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Anti-Inflammatory and Antinociceptive Potential of Phytochemicals Derived from *Urtica massaica*: A Comprehensive Review

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Abstract

Urtica massaica, commonly known as the stinging nestle belonging to the family Urticaceae is used either as a vegetable or as food additive and as medicine in traditional African societies. It is a perennial herb that grows in wet parts of Kenya highlands and whose use in treating inflammation and pain among the natives in Kenya highlands has been common. Inflammation and pain management is still a problem in the treatment processes. The two medical indications have been regularly treated using non-narcotic drugs such as non-steroidal anti-inflammatory drugs, which have proved to cause adverse side effects. Therefore, there is need to use bioactive compounds from natural sources like *Urtica massaica* as an alternative treatment. This review focused on the phytochemicals derived from the plant species *Urtica massaica*, its anti-inflammatory and analgesic effects. The mechanisms by which the phytochemicals exert their anti-inflammatory and analgesic effect was also reviewed. Information on the safety and toxicity of *Urtica massaica* was also reviewed. The references reviewed were obtained from peer reviewed scientific journal articles. These articles were searched from databases including PubMed, Google Scholar (http: //scholar.google.com) and Science Direct (http://www.science direct.com). This review focused on data published from the year 2014 up to 2024. The findings obtained indicated that *Urtica massaica* has over 50 phytochemicals, flavanoid derivatives being the main anti-inflammatory and analgesic compound. However, there is need to isolate the bioactive compounds and further investigate the mechanisms by which they exhibit their anti-inflammatory and antinociceptive effect.

Key Words: Phytochemicals; *Urtica massaica;* Safety profile; Anti-inflammatory pain

Introduction

Urtica massaica is a plant commonly known as the stinging nestle belonging to the family Urticaceae. It is a dioecious erect herb with ovate leaves and inflorescence of auxiliary groups of spike-like unbranched racemes. The plant is usually found growing in shrubs and is widely used as a vegetable by indigenous people of Kenya. *Urticaceae*, the nettle family (order Rosales), includes 54 genera and a total of 2,625 species of herbs, shrubs, small trees, and a few vines distributed primarily in tropical regions (Britannica, 2023). *Urtica massaica* products are widely used as a source of food for humans and livestock, medicine for both humans and livestock, and for other purposes such as live fencing and as a source of raw material in the traditional basket and mat weaving (Nduwamungu et al., 2023). For centuries, in Kenya, *U. massaica* has found its use as a traditional remedy for treating a variety of diseases like abscesses, wounds, pain, allergic itching, diabetes, stomachache and diarrhea (Wambui et al., 2024).

Inflammation is a complex, natural protective response towards different stimuli characterized

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by the dilation and permeation of the blood vessels with a surge in leukocytes in the tissues (Wambui et al., 2024). The current treatment involves the use of anti-inflammatory drugs, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), which have been associated with adverse side effects especially gastrointestinal ulcers (Nunes et al., 2020). Limited studies have been attempted to identify the specific anti-inflammatory compounds within the extracts of the stinging nettle leaves as well as their mechanism of action therefore, there is a growing need to explore alternative sources from medicinal plants (Nunes et al., 2020). Pain management is still a major problem with a prevalence of postoperative pain at 95.2% of the patients. The incidence of moderate and severe pain varies across the world and ranges from 14% to 55% in western countries, being the highest on the day of surgery. In low- and middle-income countries, data are scarce but prevalence goes up to 95% according to studies done in Kenya and Ethiopia (Ndebea et al., 2020). This present study is a review of the phytochemicals derived from *Urtica massaica*, which are used in the treatment of inflammation and pain.

