MOLECULAR AND CHEMICAL THERAPEUTIC FEATURES OF *URTICA SPECIES*

Mousa H. AlShuwayeb
Ahed J. Al-Khatib
Jordan University of Science and Technology, Jordan

Abstract

The present review study was conducted to review the current understanding of molecular aspects of Urtica species. We refer to the most recent published articles addressing the therapeutic potential of this plant. A wide spectrum of diseases has been associated with Urtica species including cancer, arthritis, autoimmune diseases, diabetes, and fatigue. Some molecular mechanisms and chemical properties have been discussed. Taken together, studies have confirmed the beneficial effects of Urtica all over the world and understanding of the molecular mechanisms underlying the beneficial effects opens new horizon to understand new therapeutic options. The extracts of Urtica should be prepared based on separating effective ingredients for optimal therapeutic benefits.

Keywords: Urtica, extracts of Urtica, molecular mechanisms, chemical properties

Introduction

From a historical point of view, medicinal plants have been used by human as a traditional way of providing relief to several diseases. No doubt that many plant-derived compounds exhibit significant analgesic properties. Despite the large progress that has occurred in the development of therapy, there is still a need of effective and potent analgesic drugs. In this regard, it has been widely shown that many plant-derived substances play a relevant role in the process of development of new strategies to treat complaints related with pain (Calixto et al., 2000).

This review study was conducted in the light of the fact that there is a necessity to have a monitoring of the adverse effects of herbal medicines and to establish a correlation between marker compounds and plants to guarantee the efficiency and quality of herbal medicines. One of herbal medicines that have received great attention is the Urtica which has many species including *Urtica dioica* L (Ozen and Korkmaz, 2003).

Several studies have investigated the therapeutic potential of *Urtica dioica* L. (Urticaceae), or stinging nettle. Hypotensive properties of leaves of *Urtica dioica* L have been demonstrated (Garnier et al. 1961; Ziyyat et al. 1997). Other studies pointed to anti-inflammatory effects (Reihemann et al. 1999), prostatic hyperplasia treatment (Kreski et al. 1993; Lichius and Muth, 1997**)**, diuretic (Tahri et al. 2000) and immunomodulatory activity (Delcourt et al. 1996; Musette et al. 1996; Basaran et al. 1997; Rovira et al. 1999), to alleviate rheumatic pain (Chrubasik and Eisenberg, 1999), and to serve as an adjuvant therapeutic agent in rheumatoid arthritis (Randal et al. 1999).

Many studies have suggested various mechanisms to explain the beneficial effects of *Urtica dioica*. These mechanisms include glucopyranosides (Neugebauer et al. 1995), glycoprotein (Andersen and Wolf, 1978), protein (Styprekowska and Bieganska, 1980), flavonol glycosides (Chaurasia and Witchtl, 1987; Basaran et al. 2001), carotinoids (Kudritskaya et al., 1986). Other studies attributed beneficial effects of *Urtica dioica* to biologically-active compounds, such as amino acids, caffeoyl malic acid and quinic acid (Obertreis et al. 1996). It has also been shown that essential oils, formic and acetic acid, histamine, tannins, mucilage, vitamins (A, B1, B2, C, K1, folic and pantothesic acids) to be identified as contributing to the observed medicinal effects of the plant (Tita et al. 1993). Other studies pointed to the use of *Urtica dioica* for cancer treatment positive findings (Baytop, 1984; Samur et al. 2001).

Urtica pilulifera, is a popular plant found in Palestinian and in Sinai (Ali-Shtayeh etal., 2000). It belongs to family Urticaceae and it is characterized morphologically by the stinging hairs carried by its leaves and flowers which cause irritation to the skin (Fu etal., 2006). A tea made from the leaves of Urtica pilulifera has traditionally used as a stimulating tonic, blood purifier and hemostatic and for enhancement of hemoglobin concentration (Chrubasik etal.,2007).

