Efficacy of Traditional Chinese Veterinary Medicine in the Treatment of Cognitive Dysfunction: A Systematic Review and Meta-Analysis

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ABSTRACT

The objective of this systematic review study was to assess the efficacy of traditional Chinese medicine (TCM) or traditional Chinese veterinary medicine (TCVM) in the treatment of cognitive dysfunction. The study considered the similarities in Alzheimer's disease (AD) and canine cognitive dysfunction (CCD). The initial literature search resulted in 573 relevant clinical and nonclinical studies. Three categories of controlled clinical trials in AD patients were selected for review: placebo control (20), conventional medicine control (126), and integrated treatment (183). The studies were reviewed and those that met the inclusion criteria were selected for meta-analysis. The review found that 10 placebo-controlled studies, 38 conventional medicine-controlled studies, and 38 integrated studies were qualified for meta-analysis. In placebo-controlled studies, meta-analyses based on improvements in Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) found statistical significance in the MMSE (p=8.74×10^{-7}), ADAS-cog (p=0.0085), and overall p-value (p=3.66×10^{-17}), suggesting that the TCM treatments were significantly more effective than placebo. In conventional treatment-controlled studies, results from the meta-analyses also suggest that TCM treatments were significantly more effective than conventional treatments based on the overall p-value (p=1.67×10^{-23}) and improvement in MMSE (p=0.0002). In the integrated treatment studies, the meta-analyses findings suggest that TCM-integrated treatments were significantly more effective than conventional treatments alone (overall p-value: p=1.82×10^{-48} and p=0.0050 in MMSE improvements). Based on this systematic review and considering the similarities in pathology in the human and canine, TCVM may be helpful to lessen suffering and improve the quality of life in patients with canine cognitive dysfunction.

Keywords: canine cognitive dysfunction, cognitive dysfunction syndrome, Alzheimer's disease, Chinese herbal medicine, acupuncture, traditional Chinese veterinary medicine, meta-analysis

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ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's disease
ADAS-cog	AD Assessment Scale-cognitive subscale
AP	Acupuncture
CCD	Canine cognitive dysfunction
CHM	Chinese herbal medicine
DNAP	Dry needle acupuncture
EAP	Electro-acupuncture
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
TCM	Traditional Chinese medicine
TCVM	Traditional Chinese veterinary medicine
VAS	Visual analogue scale

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Canine cognitive dysfunction (CCD) is a significant problem, as 28% of 11- to 12-year-old dogs and 68% of 15- to 16-year-old dogs show one or more signs of the disorder.[1] It is also under-diagnosed in up to 85% of potentially affected companion dogs, causing unnecessary suffering.[2] Canine cognitive dysfunction is a progressive neurodegenerative condition associated with cerebral pathology leading to a gradual decline in cognitive function.[3] In canine patients, it is reported that the pathology resembles Alzheimer's dementia, with cortical atrophy, ventricular dilatation, accumulation of amyloid-beta (Aβ) and tau protein, microvascular lesions, and decreased hippocampal volume (Table 1).[4-9] This combination of neurodegenerative lesions is clinically seen as changes in behavioral patterns and daily routines that may continue to worsen, as in AD.[10]

Canine cognitive dysfunction is typically diagnosed using owner questionnaires and rating scales based on clinical signs. These include disorientation, altered social

interaction, sleep-wake cycle disturbances, house-soiling/loss of other learned behaviors, changes in activity and increasing anxiety, represented by the acronym DISHAA.[8,11-14] The signs are similar to those seen in the stages of Alzheimer's dementia.[4] A clinically relevant screening and assessment tool, the Canine Cognitive Dysfunction Rating Scale (CCDR) is effective in differentiating severe changes associated with cognitive dysfunction from normal aging, with an overall diagnostic accuracy of 99.3%.[2] As an option, the Canine Dementia Scale (CADES) can be used to identify stages ranging from mild through moderate cognitive impairment to severe cognitive dysfunction (Table 2).[3,15,16] In patient assessment, it is also necessary to rule out diseases with similar clinical signs, such as primary behavioral conditions, other cerebral diseases and systemic diseases.[5,10]

Table 1: Comparison of neurodegenerative changes characteristic of both canine cognitive dysfunction (CCD) and Alzheimer's disease (AD)

Abnormality	CCD	AD
Cognitive decline	+	+
Brain atrophy	+	+
Neuronal damage and death	+	+
Aβ accumulation in brain parenchyma	+	+
Diffuse Aβ plaques	+	+
Dense-core Aβ plaques	-	+
Aβ accumulation in blood vessel walls	+	+
Neurofibrillary tangles formation	-	+
Microglial dysfunction	+	+
Astrocyte dysfunction	+	+
Astroglial hypertrophy and hyperplasia	+	+
Oxidative brain damage	+	+
Mitochondrial dysfunction	+	+
Cholinergic dysfunction	+	+
Impaired neuronal glucose metabolism	+	+

Adapted from: Mihevc S et al. Canine cognitive dysfunction and Alzheimer's disease-two facets of the same disease?[8]

There is a list of conventional medications and nutritional therapies that may help slow deterioration or improve CCD clinical signs.[5,11] Three drugs that have been traditionally used include selegiline, propentofylline and nicergoline. Selegiline is a monoamine oxidase inhibitor that may also have antioxidant properties.[11,14] Although selegiline may enhance neurotransmission and provide neuroprotection, it is associated with numerous side effects (e.g., gastro-intestinal, hindlimb paresis, ataxia).[11,17,18] Propentofylline improves spatial attention and is used in treating dullness, lethargy, and depressed demeanor associated with CCD.[11,19] Minimal data on adverse effects include increased body weight and decreased exploratory behavior in a rat model study.[20] Nicergoline, an α-adrenergic antagonist, improves cerebral blood flow and metabolism, but there are concerns about its side effects and limited clinical studies on its efficacy.[19,21,22] In general, experimental study results comparing efficacy and usefulness in dogs have been conflicting with these drugs.[23,24]

