

## Phytochemistry, biological activity and medicinal importance of *Urtica dioica*: A Review

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### Abstract

*Urtica dioica* (stinging nettle), a flowering plant with the herbaceous perennial habit, belonging to the 'Urticaceae' family, native to temperate Asia, Europe, and North Africa, shows now worldwide distribution. The plant has a long history of being utilized as a medicinal herb. Traditionally, it is being used widely by many medical practitioners to treat many diseases like haematuria, arthritis, nephritis, menorrhagia, and rheumatism. Although this plant's phytochemistry is complex, studies on phytochemical constituents showed the occurrence of compounds like flavonoids, tannins, saponins, proteins, amino acids, and phytosterols. Likewise, *Urtica dioica* is being used as food, fibre, manure, and cosmetics. The plant also possesses diverse pharmacological activities, including antioxidant, antibacterial, analgesic, antiviral, anti-inflammatory, hepatoprotective, anticancer, and immune-regulatory effects. This review briefs about biological activities, phytochemistry, toxicology, and pharmacology of *Urtica dioica*.

**Keywords:** phytochemicals, antioxidant, anti-inflammatory, hepatoprotective, ROS, coronaviruses

### Introduction

*Urtica dioica* of the family *Urticaceae* and genus *Urtica* [1] is a plant with perennial habit possessing quadrangular, green, and erect stem. Each corner of stem cells has lacunar collenchyma and possibly 12-20 fibrovascular bundles [2]. Plant leaves are pale abaxially, while their adaxial sides are dark green. Leaves are finely toothed with a cordate base and arise oppositely [3]. Both leaves and stems are enclosed with stinging trichomes filled with acetylcholine, serotonin, and histamine. Flowers are dioecious, brown, or green, usually borne in separate inflorescences present in the upper leaf axils. The flowering season is between May and September [1].

Usually, the biarch root is present, along with the rhizome [2].

*Urtica*'s leaf extracts have an adequate concentration of flavonoids and derivatives of caffeic acid with anti-inflammatory, analgesic, and antioxidant properties [4]. The ethanolic leaf extracts of *Urtica dioica* driven by the NF-KB inhibitory pathway regulate the release of inflammatory cytokine [4]. Stinging nettle leaves contain significant amounts of minerals, vitamins, essential fatty acids, and amino acids.

### 1. Phytochemistry

Phytochemical compounds commonly found in *Urtica dioica* are sterols, flavonoids, tannins, and volatile

compounds [5, 6]. Some amino acids, viz asparagine, aspartic acid, alanine, glutamic acid, and threonine, are found in dominating ratios [7]. Besides these, three more substances that cause smooth muscle stimulation have been reported in *Urtica*. These are histamine, acetylcholine, and 5-HT (hydroxytryptamine) [8]. The plant's rhizome shows the occurrence of an unusual lectin that is a monomeric protein, 8-5KDa in weight, and contains high levels of cysteine, glycine, and tryptophan [9]. Roots of stinging nettle contain neolivil, secoisolariciresinol, ligans, and isolariciresinol [10]. Leaf trichomes usually cause a burning sensation due to the presence of histamine, leukotrienes, 5-hydroxytryptamine (serotonin), acetylcholine, and formic acid [8]. The main components recorded in nettle plant essential oil include carvone (9.0%), carvacrol (38.2%), naphthalene (8.9%), hexahydrofarnesyl acetone (3.0%), (E)-anethol (4.7%), (E)-beta ionone (2.8%), phytol (2.7%), (E)-geranyl acetone [6]. Some biologically important compounds have also been identified in the rhizomes of common nettle, such as sterols, polysaccharides, scopoletin, isolectins, and fatty acids [5]. The rhizomes also witness the occurrence of some agglutinin isolectins that probably form a complicated mixture and vary in their amino acid contents [11]. Important phytochemical constituents found in *Urtica dioica* are listed in the Table below:

