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Screening of pharmacological uses of *Urtica dioica* and others benefits

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ABSTRACT

Background: Natural products, whether pure compounds or standardized plant extracts, offer unlimited opportunities for other drug sources due to the unequaled availability of chemical diversity. Stinging Nettle (*Urtica dioica*) is a unique herbaceous perennial flowering plant with stinging hairs. The leaf extract of nettle was one of the herbal remedies which the experimental, clinical and trials have complemented each other. It is a very well-known plant with a wide historical background use of stems, leaves and roots. It has a long history of use as power sources such as soup or curry, and also used as fiber and a medicinal plant. *Urtica dioica* has traditionally been used in the control of cardiovascular disorders especially hypertension. The leaf extract of *Urtica dioica* has been reported to improve glucose homeostasis in vivo. Nettle root could prevent some of the effects of prostatic hyperplasia. Extracts of nettle leaf are used as anti-inflammatory remedies for rheumatoid arthritis. *Urtica dioica* extract significantly increased the sensitivity of breast cancer cells to paclitaxel.
This article aims to review the very wide ranging of pharmacological effects of *Urtica dioica* extract.
Methods: Articles on PuBmed between 1980 and 2019.
Results: Description and critical review of the pharmacological effects of *Urtica dioica* and other uses.
Conclusion: The nettle is actually a plant with many qualities and uses. The interest in it is deserved and it is given by other studies and investigations.

Contents

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Abbreviations

ADA	Adenosine Deaminase
A4H	Aniline 4-hydroxylase
AP-1	Activator protein 1
BPH	Benign Prostatic Hyperplasia
CCl4	Chemokine (C—C motif) ligand 4
CRP	C - reactive protein
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic acid
EAT	Erhlich Ascites Tumor
EGF	Epidermal Growth Factor
HIV	Human Immunodeficiency Virus
IBD	Inflammatory Bowel Disease
IFNy	Interferon-y
IL-1β	Interleukin 1 beta
IL-1	Interleukin-1
IL-2	Interleukin-2
IL-4	Interleukin-4
IL-5	Interleukin-5
IL-10	Interleukin-10
IPSS	International Prostata-Symptoms Score
LDL-C	Low-density lipoprotein cholesterol
NF-kB	Nuclear Factor Kappa Beta
PAF	Platelet Activating Factor
RSV	Respiratory Syncytial Virus
SHBG	Sex Hormone Binding Globulin
TH1 and TH2	T-Helper cells 1 and 2
TNF	Tumor Necrosis Factor
U	dioica, *Urtica dioica*

1. Introduction

Urtica dioica L. (stinging nettle) is an herbaceous perennial flowering plant, belongs to the family of Urticaceae and genus *Urtica,* native to Eurasia, and it is considered therapeutically interchangeable. Nettles are a very nutritious food easier digested and high in minerals (especially iron), vitamin C and pro-vitamin A (Allardic, 1994). It is hypothesized that may also affect protein and lipid metabolism and improve their performance (Alireza et al., 2012). Historically, medicinal plants have been used by humans as a traditional means of relieving several diseases. Despite the great advances in the development of therapy, there is still a need for potent and effective analgesic drugs. In this regard, it has been widely shown that many substances derived from plant play a relevant role in the process of development of new strategies to treat complaints related with pain (Calixto et al., 2000). Numerous Studies have confirmed the good effects of *Urtica dioica* in the world. Understanding the molecular mechanisms underlying beneficial effects can open up a new horizon for new therapeutic strategies. Urtica extracts can be packaged according to the separation of effective ingredients for optimal therapeutic uses (Mousa and Ahed, 2013).

This review study was conducted in the light of studying the different uses of *Urtica dioica*.

2. Classification

This plant belongs to the plant kingdom, phylum phanerogam under phylum angiosperms-magnoliophyta, broadleaf class-magnoliopsida, Order: Rosales, Family: Urticales – Urticaceae, Sub-Family: Urticaceae, Genus: *Urtica*.

Species: We distinguish thirty species in the world except Madagascar and South Africa where the nettle is absent (Henning et al., 2014).

The plant has given its name to an entire family: the Urticaceae. The Urtica term, meaning “the one that burns” comes from the Latin urere, “burn”. By extension, the term “urticaria” means any itching similar to that caused by nettle stings. These are the species *Urtica dioica* and *Urtica urens* which are known to possess medicinal properties.

3. Distribution

Among the species of the genus *Urtica*, *Urtica dioica* L. is the largest and most widespread. Nettle grows on humus and light soils. It likes fresh, light soil and sunshine. It supports all soils, especially those containing fresh organic matter. Nettle grows ever alone, but in large compact mass away with the movements of many insects (Bertrand, 2003).

4. Collection

An aerial part of the nettle is harvested just before flowering or shortly after. The leaves contain the highest concentration of active ingredients, whereas other parts of the plant contain very little. The plant was collected in April from the region of Sidi Bouzid, Tunisia and was identified by Pr Mohamed Echaieb (Botanist in Faculty of Science of Sfax, Tunisia).

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5. Various uses of *Urtica dioica*

5.1. Therapeutic uses

5.1.1. Action on the central nervous system

Nettle is an adaptogenic herb, it acts in the central nervous system and it is an alternative (purifying) plant that detoxifies, enhances and stimulates the metabolism. It has been shown that nettle reduces spontaneous activity in rats and mice, inhibited seizures induced by drugs, and decreased the body temperature in rats (Chahardehi et al., 2012). The results of the work of Radák (2005) suggest that exercise and nettle influenced physiological brain functions. Supplementation with nettle reduces the concentration of free radicals and increases the binding of Activator protein 1 (AP-1) in the brain of Deoxyribonucleic acid (DNA). And later proved that nettle can be an effective antioxidant and anti-apoptotic supplement promoting cell survival in the brain. Toldy et al. (2009) show that the supplementation with nettle has an effective antioxidant role; in fact, it regulates the inflammatory transcription factors and may also promote learning performance in the brain. Patel et al. (2016) have shown that UD extract could be effective for stress-mediated neurological disorders (Fig. 1).

