University of Veterinary Medicine Budapest

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The development of a herbal preparation for the treatment of diarrhea in dogs

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Abstract

This thesis treats the development and therapy documentation of a phytotherapeutical preparation which can be used in treatment of diarrhoea in dogs. The Department of Botany at the University of Veterinary Medicine Budapest first implemented this topic out of an increasing demand of phytotherapy in small animal medicine. The development of this herbal remedy was based on scientific literature about the active metabolites and their therapeutical properties in veterinary medicine. In the first part we focused on the research on medicinal herbs as well as the election of five specimens targeted at the needs of the preparation. The herbs used were cultivated in Hungary and were of highest quality. During the manufacturing, the medicinal plants were processed to an easy to use, oral applicable remedy. Further the therapy was then documented by means of an uncontrolled study in Hungary, under veterinary supervision. The data was collected by the help of a questionnaire, by the dog's owner over a time period of one year (from January 2023 to January 2024). The information gathered was then handed down to the veterinarian in charge.

During therapy, data were collected on the therapeutical effect, general status of the animal and the intake acceptance of the product. A total of thirty therapies were carried out by 24 veterinarians. In case of eleven patients the fulfilled, written documentation data was used for the therapeutical effect evaluation. In case of the general status and intake acceptance six out of the eleven questionnaires were used. Based on the written information received during therapy, a positive individual perception could be seen. But a bigger amount of data would be required to underline and proof the therapeutical significance by statistical analyzation.

Absztrakt

Ez a szakdolgozat kutyák hasmenésének kezelésére használható fitoterápiás készítmény kifejlesztéséről és terápiás dokumentációjáról szól. A kisállatgyógyászatban a fitoterápia iránti növekvő igényre reagálva a Budapesti Állatorvostudományi Egyetem Növénytani Tanszékén dolgoztunk. A gyógynövénykészítmény kifejlesztése a másodlagos növényi anyagcseretermékek és azok terápiás tulajdonságairól és állatgyógyászati felhasználásáról szóló tudományos szakirodalom alapján történt. Az első részben a gyógynövények megismerésére, valamint a készítménnyel szembeni elvárásokat kielégítő öt növényfaj kiválasztására összpontosítottunk. A felhasznált gyógynövény drogok

Magyarországon termesztett, kiváló minőségű gyógynövények voltak. A gyártás során a gyógynövény monodrogokat könnyen használható, szájon át alkalmazható gyógyszerkészítménnyé dolgoztuk fel. A terápia dokumentálására egy nem kontrollált vizsgálat keretében került sor Magyarországon, állatorvosi felügyelet mellett. Az adatokat kérdőív segítségével gyűjtöttük össze a kutyák gazdájától egy éves időszakon keresztül (2023. januárjától 2024. januárjáig). Az összegyűjtött információkat a gazdák a felelős állatorvosoknak adták át.

A terápia során nemcsak magáról a terápiás hatásról, hanem az állat általános állapotáról és a terméknek a kezelt állatok általi elfogadásáról szóló információkat gyűjtöttünk. Összesen 30 terápiát hajtott végre 24 állatorvos. A terápiás hatás értékeléséhez 11 beteg írásos dokumentációs adatait használták fel. Az általános állapot és az elfogadás esetében a 11-ből 6 kérdőívet használtunk fel. A terápia során kapott írásos információkként pozitív visszajelzéseket kaptunk. A terápiás jelentőség pontos megállapításához és a statisztikai elemzéssel történő bizonyításához azonban nagyobb mennyiségű adatra van szükség.

Contents

1. Introduction

One of the oldest forms of applied medicine known to mankind is phytotherapy. The use and knowledge of medicinal herbs was based on experience gained by trial and error, this know-how was then handed down to further generations. Originally its intended use in human medicine was quickly adapted to veterinary medicine needs for the treatment of certain problems and diseases. With the establishments of the first veterinary universities in Europe in the 18th century, the medicinal plants received an increasing importance as a valuable part of therapies [1]. Ultimately known for their gentle therapeutical approach, herbal remedies are still used for the treatment of humans and animals today and with an increasing demand by pet's owners [2]. In Farm animal medicine the use of herbal preparations has already become established to a certain extent but in the small animal medicine it is an upcoming trend [3].

2. Objective

The aim of this thesis was the development of a phytotherapeutically preparation that could be used to treat diarrheal diseases. To achieve this, we used five medical herbs: agrimony herb, blackberry leaves, chamomile flowers, yarrow herb and anise fruit and used their chemical properties concerning gastrointestinal problems. The most prioritized plants were those containing tannins as a secondary metabolite due to its symptomatic improving properties as an antidiarrheal. Additionally, plants with other active compounds that have anti-inflammatory effects on the gastrointestinal tract were used. Under the lead and supervision of Dr. Ferencné Gerencsér in the Department of Botany at the University of Veterinary Medicine Budapest this herbal mixture was developed and produced. The therapy was documented with the help of a questionnaire developed by Dr. Gábor Lorászkó. Under his guidance the therapies and other assisting veterinarians involved were coordinated. For the therapy documentation we relied on the patient's owner, since they had to fill out the documentation form. The documentation was conducted in Hungary, as well as the questionnaire which was written in Hungarian to mitigate misconceptions due to the language. At the end of the therapy the filled-out documentation was handed to the veterinarian in charge and later handed in for evaluation. Prior to the advised therapy all animals underwent a veterinarian examination. With the owner's consent and veterinary monitoring, the phytotherapeutically treatment was started. In total twenty-four veterinarians participated among whom we distributed enough products for about 70 therapies but then a total of thirty therapies were carried out. With the help of this uncontrolled therapy documentation, we would like to see a positive effect of the phytotherapeutically treatment.

3. Literature review

3.1 Phytotherapy in general

The use of medicinal plants has a long tradition and has still an importance in today's medicine. The knowledge of medicinal preparations as well as their therapeutical functions are based on extensive experience in phytotherapy, which has been practiced for thousands of years in the traditional medicine all over the world. Even nowadays in human medicine many therapies rely on herbal preparations. When talking about phytomedicine, it is imperative to understand that it is not only limited to herbal mixtures but also includes developed drugs consisting of plant derivatives that have been isolated. Over time some plants lost their importance in therapy where scientific studies disproved their beneficial function. In others on the other hand we gained more interest, recognizing new potential in their metabolites. It is crucial to mention as an example, that in the tropical regions of our planet roughly 125 000 species exist. But only approximately 1% of those plants have undergone studies about their pharmacological function. So, this still shows us a future potential for the development of new drugs [4]. It is important to understand that medicinal herbs metabolites are in their natural reservoir heterogenous. The compounds always slightly differ in their composition, causing alterations in their active metabolites. Due to external environmental factors e.g. pollution of the air or the soil, naturally growing plants might be contaminated by environmental hazards like heavy metals. This is why it is crucial to use only approved medical plants which undergo quality control [5].

