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Medical Plants- Change of use with time

by

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Sammanfattning

Växter har under alla tider använts för att lindra och förhindra olika sjukdomstillstånd. När den moderna läkarvetenskapen gjorde sitt intåg så blev huskurer baserade på örter omoderna men idag så ökar intresset och användningen av örtmediciner över hela världen. Örterna används inte enbart inom homeopatin utan även i den moderna läkarvetenskapen men här så utvinns de olika ämnena från växten. Exempel på detta är *Taxus baccata* och *T. brevifolia* från vilka taxol och baccatin III utvinns för användning inom cancerbehandling.

Syftet med det här arbetet var att undersöka om användningsområdet för tre vanliga medicinalväxter har ändrats i takt med vetenskapliga framsteg och nya metoder. Varje växt fick en kortare morfologisk beskrivning följd av en presentation av den dåtida, nutida och framtida användningen av växten. Även några av de andra användningsområdena än medicin har blivit presenterade i den här rapporten och även en förteckning över de länder där dessa växter finns i kommersiell produktion.

De tre växter som undersökts är *Digitalis* för dess användning inom hjärtmedicin, *Echinacea* för dess väldigt vanliga användningsområden för att förebygga och förkorta övre luftvägsinfektioner och *Hypericum* för användning både inom den konventionella läkarvetenskapen och inom homeopatin för behandling av psykiska problem.

De tre medicinalväxter som jag valde att skriva om har mer eller mindre samma användningsområde idag som de hade då de började användas. För mer allvarliga infektioner och sjukdomstillstånd där dessa växter tidigare ansågs som mirakelbotemedel används de nuförtiden mycket sällan eller aldrig. Detta beror troligtvis på att i takt med vetenskapliga framsteg och den moderna medicinen så har mer effektiva botemedel upptäckts. I några fall så har sjukdomen eller sjukdomstillståndet mer eller mindre utrotats i I-länderna. Exempel på detta är barnsängsfeber och syfilisinfektioner av andra eller tredje graden.

Summary

Since the beginning of time, the humankind has used plants to cure all sorts of diseases, both physiological and psychological. With the entry of modern medicine the herbal remedies became unpopular but today herbal medicine is becoming more and more popular all over the world. The herbs are not only used in homeopathy but also in more conventional school medicine but here the different constituens are extracted from the plants, e.g. *Taxus baccata* and *T. brevifolia* from which taxol and baccatin III are extracted and used as cancer treatment.

The aim of the project was to see if the medical use of three medicinal plants has changed with the development of new technology and scientific progress. Each plant was given a short morphological presentation and thereafter the medical use before, today and in the future was presented. In this report some of the other ways to use the different plants are also mentioned as well as some of the countries in the world where the plants can be found in commercial cultivation.

The plants chosen are *Digitalis* for its use as a heart medicine, *Echinacea* for the very common use in both treating and preventing upper respiratory infections and at last *Hypericum* that is used both in conventional medicine and in homeopathy as a treatment for psychological disorders.

The three medical plants that I chose to write about have more or less the same area of usage today as they had from the beginning. For more serious infections and other medical conditions that are difficult to treat these plants earlier where considered as miracle cures they are no longer or to a very small extent used. This is probably due to the fact that with scientific progress and the modern medicine new and more effective cures where found. In some cases the answer is that the disease or the medical condition is more or less eradicated in the western part of the world e.g. child-bed fever and syphilis infections of second to third degree.

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Material and methods

When this project started the only thing that was clear to me was that this was going to be conducted as a literature project and that the content would be about medicinal plants. I was suggested by my supervisor to investigate and find three plants that I was especially interested in and could find information about. After some search at the library at Alnarp and at the Internet I choose three genera and within these some species. The ones that I found were *Digitalis* spp., *Echinacea* spp. and *Hypericum perforatum.*

To present the plants I made a plan, where I start with giving a morphological description, followed by the medical uses before, today and in the future. To end with I will shortly mention some of the countries where these plants today can be found in commercial cultivation.

To find the information needed the main sources was the library in Alnarp and the Internet.

Introduction

Since the beginning of time, the humankind has used plants to cure all sorts of diseases, both physiological and psychological. Today this is made visible through all de remedies and dietary supplements in our western culture and in the Traditional Chinese Medicine (TCM) as well as in the Indian medical system of Ayurveda. These are just the more commonly known users of herbal remedies but of course herbs are used in every culture all over the world.

In more conventional school medicine constituents from the herbs are used in treating different disorders. Examples of this are the *Taxus baccata* and *T. brevifolia* from which taxol and baccatin III are extracted and used for cancer treatment. *Artemisia annua* is used in producing artemisinin derivates against malaria parasites that have become resistant to ordinary medical treatments. This drug is developed from the TCM (Abrahamsson, 2003). Another plant that is well known is *Papaver somniferum,* from which opium and its derivatives morphine and codeine can be obtained, both are used as pain killers. Sadly, many of the plants used for treating various disorders have been forgotten and need to be rediscovered. Today medical companies and universities investigate the whole plant kingdom in order to find new plants to be used as treatments in various ways. Also old remedies where the functions of the plants have been forgotten are investigated (Lewis & Lewis, 2006).

This bachelor project is conducted as a literature project. The aim with the project was to see if the medical use of three medicinal plants has changed with the development of new technology and scientific progress. Each plant will be given a short morphological presentation and thereafter the medical use in the past, present and future will be presented. In this report some of the other ways to use the different plants are also mentioned as well as some of the countries in the world where the plants can be found in commercial cultivation.

The plants chosen are *Digitalis* for its use as a heart medicine, *Echinacea* for the very common use in both treating and preventing upper respiratory infections and finally *Hypericum* that is used both in conventional medicine and in homeopathy as a treatment for psychological disorders.

Digitalis purpurea, D.lanata Foxglove, Fingerborsblomma, Grekisk fingerborgsblomma

Morphology

Digitalis belongs to the family Scrophulariaceae and the subfamily Rhinanthoideae. The subfamily is characterised by having flowers with ascending corolla aestivation, meaning that in the bud the lower lip covers the upper lip (Jacobsen & Jensen, 1999). Both *Digitalis purpurea* and *D. lanata* are biennial to perennial herbs or shrublets that are native to Europe. The first year they form a rosette of basal leaves, which are lanceolate in shape. The second year a high, upright and mostly unbranched stem with unilateral inflorescence is formed, that is the flowers are formed on one side of the stem. The leaves are upright and are placed in a spiral. After fertilisation the flowers form a bi-valvate capsule, meaning that the capsule has two valves where the seeds are located (Jacobsen & Jensen, 1999; Stodola & Volák, 2000).

Digitalis purpurea has a stem that is covered in woolly hairs and the lower leaves are 10-30cm long, have a winged petiole and are ovate to lanceolate in the shape. The tip of the leaves is acute and that means the leaves end with a sharp tip. On the lower side of the leaves they are canesent i.e. they are densely covered with short, greyish-white hairs and the total height of the plant is 100 to 150cm. Flowers that are large and campanulate (formed like bells) appear on a unilateral raceme. That is when flowers are on one side of the stem and start to flower with the lowest bud first and the top at the end of the flowering period. Colour of flowers can be violet, redish, white or pale yellow with a pubescent (somewhat hairy) inside. The flowers have purple to dark red dots on the inside. (figure 1)

Figure 1. *Digitalis purpurea* (Jansson, 2006).

The flowering time for *D. purpurea* is June to August (Botaniska Trädgården, 1998; Hickey & King, 2000; Mossberg & Stenberg, 2003; Stodola & Volák, 2000; Cheers, *et al.* 2003).

For *D. lanata* the stem is tall, around 90cm in height, erect and with many sessile leaves, the leaves have no stalk. Compared to the leaves of *D.purpurea* the leaves on *D.lanata* are smaller, more narrowly lanceolate, with entire to crenate (wavy) leaf margins and they are less hairy.The bell shaped flowers are wolly, located on a terminal raceme and the colour of the flower is brownish-white where the lower lip is white and the "bell" is brownish and the woolly flowers have given this plant one of its common names, namely woolly *Digitalis*. (figure 2)

Figure 2. *Digitalis lanata* (Jansson, 2006)

The flowering time for *D. lanata* is July to August. (Botaniska Trädgården, 1998; Hickey & King, 2000; Stodola & Volák, 2000; Cheers, *et al.*, 2003).

