Department of Botany

University of Veterinary Medicine, Budapest

A trauma terápiája gyógynövények segítségével a hagyományos allopátiához képest

Therapy of trauma with the help of Herbals in comparison to traditional allopathy

By: Viola Maria Sachsenmaier

Supervisor:

Dr. Cserhalmi Dániel

Ph.D., associate professor, head of department

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Abstract

Trauma treatment is one of the most performed therapies in veterinary medicine, therefore suitable and effective medications are significant for a successful recovery of the patient. Currently, therapy with plants and herbal remedies comes more into focus again and has a rising interest, also in pet owners, due to their many possibilities of application and quite good compatibility. Therefore, this thesis deals with the comparison of the included components and their resulting effects of herbals and chemical drugs. First, the importance of herbal trauma therapy was explained, then followed by the individually worked out medicinal plants, added a shorter chapter on toxic plants with trauma-relevant active compounds, afterwards the chemical allopathy is clarified. Finally, I compare the two types of therapy finding the pro and con arguments for both types.

Absztrakt

Az állatorvosi gyakorlatban a trauma kezelése az egyik leggyakrabban alkalmazott terápia, épp ezért a megfelelő és hatékony gyógyszer kiválasztása fontos a beteg sikeres felépülése érdekében. Manapság a gyógynövényekkel és növényi alapú termékekkel való kezelés egyre nagyobb érdeklődésre tart számot az állattartók körében a különféle alkalmazási lehetőségek révén. Épp ezért a dolgozatomban szeretném összehasonlítani a növényi hatóanyagokat, illetve azok hatását a kémiai eredetű gyógyszerekkel. Először a növényi-alapú traum terápiát tekintem át, majd egyesével bemutatom a gyógynövényeket, illetve egy rövid fejezetben olyan mérgező növényeket, amelyek hatóanyagai gyógyhatással is bírnak. Végül kitérek a gyógyszeres kezelés lehetőségeire is, illetve összehasonlítom a két módszer előnyeit és hátrányait.

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Abbreviations

TCM: Traditional Chinese Medicine

EMA: European Medicine Agency

WHO: World Health Organisation

ESCOP: European Scientific Cooperative on Phytotherapy

HMPC: Committee on Herbal Medicinal Products

ESR: erythrocyte sedimentation rate

CRP: C-reactive protein

PV: plasma viscosity

IL: interleukin

TNF- α: tumour necrose factor

TGF- β: transforming growth factor-β

COX: cyclooxygenase

LOX: lipoxygenase

GABA: gamma-aminobutyric acid

NMDA: n-methyl-D-aspartate

IgE: immunoglobulin E

IgG1: immunoglobulin G1

NSAIDs: non-steroidal anti-inflammatory drugs

GCs: glucocorticoids

PLA_2: phospholipase 2

FAD: flea allergic dermatitis

mAb: monoclonal antibody

NGF: nerve growth factor

trkA: tropomyosin receptor kinase A

OA: osteoarthrosis

1. Introduction

In my thesis evaluation, I portray the different aspects of herbal treatment of trauma and the variety of herbals themselves, in comparison to another approach of trauma treatment with the common traditional allopathy and the associated drugs. Herbal treatment has been used in human medicine for quite a long time and in the last years it has also gained more attention and acknowledgment in the veterinary medicine. With the herbals' great possibilities of use, it attracts more and more pet owners, so that even some of them explicitly ask for an herbal treatment instead of just the usual chemical drugs.

I think the fact of herbal treatment getting more popular, is a great opportunity to improve the knowledge of working veterinarians in this field, eliminate some existing prejudices and to show what can be achieved by applying such natural substances. In addition, a natural treatment can be another option for some animals if there is a lack of chemical drugs, if it comes to intolerances or of course for a supporting application with other substances.

Hence the use of plants and herbs has an environmentally friendly aspect, so this topic comes up with further importance in a world that is committed to a more climate-friendly life/existence. Also, myself, I am familiar with it, since I use herbal products daily and we often/constantly treat patients with herbal preparations in our veterinary clinic at home. First, I will clarify the term trauma itself, the significance in veterinary medicine these days, the physiologic effects and what areas of treatment should be targeted. Because trauma is one of the most common treated injuries in everyday practice. Not only do I want to highlight the beneficial aspects of herbal treatment in trauma, also how to use them properly in a daily practice. So, I will introduce some selected herbals, give information about their ingredients, how to prepare them and their significant application. Following on from this, I will also explain the use of traditional chemical drugs, how their mechanisms work and what differs them to a herbal therapy. The described aspects of the preceding chapters will be summarized in a final conclusion, the beneficial and adverse considerations, thus what my closing opinion and realization on this topic is.

2. Importance of herbal trauma therapy and different aspects

For many centuries, medicinal plants have been the main important part of drug usage and application of other medical substances, in correlation to treat diseases or for general prevention. The oldest existing records of their utilisation in the Western World, also concerning the treatment of animals, were discovered in Egypt, followed by Traditional Chinese Medicine (TCM) having over 4000-year-old notes of herbal usage as medicine or the from India originated Ayurveda, thus these healing methods occur in many cultures [1]. Phytotherapy is the overarching term for medicinal plant or herb usage, it is a part of herbalism based on current phytochemical knowledge of rational medicine and derives from natural substances [2]. It describes the administration of plants and certain plant parts such as flowers, leaves, roots or stalks, sometimes seeds and fruits; being helpful due to their included chemical substances, being incorporated into preparations, to treat illnesses or maintain the patients' health. Plants own a so called 'multi-target' effect [3], caused by their complex natural combination of active ingredients, composed by a variety of chemical components. They have proven to be useful for long-term therapy, as prevention medication or in animals with multiple chronic conditions, multiplex disorders like in metabolism or disturbed wound healing [4]. Achieving a sufficient support of the animals still effective self-healing powers, in acute cases, is one of the benefits of herbal medicine. Through combinations of these herbals and their active substances, can the organisms be strengthened, what leads to an improvement of the patients' clinical state [2].

With the discovery of bacteria and viruses, in the beginning of the 19th century, chemically more aggressive agents were used like chloride, bromide, iodine or phenols, naphthalene, even mercury for disinfecting or treating microorganism infestations. Followed by the detection and fabrication of the first antibiotics, such as penicillin, the herbal therapy in medicine fell into oblivion and was considered antiquated [3]. Nowadays, more attention is paid again on the herbal therapy and its therapeutic potential, and it gains a wider popularity, not least because of people's changing attitudes towards the environment and the increasing concern towards synthetic drugs, that they might have bad impacts on their animals in long term usage. In cases of non-effective standard therapies, allergies, unwanted drug interactions, immunocompromised individuals or failure of antibiotic treatments, a therapy with herbal medicine can be profitable and promising. Frequently, chemical allopathy is not only expensive, but also entails undesirable side

effects, which can be bypassed or at least reduced by using natural based medicine. Like in the treatment of inflammatory processes, where all of the synthetic anti-inflammatory agents turn out to show unfavourable effects in longer application, for which reason further research must be done to produce more effective and tolerable decongestant medicines from herbal origin [5].

Being autotroph organisms, capable of synthesising their own dextrose or glucose and oxygen from nature and their environment, plants are essential for basic life and people as animals have taken advantage of this properties since. It was proven that animals chose herbals in correlation to their health status or in sickness, for self-medication or to improve their immune system [6]. In livestock, herbals recover a significant role having a good environmental compatibility, also with a view to the increasing number of multi-resistant pathogens, bacteria and viruses, already decreasing the effective use of some synthetic drugs. Some countries offer seminars or educational courses about phytotherapy for veterinarians, after graduating. This gives an opportunity to increase their therapeutic spectrum, but as well are they able to decide responsibly how and which medicinal plants and drugs to apply, if it is necessary and if they can be combined with synthetic ones. Otherwise without proper knowledge, it can be dangerous to administrate certain medicinal plants, although most of them are considered harmless and safe, in non-professional usage could appear unwanted and endangering side effects. That is why the owners should also be educated or enlightened in this matter, to avoid incorrect medication and such consequences. It is often species dependent, due to genetic defects and a lack of necessary glucuronidase enzymes as in cats, if herbal or synthetic treatments can be applied safely.

The veterinary usage of medicine derived from plants in treatments is regulated by law, to secure a safe possibility of application, a good quality of the products and efficacy in correlation to their fabrication methods and extracts, an assured identity of used herbs and ingredients and an adequate purity. A required approval for admission is given by the responsible authorities, since 1993 a European permit can be granted by the European Medicine Agency, shortly EMA. For member states in the European Union, a simplified registration for traditionally used herbal medicinal products, was introduced by the Directive 2004/24/EG [1]. Further committees create monographies for medicinal plants: the WHO, World Health Organisation, on international basis for traditional medicine; the European Scientific Cooperative on Phytotherapy (ESCOP) and the Committee on Herbal

Medicinal Products (HMPC) working both on improving the scientific status of herbal medicine in Europe [3].

Of course, also the phytotherapy has its limits, substitutional therapy cannot always be replaced, in examples like cancer therapy or diabetic cases. However, in such instances, it is helpful to use herbal medicine as an accompanying method of treatment, to gain better results and a faster healing process [2]. But the possibility of combining both kinds of remedies can open further doors for more treatment options.

3. Therapy of trauma

3.1. Definition of trauma, Causes and Diagnosis

The Greek term trauma defines an injury, wound, force provoked by acute, outer influences or physical harm with damage of tissue structures or functional disturbances [7]. It has several forms, like a wound or polytrauma.

Being complex, trauma can be induced by different aspects: mechanical like cuts, stab wounds, abrasions, bite and gunshot wounds, bruises, lacerations or amputations; chemical causes as combustion or electrical injuries; thermic such as chemically created burns from acids and alkalis, or by radiation [8]. It is distinguished in superficial or deeper wounds, depending on the degree and form of violence.

