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Research advances in ulcer treatment using Tunisian medicinal plants

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ABSTRACT

Ulcer is one of the most common health problems in Tunisia and rest of the world. Ulcer is characterized by the sore in the gastrointestinal tract. Medicinal plant chemicals show the better compatibility with the human body than the synthetic chemical drug. As herbal medicines are considered as safe for the treatment of illness with lesser adverse effects, economical, effective and relatively less toxic, extensive research is carried out in search for potent antiulcer agents of plant origin. Many of Tunisian medicinal plants have been experimentally validated. A comprehensive review was conducted to amass information from scientific journal articles about Tunisian medicinal plants used for the treatment of ulcer.

Keywords: *Ulcer, Medicinal plants, Tunisia, Antiulcer potential.*

1. INTRODUCTION

Ulcer is a sore on the lining of the gastrointestinal tract caused due to mucosal erosions [1]. It is a result of gastrointestinal disorder due to an imbalance between the aggressive factors like acid, pepsin, *Helicobacter pylori* and defensive factors like bicarbonate secretion, prostaglandins, gastric mucus and innate resistance of the mucosal cell factors [2]. This gastrointestinal disorder could be caused by infection with *Helicobacter pylori* bacterium and the use of non-steroidal anti-inflammatory drugs such as aspirin and ibuprofen [3]. Even the synthetic drugs of ulcer treatment, as proton pump inhibitors, H2 receptors, cytoprotectants, demulcents, anticholinergics, antacids and prostaglandin analogues, had several side effects [4]. For examples, proton pump inhibitors (omeprazole, lansoprazole) may cause nausea, abdominal pain, constipation, diarrhoea and H_2 receptor antagonists (cimetidine) may cause gynaecomastia, loss of libido [4]. As herbal medicines are considered as safe for the treatment of ulcers with lesser adverse effects, economical, effective and relatively less toxic, extensive research is carried out in search for potent antiulcer agents of plant origin [5,6]. So, the present review defines Tunisian medicinal plants that have been experimentally tested and revealed to be of some value in ulcer treatment.

2. METHODOLOGY

The search was done in electronic databases of PubMed, Scopus, ScienceDirect, and Google Scholar for studies using the key terms: Ulcer, medicinal plants, Tunisia and antiulcer potential. The references list included all scientific articles related to the ulcer subject and published from 1999 to 2016. All plant species were taxonomically validated; the latin scientific name and family were confirmed using The Plant List site (http://www.theplantlist.org/).

3. TUNISIAN MEDICAL PLANTS USED TO TREAT ULCER

1. *Apium graveolens* L.

Family: Umbelliferae

Local name: Krafess.

Description: Celery (*A. graveolens*) is a biennial plant with a height of 100 cm, a strong aroma and fleshy solid stem. Its leaves are 5 to 50 mm, triangular, diamond or a spear in shape, and their edges are saw-teeth or lobe. Each umbrella has 4 to 12 branches. The fruit of this plant is in oval shape with the wideness of 1.5 to 2 mm. It is wingless, brown, and with black lines [7]. Celery is native to Europe; the range of cultivation and consumption of celery is very extensive and it is found in most developing countries, including African, Asian and United State countries [8].

Research: Acute gastric ulcer was induced using HCl/ethanol. The volume, pH and total acidity of gastric secretion were determined by the pyloric ligature method. In addition to reference group (Omeprazole, 30 mg/kg) and control group (9% NaCl) of Wistar rats, treated groups received the essential oil of seeds isolated by supercritical CO_2 and hydrodistillation at doses (100, 200 and 300 mg/kg).. Oral administration of essential oil of *A. graveolens* seeds inhibited HCl/ethanol ulcers by 59, 93 and 98%, respectively, to supercritical CO_2 essential oil and 72, 77 and 91%, respectively, to hydrodistillation essential oil which was similar to that induced by omeprazole (71%). In the case of pylorus ligature, the essential oil reduced the volume of gastric juices and total acidity as well as increased gastric pH [9].

2. *Artemisia campestris* L.

Family: Compositae

Local name: T'gouft

Description: *A. campestris* is a perennial scarcely aromatic herb originating in Asia and now distributing to North America and North Africa [10].