Table 2: Canine Dementia Scale (CADES)

Domain	Frequency
A. SPATIAL ORIENTATION	
1. disorientation in a familiar environment (inside/outside)	
2. recognize familiar people and animals inside or outside the house/apartment	
3. abnormally respond to familiar objects (a chair, wastebasket)	
4. aimlessly wandering (motorically restless during day)	
5. reduced ability to do previously learned tasks	
SCORE (0-25)	
B. SOCIAL INTERACTION	
6. changes in interaction man/dog, dog/other dog (playing, petting, welcoming)	
7. changes in individual behavior of dog (exploration behavior, play, performance)	
8. response to commands and ability to learn new tasks	
9. irritable	
10. expression of aggression	
SCORE (0-25)	
C. SLEEP-WAKE CYCLES	
11. abnormally responds in night (wandering, vocalization, motorically restless)	
12. switch over from insomnia to hypersomnia	
SCORE x 2 (0-20)	
D. HOUSE SOILING	
13. eliminate at home at random locations	
14. eliminate in kennel or sleeping area	
15. changes in signalization for elimination activity	
16. eliminate indoors after a recent walk outside	
17. eliminate at uncommon locations (grass, concrete)	
SCORE (0-25)	
Grading Scale (Frequency of occurrence): 0 = abnormal behavior was never observed, 2 = abnormal behavior was detected at least once in the last 6 months, 3 = abnormal behavior appeared at least once per month, 4 = abnormal behavior was seen 2-4 times per month, 5 = abnormal behavior was observed several times a week	
TOTAL SCORE (A+B+C+D) = 0-95 **Normal aging (Score 0 - 7), Mild cognitive impairment (8 - 23), Moderate cognitive impairment (24 - 44), Cognitive dysfunction (45 - 95)**	

Adapted from: Vikartovska Z et al. Novel diagnostic tools for identifying cognitive impairment in dogs: behavior, biomarkers, and pathology.[16]

In traditional Chinese medicine (TCM) and traditional Chinese veterinary medicine (TCVM), cognitive dysfunction is considered a loss of *Shen* consequent to an imbalance of the Heart system.[25,26] In Chinese medical theory, the *Shen* or Spirit is housed in the Heart and is associated with mental clarity, memory and sleep. In this model, the Heart substances are essential to mental activity and brain function. The cognitive abilities are affected when Heart *Qi* or *Yin* and Blood become deficient. In TCM, there is a close relationship between the Heart and Kidney and cognition, as the Kidney *Jing* nourishes the brain while the Heart balances its activity.[27] A deficiency of Kidney *Jing*, thus, may result in cognitive impairment as well. In the Chinese medical paradigm, the Spleen is also involved in cognitive ability, as this system promotes the movement of fluids.[25,26,28] A deficiency of Spleen *Qi* causes accumulation of fluids and generation of Phlegm that is said to mist the Mind and obstruct the *Shen*. As Aβ plaques formed in the brain by accumulation of proteins are considered Phlegm or local Blood Stagnation, this pathological buildup obstructs the flow of *Qi* and impedes neuronal transmission, affecting cognitive function.

In TCM and TCVM, patterns seen in AD and CCD may include Heart and Spleen *Qi* Deficiency with Phlegm, Heart *Yin*-Blood Deficiency, *Qi*-Blood Stagnation and Kidney *Jing* Deficiency.[25-27,29-34] These imbalances in the body are addressed with TCM treatment principles of tonify Spleen *Qi* to support Heart *Qi*, tonify Heart *Qi* to support the *Shen* and tonify Heart *Yin*-Blood.[26,27] Additionally, treatment principles to address Excess include dispel Phlegm to remove obstruction of *Shen* and resolve *Qi*-Blood Stagnation. Finally, Kidney *Jing* declines with aging and since it is the origin of Kidney *Yin* and Kidney *Yang*, a deficiency of these may also be present. It is important to treat Kidney *Jing* Deficiency in these geriatric individuals by tonifying Kidney *Yin*, warming Kidney *Yang* and/or tonifying Spleen to support Post-natal *Jing*.[27]

In current research involving human patients, TCM treatment is shown to enhance cognitive function. A study on *Ba Wei Di Huang Wan* demonstrated improved cognitive function and ability to perform daily activities in elderly patients with Alzheimer's dementia and showed that it was well-tolerated.[35] In this study, a possible underlying mechanism of improved cerebral blood flow may be helpful to address the pathology of Blood Stagnation in the brain. A main TCM treatment for Alzheimer's dementia, *Bu Shen Hua Tan Yi Zhi* granules, has been shown to improve cognitive function and quality of life by replenishing Kidney Essence, resolving Phlegm, and promoting mental therapy.[34] In resolving Phlegm, this Chinese herbal medicine may be helpful to lessen Aβ plaque accumulation.[36] In addition to Chinese herbal medicine (CHM), acupuncture (AP) has proven to be an effective therapy in Alzheimer's patients. In a study involving the *San Jiao* theory of TCM, acupuncture therapy was helpful in improving cognitive function and overall clinical status with minimal side effects.[37] Also, it is reported in another study that AP treatment to replenish *Qi* and promote Blood circulation improved attention and working memory in patients with mild to moderate AD.[29]

Although there is a growing body of literature on TCM treatment of AD, there is only limited work investigating the efficacy of using TCM principles to treat CCD.[22,27] The objective of this systematic review and meta-analysis study was to assess the efficacy of TCM or TCVM, including Chinese herbal medicine and acupuncture, in the treatment of cognitive dysfunction based on the scientific evidence published to date. This research considered the similarities in AD and CCD, which would allow the extrapolation of findings in human studies to veterinary practice.

