

# Reduction of behavioural disturbances in elderly dogs supplemented with a standardised Ginkgo leaf extract

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## Summary

In this open clinical trial conducted in 10 veterinary practices, Ginkgo leaf extract was administered as a dietary supplement to 42 elderly dogs (mean age 11.4 years) at a daily dose of 40 mg/10 kg body weight for 8 weeks. The “severity of the geriatric condition” in dogs with a history of geriatric behavioural disturbances (mean duration 12 months), was significantly reduced after 8 weeks of treatment ( $P = 0.0002$ ). The positive effect was already apparent after 4 weeks. Thirty-six % of the dogs were completely free of clinical signs at study end. Overall efficacy of treatment as judged by the investigator was good or very good in 79% of the dogs. Five of six clinical sign scores (disorientation, sleep/activity changes, behavioural changes, general behaviour and general physical condition/vitality) also showed a significant decrease over the treatment period. In conclusion, these findings provide promising results that could increase the quality of life in the elderly dog and, as a consequence, that of the pet owner. The Ginkgo leaf extract appears to be an efficacious agent that provides a safe dietary supplement for the elderly dog with age-related behavioural disturbances.

Keywords: canine geriatric disorder, cognitive impairments, herbal dietary supplement, phytotherapy, *Ginkgo biloba*

## Abnahme altersbedingter Verhaltensstörungen bei Hunden nach Verabreichung eines standardisierten Ginkgoblätterextraktes

In dieser offenen klinischen Studie in 10 Tierarztpraxen wurde während 8 Wochen ein Extrakt aus Ginkgoblättern in Form eines Ergänzungsfuttermittels in einer Dosierung von 40 mg/10 kg Körpergewicht an 42 ältere Hunde (Durchschnittsalter 11.4 Jahre) verabreicht. Der «Schweregrad der klinischen Alterserscheinungen» konnte bei Hunden, welche vorgängig durchschnittlich während 12 Monaten geriatrische Verhaltensänderungen zeigten, bei 8-wöchiger Verabreichung signifikant reduziert werden ( $P = 0.0002$ ), wobei die Wirkung bereits nach 4 Wochen erkennbar war. 36% der Hunde waren am Ende der Studie vollständig frei von klinischen Symptomen. Die Gesamtwirksamkeit der Behandlung wurde durch die Prüftierärzte bei 79% der Hunde als gut oder sehr gut beurteilt. Fünf der sechs klinischen Scores (Desorientierung, Schlaf-Wach-Rhythmus, Verhaltensänderungen, Allgemeinverhalten und Allgemeinbefinden/Vitalität) wurden während der Behandlungsdauer ebenfalls signifikant verbessert. Abschliessend zeigen diese Resultate eine Erfolg versprechende Möglichkeit zur Verbesserung der Lebensqualität älterer Hunde und somit auch ihrer Besitzer. Dieser Ginkgoblätter-Extrakt scheint eine wirksame und sichere Variante zu sein, auf diätetische Weise altersbedingte Verhaltensänderungen bei älteren Hunden positiv beeinflussen zu können.

Schlüsselwörter: Alterserscheinungen beim Hund, kognitive Disfunktion, pflanzliches Ergänzungsfuttermittel, Phytotherapie, *Ginkgo biloba*

## Introduction

Experimental and clinical investigations have shown that typical age-related behavioural disturbances can occur in elderly dogs. These are assumed to result from cognitive disorders and are summarized under

the terms, “cognitive dysfunction syndrome” and “cognitive impairment”, in geriatric veterinary medicine. Geriatric behavioural changes have been classified by the following assessment scores: orienta-

tion in home and yard, social interactions, house-training, and sleep-wake cycles (Bain et al., 2001; Neilson et al., 2001). The morphological characteristics of neurodegenerative processes in the dog's brain are similar to those that have been observed in man: increased deposition of beta-amyloid proteins correlating with cognitive dysfunction and vascular alterations (Cummings et al., 1996).