Methodology

In conducting this review, literature reports on the phytochemicals derived from *Urtica massaica* used in treatment of pain and inflammation were retrieved systematically and comprehensively. Empirical online searches were done using PubMed, Google Scholar (http:// scholar. google.com) and Science Direct (http://www.science direct.com), with words including 'Phytochemicals', '*Urtica massaica*', 'Safety profile', 'Anti-inflammatory and pain' used as the main searching words. This review focused on the *Urtica massaica*-derived phytochemicals, their inflammatory and antinociception therapeutic potential. The mechanism of the phytochemicals derived from the *U. massaica* leaves in reversing nociception and modulating inflammation was also searched. Other articles and publications were obtained by tracking citations from other publications or by directly accessing journal websites. This review relied on scientific papers published between the year 2014 and 2024.

Findings and Discussion

Phytochemicals in *Urtica massaica*

A total of 24 scientific papers were searched, 83% of the literature sources were from peer reviewed journals whereas 17 % were from non-conventional literature (Figure 1).

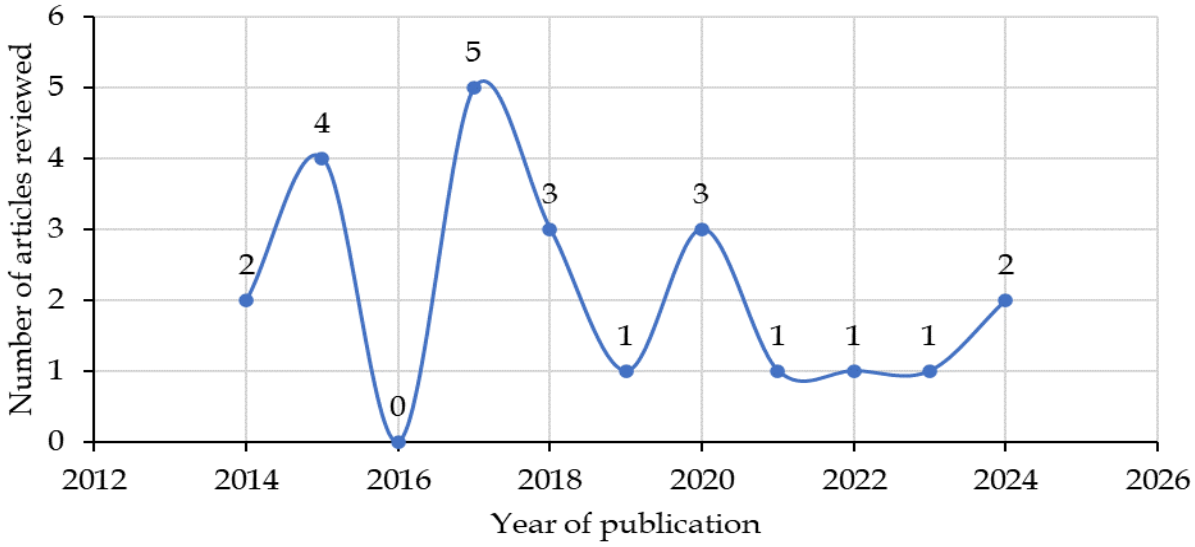

Figure 1. Trend in number of reviewed articles related to inflammation and pain treatment using *Urtica massaica* conducted over the study period 2014 - 2024

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Phytochemicals are plant metabolites produced in response to any infectious attack or as a by-product of any metabolic pathway, despite exerting beneficial effects in many ways (Taheri et al., 2022). The active chemical portions of *Urtica massaica* includes nearly fifty compounds of the lipophilic and hydrophilic fractions and whose chemical structure is known. Globally, few *Urtica* species have been screened for their phytochemical com-position, with those available so far reporting the presence of sterols, triterpenes, coumarins, phenols, lignans, ceramides, and fatty acids, amongst other minor compounds, all with a distribution varying in the various organs of the plant. Various studies on *Urtica massaica* have identified varying classes of phytochemicals. In a study by Wambui et al., (2024), Liquid Chromatography Mass Spectroscopy (LC-MS) analysis on *U. massaica* confirmed the presence of 19 phytochemicals, of which 10 and 9 were phenolic and flavonoid compounds, respectively. Beta-sitosterol, transferulic acid, dotriacontane, erucicacid, ursolic acid, scopoletin, rutin, quercetin, and phy-droxylbenzalcohol are some of the constituents found in *U. massaica* that may be applied for therapeutic purposes in communicable and non-communicable diseases (Koca et al., 2017).

