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Abstract

The aim of this study was to investigate the nutritional value of *Urtica dioica* and suggest the application of *U. dioica* as part of a healthy diet. *U. dioica*, or commonly known as stinging nettle, is a perennial plant growing almost all over the world. It prefers moist soils with a high nitrogen content. When the plant comes in contact with the skin it releases small tubes which contain irritative substances which penetrates the skin giving a rash and a burning feeling. For cultivation it can be grown with low input and can give a relatively good yield for many years. It has been used for centuries as a food source and in folk medicine. In Sweden *U. dioica* is traditionally picked in spring and used to make "nettle soup". *U. dioica* can be purchased dried as powder, in capsules or as tea for example. According to the EAT Lancet report, the consumption of meat products should be decreased whereas fruits and vegetables should be consumed in higher portions. With its highly nutritious content, *U. dioica* can be included in such a diet. It contains vitamins, minerals, essential fatty acids and has a relatively high protein content. Nine carotenoids have been detected in *U. dioica*. Pigment from *U. dioica* can be extracted and used for food coloring (E140). Nitrate has a tendency to accumulate in the plant and therefore it should not be picked on soils which have high nitrogen levels. Water extraction from *U. dioica* is a good source of anti-oxidants which are health promoting in different ways. The anti-oxidant properties of *U. dioica* are probably due to presence of phenolic compounds. *U. dioica* have antibacterial properties against certain bacteria such as *Staphylococcus aureus*. *S. aureus* bacterium have strains that are antibiotic resistant which particularly causes problems in hospitals. Therefore, it is important to develop alternatives to the traditional antibiotics. *U. dioica* even contains substances with anticarcinogenic properties. As used externally, it can be applied fresh to relieve joint pain. *U. dioica* as a part of the diet has therefore many advantages but more studies need to be done to confirm its properties and elucidate the mechanism responsible for them.

Keywords: Urtica dioica, quercetin, 5-O-caffeoylquinic acid, β-sitosterol, nitrate, phenolic compounds

Sammanfattning

Syftet med den här rapporten var att undersöka hur man kan använda *Urtica dioica* och granska dess näringsinnehåll och visa på dess roll i en hälsosam kost. *U. dioica*, eller brännässla, är en perenn växt som finns mer eller mindre över hela världen. Den föredrar att växa i fuktiga jordar med mycket nitrat. När växten kommer i kontakt med huden släpper den små rörliknande strukturer som penetrerar huden och ger upphov till utslag och en brännande känsla. Den är enkel att kultivera och kan ge en relativt bra skörd i många år. Den har använts i århundraden till mat och inom folkmedicin. I Sverige plockar man traditionellt *U. dioica* på våren och gör nässelsoppa. Man kan köpa *U. dioica* som pulver, kapslar eller te till exempel. Enligt EAT Lancet rapporten behöver människor äta en diet som är mindre köttbaserad och mer växtbaserad. Med sitt höga näringsinnehåll kan *U. dioica* inkluderas i en mer växtbaserad diet. *U. dioica* innehåller vitaminer, mineralser, essentiella fettsyror och har ett relativt högt proteininnehåll. Nio karotenoider har detekterats i *U. dioica*. Pigment från *U. dioica* kan extraheras och användas som färgämne i mat (E140). Nitrat har en tendens att ackumuleras i växten och därför bör den inte plockas på nitratrika jordar. Vattenextraktion från *U. dioica* är en bra källa till antioxidanter som är hälsofrämjande på olika sätt. Antioxidantegenskaperna är troligen främst på grund av fenolföreningar. U. dioica kan verka antibakteriellt mot vissa bakterier såsom *Staphylococcus aureus.* Inom *S. aureus* släktet finns vissa antibiotikaresistenta stammar vilka speciellt kan ge problem på sjukhus. Därför är det viktigt att ta fram alternativ till traditionella antibiotika. *U. dioica* innehåller också substanser som hämmar cancer. Utvärtes kan *U. dioica* appliceras färska där en person har ledvärk vilket kan lindra smärtan. *U. dioica* som del av dieten har många fördelar men fler studier behövs för att bekräfta dess egenskaper och tydliggöra mekanismerna ansvariga för dem.