Traditional as well as modern medical research have recognised the healing and supportive properties of whole plants and their extracts for pets and farm animals, when administered in pharmacologically active doses (phytotherapy or dietary supplementation; Reichling et al., 2004). In its countries of origin in the Far East, especially China, *Ginkgo biloba* has been used traditionally as a medicinal plant. In Europe and in the USA, the use of *Ginkgo biloba* as an active supplement in food and in medicine, has been confirmed in clinical research. The Ginkgo leaf extract used in this trial contains a complex mixture of constituents, such as terpene lactones (e.g. ginkgolides), flavonoids (e.g. quercetine, campherol) and their glycosides – these different constituent groups are all assumed to be involved in pharmacological effects supporting peripheral and cerebral blood circulation. The extract has proven its efficacy in human medicine for the symptomatic treatment of cerebral insufficiency, peripheral arterial occlusive disease (claudicatio intermittens) and disturbances of vestibular origin, such as dizziness, disturbances in equilibrium, or tinnitus. One primary indication is the symptomatic treatment of a mild to moderate cognitive performance disorder that relates to impaired peripheral and cerebral blood circulation, in an elderly population. This geriatric condition is characterized by impairments of, among others, attention, working memory, short term memory, complex reaction times and related social behaviour (Le Bars and Kastelan, 2000; WHO, 1999; ESCOP, 2003).

Today's scientific knowledge readily supports using *Ginkgo biloba* to treat dogs with age-related complaints. Closely corresponding daily dosages (up to 240 mg leaf extract per person) are recommended for humans (Le Bars and Kastelan, 2000; WHO, 1999; ESCOP, 2003). This indicates using a daily dose of 40 mg standardized dry leaf extract per 10 kg body weight. In this study, this dose was administered once daily to elderly dogs with geriatric complaints and behavioural disturbances.

## Animals, Materials and Methods

### Selection of Animals

The investigators were responsible for assessing the clinical condition of each animal at study onset, before beginning treatment and, based on this assess-

ment, decided whether inclusion of the animal into the study was appropriate. Any exceptions relating to inclusion and/or exclusion criteria had to be approved by the monitor/project leader. *Inclusion criteria* were outpatient dogs of both genders with a minimum age of 6 years for large dogs, 8 years for medium sized dogs, and 10 years for small animals, having a relatively good overall condition and geriatric clinical signs in at least two of the six score categories listed in Table 1, and whose condition was expected not to improve within two months without effective treatment. *Exclusion criteria* were poor overall condition, body temperature exceeding 39°C, and dogs whose geriatric condition was attributed to severe pain, tumours, metabolic diseases, cardiac problems, blindness, deafness, joint/skeletal disease, dogs lacking housetraining induced by a bladder-, kidney- or intestinal disease, as well as dogs being treated with either corticosteroids, anabolics, vasodilators, blood thinners, sedatives, psychopharmaceuticals, NSAIDs, cardiac stimulators, cortisone injections and dogs with recent dietary changes.

### Evaluation of efficacy and safety

The study was performed as an open multi-centre clinical trial in 10 veterinary practices. Elderly dogs

Table 1: Six clinical sign scores used to assess age-related disturbances in dogs.

Score 1	Disorientation (orientation in the immediate environment)	<ul style="list-style-type: none"> <li>wanders aimlessly</li> <li>appears lost</li> <li>gets stuck in corners</li> <li>stares into space</li> <li>does not find door</li> <li>appears to forget</li> </ul>
Score 2	Sleep and Activity Changes (sleep-wake cycle)	<ul style="list-style-type: none"> <li>wakes up</li> <li>wakes up and barks</li> <li>sleeps more during day</li> <li>sleeps less during night</li> </ul>
Score 3	House Training	<ul style="list-style-type: none"> <li>defecates indoors</li> <li>no longer signals</li> <li>forgets to defecate</li> </ul>
Score 4	Behavioral Changes (social interactions with human family members)	<ul style="list-style-type: none"> <li>does not recognize familiar people</li> <li>does not seek attention</li> <li>seeks more attention</li> <li>walks away</li> <li>does not greet owner</li> <li>does not participate</li> <li>cannot be motivated</li> </ul>
Score 5	General Behavior	<ul style="list-style-type: none"> <li>apathetic/listless</li> <li>nervous</li> <li>anxious</li> <li>aggressive</li> </ul>
Score 6	General Physical Condition	<ul style="list-style-type: none"> <li>general condition</li> <li>vitality</li> <li>appetite</li> </ul>

