antioxidant, antispasmodic, and antiplatelet activities.

Despite the various studies carried out on *C. iphionoides*, there is no comprehensive review study on constituents and biological activities of *C. iphionoides*. This study aims to collect published research conducted on the traditional use, chemical constituents, and pharmacological properties of *C. iphionoides.*

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2. Methods

The keywords *Chiliadenus iphionoides*, *Varthemia iphionoides*, traditional medicine, chemical constituents, pharmacological activities were searched through until September 2020 from journals accessible in databases such as Google scholar, Science direct, Scopus, and PubMed, database to collect the information,.

3. *Chiliadenus iphionoides* in Traditional Medicine

Many ethnopharmacological studies have shown that *C. iphionoides* is used in the treatment of various medical conditions (Table 1): stomach ailments, diabetes, male and female fertility problems, eye infection, kidney stones and as anti-inflammatory. The areal parts of *C. iphionoides* have been used for the treatment of some veterinary ailments in sheep, cows and goats such as, colic, fever, diarrhea, flatulence, pregnancy poisoning, scabies, and udder infections [14]. *C. iphionoides* is normally collected by locals, farmers and herbalists and being consumed as fresh or as dried herbs. Other than its medicinal uses, *C. iphionoides* has been used as a deodorant, a cooking spices, condiment and a herbal tea served with sugar [15]

Table 1: Different applications of *Chiliadenus iphionoides* in the traditional medicine

Ailment/use	Part used	Preparation(s)	References
Stomach ailments Intestine pain	Flowering tops, Leaves, stems	Infusion	[16-21]
Kidney stones Renal troubles	Leaves, flowers	Infusion, decoction	[16, 22, 23]
Antispasmodic	Leaves and stems	Infusion	[20]
Eye infection	Flowering tops, Leaves, stems	Infusion, soaked leaves are placed on the eye	[16, 20]

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Diabetes	Leaves and stems	Infusion	[17, 18, 20]
Anti-inflammatory	Leaves and stems	Infusion	[20, 22]
Women sterility Women fertilization Women delivery	Leaves and stems	Infusion, Vapor, lotion The Plant is burning and its vapor help women delivery	[20]
Late menstruation	Leaves and stems	Placed in a thin cloth and applied to woman's stomach	[15]
Prostate problems Testicle pains Impotence	Leaves, flowers	Decoction	[22]
Depurative To dress wound	Leaves	Cataplasm, Fresh or dried leaves are placed on the wound	[11, 19]
Urine retention	Leaves	Infusion	[11]
Acidity treatment	Leaves and stems	Infusion	[21]
Cold Influenza Fever	Leaves	Infusion bathe patient with the water of boiled leaves	[11, 15, 21]

4. Chemical Constituents

Phytochemical studies on *C. iphionoides* has resulted in the isolation and identification of different constituents, such as fatty acids, phenolic compounds, hydrocarbons, essential oils, and other secondary metabolites from the different plant parts.

The essential oils of the of *C. iphionoides* aerial parts growing in Jordan consist of 45 compounds accounting for 90.2% of the oil with monoterpenes being the most abundant constituents. The Study was performed using gas chromatography (GC) and gas chromatography mass spectrometry (GC-MS) revealed the presence of borneol as the major constituent (49.3%) followed by 1,8-cineole (8.4%), α-terpineol (3.8%), camphor (3.7%), bornyl formate (3.6%), terpin-4-ol (3.0%), bornyl acetate (2.9%), and selin-11-en-4- α -ol, that is, 2.4% [24]. The constituents of *C. iphionoides* essential oil are summarizes in table 2.

