Look For Health in Nature

PARSIMENDARU

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Pars Imen Daru Herbal Medicines Development Group

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Booklet publication date: April 2019

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Foreword

History

Pars Imen Daru pharmaceutical company was founded on June 23, 2007, by a consortium of three pharmaceutical manufacturing companies, each active in the field of production and processing of medicinal plants, feed supplements and additives for livestock, horse, poultry, fish and honey bee. The purpose of newly born company was to bring an innovative vision in the field of herbal medicine to the veterinary medicine community for effective treatment of infectious diseases and enhancement of health quality of domestic and aquatic animals. Here, at the Pars Imen Daru Pharmaceuticals, we aimed to evaluate, develop and produce the competent and high quality alternatives of the conventional synthetic medicines with a final goal of providing healthy food to improve the general health situation of people.

Research and innovation

Teaming up a group of top scientists in the country is one of the main strengths of our company. The research and development (R & D) group is formed by an eminent team of academic experts in several fields of science such as the herbal medicine, livestock, poultry, aquaculture, mycology and bacteriology. Most of our R & D members are well-known scientists with academic position (i.e. at the University of Tehran, top university of the country) and high degree of experiences in scientific researches. Although, the products of our company are inspired by the latest scientific achievements, but they are at the same time the result of the innovation and technical knowledge of the R & D group and therefore are completely unique. The sophisticated formulation of each drug which contains precisely determined amounts of ingredients with synergistic activity has been provided by the R & D team considering the most recent advances and discoveries in the field of herbal medicine and animal health.

Quality

We are proud of providing novel and effective natural solutions for most frequent and economically important health problems and infectious diseases which usually the farm owners have to face with in livestock industry.

In most cases, the positive feedback from livestock and poultry farmers has strengthened our belief that "the herbal medicine, if it is developed and produced in accordance with scientific standards, and has the high production quality then it can be the most appropriate alternative to synthetic drugs." Our products are pure herbal medicine totally inspired by the nature, and produced using standardized scientific methods under strict production principles such as GMP. Each of the products has experienced the standard protocols for developing and testing such as: drug hypothesis development by the R & D group, determining the drug composition and formulation, toxicity evaluation, pilot study, clinical trial, pharmacology, bioavailability etc., which eventually end in obtaining an official production license from a governmental authorization center (i.e Iran Veterinary Organization).

Herbal medicine for organic production in livestock industry

The synthetic drugs have many harmful and significant side effects when administered for livestock, poultry and aquatic animals. These drugs show tissue accumulation and residues and therefore can be readily transferred to end consumers (human), and cause subsequent health problems such as induction of antimicrobial drug resistance. Thus, in developed countries, the consumption of such products is decreasing every day or even is being legally forbidden. There is a long history of application of natural originated remedies by Persian physicians. The idea behind our top-selling products for ruminants, equine, poultry, honey bees and fish was originated from the old herbal medical prescriptions used by our ancients. Undoubtedly, the best way to reach a reliable and safe solution to promote the health quality of animals and as a result, producing healthy foods, is to use natural medicines to fight against livestock, poultry and fish diseases. Therefore application of our herbal/natural- based therapeutic solutions in livestock industry can be an important step in reaching the totally organic production and achieving the green production standards.

Here, we have reviewed the therapeutic/preventive products of our company briefly and provided some necessary information such as the drug composition, mechanism of action, indications, instruction of use and the results of farm evaluations. Please do not hesitate to ask us if you have any further question.

Poultry

The recommended method of use, time table and the amount/dose of poultry drugs of Pars Imen Daru Company.

	Treatment start time	Drug name	Amount/Dose	Treatment Episode Duration
1	1-3 day old	Antibiofin + Immunofin	1 liter of each drug in 1000 liter drinking water	Up to 3 days; each day 8 hours
2	One day before/after a vaccination plan	Immunofin	1 liter of drug in 1000 liter drinking water	8 hours per day
3	To prevent respiratory infections	Anzofin	1 liter of drug in 1000 liter drinking water	Up to 3 days; each day 8 hours
4	To treat the damages and symptoms of respiratory complications	Anzofin Extra	250 ml of drug in 250 liters of water to be sprayed	Up to 3 days; once in a day
5	To treat the damages and symptoms of respiratory complications	Broncofin	1 liter of drug in 1000 liter drinking water	Up to 3 days; each day 8 hours
6	Better to be started in young chicks until slaughtering time	Bioherbal	1 kg of drug in 1 ton feed	Whole growth period
7	To treat the damages and symptoms of Gastrointestinal complications	Antibiofin	1 liter of drug in 1000 liter drinking water	Up to 3 days; each day 8 hours

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BRONCOFIN

(for prevention and treatment of bronchitis in poultry)

COMPOSITION: **Broncofin** is a natural-based drug that is made up of active ingredients in eucalyptus, rosemary, thyme and other medicinal herbs. The drug is formulated in such a way that its various components empower and enhance the therapeutic effects of each other by a synergistic activity. The most important components in this drug are: 1, 8-Cineole, Camphene, Fenchone and Terpineole.

MECHANISM OF ACTION: 1, 8-Cineol belongs to class of chemicals called monoterpenoids. The molecule of Cineole can be easily inserted into the cells, and then by the inhibition of the IκBα molecule, it prevents the transfer and function of an important transcription regulator of the cell; NF-κB p65, resulting in interruption of intracellular inflammation pathways. In bronchial epithelial ciliated cells, Cineole acts through blocking the NF-κB pathway and therefore stops the expression of mucin genes which play a key role in the production of mucus polysaccharides, and thus the production of mucus decreases. Cineole reduces the mucus secretion via inhibiting the specific mucus-producing cells (Goblet cells) and thus dampens the total mucus production from the mucosal layers in the bronchus. By reducing the production of mucus, the airways open and breathing becomes more comfortable. In addition, by controlling the NF-κ B, the gene expression of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are also stopped or decreased. The cytokines cause an increase in heat and pain by recruiting the cells producing inflammatory molecules (such as macrophages and neutrophils) into the inflammatory region. Cineole almost immediately halts these reactions and reduces inflammation, heat and pain in the inflammatory area. Moreover, it was known that there are neurons (nerve terminals) within the airways (e.g. nose and bronchi) which are sensible to natural molecules. In this regard, it has been shown that treatment with natural agonists of receptors on neurons, such as Cineole causes a significant reduction in the sense of stimulation in the airways and cessation of cough reflux.

THERAPEUTIC FEATURES: The active ingredients of **Broncofin** are mucolytic (expectorant), which liquefy the mucosal secretions and facilitate the excretion of the secretions. In addition, it has strong antibacterial and anti-fungal properties and also anti-inflammatory action. Moreover, **Broncofin** can act as a superior bronchodilator in birds with severe infection in their respiratory airways (e.g. bronchitis). The dilation effect of the **Broncofin** is due to its powerful effects on inflammatory pathways and its direct relaxation effect on smooth muscle cells of bronchus.

INDICATIONS: **Broncofin** is used to prevent and treat respiratory diseases particularly bronchitis.

TARGET ANIMALS: It can be used in a variety of birds (poultry) including chicken, turkey, quail, partridge, and so on.

INSTRUCTIONS TO USE: Add a part of the drug (between 250-1000 ml) to 1000 liters of drinking water and use it for 3-5 days (8 hours a day) under the supervision of a veterinarian.

CONTRAINDICATIONS: Not to be used in conjunction with drinking vaccines.

CLINICAL TRIALS:

The results of the clinical trials on **Broncofin** are as follows:

a) The results of an in-vitro test on **Broncofin**: The table below provides a comparison of antibiotic susceptibility of *Salmonella*, *Staphylococcus aureus* and *E.coli* which was obtained by the standard disc diffusion method (a disc containing **Broncofin**). The results were presented as the values indicating the diameter of the inhibition zone for each Bacterium.

Bacteria	*E. coli*	*S. aureus*	*Salmonella*
Inhibition Zone (mm)	9.1±1.5	12±1.4	7.5±1.3

The table below represents the minimum inhibitory concentration of **Broncofin** which prevents the bacterial growth.

Bacteria	*E. coli*	*S. aureus*	*Salmonella*
MIC (µg)	1.2±0.8	2±0.9	2.5±1.1

Meanwhile, *Salmonella* and *E-coli* were resistant to chloramphenicol at the ratios of 24% and 48%, respectively. Also, they were resistant to enrofloxacin at the ratios of 20% and 77%, respectively.

b) In-vivo test results: Day old chicks (n=310) were kept under the standard conditions until the age of 43 days. The chicks in group 1 **(NI+NT)** was the negative control group (not contaminated with virus). The chicks in other groups were contaminated with the virus particles at the age of 20 days. The first clinical respiratory manifestations were onset at the age of 35 days.

The weight of the chicks (in grams) at the ages of 20, 35 and 43 was presented in the table below:

Chick age (Day)	Experimental Group				
	NI+NT	I+NT	I+Anzo	I+CT	I+S.Anzo
20	575±43	533±29	571±29	550±28	581±36
35	1087±32	1008±26	1125±40	983±42	1108±41
43	1615±28	1539±35	1660±46	1492±51	1638±39

Abbreviations; NI+NT: the group of chicks with no infection and no treatment, **I+NT:** the group of chicks with infection and no treatment, **I+Anzo:** the group of chicks with infection and Anzofin treatment, **I+CT:** the group of chicks with infection and control treatment, **I+S.Anzo:** the group of chicks with infection and simultaneously **Anzofin** treatment.

SUMMARY: In summary, the results of the farm experiments indicate that the **Broncofin** can play a significant role in the treatment of respiratory diseases in poultry; in addition, it has a preventive role in respiratory infections diseases such as bronchitis. As a complementary effect, it can also act as a growth promotion supplement.

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BRONCOFIN PLUS

(for treatment of bronchitis in poultry)

COMPOSITION: **Broncofin PLUS** is a potent herbal medicine with a broad spectrum anti-viral, antibacterial and anti-fungal properties and is made up of effective ingredients from eucalyptus, rosemary, thyme and some other medicinal herbs. The drug is formulated in such a way that its various components can enhance the therapeutic effects of each other in a synergistic manner. The most important ingredients of the drug include: 1, 8 Cineole, Camphene, Fenchone and Terpineole.

MECHANISM OF ACTION: The active ingredients of **Broncofin PLUS** have substantial anti-inflammatory properties which therefore cause a great reduction in heat sense and easier blood flow on the infected position. The more blood flow on inflamed location causes accumulation and recruitment of more immune cells in the site of the infection in which leads to control of the infection. It has also been shown that the active ingredients in **Broncofin PLUS** affect the senses of the cold, stimulate the feelings of cooling and induce a calming effect on inflamed location. It acts by inhibiting the free radicals which are released massively during stress periods after the stress hormones reached to the cells. This feature reduces the stress of chickens during highly stressed conditions. The active ingredients of **Broncofin PLUS** interrupt the cell membrane of the bacteria, and then the drug leads all the bacteria to die and thus acts as a highly effective antimicrobial agent. A distinct feature of **Broncofin PLUS** is its prominent anti-inflammatory effect which causes a great reduction in the production of mucus and also due to unique molecular structure of its components, it can also cause the rapid degradation and lysis of the mucus or sputum, and therefore the mucus cannot be accumulated and remained in airways after administration of **Broncofin PLUS**. In addition, **Broncofin PLUS** in an optimum dose can reduce the side effects following vaccination and accelerate the healing process after respiratory infection. In one word, it acts as a strong healing and disinfecting agent during the avian respiratory diseases such as bronchitis. Also, its formulation has been optimized carefully to reach maximum anti-inflammatory, bronchodilator, mucolytic, and analgesic effects.

THERAPEUTIC FEATURES: The drug helps to breathe better by opening/dilating the airways and strengthen and helps the bird's immune system to cope successfully with the disease.

INDICATIONS: For the treatment of infectious respiratory diseases in poultry.

TARGET ANIMALS: It can be administered for a variety of birds, including chicken, turkey, quail, partridge, and others.

INSTRUCTIONS TO USE: Add and mix 250 ml of the drug to 1000 liters of drinking water and use it for 3-5 days (8 hours a day) under the supervision of a veterinarian.

CONTRAINDICATIONS: Not to be used in conjunction with drinking vaccines.

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ANZOFIN

(prevention and treatment of mild respiratory lesions)

COMPOSITION: **Anzofin** is a natural-based drug that is made up of active ingredients in Rosemary, Eucalyptus, and some other herbs. The drug is formulated in such a way that its various components empower and enhance the therapeutic effects of each other by a synergistic activity. The most important constituents in the drug composition include the followings: 1, 8 Cineol, Camphene and various Sesquiterpenes.

MECHANISM OF ACTION: Camphor and Camphene are natural molecules that are chemically classified as the terpenoids. The physicochemical properties of two compounds are very similar. Both have a bicyclic structure. Camphor acts as an agonist for a number of TRP receptors. These receptors are predominantly known as microscopic thermometers. TRP receptors except their characteristic feature that is the regulation of cold and heat sensing, also have widespread attributes due to their association with various physiological functions. For instance, they also have substantial anti-inflammatory, relieving and relaxing effects. Also, since TRP receptors are predominantly found in neurons, their stimulation with natural agonists (e.g. Camphene) resulted in pain relieve and analgesic effects. In addition, it has been shown that treatment with natural agonists of receptors on neurons, such as Cineole causes a significant reduction in airways inflammation and cough reflux. Moreover, Camphor like Cineole is effective on TRP receptors.

THERAPEUTIC FEATURES: The active ingredients are mucolytic (expectorant), and therefore induce the relaxation and dilation of the airways. Also, the drug can relieve the inflammation, stop the hemorrhagic lesions and help to heal the mucosal sores in the airways.

INDICATIONS: **Anzofin** improves clinical symptoms of mild respiratory infections, facilitates respiration and prevents the progression of the disease towards acute phases.

TARGET ANIMALS: It can be administered for a variety of birds, including chicken, turkey, quail, partridge, and others.

INSTRUCTIONS TO USE: Add and mix 1 liter of the drug to 1000 liters of drinking water and use it for 3-5 days (8 hours a day) under the supervision of a veterinarian.

CONTRAINDICATIONS: Not to be used in conjunction with drinking vaccines.

CLINICAL TRIALS:

The results of the clinical trials on **Anzofin** are as follows:

a) The results of an in-vitro test on **Anzofin**: The following table represents the results of the antibiotic susceptibility testing *on Salmonella, Staphylococcus aureus* and *E.coli* by the standard disc diffusion method using the discs containing **Anzofin**. The values are diameters of inhibition zone:

Bacteria	*E. coli*	*S. aureus*	*Salmonella*
Inhibition Zone (mm)	9.3±1.3	12.5±1.3	8±1.5

And the values in following table show the minimum inhibitory concentration of the drug to prevent growth of the bacteria:

Bacteria	*E. coli*	*S. aureus*	*Salmonella*
MIC (µg)	1.3±0.5	2±0.7	2.6±0.6

b) Results of in-vivo experiments: Day old chicks (n=310) were kept under the standard conditions until the age of 43 days. The chicks were divided in 5 experimental groups as follows: Group 1 was negative control. Groups 2-5 were treatment groups. At the age 20 day old, groups 2-5 were infected by viral particles. Group 3 received **Anzofin** at the onset of the clinical symptoms. Group 4 received a routine drug at the onset of the clinical symptoms. Group 5 was treated with **Anzofin** at first day of contamination with viral particles (day 20) before the onset of clinical symptoms.

The weight of the chicks at the ages of 20, 35 and 43 was presented in the table below:

Chick age (Day)	Experimental Group				
	NI+NT	I+NT	I+Anzo	I+CT	I+S.Anzo
20	560±37	529±27	559±38	552±33	537±29
35	1075±45	995±30	1110±35	992±35	1091±51
43	1600±47	1503±47	1651±42	1503±47	1650±47

Abbreviations; NI+NT: the group of chicks with no infection and no treatment, **I+NT:** the group of chicks with infection and no treatment, **I+Anzo:** the group of chicks with infection and Anzofin treatment, **I+CT:** the group of chicks with infection and control treatment, **I+S.Anzo:** the group of chicks with infection and simultaneously **Anzofin** treatment.

SUMMARY:

In summary, the results of the farm experiments indicate that the **Anzofin** can play a significant role in the treatment of mild respiratory diseases in poultry; in addition, it has a preventive role at the early stages of respiratory infections diseases such as bronchitis and prohibits the progression of the infections. As a complementary effect, it can also act as a growth promotion supplement.

