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Review article

Pharmacological applications of *Urtica dioica*: a comprehensive review of its traditional use and modern scientific evidence

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ABSTRACT

Introduction: This review article provides a comprehensive overview of the phytochemical constituents, traditional uses, and pharmacological applications of *Urtica dioica* (UD), commonly known as stinging nettle.
Methodology: An extensive literature search was conducted to identify 278 relevant articles. After eliminating 38 duplicates, we thoroughly analysed the remaining 240 articles by examining their titles and abstracts. Finally, 126 articles were selected for inclusion in this comprehensive study on UD.
Discussion: This review explores the plant identifiable characteristics, geographical distribution and taxonomic classification. The phytochemicals found in plants include sterols, fatty acids, alkaloids, terpenoids, flavonoids, lignans, and essential oils, all of which contribute to their medicinal and therapeutic properties. It exhibits a broad range of pharmacological activities including anti-inflammatory, hypoglycaemic, antiurolithiatic, neuroprotective, antioxidant, antimicrobial, antiproliferative, and anticancer effects. UD leaves contain high levels of antioxidants, which may be useful for the treatment of breast cancer by inducing apoptosis. UD extracts *exert* a protective function by regulating blood glucose levels and β-cell activity, exhibiting insulin-like effects. It also inhibits pro-inflammatory pathways and demonstrates hepatoprotective properties following hepatectomy. UD extract inhibits the proliferation and migration of cancer cells and displays antiviral activity against rotavirus and feline immunodeficiency virus. Furthermore, UD is effective in treating chronic conditions, such as prostatitis, dandruff, and osteoarthritis, thereby reducing the need for conventional medications.
Conclusion: The diverse uses and biological properties of UD make it a subject of interest for future research.

Introduction

Urtica dioica (UD), a plant commonly known as stinging nettle, is of particular interest, with studies focusing on its medicinal benefits owing to its wide variety of phytochemical compositions, such as polyphenolic flavonoids (Hamed and Omari, 2014), and phytosterols (Smoylovska, 2017). UD has a long history of traditional use in various regions, including Turkey and Iran, and has been documented in from various ethnobotanical sources (Asadi-Samani et al., 2017; Hoseinynejad et al., 2022; Uzonur et al., 2013). Studies have shown that their aerial parts and roots have been well documented for their medicinal value. Plant leaf extracts have been reported to have anti-inflammatory (Vogl et al., 2013), antiurolithiatic (Afkari et al., 2019), and antidiabetic activities (Mukundi et al., 2017), and are considered natural therapeutic agents in various urological disorders (Kręgiel et al., 2018). Plant aerial extracts have also been reported to exert antihypertensive effects (Wright et al., 2007). The UD leaf extract, has also been studied, for its antioxidant and antimicrobial activities (Mzid et al., 2017). Plant leaf and

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Table 1
Mechanism of action of selected chemical constituents of UD extracts.

Chemical constituents		Primary medicinal benefits	References
Terpenes	Carvone	The enone form exhibits anti-parasitic activity, possibly by interacting with parasitic nucleophilic species.	(Gül et al., 2012; Krajewska and Mietlińska, 2022)
	Carvacrol	Inhibits the NF-κB signalling pathway.	(Gül et al., 2012; Krajewska and Mietlińska, 2022)
	Ursolic acid	Inhibit adipocyte adipogenesis via LKB1/AMPK pathway; Disrupts cellular lipid homoeostasis and lysosomal membrane integrity.	(Fogde et al., 2022; He et al., 2013)
Phenolics and flavonoids	Proanthocyanidins	Inhibits embryonation, hatchability, and proliferation.	(Inacio et al., 2021; Stanković et al., 2019)
	Caffeic acid/hydrocinnamic acid	Improves insulin sensitivity	(Oboh et al., 2014)
	Malic acid	Improves glucose tolerance	
	α-methyl hydrocinnamic acid	Used as preservative for food products	(Korneev, 2013)
	P-coumaric acid	Used as skin-lightening active ingredient in cosmetics	(Boo, 2019)
	Quercetin-3-O-rutinoside	This acts as insulin-mimetic in diabetes.	(Akbay et al., 2003)
Fatty acids	Vanilic acid	Responsible for antioxidant and protective effects	(Kasouni et al., 2021)
	α-linolenic acids	Alleviates metabolic syndrome and reduce weight gain	(Ou et al., 2023)
	Palmitic acids	Modulates gene expression related to lipid metabolism	(Ebrahimi et al., 2014)
Phytosterols	Campesterol	Decreases the expression levels of pro-inflammatory cytokines like IL-1 and TNF-α	(Javed et al., 2023)
	β-sitosterol	Alleviates the symptoms of BPH	(Vundru et al., 2013)

BPH, benign prostatic hyperplasia; UD, *Urtica dioica.*

root extracts have also been investigated for lipid separation and the existence of platelet-activating factors (Antonopoulou et al., 1996). It has also been found to inhibit adenosine deaminase activity in prostate tissue (Durak et al., 2004) and affect malonyl-CoA decarboxylase (Qujeq et al., 2014). Studies have reported that the methanolic extract of UD roots has significant effects on epithelial cell proliferation in human prostate cancer (Rashidbaghan et al., 2020). Additionally, the ethanolic extract of UD roots exhibits pro-fertility, antioxidant, immunomodulatory, diuretic, anti-inflammatory, antioxidant, antimicrobial, anti-ulcer, analgesic, and anti-allergic properties (Kasouni et al., 2021), suggesting its potential for the treatment of various conditions, including diabetes, prostate cancer, and urinary calculi. Additionally, the morphological characteristics and physical properties of plants have been studied to provide insights into their potential industrial applications (Lamharrar et al., 2016; Lanzilao et al., 2016). This review seeks to emphasise the pharmacological advantages of UD. Furthermore, this study will encompass the probable mechanism through which the phytoconstituents of plants may demonstrate the aforementioned advantages in human life.

A literature search was performed in from March 2023 to November 2023 articles published over a period of 25 years were surveyed with the following key words or phrases "*Urtica dioica*", "phytoconstituents of *Urtica dioica*", "pharmacological effects of *Urtica dioica*", "anticancer, antiproliferative effects of *Urtica dioica*", "clinical trials of *Urtica dioica*". A total of 278 manuscripts were extracted, 38 duplicates were removed, and 199 manuscripts were further analysed by reading the title and abstract. A total, of 126 manuscripts were selected to compile a comprehensive review. The literature search was performed using the following databases: Elsevier, Taylor Francis, ACS publications, Wiley, Springer, and Google Scholar, as they publish most research papers in specialised databases. Efforts have been made to include clinical trials reported to date for UD biological activity in human body.

Botanical description

The taxonomic classification and genetic variation of plants have been widely studied, particularly in relation to their ethnobotanical and medicinal uses (Uzonur et al., 2013). UD displays considerable variation in morphological characteristics, the stems of UD can grow up to 2 m in height and are characterised by opposite leaves that are arranged in pairs on the stems. This plant is well known for its stinging hairs, which contain formic acid and other chemicals that cause irritation upon contact and hence used as defence mechanism. UD is a dioecious plant, meaning that male and female reproductive parts are found in separate plants. The small, inconspicuous flowers of UD are greenish-yellow in colour and also characterised with an achene, dry, one-seeded fruit. In summary, the key morphological characteristics that distinguish UD include perennial habit, tall stems, opposite leaves, stinging hairs, dioecious reproduction, greenish flowers, and achene fruit. These features, along with their phytochemical composition and biological activities, contribute to the plant's use in traditional medicine and as a source of fibre (Thurston, 1974; Vertika Khare et al., 2012).

