



The Hidden Potential of Herbal Remedies and Nutraceuticals in Canine and Feline Behavioural Disorders

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ABSTRACT

Veterinary practitioners may encounter a wide variety of behavioral problems such as aggression, anxiety, compulsive behaviours, inappropriate elimination and cognitive dysfunction in daily practice. With the advance of scientific researches regarding usage of herbs and nutraceuticals in order to treat these behavioural problems, veterinarians and animal owners look for reliable sources to gain knowledge about that therapeutics. As elucidated by many published researches, neurotransmitters such as GABA, serotonin, dopamine and norepinephrine act in pathology of many psychiatric disorders and most of the modern drugs show their mechanism of action by regulating these neurochemicals. There is increasing evidence that herbal extracts and nutraceuticals act in a similar way with the conventional therapeutics however, lots of conventional medicines have remarkable side effect unlike herbal and nutraceutical therapeutics. Despite the increasing number of studies, the mechanism of action of these therapeutics has not been fully elucidated. This review aims to introduce recent scientific knowledge on herbal and nutraceutical remedies, that may be alternative treatment models in dog and cat behavioural problems.

Keywords: Behavioral disorders, Dietary supplements, Herbal, Serotonin.

öz

Kedi ve Köpeklerin Davranış Bozukluklarında Bitkisel Remedilerin ve Nutrasötiklerin Gizli Potansiyeli

Veteriner Hekimler günlük pratikte agresyon, anksiyete, kompulsif davranışlar, uygunsuz eliminasyon ve bilişsel işlev bozukluğu gibi çok çeşitli davranışsal problemlerle karşılaşmaktadırlar. Bu davranış problemlerini tedavi etmek için bitkisel remedilerin ve nutrasötiklerin kullanımına ilişkin bilimsel çalışmaların ilerlemesiyle, Veteriner Hekimler ve hayvan sahipleri bu terapötikler hakkında bilgi edinmek için güvenilir kaynaklar aramaktadır. GABA, serotonin, dopamin ve norepinefrin gibi nörotransmitterler birçok psikiyatrik bozukluğun patolojisinde rol oynar ve modern ilaçların çoğu bu nörokimyasalları düzenleyerek etki mekanizmalarını gösterirler. Bitkisel ekstraktlar ve nutrasötiklerin geleneksel terapötiklerle benzer şekilde etki ettiğine dair artan kanıtlar vardır, ancak birçok geleneksel ilacın bitkisel ve nutrasötik terapötiklerin aksine dikkate değer yan etkileri vardır. Artan sayıda çalışmaya rağmen, bu terapötiklerin etki mekanizması tam olarak aydınlatılmamıştır. Bu derleme, köpeklerin ve kedilerin davranış problemlerinde alternatif tedavi modeli olabilecek bitkisel ve nutrasötik remedilerle ilgili güncel bilimsel verileri tanıtmayı amaçlamaktadır.

Anahtar Kelimeler: Bitkisel, Davranış bozuklukları, Diyet ürünleri, Serotonin.

INTRODUCTION

Demand for etiology-based treatment options is increasing parallel to the growing behavioural problems in dogs. A recent study by Didehban et al. demonstrated that dog behavioural problems are one of the leading reasons for consulting a veterinarian and 86% of the dogs included in the study had at least one behavioural problem (Didehban et al. 2020). Veterinary practitioners may encounter a wide variety of behavioural problems such as aggression, anxiety, compulsive behaviours, inappropriate elimination

and cognitive dysfunction in daily practice. Every animal presented with behavioural complaints need to be assessed in terms of overall health and a detailed history should be taken to determine whether the behaviour is normal, abnormal or is it an underlying medical condition (Seibert and Landsberg 2008).

In human medicine, patients that suffer from anxiety, tend to seek alternative therapies due to adverse side effects of medications and collective prejudices (Liu et al. 2017). Similar tendency for alternative therapies and prejudice



for medical psychoactives are prevalent in dog owners. The Perception of dog owners against psychoactive medications and non-prescription alternative treatments was investigated and a significant majority of attendants remarked that they felt the highest comfort level with herbal and nutritional supplements, compared to medical options (van Haaften et al. 2020).

