THESIS

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The Effects of Fermented Wheat Germ Extract on the Condition and General Status in Companion Animals

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List of abbreviations

AA	Adjuvant Arthritis
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
Anti-dsDNA	Anti-double stranded DNA
BW	Body weight
CD45	Leukocyte common antigen
COX	Cyclooxygenase
dNTPs	Deoxyribonucleoside Triphosphates
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
ER+	Estrogen receptor-positive
ESR	Erythrocyte Sedimentation rate
FWGE	Fermented Wheat Germ Extract
F-6-P	Fructose-6-phosphate
GSD	German Shephard Dog
GMP	Good Manufacturing Practice
G-6-P	Glucose-6-phosphate
GL-6-P	Gluconolactone-6-phosphate
ICAM-1	Intercellular Adhesion Molecule 1
IFNγ	Interferon gamma
IL	Interleukin
ISO	International Organisation for Standardisation
HACCP	Hazard Analysis of Critical Control Points
HCR-25	Human colon carcinoma xenograft
HK	Hexokinase
HPLC	High Pressure Liquid Chromatography
Kg	Kilograms
LAC	Lactate
LDH	Lactate Dehydrogenase
MHC	Major Histocompatibility Complex
NADP	Nicotinamide Adenine Dinucleotide Phosphate (oxidised form)
NAD+	Nicotinamide Adenine Dinucleotide (oxidised form)
NK cells	Natural Killer cells
PARP	Poly (ADP-ribose) Polymerase
P.O.	Per os
PPP	Pentose Phosphate Pathway
ROS	Reactive Oxygen Species
RR	Ribonucleotide Reductase
RT-PCR	Real time – Polymerase chain reaction
SOD	Superoxide Dismutase
SLE	Systemic Lupus Erythematosus
TNF-α	Tumour Necrosis Factor – Alpha
WBCs	White blood cells
X-5-P	Xylulose- 5-phosphate
5-FU	5-Fluorouracil
3LL-HH	Lewis Lung carcinoma

1. INTRODUCTION AND AIM OF THE STUDY

In wheat grain, the kernel consists of three parts, the endosperm, the bran and the germ (Biropharma Ltd., 2015). The germ is the most nutritious part of the wheat grain kernel and has many profound benefits. Wheat germ has existed for centuries, but it is only until recently it has been used for medicinal purposes. It has a high concentration of vitamin E, omega-3 and omega-6 fatty acids which are components essential for a healthy, soft and shiny hair coat and hydrated skin. The high fibre content of wheat germ aids digestion, resulting in more nutrients being absorbed from the gastro-intestinal tract and firming of the stool. Cats and dogs need a high percentage of protein in their diet, and the high protein content of wheat germ assists in fulfilling this nutritional requirement. Many diseases that our domestic animals acquire causes immunosuppression. Immunosuppression is a term used to describe the reduction of the immune system's activity, therefore resulting in a decreased or a delayed immune response to a foreign pathogen that enters the body. Due to this, immunosuppression can have a vast array of negative impacts on animals such as loss of appetite, vomiting, decreased hair growth and an increased risk of infection. The product that I will be investigating and analysing through my thesis work *(Immunovet®)* is a specifically fermented wheat germ extract (FWGE), which is closely linked to a human supplement named *Avemar*®, used for medical purposes for cancer patients (Biopharma Animal Health Immunovet, 2018). As a future veterinarian, I have already seen many patients suffering from immunosuppression through many causes, both infectious and non-infectious. There are some drugs that are used to modulate the immune system e.g. prednisolone; however, long term usage of this drug is known to have undesired side effects. For this reason, I have taken a strong interest to gain knowledge and understanding on natural products that can modulate the immune system.

Through my thesis work, I hope to gain a better understanding on the positive effects of *Immunovet*, which will allow me to provide better treatment to diseased companion animals, aiding them to an efficient and more effective recovery. *Immunovet* is produced in a tablet form and a granulated form which is given to the animal orally (P.O.). Throughout my thesis, I will be mainly focusing on the current FWGE product, *Avemar*, and the research that I have carried out myself on companion animals taking *Immunovet* regarding the positive effects of FWGE on companion animal health.

2. LITERATURE REVIEW

2.1 The Effects of Fermented Wheat Germ Extract: Anticancer

2.1.1 Molecular Targets

In order to illustrate why the anticancer effect of FWGE occurs, it is important to first understand the molecular targets of the extract. Cancer cells proliferate and differentiate at an uncontrollable rate due to a mutation of genes, which accelerates cell division and therefore inhibits homeostasis of cells. In this manner, normal cell functions such as programmed cell death (apoptosis) are inhibited (Yadav, 2015). When there is a mass of cancer cells, it can develop into a tumour. Poly (ADP-ribose) polymerase (PARP) enzyme is essential for DNA repair and in cancer cells, the activity of this enzyme is exceptionally high (Comín-Anduix, 2002). FWGE establishes its anticancer characteristic, as it is a PARP inhibitor, thereby causing DNA fragmentation which leads to apoptosis of the cancer cells (Mueller et al., 2011). Cytostatic drugs destroy cancer cells and therefore, they are used for the treatment of cancer in the form of chemotherapy (Nichelatti et al., 2002). There are many cytostatic drugs that are used in veterinary medicine today e.g. 5-fluorouracil (5-FU), doxorubicin and dacarbazine (DTIC). Due to the high activity of the PARP enzyme that the cancer cells possess, they can be selectively sensitised by Avemar (PARP inhibitor) to these cytostatic drugs, leading to lesions in the DNA and resulting in apoptosis of the cancer cells (Boros et al., 2005). Major histocompatibility complex (MHC) molecules are surface proteins essential in adaptive immunity, as they bind to antigens derived from foreign pathogens, presenting them on the cell surface for recognition by T – cells. There are 2 major classes, MHC class I and MHC class II molecules. MHC class I molecules present antigens to cytotoxic T cell lymphocytes and MHC class II molecules present antigens to helper T cells (McDowall, 2005). Natural killer (NK) cells are cytotoxic lymphocytes that play a vital role in destroying viruses and cancer cells and do not require MHC molecules to do so (Patel, 2014). When MHC-I molecules bind to the antigen on the surface of foreign pathogens, it leads to an inhibitory effect of NK cells. Cancer cells, adapting to this, express high levels of MHC-I molecules on their surface, therefore avoiding recognition by NK cells, evading their cytotoxic function. This characteristic is particularly significant in metastatic tumours (Telekes et al., 2009). FWGE causes a down regulation of MHC-I molecules and consequently, reduces the expression of MHC-I molecules on human tumour cells (Iyer et al., 2009).

Therefore, it is hypothesised that this sensitises the cancer cells to the NK cells, allowing them to carry out their cytotoxic function and kill the tumour cells, leading to decrease in metastatic activity. Intercellular adhesion molecule 1 (ICAM-1) is an adhesion molecule, essential in immune-mediated and inflammatory processes (Boros et al., 2005). It is present in the membranes of leukocytes and endothelial cells. These molecules are important for the migration of leukocytes through the endothelial membrane and the activation of T cells (Mueller et al., 2011). The concentration of ICAM-1 molecules increases upon cytokine stimulation by tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) and is expressed by the vascular endothelium, macrophages and lymphocytes (Yashiro, 2008). There is a decreased expression of ICAM-1 on the endothelial cells of solid tumour vessels (Boros et al., 2005). This in turn, impairs trans-endothelial migration of leukocytes and therefore impairs the leukocyte infiltration into the tumour (Patel, 2014). FWGE upregulates the expression of ICAM-1 on tumour derived endothelial cells, therefore allowing for infiltration of leukocytes into the tumour. TNF-α is the principal anticancer cytokine playing a significant role in inflammation and adhesive processes.

TNF-α can destroy cancer cells directly by the induction of apoptosis and indirectly by causing a retardation of tumour angiogenesis (. Tumour angiogenesis is the proliferation of blood vessels which penetrate the growing cancer, to enable to supply the tumour with oxygen and nutrients (Yadav, 2015). FWGE increases the TNF-α secretion by macrophages, which therefore leads to an increase in cancer cell apoptosis, and a retardation of tumour angiogenesis (Mueller et al., 2011). Upregulation of TNF-α also increases the concentration of ICAM-1 molecules, increasing the migration of leukocytes to the tumorous area and allowing them to penetrate the tumour (Mueller et al., 2011). Furthermore, a study revealed FWGE causes an increased concentration of IL-1a, IL-2, IL-5 and IL-6 (Telekes et al., 2009). Cancer cells require a large amount of glucose to fuel their hypermetabolic state (Nature Education, 2014). During glycolysis, glucose-6-phosphate (G-6-P) is formed from glucose via the enzyme hexokinase (HK) (Nature Education, 2014). FWGE decreases glucose uptake both directly, and indirectly, by inhibiting glucose activation via the inhibition of HK (Telekes et al., 2009). The pentose phosphate pathway (PPP) is a metabolic pathway that uses this G-6-P to produce NADPH (Nicotinamide Adenine Dinucleotide Phosphate: in the reduced form), pentoses and ribose-5-phosphate (Boros et al., 2001). It has oxidative and non-oxidative steps. Another way that Avemar regulates tumour cell proliferation, is by reducing the rate of glucose intake for glycolysis and thereby regulating the synthesis of ribose formed during the PPP (Boros et al., 2001).

This role is significant in the ribosomal RNA fraction of cancer cells (Boros et al., 2001). Ribose is essential for the formation of ribosomal structures, while ribosomal RNA is needed for the *de novo* enzyme protein synthesis and cell proliferation of cancer cells (Boros et al., 2005). Therefore, inhibition of the formation of ribose from glucose prevents the aforementioned cycles, and highlights the mechanism whereby FWGE regulates cell tumour proliferation and growth. Furthermore, due to the tumour proliferating at a slower rate, the disease progression is slow, resulting in an increased survival rate in clinical patients (Telekes et al., 2007). Lactate dehydrogenase (LDH) is an enzyme that converts pyruvate to lactate. This reaction is reversible, so LDH can also convert lactate to pyruvate. Cancer cells have an increased activity of LDH, favouring lactate production (Telekes et al., 2007). This increased lactate production promotes cell proliferation of the cancer cells (Telekes et al., 2007). Pyruvate is utilised in the citric acid cycle to produce energy, in the form of ATP. FWGE inhibits LDH, leading to a decrease in lactate production and therefore a reduced cell proliferation of the cancer cells (Comín-Anduix, 2002). Moreover, as LDH is inhibited, the concentration of pyruvate increases, impairing glycolysis, which in turn reduces the amount of energy (ATP) produced (Telekes et al., 2007). A decrease in energy results in a decrease in tumour growth. FWGE has been found to reduce tumour growth in both aerobic and anaerobic conditions (Telekes et al., 2007). Cancer causes a malfunction in the patient's metabolism, leading to a lack of energy storage and supply, resulting in weight loss and weakness (Nature Education, 2014). Cancer patients therefore can suffer from cachexia, which can lead to treatment failure. FWGE is beneficial to cancer patients, as it decreases the chances of cachexia, by reducing glucose uptake by the cancer cells and therefore increasing weight gain. An increase in weight gain results in the metabolism of the patient being more stable, compared to cancer patients not taking FWGE. This allows these patients to tolerate invasive treatments, such as chemotherapy and surgery, to a higher degree. Ribonucleotide reductase (RR) converts ribonucleotides to deoxyribonucleoside triphosphates (dNTPs), which are precursors needed for DNA synthesis. Due to the rapid growth of cancer cells, the activity of RR is significantly higher to meet the increased requirement of dNTPs needed for DNA synthesis. FWGE works as a RR inhibitor, therefore limiting the number of dNTPs available for DNA synthesis, resulting in a decreased proliferation of the tumour (Boros et al., 2005). This effect has been shown to be considerably significant in HT29 human colon cancer and HL-60 human pro-myelocytic leukaemia cell lines (Mueller et al., 2011).

