

OVERVIEW OF BEHAVIOUR SUPPLEMENTS FOR DOGS AND CATS



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There are a variety of supplements with a potential beneficial role in behaviour medicine that are currently available for cats and dogs. Each has a different rationale and must be assessed on an individual basis. The therapeutic effects of most of the active principles of these products have been investigated in dogs and cats, although in most studies the success rates for these alternative products are consistent with a placebo effect. In animals with severe behavioural problems they must not be an alternative to behaviour medications. As for behaviour medications, **the selection and use of nutraceuticals should be advised by a veterinary surgeon and every product should be used in conjunction with a behaviour and management plan.**

The most common dietary supplements can be classified as:

1. Neuroprotective agents (including long and medium-chain fatty acids, antioxidants and free radical scavengers, mostly used in products for elderly dogs and cats)
2. Sources of energy for the brain metabolism (neuroprotective with a supposed effect in enhancing cognition)
3. Molecules of compounds that are structurally analogue to neurotransmitters
4. Precursors of neurotransmitters

It is not easy to orientate within the large amounts of commercial products that often contain a combination of active principles. It is worth considering that anything we administer to an animal and has a specific action might have side effects and the fact that these products do not need to be prescribed by a vet does not exclude them. This is also the case when they are taken in combination with other medications or special diets.

In general, supplements that have a role in neuroprotection and all the products that support cognitive functions are particularly indicated for elderly pets and young animals that suffered from developmental impairment including insufficient social exposure.

Other supplements that contain analogues or precursors of neurotransmitters might have anti-anxiety effects.

There are a number of multi-ingredient supplements available over the counter or from veterinary surgeons that share some similar active principles; the ones that have more evidence of being effective are L-tryptophan and L-theanine. **L-Tryptophan** is present in most of the available supplements with claimed calming/anxiolytic effect. Its levels can influence the synthesis of serotonin, a neurotransmitter in the central nervous system. Serotonin is implicated in mood regulation, and drugs acting via the serotonergic system are effective in treating anxiety and depression. Serotonin cannot pass the hemato-brain barrier, tryptophan is a precursor of serotonin, can be absorbed in the gastrointestinal system and easily crosses the blood-brain barrier and increases central nervous system (CNS) synthesis of serotonin. Tryptophan may interact with other behaviour modifying medications as the effects may sum up. There are no controlled studies about possible side

effects of tryptophan supplementation in dogs, while in humans occasional side effects at higher doses (70-200 mg/kg) were reported. These reported side effects were small and largely anecdotal and included tremors, nausea, dizziness and rare case of ‘serotonin syndrome’ when tryptophan was combined with serotonergic drugs.

The available supplements are not consistent as far as the content of L- tryptophan in each single dose (tablet or oral solution). In a recent study, a group of dogs was supplemented with three different percentages of tryptophan in their diet and no difference in their effect on the dogs’ behaviour was detected. The second more common ingredient in supplements that target anxiety in dogs and cats is L-Theanine. **L-theanine** is an amino acid found in tea leaves that has been shown to produce stress-reducing effects in mammals. L-theanine is a structural analogue of glutamate, an excitatory neurotransmitter in the brain, and can bind to glutamate receptors, probably reducing the glutamate excitatory effect. The relaxing action of L-theanine has been shown in laboratory animals, humans, dogs and cats.

Along with products that report specific indications for behaviour problems, dietary interventions with supplement in long chain unsaturated fatty acids, for example Nutramind®, Nutramega® or Omevio®, may influence dog reactivity, although there is no strong evidence of this action. Long chain fatty acids play a role in maintaining neuronal integrity and enhancing energy use by neurons. There is data that supports the need of these substances for normal development of the central nervous system. Furthermore, it seems that age-related cognitive decline in dogs may be associated with a decrease in omega-3 in the brain. Supplements with medium chain triglycerides seem to protect from and slow age-related cognitive decline; effects on idiopathic epilepsy in dogs, and ADHD like syndrome in dogs with idiopathic epilepsy have been reported.

In table n.1 the active components of behaviour supplements, their mechanism of action, commercial names of products and potential effects on behaviour are summarized.