3.2 The use of medical plants in the veterinary medicine

Medicinal herbalism describes the use of phytopharmaceuticals in the therapy of diseases, alleviation of symptoms of a disease, a treatment or prophylaxis. To achieve this, the whole medicinal plant or parts of it will be utilized. The therapeutic use is based on the pharmacological mechanism of the plant's phytochemical products. For this reason, phytotherapy cannot be equated to the same level as therapy forms like the Traditional Chinese Medicine or homeopathy [6]. In veterinarian medicine the use and knowledge were originally orientated from human phytotherapy. It was since adapted to animals and is still in use today. One of the interesting aspects that make those preparations valuable is that they can be applied in different veterinarian fields to produce animal medicine. Especially beneficial is the possibility to often avoid long withdrawal periods. In small animal medicine where it gains more and more popularity for therapies it is often portrayed and chosen as a natural and docile way of therapy instead of using conventional medicine [2].

One of the most key features using medical plants is their different way of function. In conventional medicine the main treatment relies on the single target approach. This means that one single active compound shows its effects by a well-described way of action. Sometimes one or two additional compounds causing the same effect can be utilized, but not more. In medicinal plants there are always multiple, similar or different active metabolites. Having an additive or synergistic effect on different pathways. This way of action belongs to the multi-target therapy [7]. All components act together, even if we don't have the whole understanding yet and we cannot take them all into account.

It is assumed that different diseases will act on different cellular targets, some alterations are known some of them unknown [6]. Based on this multifactorial pathophysiology idea, it is assumed that with the help of a multidrug preparation, there will be an improved therapeutical outcome [8]. That is why in phytotherapy the multitarget approach is significant. It is based on the synergistic and additive effects of the plant's secondary metabolites [9]. In this case, these substances will act on different cell and protein structures in an unspecific way of action [7].

In contrast to pharmaceutical preparations, which contain a single or only two active ingredients, herbal preparations are always multi-component. The many components exert their effects together, so the side effects of the individual components could be milder and, in many cases, negligible. This is none other than the multi-target theory, according to which the active ingredients of medicinal herbs exert their effect through different mechanisms of action [8]. In addition, the synergistic effect of certain secondary metabolites supports this theory and is still to be further investigated [10]. At the same time, precise knowledge of herbs and their application method is necessary, as in some cases unwanted side effects may occur.

3.3 Legal basis

The whole therapy and documentation were conducted in Hungary under veterinarian guidance and supervision.

We conducted our therapy documentation based on the freedom of veterinary practice, but not as animal experiments, since there are extensive literature descriptions of the components of the preparations we use and their effects. The dogs of various breeds participating in the testing of the product came to the treating veterinarians sick, who used the phytotherapy product under development based on the principle of freedom of treatment.

The Regulation 37/2010/EC of the European Parliament and the Council (May 6, 2009) on Community procedures for determining residue limits for pharmacologically active substances in food of animal origin does not set a limit for any plant species or its active components of our herbal mixture [11]. Although we treated dogs, this fact can be a guide.

Testing the product does not cause the animal any pain, suffering or permanent damage, so it is not considered animal testing according to Section 3, Point 9 of Act 28 of 1998 on the Protection and Welfare of Animals, which is in force in Hungary [12].

Compared to other countries in Europe, the legal background in Switzerland would be different. The use of officially approved herbal remedies is permitted by Swissmedic. The production of medical remedies such as herbal preparations needs to be produced by an approved facility as it is stated in Chapter 2, Section 2, Article 5 of 2019 in the federal act for drugs and medical devices [13].

3.4 WHO-Monographs

The WHO monographs on selected medicinal plants comprehensively describe the available information on about 160 medicinal plants. Since 1988, 100 experts originating from 40 countries have worked on the description of each herb. Medicals, pharmacists and pharmacologists have been involved in this work, its main aim was the establishment of a scientific safety standard and gathering information about the quality and efficacy of the plant and its preparations. Its documents are available for free on the site of the World Health Organization. In addition to the botanical description, they provide a detailed description of the active ingredients, drug, quality requirements, use in folk medicine and scientific use of the respective medicinal plant. The descriptions are supplemented and updated periodically [14]. Using this and based on other literature sources, I would like to present the medicinal plant components of the experimental preparation.

3.5 Phytotherapeutical basis

3.5.1 Herbal metabolites

First, when plants were biochemically analysed, the primary metabolites were evident as the substance keeping the plant alive. Being involved in tasks like growth, mitosis and storage. These primary metabolites are carbohydrates, fats, and form nitrogen metabolites proteins and nucleic acids. Then later, during further investigation another group was discovered and categorized based on their biosynthesis pathways, the secondary metabolites. Soon, it was discovered that these secondary metabolites have an important function on the plants defend mechanism, assisting the plants in the adaptation to environmental hazards and changes. Furthermore, it became clear that those substances can have certain positive or negative effects on animals after ingestion [15].

3.5.2 Primary metabolite

The primary metabolites belong to the basic substances of the plant that were first built by photosynthesis from inorganic compounds. Their numerous presences as well as their characteristics enable the daily survival of the plant. Nucleic acids, carbohydrates, proteins and fats belong to this group. So, at the same time they play a crucial role in the animal nutrition [16].

3.5.3 Secondary metabolite

The phytopharmacology's effectiveness relies on the targeted use of the secondary substances. Those consists of lower molecular natural product, resulting from specific biosynthesis pathways originating from the primary metabolism. They belong to the large compound groups e.g.: saccharides, phenoloids, polyketides, terpenoids and nitrogen containing substances. The secondary substances are recognizable as compound mixtures. Their storage and composition are influenced by the plants growing phase and organ of the plant. The compounds synthesis and storage does not always happen to be at the same place. By production of extracts and preparations it is possible to use their biological effectiveness. The most useful characteristics are the synergistic and additive effects of the secondary compounds, having a crucial rule in the phytotherapeutically treatment [1]. Based on a versatile constellation of substances with different bioactivity, secondary compounds have a wide mode of action. During evolution, the effectiveness of those substances had undergone continuous improvements. They can react by non-covalent and covalent interaction with cell-targets like bio-membranes and proteins. So, the integration into the proteins and membranes will cause protein conformation and structural modification so they have an influence on operability of enzymes as well. They cause an alteration on the rigidity and permeability in the membranes. The nonselective protein changing property of the secondary compounds gets more important in the use of phytotherapy [7]. A significant part of the secondary compounds are the so-called multi-substance mixtures like polyphenols and terpenes that play the main role in out preparation.