There is increasing evidence that herbal extracts can reduce anxiety symptoms through the regulation of neurotransmitters (Alex and Srivastava 2019). Anxiety and stress have similar development and results in humans and dogs regarding many aspects. Neurotransmitters such as GABA, serotonin, dopamine and norepinephrine mainly partake in the pathogenesis of anxiety disorders. GABA modulating phytochemicals may be an alternative to anxiolytic medications (Savage et al. 2018). Antidepressive effects of some herbal remedies via monoamine Oxidase-A enzyme (MAO) inhibition, are similar to the effects of tricyclic antidepressants (Zhang 2004).

Although rare, problems related to drug interactions and previous pathologies existing in animals should be considered when using herbal medicines in veterinary medicine. Quality, extraction method, concentration and purity have vital importance for the reliability of herbal remedies. Adverse effects due to remedies containing environmental pollutants such as heavy metals and mycotoxins also must be considered (Eritja 2014).

This review aims to introduce recent scientific knowledge on herbal and nutraceutical remedies, that may be alternative treatment models in dog and cat behavioural problems.

Herbal Remedies

Souroubea spp.

S. sympetala has been used in folk medicine to treat depression-like symptoms. Preclinical studies of *souroubea* spp. have shown an anxiolytic effect on rodents. Betulinic acid (BA) is one of the active metabolites of *Souroubea* spp. and anxiolytic effect of the herb is mainly attributed to BA. A commercial preparation which is composed of 55/45 mixture of *Souroubea* spp./ *Plantus* spp, which is equal to 1mg/kg BA for a 10kg dog has provided dose dependent decrease of plasma cortisol levels and significant anxiolytic effect on dogs (Liu et al. 2017). Chewable tablets consisting of a mixture of *souroubea* and *plantaris* at a dose of 1 mg/kg were used in the thunderstorm noise-induced fear and anxiety model of dogs, and their effectiveness in reducing anxiety in dogs was evaluated. This blind, placebo-controlled study showed that anxiety symptoms and blood cortisol levels decreased in a dose-dependent manner (Masic et al. 2021).

Canabis Sativa (Hemp)

Canabis sativa has been used by various cultures in traditional medicine for ages. *Canabis sativa* contains numerous physiologically active phytochemicals such as tetrahydrocannabinol (THC), cannabidiol (CBD), cannabigerol (CBG), and cannabichromene (CBC) (Lipnik-Štangelj & Razinger, 2020). THC binds with the cannabinoid 1 (CB1) receptors in the brain, resulting with euphoria, so it is the undesired metabolite. According to EU regulations, THC content cannot exceed 0.2% in veterinary products and hemp products are widely prescribed in USA and EU. Mechanism of action of CBD is not yet to be understood completely, but it is known that CBD modulates CB-1 receptor function, GABA, dopamine levels and serotonin function. Several human studies have shown its effectiveness on anxiety and psychotic

symptoms and it can be considered as a safe molecule (Ayati et al. 2020). Although it is used empirically, many veterinarians successfully use cannabis derivatives in many pathologies such as pain management, mood disorders, anxiety, depression, and seizures in dogs and cats (della Rocca and Di Salvo 2020). In a study on shelter dogs, effects of CBD on stress related behaviours were investigated and the results, although not statistically significant, demonstrated decrease in aggressive behaviours toward humans (Corsetti et al. 2021).

Withania Somnifera (Ashwagandha)

Withania somnifera, also known as Indian Ginseng has been studied for its neuroprotective, adaptogenic, anxiolytic and antidepressant effects. A randomized clinical trial has demonstrated the effectiveness of *withania* root extract on depression, anxiety and social dysfunction (Ayati et al. 2020). Glycowithanolides (WSG), extracted from the root of *Withania somnifera* has been used as an anxiolytic by Indians. It is thought *Withania somnifera* exhibits an effect by inhibiting protein oxidation and lipid peroxidation (Zhang 2004). Rodents treated with *Withania* presented reduced anxiety and this reduction was found similar to the effects of benzodiazepines (Alex and Srivastava 2019).

Pasiflora incarnata (Passion Flower)

Pasiflora incarnata, also known as Passion Flower is a perennial herb. Studies indicate that passion flower has effects on anxiety, reactivity, insomnia and depression-like behaviours comparable to benzodiazepines (Fonseca et al. 2020). *Pasiflora* is one of the herbal remedies that can be used to reduce stress in animals and there is no report about adverse effects, such as memory loss and collapse of psychometric functions relating to the administration of passion flower (Janda et al. 2020). A mixture containing dry extracts of *Crataegus oxyacantha*, *Passiflora incarnata*, and *Valeriana officinalis* was studied toxicologically on dogs, mice, and rats, and LD50 dose was indicated as 5g/kg and possibly more, also acute and chronic toxicity trials were conducted for 180 days and no signs of toxicity were observed at the end of the study, even with high doses and long-term use (Tabach et al. 2009). Due to the low toxicity profile and benzodiazepine like effects of the herb, Passion Flower could be a first-line therapeutic option for mild to moderate anxieties in dogs.