Dina et al (2013) conducted a study to evaluate the potential effects of ethylacetate (EA), chloroform (CHLOR) and hexane (HEXA) extracts of Urtica pilulifera as oral anti-diabetic agents as well as to evaluate their possible anti- oxidant and anti-inflammatory effects in type 2 diabetic rat model. The researchers induced the model of Type2 diabetes through a high fat diet and low dose streptozotocin (STZ). Diabetic adult male albino rats were allocated into groups and treated according to the following schedule; Pioglitazone HCL (PIO), EA, CHLOR and HEXA extracts of Urtica pilulifera at two doses of 250 and 500mg/kg were used. Control groups were included as normal and diabetic control. Blood glucose, insulin resistance, antioxidant enzymes, 8-hydroxy-2-deoxyguanosine (8-OHdG) as well as C-reactive protein and tumor necrosis factor-a levels were evaluated. Study findings indicated to significant hypoglycemia associated with antioxidant

and anti-inflammatory effects in diabetic rats in EA and CHLOR extracts of Urtica pilulifera. It is believed that these activities are responsible, at least partly, for improvements that have been seen in hyperglycemia and insulin resistance of diabetic rats. Taken together, the previous findings encourage the traditional use of Urtica pilulifera extract as an antioxidant and anti-inflammatory agent as an additional therapy of diabetes.

In a study by Zhang et al (2013), it was found that the crude polysaccharides (UA) which were obtained from *Urtica angustifolia.* The researchers investigated the anti-fatigue activity of the polysaccharides in mice and the results showed *U. angustifolia* polysaccharides had the ability to increase the swimming time, and the average swimming time of the low doses (LD), middle doses (MD) and high doses (HD) group were increased by 85.4, 114.6 and 151.2%, respectively. Furthermore, it was demonstrated that the blood urea nitrogen content of the LD, MD and HD group to be reduced by12.8, 13.6 and 19.8% compared with that of control group, respectively. Moreover, the hepatic glycogen of every treated group was higher than that of control group, increasing rates were 87.0, 469.6, and 747.8%, respectively.

Gorzalczany et al (2011) conducted a study to investigate the in vivo antinociceptive effect of Urtica circularis ethanolic extract and its isolated compounds. Antinociceptive activity was evaluated through writhing, formalin and hot plate tests in mice. The phytochemical analysis was carried out. The study findings showed that the extract had induced significant inhibition on nociception induced by acetic acid (ED50:72.2 mg/kg, i.p.) and formalin (ED50: 15.8 mg/kg, i.p.) administered intraperitoneally and also orally. It has also been found that atropine diminished the activity of the extract in the acetic acid test. In this model, it has been indicated that at dose of 10 mg/kg i.p., vitexin was the most active of the isolated compounds (inhibition of 91%), and chlorogenic acid, caffeic acid and vicenin-2 (6,8-di-C-glucosyl apigenin) produced an inhibition of 72%, 41% and 41%, respectively, whereas apigenin did not show any activity. Taken together, the previous findings indicated that Urtica circularis extract produced antinociception possibly related to the presence of vitexin, chlorogenic, caffeic acid and vicenin-2. Furthermore, the activation of cholinergic systems seems to be involved in the mechanism of antinociception of the extract.

Ghaima et al (2013) investigated the antibacterial and antioxidant activities of ethyl acetate extract of nettle (*Urtica dioica*). The researchers also investigated phytochemical screening and determination of total phenolic content. The results showed that that ethyl acetate extract of nettle had good effects on all bacterial isolates (*Aeromonas hydrophila, Salmonella typhi, Staphylococcus aureus, Bacillus cereus, Escherichia coli*) with highest

inhibition zone (24 mm) towards *B. cereus, A hydrophila* was more resistant than other bacteria. Also it was found that nettle gave large inhibition zone to *S. typhi* (22mm). Ethyl acetate of nettle had a high content of phenolic compounds (48.3mg GAE/gdw). The phytochemical qualitative screening exhibited flavonoid, glycosides, phenols, tannins and terpenoids were present in nettle alkaloid. Steroids were not present. Evaluation of antioxidant activities of ethyl acetate extract of nettle by ferric thiocyanate method (FTC) exhibited that nettle caused 76% lipid peroxidation in inhibition of linoleic acid emulsion.

