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A review of biochemical structures of Urtica dioica metabolites and their pharmaceutical effects

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ABSTRACT

Phytochemicals are chemical compounds produced by plants during the natural metabolic processes to resisting them fungi, bacteria and plant virus infections, and also consumption by insects and other animals. Phytochemicals is generally used to describe plant compounds that are under research and are often referred to as secondary metabolites. Some phytochemicals have been used as poisons and some others as traditional medicine and Nutrition. The aim of present study was to update a comprehensive review published on Urtica dioica which includes phytochemical and pharmacological synthesis. Urtica dioica or stinging nettle which is Urticaceae family herbaceous perennial, usually grows in temperate regions such as Europe, some places of Asia and western North Africa, New Zealand and North America. Its stem and leaves covered with hairs called trichomes which act like hypodermic needles and inject histamine and some other chemicals. Burning sensation during contact and contact urticaria (contact dermatitis) is visible because of it. A lot of bioactive phytochemical compounds have been identified in the methanolic extract of it.

1. Introduction

Based on our study, we can say that almost all geographical parts of the world use nettle in many different ways (Fig 1). The proliferation of human lymphocytes is stimulated by extracted water of the roots of Urtica dioica. Anti- inflammatory, antipyretic, antiasthamatic, antiulcer, anti- colitis, antiviral, anticancer, antibacterial, antimicrobial, antifungal, antiandrogenic, insecticide, immunomodulatory, genitourinary, hypo-cholesterolemic, hypoglycemic, cardiovascular effects, analgesic, natriuretic, hypotensive, hepatoprotective, antidiabetic, and anti-Alzheimer properties are evaluated [1-17]. As well as it is used for the treatment of various diseases such as arthritis, rheumatism (rheumatoid arthritis), menorrhagia, hematuria, jaundice, and nephritis [18]. Nine compounds have been isolated from Urtica dioica of China's Tibet Autonomous Region [19]. This plant contains many valuable chemical compounds such as flavonoids, proteins, and amino acids, saponins, phytosterols, and tannins [20]. The cytotoxic and genotoxic effects of nettle essential oil were evaluated and a considerable correlation has been observed between the essential oil concentration and the following: chromosomal aberrations, micronucleus abundance, apoptotic cells, necrotic cells, and dual nuclear cells [21]. This plant has been utilized in both medicine and food form in many countries especially in the Mediterranean region and it has been plenary analyzed the pharmacological, chemical, and botanical aspects [22].

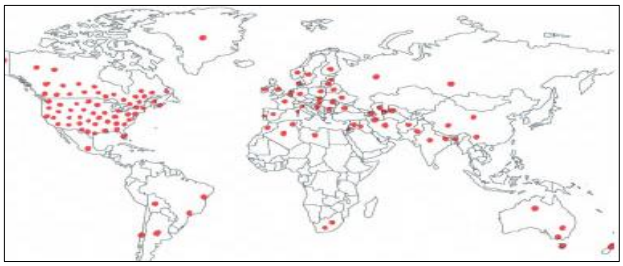

Fig. 1. Plant Distribution Map of nettle usage around the world

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2. Applications

The use of nettle in various industrial and pharmaceutical applications for health, agriculture, textile, food and dyeing purposes is significant and widespread (Table1). The leaves, stalks, and textile fiber extracts from Urtica dioica L. have been evaluated in order to consideration phenolic compositions. Large amounts of chlorogenic and 2-O-caffeoylmalic acid are in the leaves of two nettle samples. Flavonoids and Anthocyanins are present in nettle stalks. Phenolic metabolites in nettle extracts are important with regard to their biological properties (antioxidant and antiradical) [23]. Healing properties of bipod nettle Utrica dioica L. in the treatment of chronic human diseases as anemia, joints pain and skin diseases has been revealed. Number of antibacterial compounds in the leaf are greater than in other parts of plant, hereupon it is recommended to use leaves to extract them. [24].