Hypericum Perforatum (St John's wort)

Hypericum perforatum, one of the most studied herbs due to its antidepressant effects and the herb has many active metabolites. Its possible mechanism of action is attributed to inhibition of monoaminergic reuptake and inhibition of Monoamine Oxidase A (MAO-A) and MAO-B activity (Zhang, 2004). Numerous clinical studies and animal experiments demonstrated that *H.perforatum* exerts its effect through a mechanism similar to tricyclic antidepressants or serotonin reuptake inhibitors (Alex and Srivastava 2019). In a striking study comparing hypericin (one of the active ingredients of *Hypericum perforatum*, 0.05 mg/kg) and fluoxetine (1 mg/kg) in 18 dogs with tail chasing behaviour, hypericin was found to have superior clinical effects compared to fluoxetine (Mosallanejad et al. 2015). Data in human medicine has demonstrated that *hypericum perforatum* may lead to drug interaction when used concurrently with cyclosporine and many other drugs due to common enzymatic metabolism. Furthermore it could lead to serotonin syndrome when used with SSRIs and side effects such as nausea, photosensitivity, and rash, although not frequent were observed (Ng et al. 2017).

***Camelia Sinensis* (Green Tea)**

Green tea has been used by traditional medical applications and it has various pharmacological and physiological functions. It has been well documented that, L-theanine, that is a main constituent of green tea has stress and anxiety reducing, neuroprotective and antioxidant effects (Saeed et al. 2017). A study has compared the effects of a nutraceutical (green tea extract, L-tryptophane) and control diet, on stress and neuroendocrine parameters of dogs. Results of the study revealed that plasma serotonin, dopamine and beta endorphin levels of dogs in the study group were significantly higher than the control group and plasma noradrenaline and cortisol levels were significantly lower in the study group (Sechi et al. 2017).

***Melissa Officinalis* (Lemon Balm)**

Melissa officinalis has been used historically due to its anxiolytic effects. Studies performed with aqueous extract of the herb on mice, has demonstrated increased explanatory activity and sedation (Zhang 2004). In another study performed on mice, *Melissa officinalis* extract administration has shown dose dependent decrease of serum corticosterone levels, additionally increased GABA levels in mouse dentate gyrus (Yoo et al. 2011).

***Matricaria Recutita* (Chamomile)**

Matricaria is also commonly called as German Chamomile and it is a very popular herb for various diseases. It is known that among the other effects, chamomile has anxiolytic, anti-stress and anti-depressive effects. In according to the results of an animal study, chamomile extract has alleviated the anxiety and depression related to the scopolamine injection (Ioniță et al. 2019).

***Centella Asiatica* (Gotu Kola)**

Centella Asiatica has been used by Indians due to its beneficial effects on cognition and anxiety. Extracts of the herb have shown GABA receptor modulating activity, neuroprotective features and memory enhancement effect (Ceremuga et al. 2015). A study had investigated the effectiveness of Gotu kola extract for ameliorating vascular cognitive impairment (VCI) after stroke and compared its effectiveness against folic acid. Gotu kola has been found superior to folic acid in terms of memory improving and as effective as folic acid for improvement of post-stroke VCI (Farhana et al. 2016). As suggested by Wynn and Fougère (2007), 25%-40% ethanolic extract of gotu kola may be efficient for cognitive impairment of dogs and cats in a dose range of 0.4-1.5 ml per 10 kg.

***Bacopa Monniera* (Bacopa)**

As an Ayurvedic plant Bacopa has been used for centuries. Several studies have investigated antidepressant and anxiolytic activity of the plant and show that Bacopa has anxiolytic activity without adverse effects like amnesia as in benzodiazepines and has significant antidepressant effects (Gohil and Patel 2010). It is known that Bacopa has a norepinephrine decreasing effect and increasing 5-hydroxytryptamine in brain zones such as hippocampus and amygdala (Russo and Borrelli 2005). In a rat study, Bacopa extract orally at different durations of 20 to 80 mg/kg has been shown to improve memory and learning (Vollala et al. 2010).