Yohichi Kumaki et al (2011) conducted a study to investigate the effects of *Urtica dioica* agglutinin (UDA). It has N-acetylglucosamine specificity that inhibits viruses from Nidovirales in vitro. The efficacy of UDA was examined on the replication of different SARS-CoV strains in Vero 76 cells. UDA has been shown to prevent virus replication in a dose-dependent manner and reduced virus yields of the Urbani strain by 90% at 1.1±0.4_g/ml in Vero 76 cells. UDA was also tested for efficacy in a lethal SARS-CoV-infected BALB/c mouse model. The researchers infected BALB/c mice with two LD50 (575 PFU) of virus for 4 h before the mice were treated intraperitoneally with UDA at 20, 10, 5 or 0 mg/kg/day for 4 days. The results were amazing since treatment with UDA at 5 mg/kg was shown to significantly protect the mice against a lethal infection with mouse-adapted SARS-CoV ($p < 0.001$), but did not significantly reduce virus lung titers. All virus-infected mice receiving UDA treatments were also significantly protected against weight loss ($p < 0.001$).UDA also effectively reduced lung pathology scores. Furthermore, at day 6 after virus exposure, all groups of mice receiving UDA had much lower lung weights than did the placebo-treated mice. Taken together, the previous findings pointed to UDA treatment of SARS infection in mice lead to a substantial therapeutic effect that protects mice against death and weight loss. The results of this study suggested that UDA might bind to N-acetylglucosamine-like residues present on the glycosylated envelope glycoproteins, thereby preventing virus attachment to cells.

Various studies showed that stinging UDA is a small (8.7 kDa) plant monomeric lectin with N-acetylglucosamine specificity (Beintema and Peumans, 1992; Van Dammeet al., 1988) has been indicated to inhibit Nidovirales in vitro with some selectivity (van der Meer et al., 2007). In another study, Keyaerts et al. (2007) showed that UDA was shown to be a potent and selective inhibitor of SARS-CoV (Frankfurt 1 strain) with an EC50 = 1.3±0.1μM and an IC50 of >100μM, resulting in an SI > 76.9. In addition, another lectin, the mannose specific lectin Hippeastrum hybrid agglutinin (HHA), likely inhibited SARS-CoV attachment to the cells or

acted to inhibit the virus at the end of the infectious virus cycle (Keyaerts et al., 2007).

In another study, Ming Xiang (2009) conducted a study to investigate the immunosuppressive effects of HPLC qualitied ethyl acetate extract (EAE) from Urtica dentate Hand on skin allograft rejection in a murine model. The researchers established their model through placing skin allograft of C57BL/6 mice in the wound bed which was on the back of Balb/c mice. FACS was used to study the effects of EAE on dendritic cells (DCs) maturation and CD4+CD25+T regulatory cells (Tregs) differentiation. Spleen lymphocyte proliferation was used in addition to T-bet gene expression in DCs. Concentration of Th1/Th2 cytokines was monitored as markers of Th1/Th2 responses by ELISA. Study findings showed that there was a significant prolongation of skin allografts survival in a dose-dependent manner in the animals treated with EAE. It was also found that using FACS, treatment with EAE (200mgkg−1) resulted in an immature statement of DCs and stimulated the differentiation of CD4+CD25+Tregs. Additionally, the expression of T-bet gene and the proliferation of spleen lymphocytes were efficiently abated in EAE treated mice. In comparison of the model control, EAE-treated recipients showed a significant downregulation ($P < 0.01$) of Th1 cytokines (IL-2, IFN-y) and an obviously increase ($P < 0.01$) of Th2 cytokine (IL-10) in the serum, which presented in a dose-related way. Taken together, the anti-allograft rejection effect of EAE by enhancing CD4+CD25+Tregs differentiation and sustaining DCs immaturation makes EAE to be a possible choice for treating autoimmune diseases in a way of inducing a stable immunological tolerance state.

