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A Randomized Controlled Pilot Trial of Chinese Medicine (Di-Tan Decoction) in the Treatment of Alzheimer's Disease

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Abstract

Objective: This double-blind, randomized, placebo-controlled, add-on pilot study aimed at providing information for conducting a full-scale trial assessing "Di-tan decoction" (DTD), which is a traditional Chinese medicine (TCM) formula frequently used in TCM to treat symptoms that are now defined as Alzheimer's disease (AD), in treating AD in the future.

Methods: We randomly assigned 38 patients with AD to receive either DTD or placebo for 24 weeks. Primary outcome was changes in the total score of AD Assessment Scale-cognitive subscale (ADAS-cog) and secondary outcome was changes in the total score of Chinese version of the Disability Assessment for Dementia (C-DAD).

Results: Although we observed some improvement in the total scores of ADAS-cog in the DTD group comparing to the placebo group, the changes were not statistically significant. The ADAS-cog sub-scores of the DTD group also showed non-significant trends of improvement in ideational praxis (p=0.100) and in comprehension (p=0.106) comparing to placebo group. Adverse events were mild and comparable between two groups.

Conclusion: This is the first rigorous randomized control trial of DTD focusing on AD. At least five factors could explain the failure of the trends to be significant, namely length of trial, size of trial, stage of AD, palatability of the drug, and sensitivity of the scoring system. Given the limitation but with the safety and century's use of DTD, a modified pilot study is needed to support the clinical effects of DTD. In conclusion, there is no evidence supporting the efficacy of DTD to act as a single treatment for AD.

Keywords: Alzheimer's disease; Pilot study; Randomized controlled trial; Di-Tan decoction; Chinese medicine; Efficacy; Safety

Abbreviations

AD: Alzheimer's Disease; Aβ: Beta-Amyloid-Peptide; ChEIs: Cholinesterase Inhibitors; TCM: Traditional Chinese Medicine; PTOO: Phlegm Turbidity Obstructing the Orifices; DTD: Di-Tan Decoction; Ach: Acetylcholine; ChAT: Acetylcholine Transferase; AchE: Acetylcholine Esterase; CONSORT: Consolidated Standards of Reporting Trials; NINCDS/ADARA: National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; CDR: Clinical Dementia Rating Scale; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive Subscale; C-MMSE: Chinese Version of Mini-Mental State Examination; C-DAD: Chinese Version of Disability Assessment for Dementia; AE: Adverse Event; LOFC: Last-Observation-Carried-Forward; MoCA: Montreal Cognitive Assessment

Background

Alzheimer's disease (AD) is an irreversible, progressive and fatal neurodegenerative disease. Biochemically, it is characterized by accumulation of beta-amyloid-peptide (Aβ) in the brain. Symptomatically it is manifested as cognitive and memory deterioration, progressive impairment of motor skills needed in the activities of daily living as well as a variety of neuropsychiatric symptoms and behavioral disturbances [1]. It is the most common type of dementia in the elderly and imposes a great economic stress on both individuals and society [2]. The prevalence of AD is about 2% for people aged 65-69 and up to more than 25% for people aged over 90 [3]. The global AD population is predicted to increase to 114 million by 2050 if there is no new preventive intervention [4].

Cholinesterase inhibitors (ChEIs) and memantine are the two major types of pharmacological treatment for AD. While these chemicals ameliorate symptoms, they do not stop or slow the progressive neural death and malfunction in the AD brain [5]. They are also associated with unwanted effects, such as nausea, vomiting, dizziness and anorexia [6]. Given that current medication cannot halt disease progression and has undesirable side effects, patients often seek alternative treatments [7].

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When described in terms of the principles of Traditional Chinese Medicine (TCM), AD is described as: (1) deficiency of vital energy of the kidney, heart and spleen; and (2) stagnation of blood and/or phlegm [8]. The guidelines for classifying dementia into different sub-types according to the TCM theory was published in 1990 [9]. Symptoms of "phlegm turbidity obstructing the orifices" (PTOO) (Additional file 1) is considered to be one of the major contributing factors to AD, and "resolving phlegm to open the orifices" is a primary TCM strategy for treating AD [10].