3.6 Plant compounds for diarrhoea treatment

3.6.1 Tannins

Tannins are widely spread in plants. They are phenolic compounds that are water soluble and large in molecular weight between 500 and 3000 Daltons. By developing intra and inter- molecular hydrogen bonds tannins can react with carbohydrates and proteins. The astringent effect is altered by the count of hydroxyl groups. It is enhanced in case one to five hydroxyl groups are developed but will be decreased in case of exceeding the number of seven and more. The differentiation between the condensed and hydrolysable tannins is necessary. Originating from the hydrolysable group are the gallotannins and the ellagitannins. Whereupon the proanthocyanidin and catechin tannins belong to the condensed tannin group. The very complex structured proanthocyanidins are the best represented tannins in the plant. It is assumed that they have several beneficial characteristics such as anti-inflammatory effects, immunomodulation, anti-thrombotic and antioxidation effects. It is important to mention that the understanding of the exact pharmacological function and their toxicological properties are still under investigation [17].

In case of acute diarrhoea, the use of catechin and tannic acids containing drugs are recommended as first choice for phytotherapy treatment. The functionality is highly dependent on the size and complexity of the molecular structure. It can be said that small hydrolysing molecules like tannins are easier absorbable and will reach a faster systemic reaction [6]. At least 2% of tannins are contained in the dried form of *Agrimona eupatoria*. The minority of which, 3 to 21%, are condensed tannins. The other categories are hydrolysable tannins like gallotanine and agrimoniin [18]. The leaves of *Rubus fruticosus* contains about 10% hydrolysable tannins [1].

3.6.2 Flavonoids

The name comes from the Latin word flavus (= yellow). These slightly yellowish natural substances are very common in the plant world, and can be chemically derived from diphenyl-1,3-propane or 2-phenolbenzopyran. In the plant, they are formed by the intersection of the shikimate and polyketide metabolic pathways and are known as phenyl chroman derivates. Flavonoids include, among others, flavones, flavanols, chalcones, aurones, isoflavones. They contain a phenolic OH group, which can be free, methylated or glycosidically linked [19, 20].

In vitro and in vivo, flavonoids show, among other things, anti-inflammatory, antimicrobial, antiviral, antiproliferative, haemostatic, antioxidant, antispasmodic, anti-oedema and diuretic effects. In the case of silybin (found in milk thistle) and similar flavonolignans, an anti-hepatotoxic (liver-protective) effect has been demonstrated in several liver damage models. Many flavonoids interact with biopolymers, e.g. nucleic acids or enzymes, they have free radical scavenging properties and affect protein phosphorylation in the cell [1]. Chamomile includes the flavonoids apigenin and luteolin as compounds responsible for its anti-inflammatory effect.

3.6.3 Essential oil

Even though essential oils are most likely known for their odour they have some beneficial properties. Some of them have an anti-inflammatory, analgesic and anti-microbial effects to a certain extent that are important to us [21]. When essential oils were used in form of a mouth wash, an improvement of gingivitis was noticed [22]. In case of *Matricaria* a species that contains the main substances are spiroethers and turpentines. It was found out that these essential oils have a bacteriostatic effect on certain Gram-positive bacteria like *Listeria inocua* [23]. Achillea contains 0,2 – 1% essential oil, the main component is the sesquiterpene proasulene [1]. The essential oil components of *Pimpinella anisum* are not terpenoids but synthesizing throw shikimate-way, so they are phenyl-propanoids.

3.6.4 Bittering agents

When consumed, the bittering agents are well known for their bitter taste. This substance can be divided into two groups. The terpenoid and the non-terpenoid groups of which the non-terpenoids have a higher importance in the phytopharmacology as usual. In our case the terpenoid group is more important because of the stimulation of the *cortex cerebri* and so caused by the bitter sensation, enhances the excretion of gastric juice. This can cause an increase the pancreatic function and the gastrointestinal motility because of gastrin. The raised production of this hormone gastrin in turn is dependent of the already increased pepsin and hydrochloric acid concentration. Overall the bittering agents have a beneficial effect on the digestion. It is known that certain types of bittering substances as the sesquiterpene lactones and diterpenes have an additional beneficial anti-inflammatory and antibacterial effect [24]. Bittering agents are contained in *Achillea millefolium* of our plants.

3.6.5 Mucilage

Mucilages are chemically polysaccharide compounds in which several sugar molecules are connected to each other. They can bind a larger amount of water and thus they have a buffering effect. In our experiment, the mucus substances are primarily suitable for coating the inflamed mucous membrane. Many studies deal with the immunostimulant effect of mucus substances, which can also play a role in the treatment of diarrheal diseases. More recently, it has also been researched that mucus substances can be used as prebiotics, supporting the healthy functioning of the colon's bacteria [25]. Chamomile is one of the plants which contain mucilage [26].

3.7 Selection of medical plants used

To achieve the best possible result in the preparation we chose a mixture of five medicinal plants, containing the active compounds written above. *Agrimonia eupatoria* and *Rubus fruticosus* because of their tannin as a main component. In addition, plants containing essential oils as *Matricaria chamomilla* and *Achillea millefolium* were added to the preparation. *Pimpinella anisum's* main advantage is its preferred taste of dogs, facilitating the application and enhancing the acceptance of the patient's ingestion. This taste enhancing effect is more important than its therapeutical (carminative and anti-inflammatory) effect on the gastrointestinal tract.

3.7.1 Agrimoniae herba (agrimony herb)

Figure 1: a.*Agrimonia eupatoria* (https://www.medienwerkstatt-online.de) and b. its drug.

The *Agrimonia eupatoria* (Figure 1) belongs to the family of Rosaceae. The plant's occurrence spreads from Middle Asia to Middle Europe, as well as North Africa. Dry soils enriched with lime are preferred for the plant's proper development. Its harvest is recommended in the flowering months of June to July. In a dried form, the whole herb exception of the roots can be used for preparations. Main phytochemical components are tannins, flavonoids, phenolcarboxylic acids and triterpenes. There are a variety of effects, assisting in its antidiarrhoeic properties. Due to the astringent properties of tannins, a mild topical anaesthesia and surface dehydration can be expected in the gastrointestinal tract. In addition, in vitro trials showed that extracts made from the drug had antimicrobial properties. An antiviral characteristic in vitro was detected against encephalomyocard- and vaccina viruses as well as herpes-simplex viruses [1]. It is suspected that this property relies on the formation of non-water-soluble protein and tannic acid complexes. Those complexes are causing an alteration of the mucosa surface by denaturation, reducing the attachment ability for pathogens [6].

3.7.2 Rubi fruticosi folium (blackberry leaf)

Figure 2*:* a. *Rubus fruticosus* (www.medicinetraditions.com) and b. its drug balckberry leaf.