with a diagnosis of a geriatric disorder and geriatric behavioural changes were administered a daily oral dose of 40 mg Ginkgo leaf extract in tablet form per 10 kg body weight for a treatment period of 8 weeks. All animals were kept by their owners in their usual (individual) environment and received their regular food throughout the entire study. The study preparation was mixed in the food and was administered once daily by the pet owners. Three mandatory visits were conducted at the investigating veterinarian's practice on day 1 (visit 1), day 28 (visit 2), and day 56 (visit 3, end of treatment period). Seven days after day 56, a safety control was conducted. At the beginning of treatment, each canine patient (of different pedigrees) was at a unique stage of the geriatric condition and exhibited its own individual combination of clinical signs, each expressed at different degrees of severity. The geriatric condition was deemed 'steady state, limited by a possible deterioration of the condition', meaning that this condition was judged by the investigator as being unlikely to improve significantly during the study period without an effective treatment. The clinical condition of each dog was evaluated by the investigator based on the severity of a total of 27 individual clinical signs classified in six assessment scores, adapted according to Neilson et al. (2001) and Bain et al. (2001). The scores used are detailed in Table 1. The degree of "severity of the geriatric condition" and "overall efficacy of treatment" assessments were compared to pre-treatment levels and based on evaluations of the six assessment scores (efficacy parameters). A key was supplied in the protocol to ensure a uniform scoring for overall efficacy by all investigators.

Evaluations of safety and tolerability (safety parameters) were based on the occurrence of adverse events, changes between visit 1 and 3 of body weight, temperature and blood chemistry/haematology measurements. Safety was recorded up to one week

after the end of the treatment period, together with the oral acceptance of the study preparation in the food.

### Study Preparation and administration

The study preparation (film tablets containing 40 mg Ginkgo leaf dry extract, GBB101) was provided by Bogar AG, CH, [www.bogar.com](http://www.bogar.com). The standardized dry leaf extract with a drug/extract ratio of 35–67:1 was obtained from leaves of the *Ginkgo biloba* tree through a special procedure. It contains 22–27% flavonoids, expressed as flavone glycosides and 5–7% terpene lactones including 2.8–3.4% ginkgolides A, B, and C, and 2.6–3.2% bilobalide (DAB, 2000; ESCOP, 2003). The daily dose was 40 mg leaf extract per 10 kg body weight. For an extremely lightweight dog, administration every other day was allowed (1 case). Compliance with administration of the study preparation to the animals: at all visits, the pet owner showed the investigator any remaining study preparation and the signed pet owner's diary, that documented the administration. The study monitor documented all surplus study preparations returned at study end.

### Statistical analysis

The study data were analysed and reported using the SAS V8.2 statistical package. A 5% 2-sided level of significance was used throughout. For efficacy analysis, the LOCF (Last Observation Carried Forward) technique was employed for dogs that discontinued treatment prematurely. The study endpoints, comparing the dogs' condition before and after treatment, assessments of "severity of disease" and of "overall efficacy" by the investigators, were analysed using Bowker's test (Bowker, 1948; Zar, 1999; SAS PROC FREQ) to determine treatment effects. This statistical

test constitutes an extension to the McNemar test and is used when more than two data categories are present. It is suited for the type of data analysis encountered in this study because it takes into account the course of the (approximately steady state) geriatric disease for every individual animal by comparing the changes in category of severity of the clinical sign. The null hypothesis is that all changes from one category of severity to another, and vice versa, are purely coincidental and occur with the same probability. The P-value associated with the test is the probability for getting a result that is at least as asymmetric, with respect to improvements vs. deteriorations, as would be the case in the actual outcome if the null hypothesis (that the changes in severity between “before” and “after” are purely coincidental) were true. The changes in frequently occurring individual clinical sign score assessments were likewise analysed using Bowker’s test.