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ANZOFIN EXTRA

(prevention and treatment of mild respiratory lesions)

COMPOSITION: **Anzofin EXTRA** is a natural-based drug that is made up of active ingredients in *Eucalyptus globulus*, thyme and some other medicinal herbs. The drug is formulated in such a way that its various components empower and enhance the therapeutic effects of each other by a synergistic activity. The most important components in this drug are: 1, 8-Cineole, Camphene, Fenchone and Terpineole.

MECHANISM OF ACTION: 1, 8-Cineole (also called Eucalyptol) belongs to class of chemicals called monoterpenoids. The molecule of Cineole can be easily inserted into the cells, and then by the inhibition of the IκBα molecule, it prevents the transfer and function of an important transcription regulator of the cell; NF-κB p65, resulting in interruption of intracellular inflammation pathways. Many of the genes involved in inflammation pathways are regulated by the NF-κB, including the genes encoding for inflammatory cytokines and mucin. In bronchial epithelial ciliated cells, Cineole acts through blocking the NF-κB pathway and therefore stops the expression of mucin genes which play a key role in the production of mucus polysaccharides, and thus the production of mucus is prohibited. Cineole almost immediately halts immunologic reactions and reduces inflammation, heat and pain in the inflammatory area. Also, since Cineole profits from a small 3D structure with a high tendency to penetrate into the lipids and proteins, its molecule can easily penetrate into the bronchial mucosa, and therefore the molecule breaks the mucosal layers and eliminates the accumulation of mucus within the bronchi. Moreover, Cineole provides an advantageous impact on bronchial smooth muscle cells by inhibition of acetylcholine and calcium pumps which as a consequence induce relaxation of muscle cells, resolution of contraction and disappearance of airways obstruction. Thus, following opening of the bronchi, the respiration undergoes a significant improvement. So, due to its relaxation property, Cineole is also known as a strong natural bronchodilator.

THERAPEUTIC FEATURES: The actives ingredients of the **Anzofin EXTRA** can directly affect the target cells in the respiratory system and therefore cause a remarkable increase in the performance and efficiency of respiration. Also, the components of the drug can induce relaxation of bronchial muscles and excretion of mucous and secretions from the respiratory tract and ultimately facilitate the respiration. Moreover, since its strong antibacterial, anti-fungal and anti-viral properties, it has a tremendous effect on the treatment of various types of respiratory infections.

INDICATIONS: It is used to prevent and treat pulmonary inflammation and respiratory infections such as bronchitis, sinusitis, and similar diseases.

TARGET ANIMALS: It can be administered for a variety of birds, including chicken, turkey, quail, partridge, and others.

INSTRUCTIONS TO USE: Add and mix 250 ml of the drug to 50 liters of water and use it for spraying, vaporing and aerosolizing (3 episodes per day, each lasts 8 hours). The drug can also be used in drinking water.

CONTRAINDICATIONS: Not to be used in conjunction with drinking vaccines.

CLINICAL TRIALS:

Day old Ross 308 chicks (n=48) were kept under the standard conditions until the age of 43 days. The chicks were divided in 4 experimental groups. Each group of 12 chicks was also separated in three 4-chicks replicates and maintained in isolated pens. The three groups of 14 day old chicks received a bronchitis vaccine (Nobilis IB 4-91) as eye drops at 5 times of normal dose. The treatments (control drug, **Anzofin EXTRA**) were administered after vaccination day from day 15 to 20 for 5 days, twice a day and each time for 8 hours. At the day 35, the bronchial samples were obtained and investigated by two pathologists.

The results of the clinical trials on **Anzofin EXTRA** are as follows:

Experimental group	Pathologic signs
Vaccinated	**Severe bronchial lesions:** disorganized cilia, epithelial deciliation (up to 50%), degeneration, desquamation and necrosis in bronchial epithelium, infiltration of inflammatory cells in mucosal lamina propria (up to 75% of mucosal area), increased lymphocytes and granulocytes, **Mucosal lesions:** petechial hemorrhages, hyperplasia, hyperemia, mucus accumulation, heterophil infiltration into the mucus, severe edema
Vaccinated + Anzofin EXTRA	**Moderate bronchial lesions:** disorganization of cilia in some areas, epithelial deciliation (up to 25 %), increased lymphocytes replaced between epithelial cells, hyperemia, infiltration of mucosal inflammatory cells (up to 50% of mucosal area)
Vaccinated + Control drug	**Mild bronchial lesions:** disorganization of cilia in some areas, epithelial deciliation (up to 25 %), increased lymphocytes replaced between epithelial cells, hyperemia, infiltration of mucosal inflammatory cells (up to 25% of mucosal area)
No treatment (negative control, healthy)	**Minor/No bronchial lesions:** Everything seems to be normal, no inflammatory cells, no hyperemia, no mucus overproduction

The clinical results showed that the **Anzofin EXTRA**-treated chicks could resist more against the pathologic effects of bronchitis. They affected moderately by the viral invasion and the bronchial lesions was less severe than the chicks were just vaccinated against the bronchitis.

SUMMARY:

In summary, the results of the clinical experiments indicate that the **Anzofin EXTRA** can play a significant role in the treatment of respiratory diseases (particularly the bronchitis) in poultry; in addition, it has a preventive role at the early stages of respiratory infections diseases such as bronchitis and prohibits the progression of the infections.

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IMMUNOFIN

(for enhancing and stimulating the cellular immunity)

COMPOSITION: **Immunofin** is a pure natural drug containing highly effective herbs such as Echinacea, Yarrow and few other herbs. The drug formulation has an intelligent thought in its background so that its components strengthen and amplify each other's therapeutic effects in a synergistic manner. The drug contains herbal ingredients such as polysaccharides (Arabinogalactan, Xyloglycan, Echinacin), glycosides: Caffeic acid and its derivatives (Cichoric acid, Echinacoside), Alkaloids and Alkylamides. Most important ingredients of the drug belong to a family of natural compounds called Alkylamides. Some of them in **Immunofin** formulation are Isobutylamide and Methylbutylamide. Other components of the drug with significant immunomodulatory effects are Chicoric acid, polysaccharides such as Echinacin, glycosides; Echinacoside and terpenes such as Citronellol (aka Dihydrogeraniol), Humulene and Caryophyllene.

MECHANISM OF ACTION: Alkamides are among the active substances in the Echinacea, capable of inhibiting both the cyclooxygenase and lipoxygenase pathways in epithelial cells and immune cells. These pathways play an essential role in the biosynthesis of inflammatory prostaglandins, such as PGE2. Therefore, inhibiting these pathways leads to halting the production of prostaglandins (PGs). The inhibition of PGs will grant more freedom and activity to a type of powerful killer cells called Natural Killer (NK) cells. The NK cells first detect then kill the abnormal or dying cells or germs/microbes by releasing high amount of toxic molecules nearby the target cell. Moreover, Echinacea contains oligomeric substances called polysaccharides (PS). Among the PSs, Arabinogalactan can directly activate a series of special receptors on the surface of innate immune cells (e.g. macrophage), which are responsible for the detection of microbial patterns (PRR). Therefore, the microbial signal is transmitted by the receptors to the intracellular sensors and leads to activation of innate immune cells and stimulates them to produce abundant amount of inflammatory cytokines such as IL-1 and TNFα. These cytokines recruit various types of immune system cells to the site of inflammation and activate the phagocytes and killer cells (NK cells).

THERAPEUTIC FEATURES: **Immunofin** stimulates strongly the Cell-Mediated Immunity (CMI) as one of main parts of immune system which therefore participates in induction of a good level of protection after vaccination. **Immunofin** can activate both lymphocyte types; T and B and therefore can stimulate the B cells to produce abundant amounts of immunoglobulins, mainly IgG.

INDICATIONS: **Immunofin** is used as an effective immunostimulator and preventive agent against viral/bacterial infectious diseases. It is recommended to be used at first 3 days of growing period, or at least 24 hours before/after vaccination.

TARGET ANIMALS: It can be administered for a variety of birds, including chicken, turkey, quail, partridge, and others.

es; T and B and therefore can stimulate the B cells to produce abundant amounts of immunoglobulins, mainly IgG.

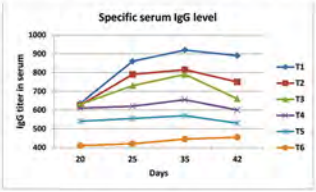
INSTRUCTIONS TO USE: Please mix 1 liter of drug per 1000 liters of drinking water and use daily for 8 hours according to expert (doctor of veterinary medicine) supervision.

CONTRAINDICATIONS: Not to be used in conjunction with drinking vaccines.

CLINICAL TRIALS:

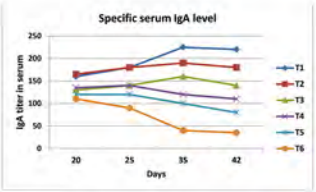
The results of the clinical trials on **Immunofin** are as follows:

The figure depicts the serum IgG antibody level after Newcastle disease vaccination in turkeys (20-42 day old). The graph shows results of a comparison between the birds administered with **Immunofin** and those received commercial probiotics.



Abbreviations; T1: the group of chicks which have been vaccinated and also treated with **Immunofin**, **T2:** the group of chicks which have been vaccinated and also received a probiotic treatment, **T3:** the group of chicks which have been vaccinated and also treated by a commercial drug (positive control), **T4:** the group of chicks have been administered with **Immunofin** but not vaccinated, **T5:** the group of chicks have been administered with a probiotic but not vaccinated, **T6:** the group of chicks without any treatment and vaccination (negative control).

The second graph below shows a comparison in serum IgA levels between the birds administered with **Immunofin** and those received commercial probiotics.



Abbreviations; T1: the group of chicks which have been vaccinated and also treated with **Immunofin**, **T2:** the group of chicks which have been vaccinated and also received a probiotic treatment, **T3:** the group of chicks which have been vaccinated and also treated by a commercial drug (positive control), **T4:** the group of chicks have been administered with **Immunofin** but not vaccinated, **T5:** the group of chicks have been administered with a probiotic but not vaccinated, **T6:** the group of chicks without any treatment and vaccination (negative control).

SUMMARY:

In summary, the results of the farm experiments indicate that the **Immunofin** can exert an impressive effect on the immune system by induction of production of protective Igs. It also can activate the T cells and make them ready and equipped against the invasion of pathogen particles particularly the viral infectious diseases. Moreover, it has a preventive role and can act as a prophylactic strategy against the viral infections diseases (e.g. bronchitis).

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ANTIBIOFIN

(natural multifunctional antibiotic; antibacterial, antiviral and antifungal)

COMPOSITION: **Antibiofin** is a pure natural drug made of highly effective herbs such as Thyme *(Thymus vulgaris)* and Ajowan *(Trachyspermum ammi)* and few other herbs. The drug contains an intelligent blend of herbal active ingredients so that its components can strengthen and amplify each other's therapeutic effects in a synergistic manner. The most important ingredients in the drug are phenolic compounds such as Thymol, Carvacrol, Paracymol and Cineole.

MECHANISM OF ACTION: **Antibiofin** contains a large amount of terpenoid phenols such as Thymol and Carvacrol. There are a lot of researches indicating that synthetic antibiotic residues in some tissues may remain for a very long time. Therefore, the antibiotics administered for the animal are deposited within the tissues and final food products. Then the drug-contaminated food products are readily transferred into the human body and blood circulation. These drug remnants are responsible for inducing the antibiotic resistance among microbial population which a human host carries within its body. To confront the problem, it was suggested by many scientists to use natural antimicrobials instead of synthetic ones. Therefore, we formulated **Antibiofin** which contains a large amount of natural terpenoid phenols such as Thymol and Carvacrol.

The natural substance; Thymol is now accepted in the EU standards as an effective antimicrobial agent but safe for humans. Both Thymol and Carvacrol are classified as monoterpenoids, since they have a carbon ring and oxygen (hydroxyl group) functionality. Evidences such as the images of the electron microscope have shown that these two monoterpenoids can be directly enclosed within the cell wall of the bacteria and, by disrupting its structure, increase the permeability of the cell wall of the bacterium. The Thymol and Carvacrol molecules are lipophilic and also have a small molecular size (just a hexagonal carbon ring with a hydroxyl group). Therefore, they are absorbed into the bacterial cellular membrane which is made of two-layer phospholipids and disrupt the structural order of the membrane (i.e. alteration of membrane fatty acids). Thus, the replacement of Thymol and Carvacrol into the cell membrane of the bacteria will mess up the regular structure of the membrane components, and the fatty acids will separate from the membrane. Following these changes and damage to the cell membrane, vital intracellular contents of the bacterial cell such as the metabolites and ions leak out of the damaged membrane. By the direct effect of Thymol and Carvacrol on bacterial cell wall proteins and molecules, shrinkage and coagulation in the bacterial wall will occur and lead bacteria to die.

The most important and deadly effect of Thymol and Carvacrol on bacterial cell wall is their capability to create pores in the membrane structure, which causes the leakage of vital substances from the bacterial cell due to a much higher osmotic pressure within the bacterial cell than the pressure in extracellular matrix. According to recent knowledge, natural antibiotics such as Thymol and Carvacrol have proven antimicrobial effects, and the drugs based on these compounds can prevent the development of various types of respiratory and digestive tract infections in industrial poultry. Actually, industrial poultry experience continuous stress during their growing period. In turn, the reduction of infection in the **Antibiofin**-treated herd causes the discontinuation of synthetic antibiotics and drugs and, as a result, in organic poultry farms, the chicken can be successfully grown completely without facing with infection challenges. Thymol and Carvacrol are also classified as antioxidants because of their phenolic nature and therefore they are very suitable for use in industrial livestock and poultry farms which are always under the high stressed conditions.

THERAPEUTIC FEATURES: active substances of **Antibiofin** inhibit the growth and proliferation of bacteria and pathogenic fungi, particularly in the gastrointestinal tract of the poultry. These substances have mild and gradual effects and therefore do not induce drug resistance in bacteria, so the drug can be used to prevent diseases in an optimal way. It can also show a synergistic effect when accompanied with other antibiotics to prevent the progression of the disease.

INDICATIONS:

- Prevention and treatment of gastrointestinal tract infections and reducing the recovery time
- Prevention of infectious diseases without inducing drug-resistance
- Prevention of the progression of the infectious diseases (without interrupting other drugs function, no contraindications)
- Acts as an effective phytobiotic and growth promoter

TARGET ANIMALS: It can be administered for a variety of birds, including chicken, turkey, quail, partridge, and others.

INSTRUCTIONS TO USE: Please mix 1 liter of drug per 1000 liters of drinking water and use it at least 3 days (every day for 8 hours) according to expert (doctor of veterinary medicine) supervision. Use it in the following conditions:

- At the first 3 days after the day-old chicks were arrived to the farm
- When the herd is challenged with an infectious diseases (i.e. digestive tract infections)
- When the herd experiences a serious stress
- 24 hours before/after an episode of vaccination to regulate the intestinal flora (as a prebiotic)

CONTRAINDICATIONS: Not to be used in conjunction with drinking vaccines.

CLINICAL TRIALS:

The antimicrobial effect of the drug was evaluated by microdilution method and subsequent counting the bacterial colony units. The table below shows the colony unit count in broiler chickens infected with Salmonella treated with **Antibiofin** and a standard drug. The day-old chicks received serial dilutions of bacterial inoculations (from 10^{-2} to 10^{-6}). The first dilution with countable colonies on the culture (<300 colonies) were recorded as the final result. We found significant therapeutic effects including reducing the burden of bacterial contamination in the stool, decreasing the relative mortality and increasing the relative weight gain in the group of chickens treated with **Antibiofin**. Interestingly, the colony count in **Antibiofin**-treated group was lower than the group treated with a routine drug.

The day of experiment	Experimental Group					
	I+Anti	I+CT	I	I+AntiB	NI+NT	NI+Anti
1	10^{-4} (95±12)	10^{-3} (153±16)	10^{-5} (175±18)	10^{-3} (165±14)	-	-
3	10^{-3} (65±9)	10^{-3} (101±11)	10^{-5} (265±20)	10^{-3} (77±4)	-	-
5	10^{-3} (114±13)	10^{-4} (127±9)	10^{-6} (147±15)	10^{-2} (43±7)	-	-
7	10^{-2} (188±17)	10^{-4} (91±11)	10^{-6} (55±7)	10^{-2} (25±5)	-	-
9	10^{-2} (78±10)	10^{-2} (170±15)	10^{-5} (133±13)	10^{-2} (11±3)	-	-

Abbreviations; for each experimental group the dilution level and the colony number of specified dilution on each of the experimental days was indicated. **I+Anti:** the group of chicks with infection which were treated by **Antibiofin**, **I+CT:** the group of chicks with infection which received a control treatment, **I:** the group of chicks with infection but no treatment, **I+AntiB:** the group of infected chicks which received **Antibiofin** two days before infection, **NI+NT:** the group of chicks with no infection and no treatment, **NI+Anti:** the group of chicks without infection but **Antibiofin**-treated.