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Table 2: The constituents of *C. iphionoides* essential oil

Sr. number	Compounds	Sr. number	Compounds
1	Borneol	23	8-Hydroxy-p-cymene
2	1,8-Cineole	24	*cis-para*-Menth-2-en-1-ol
3	α-Terpineol	25	Bergamal
4	Camphor	26	Isophorone
5	Bornyl formate	27	γ-cadinol
6	Terpin-4-ol	28	α-Fenchol
7	Bornyl acetate	29	*cis*-Jasmone
8	Selin-11-en-4-α-ol	30	*trans-para*-Menth-2-en-1-ol
9	γ-Irone	31	1,8-Dehydrocineole
10	ι-Cadinol	32	Santolina alcohol
11	Lavandulyl acetate	33	Lavender lactone
12	Geranyl acetate	34	*cis*-Linalool oxide
13	β -Oplopenone	35	*cis*-Sabinene hydrate
14	γ -Irone isomer	36	Artemisia alcohol
15	p-Cymene	37	*trans*-Linalool oxide
16	Caryophyllene oxide	38	*trans*-Sabinene hydrate
17	Viridiflorol	39	*trans* -Piperitol
18	neo-iso-Dihydrocarveol	40	*trans*-Pinocarveol
19	Yamogi alchool	41	*cis*-Piperitol
20	Chrysantemic acid	42	Linalool
21	Carvone hydrate	43	Cumin aldehyde
22	Ledol	44	Piperitone

Several compounds from different fractions of *C. iphionoides* have been isolated and identified (Figure 1). For example, varthemic acid I and II, two cyclopropane monoterpenes, have been isolated from *C. iphionoides* aerial parts [25]. The aerial parts ethyl acetate extract produced 3-oxocostusic acid an eudesmane sesquiterpene [26]. Several flavonoids have been isolated from *C. iphionoides*. Afifi et al. reported the isolation of xanthomicrol, kumatakenin, jaceidine, and 3,3′-di-*O*-methylquercetin [27]. In addition to 3,3′-di-*O*-methylquercetin and kumatakenin, Al-Dabbas et al. reported the isolation of five more 3-methoxyflavones from the aerial parts ethanolic extract: 3-*O*-methylkaempferol, 3,3'-di-*O*-methylquercetin, 3,5,6,7,4'-pentamethoxyflavone, 4'-hydroxy-3,5,6,7- tetramethoxyflavone, 5,7,4'-trihydroxy-3,6-dimethoxyflavone, and penduletin [28]. In another studies investigating the chemical constituents

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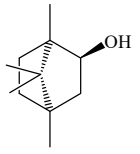
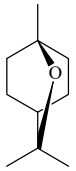
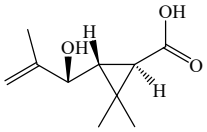
of *C. iphionoides*, resulted in the identification of apigenin, velutin, kumatakillin, quercetin-3,3′-dimethyl ether, luteolin-3′-methyl ether, taraxasterol-3-acetate, kaempferol-3-methyl ether, β-stigmasterol, vanillic acid, 3-oxocostusic acid, and β-sitosterylglucoside [25, 29].



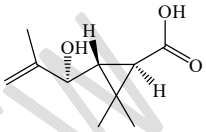
Borneol



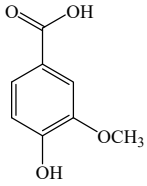
1,8-Cineole



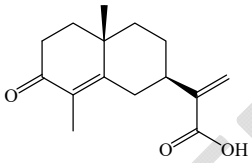
Varthemic acid I



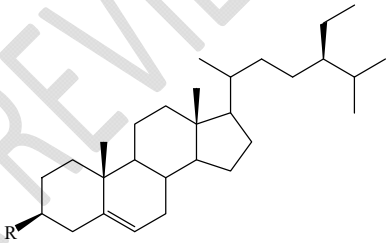
Varthemic acid II



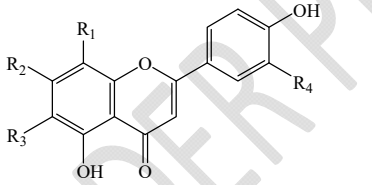
Vanillic acid



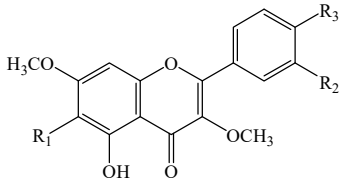
3-Oxocostusic acid



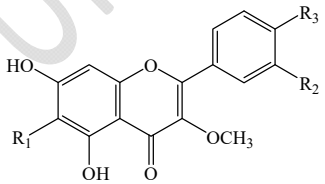
R = OAc β-stigmasterol
R = OGluc β-sitosterylglucoside



