New Approaches in Veterinary Physiology

Editor
Hikmet Yeter Çoğun

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CHAPTER I

The Effect of Various Antioxidant Substances on Fracture Healing

İsa Can UYGURALP[1]
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Introduction

The defense systems that work in the body to prevent the formation of reactive oxygen species, prevent the damage caused by these substances, and detoxify against the toxic effects of free radicals are called "antioxidant defense systems" or "antioxidants". Antioxidants are defined as substances that delay or prevent the

[1] Doktora Öğrencisi, Burdur Mehmet Akif Ersoy Üniversitesi, Veteriner Fakültesi, Fizyoloji Anabilim Dalı
[2] Doç. Dr., Burdur Mehmet Akif Ersoy Üniversitesi, Veteriner Fakültesi, Fizyoloji Anabilim Dalı
[3] Prof. Dr., Burdur Mehmet Akif Ersoy Üniversitesi, Veteriner Fakültesi, Fizyoloji Anabilim Dalı

autooxidation and peroxidation of the substrate when encountered with oxidizable substrates such as lipids, proteins, DNA, and carbohydrates even at very low concentrations in biological systems (Frankel and Meyer, 2000; Karabulut and Gülay, 2016).

Antioxidants can be found in both the fluid and membrane parts of cells. While antioxidants neutralize free radicals by giving their electrons, they do not themselves turn into free radicals even though they give electrons because antioxidants are stable in both forms (Kaur and Kapoor, 2001). These unique functions of antioxidants suggest that they can play a positive role during bone fracture healing. Thus, researchers have been investigating different antioxidants to postulate the effect of antioxidants on bone fractures. In this review, the effects of different antioxidants on fracture healing will be discussed.

Free Radicals

In atoms, electrons are located in pairs in a spatial region called an "orbital". Although most molecules have paired electrons, a small number of molecules have single electrons or missing one pair. These molecules with missing electrons interact with any electron they can find. They can either take an electron from or give an electron to that molecule. High-energy atoms or molecules carrying unpaired electrons in the outer orbit can easily exchange electrons with different molecules during physiological or pathological reactions. As a result, these molecules disrupt their structure and are defined as free radicals. Free radicals can be formed by endogenous or exogenous sources. Since free radicals have high reactivity, they cause tissue damage by reacting with polyunsaturated fatty acids in the structure of the cell membrane, nucleotides in DNA, and sulfhydryl groups of proteins (Altan et al., 2006; Altıner et al., 2017).

To maintain cellular homeostasis, there is a balance between the rate of formation of free radicals and the rate at which they are neutralized by antioxidants. This is called oxidative balance. Balancing the continuous oxidative stress by the antioxidant system

and neutralization of oxidative stress components are necessary for the organism to continue its existence. However, in some pathological conditions, more reactive radicals are formed than the cellular defense systems can neutralize. The shift of the balance between this oxidant-antioxidant system in favor of free radicals is called oxidative stress. Oxidative damage occurs when oxidative stress increases and the antioxidant system is unable to compensate for this situation. Oxidative damage plays a role in the etiology of many conditions such as diabetes mellitus, cancer, neurological diseases, and delayed fracture healing (Savaş, 2019).

Oxidative Stress and Fracture Healing

Free radicals can have a twofold effect on bone metabolism according to physiologic and pathologic conditions. Under normal conditions in the organism, free radicals produced by osteoclasts in bone tissue contribute to bone remodeling by increasing the destruction of calcified tissue. Due to fractures in bone tissue, free radicals are produced in very high amounts and have undesirable consequences on bone health (Sontakke and Tare, 2002).

Decreased blood flow due to vasoconstriction in the early period after fracture causes transient ischemia. Following these events, the reperfusion period begins with arterial vasodilation, migration of inflammatory cells (leukocytes, macrophages, and mast cells) to the area, and formation of new vessels. During this period, free oxygen radicals are produced by both inflammatory cells and osteoclasts with reperfusion. It has been reported that free oxygen radicals produced by the activation of polymorphonuclear leukocytes disrupt granulation tissue and delay fracture healing (Durak et al., 1996; Gurley and Roth, 1992;).

One of the best indicators of cellular damage caused by free radicals is lipid peroxidation. The extent of this damage can be measured by the level of malondialdehyde (MDA) released in serum or tissue. High MDA levels indicate the presence of high levels of free radicals. Various studies have shown an increase in MDA production in blood and bone tissues during fracture healing. It is

also known that lipid peroxidation increases bone resorption by directly activating osteoclasts (Garrett et al., 1990).

The Effect of Various Substances with Antioxidant Properties on Fracture Healing

N- Acetyl Cysteine. N-acetylcysteine (NAC) is a thiol that acts as the acetylated precursor of the amino acid L-cysteine. It shows direct antioxidant activity due to the ability of the free thiol group to interact with reactive oxygen and nitrogen. N-acetylcysteine is the main active ingredient approved by the Food and Drug Administration (FDA) and recognized by the World Health Organization. It has active use as a mucolytic in paracetamol poisoning and respiratory disorders. Its primary role is associated with antioxidant and anti-inflammatory activity (Yildirim, 2023).

N-acetylcysteine has many pharmacological effects on osteoblasts thanks to its antioxidant properties. It has been proven to promote bone regeneration on implant biomaterial, prevent wound infection, and enhance biomaterial-cell compatibility (Yildirim, 2023).

Jun et al. (2008) reported that glutathione synthesis accelerated and osteogenic activity increased in cell culture taken from rat frontal and parietal bones in a study conducted to observe the effect of NAC in rats. In the study conducted by Yildirim (2023), NAC administration in rats contributed to fracture healing significantly in a histopathologic manner in the group supplemented with NAC.

Alpha Lipoic Acid. Alpha lipoic acid (ALA) is an important antioxidant containing the thiol group found in physiological systems. In addition to eliminating the effects of reactive oxygen molecules, ALA is also involved in regenerating antioxidants such as vitamin C, vitamin E, and glutathione and making them reusable.

In a study by Gürsesli (2021) investigating the effect of ALA on bone resorption in osteoporotic rats, positive changes were observed in all parameters evaluated in the group given ALA orally.

It was found that there was a statistically significant increase in bone volume, trabecular thickness, and width, as well as a decrease in inter-trabecular distance. It was observed that the micro-architectural structure of osteoporotic bone was strengthened with ALA administration.

Selenium. Selenium is one of the essential trace elements for the body. Selenium deficiency has been shown to cause growth retardation and changes in bone metabolism. Low selenium intake has been reported to pose a high risk for bone diseases. It is known that 9 selenoproteins are synthesized in fetal osteoblasts and these selenoproteins synthesized by bone cells contribute to the defense of bone microarchitecture against oxidative stress. Selenium is found in the structure of enzymes that protect tissues against free oxygen radicals.

Burgucu (2016) created an experimental femur fracture in rats to investigate the effect of selenium on fracture healing and gave a high dose of selenium to one group and a low dose of selenium to the other group. In the early period, histopathologic and radiologic fracture healing was significantly better in the group given high-dose selenium. In the late period, although the average score of the group given high-dose selenium was higher, no statistical difference was reported.

Melatonin. The hormone melatonin, secreted by the pineal gland, and its secretion increase in the dark. Melatonin is a very powerful and effective radical scavenger and antioxidant. It is also responsible for the regeneration of cells, strengthening the immune system, and regulating sleep rhythm and body temperature. It forms a primary nonenzymatic defense mechanism against the destructive effects of highly reactive hydroxyl radicals (Atasoy, 2019; Delibaş and Özcankay, 1995).

Halıcı et al. (2010) created fractures in rats to investigate the effect of melatonin on fracture healing. Intraperitoneal melatonin was given to one group and the other group was considered as the controls. They reported that malondialdehyde levels in the melatonin

group were lower than in the control groups on days 3, 7, 14, and 28. They also reported that myeloperoxidase level was significantly decreased in the melatonin group compared to the control group on days 1, 3, and 7. It was also reported that fracture healing was significantly more advanced in the melatonin group and radiologically complete bone healing was observed earlier than in controls (Halıcı et al., 2010).

Vitamin E (Alpha Tocopherol). Vitamin E is a fat-soluble vitamin. The aromatic ring in its structure contains a phenolic hydroxyl group. This aromatic ring forms the active part of the molecule and gives it its antioxidant properties. The compounds that give Vitamin E activity are chemically known as tocopherol. The most important feature of vitamin E is its ability to neutralize free oxygen radicals and peroxides through its antioxidant activity. Vitamin E is the most powerful antioxidant factor that can neutralize free oxygen formed as a result of lipid peroxidation. Other antioxidant systems of the body, such as vitamin C, glutathione peroxidase, and β-carotene, are not as effective as vitamin E. Due to its high lipid solubility, vitamin E can easily diffuse into membrane phospholipids and has a stabilizing effect by protecting all cell membranes against oxidative damage (Altıner et al., 2017).

In one study, vitamin E was reported to affect the longitudinal growth of bone by increasing the amount of trabecular bone and osteoid volume by an unknown mechanism. In another study, vitamin E had a positive effect on bone tissue by increasing trabecular formation and preventing calcium loss through oxidizing agents.

Türk et al (2004) investigated the effects of vitamin E on bone fracture healing in rats. The rats in the experimental group were administered 20 mg/kg vitamin E i.p. every day, while the rats in the control group were injected with saline. The rats in both groups were sacrificed on the 15th, 46th, and 60th days. In the histopathologic and radiographic examinations, bone fracture healing was significantly better in the vitamin E-treated group compared to the

controls. The researchers concluded that vitamin E may have a positive effect on the early and late stages of fracture healing.

In another study, rabbits were administered 20 mg/kg I.M. vitamin E daily for 5 days starting 1 hour before fibula fractures. In the histopathologic examination of the tissue samples taken from the fracture site 4 weeks after the fracture, the overall fracture healing of the animals in the experimental group was better than the control group. They concluded that vitamin E applied prophylactically in the early period after the fracture would positively affect fracture healing (Keskin et al., 2010).

Durak et al. (2003) investigated the effects of vitamin E on fracture healing in rabbits. In the experimental group, 20mg/kg vitamin E was administered I.M. for 5 days starting 1 hour before the fracture. The investigators concluded that bone fracture healing was statistically significantly better in the experimental group. They reported that vitamin E positively affects healing by eliminating free radicals formed in the inflammation phase of fracture healing and that this agent can be used as a supportive drug in fracture cases.

Durmuş et al. (2008) investigated the effect of dl-alpha-tocopherol-acetate on fracture healing in experimental diaphyseal radius fractures in dogs and reported that dl-alpha-tocopherol acetate given for one week immediately after the fracture had a positive effect on fracture healing in dogs. They attributed the fact that dl-alpha-tocopherol acetate was more effective in the early period to its antioxidant effect on free oxygen radicals formed in the fracture site.

Vitamin C (Ascorbic Acid). Ascorbic acid is one of the essential water-soluble vitamins necessary for the normal metabolic functions of the human body. Ascorbic acid, a six-carbon lactone, is synthesized from glucose by many animals. Synthesis takes place in the liver in some mammals and in the kidneys in birds and reptiles. Humans, on the other hand, cannot perform this biosynthesis due to mutations in the gene encoding L-guano γ-lactone oxidase, a terminal enzyme in the vitamin C biosynthesis pathway, and must take it from outside (Uğur et al., 2020).

Vitamin C is a powerful antioxidant with the ability to donate electrons. Vitamin C stimulates the synthesis of collagen, the most important component of the extracellular bone matrix, and the formation of osteoblasts, bone-forming cells. It is also thought to reduce oxidative stress as it scavenges free radicals, which are harmful to bone health, thereby preventing bone resorption and protecting against osteoporosis. In epidemiologic studies, it has been found that patients with vitamin C deficiency have a significant increase in the risk of osteoporosis and fractures due to decreased bone formation. In addition, preclinical studies show that vitamin C has the potential to accelerate bone healing after fracture, increase type I collagen synthesis, and reduce oxidative stress parameters (DePhillipo, 2018; Uğur et al., 2020; Pınarlı, 2023).

Yılmaz et al. (2001) examined the effect of various minerals and vitamins on fracture healing. 16 rats were divided into control and vitamin C-treated groups. The right tibiae of all rats were fractured. One group received intramuscular high-dose vitamin C. On the 5th, 10th, 15th, and 20th days, two rats from each group were sacrificed and the tibias were examined under the microscope. They reported that the fracture healing stages of the vitamin C-treated group were faster than the control group.

In another study, a total of 80 aged rats with osteogenic disorders were divided into four groups with different vitamin C intake rates. The femur of each rat was fractured. Five weeks after the fracture, the femur was analyzed by mechanical and histological tests. Groups with lower vitamin C intake showed lower mechanical resistance in the healing callus and a lower rate of histological healing. Vitamin C levels in the blood during healing periods are linked to the resistance of the formed callus. Therefore, supplemental vitamin C has been concluded to improve the mechanical resistance of fracture callus in aged rats (Alcantara-Martos et al., 2007).

Taurine. Taurine (2-aminoethane sulfonic acid) is a phylogenetically ancient molecule that is widespread in the

biosphere. It is found in very high concentrations in algae and the animal kingdom but is very rare in plants. Taurine is found in many tissues, especially in polymorphonuclear leukocytes and the retina; its antioxidant properties are effective in bile acid conjugation, detoxification, membrane stabilization, osmoregulation, and neurotransmission functions; it is frequently emphasized that it has a healing role in oxidative damage such as cardiovascular diseases, macular degeneration, wound healing, and alcoholism. It is also the most abundant intracellular free amino acid in skeletal and cardiac muscle. Considering that taurine plays a role in physiological and biochemical events, it can be said that one of the most important properties of taurine is its antioxidant effect, so it should be emphasized in daily life and medical practices (Biçer et al., 2018; Karafakıoğlu, 2010).

Taurine is abundant in bone tissue and affects bone metabolism. It has been shown that taurine stimulates bone matrix formation, alkaline phosphatase, and collagen synthesis in osteoblast-like (UMR-106) cells. Taurine has also been shown to inhibit bone resorption and osteoclast formation. The effect of taurine on bone loss may be explained by its inhibition or regulation of inflammatory mediator release. Taurine can also bind directly to PGE2 and inactivate this cytokine. This inactivation also inhibits PGE2-induced osteoclast formation (Biçer et al., 2018; Karafakıoğlu, 2010).

Biçer (2010) divided rabbits into two groups in his study to observe the effect of taurine on experimental fracture healing. The experimental group was given taurine via the orogastric route. When the control group was compared with the experimental group, it was reported that the histological maturation of the callus was at a more advanced stage in the group given taurine, the radiological healing score was higher in the group given taurine on the 21st day, and a higher proportion of subjects in the group given taurine had ossified tissue in the callus. In addition to this finding, Biçer et al. (2018) also reported that the radiologic and histologic bone healing obtained in the taurine group on day 21 was significantly more pronounced in

the experimental study conducted to observe the effect of taurine on fracture healing. They also reported a decrease in MDA levels on the 7th and 14th days.

Propolis. Propolis is an apitherapeutic natural product produced by honey bees in the hive after being collected from the bark of trees, buds, and shoots of plants, insoluble in water, usually yellow, green, and brown depending on the source of collection, and the age of the propolis. It is a sticky substance mixed with beeswax, partially digested by salivary enzymes (β-glycosidase) from the bees' resin and buds. It has a very strong protective effect against bacteria, viruses, and fungi and bees use propolis in ventilation zones inside the hive, at the entrance and exit of the hive against external bacterial, viral, and fungal threats. Although propolis has low water solubility, it dissolves well in alcohol (Memmedov et al., 2017).

The chemical components of propolis are flavonoids, phenolic acids, glycosides, and aglycones. Especially flavonoids and phenolic acids are the biological components of propolis that show the main antioxidant and anti-inflammatory effects. They show antioxidant properties by inhibiting enzymes such as xanthine oxidase and capturing free radicals generated by neutrophils. In addition, the high antioxidant properties of propolis are due to its caffeic acid and derivatives of caffeic acid, ferulic acid, hydrocinnamic acids such as caffeic acid phenyl ester, hydrobenzoic acids such as protocatechic acid and gallic acid, and compounds with strong antioxidant effect in emulsion and lipid system (Çoşkun and İnci, 2020; Memmedov et al., 2017).

In an experiment, the effect of propolis on fracture healing. Rats were divided into two groups by creating an experimental fracture. In the propolis group, 2.5% liquid propolis extract was applied IM to the fracture site as 0.5 cc once after the fracture was formed, while no drug was applied to the control group. As a result of the radiologic evaluation, it was reported that the callus area in the propolis group was significantly better than the control group on all days except the 7th day and followed a gradually increasing course.

In addition, according to the results of callus matrix density evaluation; it was observed that the Bbone matrix density values in the propolis group increased on all days compared to the control values, and as a result, mineralization accelerated due to propolis. In the histopathological examination, the differentiation of bone precursor cells was faster in the propolis group compared to the controls and the callus passed from the pro-callus to the fibrocartilaginous and osseous callus faster in the propolis-administered group.