PARSIMENDARU
Herbal Medicines Development Group

BIOHERBAL

appetizer and growth promoter for poultry

COMPOSITION: **Bioherbal** is a pure natural herbal remedy made of garlic, thyme, turmeric, lemon balm *(Melissa officinalis)* and few other medicinal herbs. The drug contains an intelligent blend of herbal active ingredients so that its components can strengthen and amplify each other's therapeutic effects in a synergistic manner. The drugs therapeutic effects are mainly relied on the active ingredients from garlic such as sulfur compounds, including allicin, ajoene, allyl sulfides, and vinyldithiins. The sulfur compounds of the garlic are responsible for its well-known characteristic odor.

MECHANISM OF ACTION:

Increasing the appetite, growth, performance:

Phytochemicals in the **Bioherbal** can increase appetite in two ways: 1. by stimulating the nerve terminals (of parasympathetic nerves), an appetite stimulatory signal is transmitted to the ventromedial hypothalamus (VMH). The hypothalamus perceives the hunger and so if was stimulated, it will increase the appetite and therefore increase the intake of feed (FI). 2. Phytochemicals such as those are present in **Bioherbal** can stimulate the gastrointestinal mucosal receptors which lead to synthesizing a specific neuropeptide called Neuropeptide Y (NPY). NPY reaches to VMH through bloodstream and stimulates it which at the end causes an increase in the appetite and FI level.

Modifying the intestinal eco-system (microflora) and improving the feed absorption:

The phytochemicals such as Thymol and Carvacrol (in thyme essential oil), as the natural and very strong antibacterial, antiviral and antifungal agents, can suppress the pathogens and inhibit the intestinal enteritis and thereby reduce the local inflammation. Thus, **Bioherbal** makes a modified microbial ecosystem and provides suitable conditions for growth of beneficial bacteria within the digestive system by suppressing pathogen bacteria while promoting the proliferation of useful bacteria. In other words, **Bioherbal** acts as a kind of prebiotic.

Antioxidant effects:

Bioherbal contains a group of active ingredients called flavonoids, which are composed of several subgroups such as chalcones, flavones, flavonols and isoflavones. These compounds are strong antioxidants and prevent the fatty acids oxidation and inhibit the formation of harmful free radicals, thereby prohibit the radical-mediated protein/DNA damages. These free radicals/onions cause dangerous damages in various tissues and organs such as liver. The flavonoids can prevent oxidative stress- induced detrimental protein modifications. The protein modifications occur following oxidation-mediated kinases activation and phosphatases suppression. The superoxide dismutase (SOD) can efficiently prevents the protein damages by inhibiting the excessive accumulation of free radicals. The superoxidase (superoxide dismutase) converts harmful free radicals such as hydroxyl to less dangerous molecules such as oxygen and hydrogen peroxide. Therefore inhibition of protein damages by flavonoids leads to cell protection during the oxidative stress and maintaining of the health of the important organs.

Enhancing the immune system function and response:

Bioherbal contains additional natural active ingredients beside the appetizing and antioxidant compounds, with special immunostimulatory effects. These molecules originates from well-known immune-enhancing plant; Echinacea. Albeit, the herbal drug; **Bioherbal** is mainly an appetizer, nevertheless, the appetizing effect of the drug and increased FI level also can cause improvement of immune system function, so immunostimulatory ingredients within the **Bioherbal** act as the complementary part in the drug formulation.

THERAPEUTIC FEATURES: **Bioherbal** is a powerful growth stimulant, has a good effect on balancing the metabolism and helps for better digestion and absorption within the digestive tract, thereby improving the Feed Conversion Ratio (FCR). Moreover, the antioxidants such as Thymol, Carvacrol, Allicin and similar compounds in **Bioherbal** can increase the quality and shelf life of carcasses. In addition, thanks to a multifunctional formulation and presence of very strong antimicrobials, **Bioherbal** can also act as a kind of antiseptic/disinfectant when mixed with the chickens' diet (pellet/feed). So, **Bioherbal** can prevent the growth and proliferation of any type of pathogens in the diet.

INDICATIONS: Boosting the appetite at the time of stress, improving FCR, growth promotion, enhancing the quality and shelf life of carcass, preventing the proliferation of pathogenic bacteria in feed, stimulating the immune system.

TARGET ANIMALS: It can be administered for a variety of birds, including chicken, turkey, quail, partridge, and others.

INSTRUCTIONS TO USE: Please mix up to 2 kg of the drug per ton of the diet according to expert (doctor of veterinary medicine) supervision. It can be mixed in water readily when the farmer wants to use pellet (instead of manually-prepared diet).

CONTRAINDICATIONS: Not to be used in conjunction with drinking vaccines.

CLINICAL TRIALS:

The table below shows the FCRs of two groups of chicks; one received the **Bioherbal**, the other experienced a standard diet. It is apparent that the FCR in **Bioherbal**-treated chick was lower (better) than those not received any treatment.

Groups	Experimental days							
	5	10	15	20	25	30	35	42
Bioherbal	0.6±0.1	1.09±0.13	1.18±0.12	1.32±0.16	1.54±0.18	1.58±0.15	1.78±0.22	1.9±0.23
Negative control	0.63±0.08	1.13±0.11	1.46±0.11	1.64±0.15	1.64±0.18	1.7±0.17	1.92±0.24	2.04±0.26

In addition, for determining the bacterial count, the chicks were killed by cervical dislocation and about 1 g of ileocecal digesta content was collected from intestine of each chick. The bacteria numeration was done based on conventional (culture-based) microbiological methods and preparation of serial dilutions (10^{-3} to 10^{-7}). The results were expressed as the log10 colony forming units per gram of ileum content. As we can see in the table of results, the **Bioherbal** treatment causes an interesting change in intestinal microflora, by reducing the population of pathogen bacteria (e.g. *E. coli*) while leaving almost intact the population of useful bacteria (e.g. *Bifidobacteria, Lactobacilli*).

Treatments	Bacteria count			
	E. coli (x10^7)	*Colestridia* (x10^6)	*Bifidobacteria* (x10^7)	*Lactobacilli* (x10^8)
Bioherbal	3.09±0.52	0.66±0.1	4.12±0.6	3.61±0.72
Negative control	14.5±2.5	73.1±5.8	4.17±0.55	4.84±0.8
	Statistics			
Pooled SEM	2.62	11.65	1.56	1.22
Probability	*	*	NS	NS

Abbreviations; SEM is abbreviation of Standard Error of Mean. The * symbol means a statistically significant different between the bacterial count of ileum content in **Bioherbal**-treated and non-treated chicks.

PARSIMENDARU
Herbal Medicines Development Group

MYCOTOXIFIN

(mycotoxin-binder/absorbent for the poultry)

COMPOSITION: **Mycotoxifin** is a unique toxin binder, based on latest advances with an optimized formulation for use in poultry nutrition. The **Mycotoxifin** has been made using the state of the art technology of toxin-binders. For this purpose, special attention has been paid to the physiology of the gastrointestinal tract, the range of effects of each component of the drug, as well as the pathologic effects of mycotoxin-contamination in the nutrition of the birds. New approaches to formulate the toxin binder **(Mycotoxifin)** and the use of therapeutic active ingredients from medicinal plants (i.e. thyme, peppermint and few other herbs) along with other components such as minerals and yeast cell wall have resulted in increased efficacy and multi-dimensional effects in final product **(Mycotoxifin)**, such as toxin absorption, toxin degradation, toxin blocking and healing/repairing of the damaged intestinal tissue, thus providing a unique product. In the manufacturing processes of the product, we used ingredients with passed EU standards and special carriers which protects the ingredients and maintains the quality of the product for a long time (increased shelf life) and increases the efficacy of the components. The carrier has nutritional value and therefore can also act as a nutritional supplement for the birds and improves the growth and performance.

PATHOGENICITY OF MYCOTOXINS IN POULTRY

Mycotoxins cause a chronic illness in poultry and have a significant negative effect on growth performance. Aflatoxins reduce the successful rate of hatchery, increase the visceral and cutaneous hemorrhage, suppress the immune system responses, increase the sensitivity to infectious diseases, and induce ruffled feathers, pale beaks and shanks and atrophy of bursa fabricius. Ochratoxin reduces the production, weight of eggs and quality of egg shells, causes egg bumps or bloody spots on the eggs, growth retardation, increased FCR, renal damage/failure, polydipsia and damages to the liver. In addition, although the chickens can tolerate approximately high levels of Zearalenone (ZON) but pathologic damages are possible when they are challenged with high amounts of ZON in their diet. ZON decreases the egg production, reduces egg specific gravity, and causes weak egg shell and interior egg quality. In parent stocks, high ZON in diet causes significant reduction in egg production, enlarged abdomen due to cystic oviduct, enhanced secondary sex characteristics and lowered serum progesterone. In broilers, ZON causes enlargement of comb and wattles, prolapsus of cloaca, reduces the size and weight of the testes, and changes the behavior. Deoxynivalenol (DON) reduces the feed intake, causes loss of appetite, and induces the gastrointestinal disorders e.g. diarrhea and necrotic enteritis, decreases the resistance to environmental stress, and increases the sensitivity to infectious diseases. T-2 toxin reduces the feed intake, causes loss of appetite, reduces resistance to stress and infectious diseases, induces dryness and abnormal wings, and causes ulcers in the tip, mouth and gizzard. Fumonisin reduces the growth rate, increases the FCR, reduces the production and quality of eggs and causes the intestinal disorders e.g. diarrhea.

MECHANISM OF ACTION:

Chemically engineered clays

We have incorporated one unique, modified clay (patented), which is loaded with magnesium and potassium instead of conventional clays loaded with calcium and sodium. It has an enhanced mycotoxin absorption capacity (particularly polar ones) of about 12 times more than that by conventional organic absorbents (unmodified, intact clays).

Viable yeast

The biologically active and non-pathogen yeast, as a probiotic, can produce and release esterase, an enzyme which can transform mycotoxins and make the active groups of mycotoxins to be harmless (catalyzes or deactivates the active groups) within the digestive tract. The esterase and few other types of enzyme within the **Mycotoxifin** can transform the fumonisins and other types of mycotoxins to less toxic and even up to harmless molecules. Moreover, the yeast growth and proliferation in the intestine restricts the suitable mucosal area for the proliferation of harmful microorganisms and makes the nutritional molecules inaccessible for the microbes. Thus, **Mycotoxifin** acts as a really effective probiotic and a growth stimulant.

Yeast cell wall

In addition to the live yeasts, the **Mycotoxifin** contains also hydrolyzed yeasts (fragments of yeast cell wall). The yeasts cell wall is composed of β-glucans, mannan oligosaccharides (MOSs) and fructooligosaccharides (FOSs), and therefore can act as a prebiotic. The yeast cell wall molecules exhibit a three-axes anti-mycotoxin function; 1) they enmesh the mycotoxins even the non-polar ones within their spider warp-like interconnected structure, 2) they contribute to immune system stimulation and activation, and 3) they can be digested and absorbed, as the nutritional supplement.

Medicinal herbal ingredients

There are four pathways forming the molecular basis of anti-mycotoxin effects of herbal active ingredients of **Mycotoxifin** as followings: 1) prevention of the toxic and harmful effects of mycotoxins on the liver tissue (hepato-protective and inhibition of hepatotoxicity of mycotoxins), 2) inhibition of severe inflammatory responses; reducing the cytokine (e.g. IL-6 and tumor necrosis factor-α) production, 3) the antioxidant effect; limiting the oxidative stress by inducing the glutathione peroxidase (i.e. controls the oxidative stress) and inhibiting the production of harmful malondialdehyde, and 4) these herbal substances can accelerate the healing process of mucosal scars/wounds caused by mycotoxins. The mucosal injuries can be cured rapidly by the herbal active ingredients within the **Mycotoxifin**. These molecules have strong stimulatory effects on production, formation and rearrangement of collagens/fibrins (i.e. constitute the connective tissue) and fibroblasts.

Organic acids

Humic acids (HAs) are produced through biological/chemical reactions; during the process of humifying the organic matter of the soil (humus) which is a result of biological activity of various microorganisms. In fact, HAs are consisted of a mixture of partially and totally humified soil compounds. Therefore, HAs do not have a specific structure but are composed of several intermediate structures, mostly oxidized with negative charge. This combination of diverse structures can trap the mycotoxins as a result of their specific structural features and the negative charge, and then excrete the trapped mycotoxins from the gastrointestinal tract.

THERAPEUTIC FEATURES: Absorption/degradation of polar and non-polar mycotoxins, hepato-protective, regulation of immune function by herbal compounds, stimulating the immune response by yeast cell wall fragments, boosting healing process of mucosal wounds/injuries (i.e. formed due to histopathology of mycotoxins), prevent mold growth, prevent bacterial growth, anti-oxidant properties due to blocking the formation of free radicals.

INDICATIONS: For the feed/diet/concentrate which is suspected for mold growth or mycotoxin contamination, birds showing sub-acute/chronic clinical/post-mortem symptoms of mycotoxin damages, for prevention of mold growth in feed, for prevention of mycotoxins harmful effects

TARGET ANIMALS: It can be administered for a variety of birds, including chicken, turkey, quail, partridge, and others.

INSTRUCTIONS TO USE:

- **Broilers:** please mix 1-2 kg per ton diet.
- **Laying hens:** please mix 0.5-1 kg per ton diet.
- **Breeders** (mother hens): please mix 0.5-1 kg per ton diet.

CONTRAINDICATIONS: None.

CLINICAL TRIALS:

The table below shows the inhibition rate of two groups of chicks; one administered with the **Mycotoxifin** in their diet, the other received a diet containing routine conventional clay (i.e. Zeolite). It is clear that the inhibition rate in **Mycotoxifin**-treated chicks was much higher ($P<0.05$) than the chicks received a usual clay.

Treatment	Mycotoxin level					
	AFL-B1 (%)	AFL-B2 (%)	AFL-G1 (%)	AFL-G2 (%)	Total-AFL (%)	ZON (%)
Mycotoxifin	95±18	87±13	85±15	67±10	90±20	42±11
Commercial	61±13	55±10	56±11	82±14	60±9	24±3

Abbreviations; AFL means Aflatoxin, and ZON indicates the Zearalenone.

PARSIMENDARU
Herbal Medicines Development Group

VITA GEL

(hydrating, nutritional and antimicrobial gel for day old chicks)

COMPOSITION: **Vitagel** is composed of carefully evaluated and selected minerals, herbal and natural ingredients. The drug contains herbal components such as Thyme and Oregano. The drug also favors from its rich source of nutrients, minerals and vitamins such as the glucose, selenium, vitamin A, D3, E, K, B1, B2, B6, and B12. The drug was formulated in the form of hydrogel and therefore its main component was water. The science behind the formulation and production of drug is based on providing a synergistic blend of ingredients so that its components can strengthen and amplify each other's therapeutic effects. The drug contains two key active herbal ingredients including the thymol (mainly in Thyme), and carvacrol (mainly in Oregano).