### Ethical considerations

The study was conducted in accordance with the conditions and valid national regulations article 29/2 of the Swiss Tierschutzgesetz (TSchG) and of the Kantonales Veterinäramt Zürich. The current VICH-GL 9 guideline for Good Clinical Practice for Veterinary Products (GCPV) was followed.

## Results

### Study group composition

Forty-two elderly dogs were enrolled in the trial. Baseline characteristics and treatment records of the study population (mean and standard deviation) were as follows: age was  $11 \pm 2$  years; 19 females and

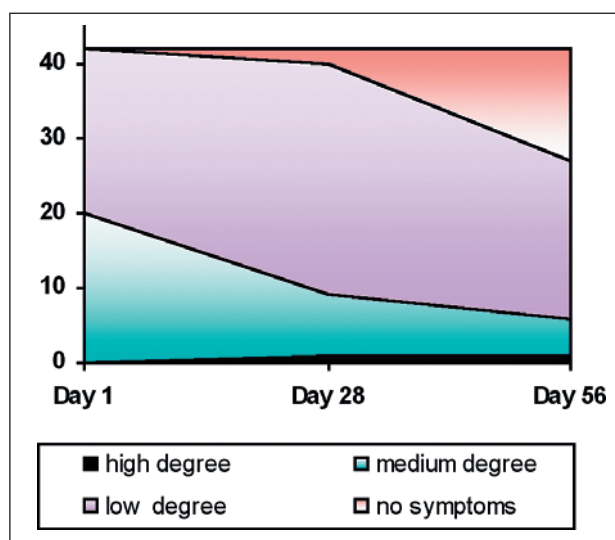


Figure 1: “Severity of geriatric condition” was significantly reduced throughout the study up to day 56 ( $n = 42$ ,  $P = 0.0002$ , Bowker’s test).

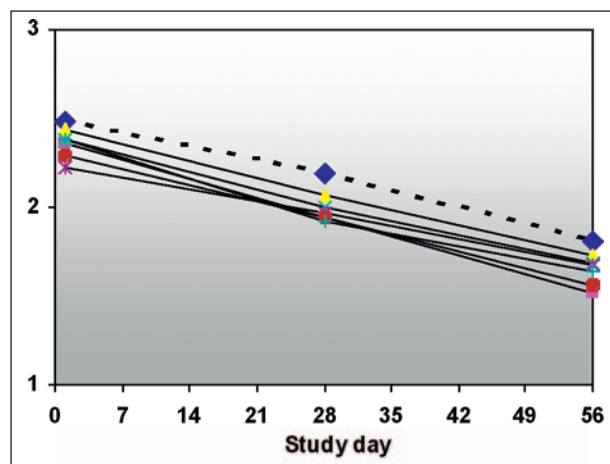


Figure 2: Course of the mean values of the six score assessments of clinical signs (score 1–6) compared with “severity of geriatric condition” during the study. Only data from dogs that expressed clinical signs in the specific assessment category at study onset are included. Evaluation according to last observation carried forward (LOCF). Degree of severity: 1 = no symptom, 2 = low degree, 3 = medium degree, 4 = high degree.