***Valeriana Officinalis* (Valerian)**

Valerian has been used in traditional and ayurvedic medicine due to a relaxant and sleep-promoting effects. Nearly 150-200 chemical metabolites have been found in valerian. Some of these constituents have been found to

have potential therapeutic effects in Alzheimer, Parkinson and epilepsy diseases. Root extract of valerian has shown cognitive enhancing and corticosterone reducing effects, in aged mice (Nandhini et al. 2018). In a study conducted on cats, responses to the use of valerian root for environmental enrichment as an olfactory stimulant were evaluated and 47% of cats responded. Results suggest that usage of valerian root may improve the quality of life in cats (Bol et al. 2017). In another study conducted on shelter dogs, the effect of olfactory stimuli on behavior was evaluated and it was shown that valerian and other olfactory stimulants significantly affect behavior, reduce vocalization and movement. Reduced vocalization and movement may be associated with reduced stress provided by the use of olfactory stimulants (Binks et al. 2018).

***Lavandula Officinalis* (Lavender)**

L. officinalis has antidepressive and sedative usage besides its various medical advantages. A study which is conducted on rats showed that extract of aerial parts of *Lavandula* possess antidepressive-like effects, anxiety and scopolamine induced memory impairment reducing effects (Rahmati et al. 2017). A study conducted on 16 cats has assessed the aromatherapeutic potential of lavender oil in reducing anxiety in cats. The study group received lavender oil by inhalation for 30 minutes. As the result, a statistically significant decrease in stress and anxiety-related behaviors was observed in the study group (Goodwin and Reynolds 2018). Due to its non-invasiveness and promising results, lavender oil can be used in cats as an additional treatment option in anxiety management.

Ginkgo Biloba

Ginkgo biloba is frequently used by humans to ameliorate age-related cognitive impairments. It is one of the most studied herbs due to its neurological effects. It is known that ginkgo has various effects on the brain including enhancement of neuronal plasticity, memory improving and protecting against ischemic neuronal death (Singh et al. 2019). A study performed on aged beagle dogs has shown that a nutraceutical preparation composed of phosphatidylserine, Ginkgo biloba, Vitamin E and pyridoxine enhanced the short-term memory performance of dogs. Along with the benefits of other substances, the study indicated that Ginkgo may possess the promote short-term retention of spatial memory thereby enhancing cognitive functions in animals (Araujo et al. 2008). In another study conducted on 46 dogs, a commercial preparation which is containing phosphatidylserine and Ginkgo biloba standardized extract has evaluated for its effectiveness and tolerability. At the end of the 3 months treatment 66% of the subjects responded to treatment with improved signs in terms of the general activity, sleep/awake cycle, house soiling, disorientation and social interactions (Cane et al. 2005).

Other Herbs

Piper methysticum is a well-known herb due to its anxiolytic effect. The main active constituent of the herb has shown the various mechanism of action such as increase of GABA-A receptor functioning, inhibition of excitatory neurotransmission and inhibition of norepinephrine uptake (Zhang 2004).

Ziziphus jujube has been used in Traditional Chinese Medicine (TCM) and laboratory studies have revealed that extract of the herb act as an anxiolytic at lower doses and sedative at higher doses (Peng et al. 2000).

Extract of the *Apocynum venetum* has an antidepressant effect and it is thought that mechanism of action of the herb is related to its effect on the central monoaminergic system, as in conventional antidepressants (Meizhu et al. 2014).

Constituent of *Atecha catechu's* nut has shown significant inhibitory effect on GABA uptake and in-vitro studies carried out with the phenolic compounds of the herb had stimulated the catecholamine release (Zhang 2004).

Table 1. Recommended herbals and nutraceuticals for behavioural problems of dogs and cats.