Research: *A. campestris* aqueous extract has potent antiulcer property. In fact, *A. campestris* aqueous extract protected against macroscopic and histological changes induced by aspirin in

stomach mucosa of rats [11]. Aspirin administration was accompanied by an oxidative stress status assessed by an increase in malondialdehyde level, a decrease in the content of sulfhydryl-groups and a depletion of antioxidant enzyme activities such as superoxide dismutase, catalase and glutathione peroxidase [11]. The *A. campestris* aqueous extract pre-treatment reversed all the effects of aspirin-induced intracellular mediators. Additionally, pre-treatment with *A. campestris* aqueous extract protected against aspirin-induced gastric oxidative stress. More importantly, aspirin administration increased plasma and tissue hydrogen peroxide, free iron and calcium levels [11]. This gastroprotection offered by *A. campestris* aqueous extract might be related partly to the safety of sulfhydryl group as well as its opposite effect on some intracellular mediators such as hydrogen peroxide, free iron and calcium [11].

3. *Carum carvi* L.

Family: *Apiaceae*

Local name: karouia

Description: Caraway (*C. carvi*) is one of the earliest cultivated herbs in Asia, Africa and Europe. Caraway seeds have remained popular as culinary spices and are also overwhelmingly used in traditional therapy since antiquity in diverse geographical areas [12].

Research: The antiulcerogenic activity of caraway seed essential oil was evaluated by the HCl/ethanol method, which caused injury to the gastric mucosa. When male Wistar rats of the reference group received omeprazole (30 mg/kg) and the control group received NaCl, three treated groups received the essential oil (100-300 mg/kg). After 30 min, all groups were treated with HCl/EtOH for gastric ulcer induction [12]. Baananou et al. [12] mentioned that *C. carvi* essential oil enhanced a significant inhibition of 47%, 81% and 88%, respectively, for three doses of essential oil used, which was similar to that induced by omeprazole (95%).

4. *Ceratonia siliqua* L.

Family: Fabaceae

Location name: Kharroub

Description: Carob (*C. siliqua*) is a slow-growth ever-green tree cultivated for years in Mediterranean countries. The carob fruit, brown pod 10-25 cm in length [13].

Research: The gastroprotective effect of carob pod aqueous extract was investigated against ethanol-induced oxidative stress in rats. Adult male Wistar rats were perorally pretreated with carob pod aqueous extract (500, 1000 and 2000 mg/kg b.w.) during 15 days and intoxicated with a single oral administration of EtOH (4 g/kg b.w.) for two hours [13]. Results showed that the *in vivo* pretreatment with carob pod aqueous extract protected against EtOH-induced macroscopic and histological changes induced in stomach mucosa. Carob extract administration also protected against alcohol-induced volume gastric juice decrease. More importantly, carob pod aqueous extract counteracted EtOH-induced gastric lipoperoxidation, reversed the decrease of sulfhydryl groups an hydrogen peroxide levels and prevented the depletion of antioxidant enzyme activity of superoxide dismutase, catalase and glutathione peroxidase [13].

5. *Juniperus phoenicia* L.

Family: *Cupressacea*

Location name: Araar

Description: *J. phoenicia* is a branched shrub up to 6 m high with a trunk up to 1 m in diameter. It is native to the northern lands bordering the Mediterranean Sea from Portugal to Palestine. It is also native to North Africa found in Algeria, Libya, Morocco, Tunisia as well as the Canary Islands [14].

Resaearch: The ulceroprotective activity of *J. phoenicea* leaf essential oil was evaluated against hydrogen chloride/ethanol-induced ulcers in rats. The antiulcer activities of 50, 75 and 100 mg/kg b.w. *J. phoenicea* leaf essential oil were investigated on 0.3 M hydrogen chloride /ethanol-induced ulcers in rats [15]. *In vivo* pretreatment with *J. phoenicea* leaf essential oil, given orally, provided dose-dependent protection against hydrogen chloride/ethanol-induced gastric ulcers in rats. Furthermore, pretreatment with *J. phoenicea* leaf essential oil significantly decreased malondialdehyde content and increased the activities of superoxide dismutase, catalase and glutathione peroxidase. Antiulcerogenic activity of *J. phoenicea* leaf essential oil could be from synergistic antioxidant and antisecretory effects. Oral use of *J. phoenicea* leaf essential oil has excellent preventive effect on induced gastric ulcer comparable to the proton pump inhibitor omeprazole [15].

