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EXPLORING THE LOCAL ANESTHETIC POTENTIAL OF *URTICA DIOICA*: PHYTOCHEMICAL BASIS AND PHARMACOLOGICAL INSIGHTS

Dr. Gunjan Jain*[1], Dr. Neha Mishra[2]

[1]PG Scholar, Department of Shalya Tantra, Pt. Khushilal Sharma Govt. Govt. Ayurvedic College and Hospital, Bhopal.

[2]Reader, Department of Shalya Tantra, Pt. Khushilal Sharma Govt. Ayurvedic College and Hospital, Bhopal.

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***Corresponding Author**
Dr. Gunjan Jain
PG Scholar, Department of Shalya Tantra, Pt. Khushilal Sharma Govt. Govt. Ayurvedic College and Hospital, Bhopal.

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ABSTRACT

Urtica dioica (stinging nettle) is a medicinal plant widely recognized for its diverse pharmacological properties. While its anti-inflammatory, antioxidant, and antimicrobial effects are well documented, emerging evidence suggests a potential **local anesthetic role** mediated by its bioactive constituents. This review provides a formal synthesis of the phytochemical composition of *Urtica dioica* and critically emphasizes its possible mechanisms and applications as a local anesthetic agent. The discussion integrates traditional usage with modern pharmacological insights, highlighting future research directions.

KEYWORDS: Urtica Dioica, Local Anesthetic Effect, Stinging Nettle.

INTRODUCTION

Medicinal plants have historically served as a foundation for therapeutic discovery. *Urtica dioica*, belonging to the family Urticaceae, has been extensively utilized in traditional medicine systems across Europe and Asia. Despite its reputation for causing transient irritation upon contact, paradoxically, extracts of the plant have been reported to exert **analgesic and desensitizing effects**, suggesting potential applications in local anesthesia.

Local anesthetics function by inhibiting nerve impulse conduction, primarily through the blockade of voltage-gated sodium channels. Natural compounds capable of modulating these pathways are of increasing scientific interest. In this context, *Urtica dioica* represents a promising, yet underexplored, candidate.

Phytochemical Composition

The pharmacological activity of *Urtica dioica* is attributed to its rich array of phytochemicals, including.

- **Flavonoids** (e.g., quercetin, kaempferol)
- **Phenolic acids**
- **Terpenoids**
- **Sterols**
- **Alkaloids and lectins**
- **Vitamins and minerals**

Additionally, the plant's stinging hairs contain bioactive substances such as.

- Histamine
- Acetylcholine
- Serotonin
- Formic acid

These compounds contribute not only to its irritant properties but also to its **neuromodulatory and analgesic effects**, which are relevant to local anesthesia.

3. Mechanisms Underlying Local Anesthetic Effects

3.1 Modulation of Nerve Transmission

Certain phytochemicals in *Urtica dioica*, particularly flavonoids and phenolic compounds, have demonstrated the ability to influence neuronal excitability. These compounds may:

- Inhibit **voltage-gated sodium channels**
- Reduce **action potential propagation**
- Decrease peripheral nerve sensitivity

Such actions are analogous to the mechanism of conventional local anesthetics like lidocaine.

3.2 Anti-inflammatory Contribution to Analgesia

Inflammation sensitizes nociceptors, thereby enhancing pain perception. The strong **anti-inflammatory activity** of *Urtica dioica* contributes indirectly to local anesthetic effects by:

- Suppressing pro-inflammatory cytokines
- Reducing tissue edema
- Decreasing nociceptor activation

This dual mechanism—direct neural inhibition and indirect anti-inflammatory action—enhances its analgesic potential.

3.3 Interaction with Neurotransmitters

The presence of histamine, serotonin, and acetylcholine suggests that *Urtica dioica* may influence.

- Peripheral pain signaling pathways
- Neurotransmitter release and receptor sensitivity

Repeated or controlled exposure may lead to **desensitization of sensory neurons**, producing a localized numbing effect.

4. Experimental Evidence

Preclinical studies have demonstrated that extracts of *Urtica dioica* exhibit:

- **Analgesic activity** in animal models
- Reduction in pain response to thermal and chemical stimuli
- Potential inhibition of nociceptive pathways

However, direct studies specifically evaluating **local anesthetic efficacy** remain limited. Most evidence is derived from broader analgesic and anti-inflammatory investigations.

5. Therapeutic Implications

5.1 Topical Applications

Extracts of *Urtica dioica* may be formulated into:

- Creams
- Gels
- Ointments

These formulations could potentially be used for.

- Minor surgical procedures
- Dermatological conditions

- Musculoskeletal pain relief

Table 1: Geographical distribution, traditional uses, and pharmacology of *Urtica* species.

No.	Species	Geographical distribution	Traditional uses	Pharmacological activities
1	*Urtica andicola* Wedd.	Turkey	Skin rashes, arthritis, fungal infections	—
2	*Urtica angustifolia* Fisch. ex Hornem.	China, Japan, Korea, Mongolia, Siberia	None known	Antifatigue
3	*Urtica ardens* Link	Bhutan, India, Nepal, Sikkim	Exorcism, jaundice, postcalving care, sprains, bones fracture, hematuria, neck sore, yolk sore	—
4	*Urtica aspera* Petrie	New Zealand	Stomach diseases, snakebites, inflammation, rheumatoid arthritis, hyperplasia, fungal infections	—
5	*Urtica atrichocaulis* (Hand.-Mazz.) C.J. Chen	China, Japan, Korea, Himalayas, Pakistan	Rheumatoid arthritis, inflammatory, antioxidant, immune-modulatory	—
6	*Urtica atrovirens* Req. ex Loisel	France, Italy, Spain	Antihyperglycemic, antioxidant, hepatic protective, antiviral, arthritis	—
7	*Urtica australis* Hook.f.	New Zealand	Skin diseases, diabetes, eczema, fungal infections, arthritis	—
8	*Urtica ballotifolia* Wedd.	Colombia, Ecuador	—	—
9	*Urtica berteroana* Phil	Chile, Bolivia, Argentina, Colombia	—	—

10	*Urtica buchtienii* Ross	Chile, Argentina	—	—
11	*Urtica cannabina* L.	Russia, Sweden, Netherlands, China, Western Asia from Siberia to Iran	—	Anti-inflammatory
12	*Urtica chamaedryoides* Pursh	United States, Mexico	—	—
13	*Urtica circularis* Sorarú	Brazil, Argentina, Paraguay, Uruguay	—	Antioxidant, anti-inflammatory
14	*Urtica deltoidea* Sw.	New Zealand	Arthritis, inflammation, antiulcer, anticancer, antimicrobial activities	—
15	*Urtica dentate* Hand.-Mazz	North America	Kidney problems, rheumatoid arthritis, kidney calculi	Antiarthritis, antiurolithiatic
16	*Urtica dioica* L.	United States, New Zealand, Turkey, Europe, Asia, North America	Injuries to reduce swelling, diuretic, flu, diabetes disease, losing weight, cold, cancers, anemic conditions, libido, induce menstruation, stomach-ache, renal and pulmonary diseases	Antiviral, antimicrobial, antioxidant, anti-inflammatory antiaging, cytotoxic/anticancer Effect on benign prostatic hyperplasia, antidiabetic, antiendometriosis, nephroprotective
17	*Urtica echinata* Benth	Bolivia, Peru, Argentina, Ecuador	—	—
18	*Urtica ferox* Blanco	New Zealand, Australia	Skin problems, hyperglycemic, antiviral, diuretic, hypotensive, antiaggregate	—
19	*Urtica fissa* E. Pritz	China, Taiwan, Egypt, Vietnam	Rheumatoid arthritis	—
20	*Urtica flabellata* Kunth	Bolivia, Peru, Ecuador, Chile, Colombia, Turkey	Skin rashes, arthritis, fungal infections	—
21	*Urtica galeopsifolia* J. Jacq. ex Blume	Russia, Ukraine, Belarus	Renal ailments, asthma, anemia, blood purification	—
22	*Urtica gracilenta* Greene		Kidney diseases, diabetes, fungal infections	—
23	*Urtica glomeruliflora* Steud.	Chile		—
24	*Urtica haussknechtii* Boiss.	Turkey		—
25	*Urtica hyperborea* Jacq. exWedd.	Nepal, India, China	Skin rashes, arthritis, fungal infections	Antioxidant
26	*Urtica incana* Blume	Peru	Skin rashes, arthritis, fungal infections	—
27	*Urtica kioviensis* Rogow.	Europe, Israel, Russia	Arthritis, hepatic protective, antiviral	—

28	*Urtica lalibertadensis* Weigend	Peru	Skin rashes, arthritis, fungal infections	—
29	*Urtica laetevirens* Maxim.	China, Japan, Korea		Anticancer
30	*Urtica leptophylla* Kunth	Costa Rica, Colombia, Peru, Bolivia, Ecuador	Skin rashes, arthritis, fungal infections	—
31	*Urtica lilloi* (Hauman) Geltman	Argentina		—
32	*Urtica longispica* Killip	Ecuador, Peru, Colombia	Cough, eczema, gout, *urticaria*, allergic rhinitis, rheumatoid arthritis	—
33	*Urtica macbridei* Killip	Ecuador, Peru		—
34	*Urtica magellanica* Juss. ex Poir.	Chile, Peru, Bolivia, Argentina, Ecuador	Allergy, arthritis	—
35	*Urtica mairei* H. Lév.	China, India, Bhutan, Himalaya, Myanmar	Kidney pain. Its extract and paste kidney diseases, diabetes, fungal infections, inflammation, arthritis	Antiprotatic hyperplasia
36	*Urtica masafuerae* Phil.	Chile		—
37	*Urtica massaica* Mildbr.	Africa	Skin rashes, malaria, eczema, skin rashes, dermatitis, diuretic	—
38	*Urtica membranacea* Poir. ex Savigny	Israeli, Europe, Algeria	—	Antioxidant, anti-inflammatory
39	*Urtica mexicana* Liebm	Mexico, Guatemala	—	—
40	*Urtica mollis* Steud.	Peru, Chile, Argentina	—	—
41	*Urtica morifolia* Poir.	Europe	—	—
42	*Urtica orizabae* Liebm.	Mexico, United States, Cuba	—	—
43	*Urtica parviflora* Roxb.	Nepal, India, United States, Western China, Bhutan, Himalaya	Arthritis, tumor, astringent, diuretic, inflammatory	Nephroprotective, antidiabetic, antioxidant
44	*Urtica pilulifera* L.	Tunisia, Israel, Cyprus, Costa Rica, Turkey, Palestine	Skin and prostate disorders, rheumatoid arthritis, diabetes, skin treatment, inflammation, arthritis, internal bleeding, anemia, excessive menstruation, hemorrhoids, rheumatism, hay fever, kidney problems, pain, skin problems, abdominal pain, internal diseases, antiasthmatic, antitumor, astringent, diuretic, galactagogue, depurative,	Antidiabetic