Quercetin. Quercetin is a crystalline solid antioxidant substance with a yellow, bitter taste and is the most common spontaneously occurring flavonoid in nature. Flavonoids are widely found in plants and quercetin is found in plants and food products such as onions, tea, coffee, ferns, and natural dyes. Quercetin has much stronger antioxidant properties compared to other flavonoids. Due to three different groups in their biochemical structure, flavonoids scavenge free radicals and gain antioxidant properties. In diseases with tissue damage due to ischemia-reperfusion, quercetin has been shown to have protective properties with its scavenging effect on free radicals (Yurteri, 2020).

Yurteri (2020) examined the effect of quercetin on fracture healing in rats with an open fracture model. The results implicated that quercetin increased the callus diameter in the group given quercetin, especially in the later period of bone healing, and also increased the callus resistance in the early and late periods. Quercetin treatment also contributed to healing histologically and biochemically in the following periods.

Ginkgo Biloba. Ginkgo biloba belongs to the Ginkgoaceae family. EGb 761 is a plant extract obtained from the leaves of the Ginkgo biloba tree. It contains chemical substances not found in other living things. The main components are 22-27% flavone glycosides (quercetin, isorhamnetin; biflavones and amentoflavone), 5-7% terpenic lactones (ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide M, ginkgolide J, and bilobalide) as well as other

components such as proanthocyanidins, organic acids (hydroxyquinurenic acid, quinolinic acid, protocatechuic and vanillic acid), ozone, ginkgolic acid, D-glucaric acid. EGb 761, especially ginkgolide B, is a molecule that antagonizes the Platelet-activating factor (PAF) and shows an antioxidant effect (Güzel, 2011).

Güzel (2011) examined the effect of ginkgo biloba (egb 761) on fracture healing in rats. He formed two groups with rats and gave Ginkgo biloba (EGb761) 60mg/kg orogastrically once a day to the experimental group and determined the other group as the control group. When the Ginkgo biloba group and the control group were compared radiologically, it was reported that there was a statistically significant difference in favor of Ginkgo biloba in terms of bone formation on the 21st day. In addition, histologically, it was reported that there was a statistically significant difference in favor of the Ginkgo biloba group on the 21st and 35th day.

Silymarin. Silybum marianum is known to have existed in Mediterranean countries and Europe since ancient times. Since 1954, scientists were aware that this plant contained flavonoids, but in the 1960s, German scientists discovered a group of active substances and named them all together 'Silymarin'. Silymarin, which has been used for the treatment of hepatitis and cirrhosis for hundreds of years and obtained from the extract of the milk thistle plant, is a polyphenolic flavonoid (Öngel, 2017).

The effect of silymarin on fracture healing in rats was examined. The rats were divided into 2 groups silymarin and control. In radiologic evaluation, there was a significant improvement in the silymarin group compared to the controls. Histopathologically, the differentiation of bone precursor cells was faster in the silymarin group compared to the control group. Moreover, the callus passed from the proximal to the fibrocartial and osseous callus faster in 21 days (Öngel, 2017).

Icariin. Icariin is a flavonoid derived from Epimedium grandiflorum, a perennial herb used for centuries in traditional

Chinese medicine as a skin tonic, aphrodisiac and anti-rheumatic. Icariin has strong anti-inflammatory and antioxidant effects.

Gürbüz (2014) examined the effects of icariin on fracture healing. He divided the rats into groups and gave various amounts of icariin to the groups except for the controls. When radiologic and histologic results were examined, it was reported that fracture healing was better in the groups given icariin. After comparing the bone mineral density measurements, it was concluded that fracture healing was better in icariin-treated groups compared to control groups.

Flaxseed Oil. Flaxseeds are rich in protein and fat, with a fat content between 35% and 45%. Flaxseed oil is a polyunsaturated fatty acid with alpha-linolenic acid as the main fatty component. It is also rich in omega-3 and fiber. Herbasetin and herbasetin-3,8-O-diglucopyranoside aglycone are isolated from flaxseed oil and responsible for the antioxidant activity of flaxseed oil (Görmez, 2018).

Görmez (2018) investigated the effects of flaxseed oil on fracture healing in rats. As a result of the experiment, flaxseed oil showed a significant antioxidant effect and radiological improvement in the early period of fracture healing. In addition, it showed a positive effect during the entire healing period histologically.

Conclusion

Fractures are common traumatic lesions and fracture repair relies on complex biological mechanisms and mechanical mediators. For a fracture repair with the desired characteristics, it is crucial to assess the fracture site and fracture type, maintain bone blood supply, and select treatment procedures that support the appropriate biological environment and optimize mechanical factors. Various therapeutic, physical, and biological treatment options are effective at different stages of the fracture healing phase. Efforts should

continue to develop new treatment modalities by creating favorable conditions and increasing the skill in fracture healing.

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CHAPTER II

Physiology of Fracture Healing

İsa Can UYGURALP[1]
Özlem YILDIZ GÜLAY[2]
Mehmet Şükrü GÜLAY[3]

Introduction

Bones are highly vascularized and innervated organs consisting of bone tissue, bone marrow, and a surrounding connective tissue-the periosteum. The bone structure is a component of the skeletal system that protects, supports, and provides movement of the body and is also a site of protection and production for specialized tissues such as bone marrow that are responsible for blood formation (Barrere et al., 2006; Tunçay, 2003).

[1] Doktora Öğrencisi, Burdur Mehmet Akif Ersoy Üniversitesi, Veteriner Fakültesi, Fizyoloji Anabilim Dalı
[2] Doç. Dr., Burdur Mehmet Akif Ersoy Üniversitesi, Veteriner Fakültesi, Fizyoloji Anabilim Dalı
[3] Prof. Dr., Burdur Mehmet Akif Ersoy Üniversitesi, Veteriner Fakültesi, Fizyoloji Anabilim Dalı

The most important function of bone tissue is to provide the rigidity necessary for skeletal movement and the protection of vital organs. Other important functions of bone tissue include providing mobility and support to the body, the formation of blood cells (hematopoiesis), providing a buffer to adjust the acid-base balance in common organ dysfunctions and acting as a storage for mineral substances such as calcium, phosphorus, growth factors, and cytokines. In addition, bone tissue stores almost all (99%) of the calcium in the body and meets the daily calcium requirement. The release of calcium from bone is essential for life as it is indispensable for muscle contraction, blood clotting, cell membrane permeability, and nerve impulse transmission (Bayliss et al., 2012; Clarke, 2008).

Nowadays, bone fractures are encountered quite frequently among mammals. Factors that cause fractures include traffic accidents, falls from height, gunshot wounds, animal fights, and man-made trauma. Thus, researchers have sought methods to improve and accelerate fracture healing. Although the number of studies on fracture healing is increasing every day, the mechanism of fracture healing is still not fully understood and attracts the attention of all researchers.

Bone Structure

Although bone has a dense and mineralized texture, it is a living tissue containing blood vessels and various cell types. There are different cell types involved in the construction and reorganization of bone. These cells are osteoprogenitor (osteoblast precursor) cells, osteoblasts, osteocytes, and osteoclasts. While bone cells other than osteoclasts originate from the stromal (mesenchymal) stem cell population of the bone marrow, osteoclasts arise from the hemopoietic cells of the bone marrow (Eşrefoğlu, 2006; Topaloğlu et al., 2017; Tunçay, 2003).

Osteoprogenitor cells. These cells are mesenchyme cells conditioned to become bone tissue. They resemble fibroblasts in shape and are precursor cells that can differentiate into osteoblasts by mitosis. In other words, they are the precursors of osteoblasts.

Some of the proliferating cells differentiate into osteoblasts. These cells are present in the periosteum, endosteum, and havers ducts. They are ready to differentiate into osteoblasts for bone formation upon stimulation. In the bone matrix, they are transformed from mesenchymal cells to osteoblasts during bone growth and fracture healing periods (Eşrefoğlu et al., 2017; Topaloğlu et al., 2017).

Osteoblasts. Osteoblasts are cubic-shaped cells that make up 4-6% of the total bone cells found on the bone surface and are known as cells with bone-forming functions. They synthesize and secrete the type 1 collagen fibers and matrix proteins of bone and form osteoid tissue that has not yet calcified. Osteoblasts have endoplasmic reticulum, Golgi, and secretory vesicles and secrete calcium-binding osteocalcin and osteonectin, glycosaminoglycans, glycoproteins, and alkaline phosphatase. Alkaline phosphatase is an important enzyme that indicates that osteoblasts are active. Their cytoplasm is rich in the enzyme alkaline phosphatase, which functions in the calcification of the matrix by precipitating calcium into the matrix as calcium phosphate. The bone matrix newly synthesized by osteoblasts and not yet calcified is called osteoid. Osteoblasts remain embedded in this osteoid tissue and when the matrix calcifies, they reduce their activity, flatten, and become osteocytes. Osteoblasts and osteocytes are non-dividing cells (Eşrefoğlu, 2006; Silva et al., 2015).

Osteocytes. Osteocytes make up 90-95% of bone cells and have a lifespan of approximately 25 years. Their function during bone formation and bone resorption has been previously described as distinct from osteoblasts and osteoclasts by their location and morphology (Silva et al., 2015).

These cells are differentiated from osteoblasts, which remain in the calcified matrix and have reduced metabolic activity. They cannot divide. After the matrix pushes the osteocytes away from each other, melon-shaped cavities form around these cells. The survival of bone tissue depends on the presence of osteocytes. As osteocytes age and die, the matrix located around these aged

osteocytes begins to deteriorate and is dissolved and resorbed by osteoclasts.

The bone matrix is highly calcified. Thus, the substance transport takes place through osteocytes. That is the reason why these cells have long appendages. Tissue fluids that contain nutrients and hormones (calcitonin, parathyroid) pass from cell to cell through these cytoplasmic extensions to ensure the nutrient supply and functioning of osteocytes located far from blood vessels (Sağlam et al., 2008; Topaloğlu et al., 2017).

Osteoclasts. Osteoclasts are formed by the combining (fusion) of monocytes from the blood. Therefore, they are multinucleated large cells (100 μm), rich in mitochondria and vacuoles. Osteoclasts are cells responsible for the resorption and destruction of bone tissue. They appear during bone formation and disappear when the bones are finalized. Since osteoclasts originate from monocytes, they are considered part of the mononuclear phagocytic system. Their cytoplasm is usually acidophilic and contains abundant lysosomes. These cells have surfaces facing the bone tissue. These surfaces contain numerous long-short, thick-thin cytoplasmic extensions with various lysosomal enzymes. Ostoclast cells excrete these lysosomal enzymes from these areas and dissolve the bone tissues by excreting various from their surface to create pits on the bone surface. These pits are called Howship's lacunae (Tresguerres et al., 2006).

Bone Tissue Types

Primary Bone Tissue (Immature). Primary bone tissues are formed during fetal development and bone repair, are transient, and transform into secondary bone tissue. In primary bone tissue, collagen strands are haphazard and the basic substance is not sufficiently hardened. In addition, osteocytes are abundant and irregularly distributed in the tissue. The lacunae in which the osteocytes are located are also rounded in shape. In adults, primary bone tissue is found in the joints of the flat bones of the skull, the

alveoli of the teeth, and the entry points of the tendons to the bones (Erdost, 2011).

Secondary Bone Tissue. Secondary bone tissues are usually found in adult bones. Bones with these tissues can be long or short, and irregularly shaped. They are called bone lamellae because they show a lamellar structure. While the collagen threads in one lamella run parallel to each other, the threads in neighboring lamellae run crosswise or spirally. This course of the threads gives secondary bones great strength. Calcium salts are deposited on the collagen threads in the form of hydroxyapatite crystals and mineralization is complete. Secondary bone morphologically exists in two forms: cortical (compact, tight) bone, which is 20% of the total skeleton, and cancellous (spongy, spongy; 80%) bone (Erdost, 2011; Tunçay, 2013).

Spongy bones have a porosity of 50-90%. They are commonly found in the epiphysis and metaphysis of long and short bones as well as in the interior parts of flat bones. Spongy bone consists of irregularly anastomosing bone trabeculae that are interrelated to each other. There are irregular spaces between the trabeculae and these spaces were filled with bone marrow. Its macroscopic appearance resembles the structure of a sponge and as a result, they are defined as spongy bone tissue. The spongy tissue is nourished by cytoplasmic extensions from the vessels in the bone marrow through canaliculi. In addition, Havers and Volkman's canals are absent in spongy bones (Erdost, 2011; Tunçay, 2013).

The body (diaphyseal region) of long bones is composed of compact bone, and there is very little spongy bone on the side facing the medullary cavity. The outer surfaces of all bones in the body are compact bone. The spongy bone in the center of short bones is surrounded by compact bone from the outside. Compact bone has a secondary bone structure and consists of cylindrical units called osteons. Osteons are located concentrically around a central canal (the Haversian canal). The haversian canal is 20-100 μm in diameter and contains 1-2 vessels. These systems are cylindrical structures,

approximately 400 mm long and 200 mm wide, which are branched within the cortical bone. The Haversian canals are surrounded by 3-7 μm thick lamellae, cells, and a hard matrix (Erdost, 2011; Tunçay, 2013). The Haversian canal contains vessels (small arterioles or a venule and sometimes a single capillary) and nerves in loose connective tissue. The lamellae arranged concentrically around the canals are called havers lamellae. Neighboring Haversian canals connect with other canals, bone marrow, and periosteum through Volkmann's canals. The vessels and nerves entering the tissue from the endosteal and periosteal surfaces travel through these canals and reach the Haversian canals. Unlike the Haversian canals, Volkmann's canals are not surrounded by concentric lamellae. Osteoblasts transform into osteocytes and settle in lacunae within the bone tissue. Lacunae are located on top of the lamellae and are connected to neighboring lacunae by canaliculi. These canaliculi, which are connected with Haversian canals, also provide the passage of substances between osteocytes and blood vessels (Eşrefoğlu, 2016; Tunçay, 2013; Stevens, 2008).

Fracture Healing

Bones are the most important elements of the skeletal muscle system. However, they may lose their integrity under traumatic conditions. The disruption of the anatomical integrity and cortical continuity of the bone due to traumatic forces is called "fracture". This phenomenon is called "fissure" if it is a simple crack. The forces that cause fracture formation can damage the bone tissue integrity as well as the surrounding muscles, tendons, ligaments, nerves, and even neighboring organs in the fracture site (Aslanbey, 2002, Prokuksi 2009; Yurtgün, 2014).

Fracture healing is a complex biological process in which the tissue integrity of the fractured bone is reconstructed and can be summarized as the formation of specialized calcified bone tissue with the activities of osteoblasts and osteoclasts; it occurs in 3 stages: inflammation, repair, and remodeling. The phases of fracture healing that start from the moment of fracture cannot be separated

histologically with precise boundaries (Altunatmaz, 2004; Balcı, 2005; Dimitriou et al., 2005; Loi et al., 2016; Remedios, 1999).

Inflammation. As with all tissue trauma, the first response to bone fractures is "inflammation". After the trauma that caused the fracture, not only the bone tissue but also the soft tissues around the bone, including regional blood vessels and muscles, are damaged. Thrombotic factors are recruited to the site of the trauma to stop and coagulate possible bleeding at the fracture site. Damage to the blood vessels of the bone disrupts osteocyte nutrition and leaves the fracture ends with lifeless cells (Buckwalter et al., 2009; Kabak et al., 2001; Marsell and Einhorn, 2011).

Inflammatory mediators released from platelets and dead and damaged cells cause dilation of blood vessels and exudation of plasma, leading to acute edema at the fresh fracture site. Polymorphous nuclear leukocytes, followed by macrophages and lymphocytes migrate to the fracture site. These cells also release cytokines responsible for angiogenesis and stimulate angiogenesis. When the inflammatory response subsides, necrotic tissue and exudate resorb. Subsequently, fibroblasts and chondrocytes emerge and begin to form the fracture callus with new matrix production (Buckwalter et al., 2009; Johnson, 2013).

Fracture treatment aims to promote healing, restore the function of the affected bone and surrounding soft tissue, and achieve a cosmetically acceptable appearance (Aslanbey, 2002; Kılıçoğlu, 2002; Sürel et al., 1996; Yalçın, 2017).

Repair and remodalization of unstable fractures. Indirect or secondary fracture healing occurs when adequate reduction is achieved at the fracture line and the fracture fragments cannot be fixed stably. Unlike primary fracture healing, callus formation is observed in secondary fracture healing (Johnson, 2013; Kılıçoğlu, 2002; Stiffler, 2004).

During injury, the rupture of blood vessels in the bone, marrow, periosteum, and surrounding tissues causes a hematoma to

form and blood to flow out of the blood vessel at the fracture site. This hematoma organization is generally considered the first step in fracture repair. Fracture hematoma is very important for secondary fracture healing. However, the effect of fracture hematoma on fracture healing is still unclear. Fracture hematoma is thought to provide a fibrin scaffold that facilitates the migration of repair cells. In addition, parathyroid growth factors (PGGA) transforming growth factors (TGF), and other active proteins secreted by platelets and cells in the fracture hematoma govern critical initial events in fracture repair. These include cell migration and proliferation and synthesis of tissue repair matrix. Loss of fracture hematoma impairs fracture healing. In open fractures or treatment with open reduction, fracture healing is delayed or absent due to the discharge of fracture hematoma (Grundnes and Reikerås, 1993; Kılıçoğlu, 2002; Ozaki et al., 2000; Sürel et al., 1996).