MECHANISM OF ACTION:

There is a natural protection mechanism in day old chicks which helps the chicks to survive for as long as until they can access to feed and water. This natural protection mechanism is based on remained egg yolk and egg white of the hatched chick which is placed in the abdominal cavity, and known as the yolk sac. The chicks remain with no access to water and feed for about 36 to 72 hours from hatching time until transportation and release into poultry house. Research has shown that the ingredients in the yolk sac meet only the minimum requirements and not all the complete nutritional requirements of the chick during the whole time of lack of access to feed and water, and in a significant percentage of the chicks the nutritional content of yolk sac is consumed within 24 to 48 hours. So chicks stay hungry and thirsty for a considerable amount of time. The growth ratio in the first week of breeding period is more important than the following weeks because at this time, some of the most important internal organs of the chick such as the liver, pancreas and intestines require about 2 to 3 times more nutrients than other organs for a proper development and growth and if not supplied, it causes an irrecoverable growth retardation which in the coming weeks cannot be compensated for even by increased protein levels. The first 2-3 days of the chick's life are critical to the growth and health of the chick. New research has shown that if the chickens are properly supplied in the early days, the chickens' immune system is also strengthened, resulting in better health and growth for the whole remained time of the growth period. Recently our company has been able to cover this nutritional gap (from hatching time until sending chicks to poultry house) based on new scientific researches. For this purpose, a type of medicinal and nutritional gel has been produced for chicks named **Vitagel**, and confirmed by the Iranian Veterinary Organization (IVO) after passing a strict review process. This drug-nutritional supplement is in the form of a hydrogel, and therefore contains significant amounts of water, thus meets all the water requirement of chicks for about 3 days (72 hours). The gel is also heated during production process and is completely sterile and safe for chicks. In addition, **Vitagel** contains herbal medicines (Oregano extract, thyme essential oil and a number of other herbs) formulated on the basis of pharmacological principles. Oregano and Thyme contain two highly effective antimicrobial phenols called thymol and carvacrol.

These two substances have significant antimicrobial potency and are comparable to well-known antimicrobial drugs such as virginamycin and similar antibiotics which are also known for their dual antimicrobial and growth promoting activity. The mentioned herbal substances exert a broad spectrum antimicrobial effect (antibacterial, antifungal and antiviral) even at low concentrations. Thymol and carvacrol also have antioxidant effects, and thus restore the physiological status of the chick body under stress conditions (heat, cold, transport). The antimicrobial and antioxidant effects of thymol and carvacrol are due to their chemical structure and the presence of an active hydroxyl group. The hydroxyl (OH) group in the molecule of these substances can rapidly absorb and neutralize free radicals produced during activated stress pathways. The small molecular structure of thymol and carvacrol and their OH group also cause these substances to easily penetrate the cell wall of bacteria and fungi and cause the death of these germs by disrupting the cell membrane. Due to the inherent tendency of these molecules to microbial cell wall, they do not harm the original cells of the host (chick). In other words, thymol and carvacrol specifically target the microbial cell not the host cells. The hydrogel also contains an energy source (glucose) and vitamins and minerals (selenium) which make it a highly potent nutritional supplement for providing the energy, vitamins and mineral requirements of day old chicks for up to 72 hours. In a nutshell, by consuming **Vitagel** a newly hatched chick which experiences the stress conditions (lack of water, and nutrition) will receive a substance that is highly potent in water, nutrients, energy and antimicrobials. **Vitagel** is made entirely of natural ingredients (herbal and organic) and even the gel has a natural origin and nutritional value. **Vitagel** is also very simple to use, just pour the gel within the tube onto the chick's box/tray. Because of its color (green), chicks are attracted to it, so they quickly tip and consume the small pieces of **Vitagel**. By using this drug, the hatchery farm owners can guarantee the health and growth of their chicks as well as a guarantee for significantly lower mortality rates during transportation of the chick to the poultry house.

THERAPEUTIC FEATURES:

Vitagel, as a rich source of water as well as vitamins, minerals, and energy, can prevent the defects due to longed stress periods (during hold over before placement, heat and humidity of the hatchery, transportation). It keeps the newly born chicks from dehydration, provides valuable nutrient source, encourages early feed intake and subsequent better feed conversion ratio (FCR), stimulates development of digestive system and reduces the early mortality rate. In addition, the drug has strong antimicrobial properties and prevents some lethal early infections in chicks such as yolk sac infection and aspergillosis (also called Brooder Pneumonia).

INDICATIONS:

The drug has been indicated for prevention of stress-mediated health problems such as dehydration in chicks. For instance, the drug can be used before/during/after stress periods such as hold over in hatchery mills, transportation, and heat stress. In addition, the drug can be applied for prevention of infectious diseases (yolk sac infection and aspergillosis) in young/newly born chicks.

INSTRUCTIONS TO USE: Please release the hydrogel by pressing the containing tube while you wearing a sterile glow onto the chick boxes/pens right after they hatched. Each tube is sufficient for 100 chicks.

CONTRAINDICATIONS: None.

Ruminants

Ruminants

PARSIMENDARU

PARSIMENDARU
Herbal Medicines Development Group

BIOHERBAL

(appetizer and growth promoter for ruminants)

COMPOSITION: **Bioherbal** is a pure natural herbal remedy made of Peppermint, Coriander, Cumin *(Cuminum cyminum)*, Lemongrass, and few other medicinal herbs. The drug contains an intelligent blend of herbal active ingredients so that its components can strengthen and amplify each other's therapeutic effects in a synergistic manner. The drug contains several key active ingredients including the menthol (mainly in Peppermint), linalool, geranyl acetate and camphor (mainly in Coriander), cuminaldehyde (mainly in Cumin) and citral and geraniol (mainly in Lemongrass).

MECHANISM OF ACTION:

Enhancing digestion performance and stimulating appetite: **Bioherbal**, thanks to its natural strong herbal ingredients, can increase appetite and improve growth performance in livestock, effectively enhances the health level at the early/mid lactation period in dairy cattle, neutralizes the harmful effects of thermal/heat stress and helps to stressed animal to rapidly restore their normal health level. Moreover, the active ingredients in **Bioherbal**, can bind to specific receptors over the mucosal layer of the intestine, stimulates them and causing the transmission of signal through parasympathetic system and therefore increases the gastrointestinal motility and tone. Also, **Bioherbal** promotes the release of the digestive secretions (e.g. bile) and thus accelerates the digestion, absorption and emptying processes within the digestive tract. Faster emptying itself stimulates the appetite. In addition **Bioherbal** does not affect the protein metabolism even protects it from degradation and also inhibits the breakdown of protein sequence to ammonia (NH3), causing prevention of protein loss in the form of hyper-production of ammonia and enhanced efficiency of nutritional material fermentation and energy production.

Balancing rumen fermentation: The compounds in **Bioherbal** have antimicrobial effects and can modify the microbial population in a positive manner; increases the useful microbial population capable of fermenting the raw nutritional materials and breaking them to small absorbable molecules. Moreover, **Bioherbal** balances the ratio of acetate to propionate to a suitable level and directs the rumen for efficient fermentation while maintaining the acetate at an appropriate level. Acetate is a precursor for the milk fat production whereas the propionate and butyrate are produced from fermented grain, and all of them belong to a class of organic compounds called volatile fatty acids (VFAs). Abnormal/hyper- fermentation can cause acidosis in rumen and suppress the milk fat production. The **Bioherbal** was carefully formulated with the goal of maintaining the very delicate balance between these VFAs, if it was used with recommended dose and therefore provides appropriate level of fermentation without turning towards acidosis.

Antioxidant effects: Some active ingredients used in **Bioherbal** have strong antioxidant activity (e.g. phenols and monoterpenoids). Their antioxidant capacity is comparable to vitamin E, a known and powerful antioxidant. It has also been proven that natural antioxidants in essential oils can synergistically empower the antioxidant activity of vitamin E. The antioxidants target the enzymes involved in reactive oxygen species (ROS) and harmful free radical production and therefore limit the development of oxidative stress (OS). The OS is responsible for predisposing the host to many metabolic defects, suppression of the immune system and challenges with infectious diseases. In addition, antioxidants improve the nutritional value of the animal feed, enhance the shelf-life of their diet, and improve the quality of carcass.

Anti-inflammatory effects: Some monoterpenoids and phenols in **Bioherbal** (e.g. linalool, menthol, camphor and citral) have the advantage of being the strong anti-inflammatory agent. These molecules directly target the intracellular and nuclear adaptors controlling the production and release of inflammatory mediators such as cytokines and chemokines. Monocytes, macrophages and T cells are affected by the active ingredients within **Bioherbal**. Regulation of immune responses and inhibition of inflammatory/stimulatory reactions of immune system lead to more tuned activity of digestive tract and a calming effect. Some of the key molecules in **Bioherbal** such as menthol, geraniol and eugenol directly bind to a class of receptors on the surface of inflammatory cells called TRPs, limiting the cells activity and reducing the release of inflammatory cytokines.

Ruminants

THERAPEUTIC FEATURES:

Bioherbal, with a group of aromatic compounds in it, restores the appetite during extreme conditions such as heat stress or transportation. Increased appetite leads to prevention of reduction of feed intake during stress periods. Also, **Bioherbal** stimulates the growth and has a facilitating effect on the metabolism procedures in livestock, resulting in better digestion and absorption of nutritional material in the small intestine and thus improving the feed conversion ratio.

INDICATIONS:

Stress periods such as the first weeks after parturition, infectious and parasitic diseases, metabolic disorders, vaccination, hoof trimming, transportation, heat stress, growth promotion, enhancing the feed conversion ratio, improving the quality and shelf life of carcasses, preventing the replication/proliferation of pathogenic bacteria.

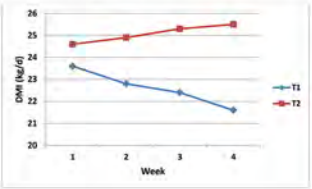
TARGET ANIMALS: cattle, sheep, goat.

INSTRUCTIONS TO USE: Please mix up to 2 kg of the drug powder per ton of the concentrate according to expert (doctor of veterinary medicine) supervision.

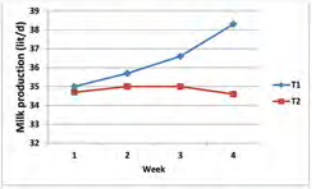
CONTRAINDICATIONS: None.

CLINICAL TRIALS:

The graph below shows the results of measuring the dry matter intake (DMI) in the two experimental groups; the animals (dairy cattle) fed with a routine diet (T2), and the animals received **Bioherbal**-mixed diet (T1). The mean DMI in the **Bioherbal**-treated group in comparison to the control group at each week was significantly higher than that in control animals ($P < 0.05$). The DMI level at two last experimental weeks (3 and 4th) was substantially higher than that in control animals ($P < 0.01$).



Moreover, the plot below shows the results of measuring the milk production in the two experimental groups as mentioned before. It is obvious that the animals fed with a diet supplemented with **Bioherbal**, could produce more milk. The milk production after 4 weeks could reach to a splendid level of around 38 liters per day. The increase in milk production at the 3 and 4th weeks of **Bioherbal** supplementing was significantly higher than that in control non-supplemented animals ($P < 0.01$).



PARSIMENDARU
Herbal Medicines Development Group

MYCOTOXIFIN

(mycotoxin-binder/absorbent for contaminated diet of the ruminants)

COMPOSITION: **Mycotoxifin (ruminant formulation)** is a unique toxin binder, based on latest advances with an optimized formulation for use in livestock nutrition. The **Mycotoxifin** has been made using the state of the art technology of toxin-binders. For this purpose, special attention has been paid to the physiology of the gastrointestinal tract, the range of effects of each component of the drug, as well as the pathologic effects of mycotoxin-contamination in the nutrition of the animals. New approaches to formulate the toxin binder **(Mycotoxifin)** and the use of therapeutic active ingredients from medicinal plants (i.e. thyme, peppermint and few other herbs) along with other components such as minerals and yeast cell wall have resulted in increased efficacy and multi-dimensional effects in final product **(Mycotoxifin)**, such as toxin absorption, toxin degradation, toxin blocking and healing/repairing of the damaged intestinal tissue, thus providing a unique product. In the manufacturing processes of the product, we used ingredients with passed EU standards and special carriers which protects the ingredients and maintains the quality of the product for a long time (prolonged shelf life) and increases the efficacy of the components. The carrier has nutritional value and therefore can also act as a nutritional supplement for the animals and improves the growth and performance.

PATHOGENICITY OF MYCOTOXINS IN LIVESTOCK

Mycotoxins inflict very harmful effects on the health of the livestock. These compounds have a negative effect on all tissues and organs (hepatotoxic, renal toxicity, gastrointestinal toxicity etc.), including the liver, kidney, CNS, digestive system and the genital system. High toxicity of mycotoxins is due to several features as follows: their high capacity in penetration into the body via different routes even from skin, the high solubility and their capability in rapidly spreading within all tissues and organs. One of the important organs in livestock animals which are affected by mycotoxins is the genital tract. Some mycotoxins, for example Zearalenone (ZON), have a molecular structure similar to sex hormones. Therefore, if the lactating cattle take ZON -contaminated diet, they will experience some typical and general damages in all organs due to ZON, as well as some organ-specific effects such as negatively affecting the reproductive system due to molecular similarity of ZON to sex-hormones, so the reproductive system (e.g. genital tract, ovary) will be affected significantly. Thus, mycotoxins such as ZON can impose many negative effects on the health of the animal due to their specific structural characteristics. Some of the harmful effects of the ZON are as follows: abortion, increased vaginal discharge, making the affected host predisposed to vaginal infections, swelling/edema of the mammary glands (udder), decreased success rate of insemination, decreased pregnancy rates, increased irregularities and hidden estrus, ovarian cysts and disruption in the production of sex hormones. Moreover, other toxins such as Aflatoxin, T-2 toxin and deoxynivalenol (DON) reduce the milk production, induce gastroenteritis, intestinal hemorrhage, rumen dysfunction, diarrhea, ketosis, contamination of milk and chronic mastitis. The strong suppressor effect of mycotoxins in milk production can impose the farmers a huge commercial loss. DON is known to be a laminitis- and lameness- inducing agent. However, one should be beard in mind that the mycotoxins can influenced the internal organs and tissues by a slow, gradual and chronic manner and therefore lately diagnosed.

MECHANISM OF ACTION:

Chemically engineered clays

We have incorporated one unique, modified clay (patented), which is loaded with magnesium and potassium instead of conventional clays loaded with calcium and sodium. It has an enhanced mycotoxin absorption capacity (particularly polar ones) of about 12 times more than that by conventional organic absorbents (unmodified, intact clays).

Viable yeast

The biologically active and non-pathogen yeast, as a probiotic, can produce and release esterase, an enzyme which can transform mycotoxins and make the active groups of mycotoxins to be harmless (catalyzes or deactivates the active groups) within the digestive tract. The esterase and few other types of enzyme within the **Mycotoxifin** can transform the fumonisins and other types of mycotoxins to less toxic and even up to harmless molecules. Moreover, the yeast growth and proliferation in the rumen restricts the suitable mucosal area for the proliferation of harmful microorganisms and makes the nutritional molecules inaccessible for the microbes. Thus, **Mycotoxifin** acts as a really effective probiotic and a growth stimulant.

Yeast cell wall

In addition to the live yeasts, the **Mycotoxifin** contains also hydrolyzed yeasts (fragments of yeast cell wall). The yeasts cell wall is composed of β-glucans, mannan oligosaccharides (MOSs) and fructooligosaccharides (FOSs), and therefore can act as a prebiotic. The yeast cell wall molecules exhibit a three-axes anti-mycotoxin function; 1) they enmesh the mycotoxins even the non-polar ones within their spider warp-like interconnected structure, 2) they contribute to immune system stimulation and activation, and 3) they have nutritional value so they can be digested and absorbed and promoted the animal growth.

Medicinal herbal ingredients

There are four pathways forming the molecular basis of anti-mycotoxin effects of herbal active ingredients of **Mycotoxifin** as followings: 1) prevention of the toxic and harmful effects of mycotoxins on the liver tissue (hepato-protective and inhibition of hepatotoxicity of mycotoxins), 2) inhibition of severe inflammatory responses; reducing the cytokine (e.g. IL-6 and tumor necrosis factor-α) production, 3) the antioxidant effect; limiting the oxidative stress by inducing the glutathione peroxidase (i.e. controls the oxidative stress) and inhibiting the production of harmful malondialdehyde, and 4) the herbal substances of the **Mycotoxifin** have the both capability of prevention and healing of mucosal damages. In the case of healing the intestinal injuries in animals that consumed mycotoxin-contaminated feed, the drug can help the animal to take advantages of a shorter healing period. In addition, the herbal ingredients of the drug have strong stimulatory effects on production, formation and rearrangement of collagens/fibrins (i.e. constitute the connective tissue) and fibroblasts.

Organic acids

Humic acids (HAs) are produced via biological/chemical reactions; during the process of humifying the organic matter of the soil (humus) which is a result of biological activity of various microorganisms. In fact, HAs are consisted of a mixture of partially and totally humified soil compounds. Therefore, HAs do not have a specific structure but are composed of several intermediate structures, mostly oxidized with negative charge. This combination of diverse structures can trap the mycotoxins as a result of their specific structural features and the negative charge, and then excrete the trapped mycotoxins from the gastrointestinal tract.