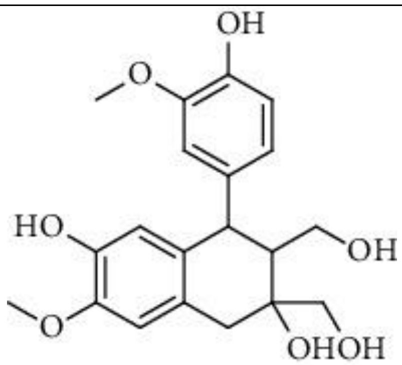
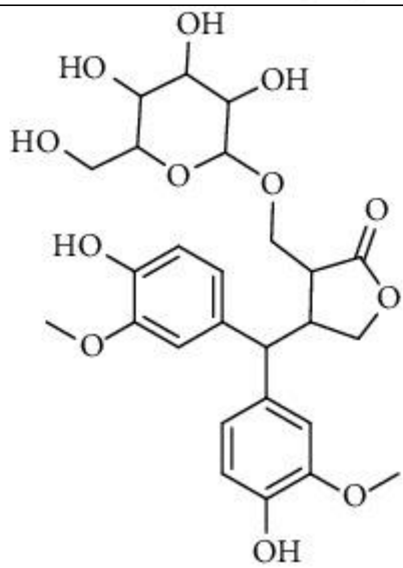
			antihyperglycemic, antidandruff	
45	*Urtica platyphylla* Wedd.	Japan, Russia	—	—
46	*Urtica praetermissa* V.W. Steinm.	Mexico	—	—
47	*Urtica pubescens* Ledeb.	Mexico	—	—
48	*Urtica rupestris* Guss.	Italy	—	—
49	*Urtica sondenii* (Simmons) Avrorin ex Geltman	Canada	—	—
50	*Urtica spiralis* Blume	Mexico	—	—
51	*Urtica stachyoides*Webb & Benth.	Spain, Mexico	—	—
52	*Urtica taiwaniana* S.S. Ying	Taiwan	—	—
53	*Urtica thunbergiana* Siebold & Zucc.	Japan, Korea, China	—	Antiaging
54	*Urtica triangularis* Hand.-Mazz.	China	—	—
55	*Urtica trichantha* (Wedd.) Acevedo & Navas	Chile, Bolivia, Peru, Japan, China	—	—
56	*Urtica urens* L.	Unite States, Mexico, Europe, Israel, New Zealand	Blood depurative, antihypoglycemic, antioxidant, hepatic protective, antiviral, diuretic, hypotensive, antiaggregate, kidney problems	Antioxidant, anti-inflammatory

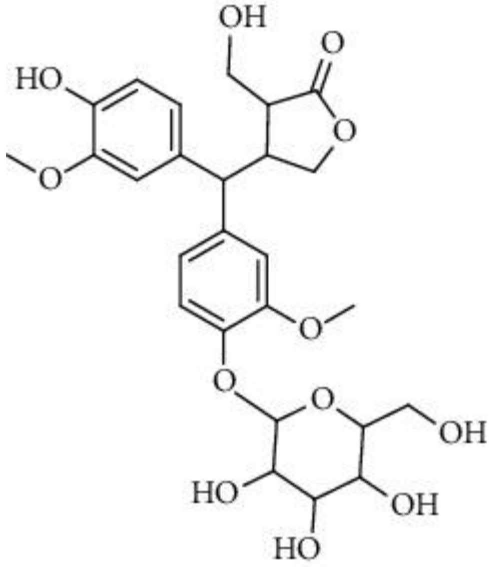
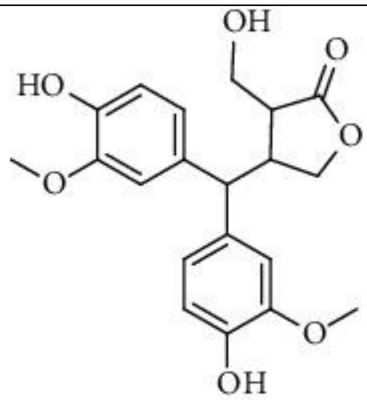
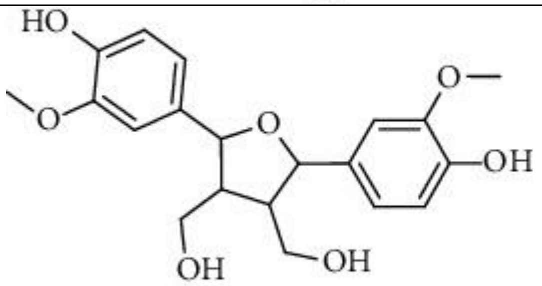
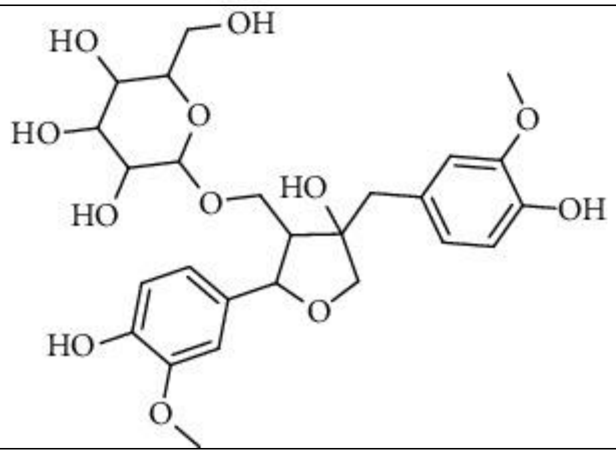
The widely distributed weedy species *Urtica dioica* is recognized as an ecological keystone species and, therefore, plays a crucial role in maintaining biodiversity within ecosystems. The genus *Urtica* exhibits a notable prevalence of island endemism, with several species confined to specific geographic regions. These include *Urtica dioica* subsp. *cypria* in Cyprus; *Urtica atrovirens* in Corsica and Sardinia; *Urtica rupestris* in Sicily; *Urtica stachyoides* in the Canary Islands; *Urtica portosanctana* in Madeira; *Urtica bianorii* in Mallorca; *Urtica domingensis* in Hispaniola; *Urtica glomerulaeflora* in the Juan Fernández Islands; *Urtica grandidentata* in Indonesia; *Urtica taiwaniana* in Taiwan; *Urtica papuana* in Papua New Guinea; and *Urtica perconfusa* in New Zealand. The occurrence of such geographically restricted species highlights island colonization as a distinctive evolutionary characteristic of this genus among flowering plants.

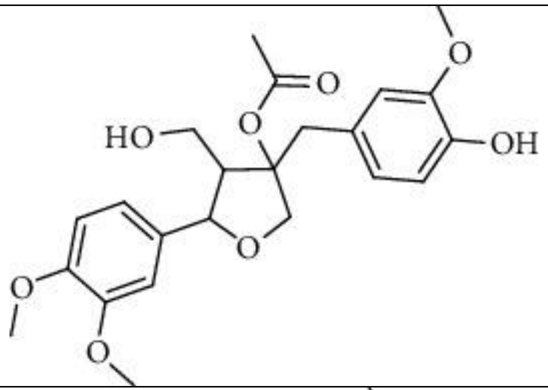
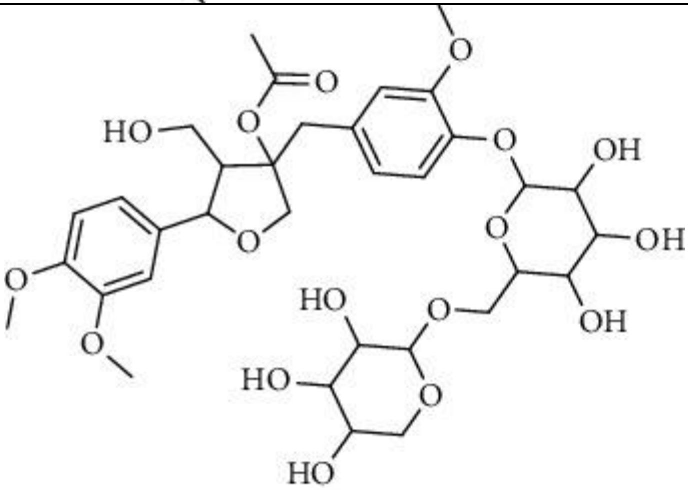
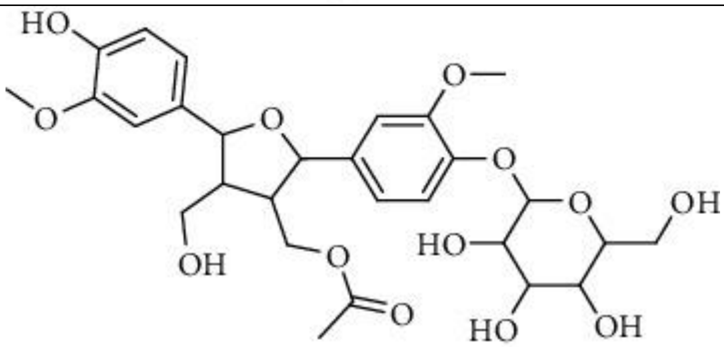
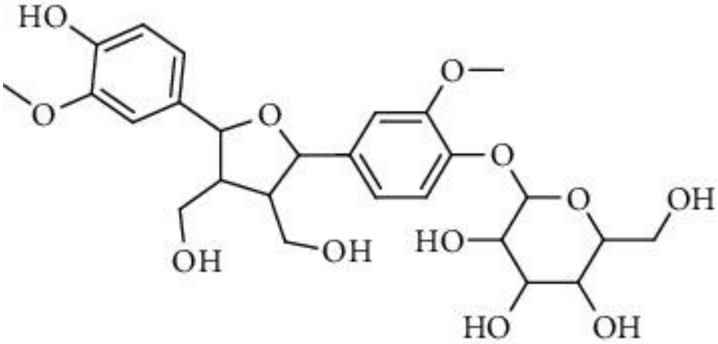
Phytoconstituents

