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Cressa cretica Pharmacognosy, and Pharmacology (A review)

Noor S. Jaafar*,[1], Iman S. Jaafar and Zainab S. Noori***

*Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
** Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.

Abstract

Cressa cretica (Shuwwayl) is a halophytic that belongs to Convolvulaceae, naturally grown in the Middle East including Iraq. Traditionally the plant is used as a paste for sore treatment, also it is used for fever, jaundice, and other illness. Regarding nonclinical use it is used as goat, sheep, and camel feed also as an oil source. Flavonoids including quercetin, kamepferol, apigenin, and their glycosides, phenolic acid as chlorogenic acid, and phytosterols mainly β–sitosterol were the most important phytochemicals that were detected in this halophyte. Crude ethanolic, methanolic extracts and ethyl acetate fraction of the areal parts were used in clinical studies and demonstrated various effects as hepatoprotective, cytotoxic, and genotoxic effect. In molecular docking studies, 3,5-dicaffeoylquinic acid showed antiviral effect vs SARS-CoV-2 (sever acute respiratory syndrome corona virus-2). The purpose of this review was to clarify and discuss all aspects regarding *Cressa cretica*.
Keywords: *Cressa cretica,* halophyte, quercetin, 3,5-dicaffeoylquinic acid .

الخصائص العقاقيرية والعلاجية لنبات*Cressa cretica*
(مراجعة)

نور صباح جعفر*[،١]، ايمان صباح جعفر و زينب صفاء نوري***

* فرع العقاقير والنباتات الطبية ، كلية الصيدلة، جامعة بغداد، بغداد،العراق
** فرع الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد،العراق

الخلاصة

الشويل هي نبات ملحي ينتمي إلى عائلة نجمة الصباح ، ينمو بشكل طبيعي في الشرق الأوسط بما في ذلك العراق. تقليديا ، يتم استخدام النبات كعجينة لعلاج القرحة ، كما أنه يستخدم للحمى واليرقان وأمراض أخرى. فيما يتعلق بالاستخدام غير السريري ، يتم استخدامه كعلف للماعز والأغنام والإبل وأيضًا كمصدر للزيت. الفلافونويد بما في ذلك الكويرسيتين ، والكاميفيرول ، والأبيجينين ، والجليكوسيدات ، وحمض الفينول مثل حمض الكلوروجينيك ، والفيتوستيرول وبشكل رئيسي – سيتوستيرول كانت أهم المواد الكيميائية النباتية التي تم اكتشافها في هذه النبات الملحي. تم استخدام المستخلصات الإيثانولية والميثانولية الخام والايثل اسيتيت في الدراسات السريرية وأظهرت تأثيرات مختلفة مثل التأثيرات الواقية للكبد والسمية للخلايا والسمية الجينية. في دراسات الالتحام الجزيئي ، أظهر حمض ٣،٥ dicaffeoylquinic-تأثير مضاد للفيروسات مقابل SARS-CoV-2. كان الغرض من هذه المراجعة هو توضيح ومناقشة جميع الجوانب المتعلقة بـ*Cressa cretica*.
الكلمات المفتاحية :

Introduction

Cressa cretica (Convolvulaceae)[(1)] is obligate halophytes which in demand for saline soil for its growth and development [(2)]*C. cretica* is a small dwarf branched shrub or subshrub typically has straight stems with white-haired, green leaves [(3)]. This subshrub has various activities and used for management of diabetes, asthma, constipation, exerts anthelmintic, and other activities which are related to the presence of different classes of photochemical as flavonoids, sterols and others[(4)].

The taxonomy of *Cressa cretica* is listed below.

Kingdom	**Plantae**
Phylum	Angiosperms
Class	Magnoliatae
Subclass	Asteridae
Family	Convolvulaceae
Tribe	Zribe Cresseae
Genus	*Cressa*
Species	*Cretica* [(5-7)]

In Arabic countries *Cressa cretica* is called Shuwwayl, Molleih [(8, 9)].Rudranti in Hindi, Rudravanti in Bengali [(10)], Bukkan [(11)]. In Iran, alaf mourcheh [(12)].

[1]Corresponding author E-mail: nooraldahan201@gmail.com
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Cressa cretica is grown naturally in the Mediterranean, in the Middle East including Iraq, Egypt, Syria and, Qatar. Australia, South America, Central and parts of South-east Asia. Also in south to northern and central Africa [11, 13-16] . It is dominant near the Arabian sea coastal region[17].