It has been reported that Urtica dentata Hand (UDH) is the root of Laportea bulbifera (Sieb.et.Zucc.) Wedd, which belongs to the family Urticaceae. UDH has been traditionally implicated as an anti-inflammatory drug, discutient, immuno-regulatory agent or as a remedy for oedema, arthrositis and some other autoimmune diseases. It is believed that UDH possess the ability to dispelling wind, eliminating dampness, promoting urination and obviating edemas (Wan et al., 2002).

Other studies have shown that the ethyl acetate extract (EAE) of UDH possessed powerful immunosuppressive abilities in vitro (Wang et al., 2007) and showed preventive action on collagen induced arthritis in mice (Xiang et al., 2006).

Ozen and Korkmaz conducted a study some metabolic effects associated with administration of extract of Urtica dioica L. The authors reported the experimental trials of two doses (50 and 100 mg/kg body wt given orally for 14 days). Study findings indicated that there were significant increased activities compared with control in liver for cytochrome b5 (cyt b5), NADH-cytochrome b5 reductase (cyt b5 R), glutathione S-transferase

(GST), DT-diaphorase (DTD), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD) and catalase (CAT). Findings also indicated that there were significantly decreased activities of cytochrome P450 (cyt P450), lactate dehydrogenase (LDH), NADPH-cytochrome P450 reductase (cyt P450 R), total sulfhydryl groups (T-SH), nonprotein sulfhydryl groups (NP-SH) and protein bound sulfhydryl groups (PB-SH).

References:

Ali-Shtayeh, M.S., Yaniv, Z., Mahajna, J (2000). Ethnobotanical survey in the Palestinian area: a classification of the healing potential of medicine. Journal of Ethnopharmacology 2073, 221–232.

Andersen S, Wold JK (1978). Water-soluble glycoprotein from Urtica-dioica leaves. Phytochemistry 17 (11):1875–1877.

Basaran AA, Akbay P, Undeger U, Basaran N (2001). In vitro immunomodulatory and mutagenic activity of the flavonoid glycosides from *Urtica dioica L*. Toxicology 164 (1–3): 171–172.

Basaran AA, Ceritoglu I, Undeger U, Basaran N (1997). Immunomodulatory activities of some Turkish medicinal plants. Phytother Res 11 (8): 609–611.

Baytop T (1984) Therapy with Medicinal Plants in Turkey, Istanbul University Press, No: 40, ˙Istanbul.

Beintema, J.J., Peumans, W.J. (1992). The primary structure of stinging nettle (Urtica dioica) agglutinin. A two-domain member of the hevein family. FEBS Lett. 299 (2), 131–134.

Calixto, J.B., Beirith, A., Ferreira, J., Santos, A.R., Filho, V.C., Yunes, R.A. (2000). Naturally occurring antinociceptive substance from plants. Phytotherapy Research 14, 401–418.

Chaurasia N, Wichtl M (1987). Flavonol glycosides from *Urtica dioica*. Planta Med (5): 432–434.

Chrubasik S, Eisenberg E (1999). Treatment of rheumatic pain with medicine in Europe. Part 2. *Urtica dioica* L.. Pain Clinic 11 (3): 179–185.

Chrubasik, J.E., Roufogalis, B.D., Wagner,H.,Chrubasik,S. (2007). Acomprehensive review on the stinging nettle effect and efficacy profiles. PartII: Urticae radix. Phytomedicine 14,568–579.