5.1.2. Action on the cardiovascular system

Testai et al. (2002) studied the cardiovascular effects of extracts of roots' nettle. The study was performed on preparations of the aorta with or without endothelium prior vasoconstricted. The aqueous and methanolic extracts of roots as well as the fractions purified showed a vasodilatory action. However, this action has not been observed in aortas without endothelium. This same fraction produced a marked decrease in the inotropic activity on guinea pigs. These results support that the stinging nettle can produce hypotensive responses through vasodilatory effects, by the release of endothelial nitrogen oxide, by a negative inotropic action and by the opening of the potassium channels (Testai et al., 2002). El Haouari et al. (2006) concluded that *Urtica dioica* has an anti-platelet action at which flavonoids are generally involved. These results demonstrate the traditional use of *Urtica dioica* in the prevention and/or treatment of cardiovascular diseases. Nettle had no effect on the blood pressure in mice, while it produced a hypotensive effect marked and bradycardia in cats (Broncano, 1983; Lasheas, 1986). In traditional therapy, Nettle is known to have an effect hypotensive. Tahri et al. (2000) had tested the hypotensive effect in rats, to whom he gave continuous infusion of an aqueous extract of nettle leaves with a concentration of 4 mg/kg/h and 24 mg/kg/h. The results of Tahri et al. (2000) show an acute hypotensive action of *Urtica dioica* defining a direct effect on the cardiovascular system. However, the hypotensive effect was reversible

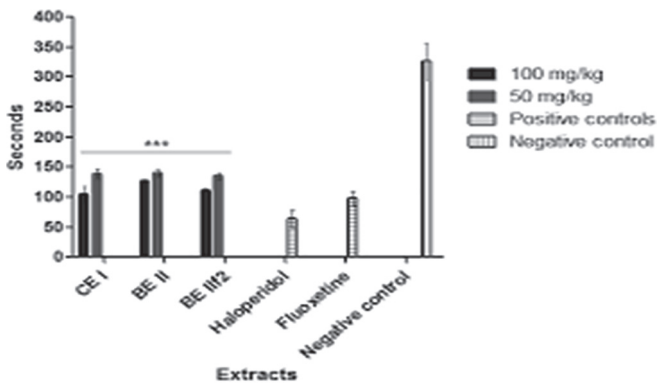

Fig. 1. Antidepressant-like effect of extracts from *Urtica dioica* in mice model of depression (Chahardehi et al., 2012).

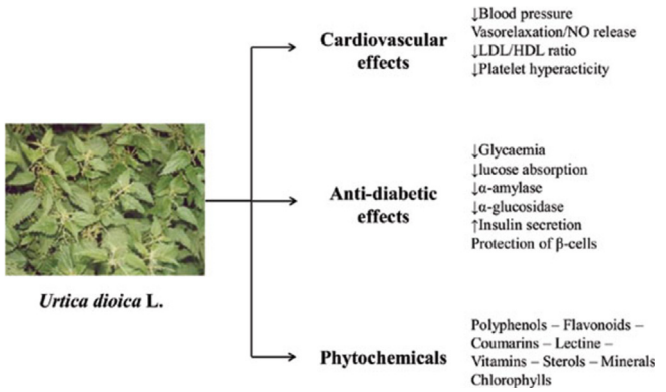

Fig. 2. Phytochemical, anti-diabetic and cardiovascular properties of *Urtica dioica* L. (El Haouari and Rosado, 2019).

after 1 h with the low concentration, while high effect concentration persisted, indicating a possible toxic effect (Kanter et al., 2003). The results show an intense hypotensive action of the nettle, which indicates direct effects on the cardiovascular system. Legssyer et al. (2002) show that nettle causes severe bradycardia that is independent of and cholinergic α-1 adrenergic effect receptors. The results of Qayyum et al. (2016) indicate that the crude methanolic extract of the UD and its fractions have an antihypertensive effect. Identification of the effects of NO-mediated vasorelaxation and calcium channel blockade explains this antihypertensive potential of *U. Dioica* and provides a potential pharmacological basis for its medicinal use in the management of hypertension (El Haouari and Rosado, 2019), (Fig. 2).

5.1.3. Anti-inflammatory action of the nettle

Wagner observed that a polysaccharide fraction of an aqueous extract of nettle root, containing 4 different polysaccharides, had shown an inhibitory activity on an induced rat paw edema (Wagner et al., 1994). They had administered the nettle dose orally and the anti-inflammatory activity was similar after 5 h that exerted by indomethacin. This anti-inflammatory activity is due to inhibition of cyclooxygenase, lipoxygenase and cytokine production (Capasso, 2003; Chrubasik et al., 2007); Fig. 3.

Shakibaei et al. (2012) demonstrate that nettle extracts exert an anti-inflammatory and anabolic effect on chondrocytes with reduction of Interleukin 1 beta (IL-1β) -induced Nuclear Factor Kappa Beta (NF-kB) activation suggesting that further studies are needed to demonstrate the efficacy of plant extracts in the treatment of osteoarthritis and other conditions in which NFL-kB plays a

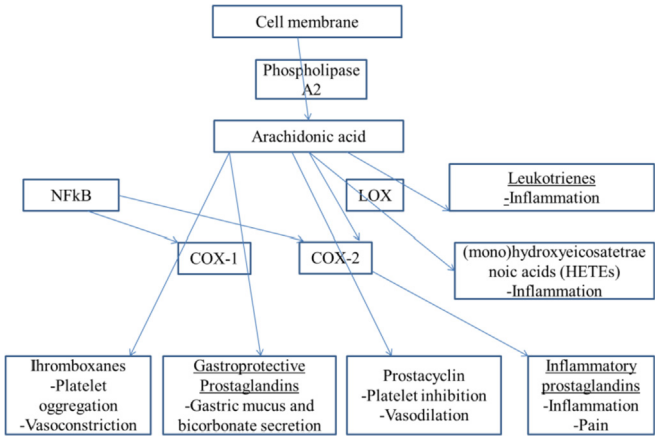

Fig. 3. Anti-inflammatory action of the nettle.

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pathophysiological role. The results of Hajhashemi and Klooshani (2013) confirm the folk use of the plant extract in painful and inflammatory conditions, which can be concluded that, the *Urtica dioica*' leaf extract has significant anti-inflammatory and analgesic activities and this study provides pharmacological evidence for its use in folk arthritis and other inflammatory complications.

5.1.3.1. Action on the metabolism of arachidonic acid. Obertreis et al. (1996) studied the effects "antiphlogistic" of an alcoholic extract of stinging nettle leaves. He isolated the cafeylmalic acid and tested in vitro on rat the inhibitory effects of the extract on the synthesis of arachidonic acid and its metabolites. The extract showed a partial inhibitory effect on 5-lipoxygenase (enzyme metabolism of arachidonic acid, pro-inflammatory molecule). Isolated phenolic acid inhibits the synthesis of leukotriene B4 in a concentration-dependent manner. The extract showed inhibition, strongly dependent on the concentration of prostaglandin synthesis. The cafeylmalic acid is a possible active substance but not the only of the plant extract in this study. In vitro, derivatives of caffeic acid and hydroalcoholic extract corresponding show inhibition of the biosynthesis of arachidonic enzymes, with a partial effect on the synthesis of 5-lipoxygenase and leukotriene B4 (Fig. 4), (Barnes et al., 2002; ESCOP, 2003; Kavalali, 2003; Wichtl and Anton, 2003).