MATERIALS AND METHODS

The search strategy was organized into a 3-step protocol. First, a search was conducted to identify protocol search terms in the title, abstract, keywords, and descriptors listed in an article using the following literature databases: Biomed Central (BMC) Complementary and Alternative Medicine, PubMed Central (PMC), Europe PMC, PubMed, Google Scholar, China National Knowledge Infrastructure (CNKI), China/Asia on Demand (CAOD), Hindawi, and the University of British Columbia library. Second, search terms identified, as well as synonyms, were used in an iterative literature search to include journals and databases associated with publications. Third, references in articles as well as the names of well-known authors in the field were then searched.

The search terms that were used initially included: canine cognitive dysfunction, cognitive dysfunction syndrome, Alzheimer's disease, Chinese medicine, herbal medicine and acupuncture. Criteria established for article selection included: 1) a controlled clinical study that investigated the efficacy of TCM/TCVM in the treatment of cognitive dysfunction, 2) the control treatment could be a negative or positive control, and 3) the study should have an outcome measure of statistical significance (*p*-value). There were several types of studies that were excluded: 1) studies in transgenic mouse models of AD, as the human AD condition may serve as a better model for CCD, 2) studies in patients with mild cognitive impairment (MCI), which is considered a heterogeneous condition and unsuitable for a meaningful meta-analysis, and 3) studies assessing the efficacy of TCM in treating only vascular dementia (a type of dementia distinct from AD), therefore not valid for AD and CCD comparison. The publications that met these study inclusion/exclusion criteria were considered for full article review to determine if they were qualified for meta-analysis.

Statistical significance outcomes derived from statistical inference on the hypotheses comparing the TCM treatment group and control group with respect to the selected assessment variables were extracted for meta-analysis. The group mean ± standard deviation (SD) of

the pre- and post-treatment differences in the selected assessment variables were also extracted for meta-analysis. In articles that only reported T statistic or 95% confidence interval of the mean pre- and post-treatment difference, the SD was calculated reversely based on the formula of the T statistic or 95% confidence interval.

The objective of the meta-analysis in a systematic review research study is to combine the results of independent, but similar, studies to obtain an overall estimate of the statistical significance. In this study, to achieve sufficient robustness, Stouffer's Z score method was applied, which first converts the *p*-value from each individual study to a Z score (inverse of normal cumulative distribution function). An overall Z score was calculated by dividing the sum of all individual Z scores by the square root of the number of studies. The overall significance (*p*-value) was calculated by the normal cumulative distribution function. If the overall *p*-value was less than 0.05, the study considered that the meta-analysis on the reviewed studies supports the study hypothesis: TCM/TCVM is effective in the treatment of cognitive dysfunction.

Under the condition that the studies that qualified for inclusion used a common outcome measurement (standardized group mean difference, correlation, or odds ratio) for testing effectiveness, the effect size model was used. Based on the effect size and variance in each study, the analysis included the estimate of homogeneity among studies. The Z statistic was calculated to test null hypothesis (i.e., TCM/TCVM treatment has the same effectiveness as the control treatment in improving cognitive function). A commercial statistical software[a] was used for all data graphic presentations and statistical analysis.

For each of the articles included in the meta-analysis, the quality of the study was assessed based on the Jadad Scale.[38,39] The scale ranged from 0 to 5 and assessed the quality of the randomized controlled trials evaluated in this study. The assessment was based on the following three criteria: (1) randomization: score 1 = mentioned, score 2 = method described, (2) blinding: score 1 = mentioned, score 2 = method described, and (3) data outcome: score 1 = fate of all subjects known (e.g., completed the trial, dropped out, excluded due to protocol deviation). A study with a Jadad score of 3 points or greater was considered high quality.

RESULTS

The initial literature search in this review resulted in a total of 573 relevant clinical and nonclinical studies. The studies were organized based on design, disease and species into categories for review. In the veterinary studies category, there were too few controlled treatment studies for a meaningful meta-analysis (1 article).[40] In the human studies resulting from the initial search, 106 assessed TCM effectiveness in MCI patients. After a careful review, it was found that MCI is considered a heterogeneous condition. These patients may progress to a dementia other than Alzheimer's, such as vascular dementia, frontotemporal dementia, Lewy body dementia, or may remain stable and show cognitive decline of normal aging.[41] The MCI patient population in a study, therefore, may not be uniform. In terms of applicability to veterinary patients, the pathology and diagnosis in the dog is unclear in the literature. It was determined that MCI as a general category is not suitable for a meaningful meta-analysis, and the relevant studies were excluded. In the initial search, 101 studies investigating the efficacy of TCM in transgenic mouse models of AD were identified. As the human AD condition may serve as a better model for CCD than experimental rodent models, these studies were also excluded. Three categories containing controlled clinical trials in Alzheimer's patients were selected for full-article review: placebo control (20 articles), conventional medicine control (126 articles), and integrated (183 articles). The studies in these categories were then reviewed, and those that met the inclusion criteria were selected for statistical meta-analysis.

Placebo Controlled Studies

The assessment found that 10 of the placebo-controlled studies were qualified for meta-analysis (Table 3).[32,42-50] All 10 studies were randomized controlled trials investigating the efficacy of CHM in treating AD patients, with treatment duration ranging from 8 to 52 weeks (mean ± SD = 20.0 ± 14.0). The sample size ranged from 13 to almost 100 per treatment group. With respect to the study quality, eight studies scored 4 or 5 on the Jadad Scale, and the remaining two scored 3 (mean ± SD = 4.1 ± 0.74).