Nyckelord: Urtica dioica, quercetin, 5-O-caffeoylquinic acid, β-sitosterol, nitrat, fenolföreningar

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1 Introduction

Nowadays, the interest in plants as medicine is growing. Many currently used and newly developed drugs are originated from plants (Morales *et al.* 2016). *U. dioica* is the Latin name for stinging nettle which belongs to the family *Urticaceae*. *U. dioica* is an herbaceous perennial flowering plant which can be found more or less all over the world. *U. dioica* is also referred to as the "common nettle" (Zeipiņa *et al*., 2014). *U. dioica* have the male and female flowers on different plants. The harvest time depends of what the nettles should be used for. For tea or for fresh consumption it is preferable to harvest early in the season. For drying, the leaves and shoots can be picked from early season to late summer. It is recommended to pick *U. dioica* in areas with short growing season or harsh winters so the plant die and therefore nitrate do not accumulate in high concentrations in the plant over the years (Upton 2013). The whole plant is used for different purposes such as for food, medicine and in textile production (Kregiel *et al.* 2018).

1.1 Defense mechanism

U. dioica is covered with small hairs that sting. The small hairs are called trichomes. When the skin comes in contact with the trichomes they break and leave small tubes which can penetrate the skin. The tubes release a fluid which contain formic acid. Formic acid is also found in stings from bees and ants. The fluid in the tubes also contain serotonin, histamine and acetylcholine. These chemicals present in the fluids are what causes the itchy and burning feeling on the skin after touching a stinging nettle. The stinging serve as a defence mechanism to protect the plant from insects (Kregiel *et al.* 2018). When *U. dioica* is processed, e.g. cooked, blanched, dried or grinded etcetera, it does not sting anymore and can serve as a food (Carvalho *et al.* 2017).

1.2 Cultivation and occurrence

U. dioica is considered as a weed in the agricultural sector since it grows fast and can cover the ground in a short amount of time and thereby compete with other crops. *U. dioica* can be cultivated with good yield for approximately 10-15 years. It is easy to grow since it does not require much work and can grow in many places. Either it can be propagated vegetative or with seeds (Di Virgilio *et al.* 2015). *U. dioica* are found in many places around the world and it is native to North America, Europe, Africa and Asia (Kregiel *et al.* 2018). *U. dioica* prefer to grow in moist soil rich in nitrogen. They can grow in soils with a lot of heavy metals and inorganic nitrates. Heavy metals can accumulate in the plant if the soil is rich in those (Kregiel et al., 2018). The rhizomes survive the winter even if the plant wither, and the rhizomes will regrow again during the spring and is therefore considered a perennial crop (Di Virgilio *et al.* 2015).

1.3 Nutritional value

U. dioica has a high nutritional value and is often more nutritious than other common garden herbs and vegetables (Zeipiņa *et al.* 2014). *U. dioica* has a relatively high protein content and a better amino acid profile than many other leafy vegetables. It is rich in minerals such as iron (Adhikari *et al.* 2016). *U. dioica* leaves are also rich in vitamin C, vitamin B and vitamin K (Zeipiņa *et al.* 2014). *U. dioica* have a high content of carotenoids among these, lutein and its isomers are the most abundant. *B*-carotene is one of the carotenoids found in *U. dioica* (Guil-Guerrero *et al.* 2003). Water extraction from *U. dioica* is a good source of antioxidants because of its high content of phenolic compounds (Gülçin *et al.* 2004). Phenolic compounds can protect the body against harmful oxidative processes and might eventually protect against cancer (Basli *et al.* 2017). *U. dioica* contains essential fatty acids (Guil-Guerrero *et al.* 2003). It also contains other substances that might help against cancer such as β-sitosterol which were shown to have effect against breast cancer cells (Awad *et al.* 2007).

1.4 Medicinal purpose

U. dioica has been used as a herbal remedy for a very long time for treating various diseases in humans (Jan *et al.* 2017). Scientific studies show that *U. dioica* have properties making it anti-inflammatory, anti-bacterial and that it can reduce abdominal pain. These studies are animal studies or studies made *in vitro*. According to Penn State Hershey Medical Center (2017) *U. dioica* is also used to treat

symptoms related to benign prostatic hyperplasia where the prostate gland is enlarged and presses on the tube that leads the urine out of the body (Penn State Hershey Medical center 2017). *U. dioica* has also been used for "urtication", the practice of putting fresh plant material on body parts that are arthritic or paralyzed. This to take advantage of the stinging properties that can "heat" limbs and stimulate circulation (Upton 2013). For a long time urtication has been used in folk medicine for treating rheumatism, arthritis and muscular paralysis (Upton 2013). Some studies have indicated that the *U. dioica* have pain relieving effects on some joint pain (Randall *et al.* 2000).