CD45 (leukocyte common antigen) is a receptor-linked protein tyrosine phosphatase, that is expressed on all leukocytes and has an intracellular phosphatase activity. CD45 has a significant role in the intracellular signal transduction of leukocytes, including apoptosis. FWGE induces apoptosis in the cells that lack CD45 and is also tumour specific (Telekes et al., 2009). This allows us to hypothesise that the induction of apoptosis caused by the extract does not involve the CD45 system.

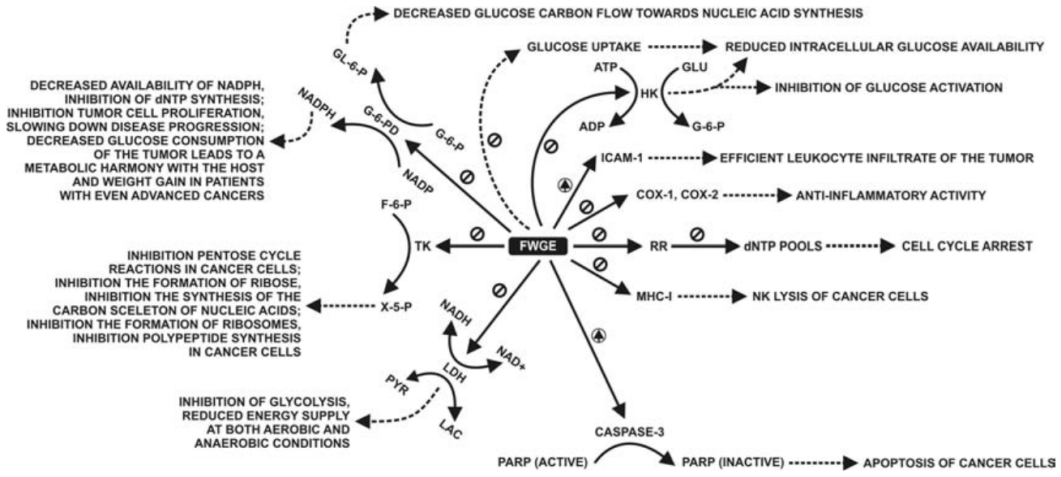


Figure 1: A summary of the molecular targets of fermented wheat germ extract (Telekes et al., 2007).

Further abbreviations: ADP = Adenosine-diphosphate; F-6-P = Fructose-6-phosphate; GL-6-P = Gluconolactone-6-phosphate; LAC = Lactate; NAD+, NADH = Nicotinamide Adenine Dinucleotide, oxidized and reduced forms, respectively; NADP, NADPH = Nicotinamide Adenine Dinucleotide Phosphate, oxidized and reduced forms, respectively; PYR = Pyruvate; X-5-P = Xylulose- 5-phosphate.

2.1.2 Drug Synergism

Owing to the molecular targets, FWGE has been found to have an anti-proliferative effect on a large range of tumours including glioblastoma, melanoma, neuroblastoma, hepatoma and tumours associated with the cervix, thyroid, testis, ovaries, head and neck (Boros et al., 2005). FWGE can be used to strongly inhibit metastases in patients with tumours. It can also have other treatment benefits when used synergistically with other compounds and drugs. Unlike most animals, humans and guinea pigs cannot endogenously produce vitamin C, and therefore it must be supplemented orally in order to meet their dietary nutritional requirement.

Vitamin C was suggested to have cancer fighting properties since the 1930s and it has been a matter of speculation since (Hidvégi, 1998). FWGE combined with vitamin C can profoundly inhibit metastases of a wide range of tumours e.g. lung carcinoma, melanoma, nephroblastoma etc. (Hidvégi, 1998). This being said, in some studies, FWGE had a stronger inhibitory effect on certain tumours when administered alone and this has been proven by research carried out by Hidvégi et al. (1999). In this study, 4 tumour models were used, grown on rats or mice: a highly metastatic variant of Lewis Lung carcinoma (3LL-HH), B16 mouse melanoma, C38 mouse colorectal tumour and a human colon carcinoma xenograft (HCR-25). Avemar treatment was started 24 hours after tumour implantation. It was dissolved in water and administered via a gastric tube. The daily dose was 3g/kg of body weight *per os*, administered in 0.1ml of water. The animals with 3LL-HH and B16 mouse melanoma, were also subject to the combined treatment of vitamin C and Avemar together. The control animals received 0.1 ml of water also via a gastric tube *per os.* The results showed that in comparison to the control animals, Avemar treatment resulted in a 71% decrease in the number of liver metastases of 3LL-HH tumour inoculated into the spleen. Moreover, the combined treatment of Avemar and vitamin C had a more pronounced inhibition of metastases. In the case of the HCR-25, Avemar treatment decreased the number of liver metastases and reduced the weight of the tumorous spleen. In the case of B16 mouse melanoma which was inoculated into muscle, there was an 85% decrease in the number of metastases, however, there was no change in the mass of the tumour which was growing in the muscle, as compared to the control group. When vitamin C was given in combination with Avemar to the B16 mouse melanoma animals, the inhibition of metastases occurred. However, Avemar administration alone, elicited a much more pronounced inhibition of metastases than the combined treatment of vitamin C and Avemar together. This allows us to speculate that in some cases, vitamin C combined with FWGE can have a significant decrease in metastatic activity when given to companion animals diagnosed with specific types of cancer. Therefore, overall, it would be advised to administer the combined treatment, as vitamin C also has profound health benefits in general. FWGE administered alongside cytostatic drugs can totally inhibit metastatic activity of the primary tumour. For example, 5-FU combined with FWGE can be used for the treatment of colorectal carcinoma and DTIC combined with FWGE can be used for the treatment of lung carcinoma. These combinations of treatment, indicate that FWGE has the potential to be used alongside chemotherapy to treat cancer in companion animals. To add to this, not only is there synergism between FWGE and chemotherapeutic drugs, but the extract poses little risk to

reduce the efficacy of the cytostatic drugs. Moreover, the addition of FWGE in long term chemotherapy, did not increase the toxic effect caused by the cytostatic drugs, reinforcing the non-toxic nature of FWGE (Hidvégi, 1998). Another study carried out by Hidvégi et al. (1999) proved that not only does FWGE have a non-toxic nature, but it also counteracts side effects caused by these cytostatic drugs e.g. weight loss. When the cytostatic drugs were used in combination with Avemar, weight loss was not observed. Tamoxifen is a drug used for the treatment of breast cancer in humans for both males and females. It is mainly used for estrogen receptor-positive (ER+) breast cancer, as tamoxifen attaches to the estrogen receptor in the cancer cell, thereby blocking the attachment of estrogen itself to the receptor (Boros et al., 2005). Tamoxifen increases the apoptosis of the cancer cells. It has been proven that this apoptosis significantly increases when used in combination with Avemar for the treatment of ER+ breast cancer (Boros et al., 2005). This suggests that FWGE could considerably enhance the efficacy of Tamoxifen. However, due to the increased risk of pyometra associated with the use of Tamoxifen, it is rarely used in veterinary clinical practice.

2.2 The Effects of Fermented Wheat Germ Extract: Immunomodulation

FWGE acts as an immunostimulant for patients that suffer from various diseases that lead to immunosuppression. This statement is proved by a study that was carried out on thymectomised mice. The thymus is a vital lymphoid organ of the immune system, as this is where the T cells mature, thus it is critical for cellular immunity. For this reason, the removal of the thymus (thymectomy) would considerably impair the immune system. In this study, carried out by Boros et al. (2005), the administration of Avemar to thymectomised mice, being severely immunocompromised, restored immune function to a degree whereby the immune response was similar to non-thymectomised mice (Boros et al., 2005). This exhibits the significant immune restorative effects of FWGE (Boros et al., 2005). This study proves that FWGE has the potential to strongly stimulate the immune system of immunosuppressed companion animals. The process of blastic transformation of B and T lymphocytes plays a key role in the immune response (Patel, 2014). Blastic transformation differentiates these lymphocytes into the different cell types to carry out different roles for immunity. FWGE increases the blastic transformation of T lymphocytes, solidifying its immune-modulating capability (Patel, 2014).

This allows us to hypothesise that FWGE has the potential to have the same effect and therefore strengthening the immune response of companion animals. Cyclophosphamide is a multifunctional drug that is used as an immunosuppressant for the treatment of immune-mediated diseases and for chemotherapy for cancer patients (Mueller et al., 2011). There are associated side effects caused by long term cyclophosphamide treatment, such as impairing the function of the bone marrow. FWGE can combat these side effects and consequently, Avemar has been proven to restore the production of thrombocytes (thrombopoiesis) and the production of erythrocytes (erythropoiesis) after long term cyclophosphamide administration (Boros et al., 2005). Immune-mediated diseases are common amongst companion animals and are consequently frequently encountered during clinical practice. Immune-mediated diseases are conditions whereby there is a dysfunction or abnormal activity of the immune system. In these diseases, the immune system overreacts and attacks normal body tissues as if they were foreign. Systemic Lupus Erythematosus (SLE) is an immune-mediated disease that is more common in dogs than cats. In SLE, antibodies are produced which form immune complexes with antigens (Ehrenfeld et al., 2001). These immune complexes deposit themselves in certain organs e.g. the kidneys (Ehrenfeld et al., 2001). Many dog breeds are affected by the disease, but the German Shephard dog (GSD) is the most predisposed breed to SLE (Ehrenfeld et al., 2001). The clinical signs observed depend on where the immune complexes are deposited within the body. The most frequent clinical signs are lethargy, weight loss, poor appetite and lameness. Lameness manifests due to polyarthritis, which is an inflammation of multiple joints (Ehrenfeld et al., 2001). Polyarthritis occurs as the immune complexes deposit in the joints, leading to inflammation. Certain immune-mediated diseases are associated with an imbalance between Th1 (T helper cell 1) and Th2 (T helper cell 2) cytokines (Ehrenfeld et al., 2001). Th1 cells produces cytokines IL-2 and IFNγ (Interferon gamma) and Th2 cells produces cytokines IL-4 and IL-10. These cytokines result in an immune response. SLE is associated with Th1/Th2 network imbalance, with a Th2 dominance and its accompanying cytokines (Ehrenfeld et al., 2001). A study carried out by Ehrenfeld et al. (2001) assessed the potential of Avemar for the treatment of SLE in naive mice. This SLE was induced by idiotypic immunisation, which involved immunising the naive mice with anti-double stranded DNA (anti-dsDNA). Approximately 2-3 months after the immunisation, anti-autoantibodies were produced which later led to clinical manifestation of the experimental SLE in the naive mice. Comparisons were made between the Avemar-treated SLE mice and non-treated SLE mice.