THERAPEUTIC FEATURES: Absorption/degradation of polar and non-polar mycotoxins, hepato-protective, regulation of immune function by herbal compounds, stimulating the immune response by yeast cell wall fragments, boosting healing process of mucosal wounds/injuries (i.e. formed due to histopathology of mycotoxins), prevent mold growth, prevent bacterial growth, prevent the harmful effects on reproductive system, and anti-oxidant properties due to blocking the formation of free radicals.

INDICATIONS: For the feed which is suspected for mold growth or mycotoxin contamination, animals showing sub-acute/chronic clinical/post-mortem symptoms of mycotoxin damages, for prevention of mold growth in feed, for prevention of mycotoxins harmful effects

TARGET ANIMALS: It can be administered for ruminants (e.g. cattle, sheep, and goat) and equine.

INSTRUCTIONS TO USE: a daily dose for each animal can be administered as follows:

- To prevent the mycotoxicosis: 7-10 g/daily/each animal
- For the moderately contaminated feed: 10-15 g/day/each animal
- For the highly contaminated feed: 15-20 g/day/each animal

CONTRAINDICATIONS: None.

CLINICAL TRIALS:

In-vitro test results:

We measured the mycotoxin absorption capacity of **Mycotoxifin** by a series of in-vitro tests. The test was done by treating the mycotoxin-contaminated rice. To run experiment, the rice was contaminated with a certain amount of a mycotoxin, placed in a container and then the **Mycotoxifin** was added to the experiment box. The box containing contaminated rice and the treatment was incubated for 24 h then a sample from the box collected. The amount of remained mycotoxin was measured by HPLC instruments.

In the box containing Aflatoxin contaminated rice, 93, 83, 85 and 69 percent of the four types of Aflatoxin including B1, B2, G1, and G2 have been absorbed, respectively after 24 h treatment with **Mycotoxifin**. Considering the sum of all Aflatoxins, a mean value about 89% of the total amount of four types of Aflatoxins was absorbed by **Mycotoxifin**. Moreover, more than half of the Zearalenone (ZON)-contaminated rice box has been absorbed after 24 h treatment with **Mycotoxifin**. Interestingly, the Aflatoxin and ZON levels were less absorbed by a commercial mycotoxin binder. The mycotoxin level in control samples (intact rice without **Mycotoxifin** treatment) remained unchanged.

The table below shows the absorption capacity of **Mycotoxifin** in two experimental groups; one is the rice sample contaminated with four types of Aflatoxins and ZON (last column) (in triplicate) and cured by **Mycotoxifin** and another is the rice samples contaminated four types of Aflatoxins and ZON and then cured by a commercial mycotoxin absorbent.

Treatment	Mycotoxin level					
	AFL-B1 (%)	AFL-B2 (%)	AFL-G1 (%)	AFL-G2 (%)	Total-AFL (%)	ZON (%)
Mycotoxifin	93±12	83±10	85±11	69±9	89±14	47±8
Commercial	58±8	50±8	51±9	78±11	58±7	21±4

Abbreviations; AFL means Aflatoxin, and ZON indicates the Zearalenone.

PARSIMENDARU
Herbal Medicines Development Group

AFTOFIN

(healing the dermal and mucosal injuries, and healing the traumatic or infected wounds)

COMPOSITION: **Aftofin** is a pure natural herbal remedy made of Peppermint, Myrtle, and few other medicinal herbs. The drug contains an intelligent blend of herbal active ingredients so that its components can strengthen and amplify each other's therapeutic effects in a synergistic manner. One of the most effective ingredients in this product is flavonoids.

MECHANISM OF ACTION: **Aftofin** is very rich in a series of unique herbal ingredients. It contains phenols (phenolic acids), tannins (proanthocyanins) and flavonoids. Anthocyanins are powerful antioxidants that actively prevent the harmful effects of oxidation reactions and free radicals. One of the effective phenols in this product is Caffeic Acid which has a strong antioxidant effect. Also, another polyphenolic found in the Myrtle Extract and present in the product, is Gallic acid. It has a strong antioxidant effect similar to Caffeic Acid. Also, the flavonoids of the **Aftofin** such as Myricetin and Quercetin and Catechin have impressive anti-inflammatory and antimicrobial effects. There are also other significant active ingredients within **Aftofin**. For instance, menthol has several beneficial effects, including anti-inflammatory, pain relief, and a feeling of coolness in the inflammation site. In short, by the four mechanisms **Aftofin** improves the health condition of the animal challenged with infection and mucosal ulcers. First, by relieving pain and reducing the temperature of inflammation and infected site, it can relieve the feelings of illness and stress and restore the animal's appetite, and subsequently boost the animal health due to better feed intake. Secondly, some herbal substances within **Aftofin** show a direct antiviral effect, and therefore can reduce the load of viruses, weaken the ability of viruses in attacking the cells and ameliorate the damage of viruses to the tissues and organs. Third, the strong antioxidants in this drug, especially the phenolic acids and anthocyanins, neutralize the toxic free radicals in the inflammation and ulceration site. The over-proliferation of viruses and over-production of free radicals are the most significant causes of progression and resistance of mucosal ulcers, which, by inhibiting the two, **Aftofin** helps the immune system and accelerates the repairing processes and wound healing. And finally, the fourth way the drug shows its action is through the stimulating the repairing/restorative cells, such as fibroblasts. Some herbal ingredients within **Aftofin** are in fact attractants and propel the fibroblasts to migrate towards the wound site and there produce specific fibers such as collagen, elastin and fibrin, resulting in the recovery of the connective tissue at the ulcer/wound site. Reconstitution of connective tissue is a fundamental step in wound healing and therefore provides the basis for full resolution of the wound.

Ruminants

THERAPEUTIC FEATURES: **Aftofin** can rapidly treat all kinds of dermal/mucosal blisters, erosions, and rashes. It also heals the ulcers on the skin, lips, and mouth which formed due to viral/bacterial/fungal primary/secondary infections. It acts as a natural antimicrobial agent with great antibacterial (gram positive and negative), antifungal and antiviral properties, even at low concentrations. Also, it has an impressive healing effect on hoof ulcers and wounds. In addition, **Aftofin** have an impressive pain-relieving and calming effect in animal challenged by painful sores/ulcers on their feet (hoof) and mouth.

INDICATIONS: The drug can be used as the complementary/symptomatic treatment for erosive and ulcerative diseases such as Foot-and-Mouth Disease (FMD), blue tongue (also known as pseudo FMD) in ruminants, and Contagious Ecthyma (also known as Orf) in sheep. Also, the drug can be used as a complementary treatment for traumatic superficial wounds/ulcers on the skin/mucosal surfaces. However, the drug is not recommended for the deep wounds.

TARGET ANIMALS: Ruminants (Cattle, Sheep, Goat)

INSTRUCTIONS TO USE: Please shake well the spray bottle before use. Then, spray the drug from a safe distance onto the wound or the infection site; in the case of FMD, spray it all over the mouth and tongue. It is recommended to repeat the procedure twice a day until complete healing/recovery. For a better response, it is suggested that to rinse the inflammation/wound site with distilled water or saline to remove the debris before spraying the drug. In fact, it is better to do a wound debridement if there is a necrosis layer on the wound. Moreover, in cases where the animal is severely affected, the spray repeats should be increased up to 2-3 times a day. If the treatment strategy contains both a topical antibiotic and the **Aftofin**, please first apply the topical antibiotic then spray the **Aftofin** on the wound site.

CLINICAL TRIALS:

Effect on oral ulcers:

Aftofin was used to treat oral ulcers formed during viral infection (FMD). By using the drug at primary stages of the disease, a good pain-relieving/antinociceptive effect was induced; the appetite and feed intake were restored. Inflammation was dampened and the healing period was significantly reduced in **Aftofin**-treated animals compared with the non-treated (control) group.

Effect on hoof ulcers:

The drug reduced the pain and inflammation dramatically; the congestion, infection and lameness were disappeared at the end of treatment period (7-day, twice a day) while there is not any improve in health condition (lameness and pain) in control group (non-treated animals).

PARSIMENDARU
Herbal Medicines Development Group

PUC (Pars Udder Cream)

(anti-inflammatory, antimicrobial, resolves the topical edema)

COMPOSITION: **PUC** is a pure natural herbal remedy consisted of active ingredients in peppermint, lavender, marigold *(Calendula officinalis)*, and few other medicinal herbs. The drug contains an intelligent collection of herbal active ingredients as well as the famous natural wound healing remedy; honey (with beeswax). So the components can strengthen and amplify each other's therapeutic effects in a synergistic manner. The most significant active ingredients of the drug are Menthol, Caffeic acid, and Helenalin.

MECHANISM OF ACTION: The active ingredients in the drug, show strong antimicrobial effects (both anti-bacterial and antifungal effects), and have extraordinary anti-inflammatory, analgesic and wound healing properties. In addition, the drug can efficiently reduce the heat and edema at the inflammation site (mammary glands) by facilitating the blood flow and blocking the inflammation signals at the molecular level. The greater blood flow in the mammary glands causes more immune cells to reach the infection site and therefore helps the animal to confront the infection. Flavonoids and saponins of the drug prevent the release of harmful enzymes and histamine. Histamine causes sensitization and swelling (edema). The drug interrupts the Histamine functions by decreasing the capillary permeability and preventing the plasma leakage into the tissues (i.e. edema) and therefore hinders worsening of inflammation and development of swelling. The drug alleviates efficiently the pain and heat due to the presence of Menthol and its desirable effect on facilitating the blood flow and cold sensing receptors. In addition, unlike the synthetic antibiotics, the bacterial resistance against Menthol is very rare due to unique structure of the ingredient as well as presence of other accompanying compounds within drug which act in synergy with Menthol. The enhancing effect of Menthol on blood flow helps the animal to confront the infection through two ways: first by reducing the heat, thereby reducing the stress of the animal, and the second by recruitment of more immune cells (phagocytes such as macrophages and neutrophils) towards the infection site.

THERAPEUTIC FEATURES: The pure natural **PUC** has strong antibacterial and anti-inflammatory properties due to incorporation of specific herbal substances, capable of rapid dermal absorption through the skin. The PUC accelerates the blood supply to the mammary glands and therefore reduces the pain and heat feeling in inflammation site; it induces the calmness and coldness sensation. Also, it acts as a complementary agent besides the classic topical/systemic antibiotic therapy and helps the animal for a faster confront against the infection in mammary glands.

INDICATIONS: The drug can be used as the complementary natural remedy for accompanying the routine antibiotic therapy against mastitis (chronic, acute, sub-clinical). It can be used to reduce the inflammation and edema in mammary glands independent of which kind of microbial agent causes the infectious.

TARGET ANIMALS: Ruminants (Cattle, Sheep, Goat)

INSTRUCTIONS TO USE: After each episode of milking, please rub a thin layer of the cream on the skin surface of the mammary glands. Please do not apply the cream on fresh scars. For the best outcome, the drug should be used as a complementary treatment besides the classic antibiotic therapy.

CLINICAL TRIALS:

Administering **PUC** for the cattle with acute mastitis significantly reduced the somatic cells count (SCC) 24 hours after starting the treatment. And after continuing the treatment for 72 hours, the SCC felled to fewer than 150,000 that is a normal range in cattle milk **(please see Fig. 1)**. Also, the California Mastitis Test (CMT) became negative in treated cows after 64 hours of treatment. The clinical symptoms such as heat, pain, and edema of the breast tissues were disappeared almost instantly after administering the PUC (few hours up to 24 hours after initiation the treatment). In conclusion, considering the CMT results, the number of somatic cells and clinical symptoms, the duration of a successful treatment plan in challenged cows was determined 72 hours (three days).

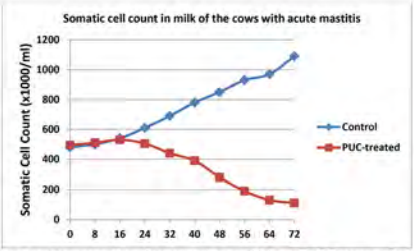


Fig 1. The plot shows the mean values of somatic cell count (SCC) in milk of the cows with acute mastitis. There were significant falls in SCC after 24-72 hours of drug application in PUC-treated animals in comparison to control animals ($P < 0.01$).

In cows with sub-clinical mastitis, the SCC and CMT results were reached to a normal range at 72 hours **(please see Fig. 2)**, therefore as a conclusion, the **PUC** treatment regimen in cows suffering from sub-clinical mastitis need to last for a longer period compared to cows with acute mastitis. Thus, it is recommended that the duration of the **PUC** application in cattle with sub-clinical mastitis is twice that of cattle with acute mastitis in order to ensure a successful treatment

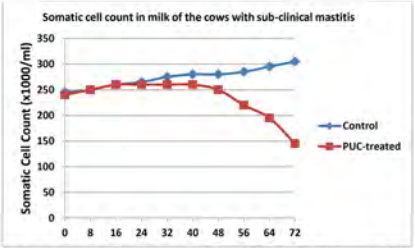


Fig 2. The plot shows the mean values of somatic cell count (SCC) in milk of the cows with sub-acute mastitis. There were significant falls in SCC after 48-72 hours of drug application in PUC-treated animals in comparison to control animals ($P < 0.01$).

PARSIMENDARU
Herbal Medicines Development Group

PUC+

(softening the udder skin, healing the skin cracks, and soothing effect)

COMPOSITION: **PUC$^+$** is a pure natural herbal remedy with almost same active ingredients in which were present in PUC. It contains constituents from peppermint, lavender, marigold *(Calendula officinalis)*, and few other medicinal herbs (e.g. *Salix alba*, Viola). However, it differs from PUC in terms of some features such as the concentration and amount of the active ingredients and herbal oils. Also, it has more amounts of specific plant extracts such as *Salix alba* and more amount of herbal oils such as the Viola flowers oil and Coconut oil. In addition, similar to PUC it has well-known natural wound healing remedy; honey (with beeswax) in its formulae. The most significant active ingredients of the drug are Menthol, Caffeic acid, Helenalin, Lauric acid, Myristic Acid, Capric acid and Salicylic acid.

MECHANISM OF ACTION: Mastitis is one of the most prevalent diseases of the dairy cows all around the world with significant and heavy costs spent for the treatment approaches. The clinical form of mastitis is generally determined by the inflammation, pain, dermal hard plaques and warmness of the breast tissue of the animal. The majority of acute and subclinical mastitis infections occur due to contagious microbes such as *Streptococcus agalactiae*, *Staphylococcus aureus* and sometimes fungal pathogens. In this regard, we have introduced an herbal remedy validated in clinical trials although it should be noted that it acts as a complementary therapeutic to PUC and routine antibiotics and covers some underestimated aspects of mastitis dermal pathology such as the dryness and hardness of the skin and dysregulated local blood circulation. A dry and hard skin is prone to dermal cracks/scars and subsequent penetration of pathogen microbes and even subsequent reoccurrence of a previously treated mastitis. An abnormal and interrupted blood circulation is usually occurred during local inflammation of cattle breast tissue (called mastitis). Thus, **PUC$^+$** was made with the goal of strengthening the PUC' therapeutic effects and prevention of reoccurrence of the mastitis. **PUC$^+$** increases the blood circulation towards the breast tissue which will be resulted in the acceleration of the tissue healing and rapid clearance of the dead cells and recruited inflammatory cells. Also, the oils (Coconut oil and Viola oil) present in the cream prevent the cracks and sores on the breasts skin which are usually formed due to infection-associated hardness. The drug contains high concentration of *Salix alba* plant extract which has a well-known anti-inflammatory compound Salicylic acid (pro-drug of the Aspirin) and therefore it stops the over-activated inflammatory procedures which then will help initiation of the healing processes. The drug also contains herbal oils such as Coconut oil and Viola oil. The first is composed of some medium-chained fatty acids such as Lauric acid, Myristic acid and Capric acid and the latter is mainly comprised of oleic acid and linoleic acid. We have incorporated both violet flowers extract and the oil in the drug formula.

Pars Udder Cream (PUC)©(ParsImenDaru Co.)

The viola extract contains flavonoids and alkaloids. It was shown in many researches that the viola have some sedative, analgesic and moisture-absorbing components such as rutin, melatoninin, methyl salicylate and mucilages. The mucilages in viola extract keep the moisture on the skin and induce soothing and calming feelings and the flavonoids facilitate the blood flow in breast tissue. The coconut oil is composed of much amount of luaric acid which is known for its antioxidant and surprising antibacterial and antifungal activity. The capric acid and myristic acid helps the lauric acid in its antimicrobial and antioxidant activity in a synergistic manner. The coconut oil is also known for its softening and healing activity on skin. The oil fills the skin cracks and makes the skin soft.