"Di-tan decoction" (DTD), a TCM formula, was developed by TCM doctor Dong Su in 1449 with the specific function of "resolving phlegm to open the orifices" [11]. It has been frequently used in TCM clinics to treat symptoms that are now defined as AD [12,13]. Some laboratory studies have shown a significant reduction in memory impairment of AD model mice treated with DTD [14,15].In the brain tissue of these mice, acetylcholine (Ach) and acetylcholine transferase (ChAT) were significantly increased, while acetylcholine esterase (AchE) was decreased [16]. The results of another study indicate that DTD may inhibit the decline of dopamine content in model mice brain tissue [17].

Nevertheless, our previous systematic review found no clinical trial studying DTD as the main intervention for treating AD. We did find AD clinical trials that had involved DTD as an intervention adjunct, but they were methodologically flawed. They not only lacked randomization, blinding and the use of control groups, but also failed to define inclusion and exclusion criteria and even the quality of the intervention medicine [18]. Thus, there is a lack of conclusive evidence for whether DTD can relieve AD clinically, and there is no basic information, such as sample size needed, for conducting a clinical trial assessing the value of DTD in treating AD.

In this double-blind, randomized, placebo-controlled, add-on pilot trial (ChiCTR-TRC-12004548, data of registration: 2012/11/21), we aimed to study the efficacy and safety of DTD in treating patients with AD. It is the first rigorous study of DTD focusing on AD, and it provides useful information for conducting a full-scale clinical trial if further study is warranted in the future.

Methods

Study design

As reported in our previous published study protocol [19], this study was a double-blind, randomized, placebo-controlled, add-on trial. Patients with mild to moderate AD were randomly assigned to a 2-week run-in period to fix their routine medication. Then they had received 24 weeks of active herbal treatment, DTD or placebo (in a 1:1 ratio) and followed for a further 6 weeks' observation period without treatment. It was carried out at the Hong Kong Baptist University Chinese Medicine Specialty Centre. It had been approved by the Ethics Committee of the Hong Kong Baptist University's Institutional Review Board (code: HASC/11-12/24). The study result was reported following the guidelines of Consolidated Standards of Reporting Trials (CONSORT).

Participants

Inclusion criteria: Adults were eligible for this study who (1) had been clinically diagnosed with AD based on the criteria of National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS/ADARA) [20] and (2) presented symptoms classified as PTOO (Additional file 1) as defined by the Guidance for Clinical Research of New Chinese Herbal Medicine [21] during a screening visit. They all had mild to moderate dementia with 0.5-2 on Clinical Dementia Rating Scale (CDR) [22] with normal liver and renal function as well as a stable medication history.

Exclusion criteria: Patients who had any other type of dementia (i.e., vascular dementia), and/or other neurodegenerative disorder (i.e., Parkinson's disease), depression (defined by a score of ≥ 8 on the 15-item Chinese version of the Geriatric Depression Scale [23]), or who were unwilling to cooperate with treatment procedures were excluded.

Study medication

The herbal medicine being studied was "Di-tan Decoction" (滌痰湯in Chinese), or DTD. It was composed of 11.42% Arisaema Cum Bile (DanNanXing膽南星 in Chinese), 11.42% Pinelliae Rhizoma (FaBanXia 法半夏 in Chinese), 9.13% Aurantii Immaturus Fructus (ZhiShi 枳實 in Chinese), 9.13% Poria (FuLing 茯苓 in Chinese), 6.84% Citri Reticulatae Pericarpium (ChenPi 陳皮 in Chinese), 4.55% Acori Tatarinowii Rhizoma (ShiChangPu 石菖蒲 in Chinese), 4.55% Ginseng Radix (RenShen 人參 in Chinese), 3.19 Bambusae in Taeniam Caulis (ZhuRu 竹茹 in Chinese), 2.29% Glycyrrhizae Radix (GanCao 甘草 in Chinese), 18.1% Zingiberis Recens Rhizoma (ShengJiang 生薑 in Chinese) and 19.36% dextin [11]. The placebo was made of caramel (2%), gardenia yellow pigment (0.05%), sunset yellow (0.02%), tartrazine (0.02%), dextrin (95%) and broad leaf holly leaf (2.91%) [24]. The DTD granules and the placebo granules had identical appearance and smell, and both were packed in sealed opaque aluminum sachets and put in zip lock bags (10 sachets each). All DTD and placebo granules were distributed by L.L. Chen with both written and verbal instructions for each participant. Patients were instructed to take the granules orally by dissolving a sachet of granules in 150ml hot water, stirring well, then drinking, two times per day, with at least two hours apart from taking any routine Western medication.