Table 1: Applications & Industrial activities of Nettle:

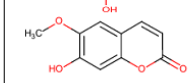
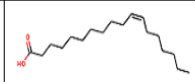
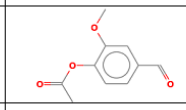
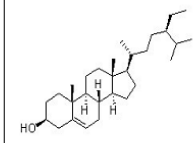
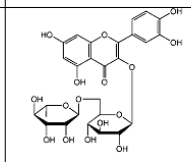
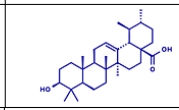
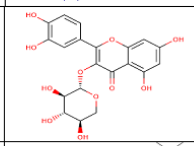
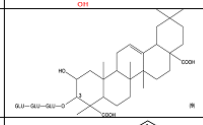
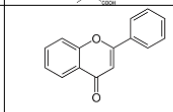
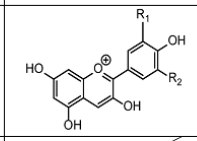
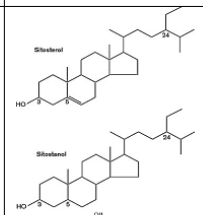
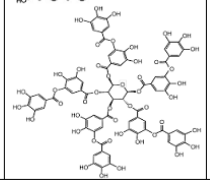
Cosmetics	Main groups of cosmetics: Preservatives, Fragrance, Musks, Phthalates, Plasticizers	[18, 22, 23, 25]
Fiber & Textiles	Fiber nettle is obtained from different sources of wild nettle (5% up to 17%, stalk dry matter)	[18, 22, 23]
Manure	Nettle exudates effect in the controlling of plants as green manure	[32]
Paint & Dyeing	Fig. 2	[18, 22]
Food	low-calorie source of essential nutrients: fatty acids, vitamins, minerals (Iron, Calcium), phytosterols, glycosides, amino acids, proteins	[20, 25, 32, 34]

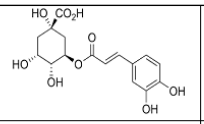
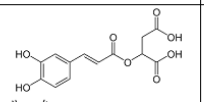
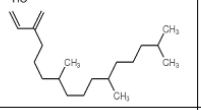
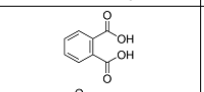
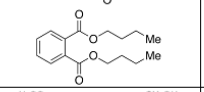
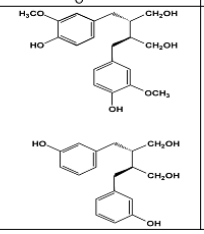
Fig. 2. Dyeing with nettles

3. Organic Chemical Analysis

Evaluation and analysis of extraction compounds in stalks, leaves, root, and textile fibers of Urtica dioica, revealed a lot of organic compounds with extensive medicinal properties (Table 2) [19-20]. The cultivation of nettle affects potentially favorable on the environment and its fiber quality has been demonstrated, hence it has a long history as a textile fiber. Dependent on the extraction method, stinging nettle contains a cellulose content around 86%. On the other hand, especially in nettle leaves, the presence of numerous active compounds, for instance, caffeic acid derivatives, ceramides, nine forms of carotenoids, essential fatty acids, vitamins, minerals, phytosterols, glycosides and proteins, have been confirmed [25]. The inhibition of pancreatic α- amylase is an important strategy for the treatment of diabetes. Some Plant may be used as therapeutic because of containing different chemical constituents with the potential for inhibition of α-amylase. Different concentrations of leaf aqueous extracts of Urtica dioica and Juglans regia Linn have been tested for α-amylase inhibition.