THERAPEUTIC FEATURES: **PUC*** is composed of a unique mixture of highly effective herbal extracts, essential oils and pure oils with soothing, softening, calming and antimicrobial effects. The active ingredients of the drug are highly concentrated so small amount of the drug for each time of application of the breast' skin is enough. Also, the drug is much greasier than the PUC which is due to its herbal oils. The herbal raw oils such as coconut oil and viola oil fills the dermal cracks/sores, eliminates the hard skin plaques and makes the breast' skin softs and fragile. Moreover, the drug returns the local blood flow to its normal state. Therefore, Mammary glands with normal soft skin and normal blood circulation are more resistant against infectious diseases.

INDICATIONS: **PUC*** can be used after a successful period of antibiotics and PUC therapy with the goal of softening and moistening the breast' skin, inducing a normal local blood circulation, and prevention of reoccurrence of mastitis.

TARGET ANIMALS: Ruminants.

INSTRUCTIONS TO USE:

After each period of milking, rub a part of the cream on the surface of cow breasts skin (according to the recommendation of an expert). Please continue the application of the drug for at least 3 days.

CONTRAINDICATIONS: None.

CLINICAL TRIALS:

Here is the summary of the results of on-farm tests of application of **PUC***:

1. In the groups receiving PUC, the pain reactions were low and the stress/unwell feeling was decreased significantly.

2. The hard skin plaques in the cows receiving PUC had been reduced leading to softness of the breast tissue.

PARSIMENDARU
Herbal Medicines Development Group

IMMUNOFIN

(immune system enhancer, rumen microbiome regulator, antioxidant for calves)

COMPOSITION: **Immunofin** is a pure natural drug containing highly effective herbs such as Echinacea, Yarrow, Peppermint and few other herbs. The drug formulation has been supported by latest advances and researches on herbal active ingredients so that these compounds are formulated in such a way that their various components intensify each other's therapeutic effects in a synergistic manner. The most important ingredients in the drug are: Alkylamides (such as Isobutylamide, Methyl Butylamide and Cichoric/Chicoric acid), polysaccharides (Echinacin, Echinacoside), and terpenes (Citronellol, Caryophyllene).

MECHANISM OF ACTION:

Effect on the immune system:

The specific polysaccharides in **Immunofin** are immuno-stimulants so the drug excites effectively the "cell-mediated immunity" and prevents or even in some cases, treats diarrhea particularly in young calves by increasing serum and mucosal IgA levels. In addition to T lymphocyte, **Immunofin** can stimulate the activated mode or provoke the proliferation of B lymphocytes so the B cells starts to produce immunoglobulins such as IgG.

Improvement of the intestinal ecosystem/microflora:

Immunofin regulates gastrointestinal flora and improves the digestion so prevents bloating in lambs and calves. Some of the phytochemicals within **Immunofin**, are effective antibacterial and strong antivirus therefore can suppress the pathogens and improve the health and growth performance of lambs and calves by creating a balanced ecosystem. By eliminating the pathogens, the drug provides suitable conditions for useful gastrointestinal bacteria. The modified ecosystem causes the reduction of denaturation and the degradation of feed proteins by pathogen microorganisms. Thereby the drug prevents the nutritional deficiency, lack of vital feed supplements and nutritional competition between pathogens and useful microorganisms and provides an appropriate background for increasing the gastrointestinal population of useful bacteria.

Antioxidant activity:

Immunofin contains potent antioxidant compounds with modulatory effect on the expression and production of protein kinases, a group of enzymes which are affected during the oxidative stress and by the action of superoxide dismutase (SOD). Proteins are major targets of reactive oxygen species (ROS) and attacked then modified by free radicals although the modifications can be both reversible and irreversible. The SOD is a key part of the cells defense mechanisms against excessive production of harmful free radicals. SOD acts as the catalyzer and eliminator of the free radicals produced during oxidation processes (e.g. the free radicals due to oxidation of the lipids). Accumulation of free radicals within a cell can be resulted in protein modifications such as; degradation/denaturation/unfolding of proteins, protein aggregation, and protein deactivation/activation. The free radicals also induce cell membrane damage, DNA damage, production of pro- and inflammatory cytokines and injuries in key organs such as liver. The cell toxicity and tissue damages can be completely inhibited with the help of strong antioxidants present in **Immunofin**. The antioxidants within the drug prevent the accumulation of free radicals by activating the anti-oxidative defense mechanisms (e.g. SOD) in cell and therefore stop the detrimental effect of oxidative stress-mediated kinases/phosphatases imbalance.

THERAPEUTIC FEATURES: Herbal compounds within **Immunofin** have multi-purpose beneficial effects and can help to improve the immune system and health of calves and lambs through different pathways. The active ingredients present in **Immunofin** help to rapid clearing of the blood from the invading pathogens and fast resolution of infections due to good antimicrobial activity. Also **Immunofin** stimulates and modulates the immune system as an immunostimulator, and prevents the oxidative stress-induced damages and complications in the challenged animal as an antioxidant. Also, **Immunofin** decreases the incidence of gastrointestinal and respiratory infections, increases feed intake and regulates the intestine/rumen function, modifies the ecosystem of the rumen (favors the increased population of useful bacteria in the rumen), reduces mortality, improves the growth performance and maximizes the mean weight of calves. In fact, the drug can be administered for young animal, as a competent alternative for prebiotics and probiotics.

INDICATIONS: Strengthens the mucosal immunity, reduces the prevalence of bacterial/viral diarrhea in new born calves/lambs, modifies the rumen/gut microbiome towards the increased population of useful microorganisms, regulates the gastrointestinal function, and helps to faster development of rumen epithelium and better fermentation.

TARGET ANIMALS: Calf, lamb, foal and other young farm animals.

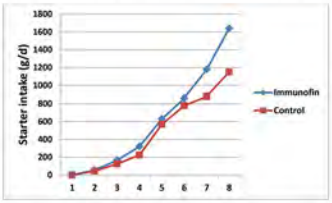
INSTRUCTIONS TO USE: The best outcome can be obtained if the drug is used in first days after birth but also it is okay if the drug is administered later. The drug dosage should be respected as follows: For calf, please add 10 ml of the drug solution each day to the milk or milk replacer. It should be started in newly born animal (from 3 days after birth) and maintained until one week after weaning from milk (transitioning the feed type from milk and starter to grain/forage and concentrate). In the case of applying the drug as the treatment for the gastrointestinal/respiratory diseases, please use a higher amount of drug daily until resolution of the illness as follows: add 15 ml of the drug into the milk or milk replacer for each head of the calves in the herd. For the lambs and kids, please use the drug under the supervision and advice of a DVM.

CONTRAINDICATIONS: None.

CLINICAL TRIALS:

We planned feeding the young (infant) calves with experimental diets from the birth time until weaning time. All calves of the experimental groups consumed the colostrum.

At first experiment, we evaluated the starter intake in two groups of calves; one was fed with a starter diet mixed with **Immunofin** (8 ml/day) and other group was fed with a routine diet (without **Immunofin**). The average total starter consumption of calves in **Immunofin**-treated group was significantly higher than that in both control and probiotic-treated groups ($P < 0.05$) (**please see Figure 1**).



At second experiment, the calves were divided in several experimental groups. Three groups of calves were fed with a starter diet containing **Immunofin** at three concentrations (4, 8 and 12 ml/day). A group of calves was received a starter diet containing a commercial probiotic (mixed into the starter) (probiotic-treated group) as a positive control, and a group of calves was just fed with milk and a standard starter (negative control group).

Then, some serologic indexes which are important in calf growth and health such as the serum levels of IgG, β-hydroxybutyrate and glucose (+ some other indices) were measured. In **Immunofin**-treated calves (at highest dose; 12 ml/day) the serum levels of IgG were increased significantly ($P < 0.05$) in comparison to both negative and positive control groups (**Please see Table 1**, the comparisons column). Although the lower doses of **Immunofin** causes an increase in IgG level but it was not significant ($P > 0.05$). Interestingly, the blood glucose level was decreased in **Immunofin**-treated calves, dose dependently. On contrast, the triglycerides (TGs) level was dampened significantly in **Immunofin**-treated calves compared to both negative and positive control groups ($P < 0.05$). In probiotic-treated group (positive control) most indices were not affected significantly (**Please see Table below**).

Parameters	Experimental groups					Pairwise comparisons		
	Negative control	Positive control	Immunofin (ml/d) 4	8	12	NC*PC	NC*IM	PC*IM
IgG (mg/ml)	10.7	11.2	13.3	13.6	15.7	0.85	0.04$^{\$}$	0.045$^{\$}$
βHB (mM)	0.197	0.2	0.215	0.218	0.222	0.45	0.3	0.4
Albumin (g/dL)	3.43	3.47	3.68	3.96	4.08	0.46	0.35	0.27
Glucose (mg/dL)	80.5	92.8	93	82.3	79.2	0.3	0.45	0.336
TG (mg/dL)	34.9	33.5	18	25.2	21.8	0.7	0.02$^{\$}$	0.04$^{\$}$

Abbreviations: NC, PC, and IM indicate negative control group, positive control group and **Immunofin**-treated group. The * symbol indicate that a statistical pairwise comparison was done. The mean values of **Immunofin**-treated calves at its highest dose (12 ml/d), was used for pairwise comparisons. The $ symbol means there was a significant difference between two groups ($P < 0.05$). The positive control calves received a commercial probiotic at the dose of 1 g/day. βHB and TG indicate β-hydroxybutyrate and triglycerides, respectively.

Equine

PARSIMENDARU

PARSIMENDARU
Herbal Medicines Development Group

ARTHIWELL

(anti-inflammatory, pain-reliever, heating effect)

COMPOSITION: **ArthiWell** is a pure natural herbal remedy consisted of active ingredients in lavender, marigold (*Calendula officinalis)*, ginger and few other medicinal herbs. In addition, *Mentha piperita* was incorporated in the drug with an accurate and adjusted concentration to induce a controlled local heating effect in synergy with Ginger. The drug contains a precisely selected collection of herbal active ingredients as well as the classic natural wound healing and skin softening remedy; honey (with beeswax). So the components can strengthen and amplify each other's therapeutic effects in a synergistic manner. Major ingredients of the drug are Caffeic acid, Helenalin, Gingerol and Menthol.

MECHANISM OF ACTION: The active ingredients in the drug, show strong antimicrobial effects (both anti-bacterial and antifungal), and have extraordinary anti-inflammatory, analgesic (pain-relieving) and wound healing properties. In addition, the drug can efficiently reduce the swelling and edema at the inflammation site by speeding up the blood flow and blocking the inflammation signals at the molecular level. The greater blood flow in the inflammation site causes more immune cells to reach the infection site and therefore helps the animal to confront the infection. Flavonoids and saponins of the drug prevent the release of harmful enzymes and histamine. Histamine causes sensitization, chemotaxis of inflammatory cells, stimulatory feedback on mast cells and other inflammatory cells, cytokine/chemokine storm and swelling (edema). The drug interrupts the histamine functions by decreasing the capillary permeability and preventing the plasma leakage into the tissues (i.e. edema) and therefore hinders worsening of inflammation and development of swelling. The drug alleviates efficiently the pain due to the presence of Menthol which directly targets the cold sensing and neural receptors. In addition, unlike the synthetic antibiotics, the bacterial resistance against Menthol is very rare due to unique structure of the ingredient. Additionally, other accompanying antimicrobial compounds in the drug form an effective synergy with Menthol in combating the resistant pathogens. Menthol, some of the monoterpenoids as well as some natural compounds such as gingerol have been known to be capable of binding or at least affecting the structural arrangement of the cold/heat receptors. The molecules show dualistic effect and the final result is dependent mainly on the concentration of the molecule or the type of the receptor. Gingerol has a similar structure to capsaicin and piperine which are found in peppers. By considering the dose-dependent variable effects of mentioned compounds on the cold/heat receptors, we have carefully determined and adjusted the concentration of the menthol and gingerol in **ArthiWell**, to be sure the drug can induce a good mild heating effect when applied topical. The drug is also enhanced to be capable of penetrating deep enough in the skin and underlying tissues and also in the synovial fluid.

Horses are naturally strong animal with usual intense physical activities and therefore are readily prone to physical injuries/traumas. At the case of joint-related diseases such as arthritis or joint inflammation, the drug disrupts the mast cell-histamine axis and immediately blocks the release of inflammatory mediators and reduces the pressure of the synovial fluid. The phenols, monoterpenoids and flavonoids of the drug are responsible for the therapeutic action in joint-related diseases. In addition, the drug is strong enough in treating any other types of injuries such as the damages due to physical over-activity (e.g. bruises, sprains, and overexertion), accidental traumas/wounds, and saddle injuries.

THERAPEUTIC FEATURES: The pure natural **ArthiWell** has strong pain-relieving and anti-inflammatory properties due to incorporation of specific herbal substances, capable of rapid dermal absorption. The analgesic (pain-relieving) activity of **ArthiWell** was dramatically enhanced in comparison to similar drugs by carefully determining the ingredients composition and incorporation of very strong anti-pain and sedative compounds such as Eugenol, and menthol. The drug also contains honey and beeswax, flavonoids and alkaloids, making the drug a highly effective wounds healing remedy. The drug can also aid the circulation and induce a local mild heating effect.

INDICATIONS: The drug can be used to reduce the inflammation and edema at the wound or inflamed site. So, **ArthiWell** is suitable for providing the sustainable recovery from a painful wound/injury. The drug is a good choice for healing the damages due to high physical activity such as bruises, sprains, sore muscles and inflamed insect bite, saddle injuries. In addition, the drug is best choice for treating local inflammatory diseases such as joint inflammation and laminitis.

TARGET ANIMALS: Equine (Horse)

INSTRUCTIONS TO USE: Please rub a thin layer of the cream on inflammation/trauma site every 8 hours until the symptoms disappear. Please do not apply the cream on fresh scars.

PARSIMENDARU
Herbal Medicines Development Group

AFTOFIN

(healing the dermal and mucosal injuries, saddle injuries, and healing the traumatic or infected wounds)

COMPOSITION: Aftofin is a pure natural herbal remedy made of Peppermint, Myrtle, and few other medicinal herbs. The drug contains an intelligent blend of herbal active ingredients so that its components can strengthen and amplify each other's therapeutic effects in a synergistic manner. One of the most effective ingredients in this product is flavonoids.

MECHANISM OF ACTION: **Aftofin** is very rich in a series of unique herbal ingredients. It contains phenols (phenolic acids), tannins (proanthocyanins) and flavonoids. Anthocyanins are powerful antioxidants that actively prevent the harmful effects of oxidation reactions and free radicals. One of the effective phenols in this product is Caffeic Acid which has a strong antioxidant effect. Also, another polyphenolic found in the Myrtle Extract and present in the product, is Gallic acid. It has a strong antioxidant effect similar to Caffeic Acid. Also, the flavonoids of the **Aftofin** such as Myricetin and Quercetin and Catechin have impressive anti-inflammatory and antimicrobial effects. There are also other significant active ingredients within **Aftofin**. For instance, menthol has several beneficial effects, including anti-inflammatory, pain relief, and a feeling of coolness in the inflammation site. In short, by the four mechanisms **Aftofin** improves the health condition of the animal challenged with infection and dermal/mucosal ulcers. First, by relieving pain and reducing the temperature of inflammation and infected site, it can relieve the feelings of illness and stress and restore the animal's appetite, and subsequently boost the animal health due to better feed intake. Secondly, some herbal substances within **Aftofin** show a direct antiviral effect, and therefore can reduce the load of viruses, weaken the ability of viruses in attacking the cells and ameliorate the damage of viruses to the tissues and organs. Third, the strong antioxidants in this drug, especially the phenolic acids and anthocyanins, neutralize the toxic free radicals in the inflammation and ulceration site. The over-proliferation of viruses and over-production of free radicals are the most significant causes of progression and resistance of mucosal ulcers, which, by inhibiting the two, **Aftofin** helps the immune system and accelerates the repairing processes and wound healing. And finally, the fourth way the drug shows its action is through the stimulating the repairing/restorative cells, such as fibroblasts. Some herbal ingredients within **Aftofin** are in fact attractants and propel the fibroblasts to migrate towards the wound site and there produce specific fibers such as collagen, elastin and fibrin, resulting in the recovery of the connective tissue at the ulcer/wound site. Reconstitution of connective tissue is a fundamental step in wound healing and therefore provides the basis for full resolution of the wound.