5.1.3.2. Action on pro-inflammatory cytokines and PAF (Platelet Activating Factor). Obertreis et al. (1996) observed that an alcoholic extract of nettle leaves reduced significantly and with dose-dependent manner, the concentrations of the Tumor Necrosis Factor (TNF-a) and of interleukin-1(IL-l); two pro inflammatory cytokines whose secretion in blood is stimulated by lipopolysaccharide. An experiment was carried out on human blood from voluntary healthy. After 24 h, the concentration of TNF-α were reduced by 50.8% and that of IL-l by 99.7%, with an aqueous-alcoholic extract at concentration of 5 mg/ml. An alcoholic extract (0.25 mg/ml) showed an inhibitory effect on exocytosis of neutrophil elastase, exocytosis induced by the Platelet Activating Factor (PAF), but had no effect on prostaglandin biosynthesis of the arachidonic cascade (Barnes et al., 2002; ESCOP, 2003).

5.1.3.3. Action on TNF kappa β. In several inflammatory diseases, transcription tumor necrosis factor (TNF) is high and would be responsible for the expression increased by some pro-inflammatory genes. Riehemann and Schulze-Osthoff (1999) showed that in vitro nettle leaf extract strongly inhibited the activation of TNF-kappa in several cell types (human T lymphocytes, macrophages and epithelial cells). It is assumed that some of the anti-inflammatory effects of nettle can be attributed to its inhibitory effect on activity of TNF-kappa B (Barnes et al., 2002; Ganber and Spiteller, 1995).

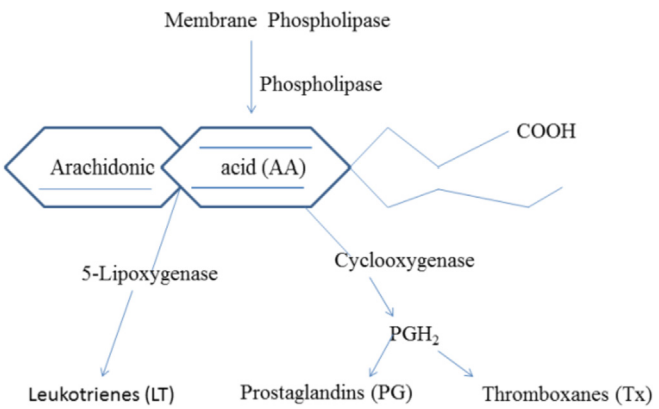

Fig. 4. Metabolism of arachidonic acid.

Table 1
In vitro antifungal activity of *Urtica dioica* L. extract against Microsporum canis determined by diameter of inhibition zone (Mikaeili et al., 2013).

Extract	Extract dose (mg.ml^{-1})			Terbinafine (8 μg ml^{-1})
	100	200	300	
Aqueous	NI	1.0 (0.00)^a	2.0 (1.00)^a	14.7 (1.30)^b
Hydroalcohol	NI	2.5 (0.70)^a	3.7 (1.52)^a	14.8 (0.98)^b

Note: Values are mean ± SD (mm, n = 3); Ni = no inhinbition zone; in rows, values with different lowercase letter are significantly different.

5.1.3.4. Action on interleukin-2 and interferon-y. T-Helper cells 1 and 2 (TH1 and TH2) regulate the cellular and humoral immune responses via cytokines. TH 1 cells produce interleukin-2 (IL-2), interferon-y (IFNy) and pro-inflammatory cytokines that induce a cascade of inflammatory reactions. The TH2 cells produce interleukin-4 (IL-4), IL-5 and IL-10. These cytokines are 2 antagonists' ways: the factors that induce TH1′ cytokines inhibit TH 2 'cytokine production, and vice versa. An aqueous extract of nettle leaves inhibits the production of IL-2 (specific TH1) stimulated by phytohemagglutinins and that of IFNy in a culture of mononuclear cells in a manner dose-dependent, 50% and 74%, respectively. In contrast, production of IL-4 by specific Th 2 was stimulated. The results imply that the extract of nettle leaves is by way of cytokines of lymphocytes T and can inhibit the inflammatory cascade in autoimmune diseases such as rheumatoid arthritis (Barnes et al., 2002; ESCOP, 2003).

5.1.4. Antifungal nettle roots

It has been shown that the extract from the roots of nettle had antifungal and anti-microbial activity and it acted in synergy with chitinase in inhibiting fungal growth. In vitro, the extract inhibited growth of several fungi pathogenic and saprophytic containing chitin (Hadizadeh et al., 2009; Mikaeili et al., 2013); Table 1.

5.1.5. Antiviral action of nettle roots

Among many plants agglutinins evaluated for their activity antiviral in vitro, *Urtica dioica*' extract was found to be a potent and selective inhibitor of the replication of human Immunodeficiency Virus (HIV (HIV-l and HIV-2)) of cytomegalovirus (CMV) and respiratory syncytial virus (RSV), (Gordts et al., 2015; Flores-Ocelotl et al., 2018); (Fig. 5).

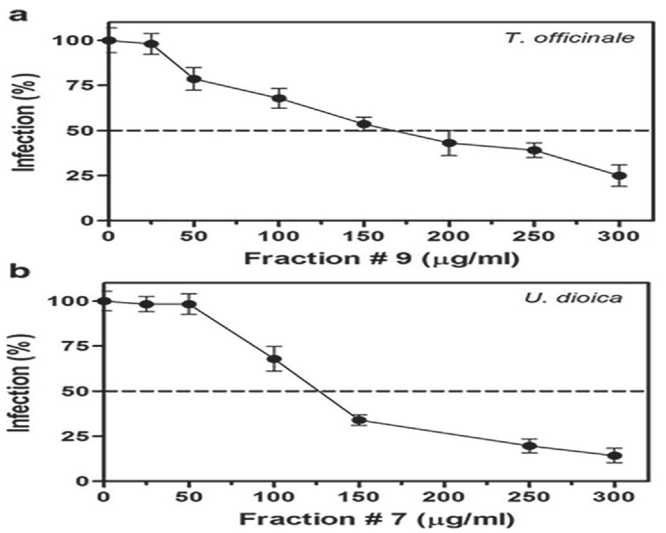

Fig. 5. *Taraxacum officinale* and *Urtica dioica* extracts inhibit dengue virus serotype 2 replication in vitro (Flores-Ocelotl et al., 2018).