Table 2: Isolated Organic Compounds from the whole herb of Urtica Dioica

Entry	Chemical material	Chemical structure	Phytochemical Status	Pharmacology
1	p-Hydroxylbenzalcohol		Phenols	Anti-inflammatory, Obesity, Brain system [44]
2	Scopoletin		Coumarin	Anti-inflammatory, Anti-cancer, Anti diabetic [45]
3	Erucic acid		Monounsaturated ω9 (omega-9) fatty acid	Inhibit elastase and thrombin, Neuropharmacological [46]
4	trans-Ferulic acid		Phenolic compound	Antioxidant, Hepatic fibrosis, antibacterial [47]
5	beta-Sitosterol		Phytosterols	Antimicrobial, Anti-inflammatory, Anticancer, Antifertility, Angiogenic, Antioxidant, Immunomodulatory, Antidiabetic, Antinociceptive [48]
6	Rutin		Bioflavonoid pigment	Antibacterial, Antiprotozoal, Antitumor, Antiinflammatory, Antiallergic, Antiviral, Hypolipidaemic, Antiplatelet, Antispasmodic, Antihypertensive [49]
7	Ursolic acid		Pentacyclic triterpene acid	Antioxidant, Antiinflammatory, Antibacterial, Antifungal [50]
8	Quercetin		Plant pigment (Flavonoid)	Antioxidant, Anti-inflammatory, Reduce swelling, Kill cancer cells, Control blood sugar, Prevent heart disease. [51]
9	Saponin		Triterpene glycosides	Soaps, Medicinal, Fire extinguishers, Dietary supplements, Synthesis of steroids [52]
10	Flavone		Flavonoids	Antioxidant, Anti-proliferative, Anti-tumor, Anti-microbial, Anti-inflammatory Anti-cancer, Anti-cardiovascular disease and Neurodegenerative disorders [53]
11	Anthocyanins		Natural phenolic pigments	Antioxidant, Antiinflammatory, Prevention of Antichronic diseases, Cardiovascular disease (CVD), Anticancers, Anti -eye diseases, Antiviral [54]
12	Phytosterols		Plant sterol and stanol esters	Lower plasma cholesterol, Anti-inflammatory, Antioxidant, Antidiabetic, Antiatherosclerotic [55]
13	Tannins		Astringent, polyphenolic biomolecules	Astringent, Hemostatic, Antiseptic, Antihemorrhagic, Sore mouth, Bronchitis, Burns, Scars of the skin, Wounds, Anti-diarrhea, Antioxidants, Anti-cancer, Cardiovascular disease [56]

14	Chlorogenic acid		Cinnamate ester	Antidiabetic, DNA protective, Neuroprotective, Anti-hepatitis B virus (HBV), Antioxidant, Anti-carcinogenesis [57]
15	2-O-Caffeoylmalic acid		Hydroxycinnamic acid ester	Cardiovascular diseases, Antioxidant, Anti-infections [58]
16	Neophytadiene		Diterpene	Good analgesic, Antipyretic, Anti-inflammatory, Antimicrobial, Antioxidant [59]
17	Phthalic acid		Natural hydrophilic substance	Dyes, Perfumes, Saccharin, Phthalates, Cosmetics [60]
18	Dibutyl phthalate		Natural Lipophilic substance	Not biologically active [61]
19	Lignans		Secondary plant metabolites (Polyphenol)	Antioxidant, Antiestrogenic, Anticancer, Anti-cardiovascular diseases Antimicrobial, Anti-inflammatory, Immunosuppressive [62]

Both plant extracts have been shown time and concentration-dependent inhibition of α-amylase and these plant extracts could provide by the successful use of plant chemicals as drug targets [26]. Qualitative and quantitative analyses indicated that phenolic acids (5-O-caffeoylquinic acid as dominant) and Flavonol glycosides (rutin, isoquercitrin, and kaempferol 3-O-glucoside) are present in the aerial parts, while lignans (secoisolariciresinol, 9,9'-bisacetyl-neo-olivil and their glucosides) were detected in the root. Selective inhibition toward cyclooxygenase and lipoxygenase branches in human platelets has been revealed by Herb and root extracts. Herb extracts were more specific toward inhibition of 12-lipoxygenase pathway while root extracts were better at inhibiting thromboxane production [27]. On the other studying, the evaluation of nettle and Probiotic effects on performance and serum composition of broiler chickens have been discussed [28].

4. Nomenclature

The nomenclatures which is used for Urtica dioica is shown in the Table 3.

Table 3: Nomenclature of Urtica dioica

Scientific Name	Common Name	Nationality of Nomenclature
Urtica dioica	(Gezik)	Kurdish
	(Gazaneh)	Persian
	(Qaraz Kabeer) (Alhareeq) (Alqariz)	Arabic
	Common Nettle	Scattered around the world
	Nettle-Leaf	
	Stinging Nettl	
	Burn-Nettle	

5. Spectral identification

In the other researches, some extraction method has been done on entire nettle stalks and/or unrated decorticated fiber of a selected fiber nettle clone, for example, chemical extraction, water retting, microbiological and enzymatic methods. In the following, morphological and mechanical properties and chemical composition have been determined on fiber samples [29]. The antibacterial and antioxidant activities of ethyl acetate extract of nettle on all bacterial isolates has been studied, also phytochemical screening and determination of total phenolic content have been investigated [30]. In vitro, a nettle extract shows inhibition of various inflammatory occurrences that make the symptoms of seasonal allergies [31]. According to the determination of proximate composition, mineral, amino acid, and vitamin contents, results have been shown that processed nettle can supply 90%–100% of vitamin A (including vitamin A as β-carotene) and is a good source of dietary iron, calcium, and protein and it has been recommended fresh or processed nettle as a high protein, low-calorie source of essential nutrients, minerals, and vitamins particularly in vegetarian, diabetic, or other specialized diets and it has hypoglycemic and hypolipidemic activity in type 2 diabetic model rats. This may be due to the histological and functional improvement of β-cells with the consequence of improved insulinemic status [32]. The main identified components of extracts in root, stem, and leaf were evaluated by FTIR and gas chromatography (GC). (Table 4 & Fig. 3) [24, 33].