- - ◆ - - Severity ( $n=42$ ,  $P=0.0002$ )
- - ◆ - - Disorientation ( $n=33$ ,  $P=0.003$ )
- - ◆ - - Sleep/Activity ( $n=41$ ,  $P=0.004$ )
- - ◆ - - Houstraining ( $n=13$ ,  $P=0.81$ )
- - ◆ - - Behavioral changes ( $n=39$ ,  $P=0.02$ )
- - ◆ - - Gen. Behaviour ( $n=34$ ,  $P=0.01$ )
- - ◆ - - Gen. Phys. condition ( $n=39$ ,  $P=0.0002$ )

23 males were enrolled; body weight was  $27 \pm 11$  kg; body temperature was  $38.4 \pm 0.3$  °C; duration of disorder prior to supplementation was  $12 \pm 8$  months; the recorded daily dose of Ginkgo extract was  $40 \pm 5$  mg/10 kg body weight; duration of supplementation of test material was  $53 \pm 12$  days.

Due to the age prerequisite in the inclusion criteria, some animals were suffering from other associated, age-related diseases that were not targeted by this investigation but nevertheless interfered with the course of the study. Five dogs prematurely discontinued the study and were carried forward for efficacy analysis. The reasons for premature discontinuation were as follows: 3 of 5 dogs had age-related diseases (see safety section), 1 dog presented with a reversible allergic skin reaction and 1 did not accept the test material. The study population consisted of 11 mixed and 31 pure bred dogs, among the latter 3 Golden Retrievers, 3 Hovawarts, 2 each of Beagles, Bobtails, German Shepherds, Irish Setters, Labradors, Poodles, Rottweilers, Tervueren, and Yorkshire Terriers, and 7 dogs of other breeds.

### Severity of geriatric condition and overall efficacy

“Severity of geriatric condition” of the dogs was assessed by evaluation of the six clinical sign scores

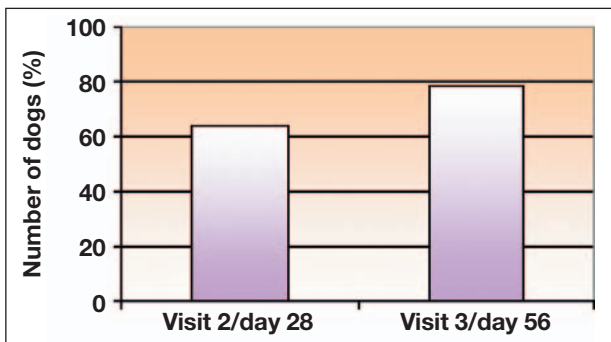


Figure 3: Assessment of "overall efficacy" in percentage of dogs during and after treatment with Ginkgo leaf extract. Improvements of the geriatric condition judged as "good" or "very good" by the investigator ( $n = 42$ ).

of Table 1, determined at 3 clinical visits, on day 1 (before), day 28 (during) and day 56 (after supplementation). Improvements, observed after 56 days of supplementation with Ginkgo leaf extract, were statistically significant (Fig. 1;  $P = 0.0002$ ). Fifteen (36%) of the animals were clearly symptom-free after 56 days of treatment.

In Figure 2, the six clinical sign scores are presented. They showed comparable progressive improvements after 28 and 56 days of supplementation with the extract and all six scores closely reflected reduction of the "severity of geriatric condition". Five of the six clinical sign assessments (scores 1, 2, 4, 5 and 6 respectively) were significantly improved after 8 weeks of supplementation with Ginkgo leaf extract: Disorientation ( $P = 0.003$ ), Sleep and Activity Changes ( $P = 0.0004$ ), Behavioural Changes ( $P = 0.02$ ), General Behaviour ( $P = 0.01$ ) and General Physical Condition ( $P = 0.0002$ ). Although score 3 (housetraining) failed to reach statistical significance due to small numbers, it is interesting to note that it blends well in the picture of the other scores. "Overall efficacy" summarizes the consistent improvements between visits, as is shown in Figure 3.