Clinical diagnosis in veterinary medicine extends the possibilities of different wounds in contusion, haematoma, excoriation, distortion, erosion, vulnus incisivum, vulnus punctum. Local ischaemia, combustion, congelation or sunburns can also be diagnosed. Besides the physical examination with auscultation, percussion, palpation; x-ray or computed tomography; ultrasound; or laparoscopy are additional ways of internal investigation. In haematology, laboratory diagnostics provide the possibility to detect trauma through increased inflammation markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and plasma viscosity (PV). Thus, possible underlying injuries can be located easily and treated quickly.

3.2. Pathophysiology of Inflammation

Depending on the location and the severity, tissue infection caused by trauma will be followed by the inflammation, a vital reaction of the body. „Inflammation is one of the most central processes required in defence of animal cells against certain injuries or microbial infections" [5], and likewise a local and systemic reaction of a biological system, caused by stimulation, which endangers physiological processes [9]. Therefore, the inflammation is supposed to remove the damaging stimulus and support healing. In addition, pro-inflammatory mediators such as histamine, IL-1 β, IL-6, IL-8, TNF- α (tumour necrose factor) and anti-inflammatory mediators like TGF- β (Transforming Growth factor-β), IL-4

and IL-10, are released from mast cells and tissues, then triggered to the affected tissue site [10, 11], just as serotonin, prostaglandins, leukotrienes, interferons, cytokines and interleukins. Mediators, which are messengers, play a crucial role starting biochemical reactions, usually in a cell. Increased permeability of vessel walls in smaller blood vessels works chemotactic on monocytes, granulocytes, lymphocytes, and increased release of other inflammation mediators, especially such as cytokines IL-1 β and TNF-α. This has a spiralling effect: cytokines cause activated macrophages to a further release of more cytokines, what helps in the elimination of bacteria and other pathogens [5].

Inflammatory responses consist of an acute or a chronic phase and are mediated by different mechanisms. These immune responses, being involved in acute inflammation, can be divided into vascular and cellular [12]. The vascular reaction leading to vasodilation, the cellular reaction leading to an increased release of neutrophile granulocytes and macrophages, so do both biological reactions direct to the production of exudate. Further following steps of the healing process contain: resorption, proliferation, remodelling and restitutio ad integrum/resolution [5]. The peak of inflammation consisting of an increased amount of lipoxins and apoptosis/phagocytosis (TGFβ1), is followed by the resolution and a return to normal tissue physiology - in a successful case. This includes the decrease of neutrophils infiltrating the concerned tissue and induction of neutrophil apoptosis, macrophages being transformed to alternative cells, cytokines and chemokines become counter regulated and finally the healing process is inducted [11]. Otherwise, if not successful, it will become an ongoing acute inflammation, finally resulting in a chronic inflammation [13], leading to enduring elevated inflammatory markers in the blood, the affected tissue can be damaged permanently and this can result in various diseases like arthritis, cardiovascular disorders, diabetes type two or even cancer.

3.3. Secondary metabolites as active plant compounds

Varied physiological changes cause the production of secondary metabolites, which of many are derivates of the primary metabolites, but both being formed during metabolic processes [14], meaning that gaining good quality herbal drugs also stands in correlation with the length of their growth periods and reaping point determination. Amount and potential of the secondary metabolites depends on the concerning plant part, roots and stem, flowers, leaves, seeds and fruits, all differing in their value of medicinal compound accumulation. During

their life span, the plants are affected by light, temperature, different soil structures, water, fertilizers and toxins like rodenticides, and other abiotic influences that trigger stress reactions, lead to changes the secondary metabolite synthesis and can have negative effects on the medicinal properties of the herb.

Firstly, the primary metabolites should be mentioned, such as amino acids, ethanol and lactic acid, being important for the plants own nutritional supply, cultivation, growth and reproduction; in addition, they play a major role in cell metabolism, especially being intensively saved in the plants storage organs and seeds [15]. On the other hand, the secondary metabolites are the actual components being responsible for the medicinal effects, healing properties, but also for the plants own defence against predators or microorganisms, in ecological ways to adapt chemically to environmental stress [16]. These include terpenoids like triterpene or essential oils; nitrogen containing compounds as alkaloids or glycosylates; and phenols like phenolic acids, flavonoids or tannins [15]. Further components are naphthalene, quinolines, phenazines or growth factors, additional plant hormones which interact with certain receptor proteins and adjust the organisms' actions, like producing more metabolites. Some glycosides, like kaempferol- or flavonoids glycosides, can inhibit pain perception mediators, this has been proven in several studies, mainly due to the lipoxygenase and cyclooxygenase pathways or processes, producing thereby the strongest analgesic action [17]. Detoxifying, astringent, antiviral and antibacterial effects have been shown in tannins; the group of flavonoids possesses anti-inflammatory, antispasmodic, digestive, antiphlogistic effects, just as antiviral actions and the cardiac glycosides, like digitalin, have an impact on the cardiovascular system [18]. Mono- and sesquiterpenoids like aucubin, which belong to the terpenoids, have shown anthelmintic and antibacterial action; diterpene alkaloids like aconitine possess antiepileptic and analgesic effects [1]. Atropine and scopolamine, being further alkaloids, have proven anticarcinogenic, antiphlogistic, anticholinergic and antispasmodic actions [18, 19]. This shows the importance of herbals and their secondary metabolites, not without reason are they used in the pharmaceutical industry for manufacturing drugs.

3.4. Targets of trauma therapy

For a successful treatment, the chosen method or product should possess the following requirements for an ideal trauma agent: reduction of inflammatory symptoms, promotion of

wound healing, being clinically approved and tested, good compatibility, less or no side effects, easy to administer and consistent.

Another character should be inhibiting the secretion of pro-inflammatory mediators, inhibiting pro-inflammatory enzymes as cyclooxygenase (COX) and lipoxygenase (LOX) and stimulating the production of cytokine TGF- β, that further inhibits pro-inflammatory cytokines, as stimulating phagocytosis, granulocyte activity and cell proliferation [5].

Utilization of multiple drugs or substances together, to enhance the mode of action and to get a quicker healing process, is an often-applied method in chemical as well as in herbal treatments. Heine [20] describes this synergistic reaction called the 'Bürgi Principle', an adding effect in the case of the simultaneous use of two or more substances, having the same function or eliminating the same symptoms, to a potentiating effect, if having different pharmacological targets.

3.4.1. Decongestant

A decongestant drug or substance can decrease the blood flow by shrinking the blood vessels and mucous membranes to their normal size and reducing congestion in general [21]. This process marks an important feature of wound healing, because if a traumatic wound is not treated effectively, it can turn into a state of chronic swelling. Therefore, the tissue is endangered for further injury, due to its rigidity and being less flexible. Prominently used decongestant drugs are the amphetamine analogues such as ephedrine and pseudoephedrine, which are generated by the *Catha edulis* and *Ephedra* plant species, combined with yeast and chemically modified [22].

3.4.2. Analgesic

Khan et al. [17] explains: „Pain represents an unpleasant sensation linked to actual or potential tissue damage. In the early phase, the sensation of pain is caused due to direct stimulation of the sensory nerve fibers. On the other hand, the pain in the late phase is attributed to inflammatory mediators." Consequently, the analgesic function is to block pain signals or change the brains reading of pain and decrease inflammation. This should happen preferably, without losing consciousness, or going into a narcotic state. Undesirable side

effects often appear in a longer treatment period against pain and inflammation, like anaemia, osteoporosis, ulcers and endocrine disturbances, caused by the usage of current synthetically produced drugs [5]. Therefore, research is done on phytoconstituents derived from medicinal herbals, having suitable analgesic actions and lesser side effects.

3.4.3. Antiphlogistic

Describes an agent or drug having the ability to reduce inflammation [23], sometimes it is also referred to decrease fever. The inflammatory response of the body is a very substantial measure to remove and kill dangerous pathogens. Long lasting inflammatory processes have mainly a chronic outcome, leading to severe defects or organ failure, so therapy with proper anti-inflammatory medication is highly advised [5]. The rise in body temperature is also a constitutional reaction of the body due to infectious, neoplastic and immunological stimulations [24], which is advantageous to counteract the respective pathogens. Though, if this process is ongoing and the fever is extremely high, the patients' health can turn into a dangerous state, why should be treated immediately with herbal or chemical drugs having antipyretic properties. Ibuprofen, aspirin or acetaminophen are the most common used chemically produced drugs in that case, having a high rate of unwanted side effects, which could be solved by utilizing safer herbal medicine, containing alkaloids, and having a more efficient effects.

4. Herbal trauma therapy and some relevant herbs

4.1. Decongestant plants

4.1.1. Achillea millefolium

Achillea millefolium is a non-poisonous plant **(Figure 1.)**, belonging to the family Asteraceae and it can be found in Europe and North Asia. Millefolii herba is known by the name ‘common yarrow’ or ‘yarrow’ [18]. The plant or subshrub is perennial, herbaceous, short hairy to glabrous and only branches in the inflorescence. A hight of 60-80 centimetres can be reached and it usually grows on meadows, pastures or roadsides. Lanceolate to linear-lanceolate, 1.5-3.5 centimetres wide green leaves are characteristic and white, rarer pinkish coloured flowers **(Figure 2.)** appear from June to September. Visited by many insects such as bees, this plant also plays an important role in the case of pollination. The fruits range from a size of one to two millimetres [25]. Used parts of the plant for drug preparations are the dried flowering shoot tips, being cut or taken as a whole.