Vascular proliferation is observed at the fracture site, although blood supply to the affected extremity increases after a short time due to vasodilation. Normally, periosteal vessels contribute more to the formation of capillary sprouts in the early stages of bone healing, whereas the nourishing medullary artery becomes more important in the later stages of the process. During the operation, when the surgeon interferes with the blood supply at the fracture site by severely stripping the periosteum or destroying the medullary system using intramedullary pins, the repair must continue with the remaining intact vessels (Buckwalter et al., 2009).

When the bone ends at the fracture site and is deprived of blood supply, necrosis develops, and the necrotic bone parts are resorbed. In some fractures, this can create a radiographically detectable cavity at the fracture site several weeks or more after the fracture. The cells responsible for this function are osteoclasts. As mentioned previously, osteoblasts develop from undifferentiated mesenchymal cells that migrate to the fracture site, whereas osteoclasts originate from monocytes in the bloodstream and monocytic precursor cells originating from the bone marrow (Buckwalter et al., 2009).

Pluripotent mesenchymal cells, probably of the same origin, give rise to fibrous tissue, cartilage, and bone at the fracture site. Some of these cells originate from damaged tissues, while others migrate through newly formed vessels at the site of injury. Cells from the cambium layer of the periosteum provide early bone formation and form the first bone. The periosteum is thicker and richer in cells in young individuals. Therefore, the periosteum plays a more dominant role in the healing of pediatric fractures. With increasing age, the periosteum becomes thinner and its effect on fracture healing decreases. Osteoblasts from the endosteal surface also contribute to bone formation, but the surviving osteocytes are not seen in the repair tissue. During fracture healing, most of the cells primarily responsible for osteogenesis appear together with the granulation tissue that replaces the hematoma (Buckwalter et al., 2009).

Mesenchymal cells at the fracture site proliferate, differentiate, and form the fracture callus, which contains fibrous tissue, cartilage, and braided bone. The fracture callus fills and surrounds the fracture site, and in the early stages of healing, it may become a hard or bony callus or softer fibrous or cartilaginous callus. At the beginning of bone formation, intramembranous bone forms at the periphery of the callus and is called a hard callus. The soft callus is mainly composed of cartilage and fibrous tissue, located in the central parts with low oxygen pressure. During enchondral ossification, bone is gradually replaced by cartilage, expanding the hard callus and increasing the stability of the fracture fragments. This process continues until new bone bridges the fracture site and continuity between the cortical bone ends is restored (Buckwalter et al., 2009).

As the mineralization of the fracture callus continues, the callus mass containing increasing amounts of braided bone begins to cover the bone ends. The increased mineral content is closely related to the increased stiffness of the fracture callus. Clinical fusion occurs with the stability of the fracture fragments, the formation of internal and external callus, and ultimately the immobilization and

painlessness of the fracture site. Radiologic fusion is observed on plain radiographs when bone trabeculae or cortical bone bridges the fracture site and is usually seen after clinical fusion. However, even at this stage, healing is not complete. The immature fracture callus is weaker than normal bone and can only reach its full strength during the remodeling period (Johnson, 2013; Tanrıkulu and Gönen, 2017).

In the final stages of repair, remodeling begins with the resorption of lamellar bone and unwanted callus, replacing the braided bone with repair tissue. In radioisotope studies, increased activity is detected in the fracture site, despite complete restoration of function and union on plain radiography. This shows that remodeling continues even years after the clinical and radiological union (Buckwalter et al., 2009; Johnson, 2013).

Repair and remodalization of stable fractures. When the fracture ends are held rigidly in contact with each other, fusion occurs without callus formation in the cortical or cancellous bone. For this to occur, there must either be a mechanical environment in which fracture motion is negligible and the fractures are in contact, or there must be only a very small (150-300 μm) gap between them (gap healing). This type of fracture healing is called primary fracture healing. This healing occurs without visible callus change and formation (Buckwalter et al., 2009; Tanrıkulu and Gönen, 2017; Johnson, 2013).

In most fractures with a rigid fixation in which the bone ends are directly joined, there are areas where the bone ends are in contact, as well as other areas with other small gaps. Healing occurs simultaneously in these contact areas and void spaces in different ways. In these areas where the bone ends are in contact, lamellar bone can form directly on the fracture line by osteon elongation. This is defined as contact healing. A cluster of osteoclasts crosses the fracture line, osteoblasts follow the osteoclasts to form new bone, and blood vessels follow the osteoblasts. The new bone matrix and blood vessels attached to the osteocytes form the haversian systems.

When gaps form that prevent osteons from extending directly across the fracture site, osteoblasts first fill the gap with braided bone. Once the voids are filled with braided bone, haversian remodeling begins and normal cortical bone structure is reestablished. Dividing colonies of osteoblasts and osteoclasts followed by blood vessels move through the braided bone in the fracture cavity, restoring the blood supply of cortical bone across the fracture site and forming lamellar bone, without the formation of a visible fracture callus. This healing is defined as gap healing. If part of the cortical bone is necrotic, the gap healed by the direct extensions of osteons heals more slowly and areas of necrotic cortical bone remain at the fracture site for a long time without remodeling (Buckwalter et al., 2009; Johnson, 2013).

Conclusion

Fractures are common traumatic lesions and fracture repair relies on complex biological mechanisms and mechanical mediators. For a fracture repair with the desired characteristics, it is crucial to assess the fracture site and fracture type, maintain bone blood supply, and select treatment procedures that support the appropriate biological environment and optimize mechanical factors. Various therapeutic, physical, and biological treatment options are effective at different stages of the fracture healing phase. Efforts should continue to develop new treatment modalities by creating favorable conditions and increasing the skill in fracture healing.

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CHAPTER III

Holistic Applications in Veterinary Medicine

Recep ASLAN[1]

Introduction

Complementary veterinary medicine consists of medical modalities based on traditional veterinary medicine. These modalities are generally integrative practices that support each other and scientific medical treatments and attract interest among animal owners and veterinarians. However, it is important that the applications within this scope are brought to scientific standards and proven. These methods are used globally in veterinary medicine, although scientific evidence of the efficacy of some modalities is not yet sufficient (Johnson, 2018).

The goal of medicine and medicine is homeostatic balance. Maintaining homeostasis, rebalancing it if it is disturbed, and sustaining mental and cognitive well-being is the aim, scope, and work of medicine. Efforts in this direction have developed a health

[1] Prof. Dr, Afyon Kocatepe University, Faculty of Veterinary Medicine, Physiology Department

memory over time, and the science and art of medicine have been formed. Most of the techniques such as medicinal and medicinal plants, some animals and animal products, blood and body fluids, surgical applications, stones and crystals, minerals such as lime, clay, some metals, cold-hot, energies, light and darkness, touch and massage, prayer, speech and suggestion are important elements of this memory and are being researched and applied in today's scientific conditions (Yıldız, 2013; Bayat, 2016; Şahan & İlhan, 2019; Ünal & Dağdeviren, 2019).

Medical approaches and practices are developing, diversifying, and changing. Beliefs, perceptions and conditioning, wars, migrations, social gains, or traumas are effective in changes and transformations. The Enlightenment period initiated a process in which scientific knowledge came to the fore in medicine and scientific findings were accepted as the only reference. Therefore, the scientific knowledge process that developed after the Renaissance and the Industrial Revolution started a period away from ancient experiences and practices (Bayat, 2016).

While trying to recognize and solve their own health problems, humans have acquired and learned some treatment methods from the animals around them by watching them. The injuries, injuries, illnesses, and births of the animals he encountered in his daily life with animals or in wars, transportation and hunting gave him new information and ideas, and healers and healers who were individuals with strong curiosity and observation skills began to attract attention in society. Observing the behavior of animals, man started the empirical treatment period by applying some animal healing reflexes to himself. With the addition of the religious knowledge and experiences that came through revelation, treatment and healing resources and procedures developed further (Smithcors 1958, Bayat 2016). Medicine based on knowledge, beliefs, healing culture and experiences acquired through revelation and inspiration continued to be widespread and effective until the 18th century; with the Enlightenment Period in the 18th century, science was accepted as separate and independent from religion, reason from belief, and

this approach also affected medicine, medical education, and medical practices. One of the important developments in the Enlightenment Period was the opening of curriculum-based schools providing medical and veterinary medicine education. The formal education based on scientific knowledge provided in these schools institutionalized the adoption of scientific medicine as the basis of medicine and the avoidance of ancient medical knowledge and practices formed by revelation, experience and tradition. In this process, in which scientific knowledge, i.e., knowledge based on findings obtained in laboratory conditions and observation, was taken as the basis, data and practices fed by belief, experience and traditions were seen as subjective fiction and were considered outside the scope of scientific knowledge. Until the mid-20th century, until the post-modern approach that started to make its impact felt in the mid-20th century, learning and practice (diagnosis and treatments) in hospitals and medical-health education institutions globally were based only on the findings obtained by modern science methods, and this approach was defined as scientific medical philosophy (Aslan, 2016; Bayat, 2016).

In every period, there have been threats and situations affecting the lives of humans and animals, and these have led to the development of medicine by increasing curiosity and questioning. Today, "integrative" or "complementary" medicine, whose scientific mechanisms are tried to be made evidence-based and supported by current technologies, is based on traditional medicine and medical experiences based on inspiration and revelation. Those who are engaged in medicine are called physicians, i.e., wise men, because of their characteristic of being nourished by faith and wisdom and their experiential qualities resulting from reasoning with wisdom. Medical knowledge is acquired through curriculum, art is acquired with each patient at the bedside, and morality is acquired through correct belief and living this belief (Bayat, 2016). The wisdom that physicians should have been a mind, and this mind is based on inspiration or revelation. There are many examples that show that traditional medicine was shaped by this wisdom mind fed by

revelation and inspiration. Akşemseddin (Şemseddin Muhammed bin Hamza), a physician, is an important physician both in our culture and in the global health culture. In his book Mâddetü'l-hayât or Mâidetü'l-hayât, Akşemseddin presented findings far ahead of the knowledge of his time, and recognised the microorganisms that cause diseases about 400 years before Louis Pastör, when there was no microscope yet; He divided diseases into hereditary and those caused by germs, i.e. genetic and microbial diseases, and noted that genetic diseases cannot be treated, while diseases caused by small germs (nuclei) invisible to the eye can be treated (Aslan & Karakuş, 2019). Considering the scientific studies suggesting that it is possible to learn through sleep and dream, which is a different state of consciousness, it is reasonable that there are treatment methods learnt through revelation, dream, and inspiration (Aslan, 2016).

Medicine and health is a scientific discipline with artistic, social and cultural characteristics. Physicians practice medicine with their technical and scientific equipment, but with the support of religion, culture, tradition, human relations, economy, literature, and art, and try to be beneficial to the patient. Every patient, whether human or animal, brings his/her life story to the physician along with his/her illness; while entrusting his/her illness to the physician's knowledge, he/she entrusts his/her emotions, mood and feelings to the physician's feelings, identity, and personality. In this case, the physician should be a person who knows the patient and the disease, not just sees them (Bayat, 2016). In a way, integrative medicine cares about this detail and this integrity. Physicians in the role of bureaucrat or technical man do not satisfy the patient in a life where materialization, and mechanization increase with the effect of rapidly developing technology. The saying attributed to Hippocrates, "If the physician is a person of wisdom, he rises to the level of divinity" (Bayat, 2016), describes a state of wisdom that can be achieved by acquiring accurate information about what is known as the soul and trying to live in accordance with that information (Dündar, 2015). The physician is the owner of wisdom; the owner of wisdom is the wise person, the one who not only knows but also lives

the truth, the one who gives peace, well-being and healing to those around him (Dündar, 2016b; Dündar, 2016a).

Human Medicine, Veterinary Medicine

The medical schools founded in 700 BC in Cnidus and later in Kos under the leadership of Hippocrates are considered as references for modern medical education (Von Staden, 1989). In our history, this process started with Gevher Nesibe Darüşşifa and Medical Madrasah. The process that developed with Tıbhane-i Amire and Cerrahhane-i Amire in the Ottoman Empire later took its modern form with Mekteb-i Tıbbiye-i Şahane, Military Baytar School and Gülhane Seririyat Hospital, and medical health education and practices were shaped by these three institutions (Aslan, 2017). The schooling process that started in France is the milestone for veterinary medicine to assume its conventional identity. When pandemics such as bovine plague, which posed a serious threat to animal existence and health, could not be prevented by human physicians, the first veterinary schools were opened in Lyone (1761) and Alfort (1764) in France and started education. The first veterinary school in the Ottoman Empire was the Military Baytar School. This school was opened in 1841 with the co-operation of veterinarians and medical doctors trained in schools in France. This school, where teachers such as Hekimbaşızade Muhiddin Bey, who graduated from Mektebi Tıbbiye, also attended classes, contains important memories in terms of the "single health" approach (Aslan, 2017).

Medicine and veterinary medicine have a common agenda, which is public health in all its aspects. The fact that humans live together with animals and must benefit from animals and their products has made it compulsory to fight against animal-human transmitted diseases, and this situation has brought the two medicines together. Although the Public Health approach was first initiated by humanitarian physicians, Veterinary Public Health was formed immediately afterwards due to the contributions of veterinary medicine to human-animal health. Due to the role of

veterinarians in the relationship between animal diseases and public health and in the protection against diseases transmitted from animals, veterinarians identified Salmonella bacteria for the first time in 1885, and in the same years, Ottoman veterinarians produced a vaccine against Bovine Plague for the first time in the world, and later updated it with dry bovine plague vaccine in the Republican period. As soon as the World Health Organization was established, Virologist Veterinarian Kaplan was assigned to WHO for the purposes of sustainable health, productivity and animal welfare, the Veterinary Public Health Unit was established within WHO, and as a result of the studies carried out in cooperation with human physicians under this unit, significant achievements have been achieved in terms of combating zoonoses, food safety and public health (Yılmaz et al., 2014; Aslan, 2017).

"One Health" is a Paradigm of Integrative Medicine

The "one health" paradigm recognizes that medicine is inseparable, that there is no mental difference between human medicine and veterinary medicine, that medical disciplines are developers and complementary to each other like modular systems, and that sustainable human, animal and environment is possible with the cooperation of all medical disciplines (Paul and Gibbs, 2014).

Of the 1415 infectious diseases caused by 538 human pathogenic bacteria and rickettsia, 307 fungi, 287 helminths, 217 prions and viruses, and 66 protozoa, 868 (61%) are zoonoses and 175 of these agents actually cause disease, of which 132 (75%) are zoonoses. Of these zoonotic agents, 35% are transmitted by direct contact, 61% by indirect contact and 22% by vectors. Since more than 60% of infectious diseases are zoonoses and that epidemics can rapidly globalize and turn into pandemics due to today's communication speed, "one health" has become a mandatory operating system to be developed and implemented (Maden, 2020). Nevertheless, the concept of "one health" is not yet at the desired level of co-operation and implementation. The complementarity that this co-ordination and co-operation will bring will accelerate the

solution of zoonoses, food and nutrition-related diseases, antimicrobial resistance, and many other global health problems. The COVID-19 pandemic has updated the necessity of this cooperation due to the contribution of veterinary researchers in the isolation of the virus and vaccine development. Previously, FAO published protocols in 2008 and the World Bank published protocols in 2010 for the reduction of animal-human related risks and the implementation of single health principles and the control of animal influenza; a successful "single health" cooperation was realized especially in the control of "HPAI H5N1" (Şeker et al., 2020). In the development of a vaccine for Covid-19, virus isolations carried out in veterinary faculties and research on the mechanisms of SARS-CoV-2 entry into cells and infection have played an important role (Maden, 2020). The first studies and successful applications of stem cell harvesting, the first announcement of the teratogenic effects of the drug containing the active ingredient Thalidomide, which was developed against pregnancy nausea in the 1950s, and even the prevention of the entry of this drug into our country were carried out by veterinary researchers (Okçuoğlu, 2020). All these show that veterinary medicine and medicine and health are not separate. The single health approach will be feasible and successful with the gathering of health disciplines under a single roof and the participation of veterinarians in health policies and practices with their ideas and experiences (Maden, 2020).

Traditional Veterinary Medicine: Folk Veterinary Medicine

Medical knowledge, accumulation and practices before modern medicine constitute traditional medicine. Traditional medicine consists of beliefs and experiences, knowledge, skills and practices whose mechanisms can be explained or not, with the aim of preventing physical and mental diseases, diagnosing, curing, and treating these diseases (Yıldız et al., 2013; Ministry of Health, 2021).