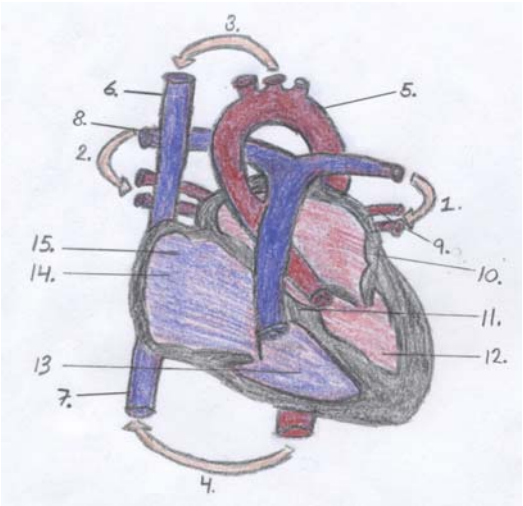
Medical use in the past

Digitalis was unknown as a medicinal plant to the ancient Greek and Romans and it was poorly known in the mainland of Europe. In Ireland it was used already during the 5th century as a cure against childbed fever. In the herbal book *Meddoygon Myddwai, Digitalis* is mentioned as a treatment for headache, tumours in the genital area and carbuncles etc (Hewe, 1952). In Wales during the 14th century *Digitalis* was used as external cover on severely infected wounds. In France and Germany *Digitalis* was found to be useful as a way to treat oedema, a disease that mostly was treated with laxative plants, e.g. bark from Alder Buckthorn (*Frangula alnus*). At this point the impact that foxglove has on the heart was not yet known (Heino, 2001). Oedema is a condition that occurs when the heart is not strong enough to pump the blood back to the heart at a sufficient pressure. When the pressure in the vena cava vessel is to low this allows fluids from the blood to leak out into surrounding tissues. It is not only the heart that is working insufficiently but also the kidney and this makes the body unable to excrete the excess fluid. The fluids fill up every empty space in the body give swollen areas causing great stress on the heart and eventually congestive heart failure. The fluids can also fill up the lung cavity and unless the patient sat upright all day and all night, he or she would drown. Because of the watery fluids filling up the body this disease

was called hydrops or more commonly dropsy (Lewis and Lewis, 2006). The plant was also used to treat carbuncles, headache, fever and for wound treating. Research has shown that extracts from the leaves have a healing effect on lesions induced by X-rays (Nielsen, 1978).

In the late 18th century medical science was puzzled why a remedy containing 20 herbs could be more efficient to treat oedema and various heart and kidney diseases than the ordinary medical treatment. The remedy came from a woman in England that treated people with herbal drugs; both the profession and the recipes had gone from mother to daughter for several generations. The doctors and the scientists tried to persuade the woman to hand them the recipe and reveal the secret. But the woman did not give them the recipes so the English and French science academies appointed a commission to investigate why this remedy was so powerful. The commission gave the English doctor William Withering the assignment to find out what the constituent/constituents of action were. After a long time, about 20 years, he found out that it was *Digitalis* that was responsible for most of the impact the remedy had on the diseases. He wrote about this in his dissertation, *An account of the Foxglove and its Medical Uses, with Practical Remarks on Dropsy, and Other Diseases* (Heino, 2001 and Hewe, 1952)

Present medical use



Digitalis is known to be very good for various heart diseases where the symptoms can be congestive heart failure (CHF) and arrhythmia. CHF is when the heart does not function sufficiently as a pump and this gives rise to either congestion of blood in the lungs or backup pressure of blood in the veins leading back to the heart. Arrhythmia is when the heart beats irregularly and there are different forms of arrhythmia. Tachycardia is when the heart beats at

Figure 3. Nr **1:**Left lung **2:**Right lung **3:**Upper body **4:** Lower body **5:** Aorta **6:** Superior vena cava **7:** Inferior vena cava **8:** Pulmonary artery **9:** Pulmonary veins **10:** Left atrium **11:** region of atrioventricular node **12:** Left ventricle **13:** Right ventricle **14:** Region of sinoatrial node (normal pacemaker) **15:** Right atrium. Figure is redrawn from Lewis & Lewis, 2006

a very fast but regular rhythm, fibrillation is an irregular, rapid twitching and atrial flutter is when only every other atrial beat travels through the ventricles (Lewis & Lewis, 2006).

Today, much of the active substances from *Digitalis* are made synthetically but in homeopathic medicines as well as to some extent conventional medicine the plant is still used.

In homeopathy, *Digitalis* is mostly used in medicals for so called old age heart, meaning a condition where the heartbeats are less powerful and regular than before, a condition that is often combined with sleeping problems and anxiety (Heino, 2001).

In commercial growing *D. lanata* is the more common because of the higher disease and cold tolerance. *Digitalis lanata* also has a higher concentration of heart glycosides corresponding to about 4 times more effective than those from *D. purpurea* (Stodola & Volák 2000).

The active constituents are extracted from the second year leaves and among these the heart glycosides (*D. purpurea*: purpureaglycosides A, B, digitoxin, gitaloxin and gitoxin and from *D. lanata*: lanatosid A, B and C, acetyldigitoxin and digoxin). The glycosides from *Digitalis* leaves strengthen and regulate the hearth rhythm and also act as strong diuretic (Stodola & Volák 2000). By increasing the contractibility of the heart muscle it results in slower but much stronger heart beats. This is done by slowing down the violently beating ventricles to a normal pace by delaying or blocking the transmission of the electric impulse through the atrioventricular node (Lewis & Lewis, 2006).

The *Digitalis* glycosides compete with potassium for binding on a enzyme called potassium-ATPase (Na^+/K^+ -ATPase) and by blocking potassium from binding to this enzyme the heart muscle is exposed to calcium for a longer period than normally. This leads to the heart contracting more forcefully (Sanchez, 2000). The effects that *Digitalis* glycosides have on the heart are induced both by the ion pumping function and the more recently discovered signal transducing function of Na^+/K^+ -ATPase. This enzyme participates in protein-protein interactions that lead to the activation of multiple growth-related signal transduction pathways. Some of these pathways play an important role in the increased contractibility of the heart that is induced by *Digitalis* (Kometiani *et al.* 2004).

The increased heart beats enlarge the amount of blood being oxygenated by the lungs, as well as the blood in general circulation with sometimes as much as 30%. The glycosides do not directly affect the kidneys, but by improving the hearth function more blood is starting to circulate in the kidneys. This will make them more effective in changing excessive water into urine (Stodola & Volák, 2000 and Lewis & Lewis, 2006).

All *Digitalis* glycosides are most often taken orally and the dosage can be as high as 70% of the toxic dose. This makes it very important to adjust the dosage after the individual patients needs. Digitoxin (figure 4) is somewhat more completely absorbed in the intestine than digoxin (figure 5) but on the other hand digoxin has a more rapid diminution of effect. Today constituents from *D. lanata* are more commonly used as prescribed medicines but for a large maintenance of doses where the patient would have been forced to take digoxin more than once daily, the longer acting digitoxin (with a half life of 5-14 days depending on dosage and the patient (Sanchez, 2000)) is still the best alternative,

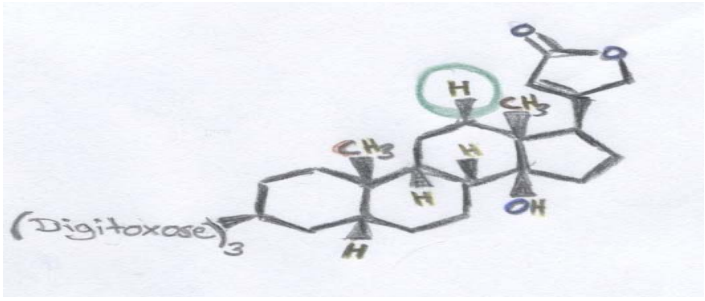


Figure 4. Chemical formula of Digitoxin. Redrawn from Sanchez 2000.

The *Digitalis* glycosides are most important in treatment and prevention of cardiac failure but they are also of value in treating certain arrhythmias and then particularly atrial tachycardia. The aim is to alter the arrhythmia to normal rhythm or to control the ventricular rate. Since digitoxin is slowly absorbed it is better to use digoxin or lantanosid C, as they are more rapidly absorbed and therefore more rapid in action, to treat these conditions (Lewis & Lewis, 2006).