Avemar was given *per os* to the mice 7 days before immunisation with anti-dsDNA and 9 weeks after immunisation as well. Down regulation of the autoantibody was observed in the Avemar treated SLE mice, in comparison with the non-treated SLE mice. A comparison of titres between the two groups revealed a 42-56% decrease in auto-antibody production in the Avemar treated SLE mice. This decreased production of auto-antibodies was noted even 4 weeks after discontinuing the Avemar treatment. The antibody response in the Avemar treated SLE mice was associated with normal values of the ESR (erythrocyte sedimentation rate), WBCs (white blood cells) and by a moderate proteinuria (less than 100 mg/dl). On the other hand, the antibody response in the non-treated SLE mice was associated with an increased ESR, leukopenia and a significantly higher proteinuria (>300 mg/dl). Serology revealed a delay in the production of cytokines IL-4 and IL-10 by Th2 in the Avemar treated SLE mice, which are associated with the development of SLE. After gathering this information, Ehrenfeld et al. (2001) concluded that Avemar can ameliorate the clinical manifestations of experimental SLE by inhibiting the Th2 response. This study allows us to hypothesise that FWGE has the potential to have the same ameliorating effect, on the clinical manifestation of immune-mediated diseases that companion animals suffer from.

2.3 The Effects of Fermented Wheat Germ Extract: Other

2.3.1 Anti-inflammatory Effect

Inflammation is a complex biological response elicited by the immune system against harmful (foreign) stimuli such as an infection, injury or irritation. Anti-inflammatory drugs are formulated to reduce inflammation by inhibiting prostaglandin production. Prostaglandins are lipid compounds that stimulate inflammation leading to pain and fever and are mainly produced by cyclooxygenase enzymes. Cyclooxygenases (COX) comprises of two enzymes, COX-1 and COX-2 (Heuser, 1980). These enzymes produce prostaglandins, thromboxane's and other inflammatory mediators. COX-2 is primarily involved in inflammation. FWGE inhibits the COX enzymes, therefore this explains the anti-inflammatory effect of the extract (Heuser, 1980). To prove the anti-inflammatory effect of FWGE, a study was carried out on rats with adjuvant arthritis (AA) by Telekes et al. (2007). AA is classed as a relevant animal model of rheumatoid arthritis (RA) which occurs in mammals.

AA has a secondary (immune-mediated) response which is associated with inflammation. RA is an immune-mediated disease, whereby the immune system mistakes some of its 'self' for 'non-self' protein (Telekes et al., 2007). Due to this, an immune response occurs producing antibodies (rheumatoid factor), forming immune complexes which deposit in the joints (Telekes et al., 2007). These immune complexes trigger an inflammatory reaction. The anti-inflammatory drugs that were used during this study were dexamethasone, indomethacin and diclofenac. The study consisted of two stages; in the first stage, the rats with AA were subject to monotherapy and were administered with different dosages of either anti-inflammatory drugs (indomethacin or dexamethasone) or FWGE. In the second stage, the same sample of rats were administered with FWGE in combination with either diclofenac or dexamethasone. The gene expressions of COX-1 and COX-2 were determined by RT-PCR (Real time – Polymerase chain reaction). Overall, the study concluded that FWGE, substantially inhibited the development of the secondary (immune-mediated) response, to a degree that was comparable to the inhibitory effect exerted by dexamethasone and indomethacin (Telekes et al, 2007). The extract inhibited the gene expression of both COX-1 and COX-2, therefore concluding that FWGE has a significant anti-inflammatory capability. This study solidifies the anti-inflammatory characteristic of FWGE. COX enzymes also contribute to tumour development due to their involvement in carcinogenesis. Therefore, FWGE can be used prophylactically, preventing the development of cancer. This characteristic has been shown to be especially efficacious in colonic cancer.

2.3.2 Safe Usage

In the current medical climate, drug safety is of upmost importance due to the serious adverse side effects available drugs can cause. Because of this, nowadays in the medical industry, it is highly desirable to find drugs or natural substances with minimal/no side effects. FWGE has been tested on many animals and humans, and in none of these patients have adverse effects been observed. Avemar has been subjected to acute toxicity studies in the rat and mouse, a subacute toxicity study in the rat, and subchronic toxicity studies in the rat and mouse, as well as genotoxicity, mutagenicity and carcinogenicity screening tests (Boros et al., 2005). None of these tests resulted in toxic effects to the patients, therefore establishing that FWGE is a non-toxic substance. This allows us to believe that FWGE would also be non-toxic when used to treat companion animals.

FWGE is safe to use, reinforced by a study that was carried out on carcinoma patients, where haematologic values with long term Avemar treatment (over 2 years) remained within normal limits. Haematological data included white blood cell count, red blood cell count, haemoglobin level, haematocrit, platelet count, erythrocyte sedimentation rate, lymphocyte count, neutrophil granulocyte count, monocyte count, eosinophil granulocyte count, and prothrombin level (Boros et al., 2005). Another aspect solidifying the extract's safe usage is, as previously mentioned, the addition of the FWGE in long term chemotherapy which did not increase the toxic effect caused by the cytostatic drugs. This also reinforces the non-toxic nature of FWGE. In addition, over the course of time that FWGE has been used, no noteworthy side effects have been detected and there have been no reports of interfering interactions with other drugs, solidifying the safety aspect of the product. This allows us to deem that FWGE is safe to use in companion animals

2.3.3 Free Radical Binding Effect

A free radical is any molecular species that has gained or lost an electron and is capable of independent existence. Free radicals are derived from normal metabolic processes occurring within the body, and a vast range of external sources such as x-ray exposure and cigarette smoking. They are unstable molecules, which are highly reactive and dangerous and can have extremely detrimental effects to the cells of the body in multiple ways. One of them being that they attack macromolecules, in which their main targets are lipids, nucleic acids and proteins. Oxygen-containing free radicals are known as reactive oxygen species (ROS) e.g. hydroxyl radical, superoxide anion radical etc. ROS break DNA strands and DNA protein cross-links, therefore inducing DNA damage. This leads to mutation and transformation of the cells in the body, which can result in cancer. Binding of free radicals can prevent these undesired effects they cause. FWGE has a strong free radical binding effect (Hidvégi et al., 1999). In particular, it has been found that the extract has a strong superoxide scavenging potential, an effect comparable to superoxide dismutase (SOD) (Hidvégi et al., 1999). SOD is an enzyme that catalyses the dismutation of superoxide radical into either oxygen or hydrogen peroxide. Therefore, this information establishes the anti-oxidant effect of FWGE, which has the potential to treat high levels of ROS in companion animals.

2.4. The Product containing Fermented Wheat Germ Extract – *Immunovet*

Immunovet is a nutritional supplement that mainly contains the natural active ingredient, fermented wheat germ extract, derived from the wheat species *Triticum vulgare.* 2-methoxy-p-benzoquinone and 2,6-dimethoxy-p-benzoquinone are the two principal bioactive molecules thought to be responsible for most of the biological properties of FWGE. Among others, these properties include an anti-cancer and an antimicrobial effect and a stimulating effect on the immune system. These bioactive compounds appear in the form of glucosides and are formed during a highly controlled biotechnological process with a special fermentation of wheat germ, by a certain strain of yeast species, *Saccharomyces cerevisiae*. *Immunovet* is a brand-new substance formed from a mixture of fractions manufactured via this complex process. It is treated with ionising energy to reach appropriate microbiological purity (Biopharma Animal Health Immunovet, 2018). It also contains maltodextrine, fructose, silicum dioxide and sodium chloride. Additionally, *Immunovet* is rich in vitamins, unsaturated fatty acids, macro- and microelements and binding peroxides.

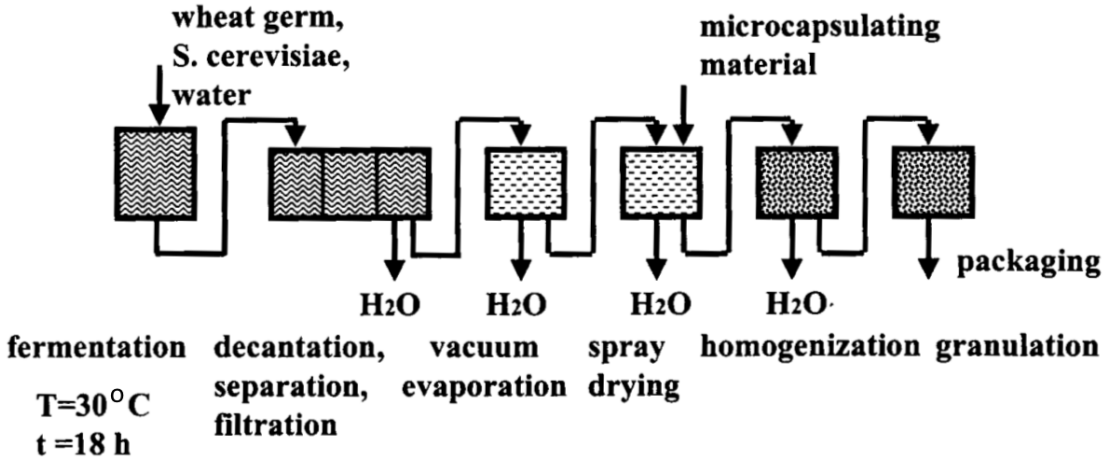


Figure 2: A flow sheet diagram of the manufacturing process of Avemar (Hidvégi et al., 1999)
where T= Temperature, t = Time

Immunovet is a multi-functional product which primarily boosts and helps the immune defence by stimulating both the humoral and cellular immunity. Due to the active ingredients present in *Immunovet*, it has an antimicrobial, anti-inflammatory, anti-cancer, antioxidant and immune strengthening effect. It also strengthens the skeletal musculature framework of the animals and due to its antioxidant effect, it acts as a free radical scavenger. Owing to its immune stimulating effect, *Immunovet* activates the immune system, especially beneficial clinically during cases of immunosuppression (Biopharma Animal Health Immunovet, 2018).