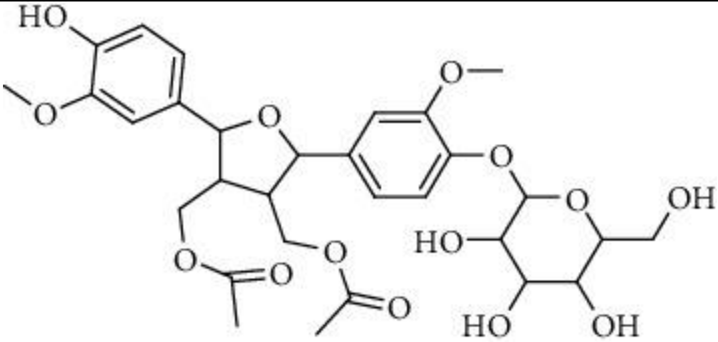
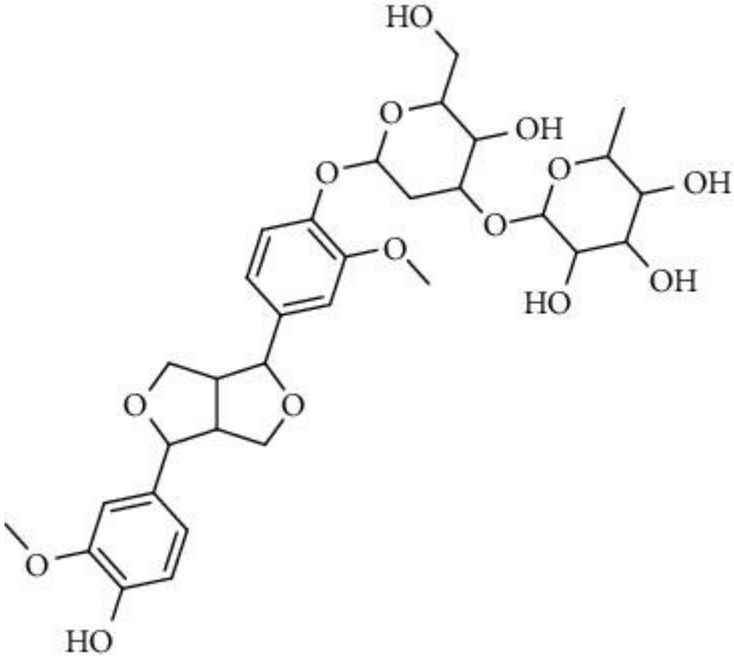
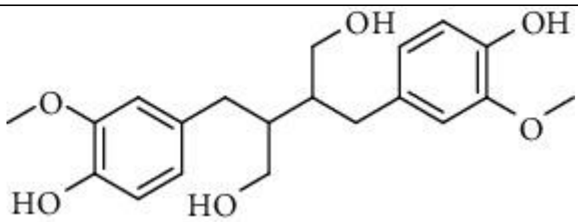
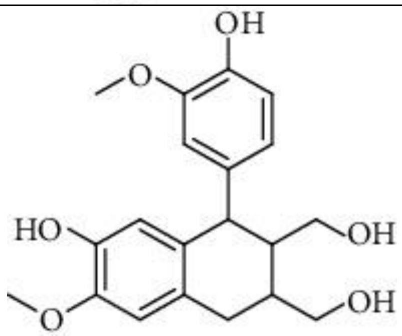
Phytochemicals are secondary metabolites synthesized by plants either in response to biotic stress, such as pathogenic attack, or as byproducts of intrinsic metabolic processes. Despite their origin, these compounds are known to exert a wide range of beneficial biological effects. The bioactive chemical composition of *Urtica* species, particularly *Urtica dioica*, comprises approximately fifty identified compounds distributed across both lipophilic and hydrophilic fractions, with well-characterized chemical structures. Although only a limited number of *Urtica* species have been extensively investigated for their phytochemical profiles, existing studies have reported the presence of diverse classes of compounds, including sterols, triterpenes, coumarins, phenolic compounds, lignans, ceramides, and fatty acids, along with several minor constituents. The distribution and concentration of these phytochemicals vary significantly across different plant organs, as documented in relevant studies.

Table 2: Lignans extracted from *Urtica*.

Sr. no.	Compound name	Structural
1.	Cycloolivil; 9′-O-b-d-Glucopyranoside	
2.	4-[Bis(3, 4-dihydroxyphenyl) methyl]dihydro-3-(hydroxymethyl)-2(3H)-furanone; (8R*, 8′R*)-form,3′, 4-Di-Me ether, 7-O-b-D-glucopyranoside	

3.	4-[Bis(3, 4-dihydroxyphenyl) methyl]dihydro-3-(hydroxymethyl)-2(3H)-furanone; (8R*, 8′R*)-form,3′, 4-Di-Me ether, 4′-O-b-D-glucopyranoside	
4.	4-[Bis(3, 4-dihydroxyphenyl) methyl]dihydro-3-(hydroxymethyl)-2(3H)-furanone; (8R*, 8′R*)-form,3′, 4-Di-Me ether	
5.	Neoolivil	
6.	3, 3′, 4, 4′, 8′, 9-Hexahydroxy-7, 9′-epoxylignan; (7S,8R, 8′S)-form, 3, 3′-Di-Me ether, 9-O-β-D-glucopyranoside	

7.	3, 3′, 4, 4′, 8′, 9-Hexahydroxy-7, 9′-epoxylignan; (7S,8R,8′S)-form, 3, 3′, 4-Tri-Me ether, 8′-Ac	
8.	3, 3′, 4, 4′, 8′, 9-Hexahydroxy-7, 9′-epoxylignan; (7S,8R,8′S)-form, 3, 3′, 4-Tri-Me ether, 8′-Ac, 4′-O-[aarabinopyranosyl-(1 ⟶ 6)-bd-glucopyranoside]	
9.	Neoolivil; 9-Ac, 4-*O*-b-D-glucopyranoside	
10.	Neoolivil; 4-*O*-b-D-glucopyranoside	

11.	Neoolivil; 9, 9′-Di-Ac, 4-*O*-b-D-glucopyranoside	
12.	Pinoresinol; (+)-form, 4-O-[a-L-rhamnopyranosyl-(1 ⟶ 2)-b-d-glucopyranoside]	
13.	Secoisolariciresinol	
14.	Isolariciresinol	

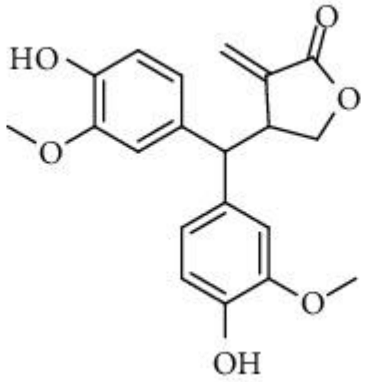
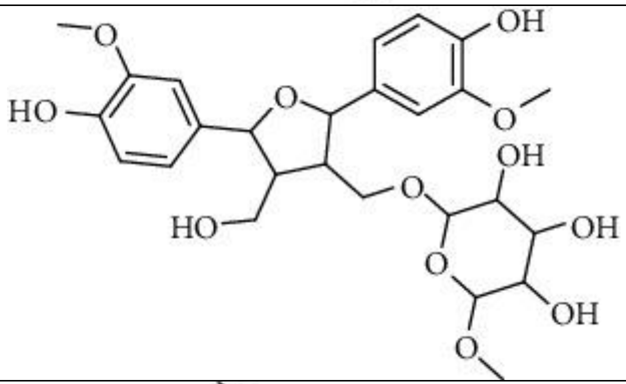
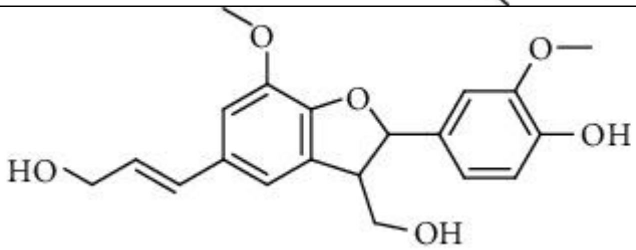
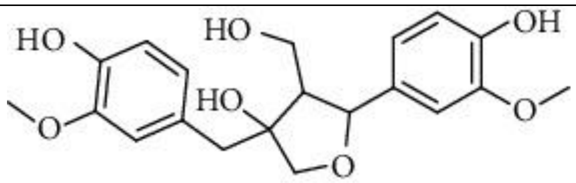
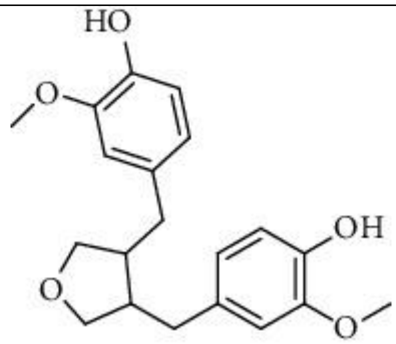
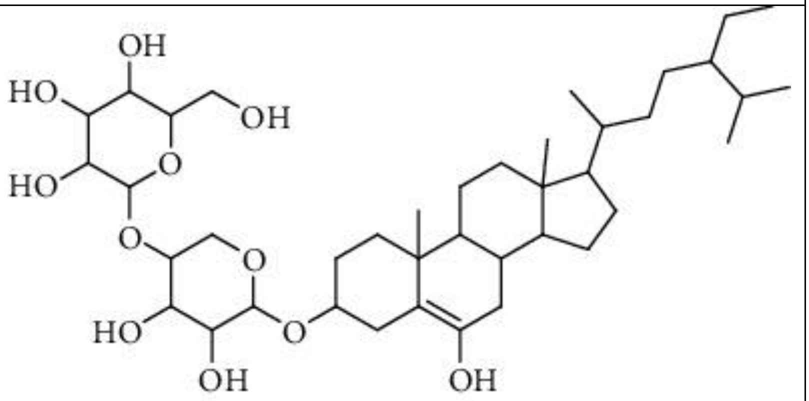
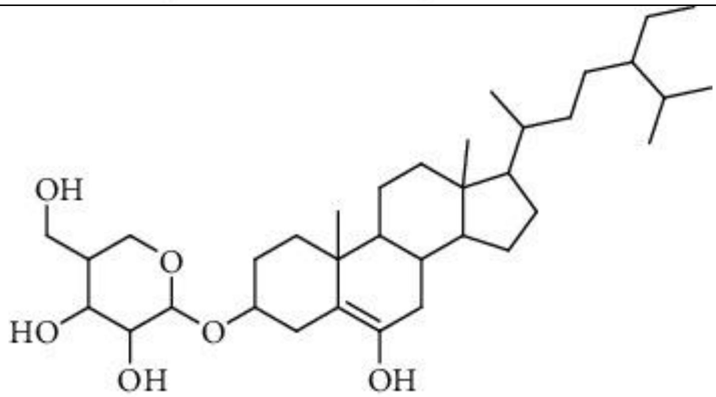
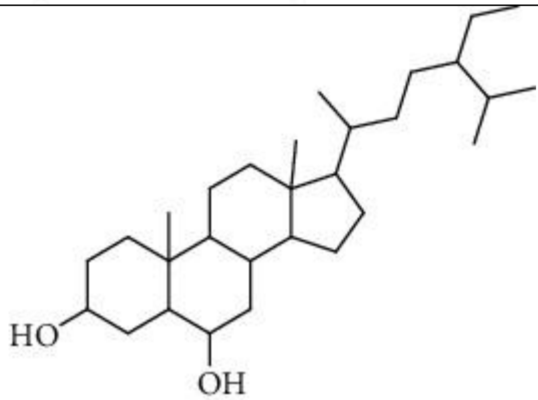
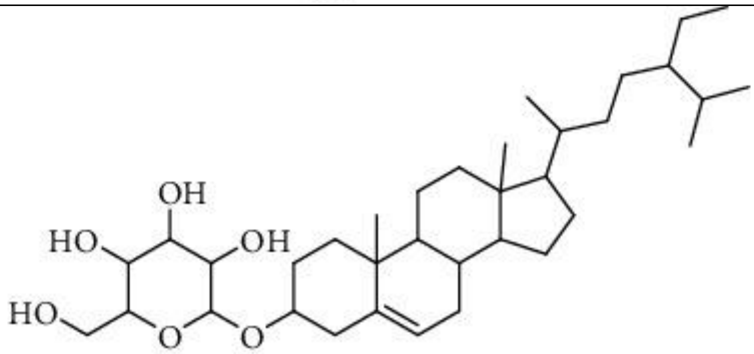
15.	Urticene; (−)-form	
16.	Neoolivil; 9-O-b-d-Glucopyranoside	
17.	Dehydrodiconiferyl alcohol	
18.	Olivil	
19.	3,4-Divanillyltetrahydrofuran	