This shrub is perennial, hairy in nature, erect from 35-40 cm height. The root is perennial woody, horizontal, geminate, has lateral branches growing upward to give rise to above-ground parts [18-20].The short-lived stems are many, erect initially and then become decumbent, these stems branched at the base [20, 21]. The leaves are highly condensed, hairy and stalkless [20-22]. Typically the leaves are obovate lanceolate to scale-like. Flowers are solitary, ovate to obovate imbricate, white or pink in color found in spicate to head like panicles at the apex of the branchlet [5, 20]. The one-seeded fruits are ovoid capsules pointed at the tip[5, 21]. The seeds are brown, glabrous in nature, and shiny to reticulate [5].

Cressa criteca grow along the coastal zone in the sandy area and marshes in combination with other halophytes. Its life cycle carries on during Summer. *C.cretica* begins to shoot or develop with June onset. Meanwhile from the June ending to the August ending flowering and fruiting period is observed[13, 23] in another reference the flowering and fruiting period is all over the year[21]. The plant gradually shrivels in September and October and producing seeds. The seeds stay dormant in the immerse soil till the next year June [18, 23, 24]. The germination of seeds occurs in Spring[18].

Salinity and humidity content influence the allocation and structure of *Cressa cretica* communities, while soil nutrients deficiency as potassium and nitrogen greatly prohibit plant growth and reproduction[25]. *Cressa crética* appears to be one of the most tolerant salt species identified so far[26] tolerating up to 800 mM NaCI[27]. The whole plant and its parts is shown in figure 1

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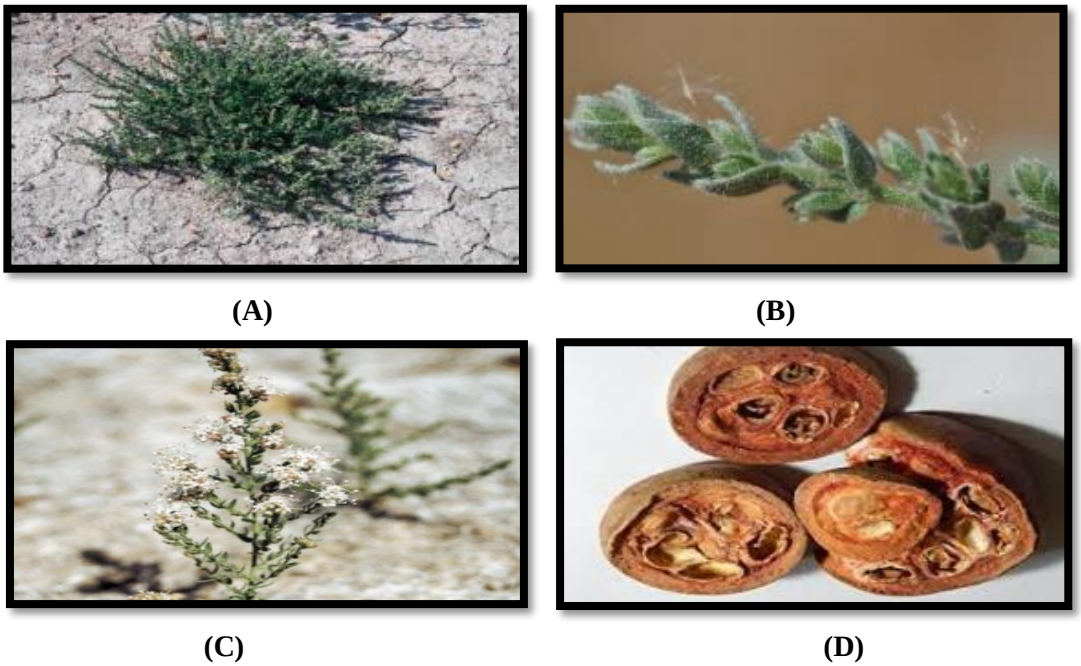

Figure 1. *Cressa cretica* (A): Whole plant, (B): Stem and leaves, C: upper flowering part, (D): Seeds [25, 28].

Ethno pharmacological action of Cressa cretica

Plants are a rich source of secondary metabolites and have been used since ancient civilization for the management of various illnesses. *C. cretica* is a well-known medicinal halophyte. In Iran, the whole aerial parts of the plant are used topically as liniment intended to produce antibacterial and antifungal effects[12]. Decoction prepared from the whole plant is anticipated to exert an antioxidant, antiviral and anti-inflammatory effect, while the paste is used topically for sore treatment[29]. Regarding the folklore utility of this halophyte; it exert expectorant, stomachic, anthelmintic, aphrodisiac actions, and for a urinary problem management. It is used for diabetes, asthma, ulcer, leprosy, constipation, and has certain properties to enrich blood[29, 30]. The whole plant is squelched in water with little black pepper and candy and the resultant blend is used to alleviate chronic fever and Jaundice [31]. In Sudan, dry leaves were triturated with sugar and used as an emetic, also aerial parts extracts or menstrum taken as a tonic. A decoction of leaves of *Vitex doniana* with cressa stems used topically for skin eruption[32].