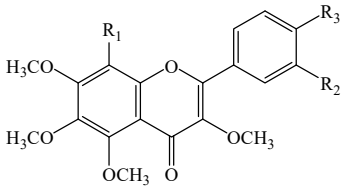
R1= R2= R3= OCH_3, R4=H Xanthomicrol
R1= R3= H, R2= R4= OCH_3 Velutin
R1= R3= R4=H, R2= OH Apigenin
R1= R3= H, R2= OH, R4= OCH_3 Luteolin-3'-methyl ether



R1= H, R2= CH_3, R3= OH Kumatakenin
R1= OCH_3, R2= H, R3= OH Penduletin
R1= H, R2= OCH_3, R3= OH 3,7,3'-tri-*O*-methylquercetin
R1= R2=H, R3=OH 5,4'-Dihydroxy-3,7-dimethoxyflavone



R1= R2= OCH_3, R3= OH Jaceidine
R1= H, R2= OCH_3, R3= OH 3,3'-Di-*O*-methylquercetin
R1= R2= H, R3= OH 3-*O*-methylkaempferol
R1= OCH_3, R2=H, R3=OH 5,7,4'-Trihydroxy-3,6-dimethoxyflavone



R1= R2= H, R3=OCH_3 3,5,6,7,4'-Pentamethoxyflavone
R1= R3= OCH_3, R2=H 3,5,6,7,8,4'-hexamethoxyflavone
R1= R2= H, R3=OH 4'-hydroxy-3,5,6,7-tetramethoxyflavone

Figure 1: Chemical structures of chemical constituents isolated from *Chiliadenus iphionoides*

5. Pharmacological Activities

The pharmacological activities of *C. iphionoides* have been studied and evaluated by a number of biological-pharmacological studies.

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5.1 Anticancer activity

The cytotoxic activity of *C. iphionoides* essential oil of the aerial parts was examined on human cancer cell lines related to prostate (PC3), breast (MCF7), and chronic myelogenous leukemia (K562) in a study conducted by Abbas et al. The essential oil was found to exhibit growth inhibition against all the studied cell lines in a dose dependent manner [30]. The cytotoxicity effect of diffident extracts of the leaves and stem of *C. iphionoides* on MCF-7 and cervical carcinoma (HeLa) cell lines was studied by Elbadry et al. The acetone, ethyl acetate, methanol, petroleum ether, ethanol, and water extracts showed to display high cytotoxic effect against HeLa cell lines with acetone extract being the most active and water extract being the least active. In the same study, it was found that the acetone and methanolic extracts exerted very strong cytotoxic effect against the MCF-7 cell lines [23]. On chronic myelogenous leukemia cell line, the essential oil of *C. iphionoides* at a concentrationa of 200 µg/mL was found to produce a higher inhibition rate compared to doxorubicin with an apoptotic effect. The ethanol, chloroform, and hexane extract *C. iphionoides* aerial parts was investigated on human myelocytic leukemia (HL-60) cell lines and was found to produce growth inhibition with hexane fraction (200 µg/mL) being the most active with 89.0 % inhibition rate [31]. The two isolated compounds 3,3'-di-*O*-methylquercetin and 5,7,4'-trihydroxy-3,6-dimethoxyflavone from *C. iphionoides* aerial parts were found to exert growth inhibition of HL-60 cell lines [28]. The ethanolic extract of *C.*

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iphionoides anticancer activity were also studied on HL-60 cells and other human cancer cell lines such as ovarian carcinoma (SKOV3), lung cancer (A549), and melanoma (BG) cells. The crude extract of *C. iphionoides* was found to exhibit a moderate cytotoxic effect to SKOV3 cells at high concentration (78 mg/mL), while the effect was very small on cancer cells BG and A549 at the same dose. At lower concentrations, the same extract was found to promote the proliferation of A549 and BG cancer cells [32]. The aerial parts dichloromethane extract inhibited the cell growth of breast cancer (EMT6, MCF-7, T47D) cell lines in diabetic and non-diabetic mice in a study by Halees et al. [33]. This activity of the dichloromethane extract suggesting that the nonpolar compounds are responsible for most of the antiproliferative activities in this plant. The antitumor activity of *C. iphionoides* water extract of on human hepatocellular carcinoma (HepG2) cells was also investigated and found to possess a significant antitumor effect and produced a moderate cell killing activity [7, 34].