5.1.6. Action of the aerial parts of the nettle on blood glucose

The lowering effect on glucose levels of the Nettle as a medicinal plant has been reported in manuscripts dating from the time of Avicenna. Recently, other studies have shown the hypoglycemic effect of Nettle. A study was conducted by Farzami et al. (2003) on islet exposed to several fractions of leaf extracts Nettle. One of the fractions caused a marked increase in insulin secretion. So a decrease in blood glucose. Furthermore, this active fraction caused an increase in insulin levels in normal and diabetic rats, injected by intraperitoneal extract. The results show that the lowering effect of glucose is due to an inducement of insulin secretion from the islets of Langerhans (Farzami et al., 2003). Another study also showed that Nettle had a significant anti hyperglycemic effect, and this effect could be caused in part by the reducing of the intestinal absorption of glucose (Bnouham et al., 2003). However, other studies have shown opposite results: the nettle extracts had produced hyperglycemic effects in the oral glucose tolerance test (ESCOP, 2003). Twelve plants were used in traditional treatment of diabetes by experimenting on diabetic mice with and without administration of streptozotocin. It turned out that the Nettle worsening diabetic condition in mice receiving streptozotocin (Farzami et al., 2003; Kavalali, 2003). Patel and Udayabanu (2013) indicate that *Urtica dioica* reversed dexamethasone induced hyperglycemia and its associated complications such as depressive behavior and cognitive dysfunction, significantly depressed the corticosteroid as mediation and diabetic status. Golalipour et al. (2011) concluded that the hydroalcoholic extract of the leaves *U. dioica*' s administration before the induction of diabetes, has a possible protective effect against deterioration of histomorphometric seminiferous tubules of diabetic rats induced by streptozotocin. Qujeq et al. (2013) indicate that the pancreas of diabetic rats show injuries of pancreatic tissue while the pancreas of diabetic rats treated with dried alcoholic and aqueous extracts of *Urtica dioica's* leaves show mild to moderate rearrangement of blocks. They find that the *Urtica dioica* can cause an appropriate repair pancreatic tissue in experimental model streptozotocin-induced diabetes. Rahimzadeh et al. (2014) states that the determination of the type of α-amylase inhibition by these plant extracts may provide successful use in chemical plants as drug targets. Patel et al. (2015) showed that a leaf extract has the potential to reverse the diabetes-mediated alteration in the muscarinic cholinergic system in the hippocampus by improving memory functions. According to the work of Gohari et al. (2018), treatment with UD in diabetic rats improves hyperglycemia by partially restoring plasma insulin levels. The data found suggest that UD inhibits islet atrophy and/or regenerates pancreatic β cells (Fig. 2).

5.1.7. Immunomodulatory activity of the aerial parts of Urtica dioica

Some major components extracts of the aerial parts of nettle such as quercetol-3-0-rutinoside, kaempferol-3-0-rutinoside and isorhamnétol-3-O-glucoside were studied for their in vitro immunomodulatory activities. All three compounds tested showed a high meaning of chemotactic effect and a strong intracellular lysis's activity. These two results confirm the immuno stimulatory activity of glycoside flavonoids on neutrophils, while suggesting that they may be useful for treating patients suffering from deficiency of neutrophil function and chronic granulocytic (Akbay et al., 2003).

5.1.8. Analgesic action and local anesthetic of the aerial parts of the nettle

A study was conducted on mice to assess the analgesic activity of an aqueous extract of nettle leaves and stems. After administration of the extract at the dose of 1200 mg/kg, mice showed a greater resistance to thermal stimulation in the test "hotplate" at 55 °C, taking 190% more time to react compared to control animals. This result suggests a peripheral analgesic activity (Tita, 1993). Our previous results justify that UD can be a valuable natural analgesic source that appears to provide potential phototherapies for various conditions. The analysis of the ethanolic extract of UD by GCMS revealed the presence of several compounds including polyphenols, flavonoids, triterpenes that can explain the analgesic effect of UD and its mechanism of action. Therefore, UD could be another therapeutic alternative to relieve pain and minimize the use of drugs that have long-term side effects (Dhouibi et al., 2017); (Fig. 6).

5.1.9. Study of external and internal application of nettle leaves in joint pain, arthritis, rheumatism and allergic rhinitis

Studies have been done to assess the effect of nettle leaves applied externally in patients with joint pain. Randall et al. (1999) performed a preliminary exploratory study on the use of external application in nettle leaves in 18 patients from the United Kingdom. They used fresh leaves nettle to relieve various joint pain (knee, shoulder, wrist, fingers, elbow, and back). All are sure that nettle was very beneficial. The results of this study were used to perform a randomized controlled test which was done in twenty-seven patients with persistent wrist pain (Randall et al., 1999). The pain relieved by daily application for one week of a sheet of stinging nettle which was compared with a white nettle leaf (or false nettle, because of its resemblance), and used as placebo. The results showed a statistically significant reduction of pain and degree of disability. Other pain parameters were evaluated, such as the number of analgesics and anti-inflammatory drugs, sleep quality, and the overall estimate of patients provide evidence of the analgesic effect. Randall et al. (2000) describes the most likely mechanism of the analgesic effect of the stinging nettle as a "thermal analgesia hyperstimulation" which lasts more than 24 h after application. The assumption is that the deep thermal hyperalgesia caused by serotonin and possibly by other chemical compounds causes a stinging nettle hyperstimulation Algic afferent fiber, causing there after an inhibitory action on the cells of the dorsal come from the spinal cord. It is believed that this action is a result of depletion and blockage of the synthesis of the nociceptive sensory nerve fibers 'substance. Several multicenter studies of post-marketing surveillance were conducted on patients suffering from arthritis or rheumatism and using a hydroethanolic extract from dried nettle leaves, at a dose of 670 mg twice/day. In each study, some patients continued to take non-steroidal anti-inflammatoircs drugs. Based on all the results, 80–95% of patients noted the effectiveness of the extract, and 93–95% noted its good

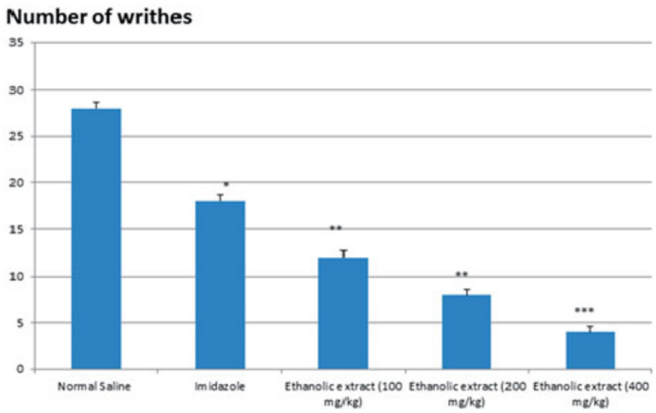

Fig. 6. Screening of analgesic activity of Tunisian *Urtica dioica* (Dhouibi et al., 2017).