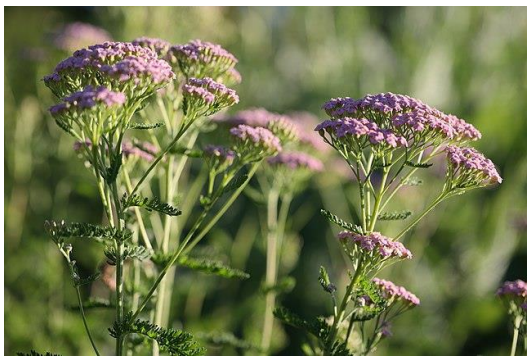

Figure 1 (left): habitus of *Achillea millefolium*. (Wikimedia Commons, 2022)

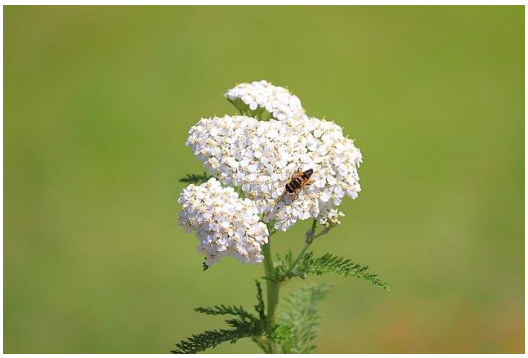

Figure 2 (right): flowers of *Achillea millefolium*.
(Wikimedia Commons, 2010)

Achillea millefolium is known as the ‘soldier weed with the many leaves’, to heal wounds, haemorrhages, ulcers and fistulas, so in folk medicine it is one of the most important herbal drugs for internal and external inflammation. In veterinary medicine its application has been proven to be successful in cramping colic of ruminants, various intestinal disturbances, liver and bile problems, rinsing of wounds, impure ulcers and injection of fistula tracts [1]. Significant is the plant not only being decongestant, but also having spasmolytic, choleretic and antimicrobial effects. Borelli et al. [26], confirmed that feature in a study on mice, with

a standardized *Achillea millefolium* extract, having a spasmolytic impact on the stomach. Main components compromise of essential oils (0,2-1%), including chamazulene, cineol and camphor; flavonoids, such as glycosides, luteolins; hydroxycoumarins; betaine; chlorogenic acids; alkamides and polyene [27]. In general, the medical usage in animals expands from inner treatment of dyspeptic issues in the gastrointestinal or genital tract and application in anorexia, to external wound treatment and mucosal membrane or skin inflammation [28]. Powder preparation for *Millefolii herba* is the simplest form and to be supplemented directly to the food. Depending on the animal species, a daily dose for oral powder is 60mg/kg BW, two to three times per day. Another method is preparing fresh plant juice, by moistening well a bunch of yarrow with water and letting it set for three hours. Then it is chopped in the blender, wrapped in a towel, the water is squeezed out and finally freshly applied. The juice should always be mixed 1:1 with water, given orally half a teaspoon per ten kilograms bodyweight.

In case of gastroenteric disease an infusion can be brewed: give one tablespoon of plant into two hundred millilitre water and let it steep for one hour. When ready, the mixture is administered before feeding. Especially in calves this is a reliable method, tending to diarrhea in the early weeks of their life, to use two tablespoons per calf three times a day [1]. Making flatulent tea is an often-used method in small animal treatment, which can also be utilized for washing wounds. Therefore, pour over one part yarrow with ten parts of boiling water and let it set for ten minutes [25]. Suitable for all species, except cats, who should be treated in all yarrow preparations with care and only with low dosage. To treat skin diseases externally, ointments can be made or in case of horses they are rubbed over with the unprepared plant, to repulse flies [29].

4.1.2. Arnica montana

Arnica montana is a perennial, deciduous flowering plant **(Figure 3.)** belonging to the Asteraceae family. Being indigenous in mountain regions, it can be found widespread on pastures, mountain meadows, acidic peat soils in the Alps and in Europe in general. Colloquial names are ‘mountain arnica’ or wolf’s bane, however this name is also associated with the highly toxic plant *Aconitum* and should not be mistaken [18, 30]. In Croatia and Germany, it is listed as ‘vulnerable’, whereas in Hungary the plant was saved from extinction by planting it man-made on artificial grasslands [31]. Its structure is unbranched or with rarer

two or four side branches at the top and it reaches a hight of twenty to sixty centimetres. Characterised by building up rhizomes as roots and a glandular stem, the plant processes light green leaves being ovate to lanceolate arranged in a rosette form. The flowering period takes place from June to August, the flowers are dark yellow and with ray and tubular florets.

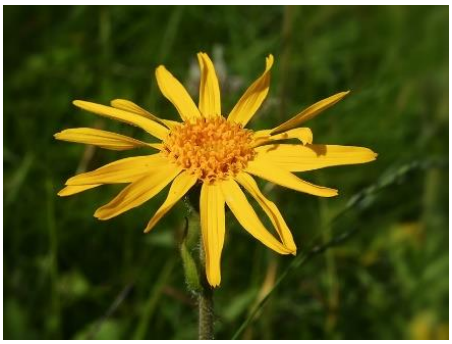

Figure 3: flower of *Arnica montana* (Wikimedia Commons, 2008)

A certain aromatic smell is typical for the four to six centimetres wide flowers. Their fruits have yellowish pappus bristles and ripe from August to October [32]. Dried inflorescence, whole or partially decomposed, are the used parts for medical therapy. The plant is noted be an old Germanic folk remedy and became popular in the 17th and 18th century, due to its mission as drug for treating injuries. It has also been used internally as a cardiotonic in veterinary medicine, in cases of distemper in dogs, or weakness due to lung and heart diseases. Nowadays the plants use is reduced to an external preparation and application [1].

One of the most important main components are sesquiterpenlactones, including helenalin and dehydrohelenalin (0.2-1.5%), which are anti-inflammatory agents. Several studies showed: „containing an α-methylene-γ-lactone moiety were shown to be potent inhibitors of carrageenan-induced oedema and chronic adjuvant-induced arthritis in rodents" [33]. Other ingredients enclose flavonoids, essential oils like thymol, fatty acids, alkane, coumarin derivates, polyene and phenol carbon acid. Besides having decongestant properties, *Arnica flos* is known to have an analgesic, absorption-enhancing, antimutagenic, hyperaemic and antimicrobial effect; caused by the sesquiterpenlactones forming covalent bonds with proteins and modifying their original characteristics [34]. The plants' analgesic action is pronounced as well, proven effective in a study on female dogs, who went under elective ovariohysterectomy or applying preparations topically, like an ointment [34, 35]. In addition, this plant has an antiphlogistic impact caused by inhibiting the following: release of inflammatory mediators, release and activity of lysosomal enzymes, activation of the

transcription factor NF-kB, chemotaxis and wandering of leukocytes [1]. Topical usage can be treatment of acute blunt trauma such as contusion, haematoma, compression, distortion or superficial phlebitis, inflammation, rheumatic discomfort of muscles and joints [28]. By isolating a polymeric complex from the flowers, a study showed antitussive and broncho dilatory properties, where the antitussive effect turned out to be lower than codeine, but the action as a bronchodilator was even analogical to the antiasthmatic drug salbutamol [36].

Arnica montana as a whole plant, possesses mediate poisonous activity, consequently cautious applications are recommended. It should not be used in open wounds and oral consumption is not suitable. Also, there have been cases of allergic skin reaction due to helenalin and helenalin acetate in guinea pigs and dermatitis after extract applications [37]. Helenalin is considered sensitizing, due to its reaction with organism-built proteins and antigens. This has a direct effect on previously damaged skin, having a disturbed protective function and should be considered in therapy [1]. A safe, reliable external method is the preparation of a compress. It has a thermic effect that activates the blood circulation by a cold stimulus and deprives the heat due to evaporation. The compress can be soaked either with an infusion, two grams of drug are brewed with one hundred millilitres water, or by an *Arnica* tincture. For the tincture one part flowers and ten parts ethanol 70% is needed, then always dilute with water and apply [1]. Ointments with *Arnica montana* are frequently prepared in veterinary medicine: a 25% tincture is made and incorporated in a suitable ointment base. BenAcet aethericum® (DE) is an in stores available finished preparation for horses, cows and sows and it's a traditionally used mixture for acute inflammations in tendons and joints.

4.1.3. Bellis perennis

Bellis perennis is an herbaceous, perennial, traditional wound herb and known by the names 'Common daisy', 'English daisy' or 'Lawn daisy'. The Latin description 'bellus' references to pretty [18]. Dieter Podlechs book 'Heilpflanzen' [25] describes lawns, meadows and grassy areas to be a frequent habitat and it is widespread over Europe, America and West Asia. It usually reaches a hight of twenty centimetres and the plant prefers moist nutritious soil, but it can handle likewise sandy ground. The dark green leaves are two to five centimetres long, spatula shaped and ordered in a flattened rosette. As a member of the Asteraceae family the plant produces white ray flowers, sometimes pinkish on the edge, with

a yellow tubular floret disc **(Figure 4.)**. Between January and December is the blooming period and the plant makes an important contribution to pollination. Special characteristics include being hermaphrodite, performing heliotropism – aligning its flowering head towards the sun, closing at night and opening in the morning [25, 38]. Wild grown or cultivated, as a non-poisonous plant the raw or cooked leaves can be used in everyday kitchen, in salads, soups or sandwiches and own a mild to acid flavour [39]. Also, the fresh or dried flowering heads are utilized for food consumption or in medical preparations.

Figure 4: flowers and leaves of Common daisy, (Wikimedia Commons)

Previously it had been employed by Crusaders in the Middle Ages, to treat wounds, broken bones or bruises [40]. In the modern world its utilization has expanded to not only treating of wounds, injuries, trauma or muscle overexertion, but also to application in haematoma, haemangioma, metrorrhagia, disorders of bleeding. The plant is declared to have value in skin therapy, further on furuncles, labial herpes, oozing eczema and urticaria [41]. A study on Wistar albino rats proved for the first time that *Bellis perennis* has a wound healing potential, without forming scars, by administering a topical ointment preparation from the flowers' n-butanol fraction [42]. *Bellis perennis* possesses mildly analgesic, anti-inflammatory, antispasmodic, antitussive, demulcent, digestive, skin softening, expectorant, laxative, ophthalmic, diuretic and tonic properties. [42]. Main components of the plant include flavonoids, which have an antioxidant effect, like flavone glycosides and apigenin, kaempferol and quercetin. Further constituents are triterpenoid saponins (2.7%), including ester triterpenoid Bellis saponins 1 and 2. The roots contain an even higher concentration. Essential oils are produced in the tubular flowers and special squamous glands of the leaves, or the petiole and more substances are tannins, acetic acid, oxalic acid, wax and inulin [43].