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5.2 Anti-diabetic activity

C. iphionoides is one of the most common medicinal plant species used diabetes treatment. Several studies have been carried out to evaluate the anti-diabetic activity of *C. iphionoides*. The whole plant parts aqueous extract was studied for its effect on blood glucose levels in normoglycemic and streptozocin (STZ) -induced diabetics rats by Afifi et al. [35]. The extract was found to significantly reduce the glucose levels of the blood by 70 % in the hyperglycemic rats and reduced the intestinal glucose absorption in both normal and diabetic rats in a dose-independent manner. Abu-zaiton et al. studied the anti-hyperglycemic and the effect of the hepatic enzymes of the essential oil isolated from *C. iphionoides* aerial parts on STZ -induced diabetic rats [36]. The essential oil showed to significantly decrease the glucose and the aspartate aminotransferase (AST) levels in rats suggesting that the essential oil possesses anti-

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hyperglycemic activity and may reduce the liver damage induced by streptozotocin. The same anti-hyperglycemic effect of the aerial parts ethanolic extract was observed by Gorelick et al. using cellular and animal models [37]. In the same study, *C. iphionoides* extract was found to increase insulin secretion of pancreatic β cells and the glucose uptake in adipocytes and skeletal myotubes. The anti-α-glucosidase and anti-α-amylase effects of *C. iphionoides* were also investigated. The aerial parts water and ethanolic extracts were found to possess a potent inhibitory effect against porcine pancreas α-amylase in both the iodine starch and the 2-chloro-4-nitrophenyl alpha-~~maltotrioside~~ degradation (CNP-G_3) assays. Further purification of the ethanolic extract by column chromatography led to the isolation of seven 3-methoxyflavons in which five of them (shown in table 3) were reported to highly inhibit the activity of α-amylase at a concentration of 100µM [38]. The dual anti-α-glucosidase and anti-α-amylase efficacies have been studied by Kasabri et al. in two separate *in vitro* and *in vivo* studies. In both studies, the aqueous extract exhibited a dual inhibition of anti-α-glucosidase and α-amylase in a concentration-dependent manner [39, 40]. The extract was also found to induce augmentations in pancreatic promodeoxyuridine (BrdU) incorporation and to enhance the glucose homeostasis by delaying the absorption of carbohydrate and induction of β-cell mass expansion *in vitro* and to exhibit antihyperglycemic in starch-fed rats confirming the therapeutic effect of *C. iphionoides*.

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5.3 Anti-bacterial Activity

Lots of studies on the antibacterial activity of *C. iphionoides* on Gram-positive and Gram-negative bacteria have been carried out. The leaves methanolic extract was evaluated against six bacterial species (*Salmonella typhimurium*, *Proteus vulgaris*, Methicillin-resistant *Staphylococcus aureus*, *Klebsiella oxytoca, Klebsiella pneumoniae*, and *Escherichia coli*) in a study by Haddad et al. using the agar well diffusion method [41]. The extract exerted an