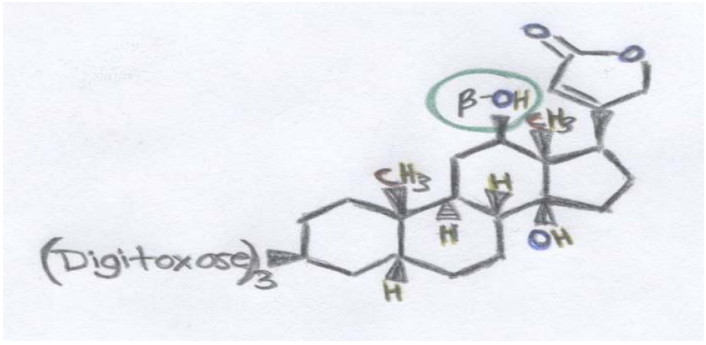


Figure 5. Chemical formula of digoxin. Redrawn from Sanchez, 2000.

The side and toxicity effects for the *Digitalis* glycosides are several and some of them are as follows: nausea, vomiting, irregular heartbeat, vision disorders such as changed colours and blurriness, headache and fatigue (Sanchez, 2000).

Glycosides from *Digitalis* are not only used for treating heart conditions but can also be used for their effect on cancer cells. In the 1960s *in vitro* studies showed that malignant cells were inhibited by cardiac glycosides. But the short-term animal tests that were conducted indicated that toxic levels of the glycosides would have been necessary to achieve an anticancer effect in humans and very little research within this area was carried out after this discovery. In 1979 observations made on cancer cells from women with breast cancer showed that the women taking *Digitalis* had more benign characteristics than the cancer cells from women that were

not on *Digitalis*. At a follow up five years later it was observed that the recurrence was 9.6 times higher for women not taking *Digitalis* compared to the ones taking the drugs. None of these findings led to much research in this area and the possible benefit of *Digitalis* glycosides needs to be further investigated (López- Lázaro, *et al.* (2005).

Future medical use.

When treating heart failure patients with atrial fibrillation the physicians often use digoxin. Digoxin does not offer rate control benefits in patients with sinus rhythm, but a study has shown that the patients may benefit from the improvement on the cardiac performance that the drug induces. Since digoxin in this investigation had no adverse effect on mortality, is readily available and inexpensive it should be used in management of heart failure patients in sinus rhythm, that is to keep the heart beat at a normal pace (Lewis and Lewis, 2006).

Another area where the glycosides from *Digitalis* can be used is when treating cancer, but this requires further research. It is not only the heart glycosides from *Digitalis* that can be useful, other heart glycosides such as oleandrin and ouabain have also been subjects for research. The heart glycosides have been shown to induce apoptosis in different malignant cells e.g. prostate-, breast-, leukemia-, and cancer in the kidney/urinary tract. It seems like that the malignant cells are more sensitive to the effects of *Digitalis* than normal cells (Haux *et al.*, 2001).

Research done by Haux *et al.* (2001) have shown that the TK-10 renal adenocarcinoma cell line that is normally considered as one of the most resistant to cancer chemotherapeutic drugs was sensitive to digitoxin. In this study this line of cancer was shown to be hypersensitive to digitoxin compared to other cancer lines which supports the findings done by Haux *et al* (2001). In this study apoptosis was found in TK-10 cells at digitoxin concentrations of 3 nM. It has been shown that high plasma concentrations (more than 21 nM) of digitoxin lowers the risk of cancer in the kidney/urinary tract. All these data suggests that digitoxin has a potential in treatment of cancer in kidney/urinary tract (López- Lázaro, *et al.* 2005). Kometiani *et al.* (2004) investigated the effect of the ion pumping and signal transducing functions of Na^+/K^+ -ATPase in human breast cancer cells. They found that digitoxin seemed to be more effective than digoxin when inhibiting the growth of the cancer cells. If the concentrations of *Digitalis* drugs are sufficiently high they alter the normal Na^+ and K^+ gradients and are then lethal to nearly all mammalian cells. This together with the findings made by López- Lázaro *et al.*

(2005) indicates that cancer cells are more sensitive to an altered Na^+ and K^+ concentration and therefore can be defeated with the use of *Digitalis* drugs.

Commercial growing

Before 1950 the Balkan countries where the major delivers of glycosides from *D. lanata* but trials in Switzerland have been successful and nowadays they deliver a *D.lanata* drug that is of the same high quality as the one from the Balkans (Hewe, 1952) The major part of the commercial growing of *Digitalis* is today in countries like USA, UK, the Netherlands, Switzerland, Germany and the former USSR as well as the Balkan countries. (FAO, 2004)

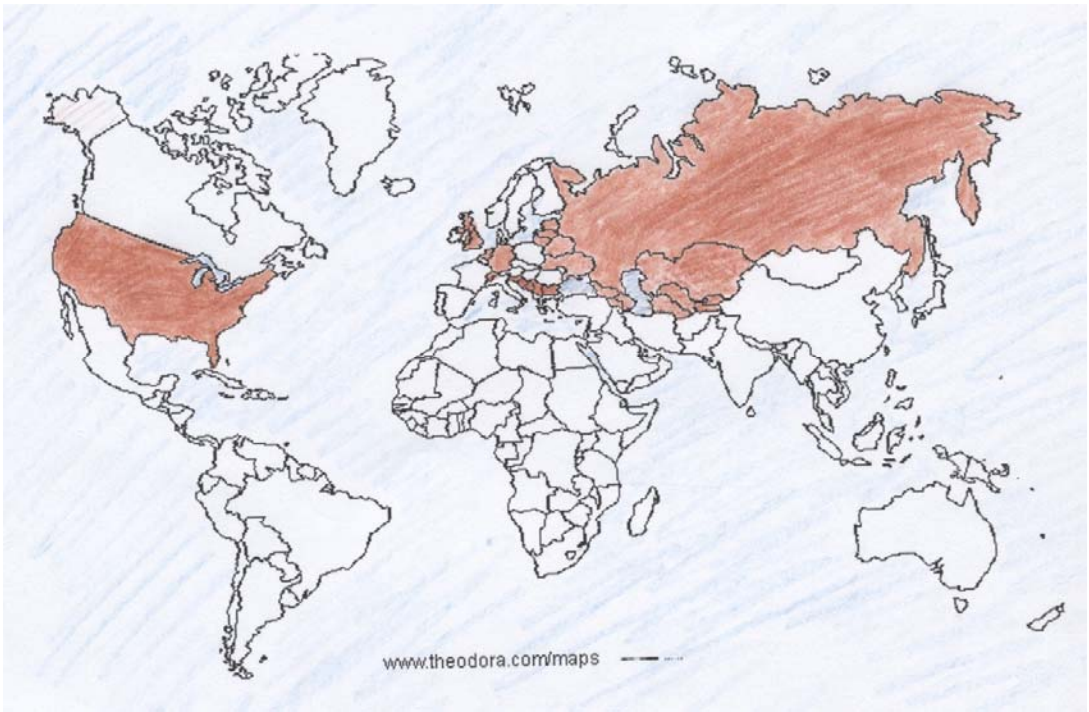


Figure 6. World map where countries with commercial production of *Digitalis* are coloured with brown. Map from www.theodora.com/maps, 2006

Echinacea purpurea, E. pallida, E. angustifolia Purple or Red Coneflower Röd Solhatt och Läkerudbeckia

Morphology

Echinacea belongs to the family Asteraceae and are herbaceous (non woody), perennial plants that originated in Northern America. The leaves are petiolate and are found in a basal rosette and the stems arise from the rootstock. *Echinacea purpurea* has a fibrous root system while *E. pallida* has a single taproot (like a carrot). The stems terminate in a long lasting inflorescence, the disk flowers (often golden brown to orange) are attached to a conical, hemispherical or occasionally flattened receptacle and the receptacle is the bottom of the inflorescence. Surrounding the bottom of the inflorescence is a ring of bracts (involucres) of 3-4 series of phyllaries (small green leaf- or scale like structures) and each disk floret is subtended on the lower side by a modified bract, that protrudes beyond the five-lobed corolla. The distinct form of the capitulum (flower head) is due to the sharply tipped bracts, this form has given the genus name derived from the Greek word for hedgehog, echinos. *Echinacea purpurea* flowers from late June to September and sometimes even longer and *E. pallida* has flowering period from May to July depending on where it is grown (McKeown, 1999). The ray florets (purple to pink) can be descending as for *E. pallida* or more erect and shorter as for *E. purpurea* but the plants have similar height of 120cm *(*Cheers *et al.,* 2003).