Geographical distribution

UD has been reported to have a broad geographical distribution (Harrison et al., 2022), the plant is native to fens and ancient woodlands and has become naturalised in different habitats, including the British Isles. UD was included in the flora of British India, indicating its presence in the Indian subcontinent during the British colonial period. The plant has been reported from the Presidency of Bombay (present-day Mumbai and surrounding areas) in Western India (De Vico et al., 2018; Taylor, 2009). In Turkey, the plant is found in all three geographical regions (Euro Siberian, Irano-Turanian, and Mediterranean), demonstrating its high adaptability to diverse geographies, including varying climates, soil types, and altitudes (Uzonur et al., 2013). The wide distribution of UD has also been studied in relation to its ecological requirements and adaptation to different soil conditions, highlighting its ability to thrive in various environmental settings (Pigott and Taylor, 1964).

Phytochemistry

UD contains a plethora of phytochemical constituents that contribute to its diverse pharmacological activity. The following section describes the phytochemical constituents of UD (Table 1).

Phenols

The plant contains a diverse range of phenolic compounds that contribute to its antioxidant, anti-inflammatory, and other bioactive properties. Studies have reported that extracts from the aerial parts of nettles are rich in polyphenols, while the roots contain oleanolic acid, sterols, and stearyl glycosides (Kręgiel et al., 2018). Caffeic acid, chlorogenic acid, 2-O-caffeoylmalic acid, ferulic acid, homovanillic alcohol, p-coumaric acid, rutin, kaempferol, isorhamnetin, quercetin,

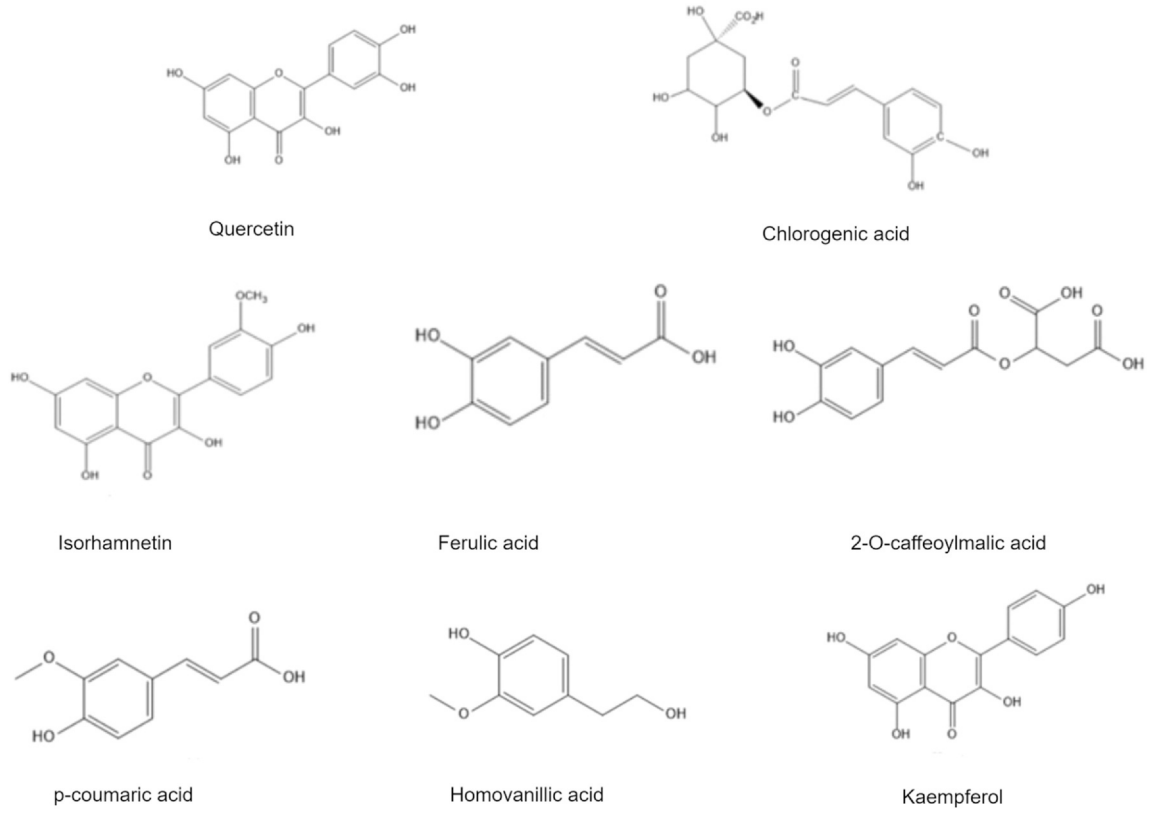

Fig. 1. Phenolic groups present in *Urtica dioica*.

isoquercetin, vanillic acid, carotenoids, essential oils, fatty acids, minerals, and vitamins have also been found in the aerial parts of UD (Maietti et al., 2021; Masłowski et al., 2022; Pinelli et al., 2008). Plant roots contain 18 different phenolic and eight different lignan components (Ötleş and Yalcin, 2012). The total phenolic content of the seed oils from UD has been determined to be in the range of 208.3–231.6 mg gallic acid equivalent (GAE)/kg oil, indicating a significant presence of phenolic compounds in the plant (Jafari et al., 2020; Kukrić et al., 2012). The leaves extracts of UD has been studied for its antioxidant activity, as it has been reported with the highest concentration of polyphenols, particularly derivatives of caffeic and p-coumaric acid (Repajić et al., 2020). Figure 1 shows the possible phenolics constituent present in plant which may contributes to its potential health benefits, including antioxidant and anti-inflammatory properties.

Alkaloids

The phytochemical composition of UD, specifically flavonoids, polyphenols, essential oils, and non-alkaloid constituents, have been extensively studied and documented. Although alkaloids are not major components of UD, there is evidence that UD contains alkaloids, such as phenols, saponins, steroids, and tannins, which exhibit antimicrobial properties (Ketema and Worku, 2020). This plant has shown potential in the treatment of conditions such as diabetes and prostate cancer, further highlighting the significance of alkaloid contents (Durak et al., 2004). However, the literature lacks confirmatory analysis of a particular alkaloid; hence, there is a strong desire for scientists to confirm the possibility of an alkaloid in either the root or leaf extracts of the plant.

Fatty acids

The fatty acid profiles of UD have also been studied and confirmed using gas chromatography-mass spectrometry (GC-MS), providing insights into the specific fatty acid constituents of the plant (Savych et al., 2021; Taheri et al., 2022). The fatty acid content of UD, particularly the presence of essential fatty acids, contributes to its potential health benefits, and is a subject of interest for further exploration in the development of therapeutic applications. Research has highlighted the presence of high levels of linoleic and α-linoleic acids in both the young and mature leaves of UD (Fig. 2).

Essential oils

The essential oils present in UD leaves have been the subject of investigation, revealing their diverse composition. Studies have identified the essential oil composition of UD, which mainly consists of hexahydrofarnesyl acetone, 1,8-cineole, α-ionone, β-ionone, farnesyl acetone, methylbenzene, (−)-limonene, 3-carene, (+)-limonene, γ-terpinene, vanillin, butyl acetate, and 1,2-benzenedicarboxylic acid (Taheri et al., 2022; Vico et al., 2018). The presence of these essential oils aligns with the traditional use of the plant as a medicinal herb and supports its potential for various therapeutic applications.