#### 1.1. Phytochemical Constituents

Table 1

Secondary Metabolites	Phyto Constituents
Flavonoids	Isorhamnetin, Kaempferol, Isoquercitrin, Rutin and Astragalol [12]. Hyperoside, Quercetrin, 2-phenyl4-benzopyrone, Hyperin, Quercetin and Apigenin [13]. Crysoeriol, Isorhamnetin, Catechin, Amentoflavon, Quercetin-3-O-glucoside, Quercetin-3-O-rutinoside, Kaempferol-3-O-glucoside [14].
Phenolic acids and Phenolics	Flavonoid, Benzoic acids, Phytosterols, Cinnamic acids, and Coumarins [15]. Caffeic acid, Chlorogenic acid, Phenylpropanoids, and Scopoletin [12]. Monocaffeoyl-meso-tartaric acid and kaempferol 3-O-rutinoside-7-O-rhamnoside [16]. p-Hydroxybenzoic acid, Vanillic acid, p-Coumaric acid, Ferulic acid, Gentisic acid, Protocatechuic acid, Esculetin, Quinic acid, Neochlorogenic acid [14]. p-Coumaroylmalic acid, Caffeoyl tartaric acid, 4-O-Caffeoylquinic acid, Caffeoylmalic acid [17].
Carotenes	Violaxanthin, Lutein, Lutein epoxide, Luteoxanthin, beta-Carotene, Hydroxyl beta-carotene [18].

Essential oils	2-methyl-2 hepten-2-one, Ethyl ketone, Acetophenone, Free alcohols, some nitrogenous substances, esters, aldehydes, and phenols <sup>[18]</sup> .
Fatty acids and ceramides	Stearic acid, Palmitic acid, Linolenic and Oleic acids <sup>[19]</sup> . Lauric acid, Myristic acid, Myristoleic acid, Heptadecanoic acid, cis-10-Heptadecenoic acid, Stearic acid, cis-9,12-Linoleic acid, Arachidic acid, $\alpha$ -Linolenic acid, Heneicosanoic acid, cis-11,14-Eicosadenoic acid, Behenic acid, Arachidonic acid, Tricosanoic acid, cis-13,16-Docosadienoic acid, Lignoceric acid, Nervonic acid <sup>[20]</sup> .
Organic acids and Carbohydrates	Malic acid, Acetic acid, Citric acid, Succinic acid, Formic acid, Inositol, Glucose, Rhamnose, Sucrose <sup>[21]</sup> .
Amino acids	Aspartic acid, Glutamic acid, Asparagine, Threonine, Alanine, Histidine, Leucine, Arginine, Phenylalanine, Proline, Tyrosine, Valine, and Isoleucine <sup>[7,15,21]</sup> .
Carotenoids	Leutin, beta-Carotene, and their isomers; Chlorophyll a and b <sup>[19]</sup> .
Steroids and triterpenoids	3- $\beta$ -Sitosterol, Sitosterol- $\beta$ -D-glucoside, (6'-O-palmitoyl)-sitosterol-3-O- $\beta$ -D-glucoside, 24R-Ethyl-5 $\alpha$ -cholestane-3 $\beta$ , 6 $\alpha$ -diol, 7 $\beta$ -Hydroxy-sitosterol, 7 $\alpha$ -Hydroxy sitosterol, 7 $\beta$ -Hydroxy-sitosterol- $\beta$ -D-glucoside, 7 $\alpha$ -Hydroxy-sitosterol- $\beta$ -D-glucoside <sup>[22]</sup> .
Other constituents	Vitamin B <sub>1</sub> , B <sub>2</sub> , B <sub>3</sub> , B <sub>6</sub> , B <sub>9</sub> , C, K, and some minerals viz. Calcium, Magnesium, Potassium, Sodium, Iron, Barium, Lithium, Nickel, and Phosphorous <sup>[13,18]</sup> .