Herbals and Nutraceuticals	Effects on Behavioural Conditions	Potential Indications	References
Pasiflora incarnata	Stress reducing and benzodiazepin-like effects	Canine and Feline Anxiety Insomnia Depressive Behaviours	(Janda et al. 2020) (Fonseca et al. 2020)
Hypericum perforatum	Inhibition of monoaminergic reuptake and inhibition of (MAO)-A and MAO-B activity	Depressive Behaviours Anxiety Tail-Chasing	(Zhang 2004) (Alex and Srivastava 2019) (Mosallanejad et al. 2015) (Ng et al. 2017)
Matricaria recutita	Anxiolytic, Antidepressive and Anti-stress	Depressive Behaviours Anxiety	(Ioniță et al. 2019).
Withania somnifera	Anxiolytic, Adaptogen and Antidepressive	Depressive Behaviours Anxiety	(Alex and Srivastava 2019) (Ayati et al. 2020) (Zhang 2004)
Canabis Sativa (CBD) I	Alteration of CB-1 receptor function, GABA and dopamine levels, and serotonin function	Depressive Behaviours Canine Aggression	(della Rocca and Di Salvo 2020) Ayati et al. 2020) (Corsetti et al. 2021)
Camelia Sinensis	Neuroprotective, stress and anxiety reducing effects	Anxiety	(Saeed et al. 2017) (Sechi et al. 2017)
Melissa officinalis	Decrease serum corticosterone levels and increase dentate gyrus GABA levels	Cognitive dysfunction Anxiety	(Zhang 2004) (Yoo et al. 2011)
Gotu Kola	GABA receptor modulation Memory enhancement and Neuroprotective	Cognitive dysfunction Anxiety	(Ceremuga et al. 2015) (Farhana et al. 2016) (Wynn and Fougère 2007)
Bacopa monniera	Increase brain serotonin and decrease brain norepinephrine Anxiolytic and Antidepressive	Cognitive dysfunction Depressive behaviours Anxiety	(Gohil and Patel 2010) (Russo and Borrelli 2005) (Vollala et al. 2010)
Lavandula officinalis	Antidepressive Anxiety reducing	Depressive Behaviours Anxiety	(Rahmati et al. 2017) (Goodwin and Reynolds 2018)
Valeriana officinalis	Relaxant, Sleep promoting, Sedative	Insomnia Feline Hyperesthesia Stress	(Nandhini et al. 2018) (Bol et al. 2017) (Binks et al. 2018)
Ginkgo biloba	Neuroprotective, Memory Improving,	Cognitive dysfunction	(Singh et al. 2019) (Araujo et al. 2008) (Cane et al. 2005)
Bovine Milk Protein derivates	Stress reducing Anxiolytic	Anxiety Depressive Behaviours	(Orlando 2018) (Beulens et al. 2004) (Beata et al. 2007)
Apoaequorin	Neuroprotective effect by intracellular calcium regulation	Cognitive Dysfunction	(Milgram et al. 2015) (Orlando 2018)
MCTs	Support brain energy metabolism	Cognitive Dysfunction Neuroprotection	(Pan et al. 2010) (Orlando 2018)
Omega-3	Neuroprotective and neuronal development	Cognitive Dysfunction	(Orlando 2018) (Kaur et al. 2020)
SAME	Cellular metabolism regulation, Cell membrane stability	Cognitive Dysfunction	(Orlando 2018)
Tryptophan	Precursor serotonin synthesis	Phobias Aggression Anxiety	(Orlando 2018)

Nutraceuticals

Bovine milk protein derivates include alpha caseozepine and alpha-lactalbumin, these compounds greatly reduced anxiety signs and plasma cortisol levels in dogs besides reduced social anxiety in cats (Orlando 2018). In a study,

rats fed with alpha-lactalbumin enriched diets have shown increased serotonin levels and increased activity levels. In the same study alpha lactalbumin has found superior to casein in terms of profitable effects on mood (Orosco et al. 2004).

It is known that a high ratio of tryptophan to other large neutral amino acids (LNAAs) in the diet is important for serotonin synthesis. Alpha-lactalbumin enriched diets increaseserum tryptophan to LNAAs ratio (Beulens et al. 2004). Numerous commercial diets that include bovine milk protein derivatives have already been available in the market. A study that compares the effectiveness of alpha-casozepine and selegiline on anxiety disorders in dogs have shown that alpha-casozepine is equivalently effective as selegiline and during the study no adverse effects were recorded regarding the use of alpha-casozepine (Beata et al. 2007).

Apoaequorin is a protein derived from jellyfish and it has a better improvement effect on cognitive functions in aged beagle dogs compared to selegiline (Orlando 2018). Apoaequorin has calcium buffering properties and thus protects against pathologies related to calcium dysregulation and excitotoxicity. In a placebo-controlled study, 23 aged beagle dogs have treated with apoaequorin and the study group has shown enhanced cognitive results. In a second study, 10 mg apoaequorin administration has been shown as effective as selegiline treatment for canine cognitive dysfunction (Milgram et al. 2015).