Sterols

Scientific studies on the phytochemical analysis of UD have demonstrated the presence of sterols among the compounds isolated from this plant (Ibrahim et al., 2018). Three steroid compounds, stigmasterol, campesterol, and β-sitosterol, have been identified in the aerial parts of the plant (Chaurasia and Wichtl, 1987; Ibrahim et al., 2018; Smoylovska, 2017). The roots of UD have also been analysed to contain sterols and steryl glycosides, which are known for their potential health benefits (Kręgiel et al., 2018). These sterols contribute to the overall chemical composition of plants and are of interest for further exploration in the development of therapeutic applications (Fig. 3).

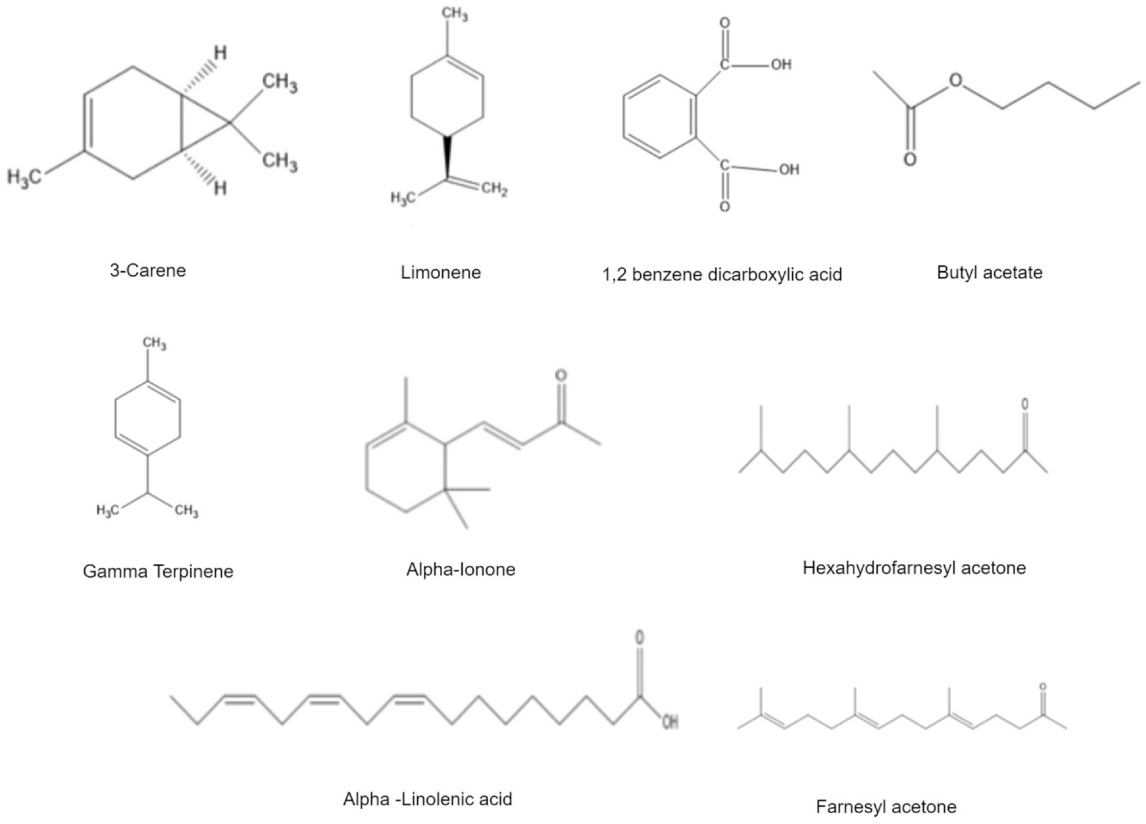

Fig. 2. Fatty acids and volatile oil present in *Urtica dioica*.

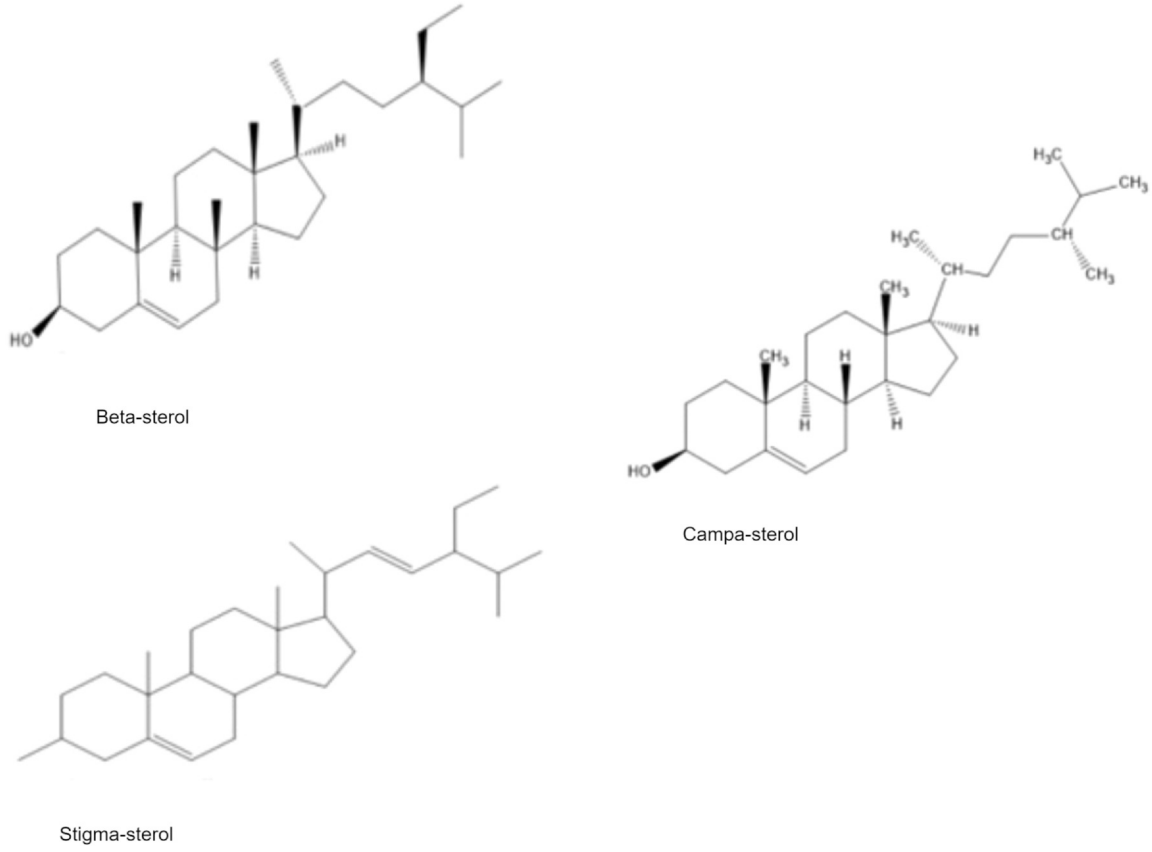

Fig. 3. Sterols present in *Urtica dioica*.