Animal health, like human health, has been supported by traditional medicine practices for thousands of years. Preparations, medicines and applications have been made in traditional veterinary

medicine against hundreds of medical conditions such as parasite control, lameness, joint and foot diseases, tendo-tendovagina, bursa and bone diseases, vertebrae, neck and head diseases, eye diseases, mouth and jaw and facial muscle disorders, skin, subcutaneous connective tissue diseases, chest, abdominal diseases, oral diseases, stomach disorders, intestinal diseases, problems related to vitamin, mineral and trace element deficiency, epidemic diseases (Brennan, 2001; Hewson, 2005; Sinmez, 2011; Abalı, 2019). Many methods such as bloodletting, leech, chiropractic, aromatherapy, phytotherapy, cupping, suggestion, musicotherapy with shepherd's pipe and tunes are known (Aslan, 2016).

Traditional veterinary medicine, which is folk veterinary medicine, has developed with veterinarians. Traditional veterinary medicine is an anonymous medicine culture with inter-communal and local traces, defined with names such as folkloric medicine, holistic medicine and ethnoveterinary medicine (Smith-Schalkwijk, 1999; Ertürk, 2006; Yiğit et al, 2013; Özyurtlu and Küçükaslan, 2019; Abalı, 2019; Gülanber, 2020). Before the current veterinary medicine education and practices, there were individuals interested in animal health in all societies. These individuals, known as "baytar" in our society, have strong research and curiosity skills, are fond of animals, recognise the animals around them, follow their movements, and stand out with their compassion and wisdom. These people, who volunteered to treat the diseases, injuries, aches, and pains of animals, were called "baytar", which means "tabib-i baytarî: animal physician" in Arabic, by the people because of the practices they developed. The treatment methods of folk baytars are based on learning, experience, and beliefs. Traditional veterinary medicine has emphasized the invisible (spiritual) dimension for disease and treatment processes in animals, and this approach has manifested itself in folk medicine all over the world (Sinmez, 2011; Abalı, 2019).

Man, who has tried to cure his own illnesses and wounds, aches and pains, anxieties and restlessness with religious knowledge, experiences, and reasoning, has started to perform these experiences

in animals with the domestication of animals. With domestication, animals have become a sustainable source of food and livelihood for humans, and have become companions in transportation and cargo carrying, normal life and wars. This situation made animal health as important as man's own health, medical knowledge and experiences were also used to heal animals and passed on to the next generations in oral and written form, thus forming the basis of today's veterinary medicine science, animal medicine (baytarlık). Although modern veterinary medicine education, practice and opportunities have shown great and important developments, folk medicine is still practised in rural areas, highlands, and hamlets and in many parts of the world in societies where transport and communication are not fast and easy (Sinmez, 2011; Boratav, 1973).

In ancient societies, life and economy are generally based on agriculture and animal husbandry. This is also the case in Turkish culture. For this reason, domestic animals such as horses, sheep and dogs have been included in coins, flags, state emblems and valuable weaving motifs due to their roles in transport, transport, food, security and trade, and folk medicine has been a respected occupation. The products, materials and techniques used to treat diseases, injuries, injuries, aches and pains of animals such as horses, dogs, sheep, goats and cows have been very important in the eyes of the people. With the transformation of nomadism into a settled lifestyle, these knowledge and experiences started to be recorded under the name of "baytarname" as of the 14th century and works containing information about the care and treatment of horses, drug preparations and applications were created (Dinçer, 1967; Kunul, 2010; Yiğit et al., 2013). The books named “Baytarname”, common animal diseases and their treatments, information on animal breeding, animal products, shoeing and blacksmithing, and animal-human relations are important topics, and sometimes the subjects are explained with pictures (Picture 1 and Picture 2), (Eliaçık, 2021).

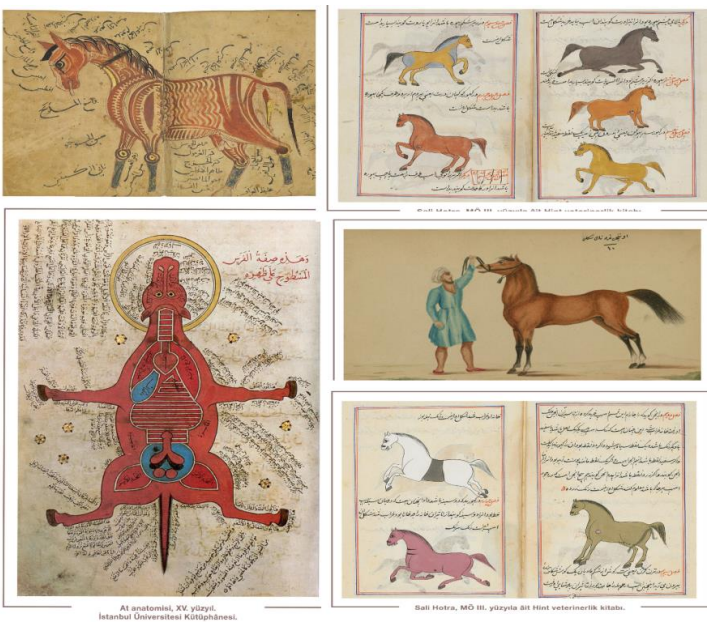

***Figure 1**: Illustrations of folk medicine in different Baytarnamas (Eliaçık, 2021)*

Folk medicine was intertwined with shepherding culture, and shepherds intervened in animals with traditional healing methods and knowledge when they realized their ailments because they knew their animals closely (Bulut, 2014; Kabak, 2018). Among the commonly used healing methods are methods such as irvasa, parpılama, prayers, cauterization, incense, moxibustion, bloodletting, homeopathy, massage, herbal emulsions, stones and crystals, animals and animal products, mines, mud, thermal and hot springs, kaval and nameler, talking to the animal, grooming (Sinmez, 2011; Aslan, 2016; Abalı, 2019).

Bloodletting is an ancient method of treatment. Hippocrates applied bloodletting in diseases and argued that the area to be bled and the color of the blood varied according to the disease. Islam has described and recommended bloodletting (hajamat) for medical purposes in hadiths. In folk veterinary medicine, in this context,

bloodletting from the ear or tail veins of animals that do not eat feed, are thought to have eaten poisonous grass, or are exposed to snake bites is still practiced (Yiğit et al., 2015); it is seen that bloodletting is used for healing in diseases such as lameness, stalling, toxication, icterus, enterotoxaemia, sheep and goat liver pain, and delibas (coenurus cerebralis) (Sinmez, 2011).

One of the elements frequently used in traditional veterinary medicine is water. Water resources such as springs, rivers and streams, hot springs, thermal and mineral waters, muds have been utilized, water resources have been respected and water has been cherished. It was seen that drinking some waters and bathing with those waters was healing for animals, reading prayers into the water and giving it to the animal to drink, washing the animal with prayed water became a treatment method (Sinmez, 2011). Today's scientific studies have revealed that water molecules are carriers of high-level information and energy, and the scientific background of reciting prayers to water has just begun to be realized (Emoto, 2005a; Emoto, 2005b).

Due to the place and importance of fire in life, which has a strong influence on life, methods such as cauterization, which utilize fire in healing, have been used, and cauterization has been one of the widely applied therapy techniques in folk medicine for warts, neoplastic formations on the skin and some other conditions. For example, animals that are thought to have delibaş (coenurus cerebralis) are usually cauterized with embers (ember fire) in areas such as the waist, neck and forehead (Yalçınkaya, 2019; Abalı, 2019).

Phytotherapy and aromatherapy are also common practices. Herbal incense, senna and some other medicinal and herbal plants have been used in folk medicine as a method of treatment. Herbs were frequently applied to animals whose productivity suddenly decreased, whose udders became inflamed (mastitis), infertile animals, and animals whose behavior suddenly changed and became irritable to their owners. Animals that are thought to be exposed to

harmful energy originating from the evil eye and envy are tried to cure the symptoms of the disease by roasting medicinal aromatic plants such as hyssop, black cumin and cloves in a pot and inhaling the incense (smoke) to the animal (Abalı, 2019; Çıblak, 2004).

Many methods such as suspending the body in large animals for fractures, dough and bandage applications in small animals and poultry; methods to stop bleeding in injuries; slurries rich in salt and minerals given to weakened animals and animals with loss of productivity, drinking olive oil in case of colitis (Figure 2) suggest that folk veterinary medicine includes practices based on scientific foundations (Sinmez, 2011; Yaşar et al., 2015; Abalı, 2019). Isolation and reunion practices for orphan lambs to be accepted to their mothers, which is one of the important breeding problems, juniper, flax, mountain plum, mistletoe, wheat bran, cholent, lice grass applied externally and internally against external and internal parasites, The paste, syrup, paste, pill and incense treatments produced from medicinal plants such as cabbage, red pepper, etc. show the sophistication of folk medicine practices and suggest that these methods are based on scientific foundations, albeit undefined (Yaşar et al. , 2015; Aslan, 2016).

The fact that the treatment methods applied to animals in traditional folk veterinary medicine are like the methods applied to humans is important in terms of showing that medicine and health are inseparable (Abalı, 2019). Due to medical conditions in which the methods and practices of conventional medicine, known as Western medicine, scientific medicine, modern medicine, orthodox medicine, etc., have difficulty in producing solutions, the demand for utilizing traditional medical methods as "complementarity" has increased in all societies, including developed societies. This situation encourages the scientific research, proof, and application of traditional and complementary medical methods (GETAT). At the current stage, GETAT methods have been taken into the process of implementation and development as a scientific medical discipline. GETAT practices have gained vitality and made a significant development in our country, as in the whole world, with the laws and

regulations of the Ministry of Health, application centers and departments of medical faculties (Ministry of Health, 2021).

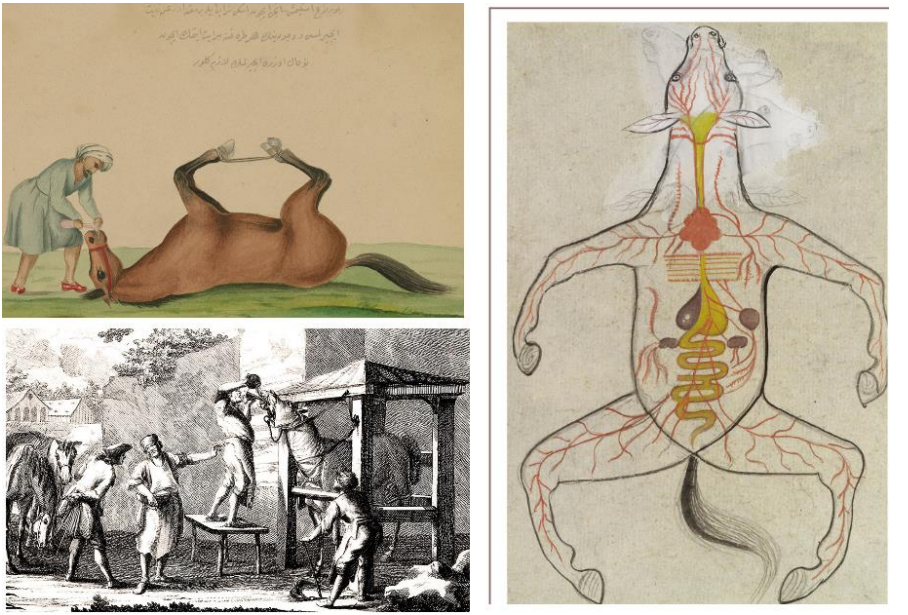

Figure 2. *Oral olive oil applications in the treatment of digestive system and colitis in horses (Eliaçık, 2021)*

Complementary Medicine Practices in Veterinary Medicine

GETAT practices in veterinary medicine disciplines are rapidly spreading all over the world, and the interest and demand for traditional complementary medical methods are increasing globally. GETAT practices are included in the literature with names such as ethnoveterinary medicine (Altınok Yipel and Yipel, 2014), folkloric veterinary medicine or folk veterinary medicine (Sinmez and Yaşar, 2011), alternative veterinary medicine (Özyurtlu and Küçükaslan, 2019), holistic veterinary medicine (Ertürk, 2006), complementary veterinary medicine (Smith-Schalkwijk, 1999), veterinary integrative medicine (Gülanber, 2020), veterinary complementary medicine (Yiğit et al, 2013). All over the world, thousands of years of folk veterinary medicine practices are being updated by making

them evidence-based and complementary medical practices are being established (Altuğ, 1998; Smith-Schalkwijk, 1999; Bath, 2006; Sinmez, 2011).

The Ministry of Agriculture and Forestry, which is known as the address of animal health policies and in which veterinarians are intensively employed, is not an institution that opens clinics, operates hospitals, and provides services prioritizing diagnosis and treatment. The veterinary medicine services of the Ministry are in matters such as protection against zoonoses and vaccinations, regulation of independent veterinary medicine services, import and export of animals, veterinary laboratory services, veterinary public health and monitoring and coordination of veterinary health products, and the requirements of laws and regulations are fulfilled in these matters (Ministry of Agriculture and Forestry, 2021). For this reason, there are no public clinics and hospitals that perform diagnosis and treatment services in the field of veterinary medicine other than universities (Aslan, 2016). GETAT comprehensive practices are carried out in veterinary faculties in Europe, USA and Far Eastern countries such as Japan, Korea and China (Gülanber 1994; Gülanber, 2008). In the clinics and hospitals of veterinary faculties in our country, GETAT is still being studied in scientific research and there are no routine practices in clinics. This situation stems from the fact that the faculties perform medicine within the framework of classical books and manuals such as The Merc Veterinary Manual due to the condition of "diagnosing and treating only with the practices accepted as the basis of scientific medicine" in the oath of veterinary medicine. In addition, the fact that veterinary faculties do not yet consider GETAT practices necessary, do not need these practices, and therefore do not have academic staff trained in GETAT practices is also an important factor. Despite this, complementary medical methods are sometimes verbally recommended to patient owners, but actual application and prescription are not made (Aslan, 2016). Including acupuncture applications, GETAT applications such as ozone, massage, phytotherapy, homeopathy, cupping, balneotherapy, reflexology,

etc. are designed and postgraduate theses and scientific research are carried out. However, the scientific findings obtained have not been transformed into practice. Routine GETAT methods are not yet applied in our veterinary faculties (Altuğ, 1998; Gülanber, 2008; Aslan, 2016; Öcal, 2018). The existing examples in this regard belong to clinics and hospitals providing private veterinary medicine services. Some private clinics and hospitals provide GETAT certification trainings in addition to applying GETAT practices (Gülanber, 2020; Gökdağ, 2021; vet hospital 2021; Urla vet, 2021; GG akademia, 2021).

Acupuncture

In veterinary medicine, acupuncture is preferred as a primary and secondary (auxiliary) treatment method in all animals but more frequently in horses, cats and dogs (Gideon, 1977; Klide et al., 1977; Doo-Seok and Oh-Nam, 1978; Chadwick, 1979; Westermayer, (1979), Janssens et al, 1979; Basko, 1983; Kleinkort and Folley, 1984; Lee and Tin, 1985); Wiebicke, 1986; Hua, 1987; Janssens, 1988; Still, 1988; Khalsa, 1989; Thoresen, 1989); Aslan and Kılıçoğlu, 1993; Rogers, 1996; Beceriklisoy and Aslan, 2005; Kemer et al.) Chinese acupuncture sources have identified 740 acupuncture points belonging to animal species in veterinary medicine. Of these, 173 belong to horses, 103 to large ruminants such as cattle and buffalo, 84 to pigs, 77 to camels, 75 to sheep and goats, 76 to dogs, 51 to rabbits, 34 to chickens and 35 to ducks (Westermayer, 1983; Gülanber, 2008) (Figure 3-6).

Scientific studies on acupuncture applications; allergic dermatitis (Craige, 1985), wound healing (Doo et al, 1984), arthritis and osteoarthritis (Glinski, 1989; Poulton, 1991), limb trauma in horses (Scanlan, 1989), disc herniations in lumbar vertebrae (Griffth, 1988), hygroma (Hall, 1989), mastitis in cattle (Holiday, 1988), anoestrus (Holiday, 1989) and postpartum uterine bleeding (Kenney, 1988a), gastric ulcers (Kenney, 1988b; Rogers, 988), megaesophagus (Weintrub, 1989b), colic pain (Kenney, 1989), idiopathic epilepsy (Klide et al. , 1987; Partıngton, 1989), chronic

back pain in horses (Martin and Klide, 1987; Klide and Martin, 1989), aerophagia in horses (Kuussaari, 1983), navicular disease (May, 1989), bilateral corneal ulcers in horses (Mc. Cormick, 1989), chronic lameness due to gold implants (Mc. Cormick, 1989), depressive mental disorders in Umbrella Cackatoo birds (Partıngton, 1989), patellar dislocations (Partıngton, 1989), hip dysplasia with gold implants (Partıngton, 1989), systemic lupus erythematosus (Schwartz, 1990), leukorrhoea (Weintrub, 1989a), anaesthesia (Still, 1987) and analgesia for laparotomy in dogs and cats (White et al, 1985), radial nerve paralysis (Weintrub, 1989c), urinary incontinence (Wurth, 1991). It is recommended that electro acupuncture and laser acupuncture should not be applied to febrile and infective patients, animals with cardiovascular problems and fractures, cachectic, epileptic, shocked and agitated animals (Gülanber, 2008).