tolerability (ESCOP, 2003). A study was conducted by Chrubasik et al. (1997) on patients with severe arthritis to compare the effects of 50 mg of diclofenac (anti-inflammatory drug) associated with 50 g of a preparation of nettle leaves with 200 mg of diclofenac. The evaluation was based on the decrease of C-reactive protein (CRP) which has a high serum concentration in acute phase, and clinical signs of acute arthritis (physical, subjective and pressure pain in patients, and stiffness. It was concluded that administration of nettle leaves could enhance the effectiveness of anti-inflammatory drugs used as anti-rheumatic. In the United States, Dr. A. Weill had recommended the use of 1–2 capsules of freeze-ground nettle leaf extract every 2–4 h against fever and allergic sinus problems (Kavalali, 2003; Mittman, 1990).

5.1.10. Action of nettle on the male reproductive system: activity of roots in benign prostatic hyperplasia

The effectiveness of extracts of nettle roots in urinary tract symptoms due to benign prostatic hyperplasia (BPH) has not been fully demonstrated. The aerial parts have no effect on the prostate but have a diuretic action (Bruneton, 1999). The BPH is characterized by an increase in the number of epithelial cells. Because the prostate surrounds the urethra, the increase in size of the prostate can block the flow of urine, resulting in a difficulty in urination with increased frequency. There are two components in these symptoms: first, static obstruction is due to the increase of size of the gland, second, the dynamic obstruction is due to activation of smooth muscle of the bladder. The therapeutic approach involves the use of drugs which affect the action and the concentration of testosterone, to reduce the size of the prostate (static obstruction) and affecting α1 'receptor antagonists on dynamic obstruction by decreasing the smooth muscle strength. Testosterone stimulated the growth of the prostate gland; it is transformed by the 5α-reductase to dihydrotestosterone (DHT), which is the active androgen hormone in the prostate. The action of testosterone on prostate can be prevented by inhibitors 5 α reductase (Capasso, 2003). SHBG (Sex Hormone Binding Globulin) is a plasma protein that binds to sex hormones (estrogen and androgen), and regulates their plasma free fraction. A study by Le Moal made in 1988 showed that the extract of the nettle was capable of specifically stimulating the proliferation of thymocytes and T lymphocytes (Le Moal and Truffa-Bachi, 1988). In 1995, Hryb et al. studied the effect of extracts of stinging nettle roots on the interaction of SHBG with its human prostatic membrane receptor. He experimented with an aqueous extract and alcoholic extract. Only the aqueous extract was active in inhibition of SHBG binding with its receptor. This inhibition was dependent on the concentration. The aqueous extract is active, it can be assumed that there is an hydrophilic compound in the roots' nettle which interferes with the binding of SHBG to its membrane receptor of the prostate (Fig. 7).

In 1995, Ganber and Spiteller have studied methanolic extracts of nettle roots for their in vitro inhibitory effect of aromatase. The inhibitory effects of aromatase have been demonstrated for a variety of compounds belonging to different classes. These compounds are the following: secoisolariciresinol, oleanic acid, ursolic acid, (9Z, IIE) −13 hydroxy-9, 11-octadecadienoic acid and 14-octacosanol (Ganber and Spiteller, 1995); (Fig. 8).

In 1997, Schottner et al. studied the binding of lignans roots' nettle and their metabolites to SHBG. The results demonstrate that the effects of nettle root extracts in BPH may be due to their content of lignans which may affect the hormone plasma by moving their binding to SHBG. Furthermore, lignans can affect the interaction of the receptor with prostatic SHBG (Schottner et al., 1997). Nettle may act by interfering with the binding of testosterone to SHBG and the SHBG with its prostate membrane receptors.

A study shows that lignin and their metabolites from the extract

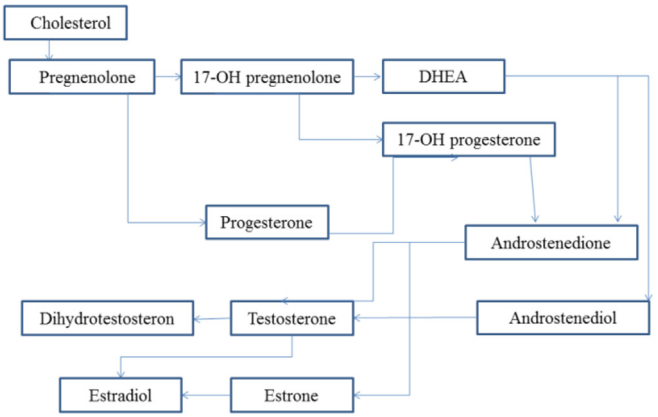

Fig. 7. Conversion of testosterone to DHT.

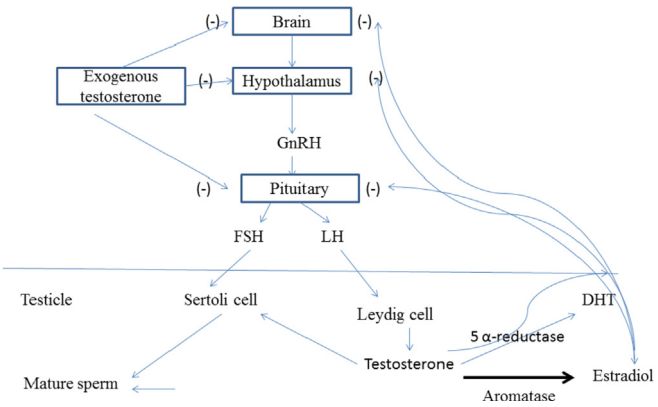

Fig. 8. Inhibition of the aromatase.