Among these studies, the most reported treatment outcomes were based on evaluation in Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) changes. To be more consistent, this meta-analysis used MMSE outcome as the primary measurement for extracting statistical significance of the study. When MMSE outcome was not presented, significance based on ADAS-cog outcome was used.

The first meta-analysis used Stouffer's Z score method that converts each observed *p*-value to a Z score. Among the 10 studies included, 8 of them concluded an efficacy with statistical significance. The overall *p*-value from this meta-analysis was 3.66×10^{-17}, which suggested that the TCM treatments were significantly more effective than placebo based on improvements in MMSE or ADAS-cog.

The second meta-analysis used the MMSE improvement data (mean ± SD and sample size) reported in the 6 studies and applied a random-effects model that incorporated the between-study variance (Table 3). The meta-analysis effect size model revealed a significant overall effect ($p = 8.74 \times 10^{-7}$). It can be concluded, based on the mean improvement in MMSE, that the evidence reported in these studies suggests that the TCM treatments were significantly more effective than placebo.

The same meta-analysis was performed on the ADAS-cog improvement data (mean ± SD and sample size) reported in the 5 studies (Table 3). The meta-analysis effect size model revealed a significant overall effect (p = 0.0085). It can be concluded, based on the mean improvement in ADAS-cog, that the evidence reported in these studies suggests that the TCM treatments were significantly more effective than placebo.

Table 3: Summary table of traditional Chinese medicine (TCM) treatment vs. placebo studies qualified for meta-analysis; Stouffer's Z score for individual studies is listed as well as overall p-value for the meta-analysis.

First Author	TCM Treatment	Cognition Test	Sample Size Test/Control	Stouffer's Z Score For TCM Efficacy*
Le Bars[42]	Ginkgo biloba extract	ADAS-cog	75 / 75	-2.81
Akhondzadeh[43]	Salvia officinalis extract	ADAS-cog	15 / 15	-3.89
Mazza[44]	Ginkgo biloba extract	MMSE	25 / 26	-1.64
Li[32]	*Tiao Xin* recipe	MMSE	30 / 15	-1.96
Akhondzadeh[45]	Saffron extract	ADAS-cog	23 / 23	-3.89
Akhondzadeh[46]	Melissa officinalis extract	ADAS-cog	20 / 15	-3.89
Zhang[47]	Huperzine A	MMSE ADAS-cog	MMSE: 98 / 99 ADAS-cog: 98 / 96	-3.29
Xu[48]	Huperzine A	MMSE	50 / 53	-1.96
Chai[49]	*Shuang Yi Ping*	MMSE	22 / 26	-0.01
Zhou[50]	Huperzine A	MMSE	13 / 13	-3.29
Overall p-value				3.66×10^{-17}

*Z score of -1.96/-3.29/-3.89 was used when the p-value was reported as $p < 0.05/0.001/0.0001$; and a Z score of -0.01 was used when the p-value was reported as $p > 0.05$; MMSE=Mini-Mental State Examination; ADAS-cog=Alzheimer's Disease Assessment Scale-cognitive subscale

Table 4: Summary table of traditional Chinese medicine (TCM) treatment vs. conventional treatment studies qualified for meta-analysis; Mini-Mental State Examination used for cognition test; Stouffer's Z score for individual studies is listed as well as overall p-value for the meta-analysis.

First Author	TCM Treatment[141-143]	Sample size Test / Control	Stouffer's Z Score For TCM Efficacy*
Chen[51]	Compound Polygonum multiflorum extract	120 / 29	-2.58
Peng[52]	*Yi Zhi Jian Nao* granules + AP: *Bai-hui* (GV-20), *Si-shen-cong*, *Da-zhui* (GV-14), and *Guan-yuan* (CV-4); Moxibustion was applied at *Guan-yuan* (CV-4)	28 / 28	-2.58
Gu[29]	AP: *Shen-ting* (GV-24), *Bai-hui* (GV-20), *Feng-chi* (GB-20), *Wan-gu* (GB-12), *Dan-zhong* (CV-17), *Zhong-wan* (CV-12), *Qi-hai* (CV-6), *Xue-hai* (SP-10), and *Zu-san-li* (ST-36)[b]	72 / 69	-2.58
Liu[34]	*Bu Shen Hua Tan Yi Zhi* granules	30 / 30	-3.29
Meng[53]	*Nao Huan Dan*	30 / 28	-1.96
Feng[54]	AP: *Bai-hui* (GV-20), *Feng-fu* (GV-16), *Shen-ting* (GV-24), *Tai-yang*, *Shang-yin-tang*, and *Da-zhong* (KID-4); EAP: *Bai-hui* (GV-20), *Shen-ting* (GV-24), and bilateral *Tai-yang*	17 / 16	-0.01
Dong[55]	*Yi Zhi Jian Nao* granules	20 / 22	-2.58
Gang[56]	*Fu Zhi San*	24 / 20	-0.01
Zhou[57]	*Shen Gui Jian Nao* liquid	34 / 34	-0.01
Lin[58]	*Tiao Xin* recipe	20 / 20	-0.01
Zhu[59]	AP: *Feng-fu* (GV-16), *Feng-chi* (GB-20), *Si-shen-cong*, *Bai-hui* (GV-20), *Yin-tang*, *Shui-gou* (GV-26), *Tai-xi* (KID-3), *Fu-liu* (KID-7), *Nei-guan* (PC-6), *Shen-men* (HT-7), *Zu-san-li* (ST-36), *San-yin-jiao* (SP-6), and *Feng-long* (ST-40); AA: *Shen-men* and Heart, Liver, Kidney, Brain acupoints	44 / 44	-1.96

Table 4 Cont.