Rubus fruticiosus, also known as blackberry (Figure 2), belongs to the family of Rosaceae. It is a widespread plant in Middle Europe with several subspecies with minor differences. The plant grows at a wide variety of locations. For therapeutical reasons the dried leaves are the most valuable part of the plant. Harvesting is recommended during the month June and July during the flowering period [1]. For a long time, the Rubi 15uestion15 folium or blackberry leaf has been used in veterinary medicine as a preventative measure as well as for therapy of diarrhoea. Main substances of content are mainly hydrolysable gallotannins between 5 to 15%. Additionally, flavonoids as well as saponins and different plant acids can be found [6].

3.7.3 Chamomillae flos (chamomile flower)

Figure 3: *a. Marticaria chamomilla* (www.biolib.de) and b. its drug.

Matricaria chamomilla (Figure 3) belongs to the family Asteraceae. This flower is one of the best known and widely used medical plants in the veterinary phytotherapy [6]. Although there is a wide appearance in the wild growth of the plant there is even cultivation of it in some countries. It is native to Europe but can be found in Northern Africa, Asia and America as well [14] . The freshly collected flower head can be used as a drug directly or in a dried form. It is recommended to harvest the flowers in the month of May to September [1].

3.7.4 Millefolii herba (yarrow herb)

Figure 4.: a. *Achillea millefolium* (www.biolib.de) and b. its drug.

Achillae millefolium (Figure 4) also known as yarrow, is part of the family Asteraceae [27]. It is native to several continents like in Europe, Northern America and Asia. The plant's herb is the recommended drug. It can be used as freshly harvested or in a dried form. The most adequate time for harvesting is during flowering in between the months of June and October [1]. The antimicrobial, antiphlogistic and spasmolytic effects of yarrow are leading indicators for its main therapeutic use in gastrointestinal problems in veterinary medicine [6]. The most important chemical substances are essential oils. Depending on the chromosome quantity the chemical composition of the essential oils is influenced. The plant contained amount can vary between 0.2% and 1.0%. Proazulene sesquiterpenes can mainly be found in plants that are diploid or tetraploid. Coloured azulenes, chamazulene and achillicine can be formed under heat treatment out of them [28].

3.7.5 Anisi fructus (anise fruit)

Figure 5: a. *Pimpinella anisum* (www.bilolib.de) and b. its drug.

Pimpinella anisum or *Anisum vulgare* named anis in English, is part of the Apiacea family [6]. After flowering, the plants fruit the so called Anisi fructus (Figure 5) can be harvested. In the dried form they can be used as drug [1]. It is wide spread within Europe and some parts of Asia and a well-known plant used in herbal medicine. Mainly used in treatment of gastrointestinal problems and respiratory diseases in human and veterinary medicine. Soon it was discovered that due to its sweet taste and odour, it enhances the palatability of preparations for dogs [6]. The most contained chemical substances are essential oils that can vary between 1.5-5% [29]. The highest concentration reaches trans-anethol about 80-94%. Methylchavicol and other low molecular terpenes can be found as well but in much lower concentrations [1]. Aniseed has a wide number of positive effects like anti-inflammatory, anti-convulsive, anti-microbial activity [29].

4. Materials and methods

4.1 Herbal drugs used

All medical plants used the so called basic unprocessed drugs, were purchased from the firm “Mamadrog”. The herbal ingredients were produced in Hungary, containing the highest quality plants. The product underwent a careful selection process, fulfilling strict quality requirements. The sent product contained the dried medical herbs packaged in 50 g bags. In total 2500 g charges were bought. For the preparation a mixture of five medicinal plants was used. It consists of *Agrimona herba, Rubi fruticosi folium, Chamomillae flos, Millefollii herba, Ansi fructus.* All the components were applied in a dried form.

4.2 Electric mill

An electric spice blender (Royal Catering RCMZ-800N; 17 cm × 9 cm; 2100 W) purchased from international firm “Expondo” was used for braking down the herbal cell wall structure, increasing the surface, increasing access to the plants active components in the dog’s gastrointestinal tract, due to the dog’s difficulty of digestion of the plants cell wall.

4.3 Primary packeting

As a primary packeting for the protection and dosing of the ground drug, a transparent, gelatine free capsule made from hydroxypropyl methylcellulose (HPMC) purchased from Slovenian online store “FutuNatura”. The appropriate size 000, in the dimensions of 25 mm length and 10 mm in diameter was chosen. The capsule consists of two parts that can be separated for filling and squeezed together afterwards resulting in a tight closure. The capsules were filled with help of a capsule charger, purchased from “FutuNatura” as well. It is compatible to the capsules size 000. This device enabled us the simultaneous filling of 100 capsules at the time with a consistent amount of 60 g of herbal preparation.

4.4 Secondary packaging

For secondary package a non-transparent, white plastic flask with 200 ml volume purchased from "Patika Pack Pharmacy Supply and Medical Aid Shop", was used for longtime storage. After filling, the container is air-tight sealed with a plastic membrane, protecting the product from environmental influences, mainly oxygen and moisture. After opening, the flask can be closed by screw top.

4.5 Manufacturing of the phytotherapeutic preparation

Prior to the manufacturing process, all the purchased herbal ingredients were visually inspected

After exclusion of any possible contamination of all sorts (Figure 6/ 1), the individual herbs were finely ground so the plant its structure is broken up by a high-power mill. Due to the friction heat during the milling process, it is crucial to set an appropriate grinding time to avoid heat damage of the drug. Accordingly, the machine was operated at 35000 rpm with a grinding time of 40 seconds (Figure 6/ 2).

In the following step, the processed individual herbal drugs were measured according to the exact percentage (Figure 6/ 3). In total three recipes were used numbered as D1, D2 and D3 of which the drug proportions were slightly changed. Then the individual components were mixed to guarantee an even distribution for later encapsulation.

Due to the increased surface caused by the milling process, it is very important to protect the preparation from external influences, potentially causing an alteration of the products quality or even spoilage. So, this is why the decision on using capsules as a primary packeting was made. Another advantage of this specific packeting, it