1.5 Consumption

U. dioica are easy to find in nature and can be picked or purchased in dried form, as a tea, as extract and in capsules for example (Penn State Hershey Medical center 2017) In some regions of Spain small shoots from *U. dioica* is used in omelettes or eaten raw (Rutto *et al.* 2013). In Sweden the shots from the first *U. dioica* in the spring are picked and used in "nettle soup" (Dags att plocka 2019).

1.6 Aim of study

The aim of this study is to investigate the health effects and common use of *U. dioica*. Specifically, the study was aimed to answer following questions:
What are the components in *U. dioica* making them healthy respectively unhealthy?
What are the actions of these components?
Which other applications can *U. dioica* be used for?

2 Method

This is a literature review in which scientific articles, reviews and reports were the main sources. The scientific databases Web of science and Scopus were searched for articles using relevant keywords such as “nettle* OR *urtica* AND nutrition”, “Nettle* OR *dioica* AND carotenoid*”.

3 Results

3.1 Nutritional value of *U. dioica* in relation to diet and health

Nepalese *U. dioica* was shown to have a protein content of 33.8% dry basis (db). The amino acid profile is better than in many other leafy vegetables. Nepalese *U. dioica* also had high amounts of minerals and its ash content was around 16.2% (db). Nepalese *U. dioica* also had high levels of minerals, e.g. iron (277 mg/100g) and calcium (169 mg/100g). It also contained potassium, phosphorus, sodium and zinc. The crude fat content was approximately 3.55% (db) and the carbohydrate content around 37.4 % (db). In the same study it was also shown that the tannin content was 0.93mg/100g (Adhikari *et al.* 2016). According to a summary on tannins by Chung *et al*. (1998), generally, tannins can have both positive and negative health effects. They can hinder normal food digestion and inhibit uptake of some minerals and vitamins. Their intake has even been associated with an increase in certain caner types. Other studies, however, suggested that tannins might have anticarcinogenic activity. In plants, the main function of tannins is to protect against infections induced by certain microorganisms. In theory this means that tannins can have a positive effect on the microbial communities in the human gastro intestinal tract. Chemical structure and amount of untaken tannins are the factors which determine the final effect of tannins on the organism. Since tannins might have some health benefits it can be beneficial to intake a smaller amount (Chung *et al.* 1998). *U. dioica* are rich in vitamins such as vitamin B, C and K (Zeipiņa *et al.* 2014).

Saturated fatty acids are found in all parts of the plant and consists of palmitic acid and stearic acid. Palmitic acid is found in high amount in all parts of the plant. *U. dioica* also contain monounsaturated fatty acids though in low concentrations. The major monounsaturated fatty acids found in *U. dioica* were palmitoleic acid, oleic acid, gadoleic acid and erucic acid. The polyunsaturated fatty acids found in *U. dioica* are linoleic acid and α-linolenic acid. The leaves are especially high in α-linoleic acid (Guil-Guerrero *et al.* 2003). Linoleic acid is an essential omega-6 fatty acid. Linoleic acid is part of cell membranes and contributes to its structure. Arachidonic acid is formed from linoleic acid which in its turn is the major precursor to

eicosanoids which are bioactive metabolites involved in many physiological processes. *α*-linoleic acid is an essential omega-3 fatty acid. Docosahexaenoic acid (DHA) derives from *α*-linoleic acid and is important for normal brain function and for the retina in the eyes (Sanders 2016).

Aqueous extract of *U. dioica* is a good source of the components with antioxidant activity. The antioxidant activity of *U. dioica* is likely due to the presence of phenolic compounds. Phenolic compounds have an ability to scavenge free radicals, superoxide and hydrogen peroxide. They also have metal chelating properties and can donate hydrogens (Gülçin et al., 2004). Phenolic compounds are present in plants and regarded as secondary metabolites because they are not directly involved in the plant growth and development. They have various functions in plants such as giving some fruits their colour and special flavour (Cheynier 2012). Some studies indicated that the antioxidant properties of phenolic compounds can even prevent cancer development because of their ability to scavenge free superoxide radicals. Because of this ability, they can also protect the physiological systems in the body from harmful consequences due to oxidative processes (Basli *et al.* 2017).