Active component	Mechanism of action	Examples of commercial name of compound	Potential behavioural effect
Long-chain polyunsaturated fatty acids Omega 3 and Omega 6 (Alpha linolenic acid, docosahexaenoic acid, eicosapentaenoic acid, arachidonic acid)	Maintain the integrity of brain cell membranes	Hill’s B/D diet Nutramind® Omevio® Nutramega® Salmon Oil Cod Liver Oil	Essential for early brain development, protective of cognitive functions (Overall, 1997; Re et al., 2008)
Medium Chain triglycerides (8-hydroxybutyrate 8-OHB)	Protect hippocampal neurons from toxicity	EN Purina Veterinary Diet	Protective of cognitive decline in epileptic dogs (Law et al., 2015; Packer et al., 2016)

Vit A	Antioxidant,	Cod liver oil	Neuroprotective
Vit E	Antioxidant	Nutromega®, Nutramind® cod liver oil	Neuroprotective
Vit B1 (Thiamine) and other complex B vitamins	Essential vitamin for the proper functioning and development of the brain and nerve cells	YuCalm®, Kalm Aid®, Adaptil®, Nutramind®	Neuroprotective
Ginkgo Biloba	Support peripheral and central blood circulation, lower blood lipids	Senilife® Nutramind®	Reduce clinical signs of cognitive dysfunction in dogs (Reichling et al., 2006)
Phosphatidylserine	Stimulates synaptogenesis, facilitates activation of neural-signals	Senilife®, Aktivait® Nutramind®	Neuroprotective, enhance cognitive functions (Araujo et al., 2008; Kim et al., 2014)
L-Theanine	Structural analogue of glutamate (brain neurotransmitter), binds to glutamate receptors	Nutracalm®, Yucalm®, Anxitane®	Improves signs of anxiety related behaviours in dogs and cats (Araujo et al., 2010; Dramard et al., 2018)
L-Tryptophan	Serotonin Precursor, passes the Blood Brain barrier and is converted to serotonin	Nutracalm® Kalm Aid®	Supposed to have similar effects as serotonergic medications, anxiolytic and antidepressant (Bosch et al., 2007; DeNapoli et al., 2000; Overall, 1997)
Oral Gamma Aminobutyric Acid (GABA)	Supposed enhanced activity of central GABA	Nutracalm®	Claimed anxiolytic effects, although there is still not enough evidence that oral GABA can pass the Brain Blood Barrier (Boonstra et al., 2015)

Vitamin C	Antioxidant	Nutracalm®	Protects brain from oxidative damage
S-Adenosyl-1-methionine (SAMe)		Novifit® Virbac®	Might support cognitive function in aging dogs (Mongillo et al., 2010)
Melatonin	Influence hormonal and physiological responses associated with sleep/wake cycles. Has antioxidant properties	Melacutin®, various over the counter products	Effects on stress and anxiety reported in rats. (Brotto et al., 2001; Sun et al., 2016).
Piper methysticum	Kavalactones active principles seem to have different actions, including increasing GABA activity in the brain and inhibition of Monoamine Oxidase type B	Calmex®	Management of stress and anxiety in dogs. No scientific evidence of efficacy. Latent liver toxicity in human beings was suspected.
Alpha-casozepine	Affinity for the benzodiazepine site of the GABA-a receptor is supposed to have an effect similar but with a much lower affinity to receptors compared to benzodiazepines	Zylkene®, Royal Canin CALM diet	Anxiolytic effect in dogs and cats (Beata et al., 2007b, 2007a; Palestrini et al., 2010)
Cannabidiol (CBD) based oil		Beaphar CBD® PURCBD® Innovet	Management of stress and anxiety in dogs. No available evidence for this use. Reported efficacy for osteoarthritis and glaucoma in dogs (Gamble et al., 2018; Harvey et al., 1991; Pattij and Vanderschuren, 2008)

Fish protein hydrolysate	Amino acids precursors of endorphins and other neurotransmitters such as serotonin and melatonin	YuCalm®	Anxiolytic effect. Non robust evidence, these supplements were reported to reduce cortisol and hyperactivity in laboratory dogs in one study
Magnolia Officinalis (extract)	Active phenolic constituents with antioxidant and neuroprotective effects	Harmonease®	Anxiolytic effect. Non robust evidence. A study reported a positive effect on noise fear in laboratory dogs. (DePorter et al., 2012)
Inositol		Adaptil® Tablets	Antidepressant and anxiolytic effect. Some evidence in humans and laboratory animals (Einat and Belmaker, 2001; Mukai et al., 2014)

Table 1. The most diffused behaviour supplements for dogs and cats.