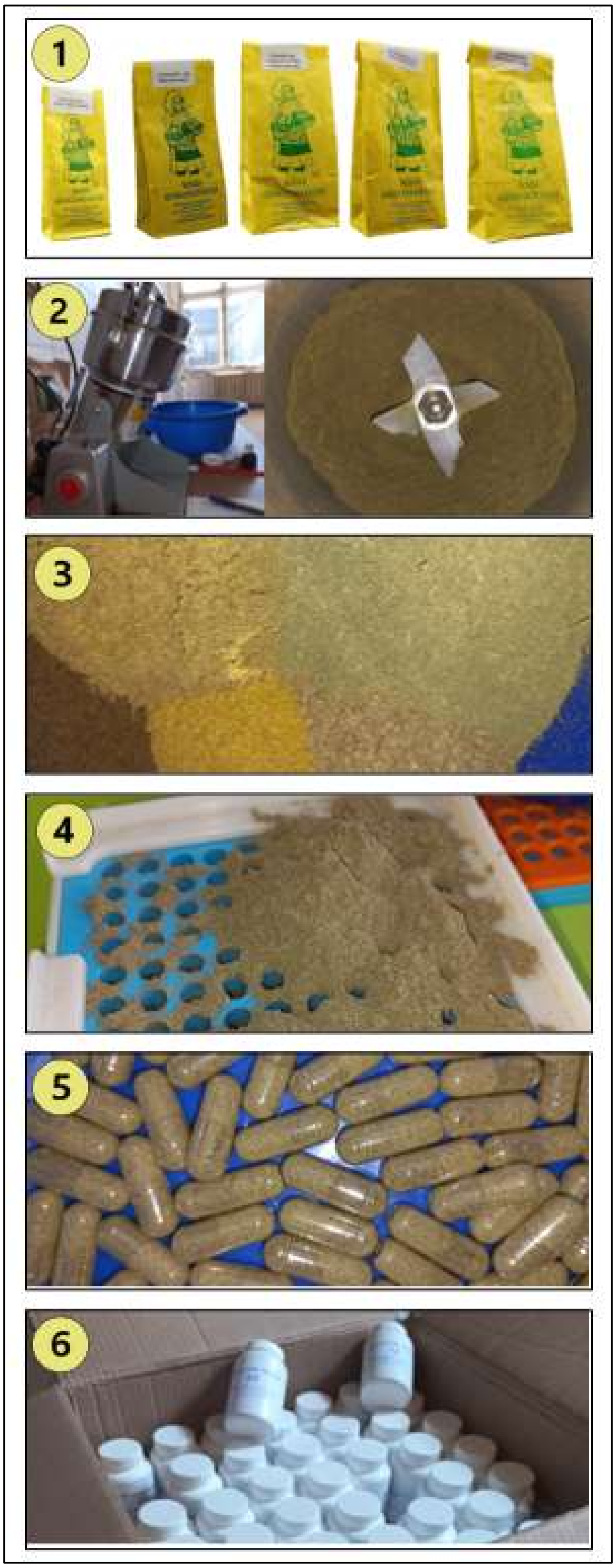

Figure 6: Flow chart about the manufacturing process.

allows the pet owner a faster, easier way of application as well as increasing the precision of daily dose of the medication. The drug mixture was filled in to hydroxypropyl methylcellulose capsules. (Figure 6/ 4 and 5). For this process a capsule charger was used. All capsules were packed with the average amount of 0.6 g drug mixture. A standard deviation not exceeding $\pm$ 0.05 g (8.3%) was accepted. Each capsule was inspected on any leaking or hull damage as well as counterchecked concerning the weight within the deviation. Capsules with a weight higher or lower than the margin, were rejected.

For longtime storage the capsules were stored in an easy to access screw top lid flask. After the filling the bottle opening was sealed by a membrane, ensuring protection from environmental influences as light, moisture and air (Figure 6/ 6).

4.6 The therapy documentation

The preparation was developed to be used on the therapy of diarrhoea in dogs. For this, voluntary veterinarians as well as pet-owners, willing to use phytotherapeutics were involved. A total of 24 veterinarians have been successfully participating in a period of 12 months.

4.7 Development of the questionnaire

To be able to evaluate the progress of the treatment, a questionnaire had to be developed. To collect data, it was essential that the patient's owners were able to evaluate the patients state of treatment. So, it was crucial to develop a comprehensive and easy to fill out form that gives valuable data about the improvement even under a non-trained circumstances. Based on the long-lasting experience of Dr. Gábor Lorászkó, the data collection form was based on a comparison system. This means that a visual faecal chart the so called Bristol Stool Scale [30] was used. In combination with written additional information.

On the first documentation form (Figure 7) accompanying the therapy, the owner was able to score the faeces assisted by comparison pictures combined with a number code. With the help of this number code, we were able to collect uniform data about the faecal consistency. Those numbers had to be written down daily. Besides this, the owner was able to describe the improvement of the animal's general status by written form based on personal impressions. But this caused too much space for personal interpretation, producing inconsistent data that was not able to be evaluated. After the first evaluation, certain weak points in the layout as well as this error causing evaluation problems, caused us to recreate the questionnnaire. Making it more uniform for the general status evaluation. In addition, a similar scoring system for the ingestion acceptance was added. After introduction of the second and final form (Figure 8) we received improved feedback.

On the top the basic data of the veterinarian in charge as well as the basic data and diagnosis of the patient was written.

On the left side, a visual fecal scoring system assists the owner analyzing the patients' feces. In the first column the days of therapy are stated. In addition, the daily general status was observed. Later on the second form, it can be seen (Figure 7) that the intake acceptance was added.

4.8 Documentation form

Place		Name	
Date		Chip	
Diagnose		Breed	
Veterinarian		Age	
Phonenumber		Sex	

Day	Feaces (1-7)	General condition
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		

1 Hard and dry. When picked up there is no residue left on the floor.
2 Solid, but not hard, segmented . No or little residue on the floor
3 Saussage like form, wet surface, little segmented or non segmented. Residue will be left on the floor, keeps its shape.
4 Wet, saussage like. When picked up residue will be left, looses its shape.
5 Sludgy pile. Residue will be left and complete loss of shape.
6 No defined shape, mushy spots. Residue left on the floor.
7 Liquid, puddle like, without firm components.

Figure 7: First questionnaire used to collect date from owners about the therapy progress. The original form was created in Hungarian, here you can see an identical translated version in English.

Place		Name	
Date		Chip	
Diagnose		Breed	
Veterinarian		Age	
Phonenumber		Sex	

Day	Feces (1-7)	General conditions? (1-5)	Intake acceptance? (1-5)
1		1 2 3 4 5	1 2 3 4 5
2		1 2 3 4 5	1 2 3 4 5
3		1 2 3 4 5	1 2 3 4 5
4		1 2 3 4 5	1 2 3 4 5
5		1 2 3 4 5	1 2 3 4 5
6		1 2 3 4 5	1 2 3 4 5
7		1 2 3 4 5	1 2 3 4 5
8		1 2 3 4 5	1 2 3 4 5
9		1 2 3 4 5	1 2 3 4 5
10		1 2 3 4 5	1 2 3 4 5

	General condition (1-5)
1	Lively, happy
2	Relatively good
3	Slack, lethargic
4	Sick impression
5	Very sick impression

	Intake acceptance (1-5)
1	Very easy consumed
2	Easy consumed
3	Not that easy
4	It was difficult
5	It was refused

1 Hard and dry. When picked up there is no residue left on the floor.
2 Solide, but not hard, segmented. No or little residue on the floor.
3 Saussage like form, wet surface, little segmented or non segmented. Residue will be left on the floor, keeps ist shape.
4 Wet, saussage like. When picked up residue will be left, looses ist shape.
5 Sludgy pile. Residue will be left and compleate loss of shape
6 No defined shape, mushy spots. Residue left on the floor.
7 Liquid, puddle like, without firm components.