Table 4: FTIR & GC-MS analysis of a sample U. dioica
Oxime-methoxy-phenyl
2,6,Nonadienal, 3, 7-dimethyl
1, 2, 3-Butanetriol
Silane,triethyl(2phenylethoxy)
Benzofuran,2,3-dihydro
2,5,5,8a-tetramethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-ol
2H-Indeno[1,2-b]furan-2-one, 3,3a, 4,5,6,7,8, 8b-octahydro-8,8-dimet
1-Dodecanamine, N,N-dimethyl
2(3H)-Naphthalenone,4,4a,5,6,7,8-hexahydro-1-methoxy
D-Fructose,diethylmercaptal,pentaacetate
[1,1-Bicyclopropyl-2-octanoic acid2hexyl- methylester
Estra-1,3,5(10)-trien-17B-ol
Cyclopropaneoctanoic acid, 2-[2-pentylcycloproyl)methyl]-methyl
1-Hydroxy-2-(2,3,4,6-tetra-O-acetyl-beta-d-glucopyranosyl)-9H-xanthe
Ethyl iso- allochlate
Neophytadiene
Phthalic acid
Dibutyl phthalate
Bis (2-ethyl hexyl) Maleate
1,2-Benzenocli carboxylic acid

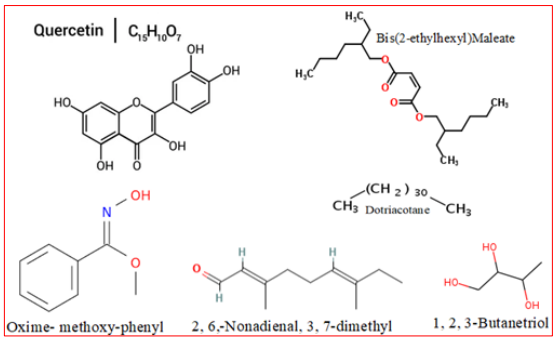


Fig. 3. Chemical Structure & Functional Groups

A high level of crude protein, crude fiber, crude fat, total ash, carbohydrate, bioactive phenolic compounds such as

gallic acid, carotenoid, and tannin has found in Stinging nettle, and energy value of about (307 kcal/100 g) as compared to wheat and barley flours [34]. Aqueous extract of nettle showed a strong glucose-lowering effect and the results indicate that it has a significant antihyperglycemic effect in the OGTT model. This effect may be caused in part by the reduction of intestinal glucose absorption [35]. Hypotensive action of U. dioica indicates a direct effect at a low dose, on the cardiovascular system and diuretic and natriuretic effects demonstrate an action on the renal function. The plant's extract seems to have a toxic effect at the higher dose [36]. The evaluation of in vivo and in vitro pharmacological actions of this plant has been done on eighteen local domestic rabbits in Erbil. For in vitro studies the effect of the plant extract on isolated pulmonary arteries and isolated urinary bladder smooth muscle and for in vivo studies, the effect of the extract on renal function has been evaluated. A significant increase in urine volume and urinary Na^+ excretion without significant changes in K^+ excretion rates and a profound drop in blood pressure and heart rate have been observed [37]. Dose-dependent antioxidant and anti-proliferative effects on MCF-7 cells has been described by Akhavan-Niaki and et al. and urtica dioica as a potential chemotherapeutic agent for breast cancer has been demonstrated [38]. Aqueous extract of Urtica dioica has been affected an inhibition on adenosine deaminase activity of prostate and it has beneficial effect in prostate cancer [39]. The antioxidant, hepatoprotective, and anthelmintic activities of methanol extract of leaves of Urtica dioica L. (MEUD) have been investigated and as well as determination of total antioxidant activity, DPPH radical scavenging activity and nitric oxide scavenging activity have been evaluated. The results of in vitro antioxidant activity indicated the extract activity comparable to standard antioxidants like α-tocopherol, ascorbic acid and BHA (Butylated hydroxyanisole). By using adult Indian earth worms (Pheretima posthuma), anthelmintic activity of the methanol extract has been explored. [40]. In the other one research, aromatase inhibition of methanolic extracts of stinging nettle roots has been investigated after appropriate chromatographic separation [41]. Formic acid, histamine, and serotonin are the known pain-inducing agents in the stinging hairs of U. dioica and also oxalic acid and tartaric acid in U. thunbergiana has been identified [42]. Additionally, it can be mentioned three smooth-muscle stimulating compounds, acetylcholine (ACh), histamine, and 5-hydroxytryptamine (5-HT) which have been detected in the sting of the nettle [43].