Recruitment procedures

All recruited patients diagnosed with AD were referred to a TCM doctor who is the Principle Investigator of the study (M. Li), or to a Research Assistant (K.K. Chua), for further assessment and recruitment. The aim, procedures, nature of study and possible side effects of DTD were explained by the PI or RA. Patients had to sign a written consent before they started the study treatment. They were informed they were free to withdraw at any time during the study.

Randomization and masking

The randomization sequence was generated by SPSS 19.0 package (SPSS, Chicago, IL) and password-protected and kept in a computer by L.L. Chen. Group allocation was simple randomization in a ratio of 1:1 to either active treatment group or placebo group. The number sequences was kept in sealed opaque envelopes and distributed to assessors. Patients, investigators and all sponsoring parties were masked to treatment allocation until the end of the study. When there was a serious adverse event, the event was discussed between the principal investigator TCM expert M. Li, and the co-investigator neurology specialist V. Mok to consider unblinding.

Outcome measurements and its assessment

The positive primary outcome of this study was a decrease [25] in the total score of Alzheimer's disease Assessment Scale-cognitive subscale (ADAD-cog) [26]. Increase in the total scores of the Chinese version of Mini-Mental State Examination (C-MMSE) [27,28] and Chinese version of Disability assessment for dementia score (C-DAD) [29] were used as secondary outcomes.

Outcome measurements were carried out during the study visits at weeks 0 (baseline), 12 (half of treatment), 24 (end of treatment) and 30 (end of observation period). Safety assessment, which included reporting of adverse events (AE), measurement of vital signs and physical examination, were carried out throughout the study. The laboratory safety screening of liver and renal function was performed at week 24.

A home diary was given to each study participant's caregiver to record treatment and changes in the participant's medical condition. Formal instruction for the home diary was given during the first visit. Revision and checking of the diary was carried out with the caregiver during each formal visit by the assessors. Compliance in taking the treatments was determined by the record of the diary and the number of the returned medicine / placebo packages.

Statistical Analysis

The differences of the total score between the measurement points and baseline in ADAS-cog, C-MMSE and C-DAD were compared between the treatment group and placebo group using the Chi-Squared test and independent sample t test, respectively. Post-hoc analysis of differences in the change of ADAS-cog and C-DAD sub-scores were also compared between the treatment group and placebo group.

To reduce the number of statistical comparisons, analyses were performed with a hierarchical approach. To begin, the change in total score of ADAS-cog at week 24 (end of treatment) for the treatment group and placebo group were compared. If the difference was deemed to be statistically significant at a 2-sided α-level of 0.1, the change of ADAS-cog total score at week 12 (half of treatment) and week 30 (end of observation period, i.e. without treatment) was compared between the treatment group and placebo group. Other outcome measurements were also analyzed in the same manner.

Missing data was input using the last-observation-carried- forward (LOFC) approach. All patients randomized with at least one post-randomization measurement were included in the primary analysis to follow the intention-to-treat principle. Analyses were done by SPSS 19.0 package (SPSS, Chicago, IL).

Results

Figure 1 is a flow chart depicting the participant screening and recruitment in this study. Demographic data and baseline scores are summarized in Table 1. A total of 66 patients were screened for eligibility, and 40 participants were enrolled between 1st December 2012 and 30th November 2014. Two patients withdrew from the study due to personal reasons after randomization and before the start of treatment. Among the remaining 38 patients (14 male; 24 female; mean ages 74.45 ± 9.01 years; mean duration of AD 2.32 ± 1.70 years), 21 were assigned to the DTD group, 17 to the placebo group. Six participants dropped out during the study due to reasons listed in Figure 1. Nineteen participants in the DTD group and 13 in the placebo group completed the study.