Figure 7. To the left is *Echinacea purpurea* and to the right is *Echinacea pallida*. Jansson, 2006

Echinacea angustifolia has a more compact growth pattern, seldom growing taller than 50cm in height. The ray florets are bent abruptly backwards (reflexed) and broad in relation to their length, length being shorter or equal to the width of the disk. The short and broad reflexed ray florets are used when distinguishing *E. angustifolia* from *E. pallida* that has narrow and long ray florets (McKeown, 1999). The disk is often large and golden brown to orange and eye-

catching, this is valid for all the different *Echinacea* species (Hansson, 2005). All *Echinacea* contain medically useful constituents to various degrees but the most used and studied are the ones mentioned above.

Medical use in the past

Echinacea came to Europe from North America and was in Europe not known as a medical plant until the 18th century. In North America the Indians used *Echinacea* to treat wounds and snake bites and it was the most used medicinal herb in USA in the end of 19th-century. In the1830´s a man called Rafinesque reported that the Sioux used *Echinacea* as a way of treating sores induced by syphilis. The first time that red and purple coneflowers occurred in a patent medicine was in Nebraska, United States of America in the 1870s, but *Echinacea* did not become popular among the Caucasian population until the eclectic school of medicine promoted its use for treatment of a great variety of diseases (Lewis & Lewis, 2006). At this point *Echinacea* was used for treating e.g. syphilis, carbuncles, eczema, tropical infections, snake and spider bites and diseases such as herpes, blood poisoning and diphtheria. (Juneby, 1999 and Lewis & Lewis, 2006). The Indians did not only use the plant for treating snakebites and wounds, they also used the root to chew on to ease and treat toothache, sore gums and throat. The Crow Indians seemed to be the only ones using *Echinacea* in the way we do today, that is to cure colds and other upper respiratory infections (Lewis & Lewis 2006).

In Europe until around 1930, *Echinacea* was used to a great extent as a treatment to various infection diseases such as blood poisoning, tuberculosis, childbed fever, and skin diseases. It was also used as an externally applied analgesic that in a miraculous way soothing pain from a burn injure (Heino, 2001). In 1915 when treating patients with tuberculosis a man called von Unruh discovered that *Echinacea* had an immunostimulating effect and this by increasing the phagocytic powers, where foreign particles are removed, of leukocytes (the white blood cells). After 1930 the chemistry and efficiency of *Echinacea* was widely explored and in 1950 an injectable product made form the fresh *E. purpurea* juice (Echinacin) was used to treat oral and respiratory infections, skin diseases, gynaecological infections and various cancers among other diseases. Later on in the 1970s it was found that Echinacin had a clinical value when treating inflammatory skin conditions but this was never proven in a controlled study.

The use of solutions solemnly containing pure *Echinacea* juice or other plant components is no longer advised because of the adverse effects on diabetics and other conditions. The solutions containing pure plant extracts are called parental and can cause, depending on

dosage, short term fever, nausea and vomiting and this because of a decline in metabolic conditions in diabetics (Lewis & Lewis, 2006).

Present medical use

Today, *Echinacea* is mostly used in the same way as ginseng. That is to prevent illness and promote well-being and not as much as a cure (Small & Caitling 1999). Recent research has shown that red coneflower relieves and shortens the duration of colds and flu like infections by early intervention rather than preventing upper respiratory infections. This is probably due to the immunostimulating effect that several constituents in *Echinacea* possess (Lewis & Lewis, 2006 and Percival, 2000).

Red coneflower has been shown to stimulate plasma cells to produce antibodies, to be analgesic, stimulate healing of wounds, have a weak antibiotic effect and stimulate the white blood cells to phagocytes, i.e. when the white blood-cells eat bacteria and viruses (Heino, 2001 and Small & Caitling 1999). Today *Echinacea* is used in immuno-potentiating therapy especially for treatment of cold and upper respiratory infections and other minor infections, e. g. in the lower urinary tract, that do not require antibiotics. (Lewis & Lewis 2006).

Both mechanistic and *in vitro* studies provide evidence that extracts and compounds from *Echinacea* stimulate the immune system and have anti-inflammatory, bactericidal and wound healing properties. The compounds that have been found to be immunostimulating, virostatic and antibacterial are the alkamides, glycoproteins, caffeic acid derivatives such as cichoric acid and echinacoside and the polysaccarides that can be extracted from *Echinacea* (Lewis & Lewis, 2006).

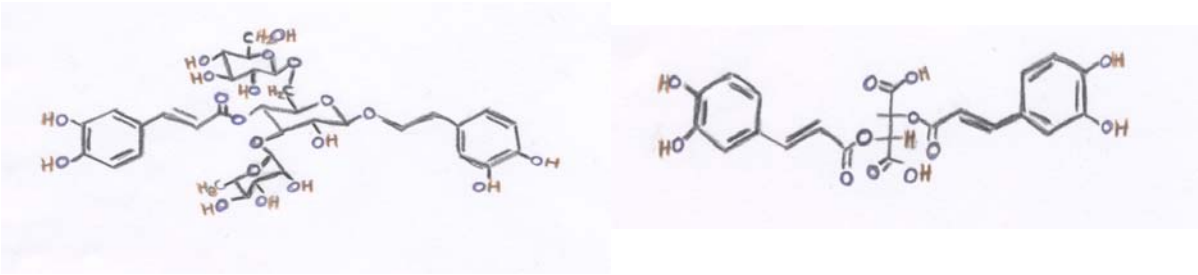


Figure 8. To the left is the chemical formula of echinacoside and to the right is the chemical formula of cichoric acid. Redrawn from Bone ,1997 and Letchamo *et al.*,1999.

German studies suggested that the benefit of *Echinacea* lies in its ability to shorten and reduce the symptoms of an illness. If a person has a healthy immune system the effect of taking *Echinacea* might be smaller than if the person has an immune disorder of some kind.

Echinacea has the potential to boost the phagocytic immune cell response but it appears that it is only fresh pressed juice and isolated polysaccharides that have this ability (Percival, 2000).

The polysaccharide fraction echinacin B enhances the healing of wounds that are difficult to heal by an enhanced formation of granulation tissue (Juneby, 1999). It is believed that the wound healing properties and then particularly for burn and photodamage of the skin is due to the capacity of its polyphenols (e.g. caffeic acid, echinacoside and cynarine) to protect the collagen from damage caused by free radicals. *Echinacea* is found to enhance the effect of penicillin and other antibiotics and can thereby decrease the time of use and dosage that is required (Lewis & Lewis 2006, and Juneby, 1999).

Even though numerous investigations, both *in vitro* and mechanistic, have found a health promoting effect of *Echinacea* this has yet not been proven in properly conducted medical investigations done on a large number of humans. So far the studies done on the health promoting effect *Echinacea* has on humans have often been conducted in small groups and with the use of non commercialized and standardized dosage forms. If the investigation has been conducted with a large number of persons the data that have been collected are mainly anecdotal and supervision of treatment as well as validation of symptoms has not been carefully controlled and this leads to results that are more or less scientifically useless (Lewis & Lewis, 2006). Many of these investigations have been performed in Germany where the market for herbal medicines is very large. More investigations needs to be performed before *Echinacea* can be said to be effective or not (Percival, 2000).

Even if the health promoting effect has not yet been proven in investigations done on humans there seem to be no hazard in an oral use of *Echinacea.* Some exceptions exist and that is if the person taking the drug has an underlying autoimmune aggression and other over reactive immune responses such as in the diseases AIDS, multiple sclerosis and tuberculosis or a hypersensitivity to asteraceous allergens. Examples given on these asteraceous allergens that can cause cross-reactivity are in North America where ragweed (*Ambrosia*) allergies are common or in Europe where chamomile (*Chamomilla*) tea drinking is common (Lewis and Lewis, 2006). Allergic reactions can be asthma, skin rashes and anaphylaxis. The most severe form of anaphylaxis is called anaphylactic shock and that condition mostly leads to death within a couple of minutes if untreated (Wikipedia, 2006).