6. Classification of Urtica dioica

We could characterize and classify Urtica dioica according to the taxonomy of it has been proposed by Henning et al. (Table 5) [63].

Table 5: Classification & Reasons

Taxonomic Level	Classification	Reasoning Behind Classification
Domain	**Eukarya**	Stinging nettles are classified as eukarya because they contain a true nucleus and membrane bound organelles.
Kingdom	**Plantae**	They are in the kingdom plantae because they are photosynthetic, and eukaryotic organism.
Subkingdom	**Tracheobionta**	Stinging nettles are classified as tracheobionta because they contain vascular tissue such as xylem and phloem.
Phylum	**Magnoliophyta**	They are in the phylum magnoliophyta, because stinging nettles are a flowering plant.
Class	**Magnoliopsida**	Stinging nettles fall into the class magnoliopsida because they are dicotyledons meaning that the plants have: two cotyledons, net-like veins, vascular tissue arranged in a ring, a taproot (main root) with smaller roots branching off of it.
Order	**Urticales**	Stinging nettles are grouped into the order urticales because they have alternating leaves.
Family	**Urticaceae**	They are in the urticaceae family because stinging nettles are members of the nettle family, in which the majority of the members have stinging hairs on their leaves and stems.
Genus	**Urtica**	Stinging nettles fall into the genus Urtica because the plants are true nettles.
Species	**Urtica dioica**	The scientific species name of stinging nettles is Urtica dioica. In Latin, Urtica means "burn" and is a reference to the burning sensation that occurs when skin is brushed against the fine hairs of the plant. Dioica is Latin for "two houses" and refers to stinging nettles having plants of both male and female genders in reference to their flowers. Also, the English word nettle is derived from the Anglo-Saxon word "noedl" which means "needle".

7. Taxonomical features

Urtica dioica is a perennial plant, and grows to 1 m at a fast rate (The maximum typical height of this plant species ranges from 2 to 4 meters.). The plant can spread vigorously and is very difficult to eradicate, and its common name is Stinging Nettle. Nettles are in leaf from March to November, in flower from May to October, and the seeds ripen from June to October, and their habitats are Woodland Garden Sunny Edge and Shady Edge [22]. The plant is well recognized for its stinging hairs, green leaves are 3-15 cm long and are coated with stinging hairs, causing irritation to the skin (Fig. 4-Fig. 8). Flowers are either male or female, thus only one sex is to be found on any one plant and the stems are often branched from the base and have long stinging hairs as well as short. The root pattern is fibrous dividing into a large number of fine roots, their edible parts are the young leaves and the seeds [4].

8. Conclusion

Even in today's world, despite rapid advances in the production of chemical compounds and drugs, attention to local plants and their use for a variety of purposes is increasing. Therefore, it makes researchers pay their efforts to this aspect of scientific research mandatory. So, consideration of promising natural sources, standardization, and clinical trials of pharmacological potential for the development of novel strategies, to cure fatal maladies is recommended. Drawing people's attention to medicinal plants, in a scientific way, lead to wiping up harmful consequences and reducing unwanted side effects of herbal treatment, and also establishing their eco-friendly relationship with the environment. A perfect packing of several chemical compounds and nutrients makes nettle responsible for bioactivities and medicinal properties and can be stated as a suitable herb candidate for more explores.

Fig. 4. Urtica dioica L. (Stinging Nettle)

Fig. 5. Urtica dioica (Leaves)

Fig. 6. Urtica dioica (Flowers)

Fig. 7. Urtica dioica (Roots)

Fig. 8. Urtica dioica (Trichomes)

Acknowledgements

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