Non clinical uses of C. cretica

This halophyte is considered suitable biodiesel due to high-level seeds oil contents besides good quality engine parameters. Also, it is used as camel, goat, and sheep feed[27, 32]. Fruits of Cressa are considered as probable supply of edible oil and safe for human use since it is free from unwanted or undesirable contents [33].

Chemical constituents

Phytochemical alkaloids, phenolic acids coumarins, tannins, and sterols were identified in this plant[16]. Others like gum, amino acids, proteins, and mucilage were identified in another study[20].

Different flavonoids were isolated from Egyptian aerial parts of C. cretica using column chromatography including; rutin, quercetin, quercetin-3-O-b-glucoside), (kaempferol-3-O-b-glucoside) and [kampferol-3-O-a-rhamnosyl- (1-6)-b-O-glucoside][16]. Apigenin, Apigenin-7-glucoside, rutin, quercetin and kaempferol were also detected by HPLC in ethyl acetate aerial parts extract of Egyptian plant, with rutin being the main flavonoid in this extract while ethanolic extract contains the same flavonoid except apigenin and Apigenin-7-glucoside is the main flavonoid in this extract[34]. The chemical structures of some flavonoids are shown in figure 2.

kaempferol 3-O-β- glucoside (Astragalin) was also isolated as the main glycoside in ethyl acetate fraction of ethanolic aerial parts extract in Iraqi plant[36].

Flavanol as catechin was also detected by HPLC in both ethyl acetate and ethanolic aerial part extract, and it is the major compound in ethyl acetate extract[34]. Phenolic acids as 3,5 dicaffeoylquinic acid and chlorogenic acids were identified in the plant[38], protocatechuic (3,4-dihydroxybenzoic acid), p-, gentisic acid (2,5-dihydroxy benzoic), chlorogenic , caffeic acid, vanillic acid,ferulic acid, sinapic (3,5-Dimethoxy-4- hydroxycinnamic acid), p-coumaric, gallic acid, and cinnamic acid were detected by HPLC in both ethanol and ethyl acetate extract of aerial parts. Chlorogenic acid is the major phenolic acid in ethanolic extract. Hydroxybenzoic acid, and gallic acid not detected in ethyl acetate and ethanolic extract respectively[34]. Chemical structures of phenolic acids (3,5 dicaffeoylquinic acid and chlorogenic acid) are shown in figure 3.

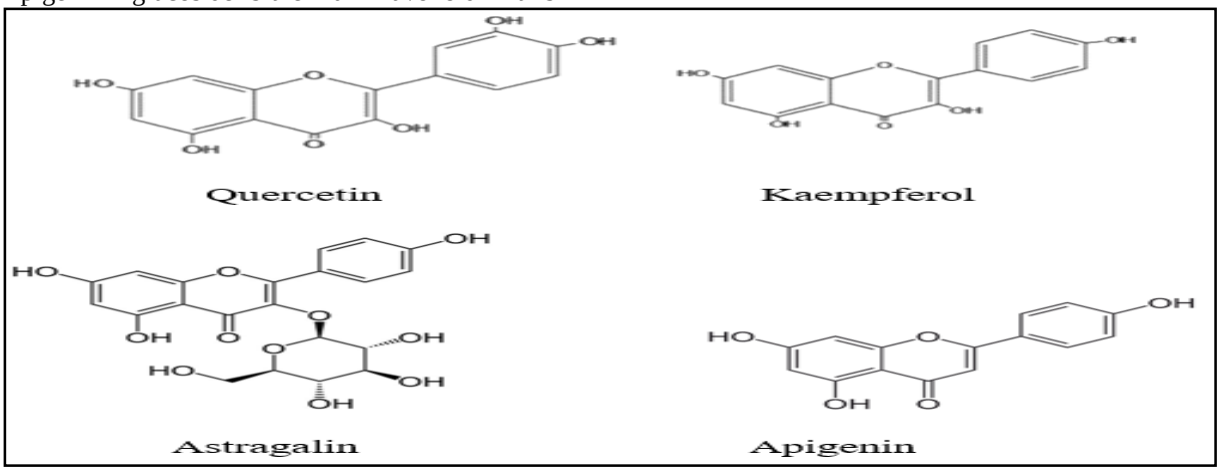

Figure 2. Chemical structures of some flavonoids [35-37].