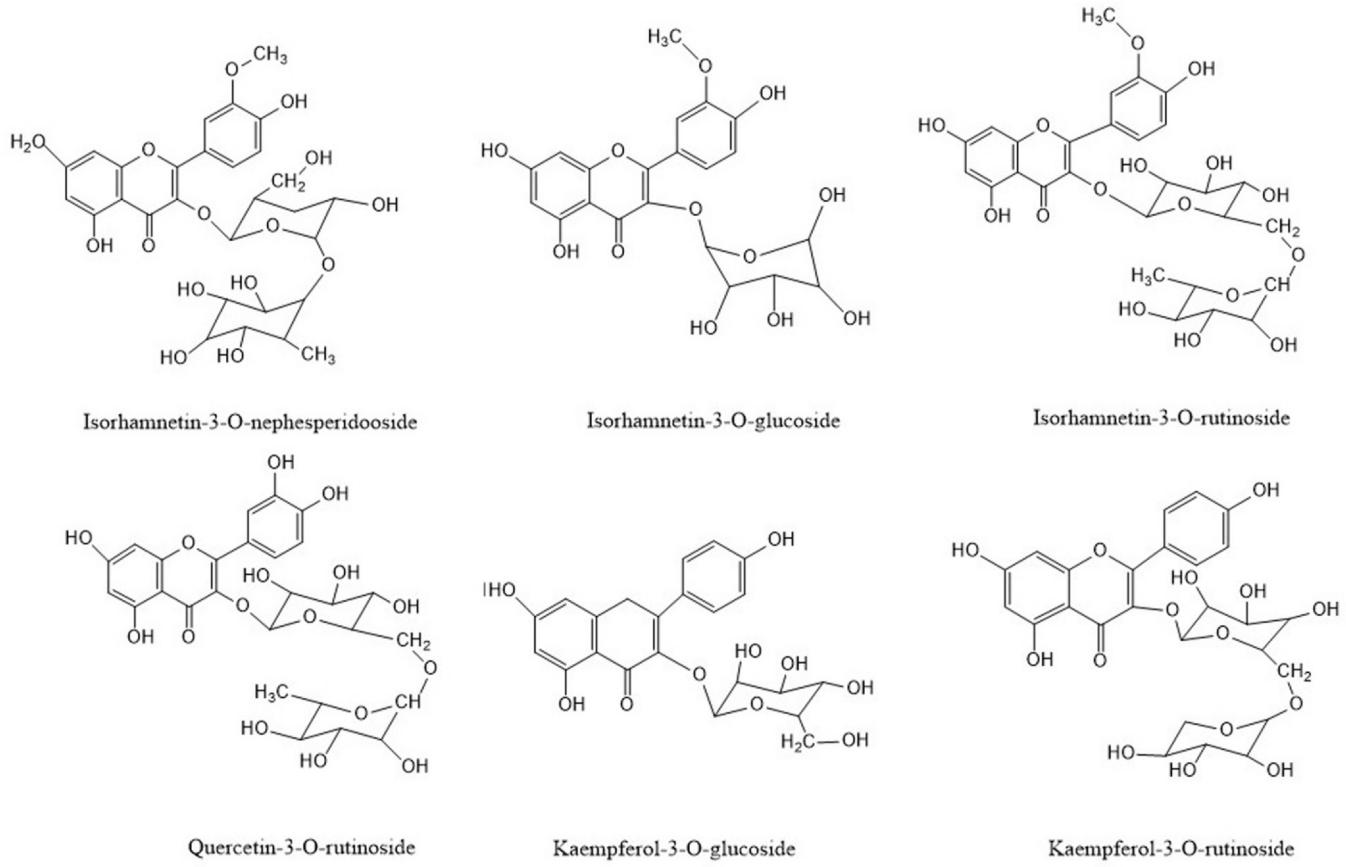

Fig. 4. Glycosides present in *Urtica dioica*.

Glycosides and lignans

UD contains a variety of lignans and glycosides that are responsible for its pharmacological properties. Glycosides such as kaempferol-3-O-glycoside, quercetin-3-O-glycoside, isorhamnetin-3-O glycoside, quercetin-3-O-rutinoside, isorhamnetin-3-O-rutinoside, kaempferol-3-O-rutinoside, and isorhamnetin-3-O-neohesperidoside have been isolated from UD leaves (Ötleş and Yalcin, 2012). Quercetin-3-O-rutinoside, also known as rutin, is a representative constituent of UD flowers (Xuan et al., 2019). These lignans and glycosides are known to possess various pharmacological activities such as antioxidant, anti-inflammatory, and immunomodulatory effects, which highlight the therapeutic potential of UD and its chemical constituents (Fig. 4).

Terpenoids

These specific terpenoids present in UD include hexahydrofarnesyl acetone, 1,8-cineole, α-ionone, β-ionone, and farnesylacetone to name a few (Kręgiel et al., 2018). Studies have reported that ursolic acid is one of the major pentacyclic natural terpenes reported in UD (Bourgeois et al., 2016). Research has shown that the hydroalcoholic extract of UD leaves, which is rich in lupeol, exhibits healing properties and is involved in the process of re-epithelialisation (Somensi et al., 2021). The identification of terpenoids in UD highlights the chemical complexity of the plant and highlights their potential for further exploration in the context of phytotherapy and drug discovery.

Pharmacological activity

Antihelminthic

The anti-helminthic mechanisms of UD are multifaceted and involve coordinated action of various phytochemical components. These mechanisms include disruption of cell membranes, impairment of helminthic growth and biofilm formation, and regulation of oxidative stress and inflammation. Essential oils derived from UD have been reported to exhibit anti-helminthic effects by disrupting the integrity of helminthic cell membranes, leading to cell lysis and death. This disruption may also be attributed to the presence of bioactive compounds such as terpenoids, which can interact with helminthic membranes, compromising their structural integrity and function (Kręgiel et al., 2018). Furthermore, the flavonoids and phenolic compounds, have been shown to possess anti-helminthic properties by inhibiting embryonation, hatchability, and proliferation and thereby interfering with helminthic growth (Lotfi Moussouni et al., 2019). These compounds can inhibit helminthic enzymes, interfere with helminthic DNA replication, and disrupt essential helminthic metabolic processes, ultimately leading to inhibition of helminthic growth and survival (Manjir Sarma Kataki et al., 2012).

Biofilms are complex helminthic communities that are highly resistant to anthelminthic agents. Studies have suggested that UD extracts can disrupt biofilm formation, thereby enhancing their anti-helminthic efficacy (Samoilova et al., 2014). The antioxidant and anti-inflammatory properties of UD may also be beneficial in the fight against helminthic infections by mitigating the oxidative stress that often accompanies such infections (Jaiswal and Lee, 2022). The extensive anti-helminthic activity demonstrated by UD underscores its potential as a natural anti-helminthic agent, and necessitates further exploration of its therapeutic applications.

Antidiabetic activity

The phytochemicals in the UD extract, such as phenolic compounds and sterols, may be responsible for its antidiabetic properties (Ibrahim et al., 2018). Phytoconstituents have been shown to have hypoglycaemic

and antihyperglycemic effects, as evidenced by their ability to decrease plasma glucose levels (Kadan et al., 2013; Khalili et al., 2017). It has also been reported the UD extract can have a protective effect on the β-cells of Langerhans, which are responsible for insulin secretion, and to modulate the main morphometric indices of the liver, indicating its potential in ameliorating diabetes-related complications (Shrestha, 2022).

This anti-inflammatory property of UD extract may be relevant in diabetes, as chronic low-grade inflammation is associated with insulin resistance and the pathogenesis of diabetes. Moreover, the alpha-glucosidase inhibitor activity of UD has been investigated, which is relevant for diabetes management because alpha-glucosidase inhibitors can help regulate postprandial blood glucose levels (Önal et al., 2005). This mechanism may contribute to the potential of the plant to control blood glucose levels in individuals with diabetes. Furthermore, UD has been reported to exert hypotensive and diuretic effects, which may have implications for its antidiabetic effects because hypertension and fluid retention are common comorbidities of diabetes (Altamimi et al., 2022). The antioxidant properties of the plant, which are believed to be associated with its unsaturated fatty acids, may also play a role in its antidiabetic effects by mitigating oxidative stress (Ahmed et al., 2022; Qayyum et al., 2016; Vogl et al., 2013).