Studies displayed antioxidant and radical scavenging, antibacterial and antifungal activities of the herb, proved by preparing aqueous and methanol extracts from aerial parts [44]. Making a tea is a homespun remedy and not only for human consumption a valuable preparation. Douse two teaspoons drug with 250ml boiling water, let it steep for ten minutes and use it as oral administration or for compresses in case of skin rashes, eczema and poorly healing wounds [25].

4.1.4. Hamamelis virginiana

Hamamelis virginiana is a deciduous, scented shrub **(Figure 5.)** or tree called Witch hazel, Common witch-hazel or American witch-hazel. It is indigenous in North America, spread further to Canada, Florida, Texas and Minnesota [18]. Cultivated in Central Europe and commonly used as an ornamental plant, it is found on rocky bands of creeks or on the edge of forests and it prefers rich soil. The shrub belongs to the Hamamelidaceae family and has the ability of being hermaphrodite, so self-fertile, having both female and male sexual organs. It can reach a hight of five to even seven metres. The treetop is broadly funnel-shaped with spreading branches, obovate to elliptical dull green leaves adorn it [45]. Flowering period lasts from September to October/November, producing bright yellow up to 1.5 centimetres long petals **(Figure 6)**. Shiny blackish brown seeds are ejected from the capsule-formed fruits, that ripe in October of the following year [46].

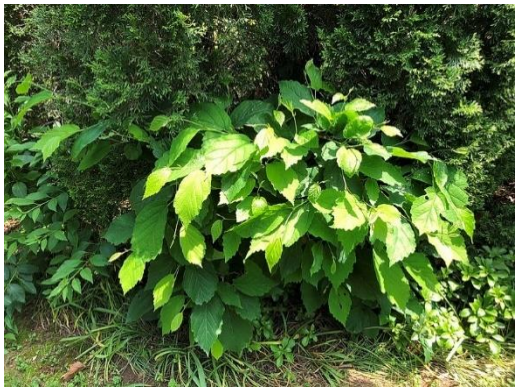

Figure 5 (left): shrub of *Hamamelis virginiana*, (Wikimedia Commons, 2022)

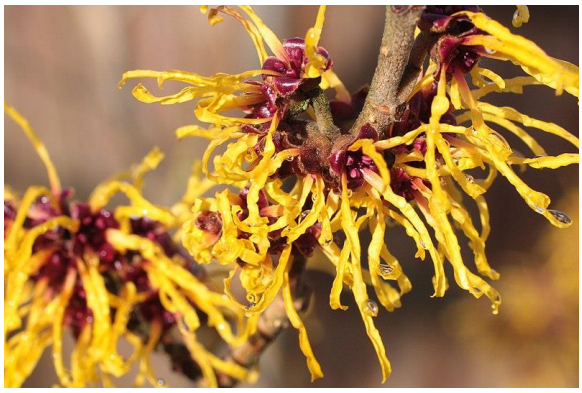

Figure 6 (right): flowers of *Hamamelis virginiana*, (Wikimedia Commons)

In former history it has been used traditionally, by the indigenous Native American population as an internal as well as external drug. This included the treatment of superficial skin wounds, skin inflammations, burns and various types of bleeding, making decoctions from boiling the shrub [47]. In veterinary medicine it has been utilized in farm animals for treating vaginitis, metritis, udder tears with milk leakage. Also, in general, to treat inflamed, painful eyes and ears, ulcers and bruises. New-borns with navel infection, ear cleaning, episiotomy and anal furunculosis especially in dogs can be successfully medicated. Inner usage in disorders of the genital- and urinary tract is also beneficial [48]. Common medical effects of the plant consist of being astringent, antipruritic, mild superficial anaesthetic, anti-inflammatory, antimicrobial, anti-secretory, vein tonic and to stop local bleeding [1]. The bark, *Hamamelidis cortex* is used to produce preparations and it contains tannins, such as gallotannins like hamamelitannin (8-12%); oligomeric proanthocyanins; essential oils. *Hamamelis virginiana* is a highly astringent/decongestant herb, what is said to be in correlation to the high amount of tannins in the bark. These substances react with the tissue proteins, which they come in touch with, like in precipitating proteins, where tannins offer antifungal and antimicrobial effects [49]. Experiments on isolated rabbit arteries being confronted with preparations of Witch hazel leaves, exhibited vasoconstrictive reactions [50], as well as lowered skin temperature in other topical applications.
A study, carried out by Touriño et al. [51], states that the polyphenolic extract made from this bark has free radical scavengering properties, acts antitumoral against melanoma cells and prevents haemolysis. For rinsing wounds, a decoction is prepared out of five to ten grams of bark, put into 250ml water, then cooked up to ten minutes. It should be applied several times a day. Another therapy is the tincture, where five parts of 60% ethanol are poured over one part of leaves, dried and crushed. The process takes two weeks to let it steep, finally it is squeezed out and filtered. To formulate an ointment, '*Hamamelis* water' is incorporated into a suitable base, like lanolin or white vaseline [1].

Antibacterial potential against strains of *Streptococcus* and *Staphylococcus* ssp. could be confirmed in a study, with the help of extracts made from the leaves [47]. Dried leaves whole or cut *Hamamelis folium*, are also made use of as various preparations. They consist of tannins (3-10%), catechin tannins; flavonoids; essential oils. Tea can be made as an inwardly preparation, where one to two teaspoons of leaves are doused with boiling water. Let it set for ten minutes, sieve it and give orally up to three times a day, this is useful in diarrheal disorders. Containing tannins which are astringent, cause diarrhea and vomitus, therefore

these inner preparations are not suitable for cats because they are more sensitive in general [1]. An external infusion is made out of leaves in proportion (1:3 to 1:10), if necessary diluted, and utilized in inflammation and wounds [1], or an infusion with one part leaves and ten parts water for compresses and rinsing [29]. None of the preparations showed any toxic impacts on tested rats and mice, no abnormalities appeared in a daily oral administration with 100 mg/kg body weight for three months, in those rats. Wynn & Fougère [48] detected an altered drug absorption as occurring interaction.

4.2. Analgesic plants

4.2.1. Hypericum perforatum

Hypericum perforatum is a scented perennial, herbaceous herb called ‘Common St. John’s wort’, ‘Chase-devil’, ‘Tipton's weed’ or ‘Rosin rose’ and it is one of the various members of the Hypericaceae family [32]. To its habitats belong wood edges, wood clearings, dry meadows, subalpine regions and it occurs in Europe, West Asia and North Africa. In many countries it is stated as an invasive weed these days [50], also does the whole plant possess toxic properties, especially in the leaves and flowers. A hight up to one metre can be reached, it has rhizomes as roots and generally several, erect, richly branched stems, with two longitudinal edges [25]. A special botanical feature regards the green and densely leaves, if held against light they appear perforated, what also refers to the Latin name ‘*perforatum*’. Those holes are secretion containers, which include essential oils. The inflorescence is umbel-like, 5-folded and yellow, having six-millimetre-long sepals and three times longer petals **(Figure 7.)**. Hypericin, the important main component, is in the flowers and visible as dark red dots or stripes [1]. From June to September lasts the flowering period and the fruits are ovoid shaped fissile capsules.

The traditional use goes back to antiquity: in Greek it was used for treatment of shingles; being known as a very effective wound healing herb it has helped in therapy of bruises, swellings, ulcers, tumours with infused oils and ointments; also urinary problems, dysentery, diarrhea, muscular rheumatism and treating of worm infestation [50].

In the last two decades, *Hypericum perforatum* has been one of the best researched and most significant medicinal herbs, especially in the direction of its antidepressant capability, not only in human medicine [52]. In veterinary behaviour therapy, notably in primates, cats and dogs; the plant has found its usage in compulsive behaviour, depression, panic attacks and anxiety, being unclean, misconduct when being alone and when combined with valerian it achieves an effect even similar to tricyclic antidepressants [1]. Nowadays its utilized internally in the treatment of gastrointestinal tract inflammation, digestive problems, diarrhea, agitation, nervousness and bronchitis [29]. Externally, the plant is helpful for wounds, insect bites, burns and ulcers, scar pain, rheum and there are medical skin care products available for the aftercare of injuries, atopic dermatitis and to support a healthy skin function [28, 29, 53].

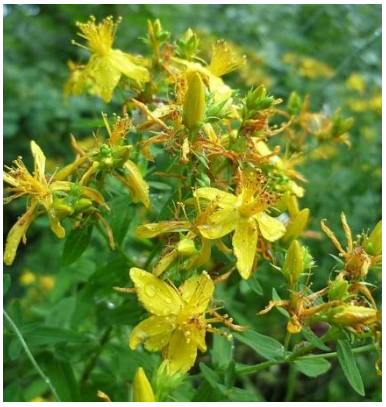

Figure 7 (left): flowers of St. John's Wort, (Wikimedia Commons, 2011)

Figure 8 (right): inflorescence being soaked in olive oil and exposed to sun light, to make herbal medicine. (Wikimedia Commons, 2013)

For drug preparation the herb itself and the dried, whole or crushed shoot tips are processed. The herb, '*Hyperici herba*', consists of the main substances naphthodianthrones, like hypericin and phloroglucinderivate such as hyperforin, adhyperforin; which are known to have anti-inflammatory, anticancer, antioxidant and antimicrobial capacities [53]. Furthermore, studies of hyperforin showed apoptosis stimulating effects ex vivo of lymphocytic β-cells in leukaemia and antitumour properties, like inhibiting highly angiogenic sarcoma in mice [50]. Hypericin is light utilising, which leads to photosensitization in poorly pigmented areas, especially in grazing animals being exposed to the sun [28], so shading or putting them into a stable during treatment is advised. Other components are biflavones; xanthone; oligomer procyanidins (up to 15%); phenol carbon acids; flavonoids (up to 4%), like hyperosid and rutosid. Mechanisms of action include inhibition of GABA and NMDA receptors, inhibition of serotonin, dopamine, noradrenalin

revival, increase of nocturnal melatonin secretion and stress decrease due to raising prolactin- and cortisol levels [1]. These features can be used in supplementary feeds for anxious and nervous animals. For inner usage a tea can be made, therefor pour over 5-30g of drug with simmering water, let it set for ten minutes and give 100ml/10 kg per bodyweight over the day [25]. Also, tinctures, powders and extract preparations are applied as antidepressants. Fresh inflorescence, '*Hyperici flos recens*', is often prepared to a red oil macerate or into wound oil mixtures **(Figure 8.)** together with lavender-, coriander-, tea tree oil; due to the differentiation of primary keratinocytes and antimicrobial as well as antiphlogistic effectiveness, it is helpful in sharp and blunt trauma, abrasions and first-degree burns [1]. Flavonoids with hyperosid (1,1%), hypericin, hyperforin, biflavones and essential oils are main ingredients in the flowers. Since the plant activates the enzyme CYP3A4, which is metabolized over many antimycotic and immunosuppressive drugs, interactions have been reported in simultaneous applications, as well in drugs being transported by the p-glycoprotein [48].