6. *Matricaria recutita* L.

Family: *Asteraceae*

Local name: Babounj

Description: Chamomile (*M. recutita*) is an annual herb with erect branching and finely divided leaves growing between 50 and 90 cm tall. The flowers are daisy-like, with hollow conical yellowish centre surrounded by silver-white to cream colored florets [16]. Chamomile is one of the important medicinal herb native to southern and eastern Europe. It is also grown in Germany, Hungary, France, Russia, Yugoslavia, and Brazil. The plants can be found in North Africa, Asia, North and South America, Australia, and New Zealand [17]. It has been included for centuries in the pharmacopeia in many countries such as Tunisia [18]. Chamomile is a safe plant used in different commercially available forms such as tea, infusion, liquid and capsules in human nutrition [16]

.**Research:** The protective effect of chamomile decoction extract in ethanol-induced ulcer on gastric mucosa in rat was investigated [18]. The administration of acute alcohol had lead to mark macroscopic and histologic changes in gastric mucosa. It also induced lipoperoxidation (486.99%), thiol group decrease (40.98%), antioxidant enzyme activity depletion such as superoxide dismutase (49.05%), catalase (46.80%) and glutathione peroxidase (38.20%) as well as an increase of tissue and plasmatic hydrogen peroxide, calcium and free iron levels. *M. recutita* decoction extract reversed all macroscopic, histologic and biochemical changes induced by alcohol administration [18]. A potential gastropreotective effect of *M. recutita* decoction extract against EtOH-induced ulcer and oxidative stress might be partially to its antioxidant properties as well as to various gastric mucosal defense mechanisms, including protection of gastric sulfhydryls and its opposite effect on some intracellular mediators such as free iron, hydrogen peroxide and calcium [18].

7. *Myrtus communis* L.

Family: *Myrtaceae*

Local name: Rihane

Description: Myrtle (*M. communis*) is an evergreen shrub or a small tree growing wild in the coastal regions, the internal hills and the forest areas of Mediterranean countries [19]. The flowering period occurs from May to June and the ripening period extends from September to January [20]. The myrtle ripe fruit is ellipsoidal in shape, dark blue in color [21]. The fruit is composed of pericarp and approximately 9 small seeds having snail shapes [22].

Research: The antiulcer activity of the myrtle seed aqueous extract on peptic ulcer model induced by ethanol in male Wistar rats was investigated. Results showed that myrtle seed aqueous extract provide *in vivo* a dose-dependent protection against ethanol-induced gastric and duodenal macroscopic and histological alterations. It also inhibited the secretory profile disturbances and lipid peroxidation, preserve normal antioxidant enzyme activities and non-enzymatic antioxidant levels. Alcohol acute intoxication increased gastric and duodenal calcium, hydrogen peroxide and free iron levels, while the treatment of myrtle berry seeds aqueous extract protected against intracellular mediators deregulation [23]. Jabri et al. [23] deduced that myrtle berry seeds aqueous extract had a potent protective effect against alcohol induced peptic ulcer in rat. This protection might be related in to part its antioxidant properties as well as its opposite effects on some studied intracellular mediators.

8. *Opuntia ficus indica* L.

Family: *Cactaceae*

Local name: Hindi

Description: Cactus pear (*O. ficus indica*) is a tropical or subtropical plant up to 2 m height. Succulent stems are flat, oval and segmented. Flowers 5-6 cm in diameter are yellow. Fruit is a false berry composed of a juicy sweet pulp containing numerous small hard-coated seeds. Cactus pear is originally grown in South America and cultivated in dry regions as an important food source [24]. Native to Mexico, this plant is widely distributed in arid and semi-arid regions of South and Central America, Africa and the Mediterranean area [25]. Cactus pear has a rapid growth, good adaptation to poor soils and low water requirement [26].