Immunovet has been formulated in a way that animals enjoy the flavour of it and therefore it can be used as a nutritious treat. Everything about *Immunovet*, from the raw ingredients to the production process, is 100% environmentally friendly. This is evident as both *Triticum vulgare* and *Saccharomyces cerevisiae* occur in nature. Furthermore, no artificial additives are used in the manufacturing process, making *Immunovet* a very healthy and pure product in comparison to how other supplements are made. As *Immunovet* is a natural product, it can be purchased without a veterinary prescription and can be given to livestock without leaving any residues in the animal's body and therefore has a 0-day withdrawal period. Moreover, it's standardised, meaning that it has a typical fingerprint chromatogram examined by high pressure liquid chromatography (HPLC) which is suitable for its identification. The product is standardised on 2,6-dimethoxy-p-benzoquinone, which is traceable with analytical methods. Another remarkable aspect of *Immunovet* is that it is beneficial to the animal's health and digestion, supporting the gastro-intestinal tract by protecting the intestinal villi and stabilising the gut's microflora. It does this by increasing the height of the intestinal villi, therefore enhancing the absorption of molecules from the intestinal tract, resulting in efficient utilisation of food. Additionally, *Immunovet* products are uniform, effective and have a high standard of quality. This is due to the manufacturing plant running under the HACCP (Hazard Analysis of Critical Control Points) system and it is ISO (International Organisation for Standardisation) 9001:2008 and is GMP (Good Manufacturing Practice) certified. During the manufacturing process, *Immunovet* has an optimal size distribution which makes the mixing dust free, resulting in a very safe product. Over the course of time that *Immunovet* has been used, no side effects have been detected and there have been no reports of interfering interactions with other drugs, solidifying the safety aspect of the product.

Proved by toxicological studies, *Immunovet* is considered as non-toxic as it does not disturb the physiological balance of the animal, even when extreme overdosing occurs (2500mg/kg of bodyweight) (Biopharma Animal Health Immunovet, 2018). To add to this, no mutagenic or genotoxic activity has been reported. *Immunovet* has a long shelf life of 2 years under normal storage conditions, making it a very stable product.

3. MATERIALS AND METHODS

A sample size of 60 companion animals were used to collect data regarding the beneficial effects of using *Immunovet*. An investigation was carried out at Rex Small Animal Hospital, which is a veterinary practice, located in the 4th district of Budapest, Hungary. The owners were advised to give their companion animal *Immunovet per os,* daily over a course of 8 weeks. All owners were given the granulated form of *Immunovet* to use. The dosage depended on the patient's weight, which was 1 measuring spoon per 10kg of body weight.



Figure 3: Photo of the granulated *Immunovet*, given to the owners during this investigation (Biropharma Kft, 2017).

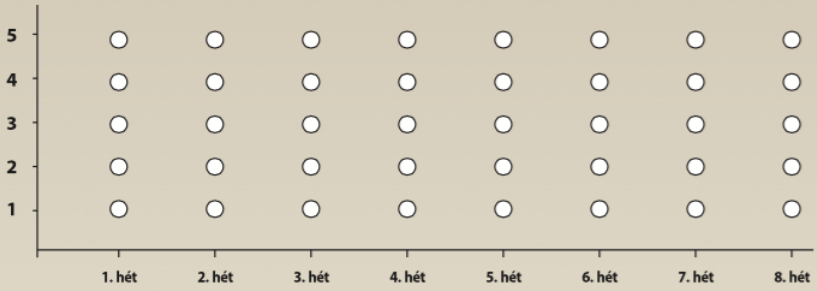
Each owner was given a questionnaire (see Figure 4 and 5) for them to keep track of the patient's progress over this 8-week period. It consisted of 10 questions which were written in Hungarian. 100 questionnaires were given to collect data on 100 patients, however only 60 of them were returned to the practice.

The translation of these question are as follows: Question 1 asks ‘How old is your animal?’. Question 2 asks ‘What species is your animal?’ with the options being either dog or cat. Question 2 then asks the owner to specify ‘What breed is your animal?’. Question 3 asks ‘What is your animals name?’. Question 4 asks ‘What was the reason for the purchase of *Immunovet*?’. The options for this question are as follows; option 1 stating ‘General immune-protection, roboration’, option 2 stating ‘For the post-operative recovery phase’, option 3 stating ‘Improvement of hair coat quality’, option 4 stating ‘Due to recurrent infectious diseases’, option 5 stating ‘Due to senior age, declining immune system’ and option 6 stating ‘Other:’ giving the owner the option to write the other reason of purchase if it was not listed in the options above. Question 5 asks for the ‘Current weight of the animal:’ in kg (kilograms). Question 5 then goes on to ask ‘How did your animals bodyweight change during the observation period of 2 months? Please write into each column, the body weight measured in the corresponding weeks. (It is advised to take the body weight of your pet on the same day each week)!’. The last part of question 5 states ‘End of the week body weight (kg)’ and has 8 empty boxes to allow the owner to write the body weight for each week, starting with the 1st week and ending with the 8th week as shown in Figure 4. Question 6 states ‘Please illustrate the alteration of your pet’s appetite in the first two weeks of treatment!’. To illustrate the alteration of the animal’s appetite, a graph is used, where the X axis represents the number of days (ranging from day 1 – day 14) and the Y axis has a score from 1-5. Option 1 states ‘minimal appetite, accepts food only by feeding, option 2 states ‘weak appetite, eats less than normal’, option 3 states ‘normal appetite’, option 4 states ‘increased appetite’ and option 5 states ‘overeating, constantly demands food’. Question 7 states ‘Please illustrate the quality changes of your pet’s hair coat during the 8 weeks of treatment!’. To illustrate the quality change of the animal’s hair coat, a graph is used in the same way as question 6. The X axis represents the weeks (from the 1st week until the 8th week) and the Y axis has options from 1 – 5. Option 1 states ‘scruffy, matt fur, areas with visible alopecia, dermal symptoms (rash, itch, redness)’, option 2 states ‘scruffy, matt fur, alopecia, but no dermal symptoms’, option 3 states ‘matt fur, but intact hair coat’, option 4 states ‘normal appearance of the hair coat’, option 5 states ‘glossy, well-groomed, immaculate hair coat’.



Figure 4: The first page of the questionnaire

7. **Kérjük, ábrázolja egy grafikonon kedvence szőrzete állapotának alakulását a kezelés nyolc hetében!**



1 ápolatlan, tompa fényű szőrzet, szembetűnő szőrhiányos területek, bőrtünetek (kiütések, kipirulások, viszketés jelei)
2 ápolatlan, tompa fényű szőrzet, szőrhiánnyal, de bőrtünetek nélkül
3 tompa fényű szőrzet, de ép bunda
4 normál megjelenésű bunda
5 fényes, ápolt, kifogástalan minőségű szőrzet

8. **Tapasztalta-e bármelyiket az alábbi viselkedési jellemzők közül kedvencén a kezelés ideje alatt (egyszerre többet is megjelölhet)?**

- ☐ Kedvencem aktívabb lett
- ☐ Kedvencem kevesebbet alszik napközben
- ☐ Kedvencem olyan dolgokat csinált, amit már régóta nem (például újra játszik más állatokkal)
- ☐ Kedvencem mozgásigénye növekedett
- ☐ Kedvencem többször hozza a játékát, hogy együtt játsszunk
- ☐ Kedvencem mozgása dinamikusabb lett

9. **Ha kedvencénél fennállt az alábbi tünetek közül bármelyik az Immunovet kezelés előtt, észlelt-e abban változást?**

Tünet	javult	rosszabbodott	változatlan maradt
Vakaródzás	☐	☐	☐
Szőrhullás	☐	☐	☐
Fülgyulladás tünetei	☐	☐	☐
Sántítás	☐	☐	☐
Szörtyögés, köhögés	☐	☐	☐
Hallászcsökkenés	☐	☐	☐
Látászcsökkenés	☐	☐	☐

10. **Tapasztalt-e kedvencénél a kezelés során mellékhatást? (pl. hányás, hasmenés, étvágytalanság).**

.....

Figure 5: The second page of the questionnaire

Question 8 asks ‘Have you observed any of the listed behavioural characteristics that your pet exhibited during the treatment?’. The options for this question are as follows; option 1 stating ‘My pet became more active’, option 2 stating ‘My pet sleeps less during the day’, option 3 stating ‘My pet has done things that it hasn’t done for a long time (e.g. plays with other pets)’, option 4 stating ‘My pet’s activity level increased’, option 5 stating ‘My pet brings its toys more often to initiate play time’ and option 6 stating ‘My pet’s movement became more dynamic’. Question 9 asks ‘If any symptom(s) persisted before the use of *Immunovet*, have you observed any change in that/those symptom(s)?’ and is followed by a table for the owner to fill out. The first column of the table lists the symptoms, which in order are scratching, hair loss, symptoms of ear inflammation, lameness, coughing, decreased hearing and decreased vision. The second, third and fourth columns states ‘improved’, ‘deteriorated’ and ‘remain unchanged’ respectively, and has boxes (as shown in Figure 5) for the owner to mark a cross accordingly. Question 10 states ‘Have you observed any side effects in your pet during the treatment? (e.g. vomiting, diarrhoea, loss of appetite).’ with a line for the owner to write, if side effects are seen.

4. RESULTS

The aim of this study was to acknowledge the beneficial effects of using *Immunovet* on the condition and general status in companion animals. After the course of 8 weeks, the owners returned the questionnaires to the practice. The data was collected and a table was formulated (see *Appendix 1*). Out of the 60 patients that were investigated in this study, 40 of them were dogs and 20 of them were cats. 2 of the dog patients did not consume *Immunovet* and therefore are not included in the results. Based on the data, overall the average patient age for dogs used in this study was approximately 6 years old and for cats was approximately 10 years old. The average weight gain over the course of 8 weeks was 0.43 kg and the average weight gain for dogs was 0.51 kg and for cats was 0.27 kg.

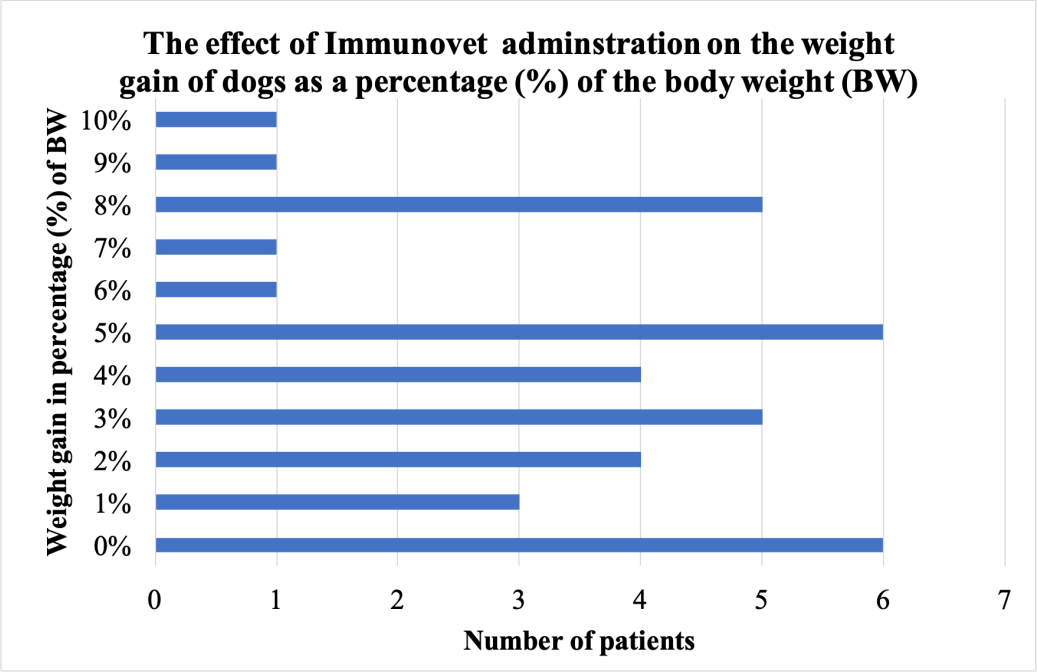


Figure 6: A bar chart demonstrating the weight gain of dogs as a percentage (%) of body weight (BW)

The weight gain as a percentage of the body weight (BW) is a more accurate way of measuring the increased weight gain of an animal. This is because the percentage takes the initial body weight into consideration, whereas the weight gain in kg does not. Figure 6 is a bar chart demonstrating the weight gain of dogs as a percentage (%) of the BW. *Immunovet* administration led to 6 patients having a weight gain of 5%, however, it also led to 6 patients having no weight gain at all.