4.2.2. Symphytum officinale

Symphytum officinale is a perennial, densely haired plant having angular winged stems **(Figure 9.)** that can reach a hight of 1,2 to 1,5 metres. It is a member of the Boraginaceae family and known under the colloquial names 'Common comfrey', 'Quaker comfrey', 'Bruisewort' or 'Consound root' [18]. The plant is native in Europe, Siberia, East Asia and has also spread over North America, where it can be found in damp meadow ditches or riverbanks.

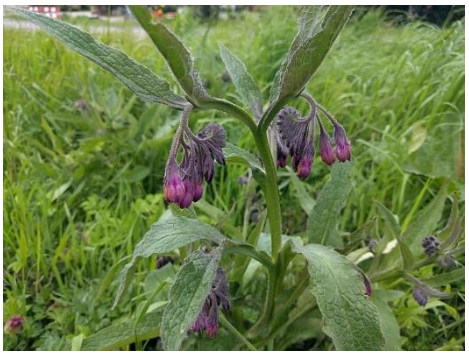

Figure 9: habitus of *Symphytum officinale*, (Wikimedia Commons, 2021)

Long pointed, lanceolate shaped, green leaves define the herb, the lowest ones reach a length up to 25 centimetres and stem wings descend to the next leaf. Having a blooming period from May to June, the red-violet or sometimes yellowish-white flowers are one to two centimetres long, with glabrous and narrow maw scales and from the corolla protruding stylus [25]. One-seeded, smooth, shiny fruits and a turnip shaped root, forming black 30 centimetres long far-reaching rhizomes. These possess slightly astringent properties and a slimy consistency when cut [54].

In fractures due to acute trauma or wound and joint sores, it has been utilized since as a medicinal plant for therapy with a long traditional history. Due to its diuretic and laxative effects, internal applications for treating intestinal ulceration, gallbladder problems and gastritis had been recorded, though to the cancerogenic and mutagenic capacities of the included pyrrolizidine alkaloids this method is strongly advised against nowadays [1]. Storebought medical products are free from these alkaloids, due to extraction methods, so they can be applied safely. A study with rats demonstrated anti-inflammatory effects in induced paw oedema, with the help of a dry extract from the plant's roots, containing rosmarinic acid [55]. *Symphytum officinale* has shown to be useful in the treatment of poorly healing wounds and bone injuries, due to one of the main components allantoin (up to 4,7%), which does not only promote the rejection of necrotic tissue, but as well the epithelisation and cell proliferation [55, 56]. It possesses analgetic, antiphlogistic and granulation-promoting effects and supports the callus formation, caused by the included glycopeptides blocking the release of prostaglandins and arachidonic acid [28]. Other contained substances are mucilage (up to 30%), tannins, amino acids, caffeic acid ester and the antimicrobial effective triterpene saponins [56]. The fresh or dried root, *Symphyti radix*, as well as the leaves can be utilized for external preparation therapy. A poultice is made out of one hundred gram roots, boiled in one litre water for ten minutes and then applied in case of distortions, contusions, tendinitis, fractures or arthritis [25]. Furthermore, a tea can be prepared from the herbage, used within a compress, or a made tincture being incorporated in ointments [28]. Due to the amount of pyrrolizidine alkaloids in the roots, the plant is considered potentially toxic, hence it should only be put on intact skin, especially in dermatological treatments of pruritic or inflammatory skin conditions [1, 50].

4.3. Antiphlogistic plants

4.3.1. Calendula officinalis

Calendula officinalis describes an annual, cultivated and non-poisonous plant, belonging to the Asteraceae family. Occurring in Asia, Europe, the Alps and Mediterranean regions, it inhabits arable land, roadsides and dumps or can be found in gardens as ornamental plant [18]. Known names are 'Scotch Marigold', 'Common Marigold', 'Ruddles' or 'Pot Marigold' and it reaches a hight up to 60cm, with an erect and hairy petiole [32]. The leaves are ovate to lanceolate shaped, green coloured and they narrow in a winged stalk. A blooming period from June to late August and two to five centimetres wide, orange to dark-yellow tubular and ray florets **(Figure 10.)**, which proceed into a disc flower typify the plant [25]. Besides being heliotropic, the fruit is an incurved achene, with multiple hooks. Although the whole herb has a stinging and resinous smell, the flowers can be used in salads or sweet-sour dishes due to their slightly bitter aromatic taste, as well as the raw leaves which possess a high mineral and vitamin content [32].

Figure 10: *Calendula officinalis* florets, (Wikimedia Commons, 2013)

In folk medicine the herb was used as a diuretic, antispasmodic, anthelmintic, promote sweat build up, or even to treat cancer and jaundice. Nowadays it finds application in gastrointestinal disorders, therapy of external wounds and inflammation of the skin or mucous membranes [29]. Several ethnoveterinary medicinal studies in rural animal husbandry showed, that *Calendula officinalis* is one of the most utilized medicinal plants, especially in Switzerland, for treating gastrointestinal diseases and wounds or ulcers in horses and cows [1]. Effective wound healing properties have been proven in multiple

animal trials, like an enhanced recovery from inflammation stages or stimulating granulation tissue, as well as having a prophylactic outcome in burns, when applied earlier [57]. Apart from promoting epithelisation and phagocytosis, collagen production, stimulating fibroblasts and the immune system in general, the plant proves to be useful in eye inflammations and conjunctivitis or for treating vaginitis and endometritis [28]. The important components for medicinal usage are situated primary in the inflorescence, consisting of triterpene saponins, which are responsible for the antiphlogistic, diuretic and antimicrobial capabilities [58]. Other substances are flavonol glycosides like quercetin, carotenoids, mucilage and essential oils.

Calendulae flos, the flowers, can be used in many ways for herbal preparations: one is the Marigold ointment, which is available over the counter in pharmacies or stores too. Fresh or dried florets parts are put in 40-50°C heated up fat, macerated for two to three hours, filtrated, bottled and then processed with beeswax for hardening [1]. Podlech [25] advises an infusion for compresses by boiling one to two teaspoons of drug in 250ml water, for ten minutes, helpful in poorly healing wounds or abscesses. Preparing a tincture from the ray florets as a wound rinse or an oil for smearing scars are further possibilities.

4.3.2. Echinacea purpurea (Echinacea angustifolia, Echinacea pallida)

Echinacea purpurea is one of the three *Echinacea* species, which are being utilized as medicinal herbs, such as *Echinacea angustifolia* and *Echinacea pallida*, having properly similar morphology and drug effects [59]. It is a perennial, herbaceous and non-toxic plant and belongs to the Asteraceae family, known by the names ‘Red sunflower’ or ‘Eastern purple coneflower’. The plant is indigenous in North America and grows on barrens, prairies or in open forests; it has been introduced into Germany, Poland and Austria a few decades ago, where the herb is mostly cultivated as a garden ornamental plant [18]. Reaching a hight from 50-120 centimetres; the stalk is hairy, brownish-green and erect; with simple, narrow to wide-lanceolate, serrated dark green leaves. The big flowering head containing orange-brownish tubular florets and crimson to purple ray florets on the edge, are a prominent characteristic, attracting many bees in the blossom period from May to October **(Figure 11.)**. It has fibrous roots and a glabrous achene with a pappus as fruit [25].

The plant has long traditional use by the natives of North America like for local treatment of burns and injuries, in toothache as an analgesic, as disinfectant in inflammation and suppuration or even as antidote in snake bites [1].

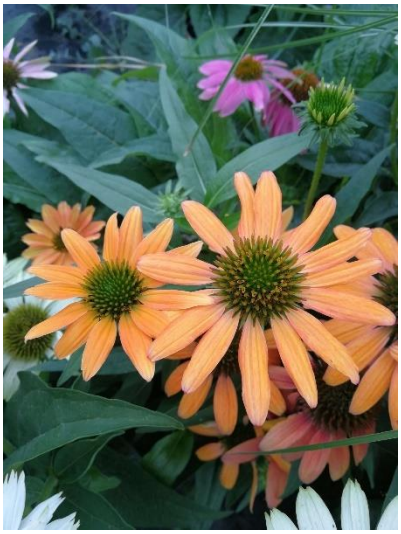

Figure 11: florets of *Echinacea purpurea*, photographed by the thesis author

Promotion and support of natural immunity like in respiratory infections, urinary tract infections, scalds, abscesses, insect bites and treating of superficial wounds are ways of application in modern western medicine these days [41]. In-vivo studies in rats showed the promotion of granulocytes and macrophages, due to the oral prescription of water-ethanol extracts from the roots, containing alkamides, polysaccharides and cichoric acid [59]. Antibacterial and antifungal properties have been proven in a dose-dependent study in mice, with the use of polysaccharides from cultures, to treat lethal dosages of *Candida albicans* and *Listeria monocytogenes* intravenously [60]. Wound healing effects of the plant are caused due to the activation of fibroblast growth and other growth factors, as well as inhibiting hyaluronidase and prevent spreading of inflammation in tissues [28]. Further reactions include increase of T-helper cells, promotion of production of cytokines and TNF, blocking inflammatory messengers and also an immunosuppressing effect in prolonged usage, as well as a local anaesthetic effect on the tongue by alkamides [54], why the plant should not be given to patients having a weak immune system. Polyyines; flavonoids; caffeic acid derivates, like cichoric acid; essential oils and glycoproteins are other components, that the roots and flowers consist of [18]. *Echinacea purpurea radix* and *Echinacea purpurea*

herba can both be utilized for herb preparations: a tincture is made out of adding one part root to five parts high-proof alcohol and leaving it for ten days [41], dry extracts or powder can be prepared from the roots, pressed juice as inner and outer applications and ointments for therapy of wounds [25].