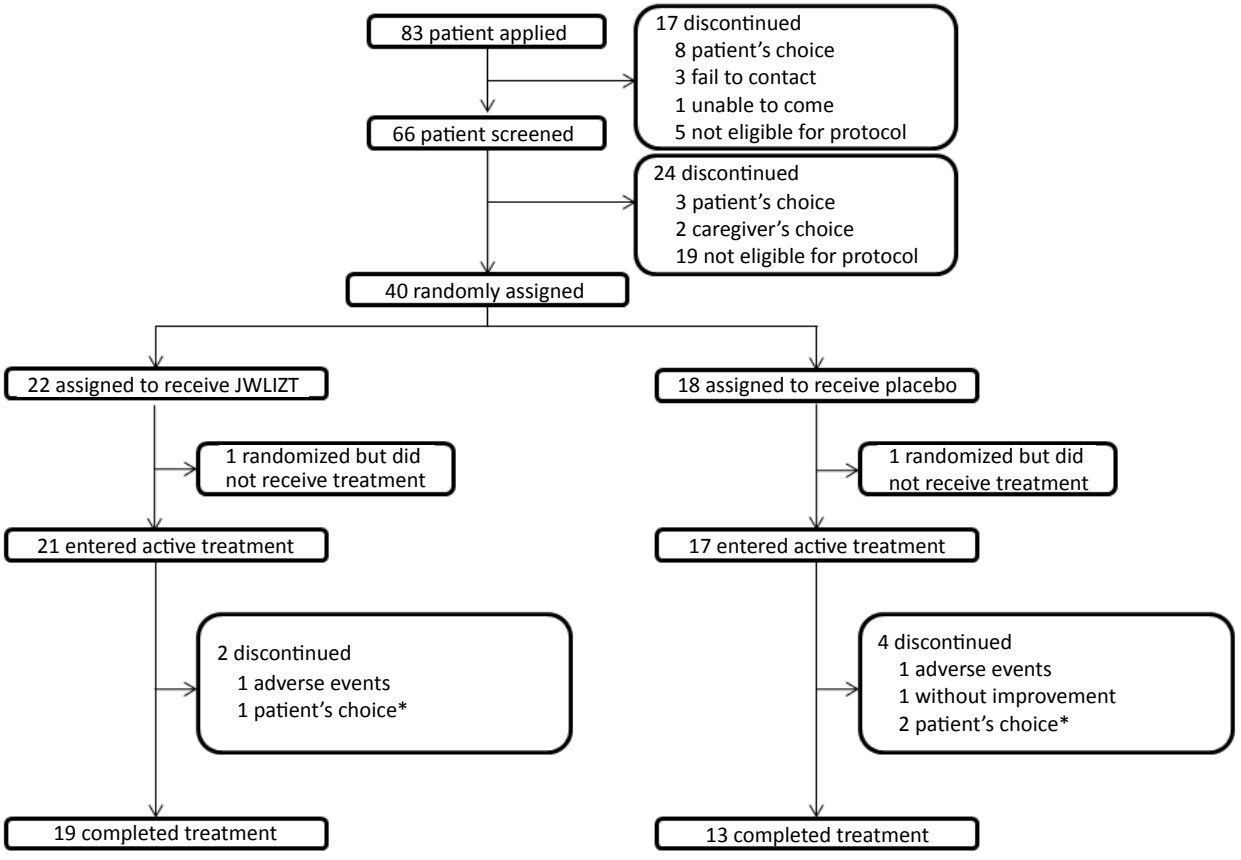

Figure 1: Patient's choice to discontinue for reasons unrelated to the study drug.

No statistically significant improvement (p=0.315, Table 2) was obtained in either group according to the primary outcome, i.e., the change in total score of ADAD-cog. However, we observed a trend of improvement, namely, a decreasing score at week 24 that suggests there may have been cognitive improvement in the DTD group compared to the control group (Table 2). Also, analyses of ADAS-cog sub-scores between the two groups reveals that the DTD group showed non-significant trends of improvement in ideational praxis (p=0.100) and