Table 3: Sterols extracted from *Urtica*.

Sr. no.	Compound name	Structural formula
1.	Stigmastane-3, 6-diol; (3β, 24R)-form, O-[b-d-Glucopyranosyl-(1 ⟶ 4)-al-arabinopyranoside]	
2.	Stigmastane-3, 6-diol; (3b, 7a, 24R)-form, 3-O-b-d-Glucopyranoside	
3.	Stigmastane-3, 6-diol; (3b, a6a, 24R)-form	
4.	Daucosterol	

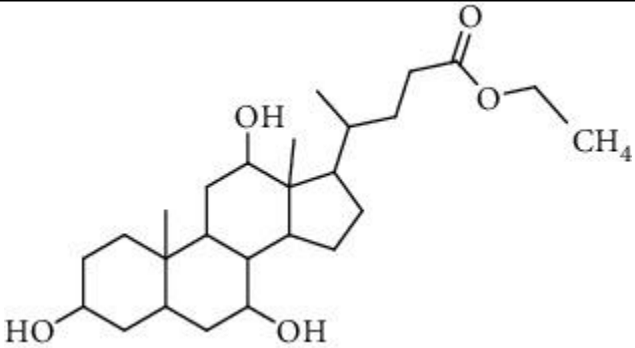
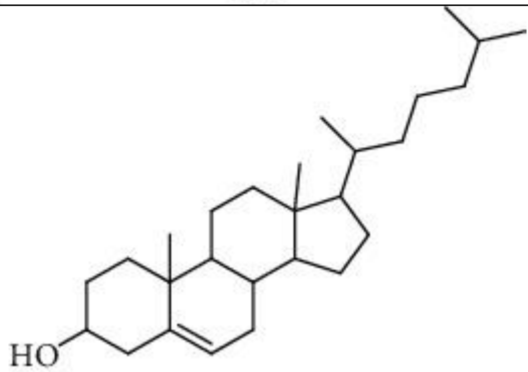
5.	Ethyl iso-allocholate	
6.	Cholesterol	

Table 4: Fatty acids isolated from genus *Urtica.*

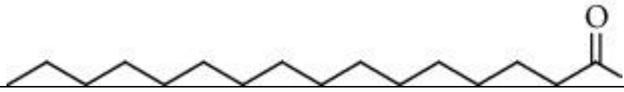
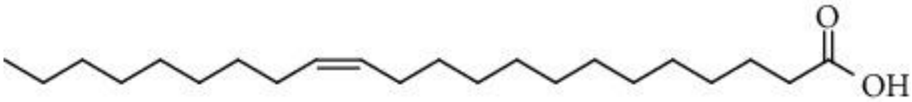
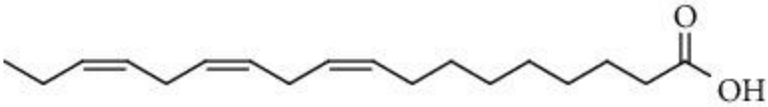
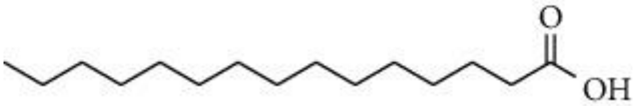
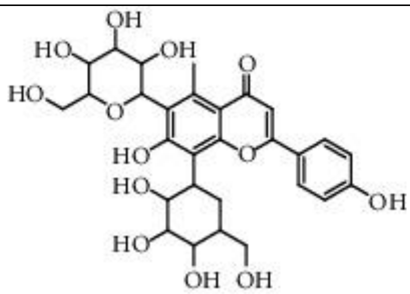
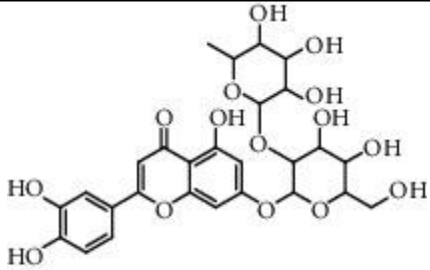
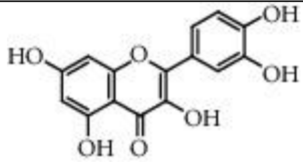
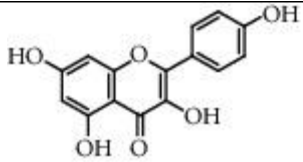
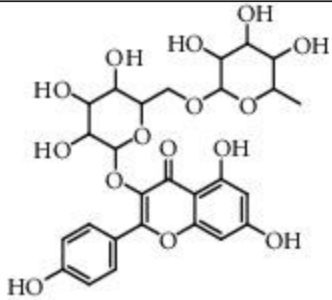
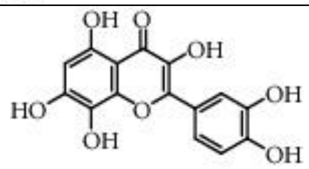
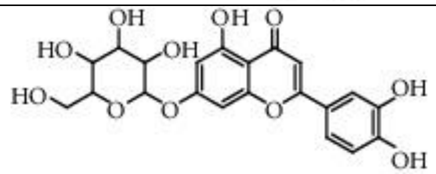
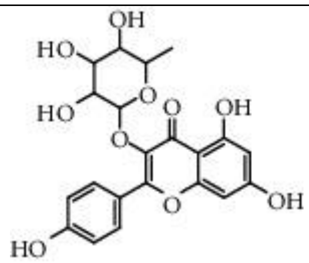
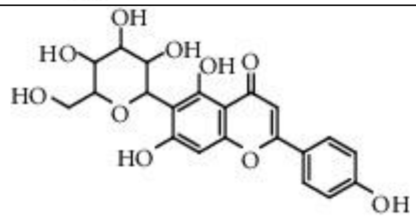
Sr.	Name	Structural formula
1	Palmitic acid	
2	Erucic acid	
3	Linolenic acid	
4	Pentadecanoic acid	

Table 5: Flavonoids isolated from genus *Urtica.*

Sr.	Name	
1.	2′, 4′, 5, 7, 8-Pentahy-droxyflavone; 7, 8-Di-Me ether	

2.	Luteolin 7-*O*-neohes-peridoside	
3.	Quercetin	
4.	Kaempferol	
5.	Nicotiflorin	
6.	Gossypetin	
7.	Luteolin 7-O-b-d-Glucopyranoside	
8.	Afzelin	
9.	Isovitexin	

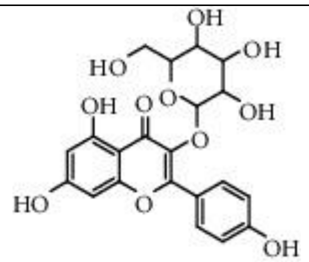
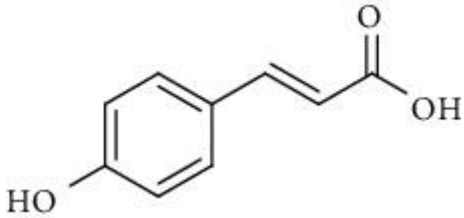
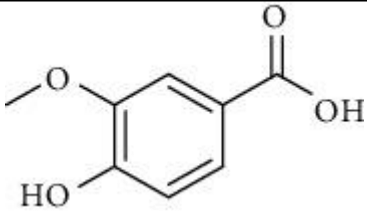
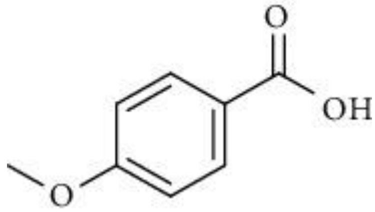
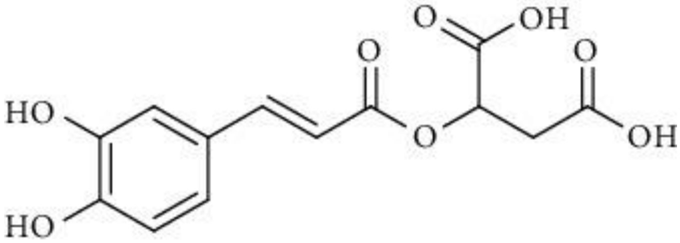
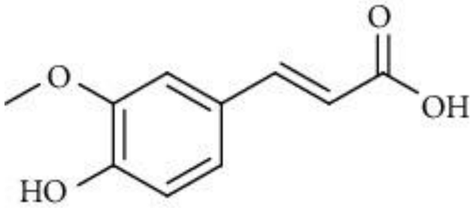
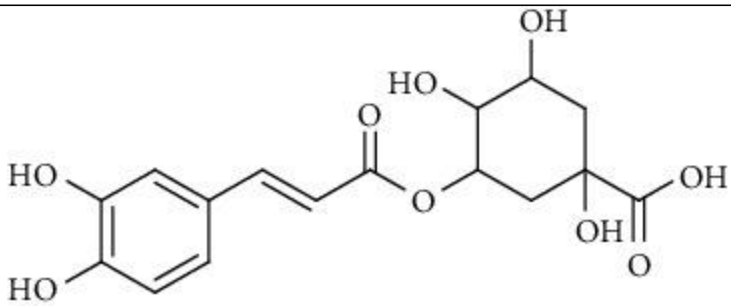
10.	Astragalin	

Table 6: Phenols extracted from *Urtica* spp.