Further establishing the products beneficial effect on the BW, 5 patients had a weight gain of 8% and 5 patients had a weight gain of 3%. A weaker effect on the BW was evident whereby 1 patient had a weight of 10%, 1 patient had a weight gain of 9%, 1 patient had a weight gain of 7% and 1 patient had a weight gain of 6%. Moreover, other patients had a varied effect on their BW whereby 3 patients had a weight gain 1%, 4 patients had a weight gain of 2% and 4 patients had a weight gain of 4%.

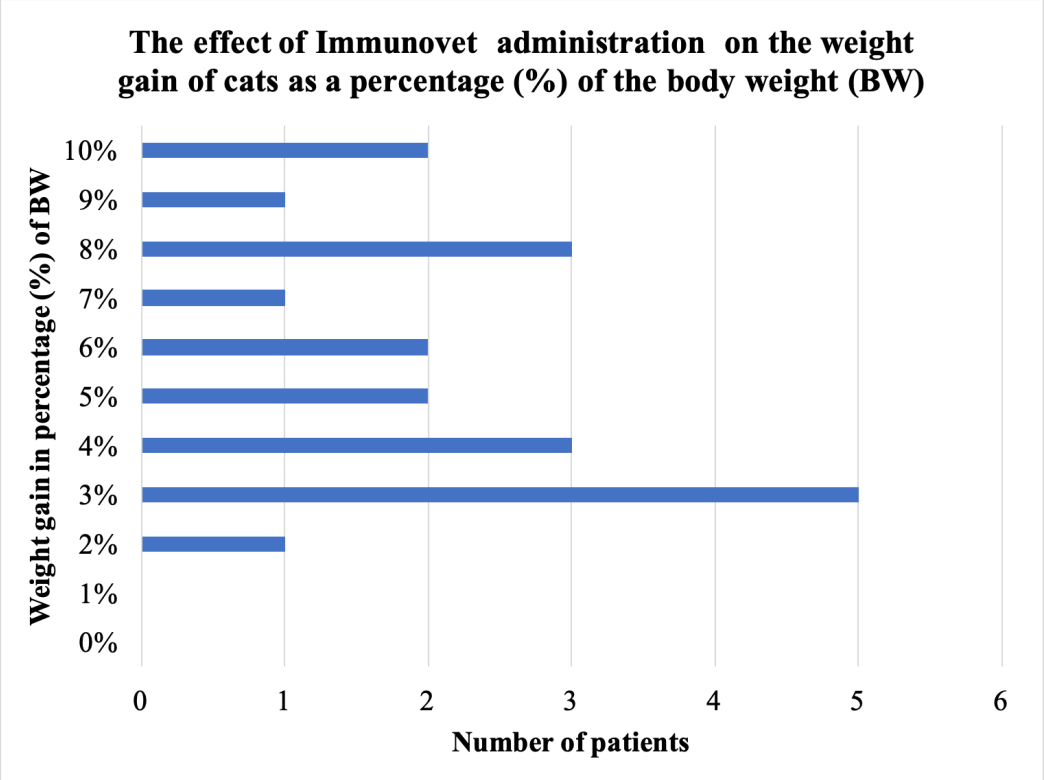


Figure 7: A bar chart demonstrating the weight gain of cats as a percentage (%) of body weight (BW)

Figure 7 is a bar chart demonstrating the weight gain of cats as a percentage (%) of the BW. *Immunovet* administration led to 5 patients having a weight gain of 3%, however, only 1 patient had a weight gain of 9%. Further establishing the products beneficial effect on the BW, 2 patients had weight gain of 10%, 3 patients had a weight gain of 8% and 3 patients had a weight gain of 4%. A weaker effect on the BW was seen whereby 1 patient had a weight gain of 7% and 1 patient had a weight gain of 2 %. Other patients had a varied effect on their BW whereby 2 patients had a weight gain of 6%, 2 patients had a weight gain of 5%.

All cats that were administered with *Immunovet* had a weight gain of some degree, proven by the fact that no cats had a weight gain of 0%, or 1% for that matter.

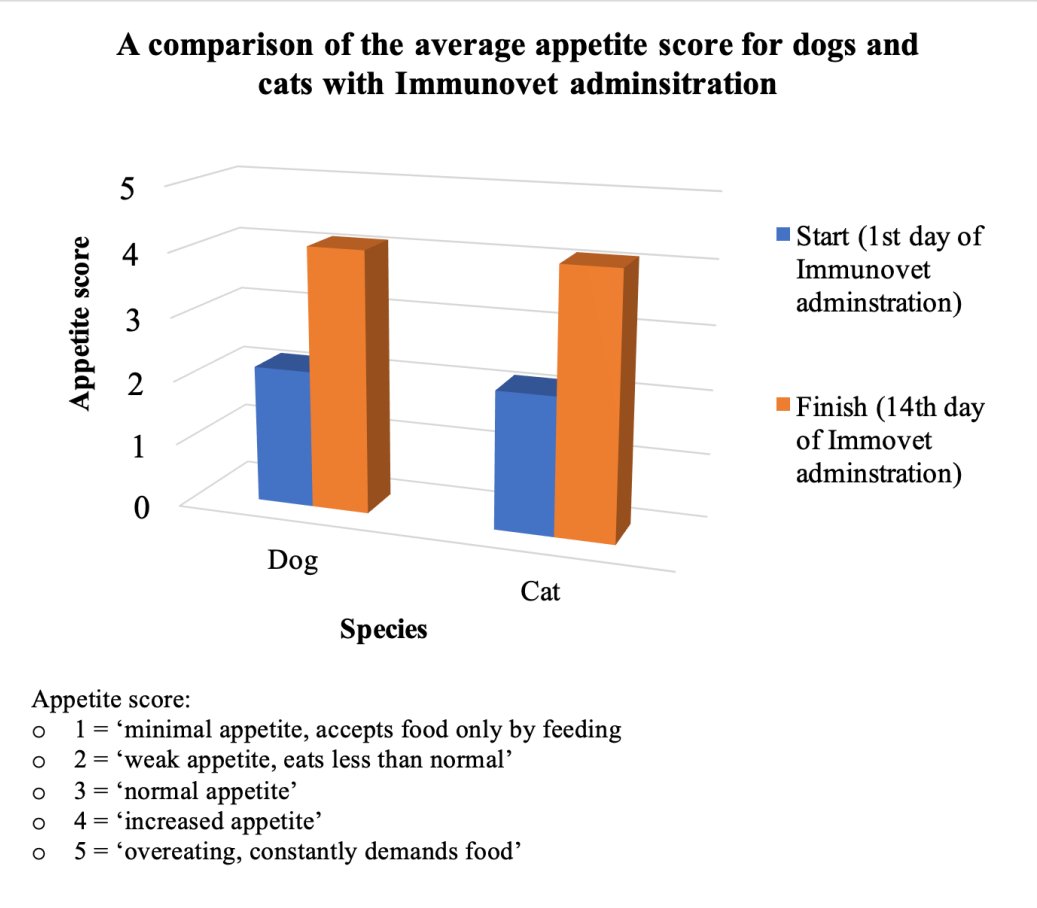


Figure 8: A column chart displaying a comparison of the average appetite score for dogs and cats

Figure 8 displays that the average appetite score for all patients started at level 2 ('weak appetite, eats less than normal'), and the mean increase over the course of 2 weeks was 2 levels, increasing to level 4 ('increased appetite'). With 14 days of *Immunovet* administration, the average appetite score increase for dogs was 2 levels and for cats was 2 levels. 19 patients whose appetite score started at level 1 ('minimal appetite, accepts food only by feeding') increased to level 4. 3 patients whose appetite score started at level 1 increased to level 3 ('normal appetite'). 5 patients whose appetite score started at level 2 increased to level 4. 1 patient whose appetite score started at level 2 increased to level 3. 17 patients whose appetite score started at level 3 increased to level 4. 8 patients whose appetite score started at level 3 did not increase.

1 patient whose appetite score started at level 4 increased to level 5 (‘overeating, constantly demands food’). 2 patients whose appetite score started at level 4 did not increase and 2 patients whose appetite score started at level 5 did not increase.

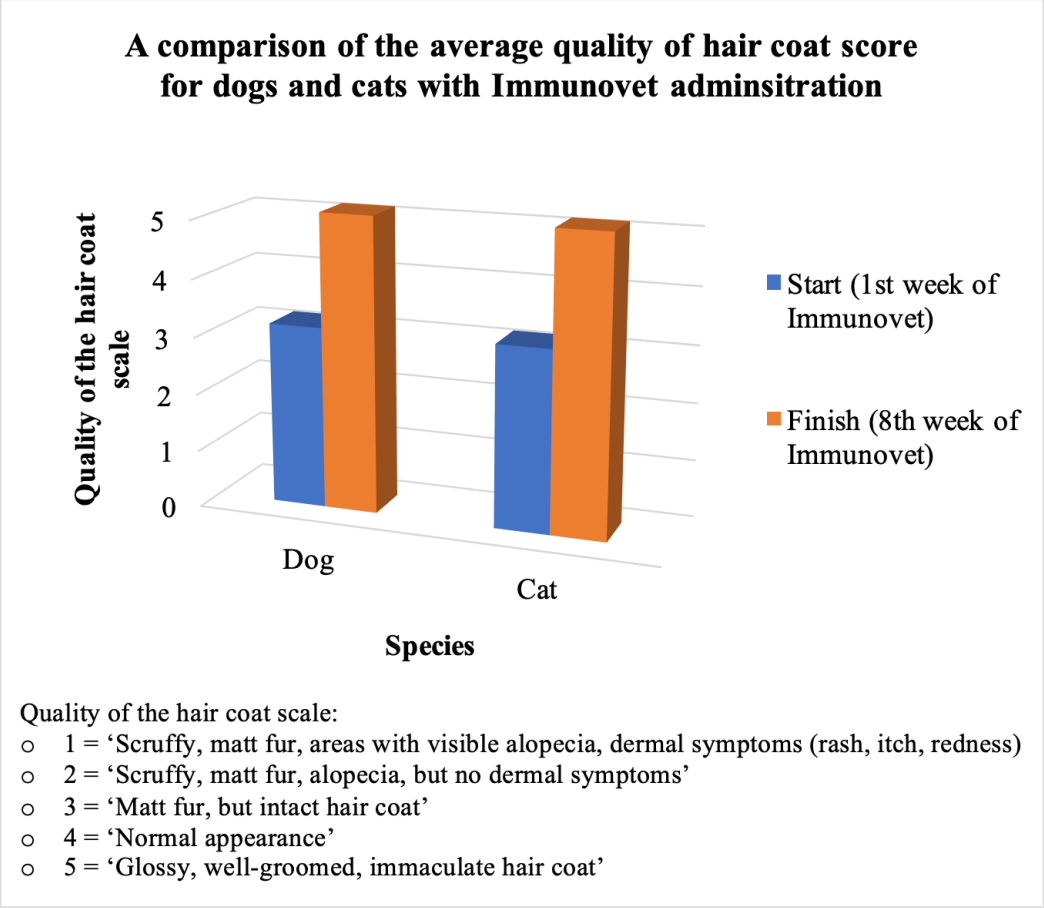


Figure 9: A column chart displaying a comparison of the average quality of hair coat score for dogs and cats