Acupuncture in horses is categorised under six headings: musculoskeletal system, neurones and nervous system, gastrointestinal system, respiratory system, urogenital system and other clinical conditions. Conditions such as thoracic and lumbar pain, sacral areas, shoulder lameness, elbow and carpal lameness, laminitis, navicular disease, nail abscess, tendonitis and paralytic myoglobinuria are musculoskeletal system applications; radial paralysis and facial paralysis and cervical ataxia and peripheral nerve paralysis nervous system applications; colic, gastroesophageal reflux, gastritis, gastric ulcer, dyspepsia, constipation, diarrhoea, ulcerative colitis, cancers, pancreatitis and hepatitis gastrointestinal applications; nosebleeds, rhinitis, sinusitis, bronchospasm and pulmonary haemorrhages are treated with respiratory system applications; anaestrus, ovarian cysts, infertility despite multiple inseminations, sperm abnormalities in men, disorders related to kidneys and urinary mechanism are treated with urogenital applications; restlessness, anxiety, fear, nervousness and skin problems are tried to be treated with acupuncture techniques within the scope of other clinical applications. Highly positive results are reported to be obtained with acupuncture in horses with paralytic

myoglobinuria, laminitis, air swallowing, radial paralysis, bronchitis, chronic respiratory diseases, anorexia, nosebleeds, anaestrus, ovarian cysts, infertility in repeated inseminations, dermatitis, corneal ulcers, navicular disease and tetanism (Glinski, 1989; Poulton, 1991; Scanlan, 1989; Griffth, 1988; Martin and Klide, 1987; Kuussaari, 1983; May, 1989; Weintrub, 1989c).

In ruminants; pneumonia, pulmonary emphysema, heart and respiratory disorders, indigestion, rumen motility disorders, colic, hepatitis, ketonuria, functional ovarian disorders, infertility, placental retention, testicular disorders, nephritis, kidney disease, mastitis, paralysis of the hind legs, contractions and embryo transfer, treatment of infertility cases, low ejaculation intensity in bulls and improvement of the number of motile spermatozoa.

Acupuncture in cats and dogs is thought to give positive results in many medical conditions including hygroma, systemic lupus erythematosus, rectal prolapse, behavioural disorders, urinary incontinence, keratoconjunctivitis sicca, megaesophagus, arthritis, rheumatoid arthritis, muscle and tendon injuries, paralysis and operative analgesia, paresis and paraplegia, cervical pain and skin problems (Gülanber, 2008).

As a result, veterinary acupuncture is used alone or in combination with conventional and other traditional treatments in many clinical problems; especially in cases where surgical intervention is not recommended, analgesic and anti-inflammatory drugs are ineffective or show side effects. In practice, it has been found that dogs react anxiously to the needling of acupuncture points, whereas horses, cats, birds and many other reactionary animals are calmer (Firebert, 2012).

Figure 3. *Acupuncture and electroacupuncture applications (Horstalk, 2021)*

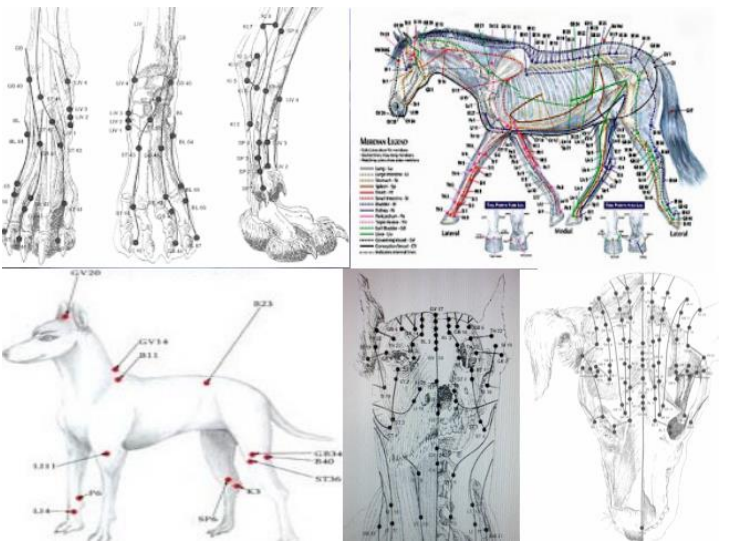

Figure 4. Aquatic points on the paw, head and body (Firebert, 2021)

Figure 5. *Acupuncture applications in koala, llama, cat and dog (Acupet, 2021)*

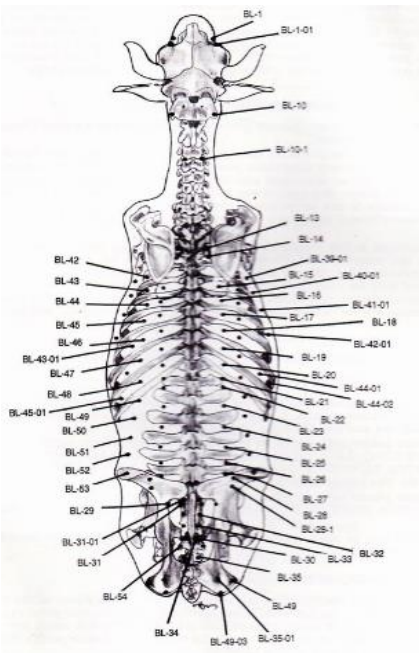

Figure 6. *Acupuncture points in cattle (Pankonin, 2021)*

Phytotherapy

The plants used in veterinary phytotherapy are plants that have been used for thousands of years for wound healing, pain relief and relaxation. In fact, the medical basis of Western medicine, known as scientific medicine, is also based on plants. For example, nonsteroidal anti-inflammatory salicylic acid from willow tree, vagal activity blocker, atropine that stimulates sinus node automatism and AV node conduction, scopolamine with anticholinergic effect that suppresses muscarinic acetylcholine receptors is a few of the hundreds of herbal preparations obtained from beautiful hawthorn, silymarin with hepatoprotective effect from milk thistle plant (Wynn and Fougère, 2007; Bayatlı, 2019; Yipel et al, 2021; Zoom, 2021).

Phytotherapy in animals is applied in forms and methods such as dietary supplementation, aromatherapy (incense, steam inhalation), tinctures, herbal teas, maceration, vaccination, and syrup. Phyto therapist veterinarians choose one of these forms suitable for the animal (Yipel et al., 2021).

Medicinal and aromatic herbs such as marjoram thistle, black cumin seed, turmeric, pipe flower, flax, cypress, juniper, fig, onion, anise, senna, cassia, mulberry, sunflower, henbane, saffron, thyme, cinnamon, and senna have been used in folk veterinary medicine for thousands of years in single or combined prophylaxis and treatment (Bayatlı, 2019). Phytotherapy is also used in today's veterinary medicine in medical conditions such as COPD, laminitis, digestive disorders, allergies and eczema, diarrhea, arthritis, liver disorders and dermatological problems, respiratory and urogenital system problems, internal and external parasite control (Figure 7) (Özkul, 2021). Horsetail (Equisetum arvense L.), echinacea (Echinacea angustifolia DC), mistletoe (Viscum album L.) as immune stimulants; Christmas rose (Helleborus L.) in parasite control; chamomile (Matricaria chamomilla L.), Yarrow (Achillea millefolium L.), Capsicum (Melissa officinalis L.), Basil (Ocimum basilicum L.); bactericidal and antifungal effect and anthelmintic in animals and against blood parasites such as Trypanosoma,

Plasmodium spp.), bitter wormwood (Artemisia absinthium L.), ragweed (Ambrosia artemisiifolia L.) and Ayvadane (Artemisia vulgaris L.) against tapeworms such as Taenia saginata, Taenia solium and worms such as Fasciola hepatica; fern (Dryopteris filix-mas L.); Christmas rose (Helleborus L.), common litter (Veratrum album L.) and tobacco (Nicotiana tabacum L.) are used for lice control in cattle (Yargeldi and Abaş, 2013; Köksal, 2018; Eren and Şar, 2020). In the treatment of digestive system diseases, bitter plants such as Chamomile, Asteraceae, salicin glycosides in White willow Salix alba L., essential oil sources such as Flax (Linum usitatissimum L.), Mallow (Malva sylvestris) are generally applied; Sinirliot (Plantago major L.), Calendula (Calendula (Plantago major L.) against diarrhea in ruminants.), Calendula (Calendula officinalis L.), Nettle (Urtica dioica L.), Medicinal marshmallow (Althea officinalis L.), Dill (Anethum graveolens L.), White willow (Salix alba L.) plants; St. John's wort (Hypericum perforatum L.) is used for skin and mucous membrane injuries and burns (Bayatlı, 2019). The fact that medical preparations alone do not give radical results in the control of internal and external parasites in cats, dogs and birds has increased the use of parasite drugs together with herbal products. It is reported that phytotherapy gives good results in the treatment of liver and kidney diseases, urinary tract problems, dermatological diseases and mastitis (Kuru and Oral, 2013).

Nowadays, plant metabolites and bioactive phytochemicals such as plant extracts, alkaloids, heterocytes, saponins, terpenes, tannins, flavonoids, flavones, lycopene, plant metabolites and bioactive phytochemicals are widely used in the treatment of chronic diseases and recurrent infections as well as organic animal husbandry and prophylaxis (Dündar and Aslan, 1999, Bayatlı, 2019). The use of plant extracts as nutritional supplements is also considered important by livestock farms for purposes such as stimulating digestion by increasing hydrolytic enzyme activities, preventing the development of pathogenic microorganisms, increasing the quality, productivity, and food safety of products such as meat, milk and eggs. Phytotherapy has an increasing use in animal

diseases alone and in addition to medical treatment due to the reasons such as supporting medical treatments, being economical and having fewer side effects compared to medical medications. Phytotherapy preparations should be made with products of medicinal value, applied in scientific dosage and with indicated methods. Incorrect applications may lead to ineffectiveness and side effects (Görgün Yaltı, 2020). Plants and herbal products used in veterinary phytotherapy have fewer side effects than drug active ingredients. In this case, the animal body is not exposed to the chemicals in the drug formulation and unwanted effects are encountered less. Since the dose is adjusted according to the characteristics of the animal, there is less risk and herbal products cause less overdose and poisoning. For the livestock sector, phytotherapy is a therapy with low cost, easy to obtain products and low risk. However, for a correct application, the veterinarian should know the plants, herbal preparations, the patient and the disease well. However, in the treatment of very severe diseases, phytotherapy should generally be preferred together with normal medication (Yipel et al., 2021; Özkul, 2021). Today, scientific data are available on the formulae of herbal drugs used in veterinary phytotherapy, the use of medicinal and aromatic plants in veterinary medicine, toxicity, and drug interactions of herbal drugs. Scientific resources containing detailed data on animal- and disease-specific dosing and pharmacokinetics, the use of herbal medicines in reproduction and productivity have been established (Wynn and Fougère, 2007).

Figure 7. *Some veterinary phytotherapy preparations used for metritis, pyometra, uterine tone regulator, depression, detox and fertility enhancement (Himalaya Drug, 2021; India Herbalist, 2021; Affordable, 2021)*

Homeopathy

Homeopathy is a GETAT method used in veterinary medicine all over the world, especially in Germany and Europe. Homeopathic preparations, remedies, are produced by diluting natural minerals, plants and body fluids and have been used for hundreds of years. The classical source of homeopathic preparations used in many diseases is Materia Medica (Cullen, 1789). Nowadays, there are many courses, books and research articles for veterinarians who want to use homeopathic therapeutics (Saxton, 1991; Hatipoğlu, 1996; Ruddock, 2007; Clausen and Albrecht, 2010; Pekmezci and Gültiken, 2015; Atam and Kızıl, 2016; Özpek and Altıntaş, 2019). Veterinary homeopathy applications include effective treatment models with only a few remedies in many simple and acute cases, although it is difficult in chronic cases (Ruddock, 2007; Dogs, 2021). Homeopathic medicines for vaccination (nosodes) are immune modulators made from tissues and other ingredients of the disease. It is known that nosodes used for prophylaxis reduce the incidence of distemper in dogs and give successful results in cases of kennel

cough, felin AIDS, felin flu, felin leukaemia (Löscher and Richter, 1993).

It is reported that homeopathic remedies can be used in veterinary medicine in many medical conditions such as allergies, urogenital problems, tumour formation and metastasis, infertility, false pregnancy, retention, mammary diseases, muscle-joint inflammation and pain, spasms, icterus, fatty liver, fever, edema, heart failure (Clausen and Albrecht, 2010; Kızıl and Atam, 2016).

Figure 8. *First aid kit used in veterinary homeopathy for dogs (Dogs, 2021).*

Trophy App

It is known that bloodletting is performed for therapeutic purposes in veterinary medicine practices, blood is generally taken from the neck, spur, armpit, and saphenous veins, and it is known that these practices continue in today's folk veterinary medicine (Yiğit et al., 2015). Cupping and cupping therapy based on bloodletting are still applied to animals under scientific conditions (Vagefi and Bassiri, 2015), (Figure 9, Figure 10). It has been

reported that cupping is applied especially in the solution of foot diseases and muscle problems of horses, in increasing running performance, in the treatment of some sheep diseases, against some sexually transmitted diseases in rams, cupping applied under the humps of tired camels energizes the animal, cupping supports the homeostatic balance of the animal in animals that have been immobilized due to prolonged transport, cage life and other reasons (Sahawaf et al., 2018; Estaity, 2019; Estaity, 2019; Altıntaş, 2019). Jaundice (leptospirosis), acute rumen acidosis, tympani, parleying, poisoning, mad head (coenurus cerebralis), malaria (babesiosis), pains, painful diseases, lumbago, enterotoxaemia (clostridiosis), gingivitis, stomatitis, Blood sampling from different parts of animals for colds, myopathy and fatigue, lung problems, hepatitis, asthma, and behavioral disorders have been used in folk veterinary medicine for years (Yiğit et al., 2015).

Figure 9. *Cup application on a donkey (Estaity, 2019).*

Figure 10*. Cup application (Estaity, 2019).*

Studies, reference books and training seminars on GETAT comprehensive applications such as massage, magnetic therapy, lasers, homeopathy, chiropractic, phytotherapy, aromatherapy and acupuncture to cats, dogs and other pets have been scientifically applied in veterinary medicine for the last fifty years, and these applications are expanding day by day with increasing level of evidence (McKibbin, 1984; Brennan & Eckroate, 2004) (Figure 11).

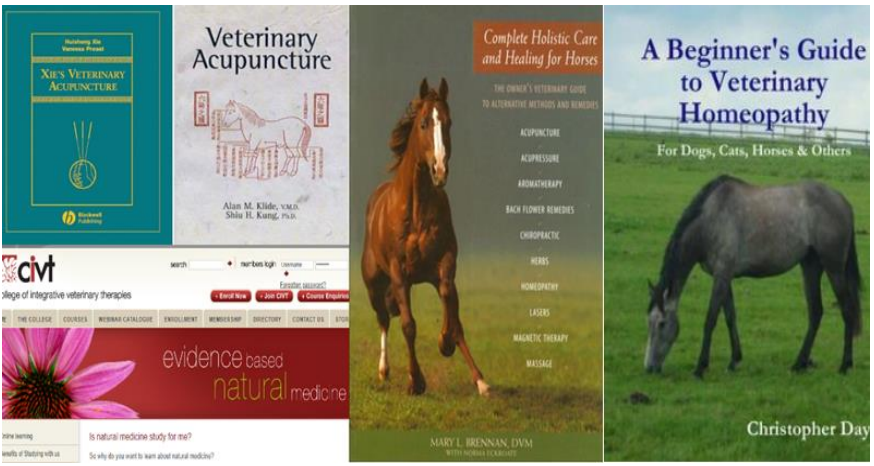

Figure 11. *Veterinary integrative therapy reference books, courses (Brennan and Eckroate, 2004; Wettown, 2018; Civt, 2021; Cobo, 2021).*

Moxibustion Application

Moxibution is the use of heat and aroma emitted from an ignited wormwood stick passed over specific acupuncture points. It is used to reduce pain, improve blood circulation, reduce dampness, warm the animal (hyperthermia) and is reported to be beneficial. However, since the moxa sticks are very hot, care should be taken to avoid burning the skin of the animal (Cheng, 1987; Yu, 1990; Zhang, 1988; Gongwang, 1996; Schell, 2013).

Reflexology

Reflexology is a type of massage based on the connection of reflex points on the feet, paws, and head with other parts of the body. In veterinary medicine, it is especially applied to cats, dogs and horses. It is thought that by massaging these points, the tension of the animal is reduced, and some medical conditions will be easier to heal (Larson, 2018; Buscher, 2021; Canine, 2021). The most common method in dogs and cats is to apply pressure to different areas on the lower part of the paw. It has been reported that

reflexology reduces stress in the animal, but factors such as malnutrition and inactivity should be eliminated. It has been reported that reflexology applications stimulate circulation, bioenergy, parasympathetic nervous system, encourage deep breathing, reduce aches and pains, but care should be taken not to hurt and pay attention to the animal's reflexes when applying the five basic types of massage (Acorda, 2006; Acorda, 2010; Larson, 2018).