Sr. no.	Compound name	Structural formula
1.	p-Coumaric acid	
2.	Vanillic acid	
3.	4-Methoxybenzoic acid	
4.	Caffeoylmalic acid	
5.	Ferulic Acid	
6.	Chlorogenic acid	

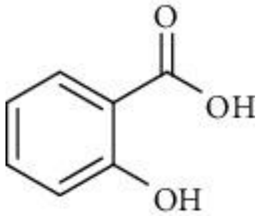
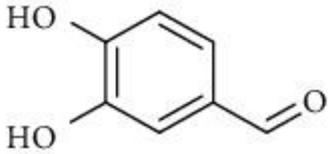
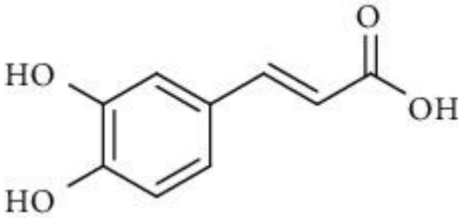
7.	Salicylic acid	
8.	Protocatechuic aldehyde	
9.	Caffeic acid	

Table 7: Alcohols isolated from genus *Urtica*.

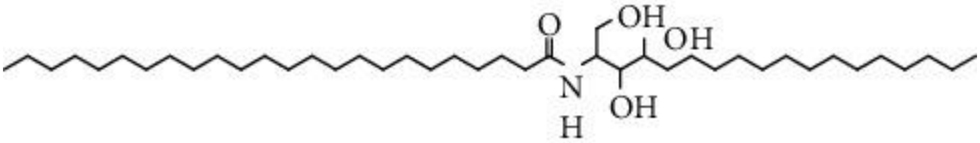
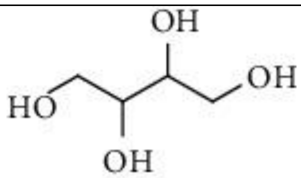
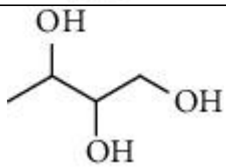
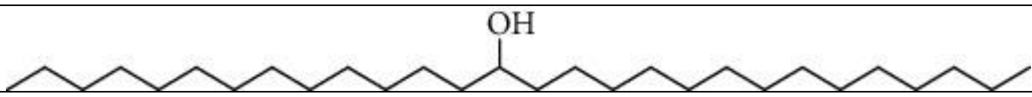
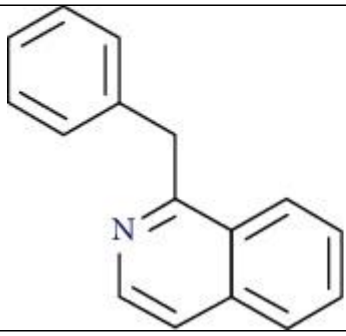
Sr.	Name	Chemical structure
1.	N-Tetracosanoylphytosphingosine	
2.	Erythritol	
3.	1, 2, 3-Butanetriol	
4.	14-Octacosanol	

Table 8: Alkaloids isolated from genus *Urtica.*

Name	Chemical structure
Benzylisoquinoline	

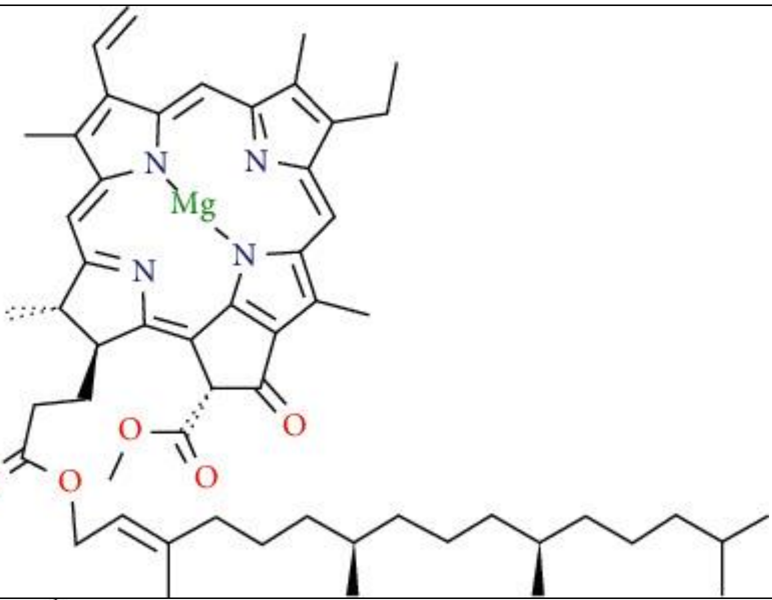
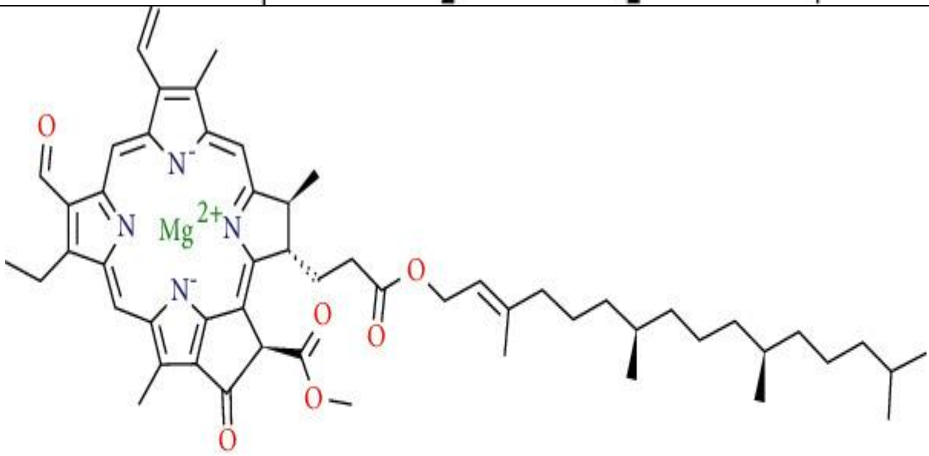
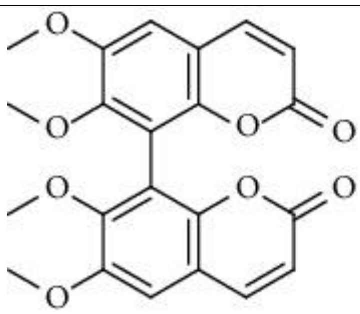
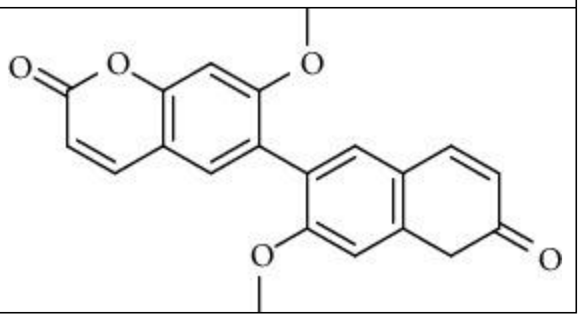
Chlorophyll A	
Chlorophyll B	

Table 9: Benzopyranoids isolated from genus *Urtica.*

Sr.	Name	Chemical structure
1.	6, 6′, 7, 7′-Tetrahy-droxy-[8, 8′-bi-2H-1-benzopyran]-2, 2′-dione; Tetra-Me ether	
2.	7, 7′-dimethoxy-6, 6′-biscoumarin	

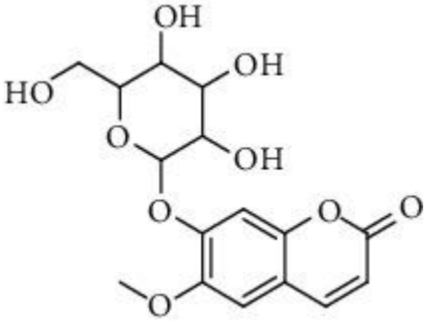
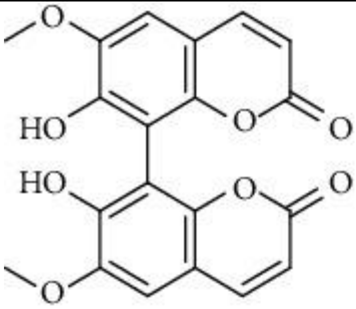
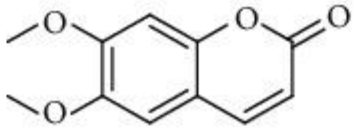
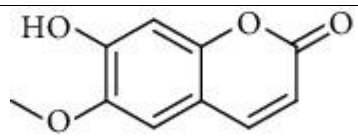
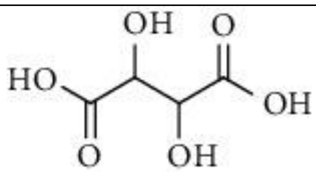
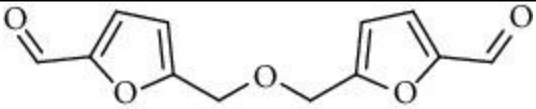
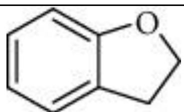
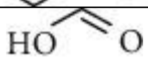
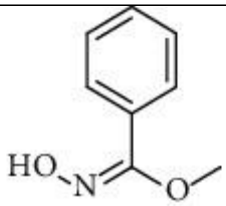
3.	Scopolin	
4.	6, 6′, 7, 7′-Tetrahydroxy-8,8′-bicoumarin; 6, 6′-Di-Me ether	
5.	Scoparone	
6.	Scopoletin	