Figure 9 displays that the average quality of the hair coat score for all patients started at level 3 (‘matt fur, but intact hair coat’) and the mean increase after 8 weeks of treatment was 2 levels, increasing to level 5 (‘glossy, well-groomed, immaculate hair coat’). With 8 week of *Immunovet* administration, the average quality of hair coat score increase for dogs was 2 levels and for cats was 2 levels. 8 patients whose quality of hair coat score started at level 1 (‘scruffy, matt fur, areas with visible alopecia, dermal symptoms (rash, itch, redness)’) increased to level 5. 2 patients whose quality of hair coat score started at level 1 increased to level 4 (‘normal appearance’). 4 patients whose quality of hair coat score started at level 2 (‘scruffy, matt fur, alopecia, but no dermal symptoms’) increased to level 5.

1 patient whose quality of hair coat score started at level 2 increased to level 4. 5 patients whose quality of hair coat score started at level 3 increased to level 5. 3 patients whose quality of hair coat score started at level 3 increased to level 4. 2 patients whose quality of hair coat score started at level 3 did not increase. 16 patients whose quality of hair coat score started at level 4 increased to level 5. 14 patients whose quality of hair coat score started at level 4 did not increase.

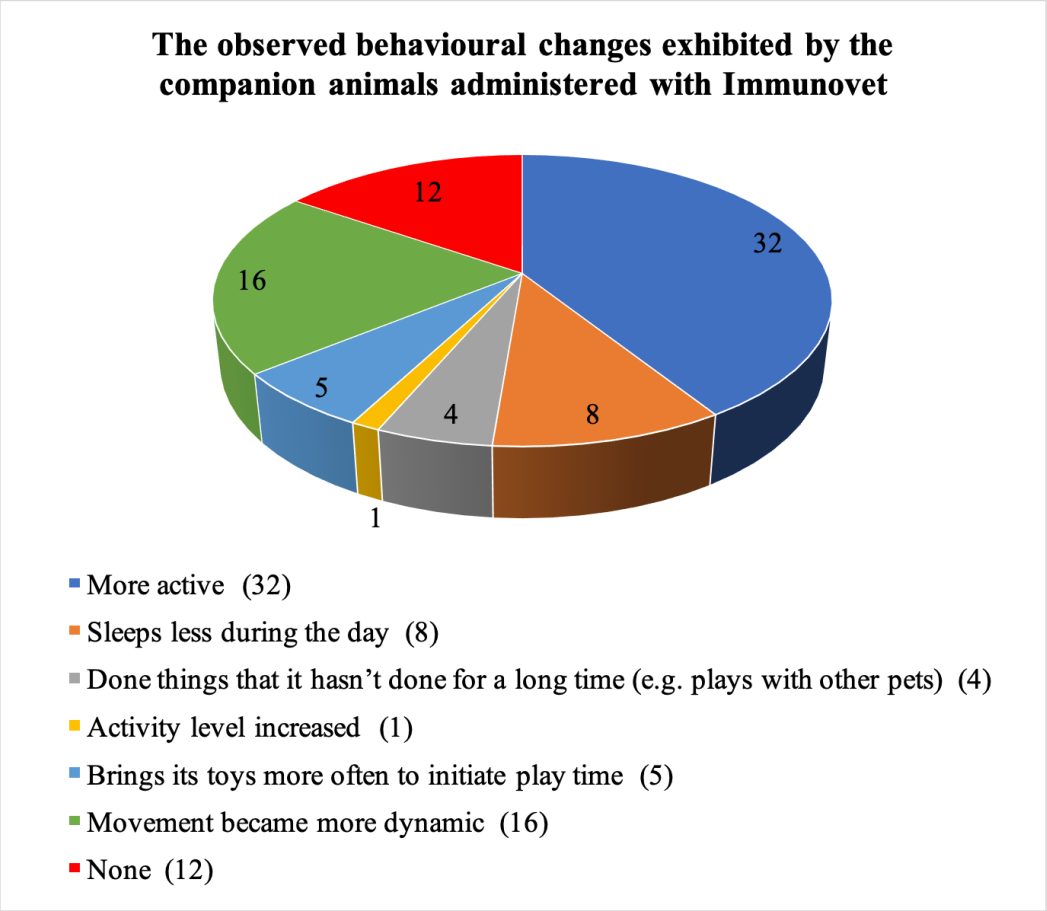


Figure 10: A pie chart showing the observed behavioural changes exhibited by the companion animals administered with *Immunovet*.

In terms of behavioural changes, patients frequently exhibited more than one behavioural change. Figure 10 shows that *Immunovet* administration had a beneficial effect on making the patient more active whereby 32 patients became more active. There was a weaker effect on the activity levels whereby 1 patient's activity level increased. However, *Immunovet* also led to 12 patients experiencing no behaviour changes at all during the investigation.

In addition, 8 patients slept less during the day, 5 patients brought their toys to initiate play time, 4 patients done things they haven't done for a long time (e.g. play with other pets) and 16 patients became more dynamic in their movement.

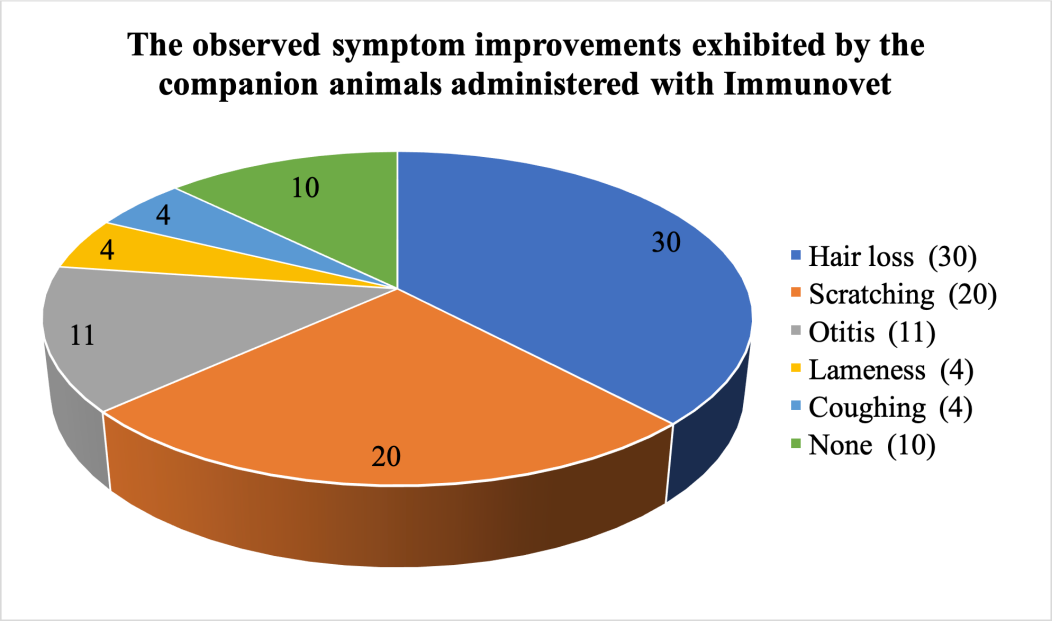


Figure 11: A pie chart showing the observed symptom improvements exhibited by the companion animals administered with *Immunovet*.

In terms of symptom improvements, patients frequently displayed more than one improvement. Figure 11 shows that *Immunovet* administration had a pronounced effect on reducing the hair loss whereby 30 patients experienced an improvement in hair loss. Another positive effect was on the reduction in scratching whereby 20 patients experienced an improvement in scratching. The product also led to 11 patients experiencing an improvement in otitis. In addition, 4 patients experienced an improvement in lameness and 4 patients experienced an improvement in coughing. However, *Immunovet* also led to 10 patients experiencing no symptom improvements. Furthermore, there were no patients experiencing an improvement in decreased hearing or decreased vision.

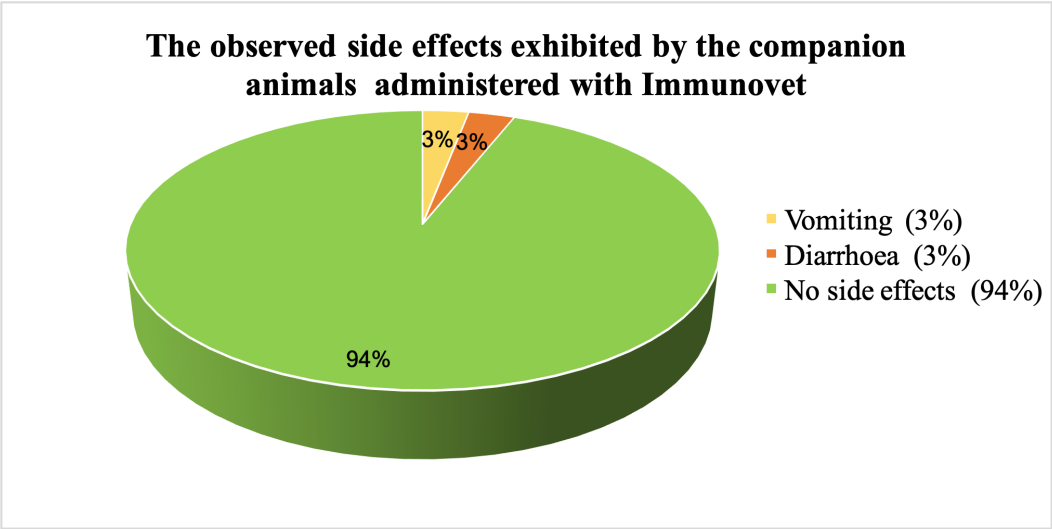


Figure 12: A pie chart displaying the observed side effects exhibited by the companion animals administered with *Immunovet*.