4.3.3. Matricaria chamomilla

Matricaria chamomilla or as other synonyms *Matricaria recutita*, *Chamomilla recutita* is an annual, non-poisonous weed or ruderal plant **(Figure 12.)**, which is categorized into the Asteraceae family [25]. Known colloquial names are ‘Chamomile’, ‘German chamomile’, ‘Hungarian chamomile’ and ‘Scented mayweed’ [18]. It is native in Europe, North-West Asia, Hungary, North America and distributed in wasteland, fields, roadsides and even subalpine regions. The plant is one of the most important traditional medicinal herbs, having nutritional, cosmetic, pharmacological and multitargeting properties in therapy, which have been used and researched for many years [61].

Figure 12: *Matricaria chamomilla*, (Wikimedia Commons)

It can grow up to 50 cm, is mostly bare, possessing green two to three pinnate leaves with linear tips. White ray and yellow tubular florets characterize the 1.5-2.5 cm large caplets, the petal base is conical and hollow, and the flowering heads are single. The flowering period lasts from May to September and a yellowish-brown achene defines the fruit [25, 50]. The plant has a typical aromatic smell, gets pollinated frequently by bees and many other insects, and is also hermaphrodite [61]. Widely deployed as folk remedy, disorders in

relation to urinary bladder, uterus, intestines and stomach are preferential areas of application. In veterinary medicine it had been used externally as clyster and cataplasm – a poultice made with paste, and it has been prepared for rinsing wounds until this day. A steam inhalation can be performed in cases of inflammation of the eyes, rhinitis, sinusitis, dry cough, acute and chronic bronchitis [1]. Further treatments were in colic, flatulence, digestive and liver problems, uterus and urinary tract spasms, eyewash, calming patients and sweat cure [18]. Externally, the plant is utilized in ulcer, furuncle and abscess therapy, also for treating infected wounds, in promotion and stimulation of tissue granulation and to remove unpleasant smells of affected skin parts [28, 29].

Brendieck-Worm & Melzig [1], explain that for drug preparation the dried flowers, *Matricariae flos*, are useful. As well the so called blue essential oil, *Matricariae aetheroleum*, which is obtained by steam distillation from chamomile inflorescence. The flowers' main components are sesquiterpene lactones, like matricin, flavonoids (0,5-3%), essential oils (0,3-1,5%), coumarins, about 10% mucilage, phenolic acids. Flavonoids and coumarin derivates are responsible for the plant's antispasmodic properties, whereas chamazulene, farnesol, bisabolol are monoterpenoids that cause the anti-inflammatory and disinfectant activity [58]. Those are constituents of the blue essential oil: α-bisabolol, chamazulene, en-in-dicycloether, bisaboloxid A and B. To the general effects of being spasmolytic, antiphlogistic, analgesic, immunostimulant, antimicrobial and promotion of wound healing, the essential oil is capable of ulcer protection and having a psychostimulant impact. Further, describe Brendieck-Worm & Melzig [1] the mechanism of action as the following: the inhibition of cyclooxygenase and lipoxygenase in the arachidonic acid cascade, by (-)-α-bisabolol and chamazulene, leads to antiphlogistic effects. Spasmolytic activities are caused by inhibiting the calcium mobilisation into the cells of smooth muscle, in the gastrointestinal tract, and mucilage is an immunostimulant. Also, antiallergic actions are shown, due to the decrease of IgE and IgG1 values. In addition, the inhibition of pepsin secretion and activity, due to (-)-α-bisabolol, leads to an ulcer protective effect even without changing the amount of stomach acid [61]. This benefits in treatment of gastric and intestinal diseases. A study in six plants with well-known antimicrobial effect, including *Matricaria chamomilla*, proved the hindering of certain cell lines in the protozoal parasite *Leishmania mexicana* [62].

Most common way of preparation is a tea infusion, where up to three teaspoons of drug are poured over with boiling water, let steep for ten minutes and then administered over the day

[25]. This method mainly brings out the healing of wounds and antispasmodic properties of the plant. Additionally, the tea is suitable for all animal species, and for making compresses or rinsing of inflamed skin and mucous membranes [28, 29]. For inhalation therapy, mix two to three tablespoons of dried flowers in one litre of hot water, and in adult animals, eucalyptus oil can be added for potentiating effects [29]. Tinctures, made of flowers and strong alcohol, are likewise usable for flushing wounds. There exist several animal care products on the market, whereby aloe vera, witch hazel, peru balsam, calendula, rosemary, sage and other herbal substances are worked together with chamomile, to support the regeneration process and metabolic activity of the stressed skin [1]. Although it is characterized as non-toxic plant, hypersensitivity reactions due to ingredients and preparations have been reported, especially in cats should be dosed carefully [28]. Often these adverse effects are caused by impurities with other chamomile species, or due to allergic cross reactions with ragweed [18], and even possible interactions in application of aspirin, anticoagulants, benzodiazepines and salicylates were detected [48].

4.3.4. Plantago lanceolata

Plantago lanceolata is a perennial, herbaceous, nutrient-rich meadow plant **(Figure 13.)**, being noted by the names ‘Ribwort plantain’, ‘English plantain’, ‘Narrowleaf plantain’, and which is a member of the Plantaginaceae family [63]. It is native to Europe and Asia but since this species has spread globally and it can be spotted on roadsides, meadows or pastures. Narrowly lanceolate, upright, green leaves are situated on a 40-centimetre high, slightly hairy peduncle; the inflorescence is spherical, greenish brown, like a long-stalked ear with a four-part chalice and crown, blooming from April to September [25]. The fruits are two seeded capsules, the plant is hermaphrodite and loam soil that is nutrient rich is preferred. Due to its varied possible ways of application, such as in therapy of wounds, to reduce fever, as a haemostatic, to cleanse blood or as an expectorant, the use of the plant goes far back to the Middle Ages and antiquity [1]. Commonly eaten by all grazing animals, the leaves *Plantaginis lanceolatae folium* contain mucilage and tannins, as well monoterpenes like aucubin, catapol and other antibiotic compounds, which show favourable gastrointestinal effects [64]. The plant is said to be one of the most helpful herbs for respiratory disorders, being used inwardly for catarrh of the upper airways due to its antimicrobial activities, the mucosal membrane is protected by the soothing mucilage in

inflammation of the throat, and by decreasing of congestion and having antispasmodic effects does it also help in asthma and allergies [1]. Astringent properties have been detected, caused by the included tannins, hence it finds application in ulcers, gastrointestinal diseases like diarrhea or bowel infections, externally in primary wound care, hoof or skin inflammations and the freshly picked leaves act against insect bites [65]. Aucubin, with its antibacterial and anthelmintic properties, is also used in the treatment of urinary tract infections and other main components in the leaves are flavonoids, phenylpropane, minerals like zinc, coumarin and the immunomodulatory polysaccharides [58]. The dried leaves and flowers, whole or crushed, can be utilized for preparations, such as making tea out of one to two teaspoons of drug for respiratory infections or to use in a compress to treat poorly healing wounds [25], preparing a pressed juice against indigestion or an infusion for gastrointestinal inflammations in calves [29].

Figure 13: *Plantago lanceolata* florets and leaves, (Wikimedia Commons)

4.3.5. Salvia officinalis

Salvia officinalis depicts a perennial, scented, evergreen subshrub which is a relative of the Lamiaceae family and it is acquainted under the names ‘Common sage’ or ‘Garden sage’ [66]. Being indigenous as a crop plant in the Mediterranean regions, it has mainly wild growth in Central Europe, and it inhabits rocky steppes and dry grasslands. The hight varies from 60-100 centimetres, it is feltlike haired with long-stalked, ovate and wrinkled greyish

green leaves **(Figure 14.)**. Notably are the violet-pink florets standing mostly loose in whorled partial inflorescences **(Figure 15.)**, they have a blooming phase from May to July and can be used as seasoning in salads or as fragrances, due to their aromatic flavour [25, 54]. It has also schizocarp fruits, with black seeds in them and can outlive dryness. ‘Salvia’ derives from the Latin word ‘salvare’, meaning healing, therefore it has been significant as a medicinal herb since the early antiquity and it was utilized against cough, gastrointestinal problems, diarrhea, stomatitis, ulcers, rheumatism or even as cataplasm [67].

Figure 14 (left): Sage leaves, photographed by the thesis author

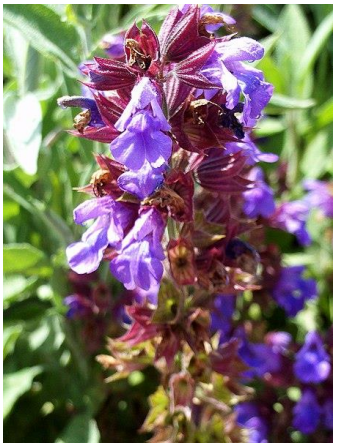

Figure 15 (right): Sage inflorescence, (Wikimedia Commons, 2009)

Until these days it plays a major role in veterinary medicine and finds application in wound treatment, weaning, inflammations of the skin or throat and mouth, diarrhea, stomach disorders and to treat increased sweat production. The most crucial chemical compounds are present in the leaves, such as hydroxycinnamic acid derivates, like rosmarinic acid, having antioxidant properties, anti-inflammatory action in topical applications on the epidermis and studies also showed the capability to prevent skin carcinogenesis and breast carcinoma caused metastasis in mice [66]. Di- and triterpenes are extensively present, whereby oleanolic and ursolic acid have antibacterial properties to block the growth of methicillin-resistant *Staphylococcus*, *Streptococcus* pneumonia resisting penicillin, *Enterococcus* being vancomycin resistant and the effect of ursolic acid was proven to be more powerful than ampicillin [68]. Flavonoid glycosides, like luteolins, apigenin, campherol are further components and besides that, the plant has antiphlogistic, appetizing, antiviral, digestion promoting, spasmolytic, choleretic and astringent effects [28]. Essential oil (1-2,5%) from

the leaves, also so called ‘Dalmatian sage oil’, which is gained by steam distillation and is rich in thujone (30-60%), camphor (14-37%) and cineol (6-16%), has mucolytic, cholagogue as well as hepatoprotective properties [1, 66], thus being helpful in liver injuries or medicating other related disorders.