Methods of Extraction

Extraction from the plant is an empirical exercise since different solvents are utilized at varying conditions such as time and temperature of extraction (Ingle et al., 2017). Further separation of bioactive components from co-extractives compounds is essential. Further fractionation of extracted compounds is done on the basis of their acidity, polarity or molecular size. All these inform the type of method of extraction used for *U. massaica*. Several extraction methods have been described:

Maceration: In this extraction procedure, coarsely powdered drug material, either leaves or stem bark or root bark, is placed inside a container; the menstruum is poured on top until completely covered the drug material. The container is then closed and kept for at least 72 hours (Azwanida, 2015).

Infusion: This is an extraction process such as maceration. The drug material is grinded into fine powder, and then placed inside a clean container. The extraction solvent hot or cold is then poured on top of the drug material, soaked, and kept for a short period of time (Ingle et al., 2017). Infusion method is suitable for extraction bioactive constituents that are readily soluble. In addition, it is an effective method for preparation of fresh extract before use (Majekodunmi, 2015).

Digestion: This method involves moderate heating during extraction process. The solvent of extraction is poured into a clean container followed by powdered drug material (Ingle et al., 2017). The mixture is placed over water bath or in an oven at a temperature of about 50^0 C. Heat is applied throughout the extraction process to decrease the viscosity of extraction solvent and enhance the removal of secondary metabolites. This method is suitable for plant materials that are readily soluble (Pandey and Tripathi, 2014).

Solvent extraction method: Solvent extraction, also called leaching, is the technique of removing one constituent from a solid by means of a liquid solvent (Hu et al., 2015). The solvent used for extraction of bioactive compounds in plants is termed as menstruum (Abubakar and Haque, 2020). The solvent to be used for extraction usually depends on the plant species, part of plant to be extracted, nature of the bioactive compounds, and the availability of solvent. Generally, polar solvents such as water, methanol, and ethanol are used in extraction of polar compound, whereas nonpolar solvents such as hexane and dichloromethane are used in extraction of nonpolar compounds (Abubakar and Haque, 2020). Solvent used in extraction is classified according to their polarity, from *n*-hexane which has been found to be have the lowest polarity to water which has the highest polarity. The following are 11 various solvents of extractions arranged according to the order of increasing polarity (Pandey and Tripathi, 2014):

Table 1. Solvents used in bioactive extraction and their polarities

Published December 2024

No.	Solvents	Polarity
1.	*n*-Hexane	0.009
2.	Petroleum ether	0.117
3.	Diethyl ether	0.117
4.	Ethyl acetate	0.228
5.	Chloroform	0.259
6.	Dichloromethane	0.309
7.	Acetone	0.355
8.	*n*-Butanol	0.586
9.	Ethanol	0.654
10.	Methanol	0.762
11.	Water	1.000

Percolation: This process involves the use of an apparatus called percolator; a narrow-cone-shaped glass vessel with opening at both ends. A dried, grinded, and finely powdered plant material is moistened with the solvent of extraction in a clean container. More quantity of solvent is added, and the mixture is kept for a period of 4 hrs. Subsequently, the content is then transferred into percolator with the lower end closed and allow to stand for a period of 24 hrs. (Pandey and Tripathi, 2014). The solvent of extraction is then poured from the top until the drug material is completely saturated. The lower part of the percolator is then opened, and the liquid allowed to drip slowly. Some quantity of solvent is added continuously, and the extraction takes place by gravitational force, pushing the solvent through the drug material downward (Ingle et al., 2017). The addition of solvent stops when the volume of solvent added reaches 75% of the intended quantity of the entire preparations. The extract is separated by filtration followed by decantation. The marc is then expressed and final amount of solvent added to get the required volume (Majekodumni, 2015).