U. dioica contain high quantities of pigment, and it is especially rich in chlorophyll (Zeipiņa *et al.* 2014). *U. dioica* leaves have a chlorophyll content of 1-5% of which 75% is α-chlorophyll and 25% is β-chlorophyll. Extraction of chlorophyll from *U. dioica* is used as a green colouring agent in food and medicine with E number E140. (Jan *et al.* 2017). In a study made on *Caenorhabditis elegans*, which is a nematode, it was shown that chlorophyll can improve resistance to oxidative stress. Chlorophyll also increased the lifespan in the nematodes with up to 25% (Wang & Wink 2016).

β-sitosterol is a phytosterol found in many plants (Awad *et al.* 2007). β-sitosterol can be extracted from the roots of *U. dioica* (Sajfrtová *et al.* 2005). An *in vitro* study on breast cancer cells showed that β-sitosterol supplementation can inhibit some sorts of tumour cells. β-sitosterol also affected tumour metastases *in vivo* by shrinking the size of them (Awad *et al.* 2007).

U. dioica extract also contain 5-O-caffeoylquinic acid (Orčić *et al.* 2014). 5-O-caffeoylquinic acid is also known as neochlorogenic acid (PubChem 2019). Neochlorogenic acid has an effect against gastric cancer according to a study made on ASG gastric cancer cells. Neochlorogenic acid inhibits the gastric cancer cells by inducing apoptosis (cell death) (Fang *et al.* 2018).

3.1.1 Carotenoids

U. dioica contain carotenoids. Nine different carotenoids were identified in a study made in Southeast Spain (Guil-Guerrero *et al.* 2003). In the leaves of *U. dioica* it was mainly lutein that was detected. Also, lutein isomers were a large part of the carotenoids. *U. dioica* can contribute to vitamin A intake since it contains beta carotene (Guil-Guerrero et al., 2003). There is a higher amount of carotenoids in

young leaves than in older ones (Zeipiņa *et al.* 2014). The main function of beta carotene is that it gets converted to vitamin A in humans. In vegetables there are no preformed vitamin A (Grune *et al.* 2010). Vitamin A plays many important roles in the body such as maintaining the functions of surface tissues, the immune system and for the eyes to be able to see when there is not much light. Vitamin A is important for healthy growth and for reproduction (Gilbert 2013). Lutein has antioxidant effects and can prevent and protect against diseases related to the eyes. Lutein can protect the retina from damaging light (Buscemi *et al.* 2018). In the leaves of U. dioica neoxanthin and violaxanthin were also found (Guil-Guerrero *et al.* 2003). Neoxanthin and violaxanthin are xanthophylls. They are present in leafy green vegetables. It seems as if only small amounts of these xanthophyll's can be absorbed by the human body (Kotake-Nara & Nagao 2011). An *in vitro* study on human prostate cancer cells showed that neoxanthin could induce apoptosis and thereby decrease the cancers cells viability. This is an indication that a high intake of foods containing neoxanthin could reduce the risk of prostate cancer (Kotake-Nara *et al.* 2001).

The nutritious components of *U. dioica* does not seem to get negatively affected by blanching or cooking (Rutto *et al.* 2013).

3.1.2 Nitrate

In *U. dioica* nitrate can accumulate and be stored in the vacuoles (Szabo *et al.* 2006). The European Commission Nitrate directive have set a limit of 50mg/l of nitrates in water. The Nitrate Directives (1991) purpose is to ensure that water in Europe keeps high quality (European Commission 2019). Nitrate is present in many foodstuffs and it is especially found in vegetables. The nitrate itself is relatively harmless but when ingested some of it changes form to nitrite and *N*-nitroso compounds which are considered toxic. These compounds can also be formed in the food before ingestion. The nitrite can react with hemoglobin and methemoglobin. This formation impairs the oxygen transport in the body. The symptoms of this is that the skin turns blue and it can even lead to suffocation. Infants are particularly susceptible to this condition. Nitrate can form carcinogenic *N*-nitroso compounds when reacting with amides or amines. These reactions can occur before ingestion, when a food product ripens, during storage, or in the stomach through enzymatic reactions. In several animal species the *N*-nitroso compounds have been shown to have carcinogenic properties (Santamaria 2006). On the other hand, an *in vitro* study showed that nitrite have antimicrobial properties against *Salmonella enteritidis*, *Salmonella typhimuirum*, *Yersinia enterocolitica*, *Shigella sonnei* and *Escherichia coli* 0157. When nitrate is ingested and converted to nitrite, the nitrite is acidified in the stomach which gives it antimicrobial properties. *S. enteritidis*, *S. typhimuirum*, *Y. enterocolitica*, *S. sonnei* and *E. coli* 0157 are involved in infective gastroenteris and this study indicates that acidified nitrite can protect against this condition (Dykhuizen *et al.* 1996).