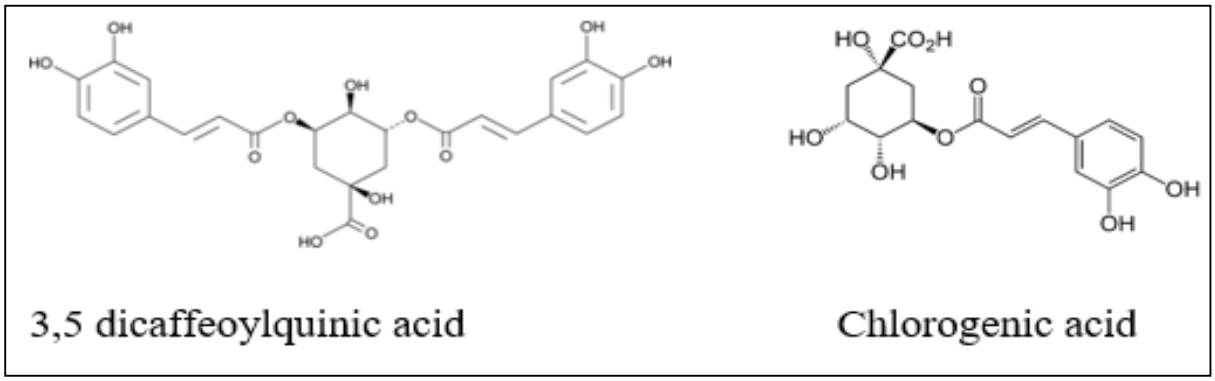

Figure 3. Chemical structures of phenolic acids (3,5 dicaffeoylquinic acid and chlorogenic acid) [39, 40].

Lignin as syringaresinol and syringaresinol-h-d-glucoside and coumarin as scopoletin[38], umbelliferon and isopimpinellin (furanocoumarin) were detected in the aerial parts[41]. The chemical structures of some coumarines (scopoletin and umbelliferone) and lignin are demonstrated in figure 4 and 5 respectively.

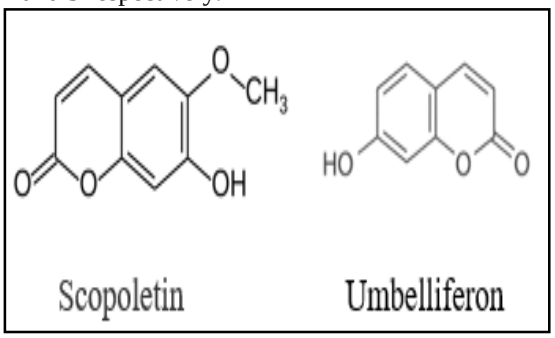

Figure 4. Chemical structure of some coumarines (scopoletin and umbelliferon) [42,43]

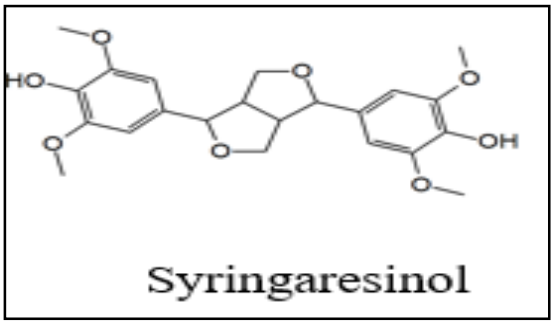

Figure 5. Chemical structure of syringaresinol (lignin) [44].

Using GC/MS Phytosterols as α–sitosterol, β -sitosterol, pentacyclic triterpenoid; β-amyrin, acid, and the terpenoids Acyclic diterpene alcohol and phytol were detected in the unsaponifiable matter of the aerial parts [34] , while campsterol, Ethyl iso-allocholate, and Cholestan-3-ol,2-methylene-,(3β,5α)- were detected in the methanolic extract of leaves[45]. The plant also contains ursolic acid[32] . β –sitosterol was the main sterol identified in the oil obtained from aerial parts, other sterols as stigmasterol, .Δ^7-avenasterol and Δ^5- avenasterol was detected in equal amounts [46]. Stigmasterol -3-O-β-D-glucoside was also identified [32]. The chemical structure of β –sitosterol (phytosterol) and ursolic acid (acidic saponin) are demonstrated in figure 6 and 7 respectively.

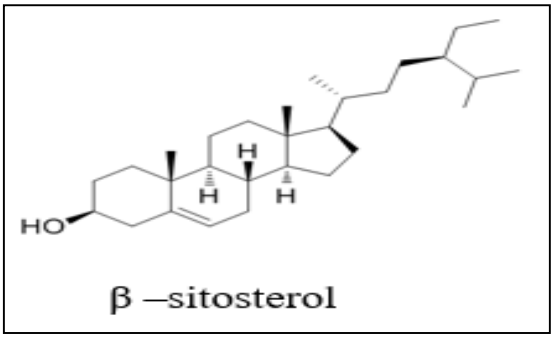

Figure 6. Chemical structure of β –sitosterol(phytosterol) [47].

