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Herbal compounds used in canine cognitive dysfunction

Gülşah Emre Mantar [1]*, Gülcan Demirel[2]

1. Graduate Education Institute, Istanbul University-Cerrahpasa, Istanbul, Turkey. **2.** Istanbul University-Cerrahpasa, Department of Animal Nutrition and Nutritional Disease, Istanbul, Turkiye. Emre Mantar , G. ORCID ID: 0009-0004-9940-3316 ; Demirel G. ORCID: 0000-0002-6864-5134

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ABSTRACT

The prevalence of chronic diseases in dogs has been increasing due to their longer life spans. One of the diseases developing with age is Canine Cognitive Dysfunction (CCD) and it is a neurodegenerative disease that affects geriatric dogs. In dogs with cognitive dysfunction, behavioral changes such as anxiety, alterations in sleep patterns, and house soiling can be observed. The treatment protocols used for CCD focus on alleviating the symptoms of the disease. Since this dysfunction cannot be cured, in addition to medications, lifestyle changes and dietary interventions are used to manage the symptoms. Herbal compounds frequently used in CCD have been the topic of recent studies. This review article presents the herbal compounds that can be used in dogs with CCD and summarizes the findings from studies on these supplements.

Keywords: dog, canine cognitive dysfunction, herbal compounds, polyphenol

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Introduction

It has been reported that the average life span of dogs, regardless of breed, has increased over the years and reached 13.6 years (Brace, 1981). The increase in the average lifespan of dogs can be attributed to advancements in veterinary medicine and balanced nutrition. It has been reported that there has been a 50% increase in the average life expectancy of dogs in Japan since 1980 (Inoue et al., 2018), and an increase in the average life expectancy in the USA between 2013-2018 (Montaya et al., 2023). The prevalence of chronic diseases in dogs has been increasing due to their increasing life span. The period after 7 years of age is considered geriatric for dogs (Harvey, 2021). Aging in dogs is a natural process and occurs over time in all living creatures, rather than a pathological process. The normal aging process does not have a significant impact on the dog's daily life but altered by cognitive disorders and chronic diseases with aging (Salvin et al., 2011).

Canine Cognitive Dysfunction (CCD) is a neurodegenerative disease that develops progressively in geriatric dogs. In order to diagnose canine cognitive dysfunction, it is necessary to rule out chronic diseases causing pain and can lead to behavioural changes, as well as conditions such as hearing and visual dysfunction. (Bellows et al., 2015). CCD is considered an under-diagnosed disease. A study conducted in 2006 reported that 14.2% of dogs exhibited behavioral changes associated with cognitive dysfunction. However, only 1.9% of these dogs were diagnosed with cognitive dysfunction in veterinary clinics (Salvin et al., 2010). Behavioral changes are observed along with cognitive dysfunctions in dogs. Seperation anxiety, new phobias, changes in sleeping cycle, house soiling, disorientation, excessive vocalization are the most common changes observed in dogs with CCD (Colle et al., 2000; Osella et al., 2007; Salvin et al., 2011a, 2011b; Fast et al., 2013). CCD is associated with

*Corresponding Author: Gülşah Emre Mantar
gulsah.emre@ogr.iuc.edu.tr

age-related oxidative damage (Ames et al., 1993; Liu and Mori, 1999; Head, 2002, 2009), reduction in brain volume (Tapp et al., 2004), accumulation of amyloid beta (Aβ) plaques (Cummings et al., 1996; Head et al., 2000; Tapp et al., 2004;), lipofuscin accumulation (Borràs et al., 1999), changes in neurotransmitters, along with an increase in monoamine oxidase B (Landberg and Araujo, 2005), increase in ventricular volume, and cortical atrophy (Su et al., 1998). Cognitive dysfunction in dogs is a similar pathology to Alzheimer's disease in humans (Head et al., 2010). With aging, Aβ plaques accumulate in the brains of dogs, similar to those seen in humans (Cummings et al., 1996a, 1996b). Amyloid deposition started in the prefrontal region at the age of 9 years and in the occipital, parietal and entorhinal cortex at the age of 14 years in a research dogs involved between 2 and 18 years of age (Head et al., 2000). Aβ proteins, polyglucosan and lipofuscin deposits increased with age (Borràs et al., 1999). In a study conducted on geriatric dogs aged 9-15 years, MRI scans were used to examine the brain tissue, revealing an increase in ventricular volume and cortical atrophy (Su et al., 1998).