Anti-inflammatory Properties

The anti-inflammatory potential of bioactive compound in *Urtica* sp. have been proved in various studies, both *in vitro* and *in vivo*. It has been deduced that the anti-inflammatory effect of *Urtica* sp. extracts is related to the presence of flavonoids, such as quercetin, kaempferol and rutin (Cuinica and Chissico, 2018). Flavanoids affect the function of T-cell, mast cell and enzyme systems involved in immune response and generation of the inflammatory process, such as inhibition of NF-kB activation, cyclooxygenase enzymes (COX-1 and COX-2) and Inducible Nitric Oxide Synthase; iNOS (Martínez et al., 2019). These secondary metabolites were found to inhibit gene expressions of pro-inflammatory mediators (TNF-α, IL-1β, IL-6, and IL-8) in human mast cells (Martinez et al., 2019). Quercetin inhibits inflammatory processes, including eosinophil and neutrophil recruitment, bronchial epithelial cell activation, mucus production and airway hyperactivity (Jefarinia et al., 2020). Flavanoid compounds inhibit macrophage derived cytokines, Nitric Oxide (NO) and Th2 cytokine production, increased IFN-γ and Th1 cytokine production in mice.

Published December 2024

Bayat et al., (2021) reported that quercetin inhibited leukocyte and eosinophil recruitment in the bronchoalveolar lavage fluid, and significantly reduced neutrophil, IL-5 and IL-4 levels. Moreover, it inhibited iNOS expression, COX-2 and NF-kB activation in IL-1β-activated rat hepatocytes (Cuinica and Chissico, 2018).

Nociception (Pain Relief) Properties

Dhouibi *et al.,* (2017) demonstrated that the leaf's ethanolic extract of *Urtica* sp. exhibits significant analgesic activity ($p < .001$) at a dose of 400 mg/kg. The analgesic activity was analysed by hot plate method, formalin test, acetic acid-induced writhing test and the tail-flick test with different doses of the ethanolic extract. In all tests, even with a low dose, it was noticed that an analgesic activity was evident. Dhouibi et al., (2017) demonstrated that *Urtica* sp. could be another therapeutic alternative for relieving pain and for minimising the use of drugs that have long-term secondary effects. Farahpour and khoshgozaran, (2015) demonstrated that *U. massaica* showed a significant reduction of pain at 30, 60 and 90 min following extracts medication. *Urtica* sp. have anti-inflammatory effect by inhibiting NF-kappa *B* which might be one of the mechanisms which impresses its antinociceptive activity. The role of tannins in antinociceptive and anti-inflammatory activities have been reported in a few reports in the recent past. Recently, it has been shown that crocins and crocus glycosides exhibited an anti-inflammatory effect on some models of inflammation and this has also been linked to Tannin's potential as a pain reliever (Hassan et al., 2017). Camilla et al., (2020) demonstrated that the analgesic and anti-inflammatory activities of flavonoids are related, at least in part, to their NF-κB inhibitory effects. Xiao et al., (2017) demonstrated that the glycosylation of flavonoids and their derivatives against their inhibitory activity on TNFα-induced NF-κB activation.

Safety and Toxicity of *Urtica massaica*

Generally, *Urtica* sp. have been reported to cause mild side effects. In a study by Yvonne et al., (2018) in which the teratogenic effect of *U. massaica* was evaluated, high doses of the *U. massaica* methanolic leaves extracts showed teratogenic activity. Oloro et al., (2015) investigated the effect that *U. massaica* aqueous extract could have on renal function, the study demonstrated that there were no significant effect on urea levels on oral administration of *U. massaica*.