Medium-chain triglycerides (MCT), it is known that in aged dogs brain glucose metabolism is altered. MCTs act as a second energy source in the form of ketones to support brain energy metabolism when given as a food additive. Beta-hydroxybutyrate, a ketone body, levels were found significantly higher in the MCT supplemented dogs (Pan et al. 2010). In a study performed on aged beagle dogs, feeding with a proportion of 5.5% MCT added diet improved cognitive test scores. In another study performed on owned dogs, 6.5% MCT containing diet has shown significant amelioration of the clinical signs of cognitive dysfunction in one month (Orlando 2018).

Omega-3 fatty acids are polyunsaturated fatty acids that are essential for the canine diet. They have beneficial properties for various conditions of dogs such as epilepsy, cardiovascular diseases, and dermatological problems (Kaur et al. 2020). Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are omega-3 fatty acids usually derived from fish oil. It is known that DHA play a crucial role in the neurological and cognitive development of puppies (Orlando 2018).

SAME (S-Adenosylmethionine) plays vital roles in cellular metabolism, cell membrane stability and neurotransmitter functions. In a study, dogs and cats with cognitive dysfunction syndrome treated with SAME have shown improvement in cognitive abilities (Orlando 2018). In cats with mild cognitive dysfunction syndrome, the administration of SAME has shown an improvement in cognitive abilities (Sordo and Gunn-Moore 2021).

Tryptophan is a dietary amino acid used in the production of serotonin. In addition to the amount in the diet, the ratio to other large neutral amino acids is also important. Owner-directed aggression score has been found higher in dogs fed with high protein diets and in fearful dogs, increased levels of plasma tryptophan metabolites and decreased levels of tryptophan have been found (Orlando 2018).

Vitamin B-6, Vitamin E, resveratrol, alpha-tocopherol, and L-carnitin are other substances that might be used to ameliorate cognitive dysfunction in dogs and cats (Sordo and Gunn-Moore 2021).

CONCLUSION

Herbal and nutraceutical remedies have many advantages in veterinary medicine such as low cost, availability and positive owner attitude, etc. Alas, people generally fixed at the opinion that, herbal remedies have no side effects. This is a crucial fault, as many herbs have various and vital side effects. The dilemma in herbal and nutraceutical remedies can be solved by choosing the right extraction, suitable dose and indication. Still there are promising therapeutic potentials in these remedies with the advances in phytochemical researches, that must be considered in veterinary medicine.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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AUTHOR CONTRIBUTIONS

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REFERENCES

- Alex A, Srivastava A (2019). Nutraceuticals for Calming and Stress. Gupta RC, Srivastava A, Lall R (Ed). Nutraceuticals in Veterinary Medicine, 417-425, Springer, Switzerland.
- Araujo JA, Landsberg GM, Milgram NW, Miolo A (2008). Improvement of short-term memory performance in aged beagles by a nutraceutical supplement containing phosphatidylserine, Ginkgo biloba, vitamin E, and pyridoxine. *Can Vet J*, 49 (4), 379-385.
- Ayati Z, Sarris J, Chang D, Emami SA, Rahimi R (2020). Herbal medicines and phytochemicals for obsessive-compulsive disorder. *Phytother Res*, 34 (8), 1889-1901.
- Beata C, Beaumont-graff E, Diaz C et al. (2007). Effects of alpha-casozepine (Zylkene) versus selegiline hydrochloride (Selgian, Anipryl) on anxiety disorders in dogs. *J Vet Behav*, 2 (5), 175-183.
- Beulens JWJ, Bindels JG, De Graaf C, Alles MS, Wouters-Wesseling W (2004). Alpha-lactalbumin combined with a regular diet increases plasma Trp-LNAA ratio. *Physiol Behav*, 81 (4), 585-593.
- Binks J, Taylor S, Wills A, Montrose VT (2018). The behavioural effects of olfactory stimulation on dogs at a rescue shelter. *Appl Anim Behav Sci*, 202, 69-76.
- Bol S, Caspers J, Buckingham L et al. (2017). Responsiveness of cats (Felidae) to silver vine (Actinidia polygama), Tatarian honeysuckle (Lonicera tatarica), valerian (Valeriana officinalis) and catnip (Nepeta cataria). *BMC Vet Res*, 13 (1), 1-15.
- Cane NEL, Pilota S, Colangeli R et al. (2005). Di Un Nutraceutico Neuroprotettivo Contenente Fosfatidilserina E Ginkgo Biloba Sui Segni Clinici Di Invecchiamento Cerebrale. 2005(October), 13-18.
- Ceremuga TE, Valdivieso D, Kenner C et al. (2015). Evaluation of the anxiolytic and antidepressant effects of asiatic acid, a compound from Gotu kola or Centella asiatica, in the male Sprague Dawley rat. *AANA J*, 83 (2), 91-98.
- Corsetti S, Borruso S, Malandrucchio L et al. (2021). Cannabis sativa L. may reduce aggressive behaviour towards humans in shelter dogs. *Sci Rep*, 11 (1), 1-10.
- della Rocca G, Di Salvo A (2020). Hemp in Veterinary Medicine: From Feed to Drug. *Front Vet Sci*, 7 (387), 1-11.
- Didehban N, Pourmahdi Borujeni M, Avizeh, R, Mosallanejad B (2020). Problematic behaviors in companion dogs: A survey of their prevalence and associated factors. *J Vet Behav*, 39, 6-13.