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antibacterial activity against all six tested bacterial species with *P. vulgaris*, *S. aureus, and K. oxytoca* being the most sensitive followed by *S. typhimurium*, while it showed limited activity against *E. coli*. The same low sensitivity against *E. coli* of *C. iphionoides* was also reported by Masadeh et al. [42]. In this study, the ethanolic extract of the whole plant exerted a comparable antibacterial activity against *Enterobacter faecalis*, to that induced by clarithromycin and less than the activity of amoxicillin with minimum inhibitory concentration (MIC) of 130 µg/mL. Abu-Hijleh et al. studied the antibacterial effect of the leaves ethanolic extract in combinations with cefotaxime using fractional inhibitory concentration (FIe) indices against four different bacterial species. The results revealed that the extract potentiated the antibacterial effect of cefotaxime against the tested Gram-positive bacteria *S. aureus* and *Bacillus subtilis* strains while this effect was not observed in the Gram-negative bacteria *E. coli* [10]. The ethanolic extract did not exert an ~~any~~ antibacterial effect against the gram-negative *Pseudomonas aeruginosa* [43]. In general, the resistant of Gram-positive bacteria is less than that of Gram-negative bacteria and this resistance may be attributed to the cell wall permeability barrier which causes a reduction of the amount of antibacterial substance entering the bacterial cell [44]. The synergistic antibacterial effect of *C. iphionoides* methanolic extract and antibiotics such as chloramphenicol, doxycycline, neomycin, nalidixic acid, and cephalexin was investigated by Darwish et al. In this study, the extract was found to enhance the inhibitory effects of the tested antibiotics against both the standard strain and to a lesser extent the resistant strain of *E. coli* [45]. The effect of the chloroform, water, hexane, ethyl acetate, and ethanolic extract of the aerial parts of *C. iphionoide* was studied by Al-Dabbas et al. against *S. aureus*, *B. subtilis*, *Salmonella enteritides*, *Micrococcus luteus*, *E. coli*, and *Bacillus cereus*, and bacterial species. Only the chloroform and ethyl acetate extracts displayed antibacterial activity against the studied bacterial species [31].

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Further purification of the ethyl acetate fraction by column chromatography led to the isolation of the sesquiterpene 3-Oxocostusic acid compound which was found to exhibit potent antibacterial activity against the six studied bacterial species [26]. The antibacterial activity of the aerial parts essential oil against *S. aureus*, *P. aeruginosa*, *B. cereus*, and *E. coli* bacterial species was studied in different food model media by Al-fawwaz et al. It was found that the essential oils exerted antibacterial effect against all used bacterial strains in all type of food media models with the highest activity was shown against *S.aureus* in tomato media [46].

5.4 Anti-fungal activity

The antifungal effect of the aerial parts essential oil of *C. iphionoides* was studied against three different fungal species (*Aspergillus niger*, *Penicillium sp.*, and *Mucur sp*) isolated from food samples using the agar well diffusion method. The results indicated that the essential oil showed a significant antifungal activity and significant reduction in the percent of germinated spores (more than 80% at 100 µg/mL) [46]. In a study by Haddad et al., the methanolic extract of this plants exhibited significant antifungal activity against 13 fungal species (*A. brasiliensis*, *A. niger*, *A. alliaceus*, *Fusarium lini*, *A. flavus*, *Rhizoupus stolonifer*, *Macrophomina phaseolina*, *Gibberella fujikuroi*, *Cephalosporum aphidicola*, *Curvularia lunata*, *Cunninghamella echinulata*, *Beauveria bassiana*, and *Cunninghamella elegans*) using the agar well diffusion method. Among the studied species, *F. lini* was found to be the most sensitive while *B. bassiana* was the most resistant to the extract [41]. Flavonoids isolated from the this plant were tested for their antifungal activity against three fungal species: *Fusarium solani*, *A.* parasiticus, and *Candida tropicalis*. Of the isolated compounds, 3',3'-di-*O*-methylquercetin and xanthomicrol exerted a high activity against the tested species while kumatakenin was only active against *C. tropicalis* and *F. solani* only [27]. In another study, the ethyl acetate, hexane, chloroform, water,

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and ethanolic extracts of *C. iphionoides* aerial parts showed potent activity against three candidal species (*C. tropicalis*, *C. glabrata*, and *C. albicans*) with ethyl acetate extract showed the highest activity among the tested extracts. Further purification of the ethyl acetate and the ethanol extracts led to the isolation and identification of 3-Oxocostusic acid, 5,7,4'-trihydroxy-3,6-dimethoxyflavon, 5,7,4'-trihydroxy-3,5'-dimethoxyflavone, and 5,4'-dihydroxy-3,7,5'-trimethoxy-flavone that were found to exhibit high anticandidal activity [47].