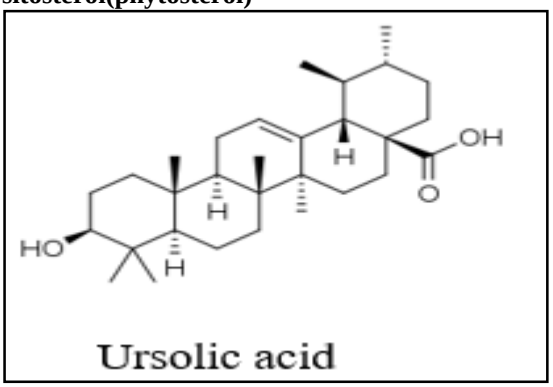

Figure 7. Chemical structure of ursolic acid (pentacyclic triterpenoids)[48].

Concerning fatty acids the following fatty acids were identified ; Octanoic acid; Caprylic acid ,14-methyl-Pentadecanoic acid, 14-methyl-Hexadecanoic acid ,9,12-Octadecadienoic acid (linoleic acid) ,5-octadecenoic acid , octadecanoic acid (stearic acid) ,nonadecanoic acid , eicosanoic acid ; arachidic acid , heneicosanoic acid, docosanoic acid , behenic acid , tricosanoic acid ,tetrecosanoic acid ,lignoceric acid , pentacosanoic acid ,hexacosanoic acid, heptacosanoic acid , octacosanoic acid . These acids are detected as fatty acids methyl ester by GC/MS in aerial parts[46]. 14-methyl-pentadecanoic acid is the major detected acid [34]. In the fixed oil obtained from Egyptian aerial parts of cressa the majority of the detected fatty acids were unsaturated. Palmitic acid is the main saturated fatty acid, while oleic acid and linoleic acid were the major unsaturated fatty acids. Regarding hydrocarbons, thirteen hydrocarbons were identified by GC/MS in the unsaponifiable matter, Hexadecene, Octadecene docosene, tricosane, eicosene, heneicosene tetracosene, tetracosane, pentacosane,hexacosane ,heptacosane , octacosane , Nonacosane. heptacosane and nonacosane represent the majority of the identified hydrocarbons[46].

5-Methyl-6-phenyltetrahydro1,3oxazine-2-thione;Adenosine , 4'-methylaminoformy -4'-deshydroxymethyl-N-; Oxyephedrine; 6-Carboxypterin; Desulphosinigrin; Cyclopentanemethylamine 2-isopropylidene-N,N,5-trimethyl-; 2,7-Diphenyl-1,6-dioxopyridazino [4,5:2',3']pyrrolo[4',5'-d]pyridin; .

Paromomycin; Strychane, 1-acetyl-20α-hydroxy-16 -methylene; 3',8,8'-Trimethoxy-3-piperidyl-2 - 2'-binaphthalene-1,1',4,4'-tetra; were the nitrogenous compound which were detected in methanolic leaves extract of cressa using GC/MS [45].

2-Isopropyl-4-(1-methyl-dodeca-2,4-dienyloxy)-benzene-1,3,5-triol and 11-methyl-dodeca-2,4,6,8,10-pentenoic acid 2,3-dihydroxy-5-methyl-phenyl ester were isolated by column chromatography from n.butanol fraction of methanolic extract *C. cretica* and identified by spectral analysis [38].

Cressa tetracosanoate, cressa tetratriacontanoic acid, creticane cressa naphthacenone and cressa triacontanone were detected in *C. cretica*[49].

Minerals as zinc, copper, and manganese were identified by atomic absorption spectroscopy using the dry ashing digestion method[34].

Aluminum, calcium, iron , magnesium, phosphorous, and Sulphur in addition to previously mentioned minerals were detected in C. cretica by atomic absorption spectroscopy and ultraviolet technique[50].

Pharmacological actions of Cressa cretica

1. Memory enhancement

Alzheimer's is a neurodegenerative disease that is related to aging. Memory loss and disturbed cognitive function are the main disease manifestations[51] . In the course of in normal aging process, there is a noticeable reduction in learning ability and memory. Khare et al (2014) investigated the effect of ethanolic extract of *C. cretica* on memory and learning in mice. Memory loss was produced by scopolamine. Orally administered doses of 200 and 400mg/kg were given for 28 days before scopolamine. The dose of 400mg/kg markedly improved the memory and learning abilities through a reduction in acetylcholine esterase activity, the antioxidant action of the plant extract plus remarkable flavonoids content. The nootropic effect of this dose (400mg/kg orally) was analogous to that of piracetam(200mg/kg intraperitoneally) which was used as a standard or reference nootropic drug[9].