In a study by Kimani et al., (2021) that evaluated the biochemical effects of *U. massaica* extract in mice, orally administered *U. massaica* at varying doses between 300 and 1000 mg/kg body weight did not affect lactate dehydrogenase (LDH) and amylase in swiss albino mice, the plant extract increased.

As for drug-drug interaction, Kőszegi et al., (2017) reported that *Urtica* sp. enhances the impact of central nervous system depressant medications. The concomitant use of *Urtica* aerial parts with sedatives, including lorazepam (Ativan), phenobarbital (Donnatal), clonazepam (Klonopin), zolpidem (Ambien), and others have been reported to cause sleepiness and drowsiness. Although the mechanism of the latter is yet to be established.

Conclusion

Urtica massaica is a promising alternative source of drug? in the management of inflammation and pain. The plant has found utility in the past in the treatment of a wide range of diseases even though scientific validation of such therapies is yet to be fully established. Inflammation and pain are joint medical challenges that still affect millions of people worldwide and the need to lower the prevalence in Kenya is not in question. The species *U. massaica* contains multiple phytochemicals that possess therapeutic significance in management of pain and inflammation. There is need to isolate the bioactive compounds, especially of flavonoid type, and further investigate the mechanisms by which they exhibit their anti-inflammatory and antinociceptive effect. There is also need to further research on the hepatotoxic effect and neurotoxic effect of flavonoid derivatives found in *U. massaica.*

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Reference

Azwanida, N.N., (2015). A review on the extraction methods use in medicinal plants, principle, strength and limitation. *Med Aromat Plants* 4 (3): 1–10.

Bayat, P., Farshchi, M., Yousefian, M., Mahmoudi, M. & Yazdian-Robati, R., (2021). Flavonoids, the compounds with anti-inflammatory and immunomodulatory properties, as promising tools in multiple sclerosis (MS) therapy: a systematic review of preclinical evidence. *International Immunopharmacology*, 95,: p. 107562.

Britannica.
(2023). www.britannica.com/plant/Urticaceae Google Scholar

Caliskan, U.K., Aka, C. and Oz, M.G., 2017. Plants Used in Anatolian Traditional Medicine for the Treatment of Hemorrhoid. *Records of Natural Products*, *11*(3).

Cuinica, L.G., & Chissico, R.B. (2018). Anti-Inflammatory Properties of Extract and Quercetin from *Urtica dioica* L. Advances in Analytical and Pharmaceutical Chemistry: AAPC-104.

Dhouibi, R., Moalla, D., Ksouda, K., Ben Salem, M., Hammami, S., Sahnoun, Z., Zeghal, K.M. and Affes, H., 2018. Screening of analgesic activity of Tunisian Urtica dioica and analysis of its major bioactive compounds by GCMS. *Archives of physiology and biochemistry*, *124*(4),.335-343.

Hassan, M.M., Shahid-Ud-Daula, A.F., Jahan, I.A., Nimmi, I., Adnan, T. & Hossain, H., (2017). Anti-inflammatory activity, total flavonoids and tannin content from the ethanolic extract of Ageratum conyzoides linn. Leaf. *International Journal of Pharmaceutical and Phytopharmacological Research*, 1(5):, 234-241.

Hu, T., Zhang, D., & Wang, J. (2015). A meta-analysis of the trait resilience and mental health. *Personality and Individual Differences, 76, 18–27.*

Ingle, K.P., Deshmukh, A.G., Padole, D.A., Dudhare, M.S., Moharil, M.P. and Khelurkar, V.C., 2017. Phytochemicals: Extraction methods, identification and detection of bioactive compounds from plant extracts. *Journal of Pharmacognosy and Phytochemistry*, *6*(1), pp.32-36.

Jafarinia, M., Sadat Hosseini, M., Kasiri, N., Fazel, N., Fathi, F., Ganjalikhani Hakemi, M. and & Eskandari, N., (2020). Quercetin with the potential effect on allergic diseases. *Allergy, Asthma & Clinical Immunology*, 16,: 1-11.