of nettle root inhibit the activity of a proteolytic enzyme, leukocyte elastase (HLE, Human Leukocyte Elastase); (Barnes et al., 2002; Bombardelli and Morazzoni, 1997; Capasso, 2003). In 1997, Lichius and Muth studied the inhibitory effects of extracts of stinging nettle roots on an experimental model of prostatic hyperplasia induced in mice. Five different extracts were tested: 20% strength methanolic extract, characterized by a low content of α-sitosterol and scopoletin and a high concentration of proteins and sugar. The experience leads to the conclusion that polysaccharides can be considered as the active compounds in this benign prostatic hyperplasia system. In 2000, Konrad et al. have studied the effects of a 20% of methanolic extract of nettle root on the proliferative activity of human epithelial and stromal prostatic cells. A significant antiproliferative effect and concentration-dependent extract was observed only on epithelial cells for seven days while the growth of the stromal cells remained unchanged (Barsom and Bettermann, 1979). Wagner et al. (1994) demonstrated that polysaccharides could block the binding of epidermal growth factor (EGF) secreted by the prostate tissue with suppression of cell metabolism and growth (Capasso, 2003). The beneficial effect observed upon treatment with an aqueous extract of roots of benign prostatic hyperplasia is probably enhanced by the presence of acidic polysaccharides and by that of a mixture of lectins immunomodulating activity, including a stimulation of cell t and TNF-α release from macrophages (Wichtl and Anton, 2003). Preliminary clinical evaluation (Stahl, 1984) carried on 30 patients (aged 51–86 years), who were treated for three weeks with a preparation containing the extract of nettle roots dosed at 150 mg. The positive effect on the symptoms associated with BPH was

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obtained with two tablets three times daily, corresponding to 900 mg of extract. The effectiveness of a root extract (600 mg, 2 times/days/20 weeks) was demonstrated in the multicenter study of 4051 patients in various stages of BPH (Stahl, 1984). Vontobel (1985) have studied the effect of a controlled placebo in 50 patients, treated with a root extract; 300 mg 2 times/day for nine weeks. Positive results were obtained by Dathe and Schmid (1987) who study the effect of placebo-control on 79 patients treated for 6–8 weeks with root extract (600 mg/day). After 4–6 weeks, the average of the urinary flow was improved by 14% and the residual urine values had fallen by 40%. Friesen (1988) reported the results in a multicenter long-term for a total of 4480 patients who received extract for 224 days on average, at doses of 600 mg twice/day for 3 months and then 600 mg daily during the remaining time. The extract improved urinary symptoms associated with BPH at 78% of patients after 3 months and in 91% of patients after 6 months. The diurnal and nocturnal urinary frequency was significantly improved as well as the mean urine output. The extract was well tolerated in 97% of patients, mild side effects, especially gastrointestinal disorders, were present in 0.7% of cases. The effectiveness of the extract of roots in improving the urinary symptoms associated with BPH was confirmed by Fieber (1988) on a limited number of patients, using ultrasound to measure the volume of the prostate and residual urine. A study was assessed the International Prostata-Symptom Score (IPSS) in patients and their evolution. 41 patients used a liquid preparation of nettle over a period of three months. This experience showed that nettle induced a significant improvement in this score and the quality of life index. There would be a decrease in intensity of symptoms: power reduced urine flow, nighttime urinary frequency, sensation of incomplete emptying of the bladder (Chrubasik et al., 2007; Kavalali, 2003). The results of Lopatkin et al. (2007) indicate that the extract of *Urtica dioica* offers an important clinically relevant over a period of at least 96 weeks and slows the natural progression of BPH. The study of Jalili et al. (2014) argued the thesis that *U. dioica* can significantly enhance spermatogenesis in rats. Nahata and Dixit (2011) concluded that the extract of *Urtica dioica* can be used as a potential candidate for treating BPH.

In addition, natriuretic and diuretic effects have also been noticed, which implies an action on renal function, the plant extract may have a toxic effect at the highest dose. The results of Sayhan et al. (2012) suggest that administration of *Urtica dioica* attenuates kidney damage. According to Moradi et al. (2015), Nettle root may prevent some of the effects of prostatic hyperplasia, so that the percentage of folded cells in the ventral lobe reduces insignificantly.

5.1.11. Cancer

Durak et al. (2004) tested the possible effects of aqueous extract of *Urtica dioica* on the activity of adenosine deaminase in the prostate tissue in patients with prostate cancer and have shown that this resulted in a significant inhibition on adenosine deaminase (ADA), an extract of *Urtica dioica* can be one of the mechanisms for the beneficial effect observed in prostate cancer. Celik and Tuluce (2007) showed that the aqueous extract of nettle can possess chemo protective effect against carcinogen exposure in rats. The fresh leaves have shown anti-tumor activity in animal studies and a strong anti-mutagenic activity in the Ames test (Karakaya, 2000). The results of Fattahi et al. (2018) demonstrated that *Urtica Dioica* induces apoptosis in breast cancer cells by influencing the expression of Ornithine decarboxylase and the genes for adenosine deaminase, and estrogen receptors. The different responses observed with these cell lines could be due to the interaction of *Urtica dioica* as phytoestrogen with the estrogen receptor (Mansoori et al., 2017); (Fig. 9).

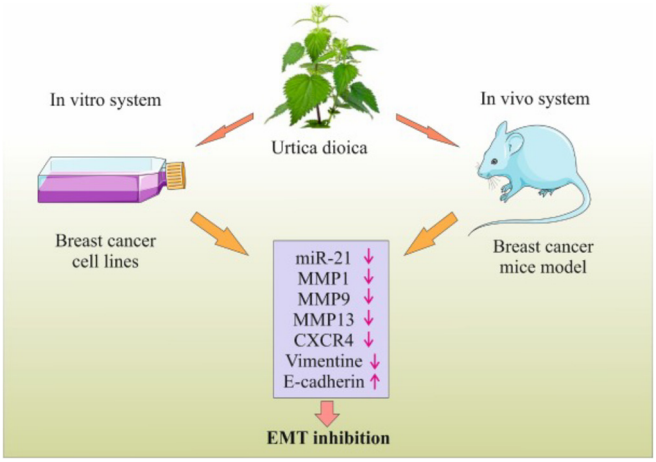

Fig. 9. *Urtica dioica* extract suppresses miR-21 and metastasis-related genes in breast cancer (Mansoori et al., 2017).

5.1.12. Action on the digestive system

Ozen and Korkmaz (2003) concluded that the application of *Urtica dioica* can have a significant effect on the enzyme systems of drug metabolism. The level of antioxidant enzymes may also recover sufficiently toxic free radicals that are produced in the normal and abnormal cellular metabolism (Marchetti et al., 2018). The results of this study could have major implications for potential chemopreventive and antioxidant profiles of the extract of this plant. Yener et al. (2009) concluded that the seeds of *Urtica dioica* have a hepatoprotective effect in rats with aflatoxicosis, probably acting through promoting antioxidant defense systems. The long-term use of *Urtica dioica* is effective in the prevention of chronic murine colitis. The study of Konrad et al. (2005) is the first to demonstrate the beneficial immunomodulatory effect of *U. dioica* experimental Inflammatory Bowel Disease (IBD) in vivo. Uyar et al. (2016) concluded that *Urtica dioica*' seed extract has a protective hepatorenal effect in broilers with aflatoxicosis, probably acting by promoting antioxidant defense systems (Fig. 10).