## 2. Biological Activity

### 2.1 Antioxidant Activity

Antioxidants obtained from *Urtica dioica* act as therapeutic and prophylactic agents by protecting from the damaging and destructive ramifications of ROS. These free radicals show a dynamic role in the pathogenesis of certain disorders like diabetes, cancer, autoimmune diseases, CDV (Canine Distemper Virus) diseases, and neurodegenerative disorders <sup>[23]</sup>. Significant results for antioxidant property in hydroalcoholic extracts of the plant have been observed. The extract has greater reducing power, superoxide anion radical scavenging, scavenging free radical, and H<sub>2</sub>O<sub>2</sub> scavenging <sup>[24]</sup>. Extracts of the plant showed higher antioxidant potential for reducing ferric equivalent to Trolox, found good at chelating metals and supplementation of *Urtica* extracts reduces oxidative stress potential at a systemic level, and it increases antioxidant capacity at the plasma level <sup>[25]</sup>. Besides antioxidants, the leaf extract exhibits antilithiasic properties and reduces the calcium oxalate crystal size in urine, proving an addition to the therapeutic application <sup>[26]</sup>.

### 2.2 Antidiabetic Activity

*Urtica dioica* is known to have anti-diabetic properties. Leaf extracts of the plant in the range of 250mg/kg, when administered to diabetic rats, showed decreased blood sugar levels in them. In induced diabetes, cold methanolic leaf extract also shows the antihyperglycemic effect <sup>[27]</sup>. Swimming exercises followed by plant aqueous extract consumption resulted in improved diabetic parameters, *in vitro* insulin or glucose uptake improvement, and *in vivo* restoration of pancreatic tissues in people with diabetes <sup>[28]</sup>. The ethanolic extract of the plant has proved to directly affect the adipocytes by increasing the expression of adiponectin and ceramidase activity, subsiding the accumulation of ceramide, and increasing insulin sensitivity through higher Akt phosphorylation <sup>[29]</sup>. By using molecular docking to study the interactions between specific enzymes accountable for diabetes mellitus type 2 (DMT2) and *Urtica dioica* phenolic compounds, the role of *Urtica dioica* as an anti-diabetic agent has been confirmed <sup>[30]</sup>. *Urtica dioica* hydroalcoholic extracts showed significant improvement in diabetic rat blood glucose levels by lowering GSK-3 beta and K-Ras levels in the blood <sup>[31]</sup>.

### 2.3 Hepatoprotective Activity

Leaf extracts of *Urtica dioica* can prevent liver damage. The suggested dosage to obtain more significant

hepatoprotective activity is 400mg/kg <sup>[32]</sup>. The plant's seed extract also protects against hepatic damage by enhancing the activity of aryl-esterase, paraoxonase, and liver tissue catalytic activity <sup>[33]</sup>. EAF (ethyl acetate fraction) of an aqueous-alcoholic extract of the plant is supposed to have substantial hepatoprotective and antioxidant potential, and Ferulic acid isolated from it imparts hepatoprotective capability <sup>[34]</sup>.

### 2.4 Diuretic Activity

Plant aqueous extract, when administered at 1g/kg (p.o) dosage, showed no diuretic activity, but a significant increase in urine output was obtained at 500mg/kg (i.p) dosage <sup>[35]</sup>. The plant's diuretic effect came to about 25% compared with hydrochlorothiazine (25mg/kg). In rabbits, natriuretic and diuretic effects by whole plant aqueous extracts have been described <sup>[36]</sup>. The plant's methanolic extract decreases the creatinine, oxalate, and urinary calcium, suggesting it being antiurolithiatic and having the potential to act as a therapeutic agent against urological problems <sup>[37]</sup>.

### 2.5 Antiviral Activity

*Urtica dioica* aqueous extract has better N-acetyl glucosamine affinity as compared to anti-HIV activity. N-acetyl glucosamine region has been observed to strongly inhibit syncytium formation between CD4<sup>+</sup>Molt/4 cells and HUT-78 cells that are permanently infected by HIV-1 and HIV-2 <sup>[38]</sup>. The plant extract at lower doses (0.5-1 micrograms/ml) shows significant inhibition on syncytia development, and further increase occurs in the inhibition level due to an increase in the concentration of extract. At higher doses, cytotoxic effects began to be observed <sup>[39]</sup>. *Urtica dioica* lectin, Agglutinin, was evaluated and shown to inhibit coronaviruses like bronchitis virus, gastroenteritis virus, I and II serotypes of feline coronaviruses, torovirus, and arteriviruses <sup>[40]</sup>. Plant nutritional extract has anti-rotaviral properties, and such activity is increased if used in combination with *Nelumbo nucifera* extract; thus, retroviral caused diarrhoea can be treated <sup>[41]</sup>. The methanolic extracts of the plant inhibit dengue virus (DENV2) serotype 2 replication, and compounds exhibiting such properties isolated are kaempferol and quercetin (flavonol glycosides), chlorogenic acid, and quercetin derivatives <sup>[42]</sup>.