3.1.3 Nitrogen fertilization effect on U. dioica

The content and chemical composition of *U. dioica* is related to geographic region, harvest time, genotype, climate et cetera (Kregiel *et al.* 2018). One study examined how fertilization with nitrogen affected the content of *U. dioica*. A study was performed in Zagreb (Croatia) where *U. dioica* was cultivated with seeds in a greenhouse without heating. The seedlings were then planted outside. The content of crude protein, potassium, iron, phenols, ascorbic acid and dry matter were examined. The study showed that crude protein, potassium and iron levels were higher when the plants were fertilized with higher amounts of nitrogen fertilization. In contrast, the content of iron, phenols, ascorbic acid and dry matter decreased with higher doses of fertilization. It was also shown that higher doses of nitrogen fertilization resulted in accumulation of nitrates in the plants. The levels of nitrogen fertilization tested were 0, 100 and 200 kg ha^{-1} (Radman *et al.* 2015). Another study examined how fertilization with nitrogen affected the content of flavonoids and phenolic acids. *U. dioica* plants were grown for three years and the different levels of nitrogen fertilization were 0, 100, 200 and 400 kg ha^{-1}. Overall the flavonoid glycoside concentration decreased with higher amounts of nitrogen added. This is, according to the report, not surprising since many flavonoids often are formed in plants when exposed to stressful conditions (such as lack of nitrogen). The addition of higher amounts of nitrogen did not give any significant effect on the levels of phenolic acids. In this study it was also confirmed that the content of dry matter decreased with higher amounts of nitrogen added (Grevsen *et al.* 2008).

3.1.4 Eventual medicinal properties

According to a study performed on rabbits, U. dioica has a diuretic effect. An aqueous extract of *U. dioica* was injected intravenously to the rabbits. After 30 minutes the injection induced an increase in sodium excretion, urine volume and total solute excretion. But the excretion of K+ did not increase significantly. The effect of the extract lasted for two hours. In the same study the effect of injection of aqueous extract from *U. dioica* on heart rate and blood pressure on rats was also examined. It was shown that the injection decreased the heart rate and systolic blood pressure significantly. The release of nitric oxide and the opening of potassium channels together with an effect on the hearts muscle contractions seems to be the cause of the lowering of the systolic blood pressure (Dizaye *et al.* 2013).

Renal ischemia/reperfusion injury (I/R) may occur after certain surgeries such as renal transplantation and other complicated surgeries (Sayhan *et al.* 2012). Ischemia/reperfusion injury is a condition where the blood can not reach an organ properly (Malek and Nematbakhsh, 2015). I/R injury results in a cascade of complex reactions eventually causing the renal cells death. I/R injury is one of the most common causes of acute renal failure and it also induces injury in the kidneys. An animal (rat) study showed that, after I/R injury, oil from *U. dioica* seeds can protect the proximal tubule from damage (Sayhan et al., 2012). The proximal tubule has many important functions in the kidney such as hormone production, certain metabolic functions and it is also responsible for keeping the body balanced regarding

nutrients, electrolytes and fluids (Curthoys & Moe 2014). It was suggested that *U. dioica* oil might even minimized the injury (Sayhan *et al.* 2012).

The NF-κB transcription factor can induce inflammation in the body by affecting the pro-inflammatory genes. NF-κB activity is raised in many inflammatory diseases. An extract from *U. dioica* can inhibit the activation of NF-κB thereby has acting as anti-inflammatory agent. The *U. dioica* extract does not seem to affect the NF-κB DNA binding but the mechanism seems rather to be that the extract inhibits the degradation of IκB. IκB is a subunit in NF-κB which inhibits the activation of NF-κB. Usually the IκB-α is proteolytically degraded and NF-κB gets activated but *U. dioica* inhibits this function. Intracellular reactive oxygen mediates needs to be formed to activate NF-κB and another inhibiting reaction might be the antioxidant properties that *U. dioica* extract possess (Riehemann et al., 1999). In a more recent study, the anti-inflammatory properties of *U. dioica* were confirmed where the mechanisms of how *U. dioica* improve the immune response were examined (Francišković *et al.* 2017).