Echinacea is not only useful to humans in a health promoting way, some of the constituents can also be used as pesticides. Echinacein is toxic to Aedes mosquito larvae and houseflies and eichinolone, which is a juvenilization compound that disrupts the growth of the large

milkweed bug and the yellow mealworm (Lewis & Lewis, 2006) *E. purpurea* is a very popular garden flower and the Swedish cultivar *E. purpurea* ´Magnus´ has become a world famous plant (Hansson & Hansson, 2005). The cultivar `Magnus` has been chosen as plant of the year by the Perennial Plant Association. This cultivar was selected by Magnus Nilsson from Paarp (Påarp) in Scania (Small & Caitling, 1999).

Future medical use.

Since the mechanism of action is unknown as well as the bioavailability, relative potency or synergistic effects of the active compounds extracted form *Echinacea* the first thing is to investigate and find answers to these questions but also to compare the effectiveness of each species. This since there is slight variations in the amount of the active constituents between the species. Variations between and among the herb species also exist due to geographical location, time of harvest, stage of development and growth conditions (Percival, 2000). So far it seems like the *Echinacea* will be used for a long time as a tool to prevent and combat upper respiratory infections.

Commercial cultivation…

The two most commonly grown *Echinacea* species are *E. purpurea* and *E. pallida*. *Echinacea* is today cultivated in Russia where the first farm commercially growing *E. purpurea* started in 1936. Russia together with Germany where among the first countries in the world that started with commercial cultivation of *Echinacea* (Juneby, 1999 and Letchamo *et al.*, 2002). *Echinacea purpurea* has since 1981 been commercially grown on a few hectares on a farm Frantsilan yrttitila, that is located in Hämeenkyrö, Finland (Byholm, 2006)

Until quite recently the major part of *Echinacea* used in USA came from wild growing populations from the Great Plains, but as this resource became smaller and smaller and the risk for extinction became greater commercial cultivation of *E. purpurea* and *E. pallida* started in the north western part of USA. Other Countries in the world where commercial cultivation is found are: western Canada, Austria, Germany, Ukraine, Yugoslavia, Finland, South Africa, Brazil, Australia and New Zeeland (Letchamo *et al.*, 2002). Small to very small production of *Echinacea* can also be found in the Netherlands, Italy, France, Sweden and Denmark (EHGA, 2004).

New countries in the world production of *Echinacea* are: Chile, Argentine, and Costa Rica and they have established field production of *Echinacea* since 1998. Experimental fields of *Echinacea* have been established in Egypt, Botswana and Zambia. *Echinacea purpurea* is the major cultivated species but both *E. pallida* and *E. angustifolia* can be found in commercial production, especially in USA and Canada (Letchamo *et al.*, 2002)

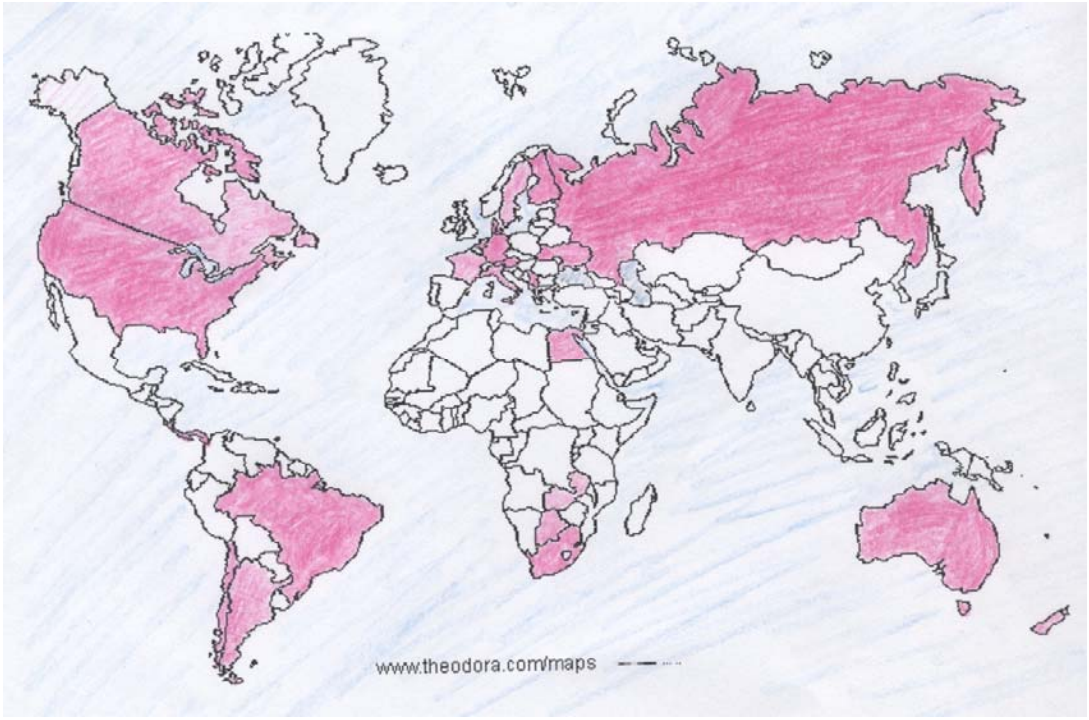


Figure 9. World map with countries growing *Echinacea* coloured in pink. Map is from www.theodora.com/maps, 2006

Hypericum perforatum St. John´s wort Äkta johannesört, Mannablod

Morphology

Hypericum perforatum belongs to the family Clusiaceae and is found in Europe, the Mediterranean area, and large areas of temperate North America, Asia and Australia as well as in tropical mountain regions. (Lewis & Lewis, 2006) It is a perennial herb, 30-50cm in height and with somewhat woody, erect stems that lack hairs and are two angular in shape. The plant has an underground stem where groups of aboveground stems are attached (Stodola & Volák 2000). The stalk is greyish violet in colour and at top densely branched. The plants have leaves that lack petioles (sessile) and are opposite, entire, narrowly ovate and lacking stipules. The leaves are around 1-2.5cm and have many transparent glandular dots. The flowers are placed in terminate compound cyme and the flower colour is yellow. A compound cyme is when the inflorescence is branched and there is more than one flower at the end of each branch. They are five-merous and with many stamens that are collected in three groups, three styles are present. The sepals are acute and often have a few black glandular dots, the petals are twice as long as the lanceolate sepals and with a few black glandular dots along the edges.

Figure 10. *Hypericum perforatum.* Jansson, 2006

The fruit is a capsule having three loculi where each locus contains many seeds (Mossberg & Stenberg, 2003; Krok & Almquist, 2003; Botaniska Trädgården, 1998; Hickey & King, 2000). *Hypericum maculatum* can easily be mistaken for being *H. perforatum*, but these two can be differentiated on the looks of the stalks and the sepals.

The stalk of *H. perforatum* has two wings giving the stalk a two-angular shape and sepals that are lanceolate, while the stalk of *H. maculatum* has four wings making the stalk four-angular and the sepals are rounded and oval.

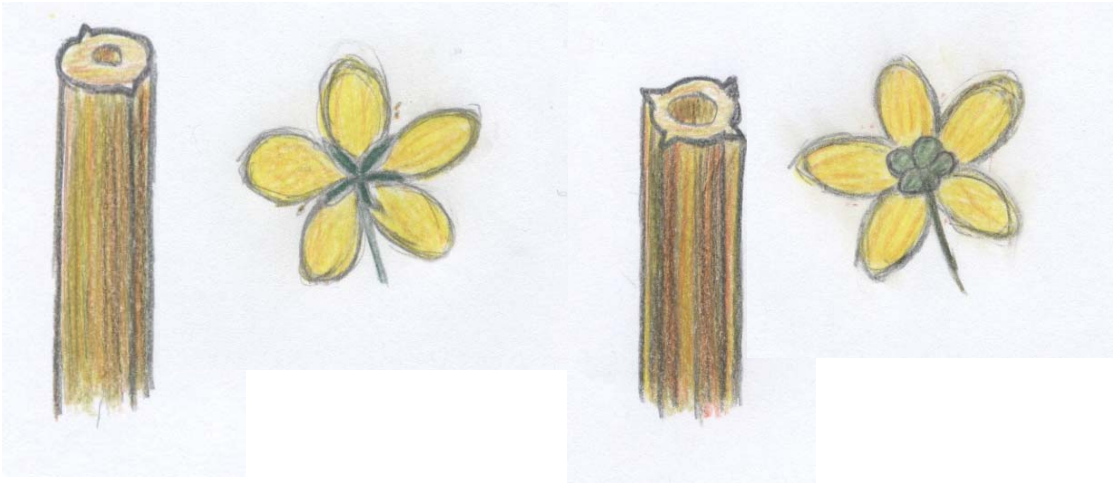


Figure 11. To the left are drawings of stalk and flower of *Hypericum perforatum* and to the right, stalk and flower of *Hypericum maculatum.* Redrawn from Stodola & Volák, 2000 and Mossberg & Stenberg, 2003.