- Eritja R (2014).** Natural Product Communications: Preface. *Nat Prod Commun*, 9 (8).
- Farhana KM, Malueka RG, Wibowo S, Gofir A (2016).** Effectiveness of Gotu Kola Extract 750 mg and 1000 mg Compared with Folic Acid 3 mg in Improving Vascular Cognitive Impairment after Stroke. *Evid-based Complement Altern*, 2016, 2795915.
- Fonseca LRd, Rodrigues R de A, Ramos A de S et al. (2020).** Herbal Medicinal Products from Passiflora for Anxiety: An Unexploited Potential. *Sci World J*, 2020, 6598434.
- Gohil KJ, Patel JJ (2010).** A review on Bacopa monniera: Current research and future prospects. *Int J Green Pharm*, 4 (1), 1–9.
- Goodwin S, Reynolds H (2018).** Can aromatherapy be used to reduce anxiety in hospitalised felines. *The Veterinary Nurse*, 9 (3), 167-171.
- Ioniță R, Postu PA, Cioacă O et al. (2019).** Anxiolytic and antidepressant effects of matricaria chamomilla hydroalcoholic extract in a rat model of scopolamine. *Farmacia*, 67 (1), 68-72.
- Janda K, Wojtkowska K, Jakubczyk K, Antoniewicz J, Skonieczna-zydecka K (2020).** Passiflora incarnata in neuropsychiatric disorders—a systematic review. *Nutrients*, 12 (12), 1-17.
- Kaur H, Singla A, Singh S, Shilwant S, Kaur R (2020).** Role of Omega-3 Fatty Acids in Canine Health: A Review. *Int j curr microbiol*, 9 (3), 2283-2293.
- Lipnik-Štangelj M, Razinger B (2020).** A regulatory take on cannabis and cannabinoids for medicinal use in the European Union. *Arhiv Za Higijenu Rada i Toksikologiju*, 71 (1), 12-18.
- Liu R, Ahmed F, Cayer C et al. (2017).** New Botanical Anxiolytics for Use in Companion Animals and Humans. *AAPS J*, 19 (6), 1626-1631.
- Masic A, Landsberg G, Milgram B et al. (2021).** Efficacy of Souroubea-Platanus Dietary Supplement Containing Triterpenes in Beagle Dogs Using a Thunderstorm Noise-Induced Model of Fear and Anxiety. *Molecules*, 26 (7), 2049.
- Meizhu Z, Yuqiu L, Dongfang S, Chunming L, Jimin Z (2014).** Antidepressant-like effects of flavonoids extracted from Apocynum venetum leaves in mice: the involvement of monoaminergic system in mice. *Afr J Pharmacy Pharmacol*, 8 (29), 765-774.
- Milgram NW, Landsberg G, Merrick D, Underwood MY (2015).** A novel mechanism for cognitive enhancement in aged dogs with the use of a calcium-buffering protein. *J Vet Behav*, 10 (3), 217-222.
- Mosallanejad B, Najafzadeh Varzi H, Avizeh R, Pourmahdi M, Khalili F (2015).** Comparative evaluation between hypericin (hypiran) and fluoxetine in treatment of companion dogs with tail chasing. *Vet Res Forum*, 6 (2), 167-172.
- Nandhini S, Narayanan KB, Ilango K (2018).** Valeriana Officinalis: a Review of Its Traditional Uses, Phytochemistry and Pharmacology. *J Pharm Clin Res*, 11 (1), 36.
- Ng QX, Venkatanarayanan N, Ho CYX (2017).** Clinical use of Hypericum perforatum (St John's wort) in depression: A meta-analysis. *J Affect Disord*, 210, 211–221.
- Orlando JM (2018).** Behavioral Nutraceuticals and Diets. *Vet Clin North Am Small Anim Pract*, 48 (3), 473-495.