Table 10: Other compounds isolated from genus *Urtica.*

Sr.	Name	Chemical structure
1.	Tartaric acid	
2.	Bis(5-formylfurfu-ryl) ether	
3.	Dotriacotane	
4.	2, 3-Dihydrobenzo-furan	
5.	Formic acid	
6.	Oxime- methoxy-phenyl	

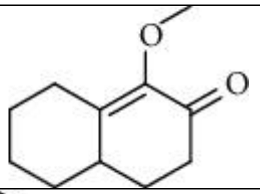
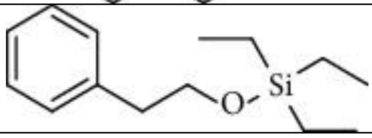
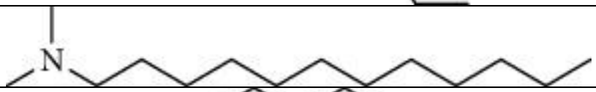
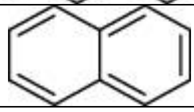
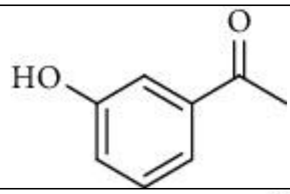
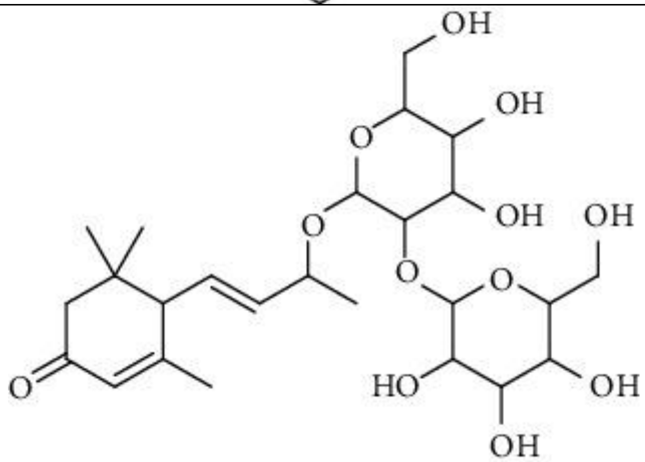
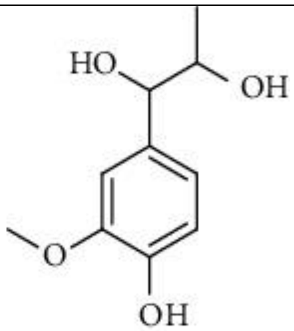
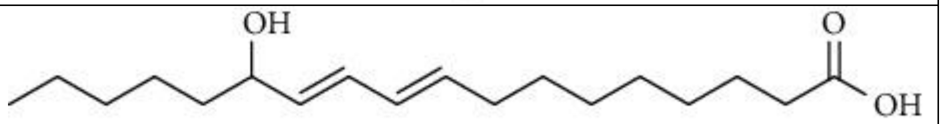
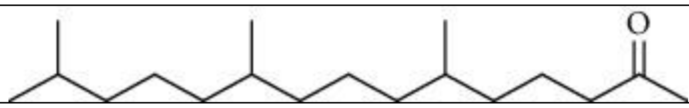
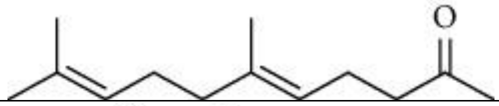
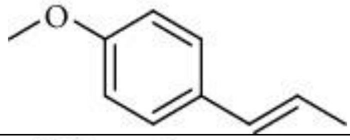
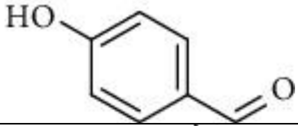
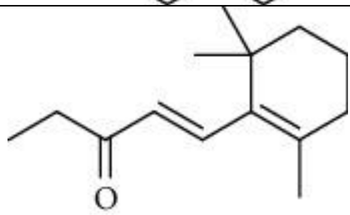
7.	1-Methoxy-4, 4a, 5, 6, 7, 8-hexahydro-2 (3H)-naphthalenone	
8.	Silane, triethyl (2-phenylethoxy)	
9.	*N*, *N*-Dimethyldo-decylamine	
10.	Naphthalene	

Table 11: Terpenoids isolated from genus *Urtica*.

Sr.	Name	Structural name
1.	3′-Hydroxyacetophenone	
2.	4,7-Megastigma-diene-3, 9-diol; (3S,6R,7E,9R)-form, 3-Ketone, 9-*O*-[b-D-glucopyranosyl-(1 ⟶ 2)-b-d-glucopyranoside]	
3.	1-(3, 4-Dihydroxyphe-nyl)-1, 2-propanediol; 3′-Me ether	
4.	(9Z,11E)-1, 3-hy-droxy-9, 11-octadeca-dienoic acid	
5.	Hexahydrofarnesyl acetone	

6.	Geranyl acetone	
7.	(E)-Anethole	
8.	*p*-Hydroxybenzalde-hyde	
9.	b-Ionone	

A wide range of bioactive constituents has been identified in *Urtica* species, contributing to their potential preventive and therapeutic applications in both communicable and non-communicable diseases. Notable compounds include β-sitosterol, trans-ferulic acid, dotriacontane, erucic acid, ursolic acid, scopoletin, rutin, quercetin, and p-hydroxybenzyl alcohol. These phytochemicals are associated with diverse pharmacological activities, supporting the medicinal relevance of the genus.

The characteristic stinging property of nettle is attributed to the liquid contained within its trichomes (stinging hairs). This fluid comprises formic acid and leukotrienes in small quantities, approximately 1% acetylcholine, histamine in concentrations ranging from 1:500 to 1:2000, and 5-hydroxytryptamine (serotonin). These components are responsible for the immediate irritant and neuroactive effects observed upon contact with the plant.

The aerial parts of *Urtica* species contain a complex mixture of chemical constituents, including essential ketones (38.5%), esters (14.7%), free alcohols (2%), nitrogenous compounds, phenolic compounds, aldehydes, β-sitosterol, formic and acetic acids, chlorophyll, phytol, vitamins, and carotenoids. Furthermore, chromatographic analyses have identified several organic acids within these tissues, such as caffeic, ferulic, caffeylmalic, chlorogenic, and sinapic acids.

Flavonoid profiling has revealed the presence of multiple glycosylated derivatives, including isorhamnetin 3-O-glucoside, quercetin 3-O-glucoside, kaempferol 3-O-glucoside, isorhamnetin 3-O-rutinoside, and quercetin 3-O-rutinoside, particularly in the flowers. In addition, β-sitosterol, β-sitosterol glucoside, and scopoletin are distributed throughout various parts of the plant.

The roots of *Urtica* species exhibit considerable chemical diversity, containing compounds from multiple classes such as polysaccharides (including glycans, glucogalacturonans, and arabinogalactan acids), fatty acids (notably (10E,12Z)-9-hydroxy-10,12-octadecadienoic acid), lectins, ceramides, terpene diols, and their corresponding glucosides.

Essential oil compositions of species such as *Urtica dioica* and *Urtica pilulifera* have also been investigated. These oils predominantly contain compounds such as hexahydrofarnesyl acetone, 1,8-cineole, α-ionone, β-ionone, farnesylacetone, methylbenzene, (−)-limonene, 3-carene, (+)-limonene, γ-terpinene, vanillin, butyl acetate, 1,2-benzenedicarboxylic acid, and 7-acetyl-6-ethyl-1,1,4,4-tetramethyltetralin.

Despite the identification of numerous bioactive compounds, the phytochemical characterization of *Urtica* species remains relatively underexplored. Further comprehensive studies are required to fully elucidate the chemical diversity and pharmacological potential of these plants.

Table 12: Chemical composition of essential oil extracted of *Urtica pilulifera* and *Urtica diorca*.

NO	Compound	*Urtica pilulifera* (RT)	*Urtica diorca* (RI)	%
1	1-(4-Isopropylphenyl)-2-methylpropyl acetate	30.5829	—	2.062
2	1-(4′-pentenyl)-1, 2-epoxycyclopentane	24.2355	—	0.1271
3	1, 2-Benzenedicarboxylic acid	32.0424	—	13.5056
4	1, 4-Diazepine	27.0528	—	0.3009
5	1,8-Cineole	13.686	—	8.2085
6	1-Penten-3-one	27.5551	—	0.3782
7	2-(1-Pentenyl)furan	—	1056	0.29
8	2, 2, 6-Trimethylcyclohexanone	—	1035	0.28
9	2, 4, 6-Trimethyl-5*H*-1, 3, 5-dithiazine	—	1199	0.30
10	2-Methoxy-4-vinylphenol	12.3214	—	0.1087
11	2-Pentylfuran	—	991	0.84
12	2-Propenoic acid	5.302	—	2.2418
13	3, 5-Dimethyl-1, 2, 4-trithiolane	—	1134	0.30
14	3-Carene	15.8651	—	3.7624
15	3-Octanone	—	988	0.28
16	5, 6-Dihydro-4-pentyl-2, 6-dimethyl-4H-1, 3, 5-dithiazine	—	1588	0.57