BEHAVIOUR SUPPLEMENTS AVAILABLE ON THE MARKET FOR DOGS AND CATS.

ADAPTIL® Tablets

The name of this oral supplement is the same as the brand of the synthetic dog appeasing pheromone but it is a completely different product. Adaptil tablets contain different active principles with different modes of action (see table 1). The main components are L-tryptophan, L-theanine, oral GABA, vitamin B (B1, B6, B12, B3) and inositol. Some studies in humans and laboratory rats showed that inositol may be beneficial for depressed patients (Einat and Belmaker, 2001; Mukai et al., 2014) but no robust evidence is available for cats and dogs. The indications are for loud noise fear, travel anxiety, vet visit anxiety. Its use is suggested in combination with a [pheromone diffuser, collar or spray](#). There is no robust evidence about the effects of this supplement as a compound of different components, but some evidence exists for some of the individual components. The only recommendation about the dose is to follow the manufacturer's instructions.

NUTRACALM®

Nutracalm components are very similar to Adaptil tablets components. L-tryptophan, L-Theanine, complex B and GABA. It also contains passiflora extracts, natural components

called flavonoids that seem to act on GABA receptors. As for Adaptil tablets, there is no robust evidence about the effects of this supplement as a compound, but some evidence exists for some of the individual components (see table 1.) .The only recommendation about the dose is to follow the manufacturer's instructions.

KALM AID®

As the previous two products, Kalm Aid's main active components are L-tryptophan and L-theanine, and a supplement of vit B1. Vit B1, or thiamine, play a fundamental role in brain functions. Insufficient intake of nutrients might happen when the dog is fed homemade diets not well supplemented or particular veterinary diets (Butterworth, 2003; Kritikos et al., 2017).The only recommendation about the dose is to follow the manufacturer's instructions.

YUCALM®

YuCalm contains L-Theanine, a special blend of natural fish protein hydrolysate, Lemon Balm and complex B vitamins. There are different formulations of this product for dogs and cats and there are tasty treats for dogs. The anxiolytic effects of natural fish protein hydrolysate was investigated in a controlled placebo study with laboratory Beagles exposed to stressful noises and mild evidence of his effectiveness on hyperactivity and cortisol level was found (Landsberg et al., 2015). Lemon Balm (*Melissa Officinalis*), has been reported as having anti-stress effects in humans (Kennedy et al., 2004; Scholey et al., 2014) and to be beneficial for gastrointestinal disorders in dogs (Russo et al., 2009). The only recommendation about the dose is to follow the manufacturer's instructions.

HARMONEASE® AND SOLLIQUIN®

The use of supplements based on *magnolia officinalis* and *Phellodendron amurense* extracts origins in Chinese medicine. Clinical studies on the efficacy of these herbal extracts in dogs and cats are limited, one study showed that Harmonease chewable tablets reduced signs of anxiety in the presence of loud noises in laboratory dogs. Solliquin, is a supplement based on a combination of *Magnolia officinalis*, *Phellodendron amurense* and L-theanine and in a study involving a very small number of dogs and cats owners reported some positive behavioural effects (DePorter et al., 2012; Landsberg et al., 2017).The only recommendation about the dose it to follow the manufacturer's instructions.

CALMEX®

Calmex® is a nutraceutical only available from veterinary surgeons. Its active ingredients are L-Tryptophan, L-theanine, B vitamins and Piper Methysticum. This latter ingredient is peculiar to this supplement and it is an herbal substance whose active principles are molecules called kavalactones that have been reported to relieve states of nervous anxiety, tension and restlessness in humans. Piper Methysticum is no longer available for human use. In 2016 in an assessment report the European Committee on Herbal Medicinal Products (HMPC) stated that benefit-risk balance of the oral use of *Piper methysticum* for the treatment of anxiety disorders is unfavourable. One of the main concerns was the potential risk of hepatotoxicity. There are no reports of liver toxicity in dogs but there is no evidence that prolonged treatments with products containing Piper methysticum are safe.

ANXITANE®

Anxitane has been suggested to relieve signs of fear and anxiety in dogs and cats. The active principle is L-Theanine is an analogue of glutamic acid, reduces the uptake of glutamate and increases GABA concentration in the Central Nervous System. As for tryptophan, there are

no studies in companion animals about what is the appropriate dose. The product is believed to be safe and the only recommendation about the dose is to follow the manufacturer's instructions.