2. *Hepatoprotective effect*

C. cretica is known to mediate a variety of effects, hepatoprotective among these. P. Thirunavukkarasu et al (2014) examined the in-vitro hepatoprotective effect of different *C.cretica* fractions that were isolated based on polarity (petroleum ether, ethyl acetate, n.butanol, and aqueous fraction). Hepatic damage was induced by CCl4, this damage manifested through an increase in hepatic transaminases, bilirubin, and alkaline phosphatase level. CCl4 causes hepatic necrosis and increased cell permeability. All the previously mentioned fractions exhibit hepatoprotective effect especially n. butanol fraction being the best protective effect. The antioxidant effect, free radical scavenging activity, and restoration on increment in glutathione level involved in the hepatoprotective effect of *Cressa cretica* [41].

El-Alfy et al (2019) showed the hepatoprotective effect of this halophyte through in vivo study on mice and rats. CCl4 was used to induce a toxic effect on the liver. The used fractions were petroleum ether, ethyl acetate, and 70% ethanolic extract. The dose used for each fraction was 500mg/kg /day for four weeks. Animals are divided into nine groups. All these fractions demonstrated hepatoprotective effect shown through perfection in liver actions, liver enzymatic and non-enzymatic antioxidant status, malondialdehyde and nitric oxide and serum transaminases, and liver histopathology. The examined fractions were safe at the used dose and up to 3gm/kg. According to this study the hepatoprotective effect in polar fraction attributed to the presence of flavonoids and phenolic acids, while in petroleum ether fraction the effect attributed to phytosterols as α–sitosterol, β -sitosterol, and to the terpenoid β-amyrin in addition to the presence of trace elements as Zn, Cu, and Mn which play an important role for antioxidant enzymatic reaction[34].

3. Antimicrobial effect

Previous studies demonstrated the antimicrobial effect of cressa extract.

Mandeel et al (2005) showed the powerful inhibitory effect of ethanolic C. cretica extract against *Penicillium citrinum* followed by *Candida albicans* using agar diffusion method[52]. Omran et al (2019) prove in a study the antimicrobial effect of three plants including *C.cretica, Origanum vulgare* L. *Rosmarinus officinalis* L. The tested microbes were *Staphylococcus aureus S. aureus, Eschrichia coli E. coli* and *Candida albicans C. albican*. Crude alkaloidal extracts of these plant were used. *C. cretica* showed the largest inhibitory effect on microbes than *Rosemarinus officinalis* and *Origanum. vulgare*, the inhibitory effect is proportional to the concentration. the most affected microbe was *S. aureus* , then *E. coli*, and *C. albicans*[53].

Pirzada et al (2009) evaluated the effect of chloroform, ethyl acetate, ethanol, methanol, and aqueous fractions of *C.cretica* methanolic extract against *Aspergillus niger, Paecilomyces varioti, Aspergillus flavus, Trichophyton rubrum* and *Microsporum gypseum*. The antifungal effect displayed by all fractions, but chloroform and aqueous fractions were the most effective. *Trichophyton rubrum* was the most affected fungi by *C.cretica* extracts[50].

Sunita et al (2012) evaluated the antimicrobial effect of different *C. cretica* fractions (hexane, ethyl acetate, and methanol) using the agar disk diffusion method. Gentamicin, tetracycline were assigned as positive controls for bacteria, and fluconazole and ketoconazole were assigned as a positive control for fungi. Among the tested fractions ethyl acetate extract had a pronounced effect than the other

fractions. *E. coli* and *K.pneumoniae* were the most affected pathogens. The antibacterial effect of ethyl acetate extract was more noticeable than the antifungal effect. *Fusarium oxysporum* was the least affected fungi as compared to *Aspergillus fumigates*, *Aspergillus niger*. *Candida tropicalis* and *Candida albicans* fill in between[54].

4. Antidiabetic effect

Traditionally *C. cretica* was used for diabetes mellitus management. Verma et al (2014) showed the antidiabetic effect of the methanolic extract of cressa in streptozotocin induced diabetic rats. Orally administered dose of 100mg/kg was given for fifteen days. Four groups were assigned, group one received distill water, group two diabetic control rats received streptozotocin, group three diabetic rats received methanolic cressa extract, and group four diabetic rats received glibenclamide. At the end of the study period in cressa extract-treated group, the blood glucose concentration markedly reduced to the normal level and the bodyweight recovered probably due to decreasing muscle wasting and regulation of lipid metabolism[55] . Kumari et al (2016) proved the anti-hyperglycemic action of methanolic extract of *C.cretica* in alloxan-induced diabetic Wistar rats. Doses of 200 mg/kg and 400 mg/kg of extract were given for 28 days. The two groups receiving these doses demonstrated a considerable lowering in glucose concentration, lipid profile, serum transaminases as compared to the control group. At the same time, there was an increase in insulin, glutathione, and high-density lipoprotein[56].

Rani et al (2020) based on molecular docking study proven the antidiabetic effect of two compounds(2-Isopropyl-4-(1-methyl-dodeca-2,4-dienyloxy)-benzene-1,3,5-triol and 11-Methyl-dodeca-2,4,6,8,10-pentenoic acid 2,3-dihydroxy-5-methyl-phenyl ester) isolated from *C. cretica* [49].