THERAPEUTIC FEATURES: **Aftofin** can rapidly treat all kinds of dermal/mucosal blisters, erosions, blisters, vesicles and rashes. It also heals the ulcers on the skin, lips, mouth, nose, sheath and udder which formed due to viral/bacterial/fungal primary/secondary infections. It acts as a natural antimicrobial agent with great antibacterial (gram positive and negative), antifungal and antiviral properties, even at low concentrations. Also, it has an impressive healing effect on tongue and mouth ulcers and wounds. In addition, **Aftofin** have an impressive pain-relieving and calming effect in animal challenged by painful sores/ulcers on their tongue, mouth, skin and feet (hoof).

INDICATIONS: The drug can be used as the complementary/symptomatic treatment for erosive and ulcerative diseases such as Vesicular Stomatitis Virus (VSV) and any other diseases with mucosal/dermal symptoms. The drug is mainly a symptomatic treatment although it has strong antiviral activity. Its antiviral activity is limited to local administration. Therefore, the drug can be used as a complementary treatment for traumatic superficial wounds/ulcers on the skin/mucosal surfaces. However, the drug is not recommended to be applied directly on the deep wounds.

TARGET ANIMALS: Equine (Horse)

INSTRUCTIONS TO USE: Please shake well the spray bottle before use. Then, spray the drug from a safe distance onto the wound or the infection site; in the case of VS, spray it all over the mouth and tongue. It is recommended to repeat the procedure twice a day until complete healing/recovery. For a better response, it is suggested that to rinse the inflammation/wound site with distilled water or saline to remove the debris before spraying the drug. In fact, it is better to do a wound debridement if there is a necrosis layer on the wound. Moreover, in cases where the animal is severely affected, the spray repeats should be increased up to 2-3 times a day. If the treatment strategy contains both the topical antibiotic and **Aftofin** please first apply the topical antibiotic then spray the **Aftofin** on the wound site.

CLINICAL TRIALS:

Effect on oral vesicles:

Aftofin was used to treat oral blisters/vesicles formed during viral infection. By using the drug at primary stages of the disease, a good pain-relieving/antinociceptive effect was induced; the appetite and feed intake were restored. Inflammation was dampened and the healing period was significantly reduced in **Aftofin**-treated animals compared with the non-treated (control) group.

Aquaculture

PI222

anesthetic, analgesic, sedative/pain reliever

PARSIMENDARU
Herbal Medicines Development Group

COMPOSITION: **PI222** contains well-known herbs with anesthetic properties (such as Clove) formulated by the support of state of the art knowledge of herbal medicine. The major active ingredients of the drug are Eugenol, Carvacrol, and Eugenol acetate which were equipped together with a precise concentration optimized for fish.

MECHANISM OF ACTION: An appropriate anesthetic for use in aquaculture should have certain characteristics, including: water-soluble, capable of inducing rapid and stable anesthesia, rapid recovery (short time of returning to normal state), no complications and stressful stimulation (e.g. Ketamine causes hyperactivity/hypersensitivity during recovery), no toxicity against human and environment, safety and wide margin between inductive and lethal doses, low cost, and availability. Anesthesia in fish is established with the goal of undergoing fisheries operations such as vaccination, examination, insemination, medical injection/intervention, surgery etc. At the normal state, any physical intervention on fish induces high level of stress and shock which can result in interruption of normal growth and higher incidence of infections. Thus, anesthesia in aquaculture is used for prevention of harmful effects of some manipulations which are routinely done in fisheries. The depth of anesthesia in fish depends on type and dose of the anesthetic drug, and can be ranged from a slight anesthesia; loss of sensation, sedation, reduction of mobility then loss of equilibrium and then full loss of sensation without reflexes and eventually medullary collapse (even death). In brief, the anesthesia in fish can be ordered in three stages including; sedation, handleable, deep anesthesia. The progression of anesthesia is directly dependent on drug dose. If the anesthetic drug dose was higher than the amount of the drug which is metabolized and cleared then the fish can reach deeper stage of anesthesia. Many synthetic anesthetic drugs have side effects and their remaining metabolites may persist for a long time in the tissues and organs of fish, which eventually they will be transmitted to humans by consumption of fish products, which is undesirable in terms of health principles. For this reason, within past years, much attention of fish farmers and scientists was drawn to natural or herbal medicine with the goal of reducing the pain, and inducing safe anesthesia in fish. Clove has been among the plants with many refers to it strong anesthetic properties. Clove is traditionally used by fish farmers and aquaculture industries, but the dosage and method of use vary according to the opinion of each farmer, and therefore unexpected outcome (e.g. lethal) or even no activity have been frequently observed during using the Clove plant material for anesthesia which is the result of inappropriate or misuse of the plant material, wrong dosage (low or high doses), and using the insoluble form of the plant material.

For this reason, **PI222** has been precisely formulated with adjusted dosage and accurate amount of herbal substances. In addition, non-toxic solvents, stabilizers, emulsifiers and co-emulsifiers have been incorporated in the drug composition, making the drug completely stable, safe and soluble. In fact, **PI222** is a combination of various herbal substances (Clove + several other herbal compounds) which act in a synergistic manner and enhance the anesthetic effect while reduce the side effects. The main ingredient within clove is Eugenol, which is usually accompanied by its derivatives such as Acetyl-eugenol. Interestingly, Eugenol has a structural similarity to some of the most famous anesthetics such as Lidocaine and Procaine. This structural similarity makes Eugenol capable of inducing anesthesia in a similar way to some of the conventional anesthetics.

There is a chemical group in the structure of Eugenol called Vanillyl moiety. Vanillyl branch which its full chemical name is 4-hydroxy-3-methoxy-benzyl, also is present in some well-known anesthetics belonged to amino-amide anesthetics.

Aquaculture

The Vanillyl-based molecules are also known as Vanilloids, can target the cells through a group of receptors called TRP, and in particular a member of these receptors, called TRPV1.

These receptors are present on the membrane of many types of cells, including immune system cells, vascular epithelial cells, smooth muscle cells as well as neurons. In neurons, the receptors affect the membrane transport of sodium ions, and therefore control the resting/action potential. Thus, vanilloids, such as capsaicin and eugenol, induce anesthesia by stimulating these receptors on the neurons. It has been discovered that eugenol is also capable of stimulating the TRPA1 in a non-specific manner which improves its anesthetic effect considering the fact that the TRPV1 is the specific target of the eugenol.

In addition, the superiority of eugenol against capsaicin is its capability to be used safely on the dermal/mucosal surfaces without any irritating impact. Moreover, Eugenol can stimulate other types of receptors/channels on neurons, such as voltage-gated calcium channels (VGCCs), sodium channels, NMDA receptors, and gamma-amino-butyric acid receptors (GABAAs). Each of these receptors also plays an important role in controlling the neurons activity, inducing the membrane depolarization and facilitating the neural message transmission. Also, Eugenol can stimulate powerful GABAAs. The opening of these ligand-gated ion receptors after the binding of eugenol as a ligand induces the entry of negative chlorine ions into the neurons and thus reduces the threshold required for initiation of an action potential. Alcohol and Diazepines reduce the stimulation threshold of neuronal system through the same receptors and therefore cause relaxation. On the other hand, eugenol also has anti-inflammatory and relaxing effects, and by blocking the danger/stress signals, it inhibits the activation processes within the immune system cells, and therefore the production and release of toxic substances such as nitric oxide as well as the release of inflammatory mediators such as chemokines and cytokines are decreased during any stressful period. Thus, eugenol causes relaxation, relief, sedation and anesthesia in fish through direct action on several types of receptors as well as through its direct action on the intracellular molecular pathways in immune system's cells.

THERAPEUTIC FEATURES: **PI222** contains sedative, analgesic and anesthetic herbal active ingredients. Eugenol as the major compound in **PI222**, is a strong anesthetic agent. However, the level of anesthesia is dependent on the dosage which is applied on the fish. Moreover, Eugenol and few other compounds within the drug are not only the anesthetic but are also anti-inflammatory, anti-microbial, and relaxing.

INDICATIONS: the drug can be a slight sedative or deeply anesthetic in a dose-dependent manner. So, in a dose-controlled way, it can reduce the stress and has a good calming effect during the transportation, blood sampling, disinfecting the ulcers, vaccination and injections. By applying a higher dose of the drug (according to dosage instructions), a deeper anesthesia can be reached. Thus serious medical interventions such as surgery can be done by induction of a deep anesthesia using the **PI222**.

TARGET ANIMALS: The drug can be used in Aquaculture and for any fisheries operations.

INSTRUCTIONS TO USE: Monitor the movements and physiologic reflexes of the fish until reaching to the desired level of anesthesia. Expose the fish to the drug for at least 1 min by gently transporting the fish into the drug-containing water in a separate container. The following dosages are approved for a medium-weighted adult rainbow trout. Please choose the appropriated dose for your fish based on mean weight of the fish under supervision of a DVM or an expert in aquaculture medicine. Please carefully follow the dosage instructions:

1. **For a slight sedation:** mix 1 ml of **PI222** per 35 liters of the water.
2. **To reach a handleable level of anesthesia:** mix 1 ml of **PI222** per 15 liters of the water.
3. **For a deep anesthesia:** mix 1 ml of **PI222** per 5 liters of the water.

CONTRAINDICATIONS: None.

IMMUNOFISH

PARSIMENDARU
Herbal Medicines Development Group

(immunostimulator, anti-inflammatory, stress reliever)

COMPOSITION: **Immunofish** is a pure herbal medicine that is made up of active ingredients from some of the most valuable herbs (mainly; Echinacea) with the goal of maximizing the immune system functions. The most important constituents are alkylamides (aka alkamides), Cichoric (aka Chicoric) acid, polysaccharides, and terpenes.

MECHANISM OF ACTION: Alkamides of echinacea are the major compounds responsible for the inhibition of the cyclooxygenase and lipoxygenase pathways in epithelial and immune system cells. The pathways are involved in biosynthesis of inflammatory prostaglandins (PGs), such as PGE2. Therefore, inhibiting the pathways resulted in halting the production of PGs. Subsequently, lack of PGs will give more freedom to the Natural Killer cells (NK cells). Then the cells will kill the target cells by releasing high levels of toxic substances near them. The target cells are abnormal or dying cells or microbes/germs which are detected by NK cells. On the other hand, echinacea contains oligomeric substances called polysaccharides (PSs) capable of regulating the immune system. Among PSs, Arabinogalactan (AG) can directly bind and activate a class of receptors on innate immune system cells such as macrophage called pattern recognition receptors (PRRs) which are responsible for the recognition/detection of microbial antigens (patterns). In fact, AG mimics the antigens of the bacteria due to its structural similarity to the PSs present in bacterial cells wall. Therefore, AG activates the phagocytes of innate immune system and also stimulates them to produce and release large amounts of inflammatory cytokines such as IL-1 and TNFα. The inflammatory cytokines can efficiently recruit the immune system cells to the inflammation site as well as acting as the feedback messengers by activating the phagocytes (macrophages and neutrophils) and NK cells.

In addition, it has been shown that alkyl amides of the echinacea, can directly bind to certain receptors on the surface of lymphocytes such as CB2. In fact, the alkylamides have been known as the cannabinomimetics due to structural similarity to cannabinoids. Some alkylamides have shown stronger affinity to bind CB2 receptors than the endogenous cannabinoids. At molecular sight, binding of alkylamides to CB2 receptors leads to activation of the nuclear transcription factor (NF-kB) through intracellular adaptors (signal messengers). Some of the most important intracellular pathways which are triggered by the alkylamides are cAMP, MAPKs, and the calcineurin pathway. Prompting the NF-kB also triggers the transcription of genes encoding cytokines such as IL-3, IL-4, IL-5, IL-10, TNFα. There is two ways for the receptor-mediated activation of T cells. In one possibility, the T lymphocytes both CB2 and TCR receptors are stimulated by their ligands simultaneously in which it leads to decrease in production of inflammatory cytokines and activation of a type of T lymphocytes called cytotoxic T cells, instead in second possibility, if T cells were co-stimulated by binding the ligands to both CB2 and CD28 receptors, then higher levels of cytokines will be produced which in turn (acting as the positive feedback agents), the cytokines activates more T cells (to produce more cytokines) and also phagocytes.

Aquaculture

THERAPEUTIC FEATURES: The drug as a wide spectrum herbal remedy has many beneficial health effects. The drug can be used in healthy fish during the growth period for boosting their immune system and prevention of infectious diseases. A well-tuned immune system itself causes better function of organs and enhanced growth rate. The drug also has a good calming effect and prevents the interruption during growth period due to stresses or extreme environmental stimuli.

INDICATIONS: **Immunofish** can be used 1-3 day(s) before any physical interventions on fish (blood sampling, surgery, vaccination etc.) until 3 days after the event. Also, the drug can be applied over whole growth period of the fish to prevent the infectious diseases and boost the health performance.

TARGET ANIMALS: fish.

INSTRUCTIONS TO USE: the drug can be used in the following schedule:

1. Use a routine 200 ml/ton feed all over the growing period
2. Use 1 liter/ton feed for one week each month during the growing period
3. Use 1.5 liter/ton feed, two weeks before a vaccination program.

CONTRAINDICATIONS: Should not be used at the same time with vaccination.

CLINICAL TRIALS: A number of fingerlings of rainbow trout *(Oncorhynchus mykiss)* (n=1200) with a mean starting weight of 20 ± 2 g were cultured in the fish farming pools with a routine diet. The fishes were divided into two experimental groups, each was planned in triplicate. A group received a diet containing an herbal treatment as following: standard feed was mixed with **Immunofish** at a ratio of 1.5 %. Also, there was a control group without **Immunofish** (negative control). The fishes were kept and cultured for 60 days. At the end of the study, the growth factors, immunological tests including measurements of serum level of lysozyme, bacteria killing potency of serum, serum level of IgG and mucosal level of IgA were measured. The results showed that the fishes treated with **Immunofish** (Echinacea) have gained a significantly better growth performance compared to the control group (Please see Table 1). Also, the level of lysozyme activity and serum bactericidal/killing potency were significantly increased in **Immunofish**-treated group in comparison to non-treated control group ($P < 0.05$). In addition, in **Immunofish**-treated fish, the mucosal level of IgA was increased dramatically ($P < 0.01$, highly significant) and the IgG levels was also elevated significantly ($P < 0.05$).

Table 1. The table shows the measurements of some biologic indices in the rainbow fish which were separated to two groups; one was fed with a diet containing **Immunofish** and the other just fed with routine diet.

Variables	Experimental groups	
	Immunofish	Control
Initial weight (g)	21.18±1.8	21.27±1.65
Mid weight (g)	51.66±3.2	40.19±3
End weight (g)	74.94±5.5	53.65±3.1
Initial length (cm)	11.33±0.75	11.42±0.08
Mid length (cm)	20.52±1.5	15.25±1.1
End length (cm)	22.1±1.65	19.8±1.3
Feed conversion ratio	1.1±0.12	1.9±0.17
Specific growth rate	1.1±1.08	0.8±0.05

Abbreviations; Mid indicates the measure of a variable in the middle of growing period, and End means the measure of a variable at the end of the growing period.

ANTIBIOFISH

(natural multifunctional antibiotic; antibacterial, antiviral and antifungal)

PARSIMENDARU
Herbal Medicines Development Group

COMPOSITION: **Antibiofish** is a pure natural drug composed of highly potent therapeutic herbs such as Thyme *(Thymus vulgaris)* and Ajowan *(Trachyspermum ammi)* and few other herbs. The drug has been made of effective herbal active ingredients which are carefully formulated with the support of latest advances in herbal medicine. The drug was created by a smart team of scientists with the goal in mind that the drug components can enhance each other's therapeutic effects in a synergistic manner. The most important constituents in the drug are phenolic compounds such as Thymol, Carvacrol, Paracymol and Cineole.