U. dioica leaves has the ability to reduce abdominal pain and it has anti-inflammatory effects on rats (Hajhashemi & Klooshani 2013). In that study, abdominal pain in rats was induced with acetic acid. Then, the rats were given different doses of *U. dioica* leaf extract (100, 200 and 400 mg/kg). The highest dose of the extract reduced the abdominal twitches with 81%. The reference painkiller used reduced the abdominal twitches by 84%. The rat's paws were injected with carrageenan to induce an inflammation. An intake of 400mg/g extract of *U. dioica* before the induced inflammation reduced it significantly (Hajhashemi & Klooshani 2013). However, if these results can be translated to human, is not known.

Urtica root extract combined with sabal fruit extract was suggested to help against some lower urinary tract symptoms. Benign prostatic hyperplasia is the most common cause to lower urinary tract symptoms which is a regular problem in older males. Benign prostatic hyperplasia can lead to difficulties with urination, incomplete emptying of the bladder and can give irritative symptoms. In a study made with both a placebo group and a group which was given sabal fruit and *Urtica* root extract, it was shown that the extracts gave positive effects regarding irritative and obstructive symptoms related to prostatic enlargement when compared to the placebo treatment. The study was performed on 249 patients where 125 was given capsules containing sabal fruit extract and *Urtica* root extract and 124 patients were given placebo. First, all patients in the study was given placebo for two weeks. Those two weeks were then followed by 24 weeks where the patients were split in the treatment- and placebo groups. After 24 weeks all the 257 patients were given sabal fruit extract and *Urtica* root extract for another 24 weeks. Sabal fruit and *Urtica* root extract seems to have a synergistic effect (Lopatkin *et al.* 2005). To the best of my knowledge the exact mechanism is still unknown. Further studies are needed to confirm the effect of sabal fruit extract and *Urtica* root extract on benign prostatic hyperplasia.

Leaves from *U. dioica* were shown to have anti-microbial activity against methicillin resistant and methicillin sensitive *S. aureus* (MRSA and MSSA). MRSA and MSSA are a significant problem regarding infections in diabetic foot ulcers. Alternatives to traditional antibiotics used against MRSA was investigated by Zenão *et al.* (2017). MRSA and MSSA were isolated from diabetic foot ulcers and the effect of *U. dioica* extracts was investigated. It was shown that *U. dioica* extract did not kill the bacteria but limited their further growth and thus could also be used to prevent the infection. The anti-microbial activity in *U. dioica* is likely related to the high content of hydroxycinnamic acids and flavonoids. One of the most important flavonoids found for anti-microbial activity was quercetin (Zenão *et al.* 2017). Studies on quercetin showed other benefits such as anti-inflammatory and antioxidant activity. Quercetin is present in many fruits and vegetables (Li *et al.* 2016). In a murine model study, it was shown that quercetin could decrease inflammation related to asthma and therefore might be possible to use for treatment of asthmatic diseases and other allergic conditions (Rogerio *et al.* 2007).

In a study in Khuzestan (Iran) it was shown that methanolic and ethanolic *U. dioica* extracts have anti-bacterial activity against *Bacillus cereus*, *S. aureus*, *Staphylococcus epidermis* and *E. coli.* It was shown that the extracts inhibited the growth of the bacteria. The target for the active substances in *U. dioica* is the bacterial cell wall where it disrupts its structure. The extracts showed the highest effect against *S. epidermis* and the lowest against *B. cereus* and *S. aureus*. In the same study it was shown that the methanolic and ethanolic extracts had no effect against *Salmonella typhi*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus mirabilis*. These Gram-negative bacteria have an outer membrane envelope that can hinder certain substances from entering the bacteria which might be an explanation for the resistance against the *U. dioica* extracts (Motamedi *et al.* 2014).

In a small study on 18 patients the effect of *U. dioica* on joint pain was evaluated (Randall et al. 1999). The patients had used *U. dioica* externally directly on the area of pain for joint pain relief. The interview revealed that 17 of the 18 patients felt that the *U. dioica* had helped with pain relief and some of them even thought that the *U. dioica* had cured them. This was, however, a study with limited number of patients and it is difficult to draw any reliable conclusion. Randomized control trials are needed for further verification of *U. dioica* effects and for elucidation of mechanisms responsible for it. There are some indications that *U. dioica* can help against certain conditions with muscle and joint pain and *U. dioica* has traditionally been used as home remedy for centuries (Randall *et al.* 1999). Another study with 27 participants with osteoarthritis examined if application of fresh *U. dioica* leaves could relieve pain at the base of index finger or thumb (Randall et al. 2000). The study was performed for twelve weeks and included a placebo group which used leaves from *Lamium album* (white deadnettle). Application with *U. dioica* had pain relieving properties compared with placebo treatment. It was suggested that the sting from *U. dioica* releases serotonin, acetylcholine, leukotrienes, histamine together with other substances which contributes to the stinging and burning feeling after touching *U. dioica* (Randall *et al.* 2000). The next study did not show any effect of *U. dioica* on chronic knee pain when applied fresh (Randall et al. 2008). 42 persons