5.1.13. Others

Ozen and Korkmaz (2009) concluded that the application of *Urtica dioica* can have a significant effect on the enzyme systems of drug metabolism. The results of Toldy et al. (2005) suggest that exercise and nettle influenced physiological brain function. Nettle supplementation reduces the concentration of free radicals and increases the binding of Activator protein 1 (AP-1) in the brain of Deoxyribonucleic acid (DNA). We can conclude from the work of Gülçin et al. (2005) that the crude extracts prepared from nettle have an activity of polyphenol oxidase very similar to other plants. The results of Özkol et al. (2012) led us to conclude that exposure to Cisplatin resulted in increased liver, protein oxidation, neutrophil infiltration, serum liver enzymes, markers of renal function and a

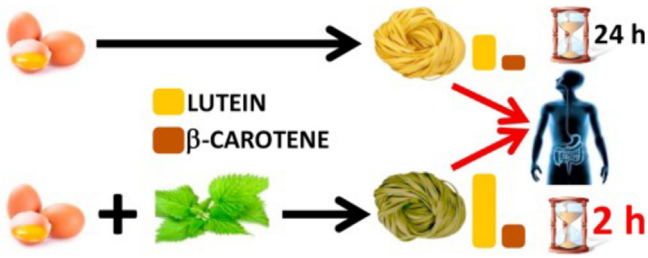

Fig. 10. Action on the digestive system of *Urtica dioica* (Marchetti et al., 2018).

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decrease in antioxidant defense systems bearing mice Erhlich Ascites Tumor (EAT). Supplementation of different doses of *Urtica dioica* has a great potential to counter Cisplatin induced hepatotoxicity, nephrotoxicity, and hepatic oxidative stress. Nettle probably neutralizes Cisplatin induced damage through its effects and antioxidant-free radical-defusing. According to Ozen and Korkmaz (2009), applying *dioica L.* can have a significant effect on the aniline 4-hydroxylase (A_4H) activity requirement cofactor and the effects of metal ions. Liver histopathologic results of Nassiri et al. (2009) reflect the *Urtica dioica* extract correlation both with liver weight and plasma TC and low-density lipoprotein cholesterol (LDL-C). These results indicate that the extract of *Urtica dioica* has cholesterol-lowering effects in animal model. Meral and Kanter (2003) concluded that the *Urtica dioica* treatments could reduce the disturbances of Chemokine (C−C motif) ligand 4 (CCl_4) induced anaemia, minerals, and the body's defense mechanism in rats treated by CCl_4.

5.2. Nutritional assessment of nettle leaves

The stinging nettle is certainly one of these primitive vegetables consumed since time immemorial. Nettle is a real nutritional plant with high levels of vitamins and minerals and has a high content and quality in protein, when it is compared to other leafy greens (Adamski and Bieganska, 1980). Nettle leaves contain a significant amount of chlorophyll and carotenoids. A rate of 4.8 mg of chlorophyll per gram of dry leaves was found. Popoval (1982) found that there were more chlorophyll and carotenoids in plants grown in the shade. The major carotenoids have been identified: β-carotene, violaxanthin, xanthophyll, Zea-xanthine-xanthine and luteal lutein epoxide (ESCOP, 2003). Hughes et al. (1980) analyzed the leaf protein levels every month of the year and found the lowest rates in the dry matter, in December (20.9%). The amino acid composition was determined by various researchers (Adamski and Bieganska, 1980); (Table 2). Analyses showed that the leaves were rich in minerals, such as iron, calcium and potassium (Table 3). The amino acid composition from the flowers nettle was determined in Table 4.

The plants lose their stinging character in drying or cooking. We must not forget that the nettle is one of those plants both in food and medicine in consuming it, it improves health. It will only be effective if one consumes a meal at least a day for 15 days to 3 weeks (Bertrand, 2003). 4 ways to prepare the nettles; to make a side dish to meat or fish dishes: stew, cream, butter, mashed. There are also other recipes with nettles: meatballs with nettles, the pancakes. Otles and Yalcin (2012) consider that the nettle is widely used in cosmetic level as well as food.

Table 2
Amino acid composition of a hydrolyzate of fresh leaves of nettle (mg/l00 g).

	Popova (1982)	Hughes et al. (1980)
Phenylalanine	5.82	6.82
Lysine	5.53	13.88
Threonine	4.61	5.40
Valine	6.31	7.21
Methionine	1.76	0.87
Cysteine	0.85	
Isoleucine	4.78	4.91
Lleucine	8.97	7.39
Tryptophan	1.28	
Histidine	4.10	2.92
Aspartic acid	9.07	10.78
Serine	6.19	4.61
Glutamic acid	13.30	13.09
Proline	4.87	4.83
Wistaria	6.25	6.59
Alanine	6.54	6.67
Tyrosine	3.87	4.03
Arginine	5.90	
Total Essential Amino Acids	39.21	

Table 3
Mineral content (mg/100 g of Nettle leaves) (Adamski and Bieganska, 1980).

Iron	13
Calcium	853
Zinc	0.9
Copper	0.52
Phosphorus	75
Magnesium	96
Manganese	3
Selenium	0.0027
Sodium	16
Potassium	532

Table 4
Amino acid composition of a hydrolyzate of proteins from dried flowers of stinging nettle (mg/100 g of Nettle flowers) (Adamski and Bieganska, 1980).

Phenylalanine	5.51
Lysine	4.67
Threonine	4.53
Valine	5.80
Methionine	1.39
Cysteine	0.35
Isoleucine	4.10
Leucine	7.18
Tryptophan	1.91
Histidine	4.52
Aspartic acid	13.15
Serine	6.87
Glutamic acid	12.32
Proline	4.21
Glycine	5.41
Alanine	6.27
Tyrosine	2.80
Arginine	6.13
Total Essential Amino Acids	35.44

5.3. Agricultural applications and gardening nettle

Whether as fertilizer treatment product, forage or livestock feed, its agricultural and horticultural uses are many and varied. The use of animal feed nettles dates back to ancient times. It was once said that nettle bringing health and vitality to the animals. Farmers take advantage of all the parts of the plant to feed the livestock, whether big or small, the chicken cow. When mixed, nettle improves palatability of other forages. Agrarian practices are amply justified by the extraordinary wealth of nettle (Table 5).