Antihypertensive action

UD has demonstrated NO-mediated vasorelaxation and calcium channel-blocking effects, offering a potential pharmacological basis for its application in hypertension management (Qayyum et al., 2016). This vasorelaxation effect is mediated by the release of endothelial nitric oxide and opening of potassium channels, and through a negative inotropic action, may contribute to the ability of the plant to lower blood pressure and alleviate hypertension symptoms (Testai et al., 2002). UD extract effectively reduces systolic and diastolic blood pressure and cardiac index by increasing the activity of superoxide dismutase and catalase without altering enzyme concentrations. The ability of UD to enhance urine flow may also contribute to its antihypertensive effect (Devkota et al., 2022). In conclusion, the antihypertensive mechanism of UD involves a combination of vasorelaxation, diuretic, and antioxidant effects, which collectively contribute to its potential in managing hypertension.

Nephroprotective activity

UD chemical constituents has potent antioxidant effects that can protect the kidneys from oxidative damage induced by various toxic agents (Cuervo et al., 2010; Gonzalez et al., 2021). The plant extracts have also been shown to inhibit adenosine deaminase activity in prostate tissues, suggesting a potential mechanism for their beneficial effects in prostate cancer (Mirzaei et al., 2019; Durak et al., 2004). The nephroprotective action of UD may be a result of its multifaceted properties, including antioxidant, anti-inflammatory, and antiulcer activities. Collectively, these properties contribute to the ability of the plant to protect the kidneys from various forms of damage and toxicity.

Anti-inflammatory activity

UD inhibits platelet aggregation, indicating its potential role in modulating inflammatory responses (Arnold et al., 2015). The immunostimulatory and anti-inflammatory activities of this plant have been attributed to its polysaccharide fraction (Li et al., 2022; Yin et al., 2019). The ethanolic extracts of UD leaves have been found to inhibit the NF-kB pathway, which regulates the release of inflammatory cytokines, thereby mitigating inflammatory processes in osteoarthritis (Riehemann et al., 1999; Shakibaei et al., 2012; Vico et al., 2018). UD leaf extracts have been shown to switch from Th-1 (T helper cells) derived responses to Th-2 responses, potentially inhibiting inflammatory events in rheumatoid arthritis and osteoarthritis (Aldridge et al., 2020). Moreover, UD leaf extract has been found to inhibit the pro-inflammatory transcription factor NF-κB, which is elevated in the synovial fluid of rheumatoid arthritis, suggesting a potential mechanism by which UD modulates inflammatory pathways in arthritis, including osteoarthritis. In addition to its anti-inflammatory effects, UD extract has antioxidant properties that may contribute to the protection of joint tissues from oxidative damage and exert a potential anti-osteoarthritis effect (Abd-Nikfarjam et al., 2021). The anti-osteoarthritis mechanism of UD may also involve the modulation of cellular pathways related to apoptosis and proliferation, as studies have investigated the interaction of UD extract with apoptosis and autophagy pathways, elucidating its antiproliferative effects (Temiz et al., 2021). Therefore, the anti-osteoarthritis mechanism of UD extract is attributed to its ability to inhibit inflammatory pathways, modulate immune responses, exhibit antioxidant effects, and potentially modulate cellular pathways related to apoptosis and proliferation. These mechanisms underscore the potential of UD as a therapeutic agent for osteoarthritis.

Hepatoprotective activity

Research has shown that UD reduces lipid peroxidation and enhances antioxidant enzyme activity, thereby protecting the liver from oxidative damage. The immunomodulatory and anti-inflammatory activities of this plant have been suggested to contribute to its hepatoprotective effects (Akbay et al., 2003). The hepatoprotective mechanism of UD is multifaceted and collectively contributes to its ability to protect the liver from oxidative damage, inflammation, and other pathological changes.

Anti-obesity activity

The antioxidant properties of UD have also been linked to its potential anti-obesity effects as oxidative stress has been implicated in the development of obesity. The ability of plants to modulate lipid metabolism and energy expenditure may also contribute to their anti-obesity effects (Haouari and Rosado, 2018). UD inhibits adipogenesis and preadipocyte proliferation, which are critical steps in obesity development (García-Carrasco et al., 2015). As discussed previously, the inhibitory effect on NF-κB activation, genetic transcription factors that activate inflammatory cytokines, and antiproliferative effects may also play a role in its anti-obesity effects (Konrad et al., 2000; Taheri et al., 2022). The anti-obesity mechanism of UD involves a combination of hypolipidaemic, antioxidant, anti-inflammatory, and antiproliferative activities, which collectively contribute to its potential in combating obesity.

Neuroprotective activity

The active compounds of the plant, such as carvacrol, have been identified as contributors to its neuroprotective properties (Jaiswal and Lee, 2022; Khazaei et al., 2020). It has been reported that UD exhibits neuroprotective effects by modulating various pathways and molecular mechanisms, as indicated by recent studies. The activation of the PI3K/Akt/Nrf2 pathway and the scavenging of free radicals are among the mechanisms attributed to the neuroprotective effects of this plant (Ali et al., 2022; Semwal, 2023; Shabir et al., 2022). The inhibitory effect of UD on adenosine deaminase activity in prostate tissue suggests potential immunomodulatory properties that may indirectly contribute to its neuroprotective effects (Durak et al., 2004).

Anticancer

The anticancer mechanisms of UD involve the coordinated action of a diverse array of phytochemicals. These mechanisms include the induction of apoptosis, inhibition of cell growth, modulation of oxidative stress, and regulation of key proteins involved in cancer cell growth and

survival (Das et al., 2020; Robertson et al., 2022). A potential mechanism underlying the anticancer activity of UD is its ability to induce apoptosis or programmed cell death in cancer cells. Studies have demonstrated that UD extracts can influence the expression of key regulatory enzymes involved in apoptosis, such as ornithine decarboxylase (ODC) and adenosine deaminase (ADA), leading to the induction of apoptosis in cancer cells, particularly breast cancer cell lines (Fattahi et al., 2018). This apoptotic effect is crucial for inhibiting the proliferation of cancer cells and suppressing tumour growth. UD extracts have demonstrated the ability to inhibit cell growth and proliferation in various cancer cell lines, including breast cancer, prostate cancer, and leukaemia (Karakol et al., 2022; Konrad et al., 2000; Mekhfi et al., 2004). The antioxidant activity of plants can help mitigate oxidative stress and DNA damage, which are associated with cancer development and progression (Badgujar et al., 2015; Liao et al., 2013). Moreover, the modulation of key regulatory proteins involved in cancer cell growth and survival, such as p53 and caspases, has been implicated in the anticancer action of UD. UD plant extracts have been shown to influence the expression and activity of these proteins (p53 and caspases), contributing to their anticancer effects (Rashidbaghan et al., 2020). UD's broad-spectrum anticancer activity of UD highlights its potential as a natural anticancer agent and underscores the need for further investigation of its therapeutic potential.

Anti-aging

Research has shown that UD extracts possess antioxidant properties that combat oxidative damage associated with aging by scavenging free radicals and inhibiting oxidative stress. These mechanisms, supported by the scientific literature, contribute to UD's anti-aging effects (Fattahi et al., 2013). This scavenging property suggests that this plant may possess potential therapeutic benefits for age-related diseases and conditions (Konrad et al., 2000; Temiz et al., 2021). Furthermore, the extracts exhibited anti-inflammatory properties essential for mitigating chronic inflammation, a key contributor to aging and age-related diseases. Plant extracts have demonstrated haemostatic potential, which is important for maintaining skin health and promoting tissue regeneration processes integral to anti-aging interventions.