If the sepals are mashed a red juice is extracted because of a flavonoglycoside called hypericin (Stodola & Volák 2000). The flowering time for *H. perforatum* is July to September (Mossberg, & Stenberg, 2003).

Medical use in the past

The usage of *Hypericum* before the modern chemistry came, can be found in the looks of the plant. The red juice that is extracted from the flowers when they are crushed, looks like blood and has given the plant many of its common names. One of the names is St. John´s wort that comes from the tale that the herb arose where the blood from John the Baptist head dripped when his decapitated head was carried to Herodes. This is not the only biblical story behind the common names of *H. perfortaum* and all these names gave the plant a place among the necessary tools to use when the church performed exorcism. The tips of the plant are especially powerful in keeping away undesired elements and bringing luck. Before the Christian names and interpretations of the plant became common the flowers where said to be derived from the sun (Nielsen, 1978 and Hobbs, 1998). All mental disorders were said to come from the devil and the person was possessed. In Norway a person with melancholy was believed to become well again if he/she had scraped their head with the fresh juice from St. John´s wort. In Sweden it was said to be a miracle cure where the patient sat up and walked

away as soon as he/she had taken this miracle medicine (Nielsen, 1978). During the middle ages branches of *Hypericum* were hanged in window and door openings to expel devils and evil spirits. The glands on the leaves were assumed to look like wounds and the plant was used by the knights of the Most Venerable Order of the Hospital of Saint John of Jerusalem (Order of St. John) when treating the wounds that the Roman Catholic knights had gained during the crusades (Stodola & Volák 2000). In year 1525 the Swiss physician Paracelsus started to use *Hypericum* to treat psychiatric disorders and since then it has been traditionally used all over Europe. The main targets where neuralgia, anxiety, depression and neurosis and later on also for treating psychovegetative disturbance and nervous unrest (Medina *et al.* 2006).

Hypericum has been used since the days of Hippocrates as a cooling and anti-inflammatory constituent in remedies (Heino, 2001). Two English herbalists from the 17th century, Gerard and Culpeper, wrote that St. John´s wort is very useful in treating and healing inwards- and deep wounds and bruises. It is also very effective to treat and open obstructions, dissolve swellings, as a treatment for snake bites and dropsy as well as a lot of other diseases and conditions. The Indians in America used several indigenous species of *Hypericum* as abortifacient, dermatological aid, antidiarrehal, general strengthener and as a febrifuge. When the European settlers introduced the St. John´s wort it was also used for these conditions (Hobbs, 1998). The Cherokee Indians gave a root infusion of *H. perforatum, H. hypericoides and H. gentianoides* as a wash to their infants in order to give them strength (Lewis & Lewis, 2006) and the Indians in North America used the leaves as a sedative (Nielsen, 1978). Other conditions the *H. perforatum* was used for in America by the European settlers and their offspring during the 19th century, but also to some extent today, was urinary affections, diarrhoea, worms, tumours, menorrhagia, hysteria and other psychological problems and disorders (Hobbs, 1998) Carl von Linné mentions in his last disputation 1776 that the flowers are good against intestine worms and a decoction on the stems is effective against hoarseness. In *Materia Medica,* von Linné recommends the usage of *H. perforatum* against bloody belching, blood in the urine, palpitations and anxiety. Palpitations are when the heart beats and can be normal, slow, fast etc. In the 19th century the St. John´s wort was used against melancholy, bed wetting and a weakening of the urine-bladder. Kristian Kneipp spoke well about the strengthening effect the herb had on the liver (Heino, 2001) In 1984 the German Commission E (commission for approval of herbal medicine) approved *Hypericum* for medical use against these psychiatric disorders (Medina *et al.* 2006).

Present medical use

The most common use of *H. perforatum* is for treatment of mild to moderate depressions e.g. during the menopause. It can also be used as an anti-spasmodic medicine at digestion problems and stopping/ obstructing diarrhoea. External use on burn wounds and other injuries those are difficult to heal (Juneby, 1999 and Juneby, 1977). The St. John´s wort have been proven to be effective to heal smaller nerve damages and it can be used in blood purifying treatments because of the strengthening effect it has on the liver. (Heino, 2001). Other medical conditions where *H. perforatum* is used are chronic inflammations in internal organs and gynaecological disorders (Stodola & Volák, 2000).

The use of *H. perforatum* as an antidepressant is due to the selective inhibition of dopamine, serotonin and norepinephrine reuptake in the CNS, central nerval system. The effectiveness of *H. perforatum* is equivalent to that of conventional antidepressants (containing e.g. fluoxetine [Prozac], maprotiline, imipramine [Tofranil] and bromazepam) when treating mild to moderate depressions. It is also used for treating depressive moods, nervous unrest and anxiety (Lewis & Lewis, 2006 and Lawvere & Mahoney, 2005). The main components behind the antidepressant effects are believed to be hyperforin and hypericin. At least hyperforin shows a broad spectrum of inhibitory effects that are affecting the reuptake of serotonin, noradrenaline, GABA, glutamate and dopamine. This can be compared to the fact that many of the other antidepressant drugs act more or less selective as inhibitors to one or several nerurotransmittors, most often serotonin (Medina *et al.* 2006).

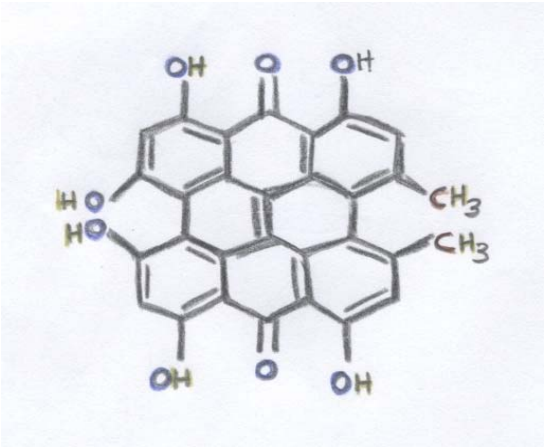


Figure 12. Chemical structure of hypericin. Redrawn from Lewis & Lewis, 2006.

Compared to the conventional antidepressants St. John´s wort has fewer side effects. The more serious of these are photosensitization and the fact that *H. perforatum* can affect and change the function of other medicines (Lewis & Lewis, 2006). Photosensitization is a condition where skin rashes and blisters appear, this side effect is most common for persons with pale skin colour (Heino, 2001). Also eyes should be protected from intense sunlight while taking medications containing *H. perforatum* and this since it can lead to changes in

lens protein leading to formation of cataracts, meaning that the crystalline lens in the eye becomes whitish and less or no light can reach the retina and vision is reduced (Lewis & Lewis, 2006).

The photosensitization effect comes from the substance hypericin but this constituent can not be removed since it has a clear antidepressant effect. This is probably because hypericin inhibits the enzyme monoamine oxidase, this substance has also been shown to be effective in treating psychosomatic diseases and problems e.g. bed wetting. But one should be aware of the fact that hypericin increases the effect of amphetamine and ephedrine which can give unwanted effects (Juneby, 1999).