ZYLKENE®

The active principle of Zylkene is alpha caseozepine, which is a product obtained by the hydrolysis of casein from bovine milk. This product is indicated to reduce stress and anxiety in dogs and cats both in the short and long term administration. The anxiolytic effect is similar to the mechanism of action of benzodiazepine, the gamma aminobutyric acid (GABA) inhibitor neurotransmitter is believed to be the target. The available studies are not supporting the efficacy of this product for short-term use, while weak evidence supports its efficacy in reducing anxiety in dogs and cats after a medium and long term administration.

MELATONIN (Melacutin®)

There is evidence that melatonin reduces stress and anxiety in rats and some studies reported these effects in humans.

Melatonin has been used in dogs for dermatological conditions (seasonal alopecia) and it was anecdotally reported to have anxiolytic effects and regulates sleep in dogs.

In dogs and cats, the optimal dose for behaviour problems, best route of administration and the duration of treatment and best time of initiation of treatment are currently unknown. The oral dose that was reported for dermatological problems was 3 mg for an average medium to large sized dog.

PurCBD® and Behaphar CBD oil for dogs and cats

These two products contain phytocannabinoid oil extracted from hemp. Behaphar also produces dog snacks with CBD oil. It is becoming more and more popular among owners for anxious and nervous dogs to administer products based on cannabidiol but there is no evidence so far for these indications. Cannabidiol is tetrahydrocannabinol (THC) free or only contains trace of this substance that is responsible for the psychoactive effects of the recreational drug extracted by Cannabis sativa; CBD does not have psychoactive effects. It was reported as effective for pain related to arthritis in dogs at the dose of 2 mg/kg twice a day. No side effects were reported but an increase in alkaline phosphatase during CBD treatment (Gamble et al., 2018). A very recent study on a hemp-based product investigated its safety and possible adverse effects in dogs and cats. At the same dose that was used for osteoarthritis (2mg/kg twice a day) eight dogs and eight cats were treated for 12 weeks. The results showed that in cats there was a persistent increase in Alanine aminotransferase (ALT) above the normal range and excessive licking and head shaking when the product was administered. No abnormal biochemistry or side effects were detected in dogs (Deabold et al., 2019). In summary, the anxiolytic effect of CBD oil are not supported by evidence so far and more studies are required to investigate both efficacy and safety of these products in dogs and cats.

NUTRACEUTICAL FOR ELDERLY DOGS AND CATS

AKTIVAIT® AND SENILIFE ®

These supplements contain phosphatidylserine and Ginkgo Biloba, C and E vitamins along with other components. Senilife also contains resveratrol and B6 vitamin; resveratrol was shown to improve cognitive impairment and reduce oxidative stress in rats (Kumar et al.,

2007). In some studies Aktivait was found effective in cognitive dysfunction in dogs (Araujo et al., 2008; Heath et al., 2007).

NUTRAMIND®

Nutramind contains phosphatidylserine and Ginkgo Biloba, Omega 3 (DHA and EPA), complex B and E vitamin.

NOVIFIT®

Novifit active principle is the S-adenosyl-1-methionine. A study showed that this product may be effective in improving social interactions and disorientation in dogs with cognitive dysfunction syndrome (Mongillo et al., 2010). This product has also been indicated to treat liver dysfunctions. It should not be administered with psychotropic drugs or tramadol (Fetrow and Avila, 2001; Iruela et al., 1993).

AROMATHERAPY

The use of aromatherapy to promote relaxation in dogs and cats is becoming more and more popular and, although there are no robust evidence that using natural oils can make dogs and cats more relaxed (or less anxious), there is no harm in using them in kennels and their positive effects might be attributed to the general benefit of providing a variety of positive sensory stimulations. The influence of olfactory stimulation in kennelled dogs was reported, in a study it was shown that dogs seemed calmer, vocalised less and spent more time resting when exposed to lavender and chamomile (Graham et al., 2005).

PET REMEDY®

Pet remedy is a blend of natural oils (valerian, vetivert, basil, sage) that is available on the market as spray or diffuser. The claimed effect is that it lowers stress-related behaviours in dogs and cats. This effect is not supported by robust evidence. No adverse effects have been reported so far, so it should be considered safe, but it should not be recommended as an alternative option to behaviour therapies with stronger evidence of effectiveness.

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