Rani et al (2020) demonstrated in a study the effectiveness of aqueous extract of whole *C.cretica* plant as antidiabetic preparation in streptozotocin-induced diabetic rats. Lab data and histopathological studies were the follow-up criteria. Doses 200mg/kg, 400mg/kg of the extract and glibenclamide treated groups display a noticeable reduction in blood glucose level. Triglyceride, cholesterol & LDL levels were decreased during and at end of the study. The dose 400mg/kg showed almost normal pancreatic cell histology as compared to 200mg/kg dose as there was some damage in these cells [57].

5. Cytotoxic effect

C. cretica exhibits a cytotoxic effect. Mutlag et al (2017) proclaim the cytotoxic effect of ethyl acetate extract of *C. cretica* through in vivo study on Albino Swiss mice bone marrow and spleen cells. Four groups were categorized each contains 6 animals. Group one was the control group received dimethyl sulfoxide (DMSO), group two received a single dose of methotrexate (20 mg), group three and four received 100mg/kg and 200mg/kg of ethyl acetate extract respectively for seven days. Ethyl acetate extract at both doses results in a remarkable decline in the mitotic index in both cell types (bone marrow and spleen) as compared to (DMSO) negative control group. mitotic index is a vital predictive factor that predicts overall survival in addition to the response to chemotherapeutic agents in most types of cancer. Ethyl acetate extract effects on mitotic index were more pronounced than that of methotrexate[58].

Fawzi et al (2019) proved the in vitro cytotoxic effect of ethanolic and ethyl acetate fractions of *C. cretica.* Different concentrations of both extracts were used vs MCF-7 Cell Line (breast carcinoma cells) and SKOV-3 Cell line (ovarian carcinoma cells). Both extracts reveled a considerable cytotoxic effect on both cell lines in a dose-dependent manner[28].

6. Genotoxic effect

Mutlag et al (2017) showed the genotoxic effect of two different doses of ethyl acetate extract of *C.cretica* . Four groups were assigned each one contains six mice. Group one was the control group received dimethylsulfoxide(negative control) group two received a single dose of methotrexate (20 mg) (positive control), group three and four received 100mg/kg and 200mg/kg of ethyl acetate extract respectively for seven days. After treatment duration, 1 mg/kg of colchicine was given intraperitoneally for each animal. Two hours later the animals were sacrificed and samples were aspirated from femur bone and spleen cells for genotoxic analysis. Both examined doses demonstrated a noticeable increment in total chromosomal aberration and chromatid break in bone marrow cells when compared to the negative control group. At the same time showed a significant reduction in total chromosomal aberration and chromatid break in bone marrow cells as compared to the methotrexate receiving group. So *C. cretica* ethyl acetate fraction has a genotoxic effect in a dose-dependent manner as compared to the negative control. The genotoxicity might be due to the presence of coumarin type of phytochemicals[59].

7. Antipyretic, and Antinociceptive Effects

One of the earliest or traditional uses of *C. cretica* was for fever treatment [31] Abdallah et al (2017) demonstrated the antipyretic effect of aqueous aerial parts extract .subcutaneous injection of Brewer's yeast was used to induce fever in mice which were pronounced 18 hours after injection. Paracetamol 150mg/kg was the standard antipyretic drug.

50mg/kg and 100mg/kg of the aqueous extract were given, these doses demonstrated a significant reduction in rectal temperature as compared to

control after 60 and 120minutes of pyrexia induction, but less effective than paracetamol.

Hot plate test and acetic acid-induced writhing test were used to evaluate the antinociceptive activity of the aqueous cressa extract in mice. The used doses 50mg/kg and 100mg/kg of the aqueous extract showed a valuable reduction in acetic acid-induced abdominal cramps (43% and 48%)in comparison to the control group. For the hot plate test, a significant rise in latency time (66% and 78%) was observed for both doses(50mg/kg and 100mg/kg) respectively as compared to the control group.

C. cretica showed writhing inhibition in acetic acid-induced peripheral nociception of 43% and 48% at doses of 50 and 100 mg/kg, respectively. The same doses increased latency time in a hot plate model of central analgesia by 66% and 78% compared to the control group respectively[60].

8. *C. cretica* and Covid 19

Previous studies reported the antiviral effect of *C.cretica(*58). Shah et al.(2021) highlighted the antiviral effect of certain active phytochemicals against the SARS-CoV-2 virus using molecular docking studies(38). Scopoletin, 3,5-dicaffeoylquinic acid, quercetin, and syringaresinol from *Cressa cretica* were used in the study. Remdesivir was used as a standard drug. The binding potential of these active compounds to serine-like protease of SARS-CoV-2 was examined followed by an investigation of the vast conformational space of protein–ligand complexes by molecular dynamics simulations. Both quercetin and 3,5-dicaffeoylquinic acid demonstrated high docking scores, and through hydrogen bonding and hydrophobic interaction combine with the active site of serine protease which is an important enzyme required for viral replication. 3,5-dicaffeoylquinic acid displayed the best interaction capacity to serine-like protease suggesting this phenolic acid as a potential antiviral agent vs SARS-CoV-2[38].