As the table shows, the nettle is rich in nutrients, while poorer cellulose as hay; we understood that the nutritional value of the stinging nettle is in these conditions significantly greater than that of a good feed (Tabardel, 2003). The nettle is a valuable ally of the gardener, who can, and thanks to a few simple applications, makes it more productive garden. The gardener will appreciate its fertilizing properties, and enhance the vitality of vegetables. Planted

Table 5
Comparison of hay and Nettle (Tabardel, 2003).

	protein	Fat	Non-nitrogenous matter	Cellulose
Hay	5.4%	1%	25.7%	15%
Stinging nettle	12.8%	4.9%	30%	6%

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Table 6
Composition of mineral manure nettle (in ppm) (Peterson, 1986).

Total Nitrogen	595
nitrate nitrogen	5
Ammonia Nitrogen	240
Organic nitrogen	350
Phosphate	20
Potassium	630
Calcium	730
Magnesium	80
Sulfate	50
Iron	2.5

between the rows of medicinal and aromatic plants, it greatly increases their content of etheric oils. The work of an English association of organic agriculture confirmed that its presence allows increased yield of fruit trees. Gardeners incorporate the compost because it enables the transformation of organic waste into humus and gives much better compost. Nettle liquid manure is used either as a fertilizer or as a preventive treatment of certain diseases or pest infestations. In 1986, Rolf Peterson, a Swedish researcher, confirms all items of the field work and give strong arguments for strong advocates of organic farming. The mineral content of the nettle manure was studied by Peterson (1986). The manure is rich in nitrogen; the phosphorus content is relatively low and its exceptionally high iron wealth (Table 6).

5.4. Industrial and domestic use of Urtica dioica

The main domestic use was, for many years, manufacturing fabric. Although their use is out of fashion, it is worth recalling textile qualities of nettle. Pinelli et al. (2008) consider that their initial results in terms of biomass and fiber yield at harvest seem positively support the feasibility of fiber nettle cultivation in central Italy, as production values are comparable to those found by German and Austrian research institutes. Bergfjord et al. (2012) had shown that the textile is made of nettle imported, probably from the Kärnten-Steiermark region, an area which had a flax production otherwise established.

Limitations: Other pharmacological effects can be discussed.

6. Conclusion

Deemed to be a 'weed', stinging nettle has always had medicinal applications, which date back to antiquity. His many virtues are used in herbal medicine: tonic, anti-inflammatory, astringent and anti-histamines. Its wealth in minerals and vitamins makes it excellent plant nutrition. Nettle is also used in animal feed and horticulture. Commonly prevalent plant, the nettle is actually a plant with many qualities and uses. The interest in it is deserved and it is given by other studies and investigations (Table 7).

Table 7
Various effects of *Urtica dioica in the literature.*

Various uses of *Urtica dioica*	
Therapeutic uses	
Action on the central nervous system	Radák, 2005; Toldy et al. (2009); Chahardehi et al. (2012); Patel et al. (2016)
Action on the cardiovascular system	Broncano, 1983; Lasheas, 1986; Tahri et al. (2000); Legssyer et al. (2002); Testai et al. (2002); Kanter et al., (2003); El Haouari et al. (2006); Qayyum et al. (2016); Haouariand Rosado, 2019
Anti-inflammatory action of the nettle	Wagner et al. (1994); Ganber and Spiteller, 1995; Obertreis et al. (1996); Riehemann and Schulze-Osthoff (1999); Barnes et al. (2002); Capasso, 2003; ESCOP, 2003; Kavalali (2003); Wichtl and Anton, 2003; Chrubasik et al. (2007); Shakibaei et al. (2012); Hajhashemi and Klooshani, 2013;
Antifungal nettle roots	Hadizadeh et al. (2009); Mikaeili et al. (2013)
Antiviral action of nettle roots	Gordts et al. (2015); Flores-Ocelotl et al. (2018)
Action of the aerial parts of the nettle on blood glucose	Bnouham et al., (2003); ESCOP, 2003; Farzami et al. (2003); Kavalali, 2003; Golalipour et al. (2011); Patel and Udayabanu, 2013; Qujeq et al. (2013); Rahimzadeh et al. (2014); Patel et al. (2015); Gohari et al. (2018)
Immunomodulatory activity of the aerial parts of *Urtica dioica*	Akbay et al. (2003)
Analgesic action and local anesthetic of the aerial parts of the nettle	Tita (1993); Dhouibi et al. (2017)
Study of external and internal application of nettle leaves in joint pain, arthritis, rheumatism and allergic rhinitis	Mittman, 1990; Chrubasik et al. (1997); Randall et al. (1999); Randall et al. (2000); ESCOP, 2003; Kavalali (2003)
Action of nettle on the male reproductive system: Activity of roots in benign prostatic hyperplasia	Barsom and Bettermann (1979); Stahl (1984); Vontobel (1985); Fieber (1988); Friesen (1988); Le Moal and Truffa-Bachi (1988); Wagner et al. (1994); Ganber and Spiteller (1995); Hryb et al. (1995); Bombardelli and Morazzoni (1997); Lichius and Muth (1997); Schottner et al. (1997); Bruneton (1999); Konrad et al. (2000); Barnes et al. (2002); Capasso (2003); Kavalali (2003); Wichtl and Anton (2003); Chrubasik et al. (2007); Lopatkin et al. (2007); Nahata and Dixit, 2011; Sayhan et al. (2012); Jalili et al. (2014); Moradi et al. (2015)
Cancer	Karakaya, 2000; Durak et al. (2004); Celik and Tuluce, 2007; Mansoori et al., (2017); Fattahi et al. (2018)
Action on the digestive system	Ozen and Korkmaz (2003); Konrad et al. (2005); Yener et al. (2009); Uyar et al. (2016); Marchetti et al. (2018)
Others	Meral and Kanter (2003); Gülçin et al. (2005); Toldy et al. (2005); Nassiri et al. (2009); Ozen and Korkmaz, 2009; Özkol et al. (2012)
Nutritional assessment of nettle leaves	Adamski and Bieganska (1980); Hughes et al. (1980); Popoval (1982); Bertrand (2003); ESCOP, 2003; Otles and Yalcin (2012
Agricultural applications and gardening nettle	Peterson (1986); Tabardel (2003),
Industrial and domestic use of *Urtica dioica*	Pinelli et al. (2008); Bergfjord et al. (2012)

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Declarations of interest

None.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Author contribution statement

Raouia Dhouibi: She wrote and she collected the data for the review.

Kamilia Ksouda and Maryem Ben Salem: Collect of data.

Zouheir Sahnoun: Vice head of laboratory where the research takes place.

Khaled Mounir Zeghal: Lab head in where the research is running.

Serria Hammami and Hanen Affes: They are the supervisors and they participate in the correction of the manuscript.

All authors read and approved the manuscript.

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