Figure 12 shows that in terms of side effects, out of the 60 patients, over the course of 8 weeks of *Immunovet* administration, approximately 3% experienced vomiting, 3% experienced diarrhoea and 94% of the patients experienced no side effects at all.

5. DISCUSSION

This section will discuss and analyse the results in further detail. The average patient age for dogs used in this study was approximately 6 years old. Regardless of being a small, medium or a large dog, 6 years old is considered as a middle-aged dog, equating to about 43 years in humans. The average patient age for cats used in this study was approximately 10 years old. For both dogs and cats, these are suitable ages to obtain reliable and trustworthy results. This is because at these ages, the animals are usually not immunocompromised, but are also liable to any disease that could affect their immune system. The average weight gain over the course of 8 weeks, was 0.43 kg. Breaking this down by species, the average weight gain for dogs was 0.51 kg, which calculated to approximately 0.06 kg weight gain a week. The average weight gain for cats was 0.27 kg which calculated to approximately 0.03 kg weight gain a week. For both species, *Immunovet* led to a sufficient weight gain, which is not too substantial but also not too small. A rapid increase in weight gain can lead to obesity, which can predispose animals to many health problems, including diabetes and heart disease.

A healthy weight is important for both species to maintain normal metabolic functions and day-to-day activities. *Immunovet* allows animals to remain at a healthy weight and increases weight gain in malnourished animals. As discussed previously, the weight gain as a percentage of the body weight (BW), demonstrated in Figure 6 and 7, is a more accurate way of measuring the increased weight gain of an animal. This is because the percentage takes the initial body weight into consideration, whereas the weight gain in kg does not. The BW of an animal is a very important factor used to determine many entities in veterinary medicine e.g. dosages of drugs. After 8 weeks of *Immunovet* administration, the average weight gain for all dog patients used in this study was approximately 4% of the BW. In general, despite the breed, this is a very respectable weight gain for a dog in an 8-week period. Demonstrated on Figure 6, 6 patients had a 5% weight gain increase in BW, which represents the category with the highest number of patients. This result proves the fact that *Immunovet* has a noteworthy weight gain effect on dogs. Generally, patients with a lower BW will gain weight quicker than those patients with a higher BW, and this can be hypothesised for Patient 50, who had a weight gain of 1kg, correlating to 10% weight gain increase in BW. Visualised in Figure 6, for 6 patients, *Immunovet* did not have an effect, therefore these patients had a 0% weight gain increase in BW. This could be expected, as not all patients will reap the benefits of the product.

After 8 weeks of *Immunovet* administration, the average weight gain for all cat patients used in this study was approximately 6% of the BW. Once again, this is a very good weight gain for a cat in an 8-week period. Exhibited on Figure 7, 5 patients had a 3% weight gain increase in BW, which represented the category with the highest number of patients. This result solidifies the fact that *Immunovet* has a remarkable weight gain effect on cats. It is crucial that an animal's appetite is adequate, so that they consume enough food to meet their nutritional requirements. A decreased appetite can lead to cachexia, which has undesired health effects. *Immunovet's* ability to enhance the appetite of dogs and cats has been demonstrated on Figure 8. This figure shows that for both dogs and cats, the average appetite score at the start (1st day of *Immunovet* administration) was level 2 ('weak appetite, eats less than normal') and increased to level 4 ('increased appetite') after finishing (14th day of *Immunovet* administration) the appetite score investigation. For this level of increase to occur after 14 days of administration, it can be said that *Immunovet* has a strong stimulating effect on the patient's appetite. It especially stimulated the appetite of approximately 33% of the patients at level 1 ('minimal appetite, accepts food only by feeding'') to level 4 ('increased appetite'). For those patients with a low appetite, it can be postulated that they could had been suffering from an underlying condition(s), most commonly of infectious origin. This study has shown that over the course of 14 days, *Immunovet* dramatically increased the appetite of these individuals, which would aid the patients to a faster recovery, as meeting the nutritional requirements allows for normal metabolic processes to occur. It also increased the appetite of approximately 30% of the patients at level 3 ('normal appetite') to level 4. This allows animals at a slightly decreased weight, to reach an ideal healthy body weight. It can be hypothesised that *Immunovet* will not reduce the appetite of companion animals, established by Patient 1 and Patient 42, where both of their appetite scores started at level 5 ('overeating, constantly demands food') and also finished at level 5. There were some patients whose appetite did not change with the administration of *Immunovet*. However, as any natural supplement or drug, the effect varies from individual to individual. Alopecia simply means hair loss and can occur due to many reasons. Examples of causes of alopecia are endocrine problems such as hyperthyroidism in cats and Cushing's disease (hyperadrenocorticism) in dogs. Immunosuppression and stress are also common causes of alopecia. Dermal symptoms (rash, itching and redness) are usually due to an allergic reaction or parasites. *Immunovet's* ability to improve the quality of the hair coat of dogs and cats has been demonstrated on Figure 9.

This figure shows that the average quality of hair coat score for both dogs and cats at the start (1st week of *Immunovet* administration) was level 3 ('matt fur, but intact hair coat') and increased to level 5 ('glossy, well-groomed, immaculate hair coat') after finishing the 8 weeks of *Immunovet* administration. These results reinforce *Immunovet's* ability to increase the quality of the hair coat. Over 8 weeks, *Immunovet* increased approximately 14% of the patients with a hair coat at level 1 ('scruffy, matt fur, areas with visible alopecia, dermal symptoms (rash, itch, redness)') to level 5 ('glossy, well-groomed, immaculate hair coat'). This shows that *Immunovet* has the ability to alleviate the poor hair coat symptom caused by the underlying diseases. *Immunovet's* high concentrations of vitamin E, omega-3 and omega-6 fatty acids are fundamental components for healthy, well-groomed, shiny hair coat, and the results support this. In terms of immunosuppression-associated alopecia, these results show that the product can stimulate the immune system and therefore led to a better hair coat. Immuno-stimulation is supported by scientific literature as previously explained in section 3. It is clear to stipulate that *Immunovet* has a more pronounced effect on the quality of the hair coat of dogs in comparison to cats. This statement is proved by the fact that 6 out of the 8 patients whose level increased from level 1 to level 5 were dogs.

However, in this study, for 10 dogs and 5 cats, *Immunovet* had no effect on the quality of the hair coat at all, establishing that the effect varies from individual to individual. The results determine the fact that *Immunovet* administration led to positive behavioural changes, visualised in Figure 10. 32 patients became more active and 8 patients slept less during the day. For companion animals, these behavioural traits are very important for the owner to be able to build and maintain its rapport and relationship with the animal. These characteristics suggest that the nutritious supplement, *Immunovet*, provided the patients with an increased energy supply, allowing them to become more active and sleep less during the day. *Immunovet's* high concentrations of omega-3 and omega-6 fatty acids decreased joint inflammation and pain and generally allowed animals to move more freely. This is supported by the behavioural change whereby the movement of 16 patients became more dynamic with *Immunovet* administration. From behavioural changes like 'my pet has done things that it hasn't done for a long time (e.g. plays with other pets)' and 'my pet brings its toys more often to initiate play time', one can hypothesise that *Immunovet* can potentially improve cognitive function and makes the animal more experimental with its thoughts and actions. However, 12 patients displayed no behavioural changes at all, reinforcing the fact that the effect varies from individual to individual. *Immunovet* can improve many general symptoms displayed in Figure 11.

There was a reduction in scratching noted in 20 patients, which reinforces *Immunovet's* action of being an anti-inflammatory product, because inflamed areas tend to be very red and itchy. The reduction in scratching also solidifies the antibacterial action of the product, as various bacterial diseases can also cause scratching. Hair loss improvement was observed in 30 patients, which emphasises *Immunovet's* immune strengthening effect and antioxidant capabilities. This symptom also coincides with the quality of the hair coat and occurs due to *Immunovet's* high concentrations of vitamin E, omega-3 and omega-6 fatty acids. There was an improvement in otitis observed in 11 patients, which highlights the antibacterial and anti-inflammatory actions of *Immunovet*. This not only supports the antibacterial action of the product, because many bacterial infections cause otitis, but also the anti-inflammatory action, as otitis is an inflammation of the ear. 4 patients were observed with an improvement of coughing. One of the causes of coughing is pneumonia, which is mainly of bacterial or viral origin, therefore, further supporting the antibacterial and immune stimulatory effect of *Immunovet*. Lameness improvement was observed in 4 patients, which supports the immunomodulation action of the product, as lameness can be caused by immune-mediated diseases such as SLE and RA. This also solidifies the anti-inflammatory action of *Immunovet*, as many orthopaedic conditions cause inflammation of the joints, resulting in lameness, and therefore can be alleviated with either anti-inflammatory substances or drugs. There were no symptoms that deteriorated, however there were no patients who exhibited an improvement with vision or hearing.

Overall, approximately 94% of patients experienced no side effects, which reinforces that *Immunovet* is a very safe product to use. Out of the sample size used in this experiment, only a small percentage of approximately 3% experienced vomiting and approximately 3% experienced diarrhoea. However, diarrhoea and vomiting could have been caused by other external factors and not *Immunovet*. These side effects could also possibly be due to these patients having an intolerance to FWGE.

6. CONCLUSION

Based on the literature review and the results collected, it can be concluded that *Immunovet* has a beneficial effect on the condition and general status of companion animals. It improves the appetite, weight gain and the hair coat of companion animals. These factors have been shown to be improved in both diseased and healthy individuals. Supplementation of *Immunovet* in an animal's diet, results in positive behavioural characteristics and many symptom improvements. The main behavioural changes that were observed were the animal becoming more active and slept less during the day. The most frequent symptom improvements were scratching, hair loss and otitis. To further conclude this article, *Immunovet* is a safe product to use due to many factors, one being it is 100% natural, and it is a non-toxic product, proved by the data collected. There were side effects observed in very few patients, reinforcing the safe usage of *Immunovet*. The antimicrobial, anti-inflammatory, anticancer, antioxidant and immune strengthening effect of *Immunovet* have been proven by both the results collected and the literature review. Through my thesis work, a better understanding on the positive effects of *Immunovet* have been established. Because of this clearer understanding, it will allow practising veterinarians to give better treatment to our companion animals. In general, it would be highly recommended to supplement *Immunovet* into a companion animals diet, due to the above reasons, and also due to the other nutritional benefits e.g. high fibre and high omega-3 and omega-6 fatty acid content. A clear conclusion from the literature review was that the anti-cancer action of *Immunovet* is very strong. During this investigation, the anticancer action was not fully targeted but, future studies could be carried out on patients with cancer and could then be reviewed on how *Immunovet* would work alongside chemotherapy and affects specific types of cancer. However, we could speculate that some of the patients could have been suffering from cancer before the administration of *Immunovet* and therefore a significant improvement was seen after the 8 week course of the product. Based on the literature review, one can hypothesise that *Immunovet* would work synergistically with chemotherapy, and not only would it decrease the undesired side effects, it poses little risk to reduce the efficacy of chemotherapeutic drugs. The results of this study are sufficient to prove the general benefits of *Immunovet*, but going forward, further studies could be carried out on how the product effects specific conditions. For example, specific bacterial infections, or inflammatory diseases and how *Immunovet* combats these conditions.