Chiropractic

Chiropractic, which is also used in veterinary medicine, includes special manipulations applied to the spine and extremities to restore normal anatomical posture (Figure 12). In chiropractic therapy, hypomobile or hypermobile joints are located by palpation to determine the range of motion and various techniques are applied to restore the normal range of motion. The modified Gonstead technique is the most widely used method in animals. This technique is the application of a low-impact, high-speed but gentle thrust at a specific contact point to increase the range of motion of hypomobile areas. Apart from the restoration of range of motion in spinal regions and increasing neural conduction, the application also has secondary effects such as nutrient delivery to intervertebral discs and toxin clearance from tissues (Taylor & Romano, 1999; Keating & Ramey, 2000; Maler, 2012; Pesch, 214).

Veterinary chiropractic techniques and theories have been adapted from human chiropractic practices documented from ancient civilizations such as Greek, Chinese, Indian, Japanese, Roman and Egyptian. Although there have been claims that the effects of chiropractic manipulations are a placebo effect, these claims have been largely discredited because of chiropractic practices applied to animals in the 1890-1900s and the findings obtained from these practices (Rome & McKibbin, 2011). Veterinary chiropractic, like human chiropractic, is a skill that must be learnt comprehensively and logically through didactic and practical training. A veterinarian or chiropractor who will apply chiropractic to animals should receive special training in addition to graduating from schools such as

veterinary medicine or animal health technician (Maler, 2012). The Veterinary Chiropractic Association (AVCA) was founded in the United States in 1989 and continues its scientific and educational activities (Taylor & Romano, 1999). The American Veterinary Chiropractic Association (AVCA) and the International Veterinary Chiropractic Association (IVCA) support approved postgraduate animal chiropractic programs. Veterinarians are accepted to these programs and animal chiropractic practices and education are provided (Rome & McKibbin, 2011; Maler, 2012). Integrative chiropractic practices, in which advanced developments have been recorded in the field of veterinary medicine in many countries, are not yet available in the clinical routine as an integrative practice in the veterinary faculties of our country.

Figure 12. *Veterinary chiropractic applications (Horse, 2021; Rogue, 2021).*

Ozone Therapy

Ozone, which is a natural disinfectant that strengthens leukocyte and lymphocyte activity, kills bacteria, viruses and fungi and leaves no waste, is applied in veterinary medicine, especially in the treatment of diseases related to the immune system. The common method is to mix 50-200 ml of blood taken from the animal with a certain dose of ozone and give it back to the animal or to inject 2-5 cc of blood into the muscle by mixing the dose of ozone. Subcutaneous application is done by injecting ozone gas under the skin with a fine-tipped needle. It can also be applied intraarticularly in the rectum, vagina, spraying into the ear and joint disorders. External application of ozone-treated liquids such as ozonated water and oil to the animal is also an application method. Ozone is also applied into or around the tumoral mass and lesion. In veterinary medicine, ozone therapy can be applied mostly in parvoviral enteritis (bloody diarrhea disease of dogs), hip dysplasia, arthritis, advanced inoperable tumors where the animal cannot receive anesthesia, wounds with large tissue loss, generalized allergy pictures, chronic ear infections, urogenital system and urinary tract diseases, genital infections, prostate problems (Vettown, 2018; Kozat and Okman, 2019; Boğaziçi, 2019; Sciorsci, 2020).

Lasers

Laser therapy has become widespread in veterinary medicine as a practice with increasing studies demonstrating efficacy and dosages. Anecdotes, clinical case reports and scientific study results suggest that therapeutic laser is effective in the treatment of skin wounds, tendon and ligament injuries, oedema, eye diseases, tumors, podiatric diseases, muscle injuries, nervous system damage and inflammation and neurological conditions, arthritis, surgical incisions and aches and pains (Pryor and Mills, 2015; Smart, 2016; Riegel and Godbold, 2017; Downing, 2017; Kelly and Johnson, 2018; Öcal, 2018; Uvet, 2021; Hasvet, 2021) (Figure 13).

Figure 13. *Laser applications in glaucoma treatment, hoof resection and melanoma removal in veterinary medicine (Hasvet, 2021; Uvet, 2021; Smart, 2016)*

Hydrotherapy

Hydrotherapy is based on the therapeutic use of sea, lake, and river waters for all animals, especially horses, large and small ruminants; these waters are known to help the treatment of leg injuries, oedema and swelling and some other diseases with an anti-inflammatory effect that increases healing in tissues and wounds. For this purpose, spas and therapy pools for animals are also utilized. In-water movements and swimming, which are performed without straining the joints and without exposing the legs to stress and shock, support the cardiovascular system and muscles in animals, so water cures and light swimming are used as a rehabilitation method for horses recovering from injuries. In addition, a simple method of hydrotherapy in the stable is to hose the animals with cold water. It has been reported that at least 20 minutes of water treatment with a hose is required for the muscles and blood vessels to respond. However, although cold water hosing is highly effective, since the

water temperature is practically uncontrolled, swimming pools and spas designed for SPA treatments with computer-controlled waters with medically adjusted temperature and mineral composition may give better results than manual washing. It has been reported that horses treated with cold water therapy have shown improvements in many conditions ranging from navicular syndrome and laminitis to severe skin lesions and stimulation of hoof growth. Drinking highly mineralized water has also been shown to be beneficial in horses. A typical equine spa is a unit with doors at either end that allow easy loading and unloading of horses. Once the horse enters the unit, it is sealed. The spa unit is then slowly filled with water, this usually takes about 2-3 minutes. A classic session is 10-20 minutes, after which the spa is emptied, and the horse is led out. Water temperatures are controlled by computer to be between 2-4 °C. Cold water hydrotherapy reduces the metabolic response of the cells in the horse, the cells require less oxygen to function, and consequently hypoxic damage is reduced. In addition, as the permeability of the horse's blood vessels decreases with cold hydrotherapy, the amount of fluid (oedema) accumulated in the injured area decreases. In addition, cold water slightly numbs the treated wound and acts as an analgesic for the area (Figure 14) (Equine Hydrotherapy, 2021; Pleasant Valley, 2021; Daily Mail, 2021).

Figure 14*. Hydrotherapy applications in horses, cats, and dogs Equine Hydrotherapy, 2021; Pleasant Valley, 2021; Daily Mail, 2021).*

Music Therapy

The history of treatment with music within the scope of complementary medicine practices in veterinary medicine is quite old and dates to shepherd pipes. The use of music in medicine-health dates to Paleolithic times. The use of music, especially in the treatment of psychic disorders, is due to the realization that it influences emotions. For this reason, music has been a treatment method applied to humans and animals since ancient times (West, 2000). Current studies in animals show that music affects not only psychology but also physiology (Lu, 2010; Aslan, 2016; Sampaio, 2017). It has been shown that music supports psychology (Wiśniewska, 2017), has positive effects in the treatment of asthma (Lu, 2010), and positively affects the development of nerve cells (Sampaio, 2017). There are reports and applications that classical music played to dairy cows increases milk yield (Bekyürek, 2009; Sputnik, 2017) and egg yield in chickens (Subaşı, 2021). Music is a rhetoric of emotion that changes from person to person and from

society to society. Today, although there is music composed for different animal species and claimed to be effective, there is a need for studies on how animals will be affected by the sound of humans and musical instruments, which animals perceive which notes, which sounds and which rhythms and which ones are positively affected. Psychologist Charles Snowdon reported that many animals enjoy music, that the sound of music arouses curiosity and gives a sense of well-being, but that different animals enjoy different types of music. For example, David Teie, with his "Music for Cats" project, has created music from the sounds cats make when purring and drinking milk, using repetitions like those used in songwriting. Music is also being created for other animal species. In fact, songs were composed for wildlife members such as monkeys; it was observed that while monkeys did not react to music listened to by humans, they reacted to music prepared for them using high-pitched monkey sounds. It has been reported that monkeys get anxious when listening to fast sounds and calm down in music containing more relaxed sounds (My Animals, 2019). Laurel Braitman works with different music styles and different animal groups within the scope of the Music for Animals project (Braitman, 2021). Videos showing the effects of the music she chooses and uses on animals can be watched on Braitman's website (http://www.musicforanimals.org/main). In one of the songs used, which bears traces of the old howling patterns of wolves, it is seen that wolves respond to music by howling. It is known that many species, including parrots, have a sense of rhythm and even percussion in nature. However, little is still known about the musical feelings and tastes of animals. This issue stands as an area where research should be intensified for animal health and welfare (My Animals, 2019). In addition, the fact that almost all the musical instruments made and used in ancient times were made of animal tissues such as skin, intestines, hair, nerves, bones and horns is also an issue that needs to be researched.

Hirudotherapy

The use of living organisms, animals, and animal products for therapeutic purposes in veterinary medicine is gaining importance. Methods such as leech (hirudotherapy) (Figure 15) (Simmental, 2021; Sobczak and Kantyka, 2014), treatment with bee products (apitherapy) (Tawfik, 2008) are being researched and applied in animals (Meregillano 2004; Tawfik, 2008; Sobczak and Kantyka, 2014; Aslan, 2016). Recently, leeches have been successfully used in veterinary medicine in the treatment of many animal diseases, especially in dogs, cats and horses. The most common indications for the use of leeches are hip and elbow dysplasia, acute and chronic arthritis, diseases associated with tendon, ligament and fascia inflammation, vertebral disorders, and treatment of scars. The treatment is a painless procedure lasting 30-120 min. depending on the size of the animal. Leeches used in medical procedures for treatment should be obtained from certified bio pharms; sterile conditions in the culture, transport and storage of leeches are important to protect the animal to be treated from microbial infections. Hirudotherapy is also used in veterinary medicine, especially in cases of injuries and postoperative venous congestion where conventional treatment is ineffective and treatment effects are very weak (Sobczak and Kantyka, 2014).

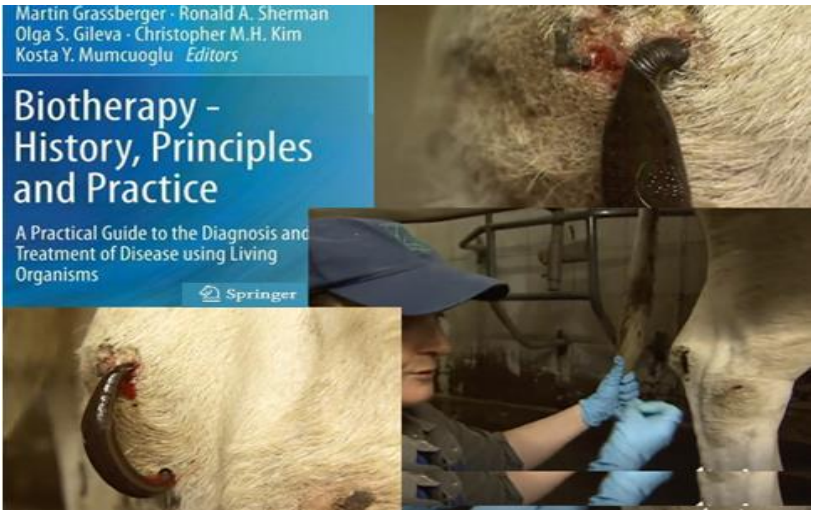

Figure 15. *Treatment with living organisms and application of hirudotherapy for wound healing in cattle (Grassberger et al., 2021; Simmental, 2021).*

Apitherapy

Veterinary medicine research on bee venom and bee products has shown that these products can be used for multiple purposes in veterinary medicine; propolis has been shown to be effective in mastitis, wound healing, diarrhea, gastrointestinal diseases, genital infections, otitis and dermatitis. An ideal propolis formulation is safe in animals; the establishment of such a formulation standard will allow for increased use of apitherapy in veterinary practice (Tawfik, 2008; Šuran et al., 2016).

Conclusions, Recommendations

Integrative veterinary medicine practices include modalities such as acupuncture (Gülanber, 2008), chiropractic (Maler, 2012), massage and reflexology (Hare, 1999; Larson, 2018), herbal therapies (Wynn and Fougère, 2007), homeopathy (Clausen and Albrecht, 2010), lasers (Kelly and Johnson, 2018), electromagnetic field (Gaynor et al, 2018), ozone (Sciorsci, 2010); cupping,

bloodletting (Estaity, 2019), leech (hirudotherapy) (Sobczak and Kantyka, 2014), cauterization/cauterization (Imrie, 2001; Thurairaj, 2014), mesotherapy (Alves, 2018), balneotherapy (Bartos et al, 2019), hydrotherapy (Ptov, 1975; Ross et al., 2001; Aslan, 2016). Medical paradigms are evolving along with human and science, and every option is tried to be updated to prevent animal suffering and to eliminate or alleviate their discomfort. It is aimed that GETAT comprehensive medical modalities will ultimately be shown to be scientific, safe, and effective and will be adapted to conventional veterinary medicine over time. Therefore, the value of GETAT modalities is also related to their scientific proof. Since success in veterinary medicine practices, whether GETAT or conventional, also depends on the practice of the physician, individual skills also affect the results (Ross et al., 2001).

In treatment, trust in the physician and the applied method affects the success. In human medicine and veterinary medicine, it is often not possible to treat diseases with a single method. It is known that conventional medicine has difficulties especially in chronic, cognitive, and mental diseases. This situation has increased the tendency towards GETAT applications in veterinary medicine. In addition, Pharmacoeconomics research aiming to reduce health expenditures and costs, which are quite high within the scope of modern medical treatment, have sought new options. Therefore, integrative medical methods have come to the fore and become an agenda again. However, scientific studies to make these methods safe and environments to apply them safely are required. GETAT education should be given in undergraduate and graduate curricula in veterinary faculties, and applications should be initiated in animal hospitals and clinics. Findings obtained from projects, thesis and other scientific studies should be subjected to systemic evaluation and a database should be created. GETAT comprehensive applications are carried out in many veterinary faculties in the world, especially in developed countries. In our country, scientific disciplines and departments of integrative veterinary medicine do not yet exist in veterinary faculties, and integrative medical methods

are not applied in faculty hospitals and clinics. Integrative medical methods are applied in the clinics of veterinarians and private animal hospitals in our country, and even courses, seminars, and certification programs for GETAT applications are organized. At this point, it can be suggested that trainings, certification processes and applications for integrative veterinary medicine GETAT applications should be carried out with the knowledge and coordination of the Ministry and Veterinary Faculties to ensure scientific, reliable, and sustainable standards.

The aim of all medical approaches is to keep the homeostatic balance within physiological limits. The source of complementary medicine approaches and practices, whether revelation or observations and experiences, should be tried to be proven within the framework of today's scientific understanding. The World Health Organization recommends that member countries integrate GETAT into their education and health policies. In our country, there is no regulation and directive on GETAT practices in veterinary medicine yet. The lack of a legal basis for integrative practices is an obstacle to their implementation in veterinary medicine. Clinics and hospitals belonging to veterinary faculties perform medication and operations within the scope of scientific medicine, and although complementary methods are sometimes recommended verbally, actual application and prescription are not performed. Postgraduate theses, projects, and scientific research within the scope of GETAT in veterinary faculties are quite high. There are also elective courses in the curriculum. Despite this, the fact that GETAT applications are not performed requires prioritizing the training of lecturers and academic staff in this field. It may be suggested to prioritize this field in the new veterinary medicine specialty education. To implement GETAT comprehensive veterinary medicine practices in veterinary faculties, it may be an important step for the Council of Higher Education to employ thematic research assistants and to train academic staff through domestic and international postgraduate education. To make veterinary medicine education and practices in our country more effective and attractive in international

competition, the establishment of GETAT departments in veterinary faculties and the establishment of a regulation on integrative practices in veterinary medicine as in human medicine should be urgently addressed. This situation has become more important today when higher education is fully opened to international students. There is no unit within the Ministry of Agriculture and Forestry to carry out GETAT practices in the field of veterinary medicine. This is because the animal health services of the Ministry of Agriculture and Forestry are not prioritized over clinics and hospitals. This situation should be reconsidered; clinics and hospitals for animal health should be opened either within the Ministry of Agriculture and Forestry or preferably within the Animal Health Department to be established in the Ministry of Health, and veterinarians to be employed should provide diagnosis and treatment services within the scope of both conventional and GETAT in animal hospitals to be opened. In addition, companies such as TARSİM, which ensures animal health, should support GETAT practices. Legal, educational, and psychological barriers to the implementation of GETAT methods in public and universities should be identified and removed. GETAT comprehensive scientific research in the fields of veterinary medicine on a global scale are quite high. A strong will is needed in our country to organize these studies and turn them into practice. Veterinary Faculties are members of the UAK Medical-Health Sciences Council. In this context, veterinary medicine should be recognized and supported as a health discipline both by the Council of Higher Education and by law, and the concept of "one health" should be initiated de facto. Implementation of the "single health" approach can end the debate on "Ministry of Health or Ministry of Agriculture and Forestry?" during the licensing of Complementary Medicine Products. Consideration of the fact that veterinary medicine education and profession is a medical field by the Ministries as well as higher education policies will accelerate and positively affect the development of integrative practices in veterinary medicine in our country.