Cardioprotective

UD extracts have been shown to have cardiovascular effects, including vasodilation and blood pressure regulation, indicating their potential cardioprotective properties (Testai et al., 2002). Inhibition of platelet aggregation by UD leaf extract may help prevent thrombotic events, thus promoting cardiovascular health. The anti-inflammatory effects of UD extract can help reduce inflammation in the cardiovascular system, which is relevant for the prevention of cardiovascular diseases (Bhusal et al., 2022; Riehemann et al., 1999). UD extracts have been found to have immunomodulatory effects and preserve epithelial integrity in heart muscle (Franciškovi ć et al., 2017; Karadeniz et al., 2007). Inhibition of adenosine deaminase activity by UD extracts may also play a role in regulating immune responses, which assists in improving cardiovascular conditions (Durak et al., 2004; Naiyila et al., 2023).

Wound healing

The literature reveals that mechanisms that support the wound-healing activity of UD-isolated extracts may be attributed to their anti-inflammatory, antioxidant, haemostatic, cell migration and proliferation, antibacterial, and signalling pathway modulation properties. These properties create a conducive environment for tissue repair and regeneration, by reducing inflammation and oxidative stress. UD extracts demonstrate haemostatic potential, which is crucial for controlling bleeding and facilitating the initial stages of wound healing (Ciftciler et al., 2020). These extracts accelerate wound healing by promoting cell migration, proliferation, and angiogenesis (Chapnick and Liu, 2014). The antiproliferative activity of the aqueous extract of UD leaves provides valuable insights into the effects of UD on cell proliferation in human cell lines. Moreover, research has shown that UD inhibited proliferation and synergised the cisplatin induced cellular toxicity in non-small-cell lung carcinoma cells, indicating a potential role for UD in modulating cellular activities and influencing its impact on wound closure activity (D'Abrosca et al., 2019; Fattahi et al., 2013). The extract can prevent infections which is considered crucial for ensuring uninterrupted wound healing. Moreover, the extracts modulate signalling pathways, such as TGF-β/BMP, which play a significant role in the regulation of wound healing processes (Guo and Wang, 2008).

Anti-diarrhoeal

Anti-diarrhoeal mechanisms include reported antibacterial effects, which can aid in combating diarrhoeal infections and reducing the pathogenic load in the gut (Dv et al., 2018; Modarresi-Chahardehi et al., 2012). As discussed previously, UD mitigates oxidative stress and inflammation in the gastrointestinal tract, contributing to the alleviation of diarrhoea (Derradji et al., 2020). UD leaf extract may have also a protective effect on the gastrointestinal mucosa, potentially reducing the severity of diarrhoea. UD extracts can help reduce gut inflammation, which is often associated with diarrhoea (Fattahi et al., 2013). The inhibition of adenosine deaminase activity by UD extracts may also play a role in regulating immune responses and inflammation, which are relevant to diarrhoeal conditions (Durak et al., 2004).

Antimicrobial

UD demonstrates a range of antimicrobial mechanisms, such as disruption of cell membranes, impeding microbial growth and biofilm formation, and modulating oxidative stress and inflammation, which collectively contribute to the ability of plants to combat a variety of microbial pathogens. One potential mechanism underlying the antimicrobial activity of UD is the disruption of microbial cell membranes. Essential oils derived from UD leaves have been reported to exhibit antimicrobial effects by disrupting the integrity of microbial cell membranes, leading to cell lysis and death. This disruption is attributed to the presence of bioactive compounds such as terpenoids, which can interact with microbial membranes, compromising their structural integrity and function (Chouhan et al., 2017). Furthermore, the phytochemical constituents of UD, including flavonoids and phenolic compounds, have been shown to exhibit antimicrobial properties by interfering with microbial growth and proliferation. These compounds can inhibit microbial enzymes, interfere with microbial DNA replication, and disrupt essential microbial metabolic processes, ultimately leading to inhibition of microbial growth and survival (Asadi-Samani et al., 2017; Gunardi et al., 2023). In addition, the antimicrobial action of UD may involve the modulation of microbial biofilm formation. Biofilms are complex microbial communities that are highly resistant to antimicrobial agents. As suggested in the anthelminthic activity, UD extracts can interfere with biofilm formation, thereby addressing the issue of antimicrobial resistance (Amirinia et al., 2021). The UD extract may also help reduce oxidative stress and inflammation associated with microbial infections, thereby supporting host defence against microbial pathogens (Semwal, 2023).

Antiviral

The antiviral activity of UD is likely mediated through multiple mechanisms, including the inhibition of viral replication, interference with viral attachment and entry, modulation of the immune response, and reduction of oxidative stress and inflammation. Collectively, these mechanisms contribute to the potential of plants in combating viral

infections. The plant has been reported to display antiviral activity against a range of viruses, including HIV, FIV, and rotavirus (Knipping et al., 2012; Manganelli et al., 2005). These findings suggest the potential of UD as a natural antiviral agent. The antiviral activity of UD can be attributed to its diverse phytochemical composition including flavonoid glycosides, lectins, and other phytochemicals. The lectins such as *Hippeastrum* hybrid agglutinin (HHA), *UD* agglutinin (UDA) and *Galanthus nivalis* agglutinin (GNA) present in *UD* have demonstrated antiviral activity against HIV-1, highlighting the potential of these compounds in combating viral infections, among (François and Balzarini, 2010; Gordts et al., 2015; Ibrahim et al., 2018). UDA is a small monomeric lectin with a molecular size of 8.7 kDa and specific affinity for N-acetylglucosamine (GlcNAc). UDA inhibits binding of the virus to its host cell receptor, thereby preventing viral entry and subsequent replication (Sabzian-Molaei et al., 2022; Saul et al., 2000). Plant extracts are capable of combatting the oxidative stress resulting from viral replication and infection (Demir and Biçim, 2019). Furthermore, the anti-inflammatory properties of plants may help regulate the immune response to viral infections, potentially reducing viral replication and severity (Costagliola et al., 2021). The immunomodulatory and anti-inflammatory activities of UD extracts have been investigated, and their effects on the mitogenic response of splenocytes and NO production by macrophages have been demonstrated *in vitro* (Harput et al., 2005).

Cosmetics

The antioxidant effects of UD extracts, as evidenced by the presence of effective antioxidant compounds, make them suitable for cosmetic formulations aimed at protecting the skin from oxidative stress and environmental damage, as demonstrated in the study. Additionally, the anti-inflammatory properties of UD extracts render them valuable for skincare products, potentially aiding the management of skin conditions and promoting skin repair. Furthermore, the antimicrobial activity of UD extracts may be beneficial in cosmetic formulations, contributing to the preservation of products, and potentially offering antimicrobial benefits to the skin. The anti-aggregant properties of UD extracts suggest their potential use in products aimed at improving microcirculation and reducing skin imperfections (Mekhfi et al., 2004; Modarresi-Chahardehi et al., 2012). The presence of phytosterols in UD extracts may offer benefits to skin health and can be utilised in skincare formulations (Smoylovska, 2017). The effects of UD on histamine-induced prolactin release, and serotonin-induced release of thyrotropin-releasing hormone suggest its potential influence on hormonal balance, which can affect skin health (Easton et al., 2021).