### Tolerability and adverse events

Overall tolerability after 8 weeks, based on the investigator's evaluation of adverse events, vital signs and haematology and blood chemistry changes in 42 elderly dogs, is presented in Figure 4 and was judged as being either "very good" or "good" for 93% of all animals. Due to the age prerequisite in the inclusion criteria, some elderly dogs were suffering from associated, age-related diseases. For 7 elderly dogs, adverse events were recorded: 4 dogs with age-related disease (suspected stroke; suspected cardiac insufficiency; arthritis flare-up; probable lung tumour) and 3 dogs with mild reversible events (allergic skin reaction; upset stomach; isolated urinary incontinence). For only one of the above events, a mild reversible

reaction of the skin, was a possible relationship to the study preparation suspected by the investigator. Average body weight and mean rectal body temperature remained stable over the 56 days of treatment. Haematology and blood chemistry changes of possible clinical relevance were suspected to be related to pre-existing conditions. One animal had to be euthanised (probable lung tumour), during the 1 week follow-up period, shortly after completing the study. There were no other adverse events reported in the 7-day follow-up safety period after completing administration of the study preparation. Assessment of acceptance of the study preparation (tablets in the food) during the study period of 8 weeks was "sufficient" to "good" in 98% of the treated dogs.

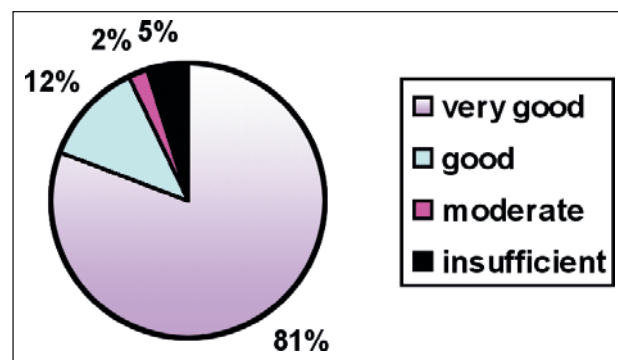


Figure 4: Tolerability of Ginkgo leaf extract after 56 days of treatment ( $n=42$ ).

### Discussion

Dogs with geriatric complaints and behavioural disturbances, probably related to cognitive impairments and cognitive dysfunction, improved remarkably after 8 weeks of diet supplementation. Consistent and pronounced improvements were already observed after 4 weeks. This study has confirmed that *Ginkgo biloba* was used to advantage as a dietary supplement to treat 42 elderly dogs with age-related complaints and behavioural disturbances in an open field trial. Improvement in an approximately "steady state" condition, where practically only slow age-related deteriorations are to be expected, is unlikely to occur without effective treatment. Dogs with symptomatic geriatric disturbances in more than one score show a significantly higher prevalence for deteriorating within 6–18 months. This was especially clear when dogs with signs of disorientation were affected (Bain et al., 2001; Neilson et al., 2001). Therefore unexpected improvements in behavioural problems related to cognitive impairments in the elderly dog, provide a strong indication for the presence of an efficacious agent. Thus the oral administration of Ginkgo leaf extract at a dose of 40 mg/10 kg body weight once daily for 56 continuous days proved to be unexpectedly efficacious as a symptomatic treatment

of behavioural disturbances, that were most likely due to age-related cognitive impairments or to the cognitive dysfunction syndrome in dogs. Five of the six typical age-related clinical sign groups (scores) showed statistically highly significant decreases and 36% of the dogs were even completely free of clinical signs after 56 days.

Although two other medications based on synthetic drugs (propentofylline/Karsivan® and nicergoline/Fitergol®), that are used for treating geriatric conditions and cognitive dysfunction in dogs are on the veterinary market as registered drugs, clinical studies with elderly dogs in the veterinary practice that could be compared with the results reported here could not be found. Publications concerning these pharmaceuticals, propentofylline and nicergoline, refer mainly to human studies in dementia and other age-associated forms of human cognitive impairment (Kittner et al., 1997; Fioravanti and Flicker, 2001). Appropriate data for elderly dogs still appear to be lacking in the current scientific literature. One comparative study (Siwak et al., 2000) on aged dogs tested in an experimental system for "locomotion", which may reflect cognitive dysfunction in part, demonstrated that the synthetic drugs mentioned above, when compared with adrafinil (human agent Olmifon®) which increases locomotion, both appear to lack efficacy in this experimental condition. In other words, proof of efficacy for treating geriatric behavioural disturbances in dogs, for the two marketed drugs, propentofylline and nicergoline, appears to be unavailable. Also data on safety and tolerability of these synthetic drugs for elderly dogs have not been reported in the scientific literature.