Herbal compounds and canine cognitive dysfunction

Increase in oxidative damage with age is considered one of the causes of Canine Cognitive Dysfunction (Head et al., 2002; Skoumalova et al., 2003). Normal activities in the brain produce oxidants or reactive oxygen species (ROS). ROS are products of mitochondrial oxygenated respiration and can contain any atom or electron. ROS are unstable and these unstable oxygen free radicals cause cell damage and loss of function. Excessive production of ROS can damage proteins, lipids and nucleoids (Ames et al., 1993). These damages lead to neuronal damage and death of neurons in the brain (Liu and Mori,1999; Floyd et al., 2001). Reducing the production of ROS may be useful for slowing down the aging process. Six weeks usage of antioxidant-enriched supplements in geriatric dogs, dogs' errors in cognitive function tests decreased, their learning abilities increased, and after 2 years of use, their memory improved and the formation of Aβ plaques decreased (Head, 2009). In a study examining seven dogs diagnosed with cognitive dysfunction, administration of supplements containing Ginkgo biloba, phosphatidylserine, pyridoxine, alpha tocopherol, and resveratrol led to a reduction in symptoms associated with cognitive dysfunction (Osella et al., 2007). Cognitive dysfunction is a progressive disease that can significantly impact a dog's quality of life. Studies suggest that early dietary supplementation with herbal compounds may help reduce symptoms and improve behavioural changes associated with cognitive dysfunction in dogs (Cotman et al., 2002; Head, 2009a, 2009b).

Polyphenol

Polyphenols are chemical compounds found in fruits and vegetables. Polyphenols are classified as flavonoids, stilbenes, lignans and phenolic acids (Naomi et al., 2023). Studies suggest that their use may be beneficial in cognitive dysfunctions due to their antioxidant effects and neuroprotective properties (Reichling et al., 2006; Fragua et al., 2017; Lee et al., 2022; Naomi et al., 2023). A study was conducted to investigate the impact of antioxidants on the cognitive function of 35 dogs aged between 8 and 14.5 years. The dogs were divided into two groups; the treatment group received supplements derived from grapes and blueberries rich in polyphenols, and the control group, consisting of 11 dogs that did not receive supplements. Within the treatment group, 12 dogs were supplemented at a dose of 240 ppm, while another 12 dogs at a dose of 480 ppm. The genes linked to oxidative stress in dogs were analyzed using the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) method, and a Delayed Nonmatching to Position (DNMP) test was performed. The results of the DNMP test showed that cognitive function improved in dogs received supplements, regardless of the dose. Dogs receiving high doses of supplements had higher levels of nuclear factor erythroid 2-related factor 2 (Nrf2), while dogs receiving low doses had higher levels of superoxide dismutase compared to other groups (Fragua et al., 2017). In the nucleus, Nrf2 binds to the gene region associated with the expression of the antioxidant response element (ARE). Through this mechanism, Nrf2 is responsible for the synthesis of antioxidants such as superoxide dismutase (Francisqueti-Ferron et al., 2019). The effects of flavonoids on cognitive function in dogs were studied using supplementation (Lee et al., 2022). Nine dogs, older than 7 years of age, were fed with a food containing honey nuts, which had cyanidin-3-O-glucoside as the active ingredient. Cognitive function tests were conducted before and after the 12-week feeding period. The dogs were received food containing 10.5 mg cyanidin-3-O-glucoside per 100 grams once a day. Weekly phone calls were made, and blood tests and weight measurements were taken at least 4 times. At the end of 12 weeks, the physical examination findings of the animals remained unchanged. However, there was a significant decrease in Aβ oligomer markers in serum. In the test for the detection of cognitive dysfunction, a significant decrease in symptoms was observed at the end of 90

days, except for one dog. At the end of 90 days, inflammation markers, including Tumor Necrosis Factor Alpha (Tnf-α), Interleukin-6 (IL-6), C-reactive protein (CRP), and Interleukin-1 Beta (IL-1β), decreased. Additionally, antioxidant levels, such as L-carnitine and glutathione reductase, increased.