Parameter	DTD group (n=21)	Placebo group (n=17)	*p*-value[a]
Age (years)	76.57 ± 8.16	71.82 ± 9.55	0.107[b]
Gender (M/F)	8/13	6/11	0.859[c]
Disease duration (years)	2.58 ± 1.81	1.99 ± 1.54	0.290[b]
ChEIs, n (%)	16 (76.2)	15 (88.2)	0.341[c]
Memantine, n (%)	2 (9.5)	1 (5.9)	0.679[c]
Baseline scores			
CDR	1.05 ± 0.67	0.77 ± 0.40	0.134[b]
MMSE	17.43 ± 5.61	16.82 ± 4.88	0.728[b]
Systolic Blood Pressure	140.88 ± 18.35	145.68 ± 22.17	0.470[b]
Diastolic Blood Pressure	72.79 ± 9.73	74.27 ± 10.50	0.656[b]
Heart Rate	65.02 ± 8.48	68.06 ± 11.72	0.361[b]

Data are expressed as mean ± S.D
[a]*p*-value was comparing the difference between two groups in baseline
[b]treatment group compared with placebo group by independent t-test
[c]treatment group compared with placebo group by Chi-square test with continuity correction

Table 1: Baseline characteristics of AD patients in DTD group and placebo group.

Cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog)Table 1			
	DTD	**Placebo**	***p*-value**
Total Score	-2.05 ± 5.26	-0.59 ± 2.98	0.315
D1 Word recall task	-0.10 ± 0.94	-0.18 ± 1.24	0.820
D2 Naming objects and fingers	0.00 ± 0.71	0.24 ± 0.66	0.302
D3 Commands	-0.14 ± 0.79	-0.12 ± 0.60	0.914
D4 Constructional praxis: figures	-0.14 ± 0.66	-0.12 ± 0.78	0.914
D5 Ideational praxis	-0.19 ± 0.87	0.35 ± 1.12	0.1
D6 Orientation	-0.14 ± 1.24	-0.53 ± 1.13	0.325
D7 Word recognition test	-0.76 ± 3.03	-0.06 ± 1.25	0.377
D8 Remembering test instructions	-0.48 ± 1.47	-0.24 ± 0.83	0.551
D9 Spoken language ability	0.00 ± 0.32	0.00 ± 0.00	1
D10 Word finding difficulty	0.05 ± 0.38	-0.06 ± 4.3	0.425
D11 Comprehension	-0.14 ± 0.57	0.12 ± 0.33	0.106
Chinese Version-Disability assessment for dementia score (C-DAD)			
Total Score	3.35 ± 7.95	4.42 ± 12.91	0.755
D1 Hygiene	2.89 ± 9.76	3.78 ± 15.23	0.828
D2 Dressing	2.04 ± 10.39	4.20 ± 8.40	0.493
D3 Continence	1.59 ± 7.27	1.96 ± 8.08	0.882
D4 Eating	2.38 ± 10.91	1.47 ± 6.06	0.76
D5 Meal preparation	7.29 ± 20.17	-5.13 ± 32.90	0.222
D6 Telephoning	10.71 ± 29.95	6.25 ± 19.36	0.607
D7 Going on an outing	-2.58 ± 26.46	2.06 ± 17.24	0.54
D8 Finance and correspondence	1.75 ± 28.27	2.94 ± 34.48	0.91
D9 Medications	3.17 ± 17.97	11.11 ± 37.09	0.399
D10 Housework	-3.57 ± 17.79	8.33 ± 25.17	0.097
D11 Leisure	0.00 ± 55.28	4.76 ± 17.82	0.760
Chinese Version-Mini-Mental State Examination (C-MMSE)			
Total Score	0.86 ± 2.85	1.94 ± 3.09	0.269
Clinical Dementia Rating Scale (CDR)			
Stage	-0.24 ± 0.33	0.09 ± 0.26	0.268

[a]*p*-value was comparing the score changes at week-24 between DTD group and placebo group by independent sample t-tests
Values are given as mean ± S.D. Values in DTD group and placebo group are the score changed in the same group between week 24 and baseline (score at week-24 minus score at the baseline)

Table 2: Outcome of DTD group and placebo group at week 24.

in comprehension (p=0.106) compared to the placebo group (Table 2). Post-hoc analysis suggested that the improvement trend continued throughout the treatment period, and declined after DTD treatment stopped (Table 3 and Figure 2).