Sage tea has been effective in inflammations of the mouth and throat, preparing one to two teaspoons leaves with cold water and then heat up to simmer [25]. Infusions for inner treatment can be used in pseudopregnancies by integrating it into the food, to inhibit the lactation or to promote the teat regression after weaning in bitches, with wet-cold compresses [1]. Calf diarrhea can as well be treated with an infusion, or to increase appetite; another method is to prepare a tincture, undiluted or as a wound flushing solution, with one glass of water mixed with one teaspoon drug [29]. Brendieck-Worm & Melzig [1] points out to pay attention due to contraindications and intolerances: sage is not suitable for cats, sage oil should not be used when epilepsy is known and sucklings, pregnant or lactating animals must not be treated inwardly due to the high amount of thujone. Moreover, various veterinary care products are available, for outer usage, often in combination with calendula flowers, thymol and hamamelis.

4.4. Plants with highly toxic components

This chapter includes plants being classified as highly toxic, although they are chemically utilized by the pharmaceutical industry and in TCM, it is not advised to create any medicinal preparations at home or on your own, as this application can be fatal.

4.4.1. Aconitum napellus

Aconitum napellus is an herbaceous, perennial, highly poisonous plant **(Figure 16.)**, known many names as ‘Aconite Monkshood’, ‘Blue Rocket, ‘Wolfsbane’ or ‘Helmet Flower’, belonging to the Ranunculaceae family [69]. It is located in the Central European mountains, where it grows on creek banks, open fields or in forests and it can reach a hight up to 1.5 metres.

The characteristic azure coloured inflorescence is branched or racemose in panicles, with wide helmet shaped upper petals which bloom from June to August; the dark green leaves have five to seven parts dispersed into lineal lobes [25]. The plant has been widely utilized in Traditional Chinese Medicine for over 2000 years, despite possessing highly poisonous chemical substances like diterpene the alkaloids aconitine and napelline, which act toxic on the cardiovascular system due to their effect on the Na+ channels, but as well having anti-epileptic and analgesic properties [58, 69]. Being antagonists on the nicotinic acetylcholine receptors, it works on the nervous system and a study showed successful growth inhibition of *Leishmania infantum*, without damaging the

Figure 16: habitus of *Aconitum napellus*, (Wikimedia Commons, 2014)

cells of the animals [70]. In case of intoxications, clinical signs are usually heart and nervous system related together with gastrointestinal disorders and the herb is extremely lethal due to final ventricular tachyarrhythmia and heart failure [19]. The whole plant, especially the seeds and roots are toxic, so reasonably making of own preparations or self-administering is strongly prohibited and only detoxified, purified bulbs and roots are permitted for clinical decoctions and oral administration. Mainly, today the herb is manufactured and incorporated into pharmaceutical drugs, to promote and enhance their effectiveness. Therefore, the plant finds its usage in oedema, diarrhea, various cardiac disorders, circulation collapse and fainting, gastroenteritis, joint pain, diseases accompanied by fever, to support tumour therapy and the analgesic activity can be helpful in wound treatment or severe traumatic injuries [18, 41]. That is why despite the plant's toxicity, with careful application, it should be considered as an important herb for veterinary medicine.

4.4.2. Atropa belladonna

Atropa belladonna depicts an extremely poisonous, herbaceous, perennial plant, being a part of the Solanaceae or Nightshade family, and which is also called ‘Deadly nightshade’, ‘Dwayberry’, ‘Belladonna’ or ‘Black cherry’ [18]. Growing on field edges, in shady woods, near bushes, it is indigenous in Central Europe, Asia and spread out to North Amerika and regions in Afrika as well. The name ‘Belladonna’ originated from the Middle Ages in Italy, when women utilized the mydriatic actions of the plant to dilate their pupils with diluted eyedrops for beauty and cosmetic purposes [19]. Alternate, ovate-elliptic, downy haired grey-green leaves are situated on an erect, woody and hairy stem and it grow up to 1.5 metres high. Having a blooming period from June to August, the inflorescence is brown violet, with a five lobed calyx and a nodding, bell-shaped corolla; the fruits are black shiny berries **(Figure 17.)** [25, 58], which can be easily confused with the edible *Prunus avium* due to their cherrylike look and sweet taste.

Figure 17: black fruits of *Atropa belladonna*, (Wikimedia Commons, 2009)

Belonging to the strongest poisonous plants, all herbal parts consist of several alkaloids like L-hyoscyamine, atropine and scopolamine, possessing parasympatholytic actions such as gastrointestinal motility inhibition, relaxation of smooth muscled organs and stimulating or depressing effects on the central nervous system [19]. Intoxications are quite common and especially sensitive and at risk are horses, cows and sheep, having symptoms such as cramps, unconsciousness, mydriasis, arousal states, hallucinations, elevated pulse, dry mucous membranes and respiratory paralysis mostly leading to a quick death [71]. Therefore, these alkaloids can only be used in manufactured, detoxified and processed forms, in certain

medications, to make the best use out of their properties. Antiphlogistic, anticarcinogenic, diuretic, mydriatic, sedative and stimulant effects find application in treating spasms, eye diseases, fever, arrythmias and cardiovascular conditions, enuresis, opium poisoning, inflammations and nervous disorders [18]. Studies in male Sprague–Dawley rats proved positive effects of the herb on wounds, a quickened collagen formation, shorter inflammation process and increased strength of the tissue [72].

5. Synthetic trauma therapy

5.1. NSAIDs

Non-steroidal anti-inflammatory drugs, also commonly known as NSAIDs, defines a class of chemical medications having the same therapeutic impacts and applications, despite being chemically diverse [73]. Possessing distinct analgesic, anti-inflammatory and anti-pyretic effects, they belong to the most frequently used drugs worldwide, usually for treating inflammation, pain and pyrexia, like in osteoarthritis, muscle spasms or rheumatic diseases [74]. They have a long history of application and have been discovered in the 19th century, due to the salicylate extraction from willow bark and later out of this the detection of aspirin/acetyl-salicylic-acid [74]. Although their popularity and wide range of use, do they possess severe side effects, such as hypertension, interfering with platelet activity, hepato- and gastrointestinal toxicities and affecting the heart and kidneys [75]. Most well-known NSAIDs in veterinary medicine consist of ketoprofen, carprofen and naproxen deriving from aryl or heteroaryl acetic acid, followed by fenemates such as tolfenamic and meclofenamic acid (Meclomen). Meloxicam and piroxicam belong to the class of oxicams, and another important drug is the pyrazolone called Metamizole [74, 75].

The principal mode of action of NSAIDs is inhibiting cyclooxygenases and intervening in the arachidonic acid metabolism, consequently they reduce the synthesis of prostaglandins, prostacyclin and thromboxane, which play a role in inflammatory pain, vasodilation and sensitize nociceptors to the effects of other mediators [75]. Important are as well the cyclooxygenase enzymes COX-1 and COX-2, being responsible for maintaining renal functions, the platelet aggregation, homeostasis and health of the gastrointestinal mucosa. Different to COX-1 being fundamentally expressed in most tissues and cells, the COX-2 is involved in lesser tissues and normally active in inflammation [76]. Therefore, so called COX-2 selective inhibitors are used for treatment, like firocoxib, robenacoxib or celecoxib; some having lesser side effects or decreased risk of gastrointestinal disorders.

Possessing analgesic actions, NSAIDs are often utilized in postoperative pain, in therapy of bone fractures – to prevent heterotopic ossification, or other orthopaedic diseases [77]. Prostaglandins play a major role in osteoclast and osteoblast formation in the process of fracture healing, thus due to their inhibition, several studies showed restrained bone formation and ingrowth with naproxen and COX-2 inhibitor rofecoxib or decreased fracture

healing with coxibs. A study on Wistar albino rats stated a decline of the wound healing properties and tissue repair after tracheostomy [78]. Though, recent scientific findings revealed a positive impact of the drugs on neurodegenerative diseases like amyotrophic lateral sclerosis or dementia, antineoplastic effects of COX-2 on colon rectal cancer, atherosclerosis risk decreasing actions and therapeutic options to treat chronic diabetic wound healing and prevent diabetes by intervening in the inflammation process [76].

Alongside the already mentioned adverse effects, further ones include peptic ulcers, due to the inhibited prostaglandin production, which generally protects the gastrointestinal mucosa, in application of COX-1 [75]. Also, in rarer cases anaphylactic reactions can appear on the skin or in the lungs, as well as urticaria or the aspirin-exacerbated respiratory disease occurring together with asthma, nasal polyps and chronic rhinosinusitis [74]. Due to those serious side effects the application of NSAIDs should be avoided in high bearing pregnant animals, patients with renal disorders, or if hypersensitivity and experienced allergic reactions with these drugs are known. Further studies and research on NSAIDs should be implemented, they have many effective properties and possibilities of application, however their severe side effects impede the treatment options especially for sensitive, pregnant or previously ill patients and so more tolerable drugs are needed.