17	5, 6-Dihydro-4-pentyl-2, 6-dimethyl-4H-1, 3, 5-dithiazine	—	1588	0.57
18	7-Acetyl-6-ethyl-1, 1, 4,4-tetramethyltetralin	32.5855	—	19.618
19	.alpha-Cetone	26.6658	—	0.9039
20	Anozol	29.1437	—	0.1346
21	Apoatropine	—	2093	0.82
22	Apoatropine	—	2093	0.82
23	Benzaldehyde	11.371	—	0.1391
24	Benzaldehyde	—	964	0.29
25	Benzofuranone	27.9014	—	0.1183
26	Benzoic acid	30.7118	—	0.873
27	Bicyclo[10.1.0]trideca-4, 8-diene-13-carboxamide	25.2741	—	0.1325
28	Bisabolene	—	1506	0.39
29	Bisomel	32.28	—	3.7872
30	Borneol	—	1171	0.31
31	Bornyl acetate	—	1283	2.14
32	Butyl acetate	6.7208	—	3.2399
33	Cadinene	—	1510	1.57
34	Cadinene	—	1516	2.37
35	Camphor	—	1145	0.27
36	Carvacrol	—	1299	0.30
37	Carvone	20.9362	—	0.1721
38	Citronellyl	19.7143	—	0.1388
39	Copaene-8-ol	—	1579	3.28
40	Decan-2-one	—	1192	0.28
41	Decanal	—	1206	0.29
42	Diethoxylated tridecyl alcohol	30.9494	—	0.1828
43	Ethylhexyl benzoate	31.187	—	0.3837
44	Farnesol	—	1715	1.88
45	Farnesol	—	1715	1.88
46	Farnesylacetone	—	1908	1.26
47	Farnesylacetone	—	1908	1.26
48	Furan-3-aldehyde	7.325	—	0.1458
49	Geranyl acetone	25.953	—	0.3483
50	Geranyl acetone	—	1448	2.22
51	Geranyl acetone	—	1448	2.22
52	Hexahydrofarnesylacetone	—	1844	31.20
53	Hexahydrofarnesylacetone	—	1844	31.20
54	Hexatriacontane	6.7208	—	11.5631
55	Humulene	—	1453	0.75
56	-Ionon β	26.822	—	0.1714
57	Ionone	—	1421	4.04
58	Ionone	—	1479	11.86
59	Isopropyl dodecanoate	—	1627	5.27
60	Isopropyl dodecanoate	—	1627	5.27
61	Lilyal	27.7113	—	1.8666

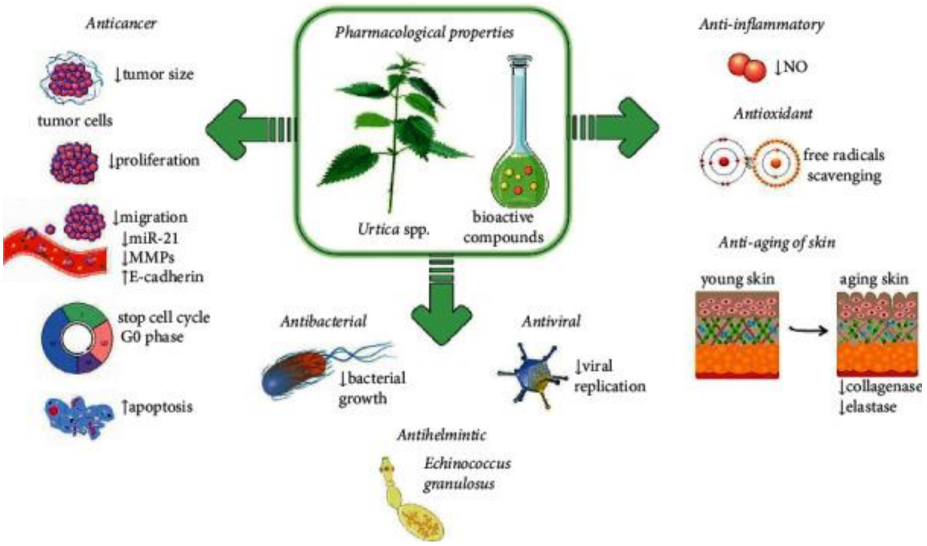
62	Limonene (−)-	13.5638	—	1.2463
63	Limonene (+)-	23.3733	—	6.7658
64	Menthol	—	1178	0.29
65	Methyl dihydrojasmonate	30.3181	—	0.8451
66	Methyl palmitate	—	1925	0.28
67	Methyl palmitate	—	1925	0.28
68	Methylbenzene	5.302	—	1.6415
69	Neophytadiene	32.3751	—	5.2683
70	n-Nonanal	15.9873	—	0.3288
71	n-Octanal	—	1004	0.30
72	Nonanal	—	1105	0.59
73	Ocimene	20.59	—	0.6869
74	Octanal	31.6555	—	2.0563
75	Octyl heptafluorobutyrate	17.9696	—	0.1347
76	p-Guaiacol	15.5392	—	0.1521
77	Phytol	—	2110	11.20
78	Phytol	—	2110	11.20
79	Safranal	—	1196	0.33
80	β-Selinene	—	1485	0.78
81	Terpinene	14.5413	—	0.1705
82	Thymol	—	1292	0.60
83	Trans-2,3-dimethylbicyclo[2.2.2]octane	22.4161	—	0.3454
84	Vanillin	21.812	—	1.7906
85	Vetivenene	—	1532	0.49
86	Vinyl	31.0445	—	0.3754
87	Xylene	8.3229	—	0.3848
88	α-Copaene-8-ol	—	1579	3.28
89	α-Humulene	—	1453	0.75
90	α-Ionone	—	1421	4.04
91	α-Longipinene	—	1347	0.30
92	α-Selinene	—	1493	0.70
93	β-2--Pinene	11.853	—	0.3957
94	β-Bisabolene	—	1506	0.39
95	β-Caryophyllene	—	1416	1.62
96	β-Cyclocitral	—	1217	0.35
97	β-Homocyclocitral	—	1254	0.28
98	β-Ionone	—	1479	11.86
99	β-Selinene	—	1485	0.78
100	β-Vetivenene	—	1532	0.49
101	γ-Cadinene	—	1510	1.57
102	γ-Terpinen	18.2615	—	0.3824
103	γ-Terpinene	18.6552	—	2.415
104	δ-Cadinene	—	1516	2.37

Table 13: *In vivo* studies of the genus *Urtica*.

Extract/compound	Doses	Route of administration	Model	Effect	Reference
Antiarthritis effect					
Total coumarins from *Urtica dentata* Hand	20, 40, 60 mg/kg	Orally every other day for 4 weeks after induction of arthritis	Collagen-induced arthritis BALB/c mice model	Dose-dependent ↓ arthritis score ↓paw swelling protect tissues against bone destruction ↓IFN-g, ↓IL-2 ↑IL-10, ↑TGF-B	[63]
Antioxidant effect					
Total 80% ethanolic extract of *Urtica dioica* L. leaves	50, 100 mg/kg	Orally daily for 14 days	Normal Swiss albino mouse model	↑cytochrome b5, ↑NADH-cytochrome b5 reductase, ↑glutathione S-transferase, ↑DT-diaphorase, ↑glutathione peroxidase, ↑glutathione reductase, ↑superoxide dismutase, ↑catalase ↓cytochrome P450, ↓lactate dehydrogenase, ↓NADPH-cytochrome P450 reductase, ↓total sulfhydryl groups, ↓nonprotein sulfhydryl groups, ↓protein-bound sulfhydryl groups	[64]
Antidiabetic effect					
Hexane, ethyl acetate and chloroform extracts of *Urtica pilulifera*	Two doses: 250 and 500 mg/kg	Orally daily for 4 weeks starting from day11 of diabetes induction	Streptozotocin and high-fat diet-induced type2 diabetes adult male albino rat model	Hypoglycemic effect - ethyl acetate and chloroform extracts ↓glucose level, ↓HbA1C, ↓ insulin resistance anti-inflammatory:	[65]

				↓CRP, ↓TNF-α antioxidant: ↓MDA, ↑GSH, ↑SOD, ↑catalase	
ZnO nanoparticles + aqueous extract of *Urtica dioica* leaves	ZnO + extract: 8 mg/dl	Intraperitoneally daily for 16 days	Alloxan-induced diabetic rat model	Both ZnO-extract and insulin (reference) ↓fasting blood glucose level in serum, while increased insulin level. ZnO-extract: ↑high-density lipoprotein ↓total cholesterol, ↓triglycerides	[66]
Antiendometriosis effect					
Hexane, ethyl acetate and methanol extracts of *Urtica dioica* L. aerial parts	100 mg/kg	Orally for 4 weeks	Surgery-induced endometriosis rat model	Methanol extract: ↓implant volumes, ↓adhesion scores ↓TNF-α, ↓VEGF, ↓IL-6; histopathological outcomes supported the results	[67]
Effect on prostate hyperplasia					
Polysaccharide fraction of *Urtica fissa*	62.5, 125, 250 mg/kg	Orally daily for 3 weeks	Testosterone propionate-induced prostate hyperplasia castrated rat model	↓prostate hyperplasia the lowest dose (62.5 mg/kg)-↓ indexes of wet weight,↓ dry weight , ↓volume by 17%, 23% and 32% highest dose (250 mg/kg)-↓indexes of wet weight, dry weight, ↓volume were further reduced by 25%, 33% and 37%; histopathological examination supported the results	[68]

Effect on nephrotoxicity					
Total 95% ethanol extract of *Urtica dioica*	Dose: 100 mg/kg	Orally daily for 10 days	Gentamicin-induced nephrotoxicity in male rabbit model	↓ serum creatinine, ↓blood urea, ↓ nitrogen antioxidant-↑glutathione, ↓malondialdehyde	[69]
Antiviral effect					
Urtica dioica agglutinin (UDA)	Three doses: 20, 10, 5 mg/kg	Intraperitoneally daily for 4 days	SARS-CoV-infected BALB/c mouse model	Treatment with UDA at dose 5 mg/kg significantly sheltered the mice against lethal infection with the virus but did not decrease virus titers in the lung; prevented weight loss and lung pathology scores of infected mice	[70]
Antiaging effect					
Total extract (50% ethanol) of *Urtica thunbergiana* leaves	Two doses: 0.1% and 1% g/kg of the animals' dry diet	Orally for 10 weeks	UVB-induced skin aging hairless mouse model	↓thinner and superficial wrinkles ↓erythema index ↑skin hydration; histopathological investigations supported the results	[71]
Anticancer effect					
Dichloromethane extract of *Urtica dioica*	Two doses: 10 and 20 mg/kg	Intraperitoneally daily for 28 days	4T1 (breast cancer cell line) allograft tumor BALB/c mouse model	↓tumor size and weight. ↑apoptosis, ↓proliferation. ↓Bcl2, ↑caspase 3; histopathology examinations supported the results	[72]



Symbols: ↑ increase, ↓decrease.