The St. John´s wort strengthens the liver and the effect can be so strong that the metabolism of many medicines is so fast that they lose their effect or become weaker (Heino, 2001). This effect on drugs is because *H. perforatum* induces a hepatic enzyme through activation of the cytochrome P450 system, this probably activates P-glycoprotein. Some of the medicines that are affected are anticoagulants, antiviral agents and contraceptives that are taken orally and this can possibly have serious consequences (Lewis & Lewis, 2006). Other side effects when taking *Hypericum* can be gastrointestinal upset (nausea and vomiting), increased anxiety or depression, headache, fatigue, minor palptations and dry mouth (Lawvere & Mahoney, 2005).

Oil made of St. John´s wort is pain killing and anti-inflammatory when used externally at treatment of joint- and muscular pain. It also increases the ability of blood to flow through the skin and makes it smooth and evens out lines (Heino, 2001). The oil is also used for treating burn and other kinds of wounds and haemorrhoids (Stodola & Volák 2000).

Some of the constituents of action in *H. perforatum* are as follows; the volatile oil has a wound healing and anti-inflammatory effect. Hyperforine, imanine and novoimanine act as antibiotics, the flavonglycosides are mildly diuretic, anti-spasmodic and strengthen the capillary walls. Some sedative effect can probably be found in biflavones and the hyperforine but this has not yet been verified by clinical tests on humans or *in vitro* (Juneby, 1999).

St. John´s wort can also be used to flavour vodka, which is quite common in the Nordic countries. The vodka gets a very nice red colour from the plant and is sometimes called “Pirkum snaps” (Nielsen, 1978).

But St. John´s wort is not only beneficial to the humans, in especially USA and Canada as well as in other countries in the world *H. perforatum* is considered a problematic weed that is difficult to get rid of (Gibson, 2000). In the beginning the farmers tried to combat the plants

with herbicides, but with little success. In 1946, the leaf-beetles *Chrysolina quadrigemina* and to lesser extent *C. hyperici* were introduced from Australia. Both leaf-beetles have a vast appetite for *Hypericum* and finally the farmers had something to use when fighting the *Hypericum* (Hobbs, 1998). *Hypericum perforatum* is also a significant cause of livestock poisoning. If the plants exist within the grazing area the animals have the sense to avoid these plants. The major problem is when livestock eats shoots that are included in weedy hay and then they can not avoid it and become poisoned. When livestock, as well as humans, get poisoned with *Hypericum* they develop severe skin lesions and necrosis because their skin becomes hypersensitive to the sunlight. This is nowadays called phototoxicity but in older literature as well as newer this is referred to as photosensitization (Gibson, 2000).

Future medical use.

A German study conducted in 2002 showed that hyperforin has the ability to reduce or stop the growth of tumours by apoptosis. This article is in German so I was not able to read the whole article but could only read the abstract. Hyperforin act as an antibiotic and has been shown to inhibit the growth of various rat and human tumour cell lines *in vivo*. It was observed that hyperforin increased the activity of caspase-9 and caspase-3 and that the apoptosis was blocked by the broad-range caspase inhibitor zVAD.fmk. It was observed that the permeability transition in the mitochondria could not be prevented by zVAD.fmk. and this indicates that mitochondrial permeabilization is a cause rather then a consequence of the caspase activation. It was also found that hyperforin is capable of releasing cytochrome c from isolated mitochondria. This discovery together with the findings concerning mitochondrial permeabilization suggests that hyperforin activated a mitochondria- mediated apoptosis pathway. The combination of an anti-tumour activity, low toxicity *in vivo* and a natural abundance of the compound make hyperforin very interesting as a potential new member of the group of anticancer plant compounds. This of course requires further investigations both *in vivo* and *in vitro* (Schempp *et al.* 2002).

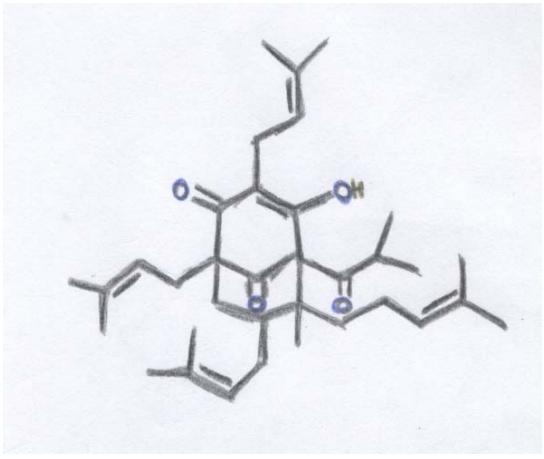


Figure 13. Chemical structure of hyperforin. Redrawn from Lewis and Lewis, 2006.

In another study done by Schempp *et al*. (2005) they studied the antiangiogenic activity of hyperforin *in vivo.* The animals used where Wistar rats that had been injected with carcinoma cells and then treated with peritumoral injections with hyperforin or a solvent. The result was that hyperforin significantly inhibited the growth of the tumours, induced apoptosis and reduced tumour vascularization. These data suggest that hyperforin can suppress angiogenesis by a direct and non-toxic effect on endothelial cells (Schempp *et al.* 2005). In another study hyperforin was found to strongly inhibit angiogenesis *in vitro* in bovine aortic endothelial cells. Hyperforin was also found to inhibit angiogenesis in the *in vivo* chorioallantoic membrane assay (Martinez-Poveda *et al.* 2005). Angiogenesis is growth of blood vessels, and the tumours secrete various growth factors to induce the angiogenesis. The capillary growth in to the tumour will provide it with nutrients and by this allowing it to grow from a small cluster of cells to a large tumour. Angiogenesis is also required for the distribution or metastasis of the tumour. Endothelial cells are much more stable than cancer cells and have a longer lifetime making them ideal targets for therapies. This since they don't carry any drug resistance to the next generation and have a slower mitosis rate than cancer cells (Wikipedia).

The anticancer effect of *Hypericum* can also be used in photodynamic therapy (PDT). That is when a photosensitizing agent, that is hopefully taken up and retained by the tumour, and visible light of a wavelength matching the drug are combined. In this study a polarmethanolic fraction (PMF) of *H. perforatum* was used as a photosensitizer and the target cancer was human bladder cancer. The tests where conducted *in vitro* on two different lines of bladder cancer, the result was positive and showed that PMF is a potent and effective photosensitizer (Stavropoulos *et al.* 2006). *Hypericum* has also been investigated for use in PDT treating early oesophageal neoplasia. The oesophageal cancer cells where preincubated with hypericin at different doses and for different time and then irradiated with light energy dose. The result was that hypericin showed strong phototoxic effects and induced apoptosis in a dose dependent way (Hopfner *et al.* 2003). Other areas where *Hypericum* can have a future potential are in treatment of inflammatory skin disorders such as dermatitis and hyperforin may have an inhibitory effect Alzheimer´s disease (Medina *et al.* 2006).

But all these new applications of *Hypericum* need to be tested and investigated both *in vitro* and *in vivo*. Another area where more research is required is how the different constituents of *Hypericum* work and how these affect the chemical components already present in the human body.

Commercial cultivation…

H. perforatum was earlier mainly collected from wild populations, and is still collected from the wild in Bulgaria to an amount of 120 tonnes in year 2004. Commercial production in field can be found in the following countries: Germany, Italy, Austria, Slovakia, UK, the Netherlands and France, with Germany as the major producer and then in a descending scale when taking the area in consideration (EHGA, 2004 and ProFound & Dürbeck, 2005). Other countries in Europe that crop *Hypericum* are Hungary and Poland but for these countries the amount of hectares is unknown, in Poland the reason for this is that it is more than 20 000 farmers that have commercial production of various medicinal plants (IENICA, 2003 and ProFound & Dürbeck, 2005). In recent years the cultivation of *Hypericum* in Poland has had some problems with red ring-root, which have forced them to change the cultivation practise (Schmidt, 2005)