Figure 8: Second and final questionnaire, accompanying the dog's treatment. Minor changes were made to the first documentation form. Especially to collect more uniform data about the general status and acceptance of the intake. Here an English translated version.

4.9 Patient examination

All dogs were examined by a veterinarian. In cases diagnosed with gastroenteropathy and diarrhoea as a leading symptom, the therapy with our medicinal herb preparation was proposed. In case of a treatment, exclusively this herbal preparation was used. If, based on the test results, the animal's health was at risk, it received medication instead of the herbal preparation and was not included in the herbal medicine research.

The application was done by the patient's owner. The recommendation was, to give the right dosage, according to the patients' needs two times a day in the morning and evening prior to feeding.

4.10 Dosage

In total three Recipes numbered as D1,¨D2 and D3 were used. The herbal mixture did not differ in composition but just small difference in proportions of the two plants containing tannins (*Agrimonia* and *Rubus*) were made to select the most effective composition. The daily dosage was in accordance with the patient's bodyweight and the severity of the symptoms.

Table 1. chart indicating the daily dosage per bodyweight.

Bodyweight (kg)	Daily dosage (g)
5-15	2
20-30	4
35-45	6

4.11 Patients

In a total of nine patients, the therapy documentation was completed in such a form that it was usable for the evaluation of experiment.

Éden, a ten-week-old male Border Collie was diagnosed with enterocolitis by Dr. Gábor Lorászkó. The patient was in therapy for twelve days that started 25.01.2023. the used recipe was D1. The data was collected according to the first questionnaire.

Léna, a ten-year-old spayed female German Sheperd was diagnosed with enterocolitis by Dr. Gábor Lorászkó. First treatment started at 26.04.2023 for ten days. The recipe used was D3. The patient was in therapy for a second time at an interval of twelve days. Second time, the therapy started on the 18.05.2023 for twelve days. The recipe used was D3. The data was collected according to the first questionnaire.
Molly, a ten-month-old spayed female Labrador was diagnosed with enterocolitis by Dr. Gábor Lorászkó. The therapy started the 09.01.2023 for five days. The recipe used was D2.The data was collected according to the first questionnaire.
Rafi, a 14-month-old neutered male Spaniel was diagnosed with maldigestion by Dr. Gábor Lorászkó. The first therapy was carried out the 09.01.2023. for 14 days. The second therapy started on the 24.01.23 after a change in recipe D1 to D2. The data was collected according to the first questionnaire.
Dante, a six-year-old male Miniature Schnauzer was diagnosed with gastroenteritis by Dr. Beáta László. The therapy started from 07.01.2024 for ten days. The used recipe was D1. The data was collected according to the second questionnaire.
Connor, an eight-year-old neutered male Cane Corso was diagnosed with enteritis by Dr. Beáta László. The therapy started from 06.01.2024 for ten days. The recipe used was D3. The data collected according to the second questionnaire.
Winny, a four-year-old neutered male mixed breed was diagnosed with gastroenteritis by Dr. Beáta László. The therapy started from 14.01.2024 for ten days. No information about used form was given. The data was collected according to the second questionnaire.
Dió, a three-year-old neutered male Bichon. No information about the veterinarian in charge or used recipe was given. The data was collected according to the second questionnaire.
Ördög, a six-year-old spayed female Foxterrier was diagnosed by Dr. Tünde Konc-Görgey. The main leading symptoms were diarrhoea and emesis. The therapy started from 25.03.2024 for nine days. No information about used recipe was given. The data was collected according to the second questionnaire.
Simba, a 15-year-old neutered male Golden Retriever was diagnosed with diarrhoea chronica by Dr. Dorottya Vladár. The therapy started from 14.12.2023 for 14 days. No information about used recipe was given. The data was collected according to the second questionnaire.

5. Results

Three different types of data were collected during the therapy. About the therapeutical effect of the preparation, about the patient's general status and about the dog's acceptance of ingestion (intake acceptance) of the herbal mixture. We summarized the collected data in an excel table and created graphs with the help of the program for better transparency of the changes.

5.1 Therapeutical effect

On table 2 in each line according to the patient's name, the average daily fecal consistency score was registered. The scoring system, reaching from one to seven of which the highest number seven corresponds with a severe diarrhoea in form of a very fluid consistency and the lowest number one correlates with hard and dry faeces. A green colour code is used to increase a better visualization of the trend during the treatment. Dark green at number seven, becoming lighter by the decreasing scoring number and increasing consistency.

In case of the patients Léna (indicated by Léna; Léna2) and Rafi (indicated by Rafi; Rafi2), the therapy was fulfilled two times because of a relapse.

Table 2. – Change of faecal consistency by days of treatment.

Name	**Form**														
	Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Éden	D1	5	4	3	5	6	4	2	5	4	4	5	4		
Léna	D3	2	2	3	2	3	3	3	2	2	3				
Léna2	D3	3	4	5	5	3	2	2	5	7	2	2	2		
Molly	D2	7	7	7	6	7									
Rafi	D1	4	4	5	4	3	4	4	4	4	4	6	6	5	5
Rafi2	D2	4	5	5	5	4	6	5	4	4	3	2	2	2	2
Dante	D1	7	6	6	4	3	2	2	2	2	2				
Connor	D3	6	6	5	4	2	2	2	2	2	2				
Winny	D?	6	6	5	4	4	2	2	2	2	2				
Dió	D?	7	5	5	4										
Ördög	D?	5	2	2	3	2	2	2	2	2					
Simba	D?	5	2	4	5	6	4	3	5	3	3	4	3	2	2

The chart below (Figure 9) shows the day-by-day improvement. It shows the percentage occurrence of each stool condition category among patients. It can be clearly seen that the appearance of diarrhoea is marked with a dark colour. It occurs in a decreasing proportion over the course of the days. The small number of questionnaires returned from veterinarians did not allow more detailed statistical calculation but by day 7, the yiz-like and residue-leaving faeces had completely disappeared. We can see that a healthy and not hard, but a solid consistency was achieved in 65% of all animals. On the 8th and 9th day, a relapse can be detected. But on the 10th day only the four faecal categories (wet, wet surface, solid not hard, healthy) are seen in our data.