13. Antidepressant effect

Herbal medicine is generally utilized to alleviate mental disorders including depression by a variety of pathways[61]. Khare et al (2016) proved the antidepressant effect of ethanolic extract of *C. cretica* using forced swim test and tail suspension test. Five equal groups of Swiss albino mice each group contains six animals. Group one received 1ml/100gm of polyethylene glycol, Group two and three received 200,400 mg/kg orally of ethanolic extract respectively, and Group four and five (positive control) received the antidepressant fluoxetine at a dose of 20mg/kg and imipramine at a dose of 15mg/kg respectively for seven and fourteen days. The immobility period was measured sixty minutes after the last dose. both doses 200 & 400 mg/kg of *C. cretica* produced considerable antidepressant indicated by a decrease in immobility times of mice in forced swim test and tail suspension test[62].

14. Antitussive effect

Indigenous people of India widely used *C. cretica* for cough and asthma management. Sunita et al show the antitussive effect of methanolic extract (2.5%w/v and 5% w/v) on male guinea pigs using the nebulized citric acid solution and also SO2 gas. Each group contains 5 animals, 0.1 g/ml of citric acid was aerosolized for 7min. the animals based on their group were exposed to normal saline (group one), 0.03gm/ml codeine solution (group two, positive control), meanwhile group three and four were aerosolized 2.5%w/v, 5%w/v)of *C. cretica* methanolic extract respectively for 7 minutes. After 10 minutes 0.1 g/ml of citric acid was aerosolized for 7min and the number of coughs was determined. Both concentrations and codeine produced a marked antitussive effect as compared to the control group, and at the higher concentration, the antitussive effect being more pronounced.

The antitussive effect was also evaluated by using SO2 gas to induce cough in mice. *C. cretica* at a used concentration (100,200,400mg/kg) produced a noticeable antitussive effect in dose -dependent manner. The dose 400mg/kg showed the most powerful effect, but less than that of codeine [63].

15. Effect on fertility

Medicinal plants either improve or deteriorate reproductive function(64) . Gupta et al. (2006) demonstrated the inhibitory effect of methanolic *C. critica* extract on male albino rat fertility. An oral dose of 100mg/kg/day was given for 60 days for one group while the other received distilled water. In *C. cretica* treated group fertility was reduced by 100%. There was a considerable decline in the testis weight. Epididymis, seminal vesicle, and ventral prostate shrink. Primary and secondary spermatocytes plus spermatids numbers were reduced. Sertoli cell and mature leydig cell counts markedly decrease.

Glycogen, cholesterol, protein, and sialic acid content of the testis was decline. Seminal vesicle fructose also, epididymis sialic acid and protein were considerably decreased. Totally all of these observations affects male rat testosterone level and spermatogenesis[65].

16. Antioxidant effect

Pryianka et al (2015) approved the in-vitro antioxidant effect of methanolic *C.cretica* extract using 1,1-diphenyl-2-picryl hydrazyl (DPPH) and hydrogen peroxide assay. The antioxidant effect is dose related, and it is attributed to the presence of polyphenolic compounds and other phytochemicals[66].

Afshari et al (2017) demonstrated the anti-oxidant effect of *C. cretica* leaf extract using 1,1-diphenyl-2-picryl hydrazyl (DPPH), ferric reduction activity potential and total antioxidant capacity assays. Aqueous and 70% hydro-ethanolic extract were prepared using different interval for extraction ranging from 3-24 hours. The anti-oxidant effect of

the extract was compared to the synthetic antioxidant BHT (Butylated hydroxytoluene).
BHT demonstrated the highest anti-oxidant effect then ethanolic extract after that aqueous extract. Also the anti-oxidant effect increase with concentration increment[3].

Conclusion

Cressa cretica is an important medicinal plant that has numerous effects. This review represents an updated information specially those concerning the phytochemicals and pharmacological activates. Experimental clinical studies confirmed its traditional uses and proved it is antimicrobial, hepatoprotective, antidiabetic, antitussive, antiviral and other effects.
Most of the clinical studies used the whole aerial parts of plant. The plant also demonstrate safety profile at the examined doses. This plant contains almost all types of phenolic compounds flavonol, flavanol, lignin, coumarins and phenolic acids. Phenolic compounds and specially 3,5-dicaffeoylquinic may has a role in treatment of COVID-19 pandemic.

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