Figure 1.

The most important pharmacological properties and potential mechanisms of bioactive compounds of *Urtica* spp. ↑: increase; ↓: decrease; NO: nitric oxide; MMPs: matrix metalloproteinases; miR-21: microRNA-21.

4. Pharmacological Activities of *Urtica dioica*

4.1. In Vitro Pharmacological Findings

4.1.1. Antiviral Activity

Current antiviral therapies are largely limited to severe infections, highlighting the urgent need for more effective therapeutic agents. The aqueous extract of *Urtica dioica* fresh bark has demonstrated significant antiviral activity against the Petaluma virus (FIV-Pet) in Crandell feline kidney (CrFK) cell lines. This effect was attributed to the inhibition of viral replication through suppression of syncytia formation at low concentrations (0.5–1 g/mL) in a dose-dependent manner.

Additionally, *U. dioica* extracts and derived N-acetylglucosamine-specific lectins exhibited inhibitory effects on syncytium formation between CD4+ MOLT/4 and HUT-78 cells infected with HIV-1 and HIV-2. These lectins also demonstrated activity against cytomegalovirus, respiratory syncytial virus, and influenza A virus, with effective concentrations ranging from 0.3 to 9 mg/mL.

Moreover, *U. dioica* agglutinin (UDA) significantly suppressed SARS-CoV replication in Vero 76 cells, achieving approximately 90% inhibition at a concentration of 1.1 ± 0.4 µg/mL.

This effect is believed to occur through interference with early stages of viral replication, particularly via binding to viral glycoproteins and preventing host cell attachment.

4.1.2. Antimicrobial and Antifungal Activity

The increasing prevalence of antimicrobial resistance necessitates the exploration of alternative therapeutic agents. Extracts of *U. dioica*, both aqueous and ethanolic, have demonstrated broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, as well as fungal species.

Tested microorganisms include *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Escherichia coli*, *Citrobacter koseri*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Micrococcus luteus*, *Staphylococcus epidermidis*, and *Candida albicans*. Activity against multidrug-resistant *Mycobacterium tuberculosis* has also been reported.

Leaf extracts prepared using advanced extraction techniques (microwave-assisted, ultrasound-assisted, and subcritical water extraction) demonstrated antibacterial activity with minimum inhibitory concentrations as low as 9.76 µg/mL against MRSA and MSSA strains. These effects are largely attributed to hydroxycinnamic acids and flavonoids such as chlorogenic acid, caffeic acid, rosmarinic acid, and quercetin.

4.1.3. Anthelmintic Activity

The ethanolic extract of *U. dioica* exhibited significant in vitro anthelmintic activity against *Echinococcus granulosus* protoscoleces, achieving 96.2% inhibition at a concentration of 4 µg/mL within 30 minutes.

Similarly, methanolic extracts demonstrated dose-dependent anthelmintic effects in studies using *Pheretima posthuma*, indicating potential applicability in helminthic infections.

4.1.4. Anticancer Activity

Urtica dioica extracts have demonstrated notable antiproliferative effects against various cancer cell lines. Significant inhibition was observed in breast cancer cell lines (MCF-7, MDA-MB-231, and 4T1) and normal fibroblast cells, with varying IC50 values.

Mechanistic studies revealed that these effects are mediated through the downregulation of oncogenic markers such as miR-21, MMP1, MMP9, MMP13, and CXCR4, alongside the upregulation of E-cadherin expression. Additionally, enhanced apoptosis was observed via modulation of Bax and Bcl-2 protein expression and induction of cell cycle arrest at the G0 phase.

Subcritical water extracts and isolated compounds, such as 5α,6β-dihydroxy-daucosterol, further demonstrated significant antiproliferative activity across multiple cell lines.

4.1.5. Antioxidant Activity

Extracts of *U. dioica* exhibit strong antioxidant properties, as evidenced by DPPH radical scavenging, reducing power, and CUPRAC and FRAP assays. These activities are positively correlated with phenolic content.

Comparative studies have shown that *U. dioica* possesses superior antioxidant capacity relative to other *Urtica* species. Methanolic and ethanolic root extracts also demonstrated significant free radical scavenging activity, supporting the plant's role in oxidative stress mitigation.

4.1.6. Anti-Inflammatory Activity

Urtica dioica extracts and isolated flavonoids have demonstrated significant anti-inflammatory effects, including inhibition of thrombin-induced platelet aggregation.

Comparative analyses among *Urtica* species indicate that *U. urens* may exhibit stronger nitric oxide inhibition. The anti-inflammatory activity of *U. dioica* is closely associated with its phenolic and flavonoid content.

4.1.7. Antiaging Activity

Extracts of *U. dioica* have demonstrated inhibitory effects on collagenase and elastase enzymes, indicating potential antiaging properties. These effects are largely attributed to the presence of quercetin and ursolic acid.

4.2. In Vivo Pharmacological Findings

4.2.1. Antiviral Activity

In vivo studies have demonstrated that *U. dioica* agglutinin provides protective effects against viral infections in murine models, reducing disease severity and improving survival outcomes.

4.2.2. Anthelmintic Activity

Methanolic extracts of *U. dioica* administered orally exhibited anthelmintic activity in mice infected with *Aspiculuris tetraptera*.

4.2.3. Anticancer Activity

Dichloromethane extracts significantly reduced tumor size and weight in murine breast cancer models, primarily through apoptosis induction and inhibition of cell proliferation.

4.2.4. Nephroprotective and Hepatoprotective Effects

Ethanolic extracts demonstrated protective effects against drug-induced nephrotoxicity and hepatotoxicity, mediated by antioxidant mechanisms and regulation of biochemical markers.

4.2.5. Cardioprotective Activity

Extracts of *U. dioica* improved lipid profiles, reduced cholesterol levels, and enhanced cardiac tolerance to ischemic conditions in experimental models.

4.2.6. Antidiabetic Activity

Extracts of *Urtica* species exhibited hypoglycemic effects, improving insulin sensitivity and reducing oxidative stress markers in diabetic models.

4.2.7. Additional Pharmacological Effects

Further studies have reported antiarthritis, antiendometriosis, antiulcer, diuretic, antiurolithiatic, immunomodulatory, and antifatigue activities.

5. Clinical Evidence

Clinical studies have provided preliminary support for the anti-inflammatory, diuretic, antiallergic, and antidiabetic effects of *U. dioica*.

- Combination therapy with nettle and diclofenac demonstrated efficacy comparable to high-dose NSAIDs in arthritis management.
- Nettle extracts increased urine output in patients with cardiovascular insufficiency.
- Moderate improvement in allergic rhinitis symptoms was observed in randomized trials.
- Antidiabetic effects were supported by improved glycemic and lipid profiles.

  However, these findings remain limited by small sample sizes, short study durations, and methodological constraints.

6. Safety, Drug Interactions, and Adverse Effects

Although generally considered safe, *Urtica* species may cause adverse effects such as skin irritation, gastrointestinal discomfort, and hypersensitivity reactions.

The plant may interact with.

- Antidiabetic medications (enhanced hypoglycemic effect)
- Antihypertensive drugs
- Central nervous system depressants

Due to insufficient safety data, its use is not recommended during pregnancy, lactation, or in pediatric populations.

DISCUSSION

The present review highlights the emerging potential of *Urtica dioica* as a source of bioactive compounds with possible local anesthetic properties, although this aspect remains comparatively underexplored relative to its well-documented anti-inflammatory and antioxidant effects. The available phytochemical and pharmacological evidence suggests that the plant exerts analgesic and neuromodulatory actions through multiple complementary mechanisms.

One of the most significant observations is the presence of diverse phytoconstituents, including flavonoids (e.g., quercetin and rutin), phenolic acids, terpenoids, and sterols, which are known to influence nociceptive pathways. These compounds may contribute to local anesthetic effects by modulating voltage-gated sodium channels, thereby inhibiting nerve impulse conduction in a manner analogous to conventional local anesthetic agents. Although direct electrophysiological studies on sodium channel blockade by *Urtica dioica* are limited, indirect evidence from analgesic and anti-inflammatory models supports this hypothesis.

In addition, the plant's strong anti-inflammatory activity plays a crucial role in reducing peripheral sensitization of nociceptors. By downregulating pro-inflammatory mediators such as TNF-α, IL-1β, and NF-κB signaling pathways, *Urtica dioica* may decrease the excitability of pain fibers, thereby enhancing its local anesthetic-like effects. This dual mechanism—direct neuronal inhibition and indirect anti-inflammatory action—positions the plant as a promising candidate for topical pain management.

Interestingly, the chemical composition of the stinging hairs, which includes histamine, acetylcholine, and serotonin, initially induces irritation but may subsequently lead to desensitization of sensory nerve endings upon repeated or controlled exposure. This phenomenon is consistent with counter-irritant or neuromodulatory effects observed in certain traditional therapies and may contribute to localized analgesia.

Despite these promising findings, the current body of evidence remains largely preclinical, with most studies focusing on general analgesic or anti-inflammatory effects rather than explicitly evaluating local anesthetic activity. There is a lack of standardized experimental models, dose optimization studies, and clinical trials specifically designed to assess nerve conduction blockade or topical anesthetic efficacy.

Furthermore, variability in extraction methods, plant parts used, and phytochemical composition presents challenges in reproducibility and standardization. Safety considerations, including potential skin irritation and hypersensitivity reactions, must also be carefully addressed when considering topical applications.

CONCLUSION

In conclusion, *Urtica dioica* demonstrates considerable potential as a natural source of local anesthetic agents, supported by its rich phytochemical profile and multifaceted pharmacological activities. The combined analgesic, anti-inflammatory, and neuromodulatory effects of its bioactive constituents provide a strong theoretical basis for its use in localized pain management.

However, the current evidence remains largely indirect and insufficient to establish *Urtica dioica* as a clinically viable alternative to conventional local anesthetics. To bridge this gap, future research should prioritize.

- Isolation and characterization of active compounds responsible for nerve conduction inhibition
- Detailed mechanistic studies, particularly involving ion channel modulation
- Development of standardized topical formulations
- Well-designed clinical trials evaluating safety and efficacy in humans

With rigorous scientific validation, *Urtica dioica* holds promise for the development of novel, plant-based local anesthetic agents that may offer safer and more accessible alternatives in clinical practice.

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