### 2.6 Anti-microbial Activity

The plant *Urtica dioica* has been used against various bacteria, be it gram-positive or negative. These bacteria

include *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Lactobacillus plantarum* 299V, and *E. coli*. The extract ranged from 9.05 to 149.33mg/ml<sup>-1</sup> showed MCB (minimum bactericidal concentration) and MIC (minimum inhibitory concentration) [43]. The methanolic extract for antibacterial activity screening in *Urtica dioica* has been analyzed on six bacterial strains viz *Pseudomonas aeruginosa*, *E. coli*, *Streptococcus pyogenes*, *S. aureus*, *Klebsiella pneumonia*, and *S. epidermis*. A prominent inhibitory activity has been revealed against *S. aureus*, *S. pyogenes*, and *S. epidermis* [44]. Patuletin, an O-methylated flavonoid obtained from *Urtica* extract, has also been screened for antimicrobial activities. The compound viz. Patuletin showed prominent activity against *S. faecalis*, *S. aureus*, *Candida albicans*, and *E. coli* with MIC of 0.02, 0.02, 0.001, and 0.002g/ml, respectively [45]. Nine crude *Urtica dioica* extracts showed antimycotic and antibacterial properties at 100mg/ml and provided a robust inhibitory effect to *Bacillus cereus*, *Acinetobacter calcoaceticus*, *B. spizizenii*, *Vibrio parahaemolyticus*, *Micrococcus* sp., *Trichophyton rubrum*, *Saccharomyces cerevisiae*, and *Aspergillus niger* [46]. Seed extracts of *Urtica dioica* and *U. pilulifera* exhibited antagonistic activity to phytopathogens and food spoiling bacteria like *Clavibacter michiganensis*, *Xanthomonas vesicatoria*, *Enterococcus gallinarum*, *Shigella* spp, and *Bacillus pumilus* [47]. Extract of *Urtica dioica* leaves, walnut husk, myrtle leaves, rose flowers and chamomilla flowers exhibited a strong inhibitory effect against *Propionibacterium acnes* causing pathogenesis of acne [48]. Leaf extracts of *Urtica dioica* used against pathogenic fungi exhibited substantial antifungal activity, and significant catalase activity was reported [49]. *Urtica* leaf extract exhibits fungicidal properties against *Fusarium* and *Aspergillus*, thus can prove an efficient biological control agent against crop and storage food pathogens [50].

### 2.7 Cardiovascular Effect

The antihypertensive property of the plant, *Urtica dioica*, has been shown by a decrease in MAP (Mean Arterial Pressure) from 96.59/0.5mmHg to 79.59/0.5mmHg on the administration of plant fraction intravenously [3]. Plant's aqueous extract has been used on thoracic aorta isolated from rat and Langerdorff rat heart simultaneously to characterize the vascular and cardiac effects [51]. Flavonoids present in *Urtica dioica* impart its antiaggregant property, and as such, epinephrine, collagen, thrombin, and ADP-induced platelet aggregation are inhibited. Hence cardiovascular diseases can be prevented or treated [52]. The crude *Urtica dioica* methanolic extracts along-with its fractions facilitate blocking of Ca<sup>2+</sup> channels and vasorelaxation, exhibiting antihypertensive capability, which can further provide a base for its usage in hypertension management [53]. *Urtica dioica* is a blood stopper component, Ankaferd hemostat, used in Turkey as a hemostatic agent and for wound healing, which acts through erythrocyte aggregation mediated by protein networks, especially fibrinogen gamma [54].