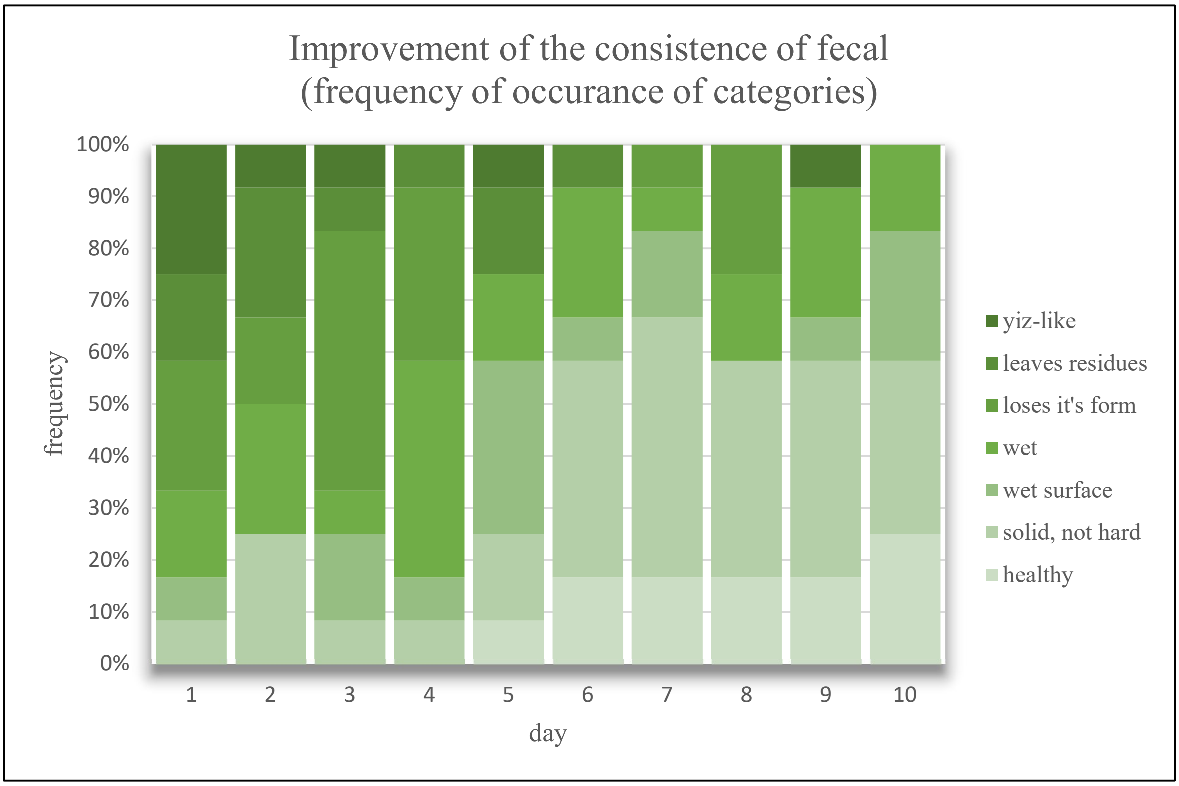

Figure 9.- On this graph the faecal improvement within ten days is shown. Lighter green colour indicates the increase of a healthy consistency. The data was used from ten patients according to table 2.

5.2 General status

Each day, owners had to rate the general condition of their dog on a scale of one to five. According to the given scoring table (Table 3), low numbers were indicating an ill appearance and the higher number a good general condition.

Table 3.- This scoring table was used for the evaluation by the pet's owner.
It was found on the second questioner form (Figure 3.)

General condition
1 – seems very ill
2 – seems ill
3 – moody, weakly
4 – relatively good
5 – very good, frisky, jolly

On table 4 information about the improvement of the general status was collected. Only information about six patients was exploitable, due to the questionnaire structure. That is why only information from the second questionnaire form (Figure 7) was used. Due to the non-reliable and not uniform answering system of the written report part of the first evaluation form.

Table 4.- This chart shows the general condition trend over 10 days. Only in case of six patients the data was sufficient to be used.

General condition on days										
Days	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Dante	4	4	4	5	5	5	5	5	5	5
Connor	4	4	5	5	5	5	5	5	5	5
Winny	3	3	4	5	5	5	5	5	5	5
Dió	1	2	4	5						
Ördög		5	2	2	3	2	2	2	2	2
Simba	4	4	4	5	5	5	5	5	5	5

In case of Dió, that had the shortest therapy time, the daily condition, that was at a very ill expression when the therapy was started, was clearly visible and improved within the four days of therapy back to a very good condition.

Interestingly in case of Ördög, that started at a good condition score between four and five, during the therapy at day five to eight there was a drop in the general condition even though the therapy showed good effects by improving his fecal consistency.

The prevalence of each category was plotted on a graph over the 10 days of treatment (Figure 10). The colour codes, which gradually changed from dark to light over the days, show that the general condition of the animals also improved over the 10 days of treatment. The category “seems very ill” occurred only on the first day where “relatively good” and “very good” status were not visible at all. And on the 9th and 10th day only these two best categories are displayed in our data.

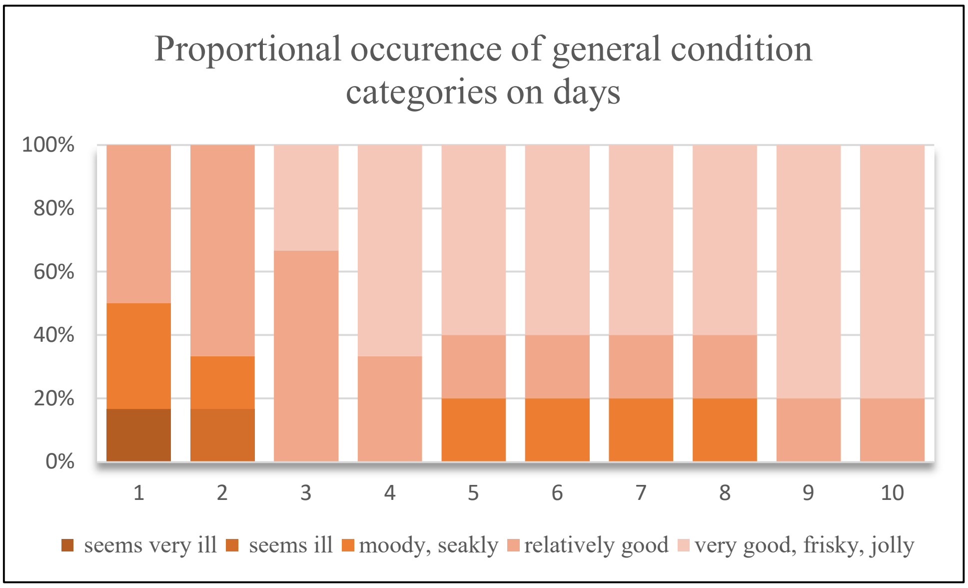

Figure 10 – This diagram shows the general condition categories per day over ten days. The lighter colour indicates the improvement. Data of six patients was used for the evaluation according to table 4.