5.2. Corticosteroids

Glucocorticoids are steroid hormones categorized as a class of corticosteroids, where also the mineralocorticoids like aldosterone belong to, but GCs are considered one of the most important and potent anti-inflammatory drugs having wide pharmacological actions [79]. Being naturally synthesised by the adrenal cortex, their discovery in the 19th century from adrenal extracts led to a broad systemic usage until this day, followed later by the inhaled glucocorticoids such as beclomethasone, for therapy of persistent asthma [80]. They possess not only anti-inflammatory properties, but they act immunosuppressive, antishock and antiallergic and previously they have found their use in treating myositis, osteoarthritis or skeletal and muscular diseases in general, but have been mainly replaced by the NSAIDs these days to treat this kind of disorders [81]. By binding to the glucocorticoid receptor, which is a ligand-inducible transcription factor that has negative and positive effects on the regulation of gene expression. The GCs have many ways of impact: they inhibit the phospholipase 2 (PLA_2) enzyme, suppress the interleukin synthesis and cell-mediated

immunity, inhibit many proinflammatory cytokines, the complement system synthesis is diminished, and leukocyte action is decreased as well [79].

Glucocorticoids are split up, due to their duration of action, in short-acting like cortisone and hydrocortisone (8-12 hours); middle-acting such as prednisolone, methylprednisolone, triamcinolone (12-36 hours); and the long-acting drugs betamethasone and dexamethasone (36-54 hours) [81]. There are various options for application: parenteral, topical, local, oral usage, inhalation or injection. Nowadays, these drugs find their application in inflammation and allergy treatments, gastrointestinal diseases and dermatological cases like FAD with prednisolone. Short-acting GCs are also generally used in feline asthma patients, chronic obstructive pulmonary diseases in horses and other respiratory disorders [81, 82]. Treatment of inflamed skin, ears and eyes with topical preparations is an often-used method. Dexamethasone, prednisolone and methylprednisolone are well absorbed in oral application, as most of the GCs, and are suitable for a prolonged therapy.

Indeed, the capacity of these extensive application possibilities results in many unfavourable severe side effects, particularly in a long-term use, such as diabetes mellitus or insulin resistance due to their inhibition of the gluconeogenesis by insulin, what can also contribute to hyperglycaemia in dairy cattle [83]. Another adverse effect is iatrogenic Cushing's disease accompanied by alopecia, polyuria, polydipsia, muscle atrophy, body fat redistribution and the animal being prone to infections [81, 84]. Addisonian-like crisis in secondary hypoadrenocorticism is a different side effect caused by a sudden termination of the GC therapy, resulting in vomiting, lethargy, diarrhea and sometimes even circulatory death. Hepatopathy, ligament degeneration, obesity, panting, cardiovascular effects, behavioural changes, laminitis in horses are further disadvantages and studies have proven impairment in wound healing and increased fracture risks in oral GC administration, due their reduction of bone mineral density [82]. Hence a careful administration of GCs is advised and the research for safer drugs in the future should be expanded. Also, possible pre-existing conditions of the animal must be taken into account, where a therapy with other more harmless substances - like herbals, can be considered/utilized as a replacement.

5.3. Monoclonal antibodies

Monoclonal antibodies, which are defined as monovalent antibodies binding to a specific target structure as in this case the Nerve Growth Factor (NGF), lead to the prevention of an impact on the TrkA-receptors and thus to a blockage of the target activity [85, 86]. Foremost created in 1975 by a hybridoma technique in mice, mAbs nowadays are gained by recombinant engineering, or in mice by single B-Lymphocyte duplications and they recently found a further therapeutic application for trauma and pain therapy in veterinary medicine [85]. Besides 'Lokivetmab', a mAb being used in the treatment of allergic pruritus, two newly approved drugs called 'Bedinvetmab' for dogs and 'Frunevetmab' for cats, offer an additional therapeutic option for pain relief in degenerative joint diseases like Osteoarthrosis. In this chronic, progressive disease, that leads to restricted mobility and reduced quality of life, the NGF plays a key role in the pain and inflammation cycle, representing one of the most important pain mediators formed excessively in damaged tissue of OA, which binds to TrkA-receptors on inflammatory cells and peripheral nerve endings [87]. Possessing a pro-inflammatory effect, increasing the pain sensitivity and sensitization of the nerves and joints to pain, as well as amplifying the pain signal are the unfavorable consequences of NGF, where the mAb can intervene effectively [88].

'Bedinvetmab' (Librela) was proven to be a safe and effective analgesic drug for dogs with OA in a placebo-controlled, randomized, multicentre and double-blind study, performed monthly via subcutaneous injection (0.5-1.0 mg/kg) for 9 months [89]. As well, it showed a solid compatibility and a decrease in the Canine Brief Pain Inventory (CBPI) score, an evaluation determined by pain interference, pain severity and quality of life. Another investigation with three inbuilt safety studies showed also an inhibition of the p75 neurotrophin receptor, such as sufficient toleration of 'Bedinvetmab' in healthy laboratory dogs - if administered monthly - and no severe side effects or anaphylactoid reactions were noticed, besides non-specific ones like anorexia and lethargy [86].

Advantageous analgesic therapy results have been shown in a placebo-controlled, double-blind, multisite, randomized study with the felinized mAb 'Frunevetmab' (Solensia), given subcutaneous monthly dosages for 3 months in cats, being diseased with OA and impaired mobility [87]. The drug was tolerated well, adverse effects only included increased skin reactions like pruritus, alopecia or dermatitis.

Summing up this research and successful therapies, mAbs involve many effective and positive aspects in treating trauma and chronic pain: possessing a durable efficacy up to 9 months, the fact that the drug is injected which is very accommodating especially in cats and being a safer option than the NSAIDs with lesser side effects [85, 89]. However, not every animal responds equally successful to this type of therapy, there is also the danger that therapeutic antibodies will be recognized by the body, immunogenicity develops and thus the mAbs will be neutralized [90]. Therefore, the way of prevention is to match them as closely as possible to the structure of their target species. The administration of mAbs must be repeated in regular intervals, being proteins, they are broken down after a certain time; aside from that Anti-NGF-antibodies should not be administered in pregnant animals, as the NGF plays a role in the development of nerve tissue and reproductive damages cannot be ruled out. In general, mAbs appear to be a safe alternative for synthetic pain killers in OA, admittedly, these drugs have been on the market only for a short period, so long-term studies have not yet been conducted and further long-lasting effects are not known.

6. Conclusion

As a result of my thesis, the following statements can be concluded. Overall, it is worth to approach trauma and chronic movement disorders with phytotherapy as it has been proven, thanks to their numerous constituents, that medicinal plants have a potent wide range of possible uses. A sustainable effectiveness could be demonstrated, especially in the external usage as tinctures, compresses, ointments or infusions for wound flushing. But also, internally by infusions or preparing tea, they can be applied effectively. Medicinal plants which were compiled with expertise, commonly act synergistic, so more comprehensive than the summation of their individual components would expect. Long-term treatment with plants, possessing mainly analgesic and antiphlogistic, is possible as well. Entailing lesser side effects than the synthetic drugs like corticosteroids or NSAIDs creates clear advantage for the phytotherapy, although NSAIDs might have a stronger action in some points and remain an important option for acute flare-ups of pain. So, it should be addressed that phytotherapy has its limits in emergency cases, taking more time to enfold the full potential. Administration of herbal medicine in combination with synthetic drugs are verified as usually unproblematic and synthetic drugs can often be reduced in their dosage within a few days' treatment. Finally, it is evident to say that therapy with medicinal plants has its value and should not be deprived, in the contrary, further investigation and research are needed, since the possibilities of application are not fully exhausted and there is still much unidentified about this topic.

7. Summary

The present topic of this study elucidates trauma therapy with an herbal approach, compared to traditional allopathy. For this purpose, I explained the importance of trauma therapy in general, what defines trauma, the causes and diagnostic possibilities, moreover the pathophysiological process of inflammation and I analysed the secondary metabolites, which are crucial for the plants' medical actions. By dividing the plants into their mode of action following plants could be highlighted: decongestant with *Achillea millefolium, Arnica montana, Bellis perennis, Hamamelis virginiana*; analgesic plants like *Hypericum perforatum and Symphytum officinale; plants* with antiphlogistic properties such as *Calendula officinalis, Echinacea purpurea, Matricaria chamomilla, Plantago lanceolata and Salvia officinalis.* In all these plants their description, included components and their resulting effects, usage and potential preparations were discussed. Additionally, I discussed plants with highly toxic constituents, if there are possible ways of use.

Thereafter I compared and evaluated the synthetic drugs - NSAIDs, corticosteroids, monoclonal antibodies - along with their history, mechanism of action, usage and adverse effects.

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Figure 14: Salvia officinalis leaves. Photographed by the thesis author.

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Thesis progress report for veterinary students

Name of student: Viola Maria Sachsenmaier

Neptun code of the student: F184XP

Name and title of the supervisor: Dr. Daniel Csecherics, head of Dept.

Department: Department of Botany

Thesis title: Therapy of trauma with the help of Herbals in comparison to traditional allopathy.

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	02	10	Discuss major chapters	
2.	2023	03	24	Literature review discussion	
3.	2023	04	19	Literature review discussion	
4.	2023	05	12	Medicinal plants review	
5.	2023	06	12	First draft review	

Grade achieved at the end of the first semester: 5

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	08	31	Corrections after first draft	
2.	2023	09.	21.	Discussing "Discussion" chapter	
3.	2023	10	07.	Bibliography corrections	
4.	2023	10	13	Final review	

5.	2023	10.	20	Finalization of the thesis/upload/typing	

Grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in 14.11.2023

I hereby confirm that I am familiar with the content of the thesis entitled

Therapy of trauma with the help of Herbals in comparison to traditional allopathy

written by **Viola Maria Sachsenmaier** (student name),

which I deem suitable for submission and defence.

Date: Budapest, 13 day 11 month 2023 year

Dr. Cserhalmi Dániel, Ph.D., associate professor, head of Botany department

Supervisor name and signature

ÁLLATORVOSTUDOMÁNYI EGYETEM
Növénytani Tanszék
1787
BUDAPEST