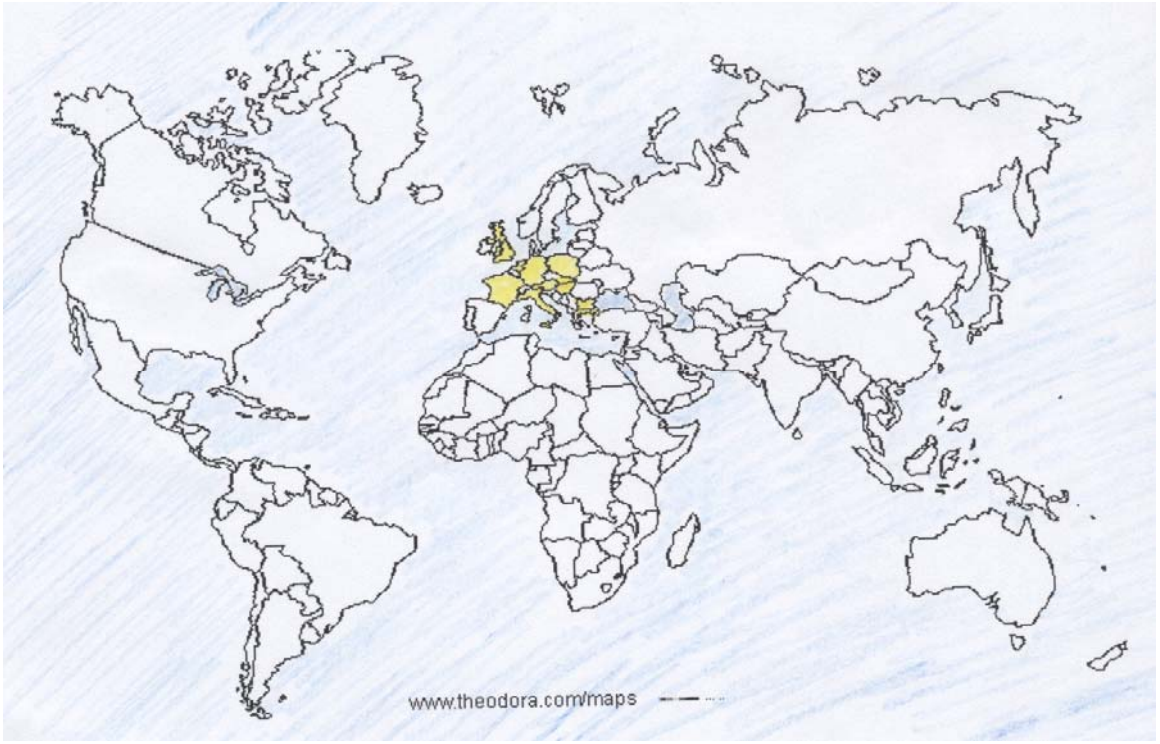


Figure 14. World map where countries with production of *Hypericum* are coloured with yellow. Map from www.theodora.com /maps.

Discussion and conclusion

Digitalis has more or less the same usage area today as it has had from the beginning that is to treat heart and kidney conditions. In Ireland it was used already during the 5th century as a cure against childbed fever, for headache, tumours in the genital area and carbuncles etc (Hewe, 1952). In Wales during the 14th century *Digitalis* was used as external cover on severely infected wounds (Heino, 2001), the usage of *Digitalis* to treat different kinds of wounds is also mentioned by Nielsen (1978). But I can't find any references concerning a modern usage of *Digitalis* as a treatment for wounds that are difficult to heal and serious infections. This can of course be due to the fact that today better and more effective drugs used for dealing with these problems exist. On the other hand, with more and more bacteria becoming resistant to various antibiotics the above mentioned use of *Digitalis* should be further investigated and perhaps some day this old usage of the plant will be applicable again.

Taking the whole picture of *Digitalis* in consideration reveals that this medical plant has been used in the same way since it was discovered more than 400 years ago. The only difference is that today it is known how and to some extent why it works. With new technologies and scientific progress new ways of action for this plant have been found and this has given *Digitalis* new areas of usage. One of these areas is as a cancer treatment but as old records mention, the plant was used already in the 5th century as a treatment for tumours in the genital area (Hewe, 1952) but they don't say whether the plant extracts are used externally or taken orally. The new research has shown that glycosides from *Digitalis* are efficient in controlling and minimizing different malignant cells in e.g., prostate and breast cancer, leucemia, and cancer in the kidney/urinary tract (Haux *et al.* 2001, López- Lázaro, *et al.* 2005,*).*

Echinacea is today used more or less solely to shorten and prevent colds and other upper respiratory infections (Lewis & Lewis 2006 and Small & Caitling 1999). This despite the fact that there is a scientific dispute going on concerning whether the plant is effective or if it is a placebo effect and whether it can prevent or if it only enhances and stimulate the immune system and in that way shortens and diminish symptoms. Recent research indicates that the plant extracts probably strengthen the immune system and diminish and shorten e.g. colds and that it has no preventative effect (Lewis & Lewis, 2006 and Percival, 2000). Even if this newer research pointed towards the fact that the plant only strengthens the immune system and has no preventive effect, more and extended research needs to be done to show what effect *Echinacea* really has on the human body. Despite this recent discovery *Echinacea* has

been proven to be useful for a number of different conditions such as other kinds of infections and inflammatory skin diseases, e.g. eczema. The reason why *Echinacea* is very little used in this area of medicine can be that the needed research does not exist and of course tradition of how the plant should be used plays a big role. This even though the plant was used during the 19th century as a cure for eczema, but the usage was not widespread (Juneby, 1999 and Lewis & Lewis, 2006).

If a plant is used for a specific condition or a specific area within the medicine it is very difficult to break that tradition, even if there are proofs that it has had a wider spectrum of areas of usage. With more research on how the different plant parts of *Echinacea* and the diverse constituents in these work and what impact they have on the human body the area of use will probably be extended.

Of the three plants that I chose to work with *Hypericum* is the one that has the longest time of use, that has been recorded and can be found in different writings and books, and it seems like that *Hypericum* has been used for psychological disorders all this time.

It was the tips of the plant that were said to be especially powerful in keeping away undesired elements and bringing luck. This since the yellow flowers reminded about the sun which was seen as a very powerful sign and the red juice that can be extracted if the flowers are crushed look like blood. All mental disorders were said to come from the devil and the person was possessed (Nielsen, 1978 and Hobbs, 1998) so this plant that was said to be derived from John the Baptiser became a very powerful tool. The Christian way of interpreting the plant was perhaps a way for the priests to handle the more pagan interpretation of the morphology of the plant so that this effective plant still could be used to help people but at the same time make them think about God and praise him.

The anticancer effect (Schempp *et al.* 2002, Schempp *et al.* 2005 and Hopfner *et al.* 2003) that has been discovered is most likely the area of use that will be given a lot of attention in the nearest future. All the areas of use need to be more carefully studied and the different mechanisms of action as well as the miscellaneous constituents so that the best healing effect can be achieved.

The three medical plants that I chose to write about have more or less the same area of usage today as they had from the beginning. For more serious infections and other medical conditions that are difficult to treat where these plants earlier where considered as miracle cures they are no longer or to a very small extent used. This is probably due to the fact that

with scientific progress and the modern medicine new and more effective cures where found. In some cases the answer is that the disease or the medical condition is more or less eradicated in the western part of the world e.g. child-bed fever and syphilis infections of second to third degree.

With the entrance of the modern medicine and schooled doctors the usage of herbals also became unpopular and was seen as unscientific, except for some cases e.g. *Digitalis*. As soon as the active constituents could be maid in a laboratory the plants were less used and the research on how they act decreased and this leads to the fact that many areas of usage are unknown and yet to be found or have been forgotten. This is not the only problem. When a compound from a plant is synthetically made it might loose some of its properties and the result is that the impact on the body can be different compared with the plant derived compound. The synthetically made compound might be a chimera of the compound in the plant and this can give the altered effect. Some of the constituents might act in a synergistic complex and if the compounds are separated from the complex the impact the drug have on the body might be altered. Instead of a beneficial effect you might not get an effect at all or an opposite effect, meaning that the compound is harmful to the body in some way. But on the other hand, if the compounds are extracted from plants and the compound is very popular the plant is in danger of becoming extinct unless it is possible to grow it commercially as with *Digitalis* and *Echinacea*.

It is not only areas of use that have been forgotten and many medicines today have active constituents that are from the beginning derived from plants but with time many of them have been forgotten.

From this project I can conclude that herbal medicines have been used for a very long time and with new technologies and scientific progress new areas of usage have been found and are still discovered and investigated, but the old applications are still valid and the main area of use. So therefore I would say that for the three plants discussed in this project the medical use has not changed with the development of new technology and scientific progress. This even if scientists are still arguing whether the plants are effective or if it is only a placebo effect, whether they have a certain area within medicine where they are effective and what constituent or constituents are responsible for the effect?

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