### 2.8 Anti-inflammatory, Analgesic and Anti-arthritis Activity

Administration of *Urtica dioica* leaf supplementation to Wistar rats resulted in NMDA (N-methyl-D aspartate) injection-induced inflammation and brain lesions. A significant decrease in NF-KB (nuclear factor kappa B)

binding capability to DNA occurs in such rats. These results suggest the prominent anti-inflammatory effect of *Urtica* leaves [55]. In rheumatoid arthritis treatment, the leaf extract of *Urtica* is used as an anti-inflammatory remedy. This anti-inflammatory consequence in rheumatoid arthritis occurs for suppression in cytokine production [56]. Leaf extracts of the plant reduce the inflammation induced by ovalbumin and lipid peroxidation within lung tissues of model rats having asthma, thus proving its protective role in airway inflammation [57]. At 400mg/kg dose, *Urtica dioica* ethanolic leaf extract exhibited potential analgesic activity owing to the presence of trimethyldecane, trimethylhexane, and methyltetradecane [58].

### 2.9 Anthelmintic Activity

The methanolic leaf extract was investigated on earthworms (*Pheretima posthuma*) for its significant anthelmintic activity. The results suggested an increase in the leaf extract's said activity at different doses of 25, 10, and 100mg/ml [32]. *Urtica dioica* extracts act against cutaneous leishmaniasis and kill the casual organism *Leishmania major* without harming macrophages in infected mice and also can boost immune responses in response to the disease [59].

### 2.10 Effect on BPH (Benign Prostatic Hyperplasia)

The nettle root's effect on BPH promoted by testosterone has been analyzed to evaluate the inhibitory potential for 5 alpha-reductase. A decrease in serum testosterone levels, urine output per week, and body weight/prostate ratio were observed. These studies strongly propose that BPH can be managed by *Urtica dioica* [60]. Bazoton uno, *Urtica dioica* root dry extract, with its anti-proliferative and antiphlogistic properties, reduces the irritative BPH symptoms and associated complications [61]. WS® 1541, a combined lipophilic fruit extract of *Sabal serrulata* and hydro-ethanolic root extracts from *Urtica dioica* is used to treat BPH and LUTS (Lower Urinary-tract Syndrome) and also exhibits anti-inflammatory and anti-proliferative properties in such cases [62].

### 2.11 Anticancer Activity

Using the XTT assay, an aqueous extract of *Urtica dioica* has been screened for cell cytotoxicity against MDA-231, MCF-7 cell lines of breast cancer. Plant root aqueous extract showed inhibition of globulin to its receptor, which is usually dose-dependent, and the direct inhibition of HeLa cell proliferation and blocking the interaction of the epidermal growth factor and its receptor [63]. The plant being anti-proliferative for breast cancer *in-vitro* is established by DNA fragmentation, increased proteins like calpastatin, calpain 1, caspase 3, Bcl-2, caspase 9, and Bax; all associated with apoptosis [64]. The plant as a nutraceutical food not only prevents but can be employed to treat different cancers, and different plant extracts not only prevent carcinogenesis but can kill the cancer cells and block metastasis by being anti-mutagenetic, cellular metabolic modulator, apoptosis inducer, and acting as an antioxidant [65]. A dose-dependent influence of *Urtica dioica* methanolic extract on colon cancer and hepatocarcinoma cell lines is shown through alteration in proliferation by variation in BAX and BCL2 expression [66]. IC<sub>50</sub> values for leaf extracts' antioxidant activity suggest *Urtica dioica* as a candidate for herbal medicine against various cancers [67].

### 2.12 Hypotensive Effect

*Urtica dioica* aqueous extract does not affect heart pressure but is undoubtedly involved in marked heart rate decrease, which causes positive effects on the heart [51]. However, if the aqueous plant extract is administered continuously (intravenously) at doses of 24 and 4mg/h, it lowers blood pressure by 38% and 15%, respectively [68].