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CHAPTER IV

Commonly Used Laboratory Anımals: Basıc Bıochemıcal, Physıologıcal And Specıes Characterıstıcs

Zeyneb KARAKUŞ[1]
Halise Betül ASLAN[2]

Introduction

Basic behavioral, biochemical, and physiological data about basic laboratory animals, which continue to play an important role in biomedical research, are important for all researchers. Technicians, animal caregivers and researchers need resources containing practical information about laboratory animals, especially rats, mice, rabbits, guinea pigs, hamsters, which are widely used in scientific research and provide findings that can be a

[1] Assistant Professor Dr., Afyon Kocatepe University, Çay Vocational School, Chemical Technology Program, ORCID ID: 0000-0002-7245-7363, zkarakus@aku.edu.tr
[2] Assistant Dr., Afyon Health Sciences University, Faculty of Pharmacy, Department of Pharmaceutical Technology, ORCID ID: 0000-0002-4285-7374 betul.aslan@afsu.edu.tr

reference for humans, during the breeding, care, and use of these animals in research. Those working in Animal Experimentation units, conducting research and thesis projects frequently refer to resources that are manuals for laboratory animals. The chapter is organized in a pattern that emphasizes the following aspects for laboratory animals. To provide simple and basic information about the important features of laboratory animals such as anatomy, physiology, hematological and biochemical indicators; to facilitate researchers to recognize the animal they work with, to observe animal welfare at the highest level and to understand the findings they will obtain; to make the care and feeding of experimental animals under the most appropriate conditions; Knowing the responsibilities of veterinarians for the health and medical needs and disease prevention of laboratory animals; procedures such as the design of experiments to be applied to animals, sample collection, measurement and evaluation of data; are important for the accuracy and success of research with laboratory animals. In addition, processes related to the procurement of animals, equipment and materials need to be well known and managed.

Laboratory Animal or Experimental Animal

Animals used in medical, biological, and other scientific research, experiments and tests are defined as 'Laboratory Animals'. Many trials and research processes are required before a drug or treatment method can be used in humans. The experimental animals produced for these processes are specially produced in laboratories or farms for use in scientific research. They are born in cages, which are artificial environments, and after being used in research, experiments and tests in this environment, their lives end in this environment. Rats, mice, guinea pigs, hamsters, hamsters, and rabbits are examples of these animals because of their widespread use. Apart from these, animals such as goats, sheep, cattle, pigs, horses and chickens are also raised and used as experimental animals in farms. However, since these animals have strong emotional bonds with humans, they are only used in some limited studies due to

ethical concerns. Studies using laboratory animals are called 'Animal Experiments'; experimental animals are frequently used in biomedical research and in testing medical and physiological hypotheses (Poyraz, 2000, Aslan & Gülay, 2022).

Laboratory Animal Discipline

This discipline has hundreds of important topics such as the correct recognition of the anatomical and physiological structures of experimental animals, their breeding and reproduction in line with these characteristics, standardization of laboratory animals in terms of environmental needs, behavior, genetic and microbiological characteristics, protection from diseases, development of the most appropriate experimental methods to be performed with these animals, improvement of experimental and application conditions, knowledge of the effects of animals against basic pharmacological agents and euthanasia. To improve the quality of experiments and ensure animal welfare, the 3R rule is a barrier that must be followed.

1. Replacement: The use of other techniques, models or methods that can be used instead of experimental animals in research.

2. Reduction: Aims to use the minimum number of experimental animals necessary to achieve the correct result.

3. Refinement: It aims to minimize factors such as pain and stress during and after the applications to the animal (Aslan & Gülay, 2022).

Animal Model

In its clearest definition, an animal model is an animal substitute for a human being. More broadly, it is defined as an animal that resembles human or other animal species in terms of biological function for the investigation of a spontaneous or induced pathology in which a normal, anatomical, or physiological structure or psychological state can be analyzed. For experiments to be appropriate and reliable, the most appropriate animal species must

be selected for that experiment. Animal models used in research are divided into 4 groups. 1. Induced models: These are animal models in which anatomical and physiological diseases and disorders are induced surgically or by a substance. 2. Spontaneous models: These are animal models that arise due to genetic and environmental reasons and can show pathology and disease symptoms like the disease in humans. 3. Negative models: Animal species, breeds, or lineages in which a particular disease has never developed experimentally or naturally. 4. Possible models: In this type of study, the target is not the disease in humans. These are models created to predict diseases that can be transmitted from animals to humans and to demonstrate a possible situation. Diseases have been seen primarily in animals and studies are conducted to identify similar diseases in humans. Animal model experiments (vivisection) are procedures performed on non-human animal species, vertebrate, or invertebrate, for scientific purposes. These scientific purposes are mainly.

- Basic biological research

- Research on forensic medicine

- Gaining vocational knowledge and skills in education

- Research for the protection of human and animal health or animal welfare

- Military research

- Research for product quality and control (Poyraz, 2000).

Animal Species Used in Experiments and Basic Experimental Procedures

Although different types of animals can be used in animal experiments, depending on the purpose and objective of the study, with the permission of the Local Ethics Committee for Animal Experiments, the most used animal species globally are rodents (mostly mice, rats, hamsters, guinea pigs, rabbits), fish, poultry, ungulates (horses, donkeys, mules), ruminants, marine mammals

and primates. In Turkey and many other countries, there are restrictions on the use of primates in experiments due to their genetic similarity to humans. Animals used in experiments are referred to as "experimental animals" or "laboratory animals" in all legal texts regulating animal experiments. However, these definitions are still controversial in many aspects in terms of animal rights. Animals used in experimental and scientific procedures in Turkey must be purchased from a "registered experimental animal producer". It is only possible to use stray animals or cats and dogs from temporary animal shelters or animal care homes in experiments if scientific justification is provided that the study should be carried out on other animals. The same applies to great tailless monkeys, which are prohibited from being experimented on. A group of animals used in experiments may be used in other studies, considering factors such as the effect of the procedure and their general health after the procedure, otherwise they are killed by the appropriate method at the end of the first study. Species-specific killing methods may differ. The aim is to prevent permanent damage or severe pain and suffering to the animal during the experiment. This killing is called "sacrifice" or "euthanasia". In the case of pain and suffering procedures that will not affect the outcome of the experiment, experimental animals may be given local or general anesthesia or painkiller preparations during these procedures (Geçmez et al., 2023).

Ethics Committees

The first rule to remember is this: It is illegal to experiment on animals without the permission of an ethics committee. The Local Ethics Committee for Animal Experiments (HADYEK) is the committee formed by public and private institutions that conduct experimental and scientific studies on animals, and the Central Ethics Committee for Animal Experiments (HADMEK) is the committee that works under the ministry and supervises all local ethics committees and approves their directives. HADYEK consists of the responsible veterinarian, officials, and representatives of the institution, while HADMEK consists of ministry bureaucrats,

academics and representatives of professional organizations and professionals. One of the 21 members of HADMEK must be a representative of a non-governmental organization active in animal protection, but the selection of members in HADMEK, which has been in operation since 2014, has been taken to court by animal rights organizations claiming that it is against the legislation. Local ethics committees review experimental and scientific studies using live animals and authorize, request changes, or reject them. HADMEK requests annual activity reports from local ethics committees and creates "Annual Statistics" reports with the information compiled from these reports. The reports include information such as the types and numbers of animals used in experiments during the year and the purposes for which these animals were used. Recent years, the number of animals used in experiments has been decreasing, especially in European countries, due to reasons such as the development and widespread use of alternative methods and the increasing questioning of the reliability and ethical dimension of animal experiments. In Turkey, a decrease of 1.92% is observed when comparing the rates between 2010 and 2017, but this decrease is quite small compared to other countries (Poyraz, 2000, Aslan & Gülay, 2022).

Animal Experimentation Centers

In countries with legal regulations on animal experiments, those who want to conduct experimental and scientific studies on animals (institutions and organizations) must obtain a work permit (license). The institution that grants this permit is the relevant ministry, which varies according to the country. In Turkey, the competent authority in this regard is the Ministry of Agriculture and Forestry. After obtaining a work permit from the ministry, public or private institutions that will conduct experiments on animals, or produce or supply animals for use in experiments, must establish their own local ethics committees and guidelines. There are around 150 licensed experimental centers in Turkey. When obtaining a work permit, the centers must specify the species they will use in

experiments and obtain permission for each species individually. Because they are obliged to provide the appropriate environment for the care and shelter of each species. Animal experiment centers also have an "Animal Welfare Unit" and the veterinarian in charge supervises the experimental procedures in this respect (Poyraz, 2000).

Physiological and Behavioral Characteristics of Experimental Animals

Rat

They belong to the rat family and are a wild brown rat variety. They are small, hardy creatures, covered with stiff, long white hair. Their tails are involved in stabilization and homeothermic regulation. The retina consists entirely of rod receptors (bacilli) and they are color blind. They are more sensitive to high frequency sounds than humans. The olfactory area of the brain is very well developed. They are animals with nocturnal (night active) biorhythms. With 6 pairs of nipples, 3 pairs of thoracic, 1 pair of abdominal and 2 pairs of inguinal, they are ready for many offspring. Rats have a pointed mouth and truncated upper lip. They have monophyodont dentition, so their milk teeth do not fall out. They have only one sharp tooth and one gnawing tooth. Together with the other teeth, which are chewing teeth, they have a total of 16 teeth. The incisors have no root and continue to grow throughout life. Therefore, they need to be filed down so that they do not grow too long. There is a gap between the incisors and chewing teeth, called a diastema in medicine. The stomach of rats is divided into two parts. With this divided stomach system, it is impossible to vomit. Since rats are unable to vomit, they are unable to orally expel any indigestible and ingested hazardous substances after ingestion. Cellulose digestion and B vitamins are synthesized in the secum. They also eat their feces for bioavailability (coprophage). Physiological feed requirement is 10-20 g/day and water requirement are 50-90 ml/kg body weight. Rations should contain

18-20% protein and 1-5% cellulose. The absence of gall bladders is important for feeding and digestion studies. Researchers should take this into consideration. Their feet and tails are completely hairless or have very little hair. They have five toes on their hind legs but only four on their forelimbs. Rats lack sweat glands, so they exude excess heat through their hairless parts (feet, ears, etc.). Females have many udders. Rats' eyes are on the sides of their heads so they can see a large area at once, but they do not have three-dimensional vision (Jain, 1993, Sharp et al., 1998, Kaya & Çenesiz, 2010).

They have a very good sense of smell. They use it not only to search for food, but also to recognize other rats in the same herd, to know when a female is ready to mate, and to know which animals calm and which animals are stressed. They have very good hearing. Like most other small rodents, rats can hear up to the ultra's hall level. The balance organs inside their ears are also very well developed, and this allows the rat to overcome seemingly insurmountable obstacles. Their taste buds are also very good, with taste sensors not only in their mouth but also in their whiskers. Water is a priority for rats, they cannot tolerate thirst. Since they can control their feed consumption, they can be fed ad libitum. Although their lifespan is approximately 24 months (maximum 36 months), the ideal period of physiological traceability for experiments and research is 9-10 months. Their physiological environment is 50-60% humidity, ideal temperature of 21±1 C (min/max 18-26 C), 12 hours of darkness and 12 hours of light (dim light). Since they are usually albinos, they are prone to cataracts in bright light. Their room/environment should be ventilated frequently, and they should be kept away from noisy environments due to their sensitivity to noise (Kelly & Masterson, 1977, Langer, 1978, Moore, 2000, Noyan, 2006, Prusky et al., 2002).

Some individual and physiological characteristics of rats are as follows (Leonard & Ruben, 1986, Schwabenbauer, 1991, Sharp et al., 1998, Öber, 2007).

Chromosome number ♀♂: 2n=42

Birth weight♀♂♂: 4,5-6.0 g.

Adult body weight ♀♂: 150-200 g.

Gestation: 21-23 days

Sexual maturity ♀♂: 40-50 days

Number of births per year: 7-9

Number of offspring in a litter: 6-14

Respiration ♀♂: 70-110 times/min

Heart rate ♀♂: 260-450 times/min

Erythrocyte (RBC) ♀♂: 6-10x106/mm3 Average 8.5x106/mm3

Hemoglobin level ♀♂: 11-17 g/100 dl

Hematocrit ♀♂: 40-50% Avg. 45

Leukocyte (WBC) ♀♂: 5-13x103/mm3

Formula Neutrophils ♀♂: 5-49% lymphocytes 43-85

Platelet ♀♂: 150-460x103 /mm3

Image 1. Rat

Rats are social animals and live in herds, with males and females mixed. Those who are friends in a herd mark each other with urine to strengthen their social bonds. Rats are adept at adapting to new environments and withstanding harsh conditions; when hungry, they will eat things like soap, leather, paper, textiles and wood, or

worms, insects, and small birds. If they have a choice between animal (meat) and plant food, they prefer plant food. If rats live in an environment where they can find everything they are looking for, only 10% of what they eat is animal food. Sexual maturity starts from the 2nd month of life but is usually completed by the 3rd-4th month. The testes, which are in the abdominal cavity in the newborn, descend into the scrotum at 4-6 weeks of age. They have a menstrual cycle, and this cycle occurs regularly every 4-5 days. Gestation period is 21 days. They give birth to 6-14 young in one litter with a birth weight ranging between 4.5-6.0 g. Lactation is 21 days. They are very fertile. They mature at six weeks of age. A female rat can conceive and breed six to eight times a year, with each pregnancy producing between 4 and 16 offspring, but only 5% of the offspring survive. If mating occurs at a time when there is not enough food, the female may hold the offspring back in the uterus, delaying pregnancy until a more favorable time. The first mating attempt is initiated by the female by producing sex hormones, the male animals smell the pheromones, the hormones. The female makes it a point to mate with as many males as possible, and the strongest and healthiest sperm are the ones she collects. Rats are also bred as pets (*Rattus rattus domesticus*), hence the different colors. The rat kept as a pet is produced from the nomadic rat. The ones used for experiments in laboratories are also from the *Rattus domesticus* species. The rat is not a mouse. They have a different place among experimental animals, especially when it comes to rabies and plague. Their survival efforts and intelligence are remarkable (Sharp et al., 1998).

The rat ovum is highly like the female ovum. The entry of sperm into the egg is therefore one of the most frequently studied subjects in rats. They run faster than rabbits. When their cage mates die, they eat them even though they have enough food. For this reason, in physiological studies and memory experiments, they may appear more intelligent when dead rats are placed in the maze instead of cheese or feed. The hairless tail acts as a kind of handle, but when held in this way, it can stick to the hand in a pulling motion. It is best to hold them from the back, grasping the whole body. If you grab

them from the back and pinch their tail with your pinky and ring finger, they will become helpless, depending on your determination. You should be prepared for the painful sound they will make. If you grab them by the tail, if you grab them not in the middle of the tail but at the very end, they will try to spin, and their spine may be damaged, and both the animal and your experiment may be wasted. When you put your hand into the cage with 5-10 of them, they may attack and bite your hand, but this is a defense instinct. They can also hurt you when it comes to their offspring. Since these animals mate out of sight and harem-type, they should be examined during the period when they have vaginal smears for mating and should be placed in their nests accordingly. Excessive stress and excessive anesthesia are the most common ways to lose them (O'Steen, 1987, Öber, 2007).

Rats become extremely aggressive when starved. If you are not careful in food restriction trials, they can pierce your finger to the bone with their 1 cm long sharp front teeth. Since rats eat their deceased and anesthetized conspecifics, if you want to take pathological samples, your experimental cage should be separate from the cage of animals that appear to be at risk. If the rats have been starved for reasons such as surgery, the anesthetic to be administered may be 2/3 of the usual dose. If you want to empty the rats' stomachs, give them diluted liquid food for 24 hours, and place the animals in cages with a wire bottom to prevent them from eating their feces. Since rats do not like to be stitched in operative trials, staplers should be used if possible. During the experiment, rats become accustomed to humans. This is a factor that complicates the sacrification process. It is necessary to be careful in choosing rats as pets, as 1 cm. tumors, which can develop in a short time (around 1 year of age) due to the excessive cancer predisposition in albino rats, cause psychological devastation in pet owners. The smell of pussy cucumber they like very much and even wake up from sleep. Rats are larger than mice and rats have coarser fur than mice. Head and body together, ears and tail are large (Sharp et al., 1998, Kaya & Çenesiz, 2010).