Research: Cactus pear methanolic root extract was investigated for its *in vivo* gastroprotective ability against 80% ethanol induced ulcer in rats. The *in vivo* pretreatment of rats with ranitidine (50 mg/kg) and 200, 400, and 800 mg/kg doses of cactus pear methanolic root extract significantly reduced the 80% ethanol induced-ulcer lesion, with a rate of 82.68%, 49.21%, 83.13%, and 92.59% respectively, and prevented the depletion of antioxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase, total glutathione. It also inhibited the increase of myeloperoxidase and malondialdehyde in rat stomach tissues when compared with ethanol group. Additionally, pretreatment with cactus pear methanolic root extract marked a dose-dependent attenuation of histopathology changes induced by ethanol [27]. Alimi et al. [27] noted that phenolic and flavonoid wealth, radical scavenging activity and reducing power have been implicated for antiulcer property of cactus pear methanolic root extract.

9. *Phlomis crinita* Cav. ssp. *Mauritanica* Munby

Family: *Lamiaceae*

Local name: Khayata

Description: The genus *Phlomis* L. comprises 12 species, which are naturalized in Europe, Asia and North Africa [28]. *P. crinita* Cav. ssp. *mauritanica* Munby (*P. mauritanica*) is a shrub with flowers having an intensely golden yellow corolla and is used in Tunisian folk medicine as a wound healing drug.

Research: This investigation of the *P. crinita* ssp. *Mauritanica* lyophilized infusion confirmed the presence of gastroprotective activity. The lyophilized extract possesseed a dose-dependent antiulcerogenic activity. When increasing the doses from 200 to 300 mg/kg, the ulcerogenesis inhibition percentage ranged from 59.15 to 91.48%. The activity of 300 mg/kg of the lyophilized infusion (300 mg of lyophilized infusion is equivalent to 2.8 g of dried leaves) was greater than that of the positive control, the cimetidine (100 mg/kg), which inhibited the ulcerogenesis by 71.48% [29].

10. *Pistacia lentiscus* L.

Family: *Anacardiaceae*

Local name: Darou

Description: *P. lentiscus* widely grows in many Mediterranean countries [30]. It is an evergreen shrub, with separate male and female plants, with a strong smell of resin, from 1 to 5 m high. The leaves are alternate, leathery, and pinnately compound (no terminal leaflet), with winged petioles and five or six pairs of deep-green leaflets. It presents very small flowers, the male with five stamens; the female is divided into 3 lobes. The fruit, which is rarely present, is a drupe, first red and then black when ripe, about 4 mm in diameter. The stems/trunks are reddish when young and become grey when older. The Gum Mastic produced by this tree is a transparent, lemon-white colored, tear-shaped natural resin [31].

Research: The antiulcerogenic efficacy of the aqueous, chloroformic, ethyl acetate and methanolic extracts from *P. lentiscus* L. leaves was investigated using the carrageenan-induced paw edema assay and HCl/ethanol-induced gastric lesions in rats. The aqueous, chloroformic, ethyl acetate and methanolic leaf extracts (50, 100 and 200 mg/kg) given intraperitoneally showed a dose-dependent antiinflammatory effect. The chloroformic, ethyl acetate and methanolic leaf extracts when administered orally (25, 50 and 100 mg/kg) exhibited an inhibition of gastric lesions in a concentration-related manner [32].

11. *Rhus tripartita* L.

Family: *Anacardiaceae*

Local name: Jdari

Description: *R. Tripartita* is low spiny bush with three toothed triangle leaflets, resembling hawthorn leaves. Inflorescence is in cymes with white flowers. Fruits start reddish green and turn to bluish black at maturity. *R. Tripartita* is a local presaharan Tunisian plant that grows largely under rainfall ranging between 100 and 600 mm/year and at altitudes ranging from 10 to 500 m [33].

Research: The antiulcer activity of methanol extract of *R. tripartita* stem was evaluated. Rats were treated with 80% ethanol (0.5 mL) to induce gastric ulcer. The results showed that the orally rat pretreatment with *R. tripartita* extract decreased significantly the ethanol gastric ulcer index value and preserved the integrity of the gastric mucosa by preventing the mucosal ulceration caused by ethanol. The *R. tripartita* extract prevented alcohol-induced decrease in stomach antioxidant enzyme activities such as catalase, glutathione peroxidase and superoxide dismutase. Total reduced glutathione and malondialdehyde tissue contents were

also reversed of *R. tripartita* extract-pretreated rats when compared with the negative control group [34].