Delcourt M, Peumans WJ, Wanger MC, Truffa-Bachi P (1996). V beta specific deletion of mature thymocytes induced by the plant superantigen *Urtica dioica* agglutinin, Cellular Immunol 168: 158–164.

Dina M.Abo-elmatty, Soha S. Essawy, Jihan M. Badr, Olov Sterner (2013). Antioxidant and anti-inflammatory effects of Urtica pilulifera extracts in type2 diabetic rats. Journal of Ethnopharmacology 145, 269–277.

Fu, H.Y.,Chen, S. J., Chen, R. F., Ding, W. H., Kuo-Huang, L.L.,Huang, R.N (2006). Identification of oxalic acid and tartaric acid as major persistent

pain-inducing toxins in the stinging hairs of the nettle, Urtica thunbergiana. Annals of Botany 98, 57–65.
Granier G, Bezanger-Beauquense L, Debraux G (1961). Resources medicinales de la flore Francaise. Vigot Freres, Paris 2: 962–964.
Haiyue Zhang, Xiaojuan Yan, Zhenling Zhao and Li Ji (2013). Analysis of the polysaccharides from Urtica angustifolia and their anti-fatigue activity. African Journal of Pharmacy and Pharmacology, 7(22): 1438-1447. DOI 10.5897/AJPP12.170.
Kais Kassim Ghaima, Noor Makie Hashim, Safaa Abdalrasool Ali (2013). Antibacterial and antioxidant activities of ethyl acetate extract of nettle (*Urtica dioica*) and dandelion (*Taraxacum officinale*). Journal of Applied Pharmaceutical Science, 3 (05): 96-99.
Keyaerts, E., Vijgen, L., Pannecouque, C., Van Damme, E., Peumans, W., Egberink, H., Balzarini, J., Van Ranst, M.(2007). Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antiviral Res. 75 (3), 179–187.
Krzeski T, Kazon M, Brokowski A, Kuczera J (1993). Combined extracts *Urtica dioica* and *Pygeum african* in the treatment of hyperplasia: double-blind comparison of two doses. Clin Ther 6: 1011–1020.
Kudritskaya SE, Fishman GM, Zagorodskaya LM, Chikovani DM (1986). Carotinoids *Urtica dioica* L. Khimiya Prirodnykh Soedinenii 5: 640–641.
Lichius JJ, Muth C (1997).The inhibiting effect of *Urtica dioica* root extracts on experimentally induced prostatic hyperplasia in the mouse. Planta Med 63: 307–310.
Ming Xiang, Wen-Rui Hou, Sheng-Nan Xie, Wei-Dong Zhang, Xin Wang (2009). Immunosuppressive effects of an ethyl acetate extract from Urtica dentata Hand on skin allograft rejection. Journal of Ethnopharmacology, 126, 57–63.
Musette P, Galelli A, Harbre H (1996). *Urtica dioica* agglutinin, a V beta 8.3-specific superantigen, prevents the development or the systemic lupus erythematosus like pathology of MRL Ipr/Ipr mice. Eur J Immunol 26: 1707–1711.
Neugebauer W, Winterhalter P, Schreier P (1995). 3-Hydroxyalpha- ionyl-beta-d-glucopyranosides from stinging nettle (*Urtica dioica* L.) leaves. Nat Prod Lett 6 (3): 177–180.
Obertreis B, Giller K, Teucher T, Behnke B, Schmitz H (1996). Anti-phlogistic effect of *Urtica dioica* folium extract in comparison to caffeoyl malic acid. Arzneimittel Forschung 46: 52–56.
Randall C, Mccthan K, Randall H, Dobbs F (1999). Nettle sting of *Urtica dioica* for joint pain: an exploratory study of this complementary therapy. Compl Ther Med 7:126–131.