Mouse (Mice)

Mouse is the common name for many small mammals, primarily house mice (Mus musculus), of the order Rodentia, suborder Myomorpha. Laboratory mice are small animals developed from house and field mice, with small bodies and ears that can be considered large for their hard hairy bodies. Mice used in laboratories are mammals belonging to the order Rodentia, usually of the species Mus musculus, which are bred for different scientific research models, as well as for breeders. In scientific research, the mouse is the most widely used mammalian research animal model. They are widely used in research in genetics, physiology, biochemistry, pharmacology, toxicology, psychology and even all medical disciplines and other biological chemical scientific disciplines. The mouse belongs to the class Euarchontoglires, which includes humans. This close relationship, high homology in relation to humans, ease of care and handling, and high reproductive rates make mice particularly suitable models for human-oriented research (Geçmez et al., 2023).

Their life span averages 18-24 months but can vary widely depending on genetic and environmental factors. Their feet have 4 toes in front and 5 toes behind. Tail length and body length are almost equal. They can escape very fast and reproduce very fast. The tooth order is 1/1. 0/0/0/0/0/0/0/0/0/0/0/0/3 and the first molars are longer than the others. Incisors grow continuously and wear down with use. They have two small lined external jaw pouches that run from their cheeks down to their shoulders. Mice carry food in these pouches and when they need to clean them, they turn them inside out and clean them. Because their incisors are constantly growing, worn surfaces are quickly replaced. They eat a wide variety of foods such as grains, roots, fruits, grasses, and insects. They do not see color. Although their sense of hearing and smell are well developed, their sense of sight is weak. Their lungs have one lobe on the left and 4 lobes on the right. Like rats/rats, they are nocturnal, active at night. Cold increases their basal metabolism up to 3 times, while temperature increase decreases metabolism. Juveniles lack

homeothermic regulation until they are 20 days old and cannot control their body temperature. They are also widely used in laboratory experiments due to the high similarity between the genetic makeup of mice and humans and their reproductive rate (Kaya ve Çenesiz 2010).

Image 2. Mice

Some genetic, physiological, and individual characteristics in mice are presented below (Geçmez 2023).

Hematocrit ♀♂: 42-50%,

Hemoglobin♀♂ :12-15 g/100,

Erythrocyte (RBC) ♀♂: 6-12.5x106/mm3

Platelets ♀♂ :160-410x103 /mm3

Leukocytes ♀♂:

Lymphocytes: 60-80%

Neutrophils: 18-20%

Monocytes: 1%

Eosinophils: 1-2%

Basophils: 0.5

Blood glucose ♀♂: 124-262 mg/d

Blood clotting time ♀♂: Start: 24"-40" End: 1'.40"-3'.35"

Red blood cell membrane stability (% NaCl) ♀♂:

Hemolysis onset (min. strength) 0.54

End of hemolysis (max. resistance) 0.42

Chromosome numbers ♀♂: 2n=40,

Average life expectancy: 18-36 months

Feed Consumption: 15g/100g/day

Water Consumption: 15ml/100g/day

Respiratory Rate: 94-163 /min.

Heart Rate: 325-780/min

Blood Pressure: 130/90 mmHg

Blood Volume: 76-80 ml/kg

Body Temp: 36.5-38.0 0C

Urine volume: 1-1.5 ml/day

Pregnancy: 19-21 days

Birth weight ♀♂: 1-2 g

Lactation period: 18-21 days

Weight in adult ♀♂: 20-40 g

Number of offspring in one litter: 7-12

Oestrus: 25-28 days

Full Sexual Maturity: 7-9 weeks

False pregnancy: 10-13 days

Cycle Length: 4-5 days

Interval between births: 3-5-6 weeks

Weaning Age: 21-28 days

Rabbit

Rabbits belong to the family of mammals, rodents and rabbits, their hind legs are longer than their front legs, and they have a well-developed sense of sight, hearing and smell. They differ from rodents by having 2 pairs of well-developed incisors in their upper jaws. Breeds range in weight from 1 kg to 6 kg. Life span can be up to 15 years in different breeds. The ideal productivity period is limited to 3-4 years. The lung has 4 right and 2 left lobes. For proper physiological life, they should be kept in a 12 hours dark 12 hours light environment, 15-20 0C optimal temperature and approximately 50% humidity. They urinate frequently and profusely. Urine pH =8.2 under free feeding and around 6-7 under supervision. Albuminuria is physiologic and urine is immediately precipitated. Herbivores. They like to consume pellet feed and seasonal greens. Coprophagy is present. They usually eat the soft feces they produce in the morning. Daily food requirement is 50 g/kg body weight. A healthy rabbit's stomach is not empty. They do not vomit physiologically (Kaya ve Çenesiz, 2010).

Rabbit is the common name of the mammalian species of the rabbit family Leporidae, classified in the order Lagomorpha. The care of the young is very low. After 7 days of nursing, the mother rabbit lets the baby rabbit go. The rabbit family includes about 60 species. Their tails are covered with long hair. Ears and hind legs are elongated. Some of them live in burrows under the ground. Rabbits are distinguished from the pika of the family Ochotonidae by their small furry tails, long ears and hind legs. All members of genera other than Lepus are commonly called island rabbits. Sage hares live in burrows of other animals or in burrows that they dig themselves, while rabbits live in tall grass and brush. Among rabbits, the white-furred greenhouse rabbit has the most striking features and has made its mark in the 21st century. In addition, some species have very good hearing. They react with surprise to all kinds of sounds. This is why wild rabbits are startled when approached by members of their own species or other creatures. They are native all over the world except Oceania. Their arrival in Oceania poses a great threat to

native mammals. Rabbits are herbivores. They are animals that feed on plant foods. They usually eat cabbage, fresh grass, carrots, radishes, radishes, dill, lettuce, salad, artichoke and cauliflower leaves, Brussels sprouts, green beans. However, it is important not to give too much food that contains sugar (for example carrots). The age of puberty is 6 months in large breeds and usually 9 months in others. They show stimulated polyestrous, reflexive ovulation (due to mating). Gestation period is 30-32 days. They give an average of 7-8 offspring in one litter. Lactation period is approximately 30 days (Geçmez et al., 2023).

Image 3. Rabbit

Some of its physiologic features can be listed as follows (Geçmez et al., 2023):

Chromosome numbers: 2n=44

Live Weight

Male: 2-5 Kg

Female: 2-6 Kg

Birth Weight: 30-300 g

Life Span: 5-6 years

Feed Consumption: 5g/100g/day

Water Consumption: 5-10ml/100g/day

Volume of urine excreted: 50-75 ml/kg/day

Body Temperature: 38.0-39.6 C

Pregnancy Period: 29-35 days

Age at pupping

Small breeds: 6-9 months

Large breeds: 3-4 months

Weaning Age: 6-8 weeks

Number of offspring in one litter: 6-7

Solid feed. Age: 3 weeks

Opening of the eyes: Day 10

Ideal lifetime: 4 years

Respiratory rate ♀♂: 35-56 times/min (for 2-4 kg)

Blood Pressure ♀♂: 90-130 / 60-90 mmHg

Blood Volume ♀♂: 57-65 ml/kg

Heart rate (pulse) ♀♂: 130-320 times/min

Erythrocyte ♀♂: 5-8 x106/mm3

Hematocrit ♀♂: 40-50% (quite high)

Platelet ♀♂: 250-750x103/mm3

Leukocyte ♀♂: 3-12.5x103/mm3

Neutrophil leukocyte formula ♀♂: 30-65

Lymphocyte formula ♀♂: 28-85

Blood clotting time:

Onset of clotting 1'-15" - 1'-42"

End of clotting 5'-40" -7'-0

Red blood cell fragility (%NaCl)

Hemolysis onset 0.49 (0.48-0.54)

(minimal durability)

End of hemolysis 0.42 (0.40-0.44)

Guinea pig

The guinea pig or guinea pig (Cavia porcellus) is a stocky, domestic rodent with fur of many colors and shapes. It is a very popular pet, especially in the Americas and Europe. Central and South America is the home of the wild guinea pig, the ancestor of the domestic guinea pig. Wild guinea pigs and other guinea pig species have spread throughout South and Central America. The guinea pigs are the largest family of rodents, consisting of species such as the wild guinea pig, mara (pampas rabbit), capybara (water boar). The remains of the first domestic guinea pigs from about ten thousand years ago were found in Peru. It is thought that guinea pigs were kept for their meat in South America at that time. In the 19th century, when the Spanish discovered South America, domestic guinea pigs began to be transported to Europe. Over time, they became a pet animal in Europe and around the world. They have a large head, small ears, and thin short hair. They have a stocky body with short legs and do not carry a tail. Their front legs have 4 toes and hind legs have 3 toes. Fingertips are clawed. Adult body weight; males: 900-1000 g., females: 700-900 g. range (Kaya ve Çenesiz, 2010).

Guinea pig is an animal that eats only vegetable feed and rarely drinks water because it usually meets its water needs from the ration. As in all rodents, incisors are continuously elongated in guinea pigs. A pair of nipples in the inguinal region. They are

sensitive to noise stress and sudden movements and are very disturbed. The optimum temperature for physiological life should be 18-22 C, with 45-70 % humidity. The temperature should not rise to 30 C. As in rats, mice and rabbits, the environment should be ventilated 8-20 times per hour. Lighting should be done with 12-12 periods. Typical herbivore (eats cabbage, lettuce, zucchini etc.) Lactobacilli are dominant in the intestinal microflora. Feed consumption is 6g-100g body weight/day. Pellet feed and quality dry grass can be given. They should get enough vitamin C. Guinea pigs, just like humans, cannot produce vitamin C in their own bodies. For this reason, vitamin C supplements should be included in the ready-made feeds that should be given to guinea pigs. They should also be fed with fruits and vegetables rich in vitamin C such as tomatoes and parsley from time to time. Pellet feed should contain 20-30% protein and 10-18% cellulose. The stomach contents empty in about 2 hours, while the passage time through the digestive tract is about 20 hours. They consume 10-15 ml/100g of water daily. Tap water can be given. Guinea pigs hide in nature and collect their food, which consists of all kinds of grasses, seeds, roots and flowers. In times of danger, they flee to their burrows, which are never far away. They are typical vegetarians, feeding on grass, seeds, fruits, vegetables, roots and twigs. The ready-made guinea pig food sold in many pet stores consists of seeds, pressed grasses and spices (pellets). They also include nuts such as peanuts or seeds (Geçmez et al., 2023.

Image 4. Guinea pig

In nature, guinea pigs live in large families of one male and one female. When the male cubs become adults, they either stay in the clan by fighting with the dominant male at the head of the clan, or they leave the clan and form their own harem. There are strong bonds between family members. They travel together and eat together. They constantly communicate with each other by making sounds that people can hear. If a family member loses sight of or loses other members of the group, they call for help with a very loud call. Especially the young ones make this sound a lot when they lose their mother. Guinea pigs are social animals. For this reason, it is not right to feed guinea pigs alone in any way. In some countries it is even considered a crime to keep guinea pigs alone. It's ideal to feed at least two guinea pigs together. Guinea pigs meet their daily fiber needs from grass. For this reason, guinea pigs kept at home should be given grass and hay every day. They should also always have clean, fresh water in their cages. Guinea pigs need large spaces. For this reason, their cages should be as big as possible. They should not be kept outside in winter and cold weather. Their cages should always be stocked with grass, hay, and ready-to-eat feed. Guinea pigs should be released for at least one hour every day. Be careful of cables and poisonous flowers in the environment where they are released. Some physiological characteristics can be listed as follows (Kaya ve Çenesiz, 2010, Geçmez et al, 2023):

Chromosome number: 2n=64

Live Weight

Male: 900-1200 g

Female: 700-900 g

Life Span: 4-5 years

Feed Consumption: 6g/100g/day

Water Consumption: 10ml/100g/day

Body Temperature: 37.2-39.5 0C

Rectal temperature: 37.9 C (36.0-40.5)

Age at maturity: 55-70 days

Cycle Length: 15-17 days

Pregnancy Period: 59-72 days

Duration of Estrus: 6-11 h

Weaning Age: 14-21 days

Lactation Period: 21 days

Time Between Births: 96.3 days

Birth Weight: 60-100 g

Respiratory rate ♀♂: 69-104/minute

Heart rate (pulse) ♀♂: 230-380/minute

Blood volume ♀♂: 69-75 ml/kg

Blood pressure ♀♂ :80-94/55-58 mmHg

Hematocrit ♀♂: 45%

Red blood cell ♀♂ :4.5-7.0 x106/mm3

Leukocyte ♀♂: 9-10x103 mm3

Neutrophils ♀♂: 28-34

Lymphocytes ♀♂: 39-70

Platelet♀♂: 250-850x103 /mm3

Hamster (Golden Hamster)

Hamsters are the animal in protection status at risk (EN). They belonging to the order Rodentia and subfamily Cricetinae, form a diverse group that includes 19 different species divided into seven genera. These animals are widely favored as cuddly little pets. The best known of the hamster species is the golden or Syrian hamster (Mesocricetus auratus), which is often the leading pet species. Other common domestic hamster species include the

Campbell's dwarf hamster (Phodopus campbelli), the winter white dwarf hamster (Phodopus sungorus) and the Roborovski hamster (Phodopus roborovskii). The hamster was discovered in 1930 in a town near Syria. The original hamster, that is, the hamster before it was bred to obtain different color and coat varieties, is a short, soft-haired, yellowish-brown animal. It has blackish spots on its back and cheeks, and its abdomen is gray, white. Hamsters with different colors and coat lengths, which are now kept in homes as pets, were later obtained through selective breeding. They usually feed on fruits, vegetables, and grains. In their natural habitat, they are prey to animals such as owls, hawks, and ferrets, as well as hunted by humans. They are 10 to 15 cm tall and weigh around 150 g. They live for about 2 years. They do not like very loud noises. The most interesting features that distinguish hamsters from other rodents are the pouches on their cheeks. Hamsters collect their food in these pouches and carry it to their burrows where they store it. In a hamster's pouch, a hamster sometimes carries half its body volume of food to protect its young. Another interesting feature of hamsters. They eat their own feces because their digestive system is not able to fully break down and utilize the nutrients in the food in the first session. In their natural habitat, hamsters usually stay underground during the day to avoid predators, becoming more active during the twilight periods between day and night. They feed primarily on seeds, fruits, and plants, and occasionally consume nesting insects. Their physically robust build includes distinguishing features such as cheek pouches that extend to their shoulders, which are used to carry food to their burrows. They also have a short tail and fur-covered feet (Kaya ve Çenesiz, 2010).

It is a short-legged, stocky rodent with marsupial cheeks. The hamster's skin is flexible and loose, as it is not fully adhered to its body. It's almost like a loose-fitting dress. The eyes are bright and perfectly round, they do not see color and their sense of sight is not well developed. Their sense of hearing and smell are very good, and their sense of smell is well developed. Feet are suitable for grasping and gripping and climbing. They have 4 toes on their front feet and

5 toes on their hind feet. The tail is shorter than 1 cm and blunt. In the long-haired ones, the tail is completely under the feathers. Their height is 10 15 cm, and their weight is around 150 gr. Golden hamster (Syrian hamster) is mostly used in laboratories. It is widely used especially in tumor research. Adult live weight is 100-150 gr. Although males sometimes live up to 4 years, their lifespan is 1.5-2 years. They are known for their wheel spinning movement in the cage. Cannibalism is common in the first week in newborns. They eat their food at night. Gestation period is 16 days on average. The number of offspring in a litter is 6-9. Hamsters become mature at 1.5-2 months of age and can be used for breeding (Geçmez et al., 2023).

Image 5. Hamster

Some physiological characteristics and parameters for hamsters are as follows:

Ideal ambient temperature: 20-24 C

Humidity: 50-60

Ventilation: 0-15 hours

Light Dark phase period: 12-12 hrs.

Adult body weight: ♂ 120-140 g ♀ 140-1460 g

Life expectancy: 2-3 years

Water consumption: 8-10 ml/day

Puberty: ♀ 4-6 ♂ 7-9

Estrus cycle: 4 days

Duration of estrus: 2-24 days

Gestation period: 15-17 days

Number of offspring born in one litter: 6-8

Birth weight: 2-3 g

Weaning weight: 30-40 g

Age at weaning: 20-22 days

Hemoglobin: 10-18 g/100ml

Hematocrit: 36-60

Red blood cell (RBC): 4.5-7.2 x106/mm3

Leukocytes: 3-11 1000/mm3

Blood volume: 80 ml/kg

Fasting serum glucose: 60-150 mg/100ml

Heart rate: 250-500 /min

Respiratory rate: 40-120 /min

Body temperature: 37-38 C

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Internet resources for images

Rat:https://terra.oregonstate.edu/2012/10/ten-discoveries-at-oregon-state/white-rat-on-white-background/ (Access Date: 11/12/23)

Mice:https://www.criver.com/products-services/research-models-services/animal-models/mice/humanized-mice?region=3616 (Access Date: 11/12/23)

Rabbit: https://www.petguide.com/breeds/rabbit/new-zealand-rabbit/ (Access Date: 11/12/23)

Guinea pig: https://www.thesprucepets.com/guinea-pig-care-1236838 (Access Date: 11/12/23)

Hamster: https://www.petburada.com/blog/icerik/hamster-isimleri (Access Date: 11/12/23)