Wang[60]	EAP: *Da-zhui* (GV-14) and *Bai-hui* (GV-20)	36 / 36	-1.96
Zhao[61]	AP: *Da-zhui* (GV-14) and *Bai-hui* (GV-20)	16 / 16	-1.96
Chen[62]	*Shen Fu* in *Yang-Qi* Deficiency; *Shen Mai* in *Yin-Qi* Deficiency; administered with deproteinized calf blood, IV injection	33 / 33	-1.96
Zhao[63]	*Bu Shen Yi Sui* + acupoint embedding at bilateral *Xin-shu* (BL-15), *Jue-yin-shu* (BL-14), *Gan-shu* (BL-18), *Shen-shu* (BL-23), *Zu-san-li* (ST-36), and *Feng-long* (ST-40); *Qi-hai* (CV-6)	30 / 30	-0.01
Chen[64]	*Wen Pi Tong Luo Kai Qiao* decoction[c]	40 / 40	-1.96
Guo[65]	*Yin Xing Ye* (Ginkgo biloba leaf), *Ren Shen* (Ginseng root), and *Yin Yang Huo* (Epimedium)	140 / 70	-2.58
Zhong[66]	*Bu Qi Huo Xue* decoction[c]	40 / 40	-2.58
Zhou[67]	*Bu Shen* recipe	34 / 34	-0.01
Liu[68]	AP: *Yin-tang* and bilateral *Ying-xiang* (LI-20)	40 / 40	-0.01
Yang[69]	*Tiao Xin* recipe	31 / 28	-1.96
Zhai[70]	*Yi Qi Cong Ming* decoction	30 / 30	-2.58
Huang[71]	*Bu Shen Yi Sui* formula	34 / 34	-2.13
Zhang[72]	*Di Huang Yin Zi*	30 / 30	-0.01
He[73]	*Bu Yang Huan Wu* decoction[c]	35 / 35	-1.96
Li[30]	*Dang Gui Shao Yao San* + AP[b,c]; EAP at main acupoints: *Bai-hui* (GV-20), *Si-shen-cong*, *Feng-chi* (GB-20), *Shen-shu* (BL-23)	35 / 14	-2.58
Li[74]	*Shi Quan Da Bu* decoction	20 / 20	-2.58
Zhu[75]	*Yi Zhi Jian Nao* granules + AP: *Bai-hui* (GV-20) and bilateral *Shen-shu* (BL-23), *Xue-hai* (SP-10), and *Ge-shu* (BL-17)	20 / 20	-1.60
Na[76]	Reinhartdt and sea cucumber capsule	33 / 32	-0.01
Wang[77]	*Tiao Xin* recipe	34 / 34	-0.01
Jiang[78]	*Jian Nao San* + AP: *Nao San Zhen* at *Nao-hu* (GV-17), *Nao-kong* (GB-19); *Zhi San Zhen* at *Shen-ting* (GV-24), *Ben-shen* (GB-13); *Nie San Zhen* in temporal area	20 / 20	-0.01
Xie[79]	*Bu Shen Huo Xue Hua Tan* formula	30 / 28	-1.96
Liu[80]	Huperzine A	23 / 18	-2.58
Bi[81]	EAP: *Zu-san-li* (ST-36) and *Feng-long* (ST-40)	37 / 37	-1.96
Ni[82]	*Jia Wei Zuo Gui Wan* + EAP[b]: *Da-zhui* (GV-14), *Bai-hui* (GV-20)	33 / 32	-1.96
Yu[83]	*Bu Shen Huo Xue Hua Tan* formula	42 / 40	-1.96
Luo[84]	*Qu Tan Hua Yu* prescription	40 / 40	-2.58
Dong[85]	*Yi Zhi Jian Nao* granules	50 / 50	-2.58
Overall *p*-value			1.67×10^{-23}

*Z score of -1.96/-2.58/-3.89 was used when the *p*-value was reported as $p < 0.05/0.01/0.001$; and a Z score of -0.01 was used when the *p*-value was reported as $p > 0.05$; [b]=additional acupoints per syndrome; [c]=additional herbs per syndrome; AA=auricular acupuncture

Conventional Treatment Controlled Studies

In this study category, the assessment found that 38 studies were qualified for meta-analysis (Table 4).[29,30,34,51-85] Among the studies qualified for inclusion, the most reported treatment outcomes were based on the evaluation in MMSE improvements. The meta-analyses for this category of studies used MMSE outcome as the measurement for extracting statistical significance (*p*-value) and the effect size (group difference) of each study. Among these studies, 25 investigated CHM, 7 were on AP [dry needle (DNAP) or electro-acupuncture (EAP)], and the remaining 6 studied treatments that combined CHM and AP (DNAP, EAP, acupoint embedding, or moxibustion). The treatment duration ranged from 3 to 48 weeks (mean ± SD = 11.9 ± 6.9), and the sample size ranged from 16 to 140 in the TCM group and 14 to 70 in the control (conventional treatment) group. Examination of the study quality showed poorer quality than the placebo-control studies, with the majority of studies (32/38 = 84%) having a Jadad Scale score of 2 or 3 (mean ± SD = 2.66 ± 0.81).

Among the 38 studies, 26 of them concluded a statistical significance with better MMSE improvements over those of the conventional treatment. The overall *p*-value from this meta-analysis was 1.67×10^{-23}, which concluded that, based on the statistical significance of improvements in MMSE, these reported studies suggest that the TCM treatments were significantly more effective than conventional treatments. The meta-analysis using the MMSE improvement data reported in 24 studies revealed a significant overall effect with the random-effects model ($p = 0.0002$). Based on the mean improvement in MMSE, the evidence reported in these studies also suggests that the TCM treatments were significantly more effective than conventional treatments.