Safety data provided in this study demonstrate, that 42 elderly dogs supplemented daily with the Ginkgo leaf extract for two months did not exhibit any serious side effects that could be associated to the Ginkgo extract. Only one dog had a mild reversible skin reaction that was suspected to be related to the study preparation. Other adverse events that also occurred appeared to be due to the age prerequisite in the inclusion criteria, as some elderly dogs were suffering from associated, age-related diseases that accompanied the course of the study.

In conclusion, our findings in an open multi-centre clinical trial in the veterinary practice provide promising results that could tremendously increase the quality of life of the elderly dog. The Ginkgo leaf extract appears to be an efficacious agent that provides a safe dietary supplementation for the elderly dog with age-related behavioural disturbances.

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### Diminution des troubles du comportement lié à l'âge chez le chien avec l'utilisation d'un extrait standardisé de feuilles de ginkgo

Dans cette étude ouverte conduite dans 10 cabinets vétérinaires, un extrait de feuilles de ginkgo sous forme d'un complément alimentaire a été distribué pendant 8 semaines à la dose de 40 mg/10 kg à 42 chiens âgés (âge moyen 11,4 ans). La «gravité des symptômes cliniques de vieillissement» chez des chiens qui présentaient en moyenne des troubles gériatriques du comportement depuis 12 mois, a été significativement réduite après une application durant 8 semaines ( $P=0,0002$ ). L'effet étant déjà visible après 4 semaines. 36% des chiens ne présentaient plus de symptômes cliniques à la fin de l'étude. L'efficacité générale du traitement a été considérée par les vétérinaires comme bonne ou

### Diminuzione nei cani dei disturbi di comportamento dovuti all'età dopo somministrazione di un estratto standardizzato di foglie di ginkgo

In questo studio clinico effettuato in 10 studi veterinari è stato somministrato durante 8 settimane a 42 cani anziani (età media 11.4 anni) un estratto di foglie di ginkgo sotto forma di nutrimento complementare in dosi di 40 mg/10 kg di peso corporeo. Il «grado di gravità dei segni clinici di invecchiamento», in cani che mostravano cambiamenti di comportamento dovuti all'età durante i precedenti 12 mesi, è risultato dopo 8 settimane di somministrazione significativamente ridotto ( $P = 0.0002$ ) anche se l'effetto era già riconoscibile dopo 4 settimane. Il 36% dei cani alla fine dello studio erano completamente esenti da sintomi clinici. Dai veterinari dello studio l'efficacia generale della cura è

très bonne chez 79% des chiens. 5 des 6 paramètres (désorientation, rythme veille sommeil, changement de comportement, comportement général et état général/vitalité) ont également été améliorée de façon significative durant le traitement. En conclusion ces résultats montrent une possibilité intéressante d'améliorer la qualité de vie des chiens âgés et, partant de leur propriétaires. Cet extrait de feuille de ginkgo semble être une possibilité efficace et sûre d'influencer positivement, par la voie diététique les troubles du comportement chez les chiens âgés.

stata valutata, nel 79% dei cani, con buono o molto buono. 5 dei 6 score clinici (disorientamento, ritmo veglia-sonno, modificazioni del comportamento, comportamento generale e stato generale/vitalità) sono significativamente migliorati durante il periodo della cura. Per concludere questi risultati mostrano la reale possibilità di successo nel miglioramento della qualità di vita dei cani anziani e quindi anche dei loro proprietari. Questo estratto di foglie di ginkgo risulta essere una variante efficace e sicura per influenzare positivamente sotto l'aspetto dietetico i cambiamenti di comportamento dipendenti dall'età nei cani anziani.

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