In the secondary analysis, there were no significant differences in the change of total score and sub-scores of C-DAD or C-MMSE at week 24 (Table 2). A trend of slowing the disease progress was observed in the DTD group in the CDR stage at the end of the whole trial; however, the change was not statistically significant (Table 3 and Figure 3).

As for withdrawal and adverse events, six patients (2 (9.5%) [DTD] vs. 4 (23.5%) [Placebo], p=0.239) discontinued treatment after randomization. Among these 6 patients, 2 withdrew because of AE (1 in each group). During the treatment phase, two patients (9.5%) in the DTD groups and two patients (11.8%) in the placebo group had serious AE: one patient had hyperglycaemia (placebo), one had skin rashes (placebo), one had cramp (DTD), and one fell (DTD). Liver and renal functions were normal in the two groups at the end of treatment. No deaths were recorded during the trial. AE were reported by at least 5% of patients in each group, as shown in Table 4. Nausea and vomiting may be a possible AE for DTD.

Parameter	Week 12		Week 24		Week 30	
	DTD	Placebo	DTD	Placebo	DTD	Placebo
ADAS-cog Total score	-0.81 ± 4.30	-1.00 ± 3.14	-2.05 ± 5.26	-0.59 ± 2.98	-1.90 ± 5.31	-0.12 ± 3.31
	p-value=0.880		p-value=0.315		p-value=0.235	
C-DAD Total score	2.68 ± 9.38	2.20 ± 12.99	3.35 ± 7.95	4.42 ± 12.91	1.85 ± 7.31	2.18 ± 11.08
	p-value=0.918		p-value=0.755		p-value=0.913	
C-DAD D10 Housework	-1.98 ± 24.14	-1.47 ± 25.72	-3.57 ± 17.79	8.33 ± 25.17	1.59 ± 23.07	0.98 ± 24.63
	p-value=0.950		p-value=0.097		p-value=0.938	
C-MMSE Total score	1.00 ± 2.88	1.71 ± 2.62	0.86 ± 2.85	1.94 ± 3.09	1.43 ± 2.06	1.35 ± 3.08
	p-value=0.439		p-value=0.269		p-value=0.929	
CDR stage	0.00 ± 0.16	0.03 ± 0.12	-0.24 ± 0.33	0.09 ± 0.26	-0.48 ± 0.31	0.06 ± 0.17
	p-value=0.532		p-value=0.268		p-value=0.214	

[a]p-value was comparing the score changes at different time point between DTD group and placebo group by independent sample t-tests
Values are given as mean ± S.D. Values in DTD group and placebo group are the score changed in the same group between different time point and baseline (score at different time point minus score at the baseline)

Table 3: Further analyses of the general condition throughout the whole trial.

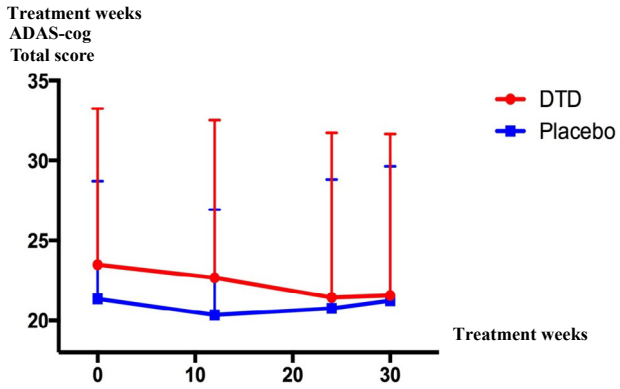

Figure 2: ADAS-cog total score throughout the whole AD trial.

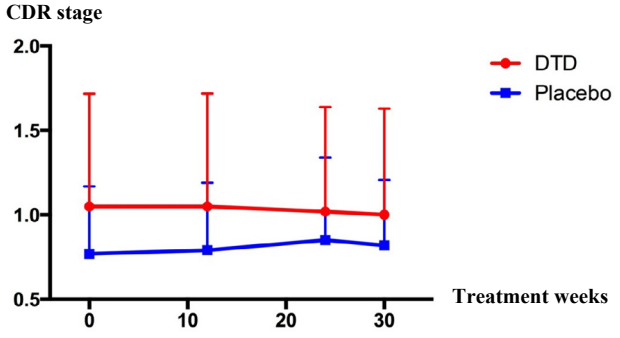

Figure 3: CDR stage throughout the whole AD trial.