Integrative Treatment Studies

The assessment for this study category found that 38 of the integrated studies were qualified for meta-analysis (Table 5).[31,86-122] Among these studies, again most studies reported treatment outcomes based on evaluation in MMSE improvements. The meta-analysis for this category extracted the statistical significance (*p*-value) and treatment effect data from the MMSE improvements reported in the study. Among these studies, 31 investigated integrative treatments with CHM, 6 with AP (DNAP, moxibustion) or transcutaneous electrical nerve stimulation (TENS), and the remaining 1 studied integrative treatment that included both CHM and AP (DNAP). With the exception of one study (Shi et al.), the treatment durations were very similar to those in "TCM vs. conventional" studies, ranging from 4 to 96 weeks (mean ± SD = 16.8 ± 16.6).[121] The sample size ranged from 20 to 90 in the integrative group (mean ± SD = 40.3 ± 16.1) and from 20 to 799 in the control (conventional treatment) group (mean ± SD = 60.0 ± 124.2). One study with 799 control subjects was an outlier.[99] Inspection of the study quality showed poorer quality than the studies in both previous categories, with the majority of studies (33/38 = 87%) having a Jadad Scale score of 2 or 3 (mean ± SD = 2.24 ± 0.68), and no studies having a Jadad Scale score of 4 or above.

Table 5: Summary table of traditional Chinese medicine (TCM)-integrated treatment vs. conventional treatment studies qualified for meta-analysis; Mini-Mental State Examination used for cognition test; Stouffer's Z score for individual studies is listed as well as overall *p*-value for the meta-analysis.

First Author	TCM Treatment[141-143]	Sample size Test / Control	Stouffer's Z Score For TCM Efficacy*
Hu[31]	*Bu Shen Tong Luo* decoction[c]	40 / 40	-2.58
Wang[86]	*San Jiao* AP: *Dan-zhong* (CV-17), *Zhong-wan* (CV-12), *Qi-hai* (CV-6), *Xue-hai* (SP-10), *Zu-san-li* (ST-36)	55 / 54	-2.58
Luo[87]	*Nao Shuan Tong*	40 / 40	-1.87
Zheng[88]	*Xing Zhi San*	90 / 90	-1.96
Cai[89]	Compound *Hai She* capsule	42 / 42	-1.96
Chen[90]	*Huo Xue Rong Luo* tablet	30 / 30	-1.96
Liang[91]	*Bu Shen Yi Zhi* granules	64 / 64	-1.96
Zhu[92]	*Nao Mai Tai* capsule + *Yi Shen Jian Nao* decoction	31 / 30	-2.58
Wei[93]	*Dan Hong* injection	53 / 53	-1.96
Zhi[94]	Compound *Hai She* capsule	30 / 30	-2.58
Jiang[95]	*Jian Nao San*	25 / 25	-1.96
Li[96]	TENS	29 / 29	-3.29
Li[97]	*Deng Zhan Sheng Mai* capsule	28 / 28	-1.72
Miao[98]	Chinese herbs to balance *Qi* and nourish Blood	67 / 69	-1.96
Canevelli[99]	Ginkgo biloba extract	29 / 799	-2.75
Zhou[100]	Reinhartdt and sea cucumber capsule	24 / 21	-2.58
Yin[101]	Curcumin	30 / 30	-2.58
Liu[102]	*Xing Chi* decoction + AP: *Si-shen-cong*, *Bai-hui* (GV-20), *Shen-men* (HT-7), *Zu-san-li* (ST-36), *Shen-ting* (GV-24), *Nei-guan* (PC-6), *He-gu* (LI-4), *San-yin-jiao* (SP-6), and *Tai-xi* (KID-3)	20 / 20	-1.96
Li[103]	Compound *Cong Rong Yi Zhi* capsule	49 / 49	-1.96
Yin[104]	Scalp AP on a line from *Qian-ding* (GV-21) to *Xuan-li* (GB-6) and on a line from *Bai-hui* (GV-20) to *Qu-bin* (GB-7)	30 / 30	-2.58

Table 5 Cont.

Guo[105]	*Bu Shen Yi Sui* decoction	30 / 30	-3.92
Jin[106]	AP: *Si-shen*	26 / 26	-1.96
Zhang[107]	*Shen Gui Yi Zhi Fang*	75 / 75	-1.96
Huang[108]	Ginkgo biloba extract	40 / 40	-1.96
Dong[109]	*Yi Zhi Jian Nao* granules	20 / 20	-1.96
Qiu[110]	*Bu Shen Yi Zhi* decoction	37 / 37	-1.96
Li[111]	*Xing Nao Jing*	52 / 48	-1.96
Han[112]	*Gu Ben Qu Tan Yu* decoction	30 / 30	-1.96
Li[113]	*Di Dang* decoction	40 / 40	-1.96
Huang[114]	Ginkgo biloba extract	40 / 40	-1.96
Wei[115]	*Lei Huo* moxibustion: *Shen-que* (CV-8), *Zhong-wan* (CV-12), *Guan-yuan* (CV-4), and *Bai-hui* (GV-20); bilateral *Tian-shu* (ST-25), *Zu-san-li* (ST-36), and *Yong-quan* (KID-1)	25 / 25	-1.35
Lang[116]	*Wen Pi Tong Luo Kai Qiao* decoction[c]	70 / 63	-1.96
Wang[117]	*Di Huang Yin Zi*	38 / 38	-2.46
Xue[118]	*Bu Shen Hua Tan Qu Yu* recipe[c]	47 / 47	-7.77
Zhang[119]	Compound *Dan Shen* tablet	50 / 50	-1.96
Tian[120]	AP: *Si-shen-cong*, *Bai-hui* (GV-20), *Shen-ting* (GV-24), *Yin-tang*, *Ren-zhong* (GV-26), *Feng-fu* (GV-16), *Shen-men* (HT-7)[b]	35 / 35	-2.58
Shi[121]	GRAPE Chinese herbal formula	30 / 26	-3.29
Li[122]	*Bu Shen Ping Gan* recipe	44 / 34	-1.96
Overall *p*-value			1.82×10^{-48}