with chronic knee pain participated in the study. The placebo group received *Urtica galeopsifolia*. *U. galeopsifolia* is very similar to *U. dioica* but is not supposed to sting. Some patients however reported that the treatment with *U. dioica* reduced the pain (Randall *et al.* 2008).

In a study on rats *U. dioica* was tested for its wound healing properties individually and in combination with *Sambucus ebulus* (Babaei *et al.* 2017). *S. ebulus* is also known as dwarf elder or danewort. *S. ebulus* has been used as a medicinal herb in folk medicine since ancient times (Jabbari *et al.* 2017). It was shown that *U. dioica* can facilitate wound healing, probably partially due to its anti- inflammatory and anti-bacterial properties. Compared to the control group, administration of only *U. dioica* had wound healing properties; this effect further increased when combined with *S. ebulus*. The combination of *U. dioica* and *S. ebulus* seems to have a synergistic effect which makes the two plants effective for wound healing (Babaei *et al.* 2017). However, human studies investigating the possibility to use these plants for wound healing are lacking.

3.2 Phytoremediation

It has been shown that *U. dioica* can be used for phytoremediation. A study where several plants were tested, *U. dioica* was shown to be effective in its uptake of chromium. Chromium is widely used in many industries and often contaminates the surrounding environment. Chromium can leach out to drinking water and accumulate in soil. *U. dioica* was shown to be effective in accumulating chromium and survive even when exposed to high levels (200 mg/l and 500 mg/l solutions) (Shams *et al.* 2010).

One of the industries that uses, and leaches lead out in the environment is the battery industry. Soil from around battery factories and recyclers was taken and compared to normal soil. *U. dioica* plants were planted in both kinds of soils. It was shown that *U. dioica* in the contaminated soil could both accumulate and tolerate high levels of lead. Thus, *U. dioica* can be used for removal of lead in contaminated soils (Grubor 2008). However, more studies are needed to identify and suggest how it can be performed in practice in large areas.

4 Discussion

As it seems, *U. dioica* can theoretically be used in many different areas, such as in medicine, as part of a healthy diet and in phytoremediation.

Antibiotic resistance has become a problem all over the world because of the high amounts of antibiotics used and microbes ability to develop resistance mechanisms (Davies & Davies 2010). The first resistant strains were found in hospitals. One of the first ones found was *S. aureus* in hospitals in London in 1940s', and since then more and more resistant strains have been detected. Simply explained, when bacteria are exposed to antibiotics, the ones that are susceptible are inhibited and the ones that are resistant keep living. These resistant bacteria can then spread their resistant genes to other bacteria (Levy & Marshall 2004). One way to reduce the widespread resistance might be to develop alternatives to antibiotics or find compounds that can be used together with antibiotics. Since extract from *U. dioica* has been found to inhibit the growth of bacteria such as MRSA, MSSA, *B. cereus*, *S. epidermis* and *E. coli* this can be a helpful tool in the work against resistant bacteria (Zenão *et al.* 2017) (Motamedi *et al.* 2014).

The EAT-Lancet commission is a report on how the world's population can be fed in a sustainable way. In this report a healthy and environmentally friendly diet is recommended. 820 million people does not have enough food today and even more people have a poor diet resulting in deficiencies in macro and micronutrients. The diet recommended in the report is high in vegetables, fruits, whole grains, legumes, nuts, unsaturated oil with an addition of a small amount of seafood and poultry (Willett *et al.* 2019). There are approximately 30 000 edible plant species in the world, but humans only cultivate 150 of them. 30 of these make up the majority of what humans eat. To include more wild plants is a sustainable way to make the diet more diversified and create more sustainable agriculture. Many crops have been lost through the history and since we rely today on only a few crops, this makes the food industry and humans more sensitive to the negative effects of global environmental change (Shelef *et al.* 2017). *U. dioica* with its high nutritional value (Zeipiņa *et al.* 2014) are found wild all over the world (Kregiel *et al.* 2018). If cultivated, it is easy to grow and can give a relatively high yield for many years (Di Virgilio *et al.* 2015). *U. dioica* has a higher content of protein and bioactive compounds than wheat and barley (Adhikari *et al.* 2016). It is also rich

in vitamin B, C and K (Zeipiņa *et al.* 2014). To meet the criteria for a healthy and environmentally friendly diet that EAT Lancet has set up, one alternative is to add wild plants such as *U. dioica* to the diet which are healthy and easy to find in nature where they are part of the local flora. Considering the recommended diet contains less meat, alternative protein rich food sources are important.