- Orosco M, Rouch C, Beslot F et al. (2004).** Alpha-lactalbumin-enriched diets enhance serotonin release and induce anxiolytic and rewarding effects in the rat. *Behav Brain Res*, 148 (1–2), 1-10.
- Pan Y, Larson B, Araujo JA et al. (2010).** Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs. *Br J Nutr*, 103 (12), 1746-1754.
- Peng WH, Hsieh MT, Lee YS, Lin YC, Liao J (2000).** Anxiolytic effect of seed of Ziziphus jujuba in mouse models of anxiety. *J Ethnopharmacol*, 72 (3), 435-441.
- Rahmati B, Kiasalari Z, Roghani M, Khalili M, Ansari F (2017).** Antidepressant and anxiolytic activity of Lavandula officinalis aerial parts hydroalcoholic extract in scopolamine-treated rats. *Pharm Biol*, 55 (1), 958-965.
- Russo A, Borrelli F (2005).** Bacopa monniera, a reputed nootropic plant: An overview. *Phytomedicine*, 12 (4), 305-317.
- Saeed M, Naveed M, Arif M et al. (2017).** Green tea (Camellia sinensis) and L-theanine: Medicinal values and beneficial applications in humans—A comprehensive review. *Biomed Pharmacother*, 95 (September), 1260-1275.
- Savage K, Firth J, Stough C, Sarris J (2018).** GABA-modulating phytochemicals for anxiety: A systematic review of preclinical and clinical evidence. *Phytother Res*, 32 (1), 3-18.
- Sechi S, Fiore F, Cocco R et al. (2017).** Effects in dogs with behavioural disorders of a commercial nutraceutical diet on stress and neuroendocrine parameters. *Vet Rec*, 180 (1), 18.
- Seibert LM, Landsberg GM (2008).** Diagnosis and Management of Patients Presenting with Behavior Problems. *Vet Clin North Am Small Anim Pract*, 38 (5), 937-950.
- Singh SK, Srivastav S, Castellani RJ, Plascencia-Villa G, Perry G (2019).** Neuroprotective and Antioxidant Effect of Ginkgo biloba Extract Against AD and Other Neurological Disorders. *Neurother*, 16 (3), 666-674.
- Sordo L, Gunn-Moore DA (2021).** Cognitive Dysfunction in Cats: Update on Neuropathological and Behavioural Changes Plus Clinical Management. *Vet Rec*, 188 (1), 30-41.
- Tabach R, Rodrigues E, Carlini EA (2009).** Preclinical toxicological assessment of a phytotherapeutic product – CPV (based on dry extracts of *Crataegus oxyacantha* L., *Passiflora incarnata* L., and *Valeriana officinalis* L.). *Phytother Res*, 23, 33-40.
- Van Haften KA, Grigg EK, Kolus C, Hart L, Kogan LR (2020).** A survey of dog owners' perceptions on the use of psychoactive medications and alternatives for the treatment of canine behavior problems. *J Vet Behav*, 35, 27-33.
- Vollala VR, Upadhyaya S, Nayak S (2010).** Effect of Bacopa monniera Linn. (brahmi) extract on learning and memory in rats: A behavioral study. *J Vet Behav*, 5 (2), 69-74.
- Wynn SG, Fougère B (2007).** Veterinary herbal medicine. Elsevier Health Sciences, Missouri.
- Yoo DY, Choi JH, Kim W et al. (2011).** Effects of Melissa officinalis L. (Lemon Balm) extract on neurogenesis associated with serum corticosterone and GABA in the mouse dentate gyrus. *Neurochem Res*, 36 (2), 250-257.
- Zhang ZJ (2004).** Therapeutic effects of herbal extracts and constituents in animal models of psychiatric disorders. *Life Sci*, 75 (14), 1659-1699.