* Z score of -1.96/-2.58/-3.89 was used when the *p*-value was reported as $p < 0.05/0.01/0.001$; and a Z score of -0.01 was used when the *p*-value was reported as $p > 0.05$; [b]=additional acupoints per syndrome; [c]=additional herbs per syndrome

Among the 38 studies, 35 of them concluded a statistical significance with better MMSE improvements over those with conventional treatment alone. The overall *p*-value from this meta-analysis was 1.82×10^{-48}, which was again extremely significant. The meta-analysis effect size model with MMSE improvement data (15 studies) also revealed a significant overall effect ($p = 0.0050$). It can be concluded, based on the mean improvement in MMSE, that the evidence reported in these studies suggests that the TCM-integrated treatments were significantly more effective than conventional treatments alone in treating AD patients.

DISCUSSION

Traditional Chinese medicine has been used in treating dementia for thousands of years. There are numerous prescriptions in the historical records, such as *Kai Xin* powder, *Nao Ling* decoction, *Yi Zhi* decoction, *Huan Nao Yi Cong* decoction, and compound formula Rehmannia that were used to improve memory/intelligence and treat dementia without noticeable side effects.[123] The objective of this study was to determine the effectiveness of TCM in the treatment of cognitive dysfunction with application to veterinary patients. As there are few studies in the veterinary field related to cognition, the findings of an extensive literature search, review, and meta-analyses of controlled clinical trials in Alzheimer's patients was conducted, as humans and canines share a similar pathology and clinical signs.[4,5,8]

The literature search identified a total of 329 articles in Alzheimer's patients and 14 in veterinary subjects for full article assessment. In human studies, the assessment resulted in 86 studies qualified for meta-analysis. These studies were classified into 3 categories based on the study hypothesis tested with respect to TCM efficacy. As only 1 veterinary study met the inclusion criteria, meta-analysis was performed on human studies.[40]

By performing statistical meta-analysis to calculate the overall statistical significance based either on the reported *p*-values or through effect size model on the most reported treatment outcome measurements, this systematic review study found that 1) TCM treatments were significantly more effective than placebo; 2) TCM treatments were significantly more effective than conventional treatments; and 3) integrating TCM with conventional treatments was significantly more effective than the conventional treatments alone, all with statistical significance $p < 0.01$.

The findings in this study are consistent with those in analyses conducted by several authors, although certain aspects of the methodology may differ. In a meta-analysis

of randomized controlled trials conducted by Kim and Cho, the effect of *Dang Gui Shao Yao San* as compared with a vitamin E placebo was assessed in patients with dementia.[124] In a subgroup analysis of Alzheimer's patients, a significant difference was seen in the MMSE favoring *Dang Gui Shao Yao San* (2 trials; $p < 0.00001$). In view of the findings, it is suggested that *Dang Gui Shao Yao San* is effective in improving cognition and accompanying symptoms of dementia with a low risk of side effects. A similar result was seen in a meta-analysis reported by Weinmann et al. comparing the effects of Ginkgo biloba with placebo in the treatment of dementia.[125] In this study, a subgroup analysis of controlled trials in Alzheimer's patients found a significant difference in favor of Ginkgo in the ADAS-cog and Syndrom-Kurztest combined (6 trials; $p = 0.02$). Another meta-analysis on randomized controlled trials compared the effects of Chinese herbal medicine and conventional medicine on cognition and activities of daily living in patients with Alzheimer's dementia.[126] The results indicated that CHM had a significant effect on cognition, as measured by MMSE (23 trials; $p < 0.001$). Of interest in a separate analysis, CHM was more effective in improving cognition than the cognition enhancing pharmaceutical, donepezil (20 trials; $p < 0.001$).[126]

Meta-analysis has also been reported on the efficacy of AP combined with CHM compared with conventional medicine in Alzheimer's patients.[127] A summarized analysis on studies using AP or acupoint embedding combined with one of several herbal recipes demonstrated that combined TCM was superior to conventional medicine in improving the MMSE score (11 trials; $p = 0.004$). Another meta-analysis assessed the efficacy of AP alone and integrated with conventional medicine in patients with Alzheimer's dementia.[128] In a combined analysis of trials, the results showed that AP was more effective than conventional medicine in improving MMSE score (6 trials; $p = 0.02$). A pooled analysis indicated that AP combined with donepezil was superior to donepezil alone in improving cognition as assessed by MMSE (3 trials; $p < 0.00001$). Positive outcomes of meta-analysis on the efficacy of acupuncture and moxibustion combined with conventional medicine in the treatment of AD were also reported.[129]

There are, however, some studies that concluded partial agreement with this systematic review. For example, 2 meta-analysis studies on huperzine A versus placebo found no evidence of significant difference in ADAS-cog improvements, and 2 studies found no significant difference between CHM and donepezil in MMSE score improvements.[130-133] In these reports, many of the analyses included fewer studies in comparison to this systematic review. It is possible that a small sample size may have reduced the power and increased the margin of error in these cases.