Many medications are known to have side effects. For example, Furosemide which has a diuretic effect and is prescribed to patients with edema and volume overload problems. Some side effects include pancreatitis, diarrhoea, tinnitus and abdominal cramping (Khan & Siddiqui 2019). *U. dioica* are shown to have a diuretic effect (Dizaye *et al.* 2013) and could be an alternative to strong diuretic medicines with many side effects. Also, *U. dioica* did not significantly affect the excretion of potassium as Furosemide does. So therefore if *U. dioica* is used for diuretic purposes supplementation with potassium might not be needed (Dizaye *et al.* 2013). Another medicinal effect of *U. dioica* is that it is anti-inflammatory which can make it useful in rheumatoid arthritis (Riehemann *et al.* 1999).

How to heal wounds faster is one major question in modern medicine. The process of wound healing is an advanced process and there are many factors affecting it. To be able to use plants that are easy to find in nature such as *U. dioica* might be a cost effective way with fewer adverse effects (Babaei *et al.* 2017).

The chemical composition of *U. dioica* is affected by many different factors such as nitrogen levels in the soil (Grevsen *et al.* 2008; Radman *et al.* 2015) climate, harvest time, processing etcetera (Kregiel *et al.* 2018). This makes it possible to affect the chemical composition depending on what the plant will be used for. For example the flavonoid content can be affected by how much nitrogen is added to the soil (Grevsen *et al.* 2008). This property of *U. dioica* can be utilized if certain compounds will be extracted or if it's supposed to be used as a food with extra high content of certain nutrients. *U. dioica* which grow on nitrogen rich soils might not be suitable for consumption. They can contain high levels of nitrate which can have negative effects on human health (Santamaria 2006).

If a soil contains high levels of certain heavy metals these might need to be removed by remediation. Methods usually used are excavation, thermal treatment and chemical soil washing. These methods might damage the area and are usually expensive. Phytoremediation is an attractive alternative to these earlier used methods (Prasad & Hagemeyer 1999). Chromium is used in many industries and can be a problem if it leaches out in nature. The ability of *U. dioica* to take up chromium (Shams *et al.* 2010) and lead (Grubor 2008) can be an alternative to the older methods. The use of plants for remediation is less expensive in comparison to other methods (Shams *et al.* 2010).

U. dioica has been used for centuries for healing different medical conditions but scientific studies on its properties are limited. Even though many studies showed positive effects of *U. dioica* on certain diseases and medical conditions further

studies are needed to evaluate if *U. dioica* has any side effects or interact with other medications. Additionally, in many studies made regarding the properties of *U. dioica* the mechanisms are not fully known. The biochemical composition of *U. dioica* is determined by geographical region, which is worth considering if picking for food consumption, especially if it grows on nitrogen rich soils. Generally, very few studies were performed on the comparison of the properties and health effects of *U. dioica* in relation to geographical region, genetic variations et cetera. Most studies were performed using laboratory animals which gives an indication on what *U. dioica* can be used for. Studies on humans are however urgently needed to confirm that it has the same effect on humans as on laboratory animals.

5 Conclusion

U. dioica has a high nutritional value and can be part of a healthy diet. Surprisingly, the use of *U. dioica* is nowadays limited. However, it can have various application. The presence of high levels of bioactive compounds such as flavonoids make *U. dioica* an excellent candidate as functional food to prevent the development of several diseases. Currently, the mechanisms of action of these compounds, especially as related to reduced risk of disease in individuals, are not completely understood and further studies are needed. Since *U. dioica* can accumulate some substances that might not be healthy in high doses. Thus, more studies are needed to evaluate an optimal dose of *U. dioica* in human diet. Another interesting possible application of *U. dioica* is its potential use in phytoremediation which is more environmentally friendly and less expensive than traditional currently used methods.

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