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5.5 Antioxidant activity

C. iphionoides is considered as a potential source of natural antioxidants. The ability of this plant in inhibiting free radicals might be attributed to the high content of polyphenols and flavonoids. Isolated flavonoids from *C. iphionoides* such as, 5,4'-dihydroxy-3,7,3'-trimethoxyflavone, 5,7,4'-trihydroxy-3,3'-dimethoxyflavone, and 5,7,4'-trihydroxy-3,6-dimethoxyflavone were found to exhibit a potent free radical scavenging activity by DPPH (1,1-diphenyl-2-picrylhydrazyl) assay with an inhibition of more than 60% at 200 µg/ml [38]. The same antioxidant activity of 5,7,4'-trihydroxy-3,6-dimethoxyflavone and 5,7,4'-trihydroxy-3,3'-dimethoxyflavone was also reported in other studies [48, 49]. The antioxidant activity of hexane, ethyl acetate, and ethanolic extracts from *C. iphionoides* aerial parts was investigated by using different methods such as linoleic acid, reducing power, DPPH and ABTS (2, 2`-azinobis (3-ethylbezthiazoline-6 sulphonic acid) radical-scavenging activity [48]. The results of this study revealed that the three extracts exhibited variable antioxidant activities with the ethanolic extract being the most effective as antioxidant out of the all methods used. In another study, the ethanolic and water extracts of the aerial parts were found to exhibit similar antioxidant activity to BHT (butylated hydroxytoluene) with an IC_{50} of 50 µg/mL on DPPH radical-scavenging activity while the inhibition of the hexane and chloroform extracts was insignificant. All extracts were found to highly inhibit

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linoleic acid peroxidation with the ethanol extract exerted the highest percent of inhibition [31]. In another study, the water and the alcoholic extracts were reported to have a moderate activity against DPPH and ABTS free radical scavenging with IC_{50} values of 40.6 and 53.2 µg/mL, respectively [50]. The relation between the antioxidant activity and ~~the extracts content~~ of phenolic compound was studied by using the accelerated oven storage method on soybean oil and beef tallow, DPPH-radical scavenging activity and the linoleic acid system. This study demonstrated that the higher the polarity of the extract displays the higher antioxidant activity and these antioxidant activities are directly related to the content of the phenolic compound of the extracts [49]. The correlation between the total phenolic content of the methanolic and water extracts of *C. iphionoides* and its antioxidant activity were also reported by other study [51]. Since the DPPH radical scavenging activity could be affected by certain salts presented in the plants extract, Al-Dabbas et al. studied the effect of the desalted water extract of *C. iphionoides* on DPPH radical-scavenging activity. The results revealed that the crude water extract exhibited much higher activity than that of the desalted extract indicating that the existence of inorganic ions may elevated the DPPH radical-scavenging activity of the extract [52]. The ethanolic extract of *C. iphionoides* was studied for its protective effect against oxidative DNAdamage using *in vitro* 8-hydroxydeoxyguanisine assay in cultured human lymphocytes and was found to increase oxidative DNA damage and to increase the levels of 8-OH-dG indicating mutagenic properties of the extract on DNA [53].

Comment [DCP44]: Expunge

Comment [DCP45]: Change to; the content of the extract

Comment [DCP46]: Include a comma

Comment [DCP47]: Change to; other studies

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Comment [DCP50]: Improperly spacing

Comment [DCP51]: Wrong spelling, replace with; hydroxydeoxyguanosine

5.6 Antispasmodic activity

C. iphionoides is used traditionally for the treatment of gastrointestinal disorders. The aqueous and the ethanolic extracts of the leaves have been studied on isolated rabbit ileum for its antispasmodic effect [54]. In this study, acetylcholine (ACh) was used to investigate the

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antispasmodic effect and mode of action of the extracts. Both extracts caused a decrease in the amplitude and the tone of spontaneous contraction in a concentration-dependent manner. At a concentration of 13.2 µg/mL, the ethanolic extract exerted a maximum intense relaxation effect of about 65% while the effect of the water extract was lower. Other studies evaluated the antispasmodic effect of compounds isolated from *C. iphionoides*. For instance, the effect of the flavone 3,3'-di-*O*-methylquercetin was evaluated by Abdalla et al. on guinea-pig isolated ileum, trachea, and main pulmonary artery and was found to cause the relaxation of the trachea and the adrenaline-contracted main pulmonary artery and a reduction of the tone and the phasic contractions of the ileum and the isolated trachea in a dose dependent manner. The inhibitory effect of 3,3'-di-*O*-methylquercetin may be due to its ability to inhibit the agonist-induced release of calcium ion from intracellular stores or that it inhibits the released calcium ion from binding to intracellular receptor proteins [55]. In another study, xanthomicrol and jaceidin isolated from *C. iphionoides* were also found to exhibit antispasmodic activity on the intestinal smooth muscles of rabbits in a concentration dependent manner [56].