MECHANISM OF ACTION: **Antibiofish** contains a large amount of terpenoid phenols such as Thymol and Carvacrol. The natural substance; Thymol is now accepted in the EU standards as an effective antimicrobial agent but harmless for humans. Both Thymol and Carvacrol are classified as monoterpenoids, since they have a carbon ring and oxygen (hydroxyl group) functionality. Evidences such as the images of the electron microscope have shown that these two monoterpenoids can be directly enclosed within the cell wall of the bacteria and, by disrupting its structure, increase the permeability of the cell wall of the bacterium. The Thymol and Carvacrol molecules are lipophilic and also have a small molecular size. They are almost similar but the only difference is the location of hydroxyl group on the hexagonal carbon ring. This structural difference makes the thymol more hydrophobic and Carvacrol more biologically active. Hydrophobic and lipophilic nature of the both molecules makes them very prone to be absorbed into the bacterial cellular membrane which is made of two-layer phospholipids. As a result, Thymol and Carvacrol can disrupt the structural order of the membrane (i.e. alteration of membrane fatty acids). Thus, the replacement of Thymol and Carvacrol into the cell membrane of the bacteria will mess up the regular structure of the membrane components, and the fatty acids will separate from the membrane. Following these changes and damage to the cell membrane, vital intracellular contents of the bacterial cell such as the metabolites and ions leak out of the damaged membrane. By the direct effect of Thymol and Carvacrol on bacterial cell wall proteins and molecules, shrinkage and coagulation in the bacterial wall will occur and lead bacteria to die.

The most important and deadly effect of Thymol and Carvacrol on bacterial cell wall is their capability to create pores in the membrane structure, which causes the leakage of vital substances from the bacterial cell due to a much higher osmotic pressure within the bacterial cell than the pressure in extracellular matrix. According to recent knowledge, natural antibiotics such as Thymol and Carvacrol have proven antimicrobial effects, and the drugs based on these compounds can prevent the development of various types of infectious diseases. In addition, **Antibiofish** not only can protect the fish from internal/systemic infectious diseases but also can disinfect the environmental water where the fish were cultured. By disinfecting the water, the drug can also protect the fish from dermal infectious diseases.

THERAPEUTIC FEATURES: active substances of **Antibiofish** inhibit the growth and proliferation of bacteria and pathogenic fungi, particularly in the gastrointestinal tract and the dermal surfaces. These substances physically manipulate the structure of bacterial cell wall and therefore do not induce drug resistance in bacteria, so the drug can be used to prevent diseases in an optimal way. It can also show a synergistic effect when accompanied with other antibiotics to prevent the progression of the diseases.

INDICATIONS:

- Prevention and treatment of gastrointestinal tract and dermal infections without emergence of drug-resistance and reducing the recovery time
- Prevention of the progression of the infectious diseases (without interrupting other drugs function, no contraindications)
- Acts as an effective growth promoter
- As a water disinfectant can be used in fish farming pools

Aquaculture

TARGET ANIMALS: Fish.

INSTRUCTIONS TO USE:

1. For the prevention of bacterial diseases, please mix 100 ml of the drug in 100 kg of the feed.
2. For the prevention of fungal diseases, please mix 2 liters of the drug in 1000 liters of the pool water.

CONTRAINDICATIONS: Should not be used at the vaccination time.

CLINICAL TRIALS:

Clinical trial with **Antibiofish** was done on rainbow trout in two separate experimental plans. In first plan, fishes received the drug before challenging with a bacterial infection and in second plan; fishes received the drug after infection. The results are as follows:

1. Pre-infection treatment: Fishes (n=10) of each separate group received **Antibiofish** (i.e. mixed in feed) in a different concentration (T3; 2mg/kg feed, T2; 1mg/kg feed, T1: 0.5mg/kg feed) and maintained for two months. The control fishes just fed with a normal diet without drug. At the end of the growing period, fishes were infected with *Yersinia ruckeri* (KC291153). The mortality rate after 10 days (of infection) was measured. The mean death count in **Antibiofish** -treated fishes (all concentrations) was significantly lower than that in control fishes ($P < 0.05$). The results were concluded in the table below:

Table 1. The table shows the death count (mortality rate) in infected fishes.

Replicates	Treatment groups			
	T1	T2	T3	Control (no drug)
Rep1	6	5	6	10
Rep2	5	5	6	10
Rep3	5	5	5	10

Abbreviations; Rep1, 2, and 3 indicate the replicate number. T1, 2, and 3 indicate the number of treatment groups.

2. Post-infection treatment: Fishes (n=10) of each group was infected with *Yersinia ruckeri* and after 24 h, they treated with diet containing **Antibiofish** at three different concentrations (T3; 2mg/kg feed, T2; 1mg/kg feed, T1: 0.5mg/kg feed) and maintained for 10 days. For control fishes, a commercial routine antibiotic (Florfenicol) was administered. The mortality rate after 10 days (of infection) was measured. The mean death count in **Antibiofish** -treated fishes (all concentrations) was significantly lower than that in control fishes ($P < 0.05$). The results were concluded in the table below:

Table 2. The table shows the death count (mortality rate) in infected fishes.

Replicates	Treatment groups			
	T1	T2	T3	Positive control
Rep1	5	6	5	10
Rep2	6	5	5	10
Rep3	6	6	5	10

Abbreviations; Rep1, 2, and 3 indicate the replicate number. T1, 2, and 3 indicate the number of treatment groups. The fishes in positive control group were fed with a diet containing a commercial drug similar to **Antibiofish**

BIOHERBAL

(appetizer, growth promoter, gut flora regulator for aquaculture)

PARSIMENDARU
Herbal Medicines Development Group

COMPOSITION: Bioherbal is an innovative blend of active ingredients from garlic, thyme, peppermint, lemon balm *(Melissa officinalis)* and few other medicinal herbs. The active ingredients of the drug were selected by spending special solicitude so that its components can boost each other's therapeutic effects in a synergistic manner. The composition and the amount of the ingredients have been carefully evaluated and optimized to be used in aquaculture. Sulfur compounds (e.g. allicin, ajoene, allyl sulfides, and vinyldithiins) are responsible for most of the biologic activities and also the characteristic odor of the drug.

MECHANISM OF ACTION:

Increasing the appetite, growth, performance:

Improving the gut mucosal immunity, gut flora and appetite is dependent on several factors. One of these factors is the microbial composition of gut flora. Some natural substances in **Bioherbal** such as thyme and peppermint are multifunctional and can directly increase appetite through the receptor-mediated mechanisms and also direct the microbial composition of the intestines towards an increased population of useful bacteria. So the population of infectious/pathogen microorganisms reaches zero or very low and the number of beneficial microbes capable of catalyzing the complex nutritional molecules and producing new useful nutrients is also increased. Some ingredients within **Bioherbal**, such as Carvacrol and Menthol, have well-known neuro-therapeutic effects. These effective herbal agents can stimulate specific receptors on neurons. Stimulation of these receptors affects the parasympathetic pathway and as a response, it causes an increased appetite while it also induces the calming and anti-stress effects in fish. Therefore the drug initiates a stimulatory pulse in neurons and then the pulse is transmitted through the parasympathetic nerves towards the ventromedial hypothalamus (VMH). The hypothalamus perceives the hunger and so if is stimulated, it will increase the appetite and therefore increase the feed intake (FI). Moreover, the phytochemicals such as those are present in **Bioherbal** can increase the appetite through a second method; by stimulating the neural receptors in the gastrointestinal mucosa, a specific neuropeptide called Neuropeptide Y (NPY) is released. NPY reaches to VMH through bloodstream and stimulates it which at the end causes an increase in the appetite and FI level.

Modifying the intestinal eco-system (gut flora) and improving the feed absorption:

On the other hand, phytochemicals such as Carvacrol, Thymol are known as strong antibacterial, antifungal, and antiviral agents and can selectively suppress the pathogen microbes in fish intestines without affecting the beneficial bacteria. As a result, by reducing the pathogens and creating favorable conditions for the growth of beneficial bacteria, this group of bacteria can take place and increasingly grow in the intestines and therefore in other words, the drug acts as a kind of efficient prebiotic. Therefore, by adding the **Bioherbal** into the water of fish farming pools, at first stage, it disinfects the water of the pools and then it reduces the saprophytic (opportunistic) microbes (bacteria and fungi) reside on the fish body surface and on the gills; it modifies the superficial microbial composition and provides the favorable conditions for growth of the useful bacteria. After being consumed by fish, **Bioherbal** also destroys the intestinal pathogens and after absorption in circulation, it will eliminate the microbial invaders present in tissues and bloodstream.

As a result, reduction of gut pathogens leads to remaining of more available nutrients. On the other hand, even more nutrients are also produced by useful microbes in the intestines. Subsequently, less toxic substances are produced in the intestines, more nutrients are available for the fish and by reducing the local mucosal inflammation in the intestines, absorption of nutrients will be efficiently improved. Moreover, the drug prevents any damages to the intestinal villi due to pathogens, and it provides the suitable conditions for better development and growth of intestinal villi and crypts. Also, it causes more secretion of digestive enzymes and therefore enhances the feed absorption ratio.

THERAPEUTIC FEATURES: **Bioherbal** can effectively improve the appetite and increase the FI by stimulating the neural pathways and neurotransmitters involved in the triggering the appetite. It was approved that some of the herbal active ingredients are ligands of specific receptors on neurons, mucosal epithelial cells and immune system cells. These ingredients which were also incorporated within the **Bioherbal** composition can directly bind and transmit the stimulatory signal to the target cells. Thus, the drug not only acts as a highly strong appetizer but also can enhance the gastrointestinal functions by increasing the gastric secretions and intestinal absorption. The drug also contains antimicrobials which there are not bacterial resistance reports against them until today. Therefore, the drug also can balance the population of useful and pathogen microbes in gastrointestinal tract.

INDICATIONS: The drug can be used to stimulate effectively the appetite and increase FI, to enhance the health condition, promote the growth ratio, regulating the gut functions, modifying the gastrointestinal flora by preventing proliferation of pathogens, and prevention of gastrointestinal infectious diseases.

TARGET ANIMALS: aquaculture.

INSTRUCTIONS TO USE: The drug is available in both powdered and liquid forms. Please mix 100 g of the powdered drug per 100 kg of the feed/diet according to advisement of expert (doctor of veterinary medicine) or dissolve 100 ml of liquid drug into the 100 kg of feed/diet.

CONTRAINDICATIONS: Not to be used at the vaccination time.

CLINICAL TRIALS:

Clinical trial with **Bioherbal** was done on rainbow trout in two experimental treatment groups and a control group. A group of fishes (n=30) received the drug at low concentration (1 mg/kg feed) and the other, was fed with a diet containing high dose of drug (2 mg/kg feed). The control group was just fed with a standard fish diet without drug. After two months of growing period, the growth indicators were measured. Interestingly, we found that the growth indices were dose dependent and at higher doses better results were obtained. The final weights at both **Bioherbal** doses were significantly higher than that in control group ($P < 0.05$) (Please see Table 1). The results are as follows:

Measured parameters	Treatment groups		
	Bioherbal (low dose)	Bioherbal (high dose)	Control
Final weight (g)	147.1±11.5	155±12.8	125.7±8.4
Feed conversion ratio	1.02±0.12	1±0.1	1.21±0.11
Final length	22.9±3.3	23.53±2.7	22.4±3
Temperature-based Antibiofish growth rate	0.187±0.02	0.194±0.03	0.168±0.02
Survival rate	94.5±13.4	95.17±11.5	88.37±10.1

Honey Bee

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VARROCIDE

(acaricide, scabicide, mite killer)

COMPOSITION: **Varrocide** is a pure herbal drug composed of active ingredients from two phenol-rich herbs including thyme and lavender, and some other medicinal herbs with the goal of eliminating the mite *(Varroa destructor)* contamination in beehives. **Varrocide** contains highly potent antimicrobial, acaricide and insecticide compounds. The most important ingredients in this drug are phenolic compounds such as thymol, carvacrol and linalool.

MECHANISM OF ACTION: **Varrocide** contains two very strong phenolic substances called thymol and carvacrol. A wrong concentration of the ingredients can result in toxicity to honey bees. Therefore, concentration of two phenols which are mainly present in the thyme essential oil, was precisely determined and incorporated in the final drug. **Varrocide** also contains linalool and some other monoterpenoids which are usually found in lavender essential oil and have significant antimicrobial activities and similar to thymol and Carvacrol, have specific strong smell. One beneficial superiorities of the **Varrocide** is its dual effect on both mites and honey bees; it destroys the mites while empowers the bees against infectious diseases. **Varrocide** exerts its acaricidal activity though two ways. The first method is to interfere with olfactory sensors of the ticks. Mites can recognize the bees by sensing the specific smell of the bees, then ride on the bee's body. Naturally occurring phenolic compounds and some aromatic substances present in the thyme and lavender essential oil have a very strong odor. These phenolic substances stick with tentacles and olfactory sensors, interfere with the operation of the sensors, and eventually confuse the tick to find and ride on the bees.

Thymol as one the major active ingredients in **Varrocide**, can sensitize the GABA-activated RDL receptors of the Varroa mites to be readily activated by other aromatic substances present in **Varrocide** such as phenolics and monoterpenoids. This forms a synergy between the aromatic active ingredients of the **Varrocide** and as a result, the drug can interrupt the olfactory system of the mite and therefore the mite will be strayed and also lost the bees. Thus, a short time after applying the **Varrocide**, the mites will be highly sensitized to all odors present in the beehive environment and as a result, the normal function of their chemo-sensing and olfactory systems will be disrupted. In addition, other natural ingredients in **Varrocide**, including Carvacrol and α-terpineol can specifically target the TRPA1 receptor in Varroa mites. Stimulation of TRPA1 receptor disrupts the normal function of the nervous system in gastrointestinal tract and also decreases the reproduction capability of the mites. On the other hand, **Varrocide** also contains an herbal substance called linalool. Similar to other phenolics, it can affect the chemical and olfactory receptors of the tick, but it also has a distinct and deadly feature. It can penetrate into the mite internal circulation (called hemolymph) and cause poisoning and death. Additionally, it profits from its strong antimicrobial properties and therefore it can disinfect the hive environment, and prevent the bacterial and fungal infectious diseases in bees.

THERAPEUTIC FEATURES: **Varrocide** is an herbal remedy with strong acaricide and ectoparasiticide activities. Its specific target is *Varroa destructor*; the most important parasite of the honey bees. The drug has no side effects which usually seen by using chemical anti-mite drugs; such as remaining residues in bee body and accumulation in honey and beeswax, and does not cause fungal or bacterial resistance, and therefore is safe for honeybees and humans. It should be noted that the drug has an herbal source contains the controlled amount of ingredients; therefore, it does not affect the quality and hygiene of honey.

INDICATIONS: For the prevention and treatment of parasitic diseases of the bee (e.g. *Varroa destructor*).

TARGET ANIMALS: Honey bee.

INSTRUCTIONS TO USE:

Spray the drug directly onto the bees in the space between the combs in which each comb side should receive sufficient amount of the drug for all the residing bees; 30-50 ml per hive that should be equally sprayed in comb sides (4-5 ml per bee space/comb side). The best time for applying the drug is at the sunset when the all bees returned hive. Please use the drug in order to the following instructions;

- **Therapeutic:** use the drug every other day for up to one week.
- **Preventive:** In months which the mites are not common, one episode of applying the drug in each 2-week is enough for prevention of the mite challenge but in months known for mite invasion, apply the drug in all hives every week regularly before they were infected by the mite.

CONTRAINDICATIONS: None.

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Future Products

Here is a list of our products that passed all testing procedures and also evaluated by the governmental veterinary organization and now are obtaining their manufacturing license to be supplied to the market:

1. Anti-coccidiosis for poultry

Therapeutic properties: Stops the proliferation of oocysts and heals the intestinal lesions.

2. Herbal GastroBoost

Therapeutic properties: It is a gastrointestinal cleaner and enhancer. It promotes repairing and recovery of damaged intestine crypts and villi. It returns back the intestines to their normal and fresh state. It has also strong anti-inflammatory activities and therefore prevents and heals the gastrointestinal inflammatory diseases. In addition, the drug has a good therapeutic effect in the treatment of intestinal hyperaemia, bloody intestines, and mucosal hemorrhage in poultry.

3. Liver and kidney promoter.

Therapeutic properties: It is a complementary treatment when the animal challenged by poisoning. The drug is a therapeutic choice for any type of poisoning which had a negative effect on liver and kidney. However, the drug can also be incorporated in animal diet at any time as a liver and kidney function enhancer and promoter. It also prevents the toxicity and pathology of mycotoxins on the liver. In addition the drug cleans the kidney and increase urine and boosts the renal excretion of toxic metabolites.

4. Herbal Repellent for Equine

Therapeutic properties: It repels the pesky insects (e.g. flies, mosquitoes, beetles etc.).

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Booklet publication date: April 2019