Antioxidant activity

Extracts derived from the leaves and roots of UD have demonstrated potent antioxidant properties that are crucial for wound healing and other important biological processes (Jaiswal and Lee, 2022). These extracts have exhibited anti-inflammatory and antioxidant effects with potential applications in cancer treatment, as they promote apoptosis in leukaemia cells (Hodroj et al., 2020). Studies have revealed the antioxidant potential of UD aerial and root extracts, which have been shown to decrease lipid peroxidation and increase antioxidant enzyme levels, thereby protecting the liver. UD root extract has been shown to reduce atretic follicles and mitigate the adverse effects of retinoic acid on oocyte maturation, highlighting its role as a natural antioxidant agent (Shabir et al., 2022). Research has emphasised the high antioxidant activity of UD extracts, which may be attributed to their high polyphenolic content (Yousuf et al., 2022). UD root extracts have shown anti-inflammatory and antioxidant activities with potential applications in conditions such as asthma and oxidative stress-related diseases (Zemmouri et al., 2017).

Toxicological evaluation

It must be emphasised that the use of UD extracts has been linked to various health benefits, although there are also toxicological concerns and adverse effects. Research has shown that UD extracts possess antagonistic properties against the histamine-1 receptor and suppress prostaglandin formation by inhibiting key enzymes, such as COX-1, COX-2, and haematopoietic prostaglandin D2 synthase, which are pivotal in pro-inflammatory pathways (Vogl et al., 2013). Studies have demonstrated that UD extracts induce apoptosis in breast cancer cells by influencing the expression of specific genes, which may have implications for cellular processes and homoeostasis (Fattahi et al., 2018). UD has been identified as a galactagogue associated with galactorrhea in non-breastfeeding women, indicating its potential hormonal effects (Easton et al., 2021). UD extracts have been investigated for their antimicrobial activity, which may have implications for microbiota and microbial balance. The reported toxicological issues and adverse effects of UD extracts must be considered when assessing their suitability for various uses such as medicinal and cosmetic applications. Additional research and thorough toxicological studies are essential to fully comprehend the safety profile and potential risks associated with the use of UD extract.

Clinical trials/research

The clinical trials/research conducted so far has been compiled, as shown in Table 2 below.

Table 2 provides an overview of the outcomes of several studies that investigated the effects of UD and other extracts in addressing diverse health conditions. Clinical trials indicate that UD offers significant benefits to individuals with benign prostatic hyperplasia (BPH) (Lopatkin et al., 2005), osteoarthritis (Jacquet et al., 2009), rheumatoid arthritis (Abd-Nikfarjam et al., 2021), chronic prostatitis/chronic pelvic pain syndrome (Cai et al., 2022), and hypertension (Samaha et al., 2019). The antioxidant properties (Riehemann et al., 1999), extend its anticancer activity by reducing metastasis-related gene expression (Mansoori et al., 2017), and decrease proliferation in HL-60 cells (Temiz et al., 2021), antimicrobial activity (Amirinia et al., 2021), and cosmetic applications in treating dandruff (Sahraie-Rad et al., 2015).

Limitations to the study

It has been established that UD possesses various therapeutic properties, the majority of research conducted thus far has focused on crude plant extracts rather than isolated compounds. Consequently, further investigations are necessary to identify and isolate the active constituents that contribute to the therapeutic potential of UD. There exists a paucity of clinical trials and human studies involving UD, with the majority of current research consisting of *in vitro* and animal studies. Therefore, there is an urgent need for more rigorous clinical trials and human studies to validate the health benefits of UD observed in preclinical studies. Despite the limited number of well-designed human trials, various pharmacological activities of UD have been reported, although the precise mechanisms underlying these activities remain unclear. Therefore, further mechanistic studies are required to improve our understanding of the molecular mechanisms by which UD and its constituents exert their respective pharmacological effects. Although plants have been widely studied for their medicinal properties, few studies have focused on optimising their cultivation and agronomy. Moreover, further research is needed to determine the best cultivation practices, harvesting times, planting densities, and other factors that can maximise the yield and quality of medicinal compounds. Similarly, the exploration of genetic diversity among ecotypes of UD from various geographical regions has received relatively little attention.

Table 2
A compilation of the clinical trial/research conducted so far for *Urtica dioica*.

Effects	Phytoconstituents or plant extract used	Methods	Observation	References
Effects on lower urinary tract symptoms caused by Bening Prostate hyperplasia	Urtica roots (The activity may be because of phytosterols).	Double-blind clinical trial was conducted. The participants received two capsules/d of PRO (120 sabal fruit extract and UD root dry extract).	Subjects in the PRO 160/120 group exhibited a significantly greater decrease in their total I-PSS score compared to those in the placebo group ($P < 0.01$). Furthermore, the PRO 160/120 treatment demonstrated a distinct superiority over placebo in ameliorating the obstructive and irritative symptoms associated with benign prostatic hyperplasia (BPH).	(Lopatkin et al., 2005)
Effects on osteoarthritis (OA)	Urtica roots (The activity may be because of selenium).	Double-blind parallel-groups clinical trial compared Phytalgic® (fish oils rich in omega-3 and omega-6 fatty acids, UD (the common nettle), zinc and vitamin E) to a placebo for 3 months, in 81 patients with OA.	Three capsules for 3 months along with the OA drugs reduced the dose as analysed using Western Ontario-McMaster University Osteo-Arthritis Index (WOMAC) function scales.	(Jacquet et al., 2009)
Effects on osteoarthritis	Urtica roots (The activity may be because of selenium).	Clinical trials over patients with rheumatoid arthritis with 1 200 mg dried extract of UD per day.	3 months UD extracts, in combination with conventional treatment, can significantly decrease the level of blood inflammatory markers, improve therapeutic benefits and decrease RA-related complications.	(Abd-Nikfarjam et al., 2021)
Anti-dandruff effects	Urtica roots (The activity may be because of 5-α-reductas enzyme, β-sitosterol and ursolic acid)	The combination of UD with other extracts tested on 30 patients with dandruff on hair within a period of 2 months.	Daily application led to the effective removal of dandruff. The inhibition of the 5-α-reductase enzyme by *U. dioica*, coupled with its promotion of blood flow to nourish follicles through the presence of β-sitosterol and ursolic acid, contributes to this effect.	(Sahraie-Rad et al., 2015)
Efficacy in chronic prostatitis/chronic pelvic pain syndrome	Possible UD leaves extracts as it contains flavonoids.	The treatment group received PROSTAFLOG® for 4 weeks. The primary outcomes were improvements in NIH-CPSI scores of at least 65% and reductions in IL-8 levels by at least 25.	Both groups exhibited substantial enhancement in NIH-CPSI score and pain domain following treatment; however, the PROSTAFLOG group evinced more substantial progress in comparison to the Ibuprofen group. Elevated levels of IL-8 is modulated by UD extract, possibly leaves.	(Cai et al., 2022)
Antihypertensive effects	UD leaves extracts mainly containing phenolics.	The single-blind trial was conducted to study effects of plant extracts on the systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). Additionally, kidney and liver function tests were conducted every fourth week of the trial.	The phenolic compounds in UD leaves extract may exhibit significant antioxidant activity and vasorelaxant properties, which may reduce systolic blood pressure (SB), diastolic blood pressure (DBP) and mean arterial pressure (MAP) from 104 to 95. Additionally, supplementation with UD was also found to increase plasma antioxidant capacity and decrease systemic oxidative stress, which may play a role in its ability to lower blood pressure.	(Samaha et al., 2019)
Anti-inflammatory effects	UD leaves extract contains antioxidants.	Stinging nettle extract, when administered in a dose of 375 μg of its dry mass, demonstrated the ability to suppress NF-κB and AP-1 activity, which in turn reduced the production of.	Stinging nettle extracts inhibit NF-UB activation in various cell types and under different stimuli by preventing its inhibitory subunit IU UB-K degradation. The study shows that stinging nettle leaf extracts prevent the activation of proinflammatory transcription factor NF-UB in response to multiple stimuli.	(Riehemann et al., 1999)
Anticancer effects	UD leaves extract may contain flavonoids and phytoestrogens.	The effect of UD on MCF-7 and MDA-MB-231 breast cancer cell lines was studied using TaqMan real-time PCR and ELISA to measure ADA and ODC1 enzymes.	Compare ADA and ODC1 concentrations in MCF-7, MDA-MB231, and Fib cells with different UD extract concentrations (0.75 mg/ml, 1.5 mg/ml, and 3 mg/ml.). UD triggers apoptosis in breast cancer cells by modulating ODC1, ADA, and estrogens receptor gene expression.	(Fattahi et al., 2018)
Antimicrobial effects	Hydro alcoholic extract of UD stems and leaves.	This study compares biofilm inhibition of *Streptococcus mutans* and *Candida albicans* by *UD, Equisetum arvense,* and *Punica granatum* peel extracts, with chlorhexidine as the control.	The UD extract showed the strongest inhibition of biofilm formation for both *Streptococcus mutans* (eight times than MIC) and *Candida albicans* (four times than MIC). Nettle extract inhibits biofilm formation.	(Amirinia et al., 2021)
Antiviral effects	Not available.	UD extracts were *in vitro* tested on MA-104 cells, while simultaneously examining the impact of simian	The IC50 values for the extracts were 46, 116, 129, and 150 μM, and 1 mg/ml showed 50% inhibition of	(Knipping et al., 2012)