Considering that the pathology is similar in CCD and AD, traditional Chinese medicine as a therapy may be helpful in veterinary clinical practice. A few veterinary reports describe the use of Chinese herbal medicine in treating clinical signs of CCD. One veterinary study, that met the present systematic review and meta-analysis criteria, was a randomized double-blind controlled study reported by Hielm-Bjorkman et al.[40] The authors evaluated the effect of Panax ginseng in combination with brewers' yeast in older dogs showing geriatric clinical signs. The patients were assigned to receive either Panax ginseng combined with brewers' yeast (n = 41) or brewers' yeast alone as a control (n = 39). The efficacy was measured with questionnaires and visual analogue scales (VAS) associated with mental and physical variables. At the end of the 8-week study period, the Panax ginseng group significantly improved in comparison with control in 4 of the 7 mental variables: alertness-interest in surroundings, forgetfulness, alertness VAS and quality of life VAS ($p = 0.008$, $p = 0.027$, $p = 0.041$, and $p = 0.012$, respectively). There was no significant difference in physical variables between groups ($p > 0.05$), and no side effects were observed during the study period. It was concluded that Panax ginseng plus yeast is superior to yeast alone in improving the quality of life of the patients. This study is of interest, as Panax ginseng has been used as a tonic in traditional Chinese herbal medicines for thousands of years.[134] The ginseng root contains numerous identified ginsenosides that are likely to be the active ingredients.[40] Effects have been associated with the ginsenoside Rb1, a neuroprotective molecule that has been shown to increase neural proliferation and differentiation of progenitor cells in the dentate gyrus of the hippocampus.[40]

In China, extracts from the leaves of Ginkgo biloba have also been used therapeutically for centuries.[135] It is reported that the Ginkgo leaf extract contains terpene lactones and flavonoids that may be involved in pharmacological effects supporting cerebral blood circulation.[22] In an open 8-week clinical trial conducted in 10 veterinary practices, Reichling et al. assessed the efficacy of Ginkgo leaf extract in reducing behavioral disturbances in 42 elderly dogs with cognitive decline.[22] The severity of the geriatric condition and overall efficacy rate were based on 6 protocol determined clinical signs. Study findings demonstrated that 5 of the 6 signs were significantly improved: disorientation, sleep and activity changes, behavioral changes, general behavior, and general physical condition ($p = 0.003$, $p = 0.0004$, $p = 0.02$, $p = 0.01$, and $p = 0.0002$, respectively). The overall severity of the geriatric condition in the patients was significantly reduced, with a positive effect apparent at 4 weeks ($p = 0.0002$). In this assessment, 15 (36%) of the patients were free of clinical signs at the end of the treatment period, and overall efficacy of treatment was good or very good in 79% of the dogs, as judged by the investigator. No serious side effects related to the Ginkgo extract were seen in the patients. The study concluded that Ginkgo leaf extract as a dietary supplement appears to be safe and effective in the treatment of elderly dogs with cognitive disturbances and may considerably increase their quality of life.[22]

In this systematic review, there are limitations to consider. First, the intention of the study was to assess the effectiveness of TCVM in treating patients with CCD. After an extensive literature review, very few clinical trials on this topic could be identified in the veterinary field. As a result, the assessment was based on Alzheimer's studies, as the human and veterinary patients share a similar pathology. Second, various traditional Chinese medical therapies were included in the analyses, and specific treatments were not assessed. Finally, an assessment of study quality was performed using the Jadad scale. In this scale, the placebo-control studies showed a median score of 4, indicating that the studies may be classified as good quality and adequately reported overall. The median Jadad score decreased to 3 in the conventional treatment-control studies and down to 2 in the integrated studies. The decreased quality as estimated by the Jadad score in these latter 2 study categories may be associated with the difficulty of blinding AP treatments in these groups.

Table 6: The incidence of Chinese herbal medicines with statistical significance of efficacy in more than one study

Chinese Herbal Medicine	Statistically Significant Studies	Non-Statistically Significant Studies
Ginkgo biloba	4	1
Tiao Xin	2	2
Huperzine A	4	1
Yi Zhi Jian Nao	4	1
Bu Shen Yi Sui	2	1
Wen Pi Tong Luo Kai Qiao	2	0
Hai She (Reinhartdt + sea cucumber)	3	1
Bu Shen Huo Xue Hua Tan	2	0
Bu Shen Yi Zhi	2	0

To provide new knowledge and a better understanding of CCD, studies with large samples, high quality designs, and accurate patient reporting are needed to support the findings of this systematic review. It would also be helpful to continue research on the mechanisms of action underlying the clinical improvement associated with AP and CHM treatment of cognitive dysfunction in animals. In a recent study, 2 aged dogs without clinical signs showed cerebral Aβ angiopathy, a lesion associated with early pathogenesis of CCD.[136,137] It is possible that the development of neuropathological lesions may precede clinical signs by a long period of time in the dog, as occurs in AD.[137] In some studies, it is suggested that $A\beta_{1-42}$ plasma level is a possible diagnostic biomarker, as the levels may differ in cognitively impaired and unimpaired dogs.[12,13,138] A recent study found that neurofilament light chain serum level, a central biomarker for neurodegeneration, may help in early diagnosis of CCD in elderly dogs.[16] In clinical practice, there is a need for concise, practical tests to evaluate canines for CCD and measure response to treatment in an objective way.[3,139]

In future studies on the efficacy of Chinese herbal medicine in treating CCD, it appears that Ginkgo biloba, *Tiao Xin*, huperzine A, *Yi Zhi Jian Nao*, *Bu Shen Yi Sui*, *Wen Pi Tong Luo Kai Qiao*, compound *Hai She*, *Bu Shen Huo Xue Hua Tan*, and *Bu Shen Yi Zhi* may be the most promising herbals based on the demonstration of effectiveness in human clinical trials in this study (Table 6).

In conclusion, the findings in this systematic review combined with the evidence in the literature for humans and dogs, support the idea that TCM is effective in the treatment of cognitive dysfunction with few side effects. It may also minimize the side effects of conventional medications.[78,109,140] These benefits may be helpful to lessen suffering and improve the quality of life of animal patients in their aging years. It is hoped that this study will lead to new knowledge and awareness of the potential benefits of TCVM therapy in treating CCD.

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FOOTNOTES

a. R version 3.5.2. The R Foundation for Statistical Computing, Vienna Austria; http://www.R-project.org

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