Reihemann K, Behnke B, Schulze-Osthoff K (1999). Plant extract from stinging nettle *(Urtica dioica)*, an antirheumatic remedy, inhibit the proinflammatory transcription factor. FEBS Lett 442: 89–94.
Rovira P, Buckle M, Abastado JP, Peumans WJ, Truffa-Bachi P (1999). Major histocompatibility class I molecules present *Urtica dioica* agglutinin, a superrantiden of vegetal origin to lymphocytes. Eur J Immunol 29: 1571–1580.
S. Gorzalczany, C. Marrassinib, J. Mi˜no, C. Acevedo, G. Ferraro (2011). Antinociceptive activity of ethanolic extract and isolated compounds of Urtica circularis. Journal of Ethnopharmacology, 134, 733–738.
Samur M, Bozcuk HS, Kara A, Savas B (2001). Factors associated with utilization of nonproven cancer therapies in Turkey. Supportive Care in Cancer 9 (6): 452–458.
Styprekowska E, Bieganska J (1980). Investigations on an increase of extraction yield of protein from *Urtica dioica* L. leaves. Herba Polonıca 26 (3): 171–176.
T. Ozen and H. Korkmaz (2003). Modulatory effect of Urtica dioica L. (Urticaceae) leaf extract on biotransformation enzyme systems, antioxidant enzymes, lactate dehydrogenase and lipid peroxidation in mice. Phytomedicine 10: 405–415.
Tahri A, Sabah Y, Legssyer A, Aziz M, Mekhfi H, Bnnouham M, Ziyyat A (2000). Acute diuteric, natriuretic and hypotensive effects of a continuous perfusion of aqueous extract of *Urtica dioica* in the rat. J Ethnopharmacol 73: 95–100.
Tita B, Facecendini P, Bello U, Martinoli L, Bello P (1993). *Urtica dioica* L: Pharmacological effect of ethanol extract. Pharmacol Res 27: 21–23.
Van Damme, E.J., Broekaert, W.F., Peumans, W.J., (1988). The Urtica dioica agglutinin is a complex mixture of isolectins. Plant Physiol. 86 (2), 598–601.
Van der Meer, F.J., de Haan, C.A., Schuurman, N.M., Haijema, B.J., Peumans, W.J., Van Damme, E.J., Delputte, P.L., Balzarini, J., Egberink, H.F. (2007). Antiviral activity of carbohydrate-binding agents against Nidovirales in cell culture. Antiviral Res. 76 (1), 21–29.
Wan, D.R., Chen, J.C., Yu, H.H. (2002). Urtica dentata Hand. In: Fu, S.X. (Ed.), Flora Hupehensis Tomus, 2nd ed. Hubei Science and Technology Publisher, Wuhan, pp. 234–238.
Wang, X., Zou, X.L., Su, Z.Q., Yao, Y., Xiang, M. (2007). Effects of the immune inhibitory active component of traditional Chinese medicine on murine BM-DCs. Chinese Journal of Experimental Surgery 24, 1414–1416.

Xiang, M., Tao, E., Chu, T., Yuan, S.Y., 2006. Preliminary study on preventing effects of the active component of Honghuoma on CIA model. Chinese Journal of Hospital Pharmacy 10, 1201–1205.

Yohichi Kumaki, Miles K. Wandersee, Aaron J. Smith, Yanchen Zhou, Graham Simmons, Nathan M. Nelsona, Kevin W. Bailey, Zachary G. Vest, Joseph K.-K. Li, Paul Kay-Sheung Chane, Donald F. Smee, Dale L. Barnard (2011). Inhibition of severe acute respiratory syndrome coronavirus replication in a lethal SARS-CoV BALB/c mouse model by stinging nettle lectin, Urtica dioica agglutinin. Antiviral Research 90, 22–32.

Ziyyat A, Legssyer A, Mekhfi H, Dassouli A, Serhrouhni M, Benjelloun W(1997). Phytotherapy of hypertension and diabetes in oriental Morocco. J Ethnopharmacol 58: 45–54.