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5.7 Anti-inflammatory activity

The anti-inflammatory activity of aqueous and methanolic extracts of the leaves of *C. iphionoides* was investigated *in* both prostate cancerous PC3 cells and non-cancerous fibroblast MRC-5. The pre-treatment with water extract at 125 µg/mL, significantly reduced the interleukin-6 (IL-6) in response to the bacterial proinflammatory agent LPS (bacterial lipopolysaccharides) in MRC-5 cells but it was not effective in the PC3 cells. In contrast, the methanolic extract at the same dose was able to significantly reduce the IL-6 levels induced by LPS in the PC3 cells but had no effect in MRC-5 cells [5].

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5.8 Antiplatelet activity

The antiplatelet activity of four flavonoids obtained from the water extract of *C. iphionoides* aerial parts was investigated for their *in vitro* antiplatelet activity on collagen and adenosine diphosphate (ADP) induced platelet aggregation of human platelet-rich plasma (PRP) by Afifi and Aburjai [57]. The isolated compound xanthomicrol was found to exhibit potent antiplatelet activity on collagen-and ADP-induced platelet aggregation. Compounds 3,3'di-*O*-methylquercetin and kumatakenin were reported to exhibit high activity in both types of induction while jaceidine were found to be inactive when platelet aggregation induced by ADP and a very weak activity by collagen induction. The antiplatelet activity of the volatile oils, water, and ethanolic extracts was also studied. Only the water extract showed antiplatelet activity with a dose-dependent manner against both collagen and ADP while the ethanolic extract and the volatile oil did not exhibit any antiplatelet activity.

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5.9 Allelopathic activity

The allelopathic activity of water extract from the leaves of *C. iphionoides* was investigated on germination and early seedling growth and seedling dry weights of six different plant species. The results showed that germination percentage of wheat, lentil, barley, pepper, and tomato was significantly altered in a dose dependent manner while chickpea showed slight enhancement when treating with a high concentration of the extract. The aqueous extracts of *C. iphionoides* significantly affected the seedling dry weights of the tested species with wheat and tomato being the least affected followed by pepper, barley, and lentil while in the case of chickpea there was a small increase in the dry weight of its seedlings. The results revealed that *C. iphionoides* contain growth inhibitors that depend on the concentration of the extract and the type of the species [58].

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In another study, the water shoot extract caused a reeducation in the wheat seed germination and the growth of shoot and root [59].

5.10 Anthelmintics activity

The anthelmintic activity of *C. iphionoides* has been investigated. The ethanolic extract of the areal parts was tested against larval exsheathment inhibition assay using two species of parasitic nematodes (*Trichostrongylus colubriformis* and *Teladorsagia circumcinta*, 80:20). The extract was found to exhibit an inhibitory effect of 29 % on the third stage larvae of the nematodes at dose of 100 mg/mL [60].

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5.11 Other studies

The acaricidal activity of the crude extract (70% ethanol) of *C. iphionoides* was examined against *Tetranychus cinnabarinus* the carmine spider mite and showed to cause mite repellency and a significant decrease in number of laid eggs [61]. The mathanolic extract of the aerial parts was screened for its pancreatic lipase (PL) and hormone sensitive lipase (HSL) inhibitory effects in two separate studied. The extract showed poor PL activity, with an IC50 greater than 1000 µg/mL [62] and poor HSL inhibitory effect with 23.6 % of inhibition at 200 µg/ml [63]. The mathanolic extract also did not exhibit any significant acetylcholinesterase and butyrylcholinesterase inhibitory activity [64].