5.3 Acceptance of product

A herbal preparation, which must be administered daily by the owner of the animal, has the very important property that the animal accepts it. In testing our formulation, acceptance was also scored on a scale of five using the values in Table 5.

Table 5 - This scoring aid was part of the second questionnaire (Figure 8.)

Administration of product
1 - unsuccessful
2 - hardly succeeded
3 - a bit of protest but successful
4 - easily administrated
5 - gladly accepted

In table 6 information about the consumption of the preparation was gathered. Only data from the second questionnaire form was used. The acceptance was evaluated on a scale of five to one, where “five” indicated the easiest acceptance and “one” indicated complete rejection by the animal. The administration and the acceptance of the product played an important part for a successful therapy. Interestingly most patients showed minor to non-problems with the consumption of the preparation. As seen in this table the administration and acceptance of the preparation was positive over the ten days.

Table 6 - contains information about the intake acceptance over 10 days. Data was collected from second questioner form (Figure 8).

Acceptance of product										
Days	1	2	3	4	5	6	7	8	9	10
Dante	3	4	5	5	5	5	5	5	5	5
Connnor	3	4	5	5	5	5	5	5	5	5
Winny	3	4	4	4	4	4	5	5	5	5
Dió	2	2	2	2	2					
Ördög	4	4	4	2	2	1	1	2	5	5
Simba	5	5	5	5	5	5	5	5	5	5

An exception was patient Dió. The only patient where the intake was hardly (marked with brown) successful during therapy. But this animal also showed a significant improvement in faecal consistence (7 → 2, as shown in the table 2) and general condition (1 → 5, as shown in the table 4) after four days. We can therefore consider that the therapy was successful despite the low acceptance, within 4 days.

Ördög started with a good intake but then during therapy there was a decrease from day four to eight. Even at day six and seven the administration was unsuccessfully. In this case, the general condition of the animal deteriorated significantly (5 → 2, as shown in the table 3), even though the consistency of the faeces improved (5 → 2, as shown in the table 2) during treatment.

However, with these two exceptions, an improvement in faecal consistency was followed by the improvement of general status.

6. Conclusion

The main goal of the production of a phytotherapeutic preparation for the treatment of diarrhoea in dogs, posed certain difficulties that had to be addressed. First, the right herbal components had to be selected by their functional properties. To reach a good bioavailability of the active metabolites the right preparation form had to be chosen. Enabling a proper storage and easy application by the owner. For this the used method of encapsulation proved as successful. The development of a reliable questionnaire was challenging. To reach an easy to comprehend form with a comparison and scoring system. Identifying stool quality using images numbered one to seven proved to be reliable. The first existing assessing part about the general status delivered inadequate results and had to be changed to an easier scoring system consisting of a list of five points to decrease subjective interpretation of text-answers. This proved to be a reliable system that was used for the rest of the study. The questionnaire was handed to the owners to document the proceeding therapy in a printed form. One of the biggest issues that developed for the data collection was the unreliable returning of the filled-out papers. Even though a total of 30 therapies were carried out only a minority of nine completed questionnaires were handed in. So, it should be considered to think about a possible change in the way of the data gathering. It might be more practical to make it available in an electronic form so it could be filled out on a mobile device right on sight, without delay, making it more user friendly.

The overall individual impression based on the oral feedback of owners and veterinarians during the therapy documentation was positive. But due to a very small number of data collected and the uncontrolled manner of the therapy documentation, it is hard to proof the positive trend as well as the significance.

Nevertheless we conclude that the treatment shows promising features despite the small sample size. The dogs generally accepted the product well, and there were usually no significant problems with the administration. We could not support the effectiveness with statistical analysis, but the small amount of data shows improving trend in both, the general condition of the animals and in the faecal consistence. We assume that it is possible to achieve results that can be supported by statistical methods with a larger number of animals and stricter data collection. We hope that with the specific attention to avoid to the expounded problems, the effectiveness of the phytotherapeutically preparation might be able to be described and supported by statistical analysis.

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8.1 Image source directory

Figure 1 a.– https://www.medienwerkstatt-online.de/lws_wissen/vorlagen/showcard.php?id=6721&edit=0 (accessed 2024.10.25)
Figure 1 b. – Personal picture of drug made by Dr. Gábor Lorászkó

Figure 2 a.– https://www.medicinetraditions.com/rubus-fruticosus-blackberry-free.html (accessed 2024.11.20)
Figure 2 b. – Personal picture of drug made by Dr. Gábor Lorászkó

Figure 3 a. – http://www.biolib.de/koehler/KAMILLE.jpg (accessed 2024.11.20)

Figure 3 b. – Personal picture of drug made by Dr. Gábor Lorászkó

Figure 4 a.–http://www.biolib.de/koehler/SCHAFGARBE.jpg (accessed 2024.11.23)

Figure 4 b. – Personal picture of drug made by Dr. Gábor Lorászkó

Figure 5 a. – http://www.biolib.de/koehler/ANIS2.jpg (accessed 2024.11.23)

Figure 5 b. – Personal picture of drug made by Dr. Gábor Lorászkó

Figure 6 – Flow-chart compiled from personal photos using PowerPoint (version 2410)

Figure 7 – Questionnaire prepared by Dr. Gábor Lorászkó

Figure 8 – Improved questionnaire prepared by Dr. Gábor Lorászkó

Figure 9 – Graph generated of own data using Excel (version 2410)

Figure 10 – Graph generated of own data using Excel (version 2410)

Thesis progress report for veterinary students

Name of student: Elias Johannes Schwab

Neptun code of the student: B2YNVS

Name and title of the supervisors:

Ferencné Gerencsér, senior academic staff, Department of Botany and

Dr. Gábor Lorászkó, associate professor, Department of Anatomy & Histology

Thesis title: The development of an herbal preparation for the treatment of diarrhea in dogs

Consultation – 1st semester

Timing				Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	03	29	Select the topic	
2.	2022	09	15	Literature and work phases	
3.	2022	09	29	Experiments with the capsule charger	
4.	2023	02	14	Planning the trial of capsules	
5.	2023	09	27	Time planning for further work phases	

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.	2024	02	13	Evaluation of first feed-back sheets	
2.	2024	09	10	Structure of the thesis	

3.	2024	10	05	Improvement of feed-back sheets	
4.	2024	10	12	Work on graphs and tables	
5.	2024	11	19	Final editing of text and figures	

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 find suitable to defence,

....

signature of the supervisors

Signature of the student: ....

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

Date of handing the thesis in 27.11.2024

ÁLLATORVOSTUDOMÁNYI EGYETEM Növénytani Tanszék BUDAPEST