### 2.13 Toxicological studies of *Urtica dioica*

It is solely non-lethal if the plant oil dose reaches about 12.8ml/kg [69]. In rabbits, 50% plant ethanolic extract was given orally for 10 days; initially, there was occasional diarrhea, body weight decreased by 4%, but later on, death occurred on prolonged treatment. Before death, these rabbits experienced an increase in respiration [38].

### 2.14 Agricultural, Agronomic, Economic and Ecological uses of *Urtica dioica*

In Spain, many ethnobotanical studies support the usage of *Urtica dioica* slurry in organic farming. The slurry is being used widely as fertilizer for cultivation in horticulture. Also, stinging nettle has been described as useful for industrial purposes [70]. Stinging nettle has tremendous applications in medicine, food/feed, and cosmetics [70]. Many studies have shown the agronomic value of stinging slurry, which is used as fertilizer, mostly in Spain [71]. Solid green manure obtained from nettle plant contained heavy B (Boron) concentrations, and low green manure C: N ratios had a drastic influence on the plant's production [72]. Earlier stinging nettles had broader use in many rural areas as nutritious food, primarily during spring, but nowadays, they are used mainly in the recipes of many dishes like they are mixed with potatoes, nutmeg, and fromage blanc to get nettle nouvelle [73]. *Urtica* plants can be cooked or boiled as fresh vegetables that supplement the soups or make vegetable salads or cooked as a herb [74]. Some evidence supports the usage of nettle leaves in milk coagulation to make fresh cheese [75]. Compared to wheat and barley flour, nettle flour contains more significant amounts of calcium, proteins, fats, ash, and crude fibres [74]. Herbal liquors are also made by nettles [76]. The oat and nettle extracts are often used as additives in fruit juice and beverages to enhance the nutritional content in drinks while ingesting raw leaves of nettle as juice or puree may cause allergic reactions [77].

### 2.15 Veterinary Uses

*Urtica* species show positive effects on productivity and health in cows and poultry as well. In some areas of Europe, there is a custom of providing fresh leaves of *Urtica* plant to poultry and pigs. However, some scientists claim that common nettles do not affect abdominal, breast, and thigh fat [78]. Further studies on broilers showed that providing 1-2% nettles and regular supplementation causes positive impacts on their carcass traits, biochemical aspects, and general performance [78]. In lactating cows, the milk production was preserved when the usual dry grass was replaced by nettles in their diets [79]. In these cows, the supply of nettle haylage and a regular diet has proven beneficial by changing their rumen's pH. In chickens, the alcoholic extract obtained from the nettle plant is known to increase the leucocyte count from 15400-17125 cells/mm<sup>3</sup> [80]. It can potentially induce higher disease resistance in broilers, thereby reducing economic losses. It is worth mentioning that the WHO has described "*Urtica*" as a

valuable herb for its potential uses in medicine [81]. The European Commission Directorate-General for Health and Food Safety believes *Urtica* species as a plant not having any immediate or delayed hazardous effects on animal or human health and potentially does no harm to the environment [82].

### Conclusion

*Urtica dioica* is cosmopolitan in distribution. Trichomes present on the plant stems and leaves are loaded with numerous chemicals, viz histamine, serotonin, and choline, causing a stinging feeling upon contact. Besides, the plant is reported to deliver several health aids for humans and cattle as well. Much evidence supports the importance of stinging nettles in treating numerous diseases like anaemia, eczema, gout, and the treatment of painful joints and muscles. The plant also possesses specific pharmacological characteristics such as analgesic, antiandrogenic, anti-inflammatory, anti-hyperglycemia, anticancer, and antiviral activities. *Urtica dioica* plant parts confer antimicrobial, antioxidant, and pro-health benefits. Nettles are commonly employed in making tea, juice, or consumed as a vegetable. Feed and fodder obtained from *Urtica* extracts show positive benefits for poultry and increase cattle productivity as well. Extensive studies on *Urtica dioica* are required to enlist all the possible benefits obtained from the plant. There is scope for developing new therapeutic drugs from *Urtica dioica* and the research that will pave the way for its commercial utilization

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