12. *Teucrium ramosissimum* Desf.

Family: *Lamiaceae*

Local name: Hachichet Belkacem

Description: *T. ramosissimum* is a native and endemic medicinal plant from South of Tunisia traditionally used in such diverse applications as the treatment of gastric ulcer, intestinal inflammation and particularly as cicatrizing in external use [35].

Research: The antiulcerogenic activity of chloroform and ethyl acetate leaf extracts from *T. ramosissimum* was assayed. Antiulcerogenic activity was examined on rat ethanol-induced ulcerogenic model. Compared with the control cimetidine, leaf extracts from *T. ramosissimum* exerted different protective effects against ethanol-induced ulcerogenesis. The ethyl acetate extract of *T. ramosissimum* showed to possess the highest protective effect with 81.04% inhibition against ethanol-induced ulcerogenesis at the concentration of 300 mg/kg. Even the weakest antiulcerogenic effect was observed for chloroform extract (56.94%) at the lowest dose [35].

13. *Thymus hirtus* sp. *algeriensis* Boiss. et Reut.

Family: *Lamiaceae*

Local name: Masoukcha

Description: *T. algeriensis* is prolific in Mediterranean regions, mostly in North Africa, has been widely used in traditional medicine as an antiseptic and antispasmodic [36].

Research: The antiulcerogenic activity of *T. algeriensis* essential oil was examined on rat HCl/ethanol-induced ulcerogenic model (0.3 M HCl/60% ethanol). Results showed that the dose of *T. algeriensis* essential oil found to be effective at 180 mg/kg b. w. Oral administration of *T. algeriensis* essential oil inhibited HCl/ethanol-induced ulcers and significantly reduced lesion index in ulcer induced rats. Furthermore, pretreatment with *T. algeriensis* essential oil essential oil significantly increased the activities of superoxide dismutase, catalase and glutathione peroxidase [36]. Guesmi et al. [36] had also mentionned that female rats had a greater resistance to ulcers and gastric lesions occurred less often than in males.

14. *Ziziphus lotus* Desf.

Family: *Rhamnaceae*

Local name: Sedra

Description: Jujube (*Z. lotus*) is a deciduous shrub up to 5 m, with shiny green leaves about 5 cm long. The edible fruit is globosely dark yellow drupe having 1.5 cm diameter. As a tropical and subtropical plant, *Z. Lotus* grows generally in arid and semiarid countries and is widely distributed in China, Iran, Africa, South Korea, and Europe like Cyprus, Spain, Greece, and Sicily [37]. In Africa, *Z. Lotus* is abundantly present in Mediterranean region like Algeria, Morocco, Tunisia, and Libya.

Research: Oral administration of aqueous extracts of *Z. lotus* root barks (50-200 mg/kg), leaves (50-200 mg/kg) and fruits (200-400 mg/kg) produced a significant and dose dependent inhibition to the acute ulcer induced by HCl/ethanol solution [38]. Borgi et al. [38] showed that the administration of methanolic, ethyl acetate and chloroformic leaf extracts at the dose of 200 mg/kg exhibited a significant inhibition of gastric lesions by 45%, 76% and 33%, respectively. Methanolic and ethyl acetate root bark extracts significantly reduced the gastric lesions by 47% and 41%, respectively. However, the chloroformic root bark extract had no significant activity (19%). The effect of all extracts was compared with cimetidine (100 mg/kg, 62%) and omeprazole (30 mg/kg, 93%).

4. CONCLUSION

To the best of our knowledge, there has been no comprehensive review incorporating Tunisian medicinal plants with the effectiveness in ulcer. In fact, this article presents a review on Tunisian medicinal plants with potential antiulcer activity which may be useful to the health professionals, scientists and scholars working in the field of pharmacology and therapeutics to develop new drug formulations to treat ulcer diseases.

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