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Table 3: The pharmacological effects of *C. iphionoides*

Pharmacological effects	Part used	Type of extract/ Isolated compounds	Reference
Anticancer	AP	Essential oil (borneol)	[30]

		Essential oil	[30]
		Hexane, chloroform, ethanol extract	[31]
		5,7,4'-trihydroxy-3,6-dimethoxyflavone 3,3'-di-*O*-methylquercetin	[28]
		Essential oil	[30]
		Dichloromethane extract	[33]
		Aqueous extract	[7]
	L, S	Acetone extract Ethanolic extract Petroleum ether extract Methanolic extract Ethyl acetate extract Boiled water extract	[23]
	WP	Aqueous extract	[35]
	AP	Essential oil	[36]
		Ethanolic extract	[37]
Antidiabetic		Ethanolic extract Aqueous extract 5,7,4'-trihydroxy-3,6-dimethoxyflavone 5,7,4'-trihydroxy-3,3'-dimethoxyflavone 5,4'-dihydroxy-3,6,7-trimethoxyflavone 5,7,4'-trihydroxy-3-methoxyflavone 5,4'-dihydroxy-3,7-dimethoxyflavone	[38]
		Aqueous extract	[39, 40]
	L	Methanolic extract	[41]
		Ethanolic extract in combinations with cefotaxime	[10]
	WP	Ethanolic extract	[42, 65]
Antibacterial		Methanolic extract in combinations with different antibiotics (chloramphenicol, neomycin, doxycycline, cephalexin, nalidixic)	[45, 66, 67]
	AP	Ethyl acetate extract Chloroform extract	[31]
		3-Oxocostusic acid	[26]

		Essential oil	[46]
		Aqueous extract	[68]
	L	Methanolic extract	[41]
		20% ethanol water extract	[69]
	WP	Xanthomicrol Kumatakenin 3',3'-di-*O*-methylquercetin	[27]
	AP	Essential oil	[46]
Antifungal		Ethyl acetate extract Hexane extract Chloroform extract Aqueous extract Ethanolic extract 3-Oxocostusic acid 5,7,4'-trihydroxy-3,6-dimethoxyflavon, 5,7,4'-trihydroxy-3,5'-dimethoxyflavone 5,4'-dihydroxy-3,7,5'-trimethoxy-flavone	[47]
Antiinflammatory	L	Aqueous extract Methanolic extract	[5]
	AP	Ethanolic extract	
Antiplatelet		Aqueous extract 3,3'di-*O*-Methylquercetin Kumatakenin	[57]
	AP	5,7,4'-trihydroxy-3,6-dimethoxyflavone 5,7,4'-trihydroxy-3,3'-dimethoxyflavone 5,4'-dihydroxy-3,7,3'-trimethoxyflavone 5,4'-dihydroxy-3,6,7-trimethoxyflavone	[38]
Antioxidant		5,7,4'-trihydroxy-3,6-dimethoxyflavone 5,7,4'-trihydroxy-3,3'-dimethoxyflavone Ethyl extract Hexane extract Ethanol extract Phenolic compound contents	[48, 49]
		Aqueous extract Ethanolic extract	[31]
	WP	Methanolic extract	[50]

		Aqueous extract	
	L	Ethanolic extract	[54]
		Aqueous extract	
Antispasmodic	WP	3,3'-di-*O*-methylquercetin	[55]
		Xanthomicrol	[56]
		Jaceidin	
Allelopathic	L	Aqueous extract	[58, 68]
Anthelmintics	AP	Ethanolic extract	[60]

AP: aerial part, L: leaves, WP: whole plant, S: stem

6. Conclusion:

Available researches have shown that different extracts and active ingredients of *Chiliadenus iphionoides* exhibit different pharmacological properties such as anticancer, antidiabetic, antimicrobial, antioxidant, antispasmodic, and antiplatelet activities. Phytochemical studies have shown the presence of many valuable compounds, such as volatile compounds, flavonoids and phenolic compounds which play a crucial role in human health, therefore, clinical trials should be conducted to investigate the beneficial effects in human models and develop new drugs from the active ingredients of this plant.

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