Plant extracts

In a study examining the effects of antioxidant supplements on oxidative stress in geriatric dogs, a supplement containing various carotenoids and polyphenols was used. The supplement included extracts from Grifola frondosa, Curcuma longa, Carica papaya, Punica granatum, Aloe vera, Polygonum cuspidatum, Solanum lycopersicum, Vitis vinifera, and Rosmarinus officinalis. The study was conducted over a period of 6 months to evaluate the effects of supplements on reactive oxygen metabolites, biological antioxidant properties, oxidative stress, and brain-derived neurotrophic factor (BDNF) in dogs. Blood analyses were performed before and after the diets were introduced. The results showed a decrease in reactive oxygen metabolites in the two groups of dogs that received supplements, while no change was observed in the other two groups that did not receive supplements. According to the report, brain-derived neurotrophic factor (BDNF) increased in two groups of dogs that received supplements, while it remained unchanged in the other two groups (Sechi et al., 2015). Ginkgo biloba is one of the oldest living trees. Extracts from its leaves are used in the treatment of Alzheimer's disease in humans (Amieva et al., 2013). The leaves of Ginkgo biloba contain flavonoids and terpenes as active ingredients (Gold et al., 2002). Terpenes act as antagonists of platelet activating factor and suppress platelet accumulation (Koltai et al., 1991). The extract obtained from the leaves of Ginkgo biloba contains flavonoids, which have been demonstrated to possess antioxidant properties (Oyama et al., 1994). The use of Gingko biloba supplementation in cognitive dysfunction in animals is being studied. Studies on mice have investigated the use of Gingko biloba supplementation in cognitive dysfunctions, and have observed positive effects on cognitive function that deteriorates with age (Stackman et al., 2003) and improves memory (Stoll et al., 1996; Tadano et al., 1998). In a study, 42 geriatric dogs with an average age of 11.2 years and age-related cognitive dysfunction were given 40 mg of Gingko biloba extract per 10 kg body weight for 8 weeks. Positive changes were observed in the dogs' behavior within the first 4 weeks. At the end of 8 weeks, a significant improvement in the dogs' general condition was reported, and clinical symptoms such as disorientation, changes in sleep and activity, and behavioral changes disappeared in 36% of the dogs (Reichling et al., 2006).

Phosphatidylserine

Phosphatidylserine is a phospholipid found in the structure of cell membranes. It is abundant in the nervous system and plays a role in maintaining the normal function of the cell membranes of the nervous system (Ramesh et al., 2019). Soybeans are one of the natural sources of phosphatidylserine (Kid, 1996; Ye et al., 2020). According to recent studies (Crook et al., 1992; Zhang et al., 2015; Ye et al., 2020), phosphatidylserine supplements may be used in the treatment of cognitive dysfunction. Several studies have investigated the relationship between acetylcholinesterase and Alzheimer's disease (Talesa, 2001; Herholz, 2008; Singh et al., 2013), and it has been observed that acetylcholinesterase activity may be associated with the accumulation of amyloid plaques (Talesa, 2001). One of the drugs used in human Alzheimer's disease is an acetylcholinesterase inhibitor (Moreta et al., 2021). Low concentrations of phosphatidylserine stimulated ATPase and acetylcholinesterase, while high levels of phosphatidylserine inhibited these enzymes in dogs (Tsakiris and Deliconstantinos, 1984). A study was conducted on rats with Alzheimer's disease. One group of rats was designated as the control group, while two groups with Alzheimer's disease were given phosphatidylserine supplementation at doses of 30mg/kg and 15mg/kg, respectively. The study examined the effects of phosphatidylserine supplementation on cholinesterase, hydroxyl radicals, and superoxide dismutase. When comparing the supplemented group to the control group, the rats given phosphatidylserine had increased levels of hydroxyl radical inhibition and superoxide dismutase, and decreased levels of acetylcholinesterase (Zhang et al., 2015). One study showed that supplementing phosphatidylserine for 12 weeks improved memory in aged mice (Zanotti et al., 1989).

A study was conducted to investigate the effects of supplements on the memory of dogs. Five female Beagle dogs, aged between 7 and 12.7 years, were given capsules containing 25 mg of phosphatidylserine, 24 mg of Ginkgo biloba extract (24%), 20.5 mg of pyridoxine, and 33.5 mg of d-alpha-tocopherol at a rate of 1 capsule per 5 kilograms BW for 70 days. DNMP tests were used to assess the short-term visual memory of the dogs and found that the memory of the dogs in the supplemented group improved .Additionally, the effects on memory were reported to continue for 70 days after the

supplements were stopped. The conclusion of the study was that the use of dietary supplements before the onset of pathological changes in the brain may contribute to the maintenance of cognitive function (Araujo et al., 2008).

Lycopene

Lycopene is a carotenoid pigment found in fruits and vegetables, such as tomatoes, papaya, and watermelon. It is known for its antioxidant and anti-inflammatory effects, which play a neuroprotective role in the nervous system and support cognitive function (Zhao et al., 2018; Chen et al., 2019 Lycopene reduced Aβ accumulation and oxidative stress and improved memory in aged mice (Zhao et al., 2018). In diabetic rats, an increase in acetylcholinesterase levels, a decrease in superoxide dismutase, and an increase in TNF-α have been observed in the brain. There was a prevention of the increase in acetylcholinesterase levels, a decrease in TNF-α levels, an increase in superoxide dismutase levels, and positive developments in cognitive tests in lycopene supplemented diabetic rats (Kuhad et al., 2008). In a study of geriatric dogs , an antioxidant-rich supplement containing papaya and tomato was used and results showed decreased reactive oxygen metabolites and increased neurotrophic factor levels (Sechi et al., 2015).