Kőszegi, K., Kocsis, J.M., Vatai, G. & Bekassy-Molnar, E., (2017). Antimicrobial Effects of the Stinging Nettle (*Urtica Dioica* L.). *Analecta Technica Szegedinensia*, 11(2):, 10-15.

Majekodunmi, S.O., (2015). Review of extraction of medicinal plants for pharmaceutical research. *Merit research journal of medicine and medical sciences*, 3(11):,.521-527.

Martínez, G., Mijares, M.R. & De Sanctis, J.B., (2019). Effects of flavonoids and its derivatives on immune cell responses. *Recent Patents on Inflammation & Allergy Drug Discovery*, 13(2),: 84-104.

Ndebea, A.S., van den Heuvel, S.A., Temu, R., Kaino, M.M., van Boekel, R.L. and Steegers, M.A., 2020. Prevalence and risk factors for acute postoperative pain after elective orthopedic and general surgery at a tertiary referral hospital in Tanzania. *Journal of Pain Research*, 3005-3011.

Nduwamungu, J., Ugirabe, M.A., Mahoro, J., Dusingize, M.C., Kabarungi, M., Irimaso, E., Maniraho, E., Mugemangango, C., Ruhimbana, C., Senyanzobe, J.M.V. and Mugunga, C., 2024. New insights into the indigenous knowledge of the uses of the

common stinging nettle (Urtica massaica Mildbr.) in Rwanda. *Cogent Food & Agriculture*, *10*(1), 2306722.

Nunes, C.D.R., Barreto Arantes, M., Menezes de Faria Pereira, S., Leandro da Cruz, L., de Souza Passos, M., Pereira de Moraes, L., Vieira, I.J.C. & Barros de Oliveira, D., (2020). Plants as sources of anti-inflammatory agents. *Molecules*, 25(16):,.3726.

Joseph, O., Kihdze, T.J., Katusiime, B., Imanirampa, L., Waako, P., Bajunirwe, F. and Ganafa, A.A., 2015. Toxicity of four herbs used in erectile dysfunction; *Mondia whiteii, Cola acuminata, Urtica massaica, and Tarenna graveolensin* male rats.

Pandey, A. & Tripathi, S., (2014). Concept of standardization, extraction and pre phytochemical screening strategies for herbal drug. *Journal of Pharmacognosy and phytochemistry*, 2(5): 115-119.

Taheri, Y., Quispe, C., Herrera-Bravo, J., Sharifi-Rad, J., Ezzat, S.M., Merghany, R.M., Shaheen, S., Azmi, L., Prakash Mishra, A., Sener, B. and Kılıç, M., 2022. *Urtica dioica*-derived phytochemicals for pharmacological and therapeutic applications. *Evidence-based Complementary and Alternative Medicine*, *2022*(1), 4024331.

Wambui, J., Ikedi, R.I., Macharia, R.W., Kama-Kama, F. & Nyaboga, E.N., (2024). Phytoconstituents of Kenyan stinging nettle (*Urtica* sp.) and their molecular docking interactions revealed anti-inflammatory potential as cyclooxygenase-2 inhibitors. *Scientific African*, 23:, p.e02088.

Woldehaimanot, T.E., Eshetie, T.C., Kerie, M.W., Burney, R.E. (2014). Postoperative pain management among surgically treated patients in an Ethiopian hospital. *PLoS ONE*. 9(7):e102835. doi:10.1371/journal.pone.0102835

Xiao, J., (2017). Dietary flavonoid aglycones and their glycosides: Which show better biological significance?. *Critical reviews in food science and nutrition*, 57(9),: 1874-1905.

Yvonne, W.W., Maina, M.J. & Mwaniki, N.E., (2018). Teratogenic potential of *Urtica massaica* (Mildbr.) and Croton megalocarpus (Hutch) in mice. *The Journal of Phytopharmacology*, 7(6):, 460-463.