(*continued on next page*)

Table 2 (*continued*)

Effects	Phytoconstituents or plant extract used	Methods	Observation	References
		rotavirus infection on the loss of transepithelial resistance (TER) of Caco-2 cells.	infection. The positive control was hyperimmune colostrum (HIC). The aqueous extracts of *Nelumbo nucifera Gaertn.* fruit, UD L. root, *Aspalathus linearis* (Burm.f.) R. Dahlgren leaves, *Glycyrrhiza glabra* L. root, and *Olea europaea* L. leaves displayed strong antiviral activity against rotavirus. The UD extract inhibited infection by 57%.	
Antiviral effects (Feline immunodeficiency virus (FIV))	UD aerial stem extract containing lectins.	The utilisation of 0.5–1 g per millilitre of UD extract was implemented. The investigation involved assessing the efficacy of *Parietaria diffusa*, *Sambucus nigra*, and UD preparations against FIV infection.	UD demonstrated effective inhibition of syncytia formation, due to the possible effect of N-acetylglucosamine-specific lectin which a strong was a strong inhibitor of syncytium formation.	(Uncini Manganelli et al., 2005)
Anticancer effects (breast cancer)	UD leaves extracts possible containing antioxidative phenolics.	The UD extract concentrations in this study ranged from 5 to 30 ug/ml, and the IC50 value of UD was determined. MCF-7, MDA-MB-468, and MDA-MB-231 cells were treated with UD extract at concentrations of 5–30 ug/ml for 48 H.	The UD extract displayed anti-mutagenic properties due to its secondary metabolites. Flavonoids in UD reduced Ki-67activity, activated Caspase-3 hence induced apoptosis in tumoral tissues causing DNA damage, cytoplasmic shrinkage, and membrane blebbing.	(Karakol et al., 2022)
Anticancer effects (metastasis related gene expression)	UD leaves dichloromethane extract.	An extract of UD at a concentration of 10–70 mg/ml was utilised for the MTT assay and scratch test on normal cell lines (HFFF2) as well as marginal normal tissues derived from breast cancer cell lines.	The extract exerts an inhibitory effect on breast cancer cell proliferation and suppresses cancer cell migration. UD extract can activate apoptosis, exhibits the ability to decrease miR-21 expression, which consequently leads to a significant reduction in the overexpression of MMP1, MMP9, MMP13, vimentin, and CXCR4, and an increase in E-cadherin levels in the tumoral group.	(Mansoori et al., 2017)
Antiproliferative effects	Hydro alcoholic extract of UD stems and leaves.	The investigation of the genetic and molecular activities and antiproliferative effects of UD extracts on HL-60 cells at a 100 µg/ml dose.	The UD extract showed a significant reduction in HL-60 cell proliferation, due to increased NO levels, increased P53 expression triggering the apoptotic process.	(Temiz et al., 2021)
Antidiabetic effects	Hydro alcoholic extract of UD leaves.	The study reported a clinical trial to evaluate the antidiabetic effects of 100 mg kg^{-1} UD extract on 50 patients.	The serum levels of SOD in the intervention group was higher, suggesting that the hydro-alcoholic extract of Nettle may provide protection against cardiovascular disease in type 2 diabetes patients.	(Namazi et al., 2012)
Antioxidant and antiproliferative effects	Hydro alcoholic extract of UD leaves containing polyphenolics.	Antioxidant activities were evaluated for 12 mg/ml, 6 mg/ml, and 3 mg/ml using both the MTT and FRAP assay on breast cancer cells.	The UD extract exhibited dose dependent activity showing strong antioxidant properties and inhibiting breast cancer cell growth. The extract activates caspase-9 and caspase-3, which suppress MCF-7 breast cancer cell growth. Additionally, it enhances the activity of calpain 1, calpastatin, Bax, and Bcl-2 proteins.	(Fattahi et al., 2013)

UD, *Urtica dioica*.

Conclusion

This review article provides an overview of the phytochemical constituents, traditional use, and pharmacological applications of UD, also known as stinging nettle. This article highlights the broad range of pharmacological activities of UD, including anti-inflammatory, hypoglycaemic, antiurolithiatic, neuroprotective, antioxidant, antimicrobial, antiproliferative, and anticancer effects. UD leaves contain high levels of antioxidants, which may be useful for the treatment of breast cancer by inducing apoptosis. The current state of research on UD reveals its potential for various pharmacological activities; however, there are significant gaps in our understanding of its specific active compounds, mechanisms of action, clinical efficacy, agronomic practices, and genetic diversity. Addressing these research gaps is essential to unlock the full therapeutic potential of the stinging nettle and optimise its use as a medicinal plant. This article concludes that the diverse uses and biological properties of UD make it a subject of interest for further research.

Ethics approval

This study did not involve any human participants or animals in any phase. The authors assert that all sources have been duly credited and due diligence has been exercised to ensure the accuracy and reliability of the information. The objective of this research is purely academic, with the intention of synthesising and presenting existing knowledge in a clear and concise manner as a comprehensive review. The authors are dedicated to promoting ethical research practices and transparency in scholarly works.

Author contributions

Butool Fatima: Writing – review & editing, Validation, Investigation. **S Jayakumari:** Writing – original draft, Visualisation, Supervision, Methodology, Conceptualisation. **Md Alimoddin:** Writing – original draft, Visualisation, Software, Methodology, Investigation. **Mohammed Tahir Ansari:** Writing – review & editing, Visualisation, Methodology, Conceptualisation. **Rajesh Sreedharan Nair:** Writing – review & editing, Resources, Methodology. **Sajid Ali:** Writing – review & editing. **Farheen Sami:** Writing – review & editing, Software. **Sadat Ali:** Supervision, Methodology, Conceptualisation. **Nadeem Hasan:** Writing – review & editing, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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