Alpha lipoic acid

Alpha-lipoic acid plays a role in mitochondrial energy metabolism and has antioxidant, anti-inflammatory properties, and effective in maintaining cognitive function (Shay et al., 2009). Twenty-four beagles between the ages of 8.05 and 12.35 years were administered tocopherol, alpha-lipoic acid, L-carnitine, vitamin C supplements and spinach, carrot pieces, orange, grape, and citrus pulp. The dogs also underwent behavioral enrichment treatment, which included socializing with other dogs, playing with toys, and walking activities. The study aimed to analyze the effects of antioxidant use, behavioral enrichment, or both on cognitive function by examining Aβ deposits in the brain. The study showed that the decrease in the Aβ plaque accumulation was more pronounced in the dogs that received both antioxidant and behavioral enrichment treatments than in the dogs that received behavioral enrichment alone (Pop et al., 2010). A later study analyzed reactive oxygen species in 24 beagle dogs taking the same supplements and found that ROS levels were higher in the brains of older dogs, while mitochondrial ROS levels decreased in dogs taking antioxidant supplements (Head et al., 2009). In a study involving dogs aged between 7.6 and 8.8 years, supplementation with alpha lipoic acid and L-carnitine resulted in improved cognitive function test scores. Result suggests that these supplements may slow down mitochondrial deterioration and could potentially be used to treat cognitive dysfunctions (Milgram et al., 2007). A study investigated the effects of alpha lipoic acid, L-carnitine, and antioxidants on cognitive function in dogs. The results showed that dogs given L-carnitine and alpha lipoic acid improved on cognitive function tests (Snigdha et al., 2016).

Curcumin

Curcumin is a polyphenolic compound derived from the plant Curcuma longa, commonly known as turmeric (Farooqui, 2016). It is known for its antioxidant properties and neuroprotective effects through its interaction with amyloid oligomers (Farooqui, 2016; Akinyemi et al., 2017). Research has demonstrated that curcumin can reduce neuroinflammation and may be effective in treating cognitive dysfunctions. A study investigated the effect of curcumin on neuroinflammation in mice injected with lipopolysaccharide, a known cause of neuroinflammation. The results demonstrated that curcumin reduced neuroinflammation (Sorrenti et al., 2018). Curcumin inhibits acetylcholinesterase and provides protection against cognitive impairment (Akinyemi et al., 2017). In mice treated with curcumin, brain-derived neurotrophic factor (BDNF) increased and Aβ accumulation decreased (Okuda et al., 2019). Curcumin has been reported to interact with Aβ oligomers and reduce their toxicity (Rao et al.,2015; Thapa et al., 2016). A study conducted on individuals aged between 50 and 80 years found that supplements containing curcumin resulted in improved memory and reduced stress levels (Cox et al., 2020). These studies suggest that curcumin may slow the pathologies caused by oxidative damage and Aβ plaque accumulation, which are associated with cognitive dysfunction. Ten dogs aged nine years or older diagnosed with cognitive dysfunction were evaluated based on specific behavioral factors (disorientation, sleep, socialization, house soiling, anxiety, activity, excessive vocalization, etc.). The dogs were administered supplements containing SAMe, phosphatidylserine, curcumin, coenzyme Q10, vitamin E, and zinc for a period of two months. At the end of the first and second months, the cognitive function test was repeated based on the initial scoring to evaluate the dogs' cognitive functions. The results showed that all dogs had improved cognitive function scores (Dewey et al., 2023). The study indicates that reducing oxidative damage may be beneficial for cognitive dysfunction. In an another study, dogs with

an average age of 9 years were given a herbal mixture rich in antioxidants, including curcumin (Sechi et al., 2015). The researchers evaluated reactive oxygen metabolites and BDNF levels in dogs given antioxidant-rich supplements. The study reported a decrease in reactive oxygen metabolites and an increase in BDNF levels in dogs received antioxidant-rich supplements. The data suggests that a diet enriched with antioxidants may be beneficial in the management of cognitive dysfunction in dogs.

Conclusion

Nowadays, there is a continued search for alternatives to improving the quality of life, both in animals and in humans, in addition to the use of traditional treatment methods. Recent studies have demonstrated that herbal compounds are effective in slowing the progression of pathologies that cause cognitive impairment. Polyphenols, which are well known for their antioxidant properties, are becoming increasingly prominent in the research literature. The results of the studies showed that oxidative damage in geriatric dogs can be reduced by supplements containing these herbal compounds. Several studies have shown that herbal supplements can improve memory and cognitive function in dogs. Based on those findings, adding herbal compounds to a dog's diet before the onset of impairment may be more effective in reducing symptoms of cognitive dysfunctions in dogs. To obtain more conclusive results, further studies should be conducted on a larger scale. Given the limited number of studies in this area, further research is needed to provide more definitive results regarding the use of herbal compounds for the treatment of cognitive dysfunction in dogs.

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