7. SUMMARY

Immunovet is a product that is made from fermented wheat germ extract (FWGE), which possesses many health benefits to companion animals due to its molecular targets in the body. The molecules thought to be responsible for many of the biological benefits are 2-methoxy-p-benzoquinone and 2,6-dimethoxy-p-benzoquinone, however this has not yet been confirmed. FWGE has a significant anticancer, antimicrobial, anti-inflammatory, antioxidant and immune strengthening effect.

In this study, a sample size of 60 companion animals were used to collect data regarding the beneficial effects of using *Immunovet*. The owners were given the granulated form of the product, and over the course of 8 weeks, 1 measuring spoon/ 10kg body weight was given *per os*. Each owner was given a questionnaire for them to keep track of the patient's progress over this 8-week-period. The weight gain, the animals appetite, the animals quality of hair coat, the behavioural changes and symptom improvements were noted on the questionnaire during this period. The main findings were that *Immunovet* increases the weight, stimulates the appetite, improves the quality of the hair coat, inflicts positive behavioural changes and improves general symptoms of companion animals. To conclude, based on the literature review and the results collected, *Immunovet* had a beneficial effect on the condition and general status of companion animals. The anticancer, antimicrobial, anti-inflammatory, antioxidant and immune strengthening effect were proven by both the results collected and the literature review. Overall, this allows one to assume that *Immunovet* would be very beneficial to use in clinical practice today, to alleviate certain problems that companion animals face e.g. inflammation, bacterial infection and many more. Furthermore, *Immunovet* would operate synergistically with other drugs that are used during treatment of diseases, and even has the potential to potentiate these drugs.

8. ÖSSZEFOGLALÁS

Az Immunovet egy olyan termék, ami erjesztett búzacsírakivonatból készül (FWGE). Az FWGE számos kedvező hatással bír háziállataink szervezetére. A molekulák, amelyek a fő hatásokért felelősek, a 2-metoxi-p-benzokinon és a 2,6-dimetoxi-p-benzokinon, de emellett a kivonat más, nem ismert hatóanyagot is tartalmazhat. Az FWGE jelentős rákellenes, vírusellenes, gyulladáscsökkentő, antioxidáns és immunerősítő hatással rendelkezik.

Jelen dolgozatban szereplő felmérésben 60 kedvtelésből tartott állat (kutya és macska) adatait gyűjtöttük össze, és vizsgáltuk az Immunovet jótékony hatásait. Az állatok a granulátum gyógyszerformát 8 héten keresztül, 1 mérőkanál/10 testtömeg-kg adagban kapták szájon át. A tulajdonosok egy kérdőív rendszeres vezetésével regisztrálták háziállataik súlygyarapodását, táplálékfelvételét, a szőrzet minőségének és a kondíciónak az alakulását. A fő megfigyelések szerint az Immunovet növelte az étvágyat és a testtömeget, javította a szőrzet minőségét, pozitív viselkedési változásokat okozott és számos kedvező hatással rendelkezett az állatok szőrzetének és mozgásának alakulása szempontjából. Összefoglalva, az összegyűjtött eredmények alapján az Immunovet jótékony hatással volt az állatok általános állapotára. A rákellenes, antimikrobiális, gyulladáscsökkentő, antioxidáns és immunerősítő hatások további feltárására további vizsgálatok szükségesek. Az Immunovet tehát egy potenciálisan szóba jövő táplálékkiegészítő az állatok általános állapotának javítására, étvágyuk és testtömegük gyarapítására. Továbbá, számos más előnyt is feltételezünk, melyek tisztázása későbbi vizsgálatok feladata.

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11. APPENDICES

11.1 Appendix 1: Results

The following, is the table of the results collected from the 60 patients examined during this investigation.

Patient	Breed	Age (Years)	Weight gain (kg)	Weight gain (%) of BW*	Appetite			Quality of hair coat			Behavioural changes observed	Symptoms improved	Side effects observed
					Start	Finish	Change	Start	Finish	Change			
Patient 1	Dog	1	0.3	2%	5	5	0	4	5	1	More active, sleeps less during the day, brings its toys more often to initiate play time	Hair loss	None
Patient 2	Cat	15	0.2	4%	3	3	0	3	5	2	Sleeps less during the day	Scratching, hair loss	None
Patient 3	Dog	10	0.2	3%	3	4	1	4	5	1	More active, sleeps less during the day	None	None
Patient 4	Dog	1	0.8	5%	1	4	3	1	5	4	More active, movement became more dynamic	Hair loss	None
Patient 5	Cat	17	0.1	3%	3	4	1	3	3	0	None	Coughing	None
Patient 6	Cat	10	0.3	3%	1	4	3	3	3	0	More active, movement became more dynamic	None	Vomiting
Patient 7	Dog	14	1.5	8%	3	4	2	4	5	1	None	Otitis	Vomiting
Patient 8	Dog	1.5	0.3	3%	3	4	1	3	5	2	More active	Scratching, hair loss, otitis	None
Patient 9	Dog	5	0.2	2%	1	4	3	1	5	4	Sleeps less during the day, more active	Hair loss, otitis, lameness	None
Patient 10	Dog	1.6	0.4	3%	1	4	3	1	5	4	Done things that hasn't done for a long time (e.g. plays with other pets), brings its toys more often to initiate play time	Scratching, hair loss	None
Patient 11	Dog	1	0.4	3%	1	4	3	2	5	3	More active, movement became more dynamic	Scratching, hair loss, otitis	None
Patient 12	Dog	10	0.1	1%	1	4	3	1	5	4	More active	Scratching, hair loss, otitis	None
Patient 13	Dog	2.5	0.1	1%	1	4	3	1	5	4	More active, movement became more dynamic	Scratching, hair loss	None
Patient 14	Cat	13	0.2	3%	1	3	2	4	4	0	More active	None	None
Patient 15	Dog	3	0.7	5%	2	4	2	2	5	3	Done things that hasn't done for a long time (e.g. plays with other pets), activity level increased	Scratching, hair loss, coughing	None
Patient 16	Dog	14	0.8	5%	1	4	3	1	5	4	More active	Lameness	None
Patient 17	Dog	14	3	8%	2	4	2	1	4	3	None	Otitis	None
Patient 18	Cat	8	0.6	10%	2	4	2	4	5	1	More active, sleeps less during the day	Hair loss	None
Patient 19	Cat	9	0.2	3%	3	4	1	3	5	2	More active, movement became more dynamic	Scratching, hair loss	None
Patient 20	Dog	12	1.4	6%	3	3	0	4	5	1	Movement became more dynamic	Scratching	Diarrhoea

Patient 21	Dog	9	0.2	3%	3	4	1	4	4	0	Sleeps less during the day	Otitis	None
Patient 22	Dog	5	0.5	4%	2	4	2	3	5	2	Movement became more dynamic, more active	Scratching, hair loss, otitis	None
Patient 23	Dog	10	0.2	2%	3	4	1	4	5	1	Done things that hasn't done for a long time (e.g. plays with other pets)	Scratching, otitis	Diarrhoea
Patient 24	Cat	11	0.4	4%	2	4	2	2	5	3	None	Otitis	None
Patient 25	Dog	6	0.5	5%	3	4	1	4	5	1	More active, movement became more dynamic	None	None
Patient 26	Cat	3	0.3	7%	3	4	1	1	5	4	None	Hair loss	None
Patient 27	Cat	9	0.1	3%	3	3	0	2	5	3	Sleeps less during the day	Hair loss	None
Patient 28	Dog	4	0.5	2%	3	4	1	3	4	1	None	Otitis	None
Patient 29	Cat	7	0.2	5%	1	4	3	1	5	4	More active	Scratching, hair loss	None
Patient 30	Cat	8	0.3	6%	3	4	1	2	4	2	More active, movement became more dynamic	Scratching, hair loss	None
Patient 31	Dog	1	0	0%	4	4	0	4	5	1	More active	Scratching	None
Patient 32	Dog	4	0	0%	3	3	0	4	4	0	More active	Scratching	None
Patient 33	Dog	5	0	0%	3	3	0	4	4	0	More active	Scratching	None
Patient 34	Dog	11	0	0%	4	4	0	4	4	0	None	Scratching	None
Patient 35	Dog	8	1	5%	3	4	1	4	4	0	More active	Scratching	None
Patient 36	Dog	3	0.5	4%	3	4	1	4	4	0	More active	Scratching	None
Patient 37	Dog	7	0.1	3%	4	5	1	3	4	1	More active	Hair loss	None
Patient 38	Cat	14	0.3	8%	3	3	0	4	4	0	More active	Hair loss	None
Patient 39	Dog	4	0.5	7%	1	4	3	4	4	0	More active	Hair loss	None
Patient 40	Cat	11	0.2	8%	3	3	0	4	4	0	None	None	None
Patient 41	Cat	10	0.4	9%	1	4	3	4	4	0	None	Hair loss	None
Patient 42	Dog	10	0.1	1%	5	5	0	4	4	0	None	None	None
Patient 43	Dog	7	0.5	4%	3	4	1	4	5	1	Playing again	Lameness, coughing	None
Patient 44	Cat	7	0.2	4%	3	4	1	4	5	1	Done things that hasn't done for a long time (e.g. plays with other pets)	Scratching	None
Patient 45	Dog	6	0.4	4%	3	4	1	4	5	1	Movement became more dynamic, brings its toys more often to initiate play time	None	None
Patient 46	Did not eat Immunovet												
Patient 47	Cat	10	0.4	8%	3	4	1	3	5	2	Movement became more dynamic	Hair loss	None
Patient 48	Dog	6	0.3	9%	1	4	3	1	4	3	More active	Hair loss	None

Patient 49	Dog	3	0.3	8%	1	4	3	4	4	0	More active	Hair loss	None
Patient 50	Dog	8	1	10%	1	4	3	4	4	0	More active	None	None
Patient 51	Dog	1	0.2	5%	3	3	0	4	5	1	More active	None	None
Patient 52	Cat	5	0.4	10%	1	4	3	3	4	1	More active	Hair loss	None
Patient 53	Dog	4	0	0%	2	3	1	3	5	2	More active, movement became more dynamic	Lameness	None
Patient 54	Cat	15	0.2	5%	1	3	2	3	4	1	Sleeps less during the day, movement became more dynamic	Hair loss, coughing	None
Patient 55	Dog	10	0	0%	1	3	2	4	5	1	More dynamic	None	None
Patient 56	Cat	10	0.3	6%	1	4	3	4	5	1	More active, more dynamic, more frequent playing	Hair loss	None
Patient 57	Dog	1	1	8%	1	4	3	4	5	1	Movement became more dynamic	Hair loss	None
Patient 58	Cat	2	0.1	2%	1	4	3	3	5	2	Nome	Hair loss	None
Patient 59	Dog	6	1.5	8%	1	4	3	4	5	1	None	Hair loss	None
Patient 60	Did not eat Immunovet												

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