Adverse events	No. of patients (%)	
	DTD (N=21)	Placebo (N=17)
Joint pain	1 (4.8)	4 (23.5)
Back pain	0 (0.0)	3 (14.3)
Skin rashes	2 (9.5)	2 (11.8)
Abdominal pain	1 (4.8)	2 (11.8)
Nausea and Vomiting	3 (14.3)	1 (5.9)
Diarrhea	1 (4.8)	2 (11.8)

Table 4: AE reported by >10% of AD patients in each group.

Discussion

In this study, results did not confirm the hypothesis that DTD improves the cognitive and daily activity including motor abilities of AD patients, as represented by the total score of ADAS-cog and total score of C-DAD. However, results did reveal a trend, which suggests an effect. A number of factors could explain the failure of this study to capture the beneficial effect of DTD.

Analyses revealed a trend of reduced cognitive impairment in the ADAS-cog total scores, and a trend of improvement in daily activity was suggested by C-DAD total score. Also, a trend of improvement in ideational praxis and comprehension is suggested by changes in the ADAS-cog sub score. Discontinuation due to AE occurred with the same frequency in the DTD group (1 patient) as in the placebo group (1 patient). DTD was well tolerated.

Although these trends suggest that DTD may be effective, this study has not fully captured its beneficial effect. Several factors could explain the failure to see significant results, as are described below.

Length of study

The most likely reason is the length of study. TCM works slowly in general. Its effect is gentler as well as more comprehensive compared to pharmaceuticals. Besides, AD is a slow, progressive disease; it may not be reasonable to see a protective effect, in a relatively short treatment period.

Sample size

The sample size in this study may have been too small to detect the effect of DTD. In fact, dementia patients in Hong Kong are much likely to present as a mixed dementia of AD and vascular dementia. It is difficult to recruit pure AD subjects. We should increase the sample size by either extend the recruitment period, or conduct in a multi-center design to increase the chance recruiting AD subjects.

Severity of AD

We aimed at recruiting mild to moderate AD patients, but most of the recruited subjects were only in mild condition. In fact, it is quite difficult to recruit AD patients in Hong Kong. AD patients must get the support and approval from their caregivers in order to participate in our clinical trial. As a number of moderate AD patients in Hong Kong have been sent to nursing homes, their caregivers often refuse to support them participating in an out-patient clinical trial. Future clinical trials carried out in a nursing home or hospital could be a possible way to recruit more moderate or even advanced AD patients.

Sensitivity of assessment tool

While some improvement trend in cognitive had been observed by ADAS-cog and CDR, it is strange that this trend was not supported by the total score of C-MMSE. C-MMSE is one of the most commonly used assessment tools for dementia; it is used as a standard measurement in most disciplines. It is doubtful that AD patients had already developed learning effect on C-MMSE even before they participated in our trial. This may have reduced the assessment accuracy of C-MMSE. A more sensitive, lesser used but valid cognitive assessment scale, like the Montreal Cognitive Assessment (MoCA) [30], could be used to replace C-MMSE in the future study.

Adverse events

For the AE, there were two more patients in DTD group (3 patients) who had nausea or vomiting compared to the control group (1 patient). All four patients complained about the bitter taste of the medicine. Although both the DTD granules and placebo granules had identical smell, they differed in bitterness and the tolerance of bitter differs among people. Thus, it appears worthwhile to try to make the taste of DTD more palatable. This may also reduce the AE of nausea and vomiting.

Conclusion

This randomized trial was the first rigorous testing of DTD for the treatment of AD patients. DTD was safely tolerated with few side effects. Although there were no significant differences in the primary and secondary outcomes, an improvement trend was observed throughout the trial, as revealed in chances in the ADAS-cog total scores, C-DAD total scores and CDR stages. At least five factors could explain the failure of these trends to be significant, particularly length of trial, size of trial, stage of AD, palatability of the drug, and sensitivity of the scoring system. Given the limitation but with the safety of DTD and its centuries of use in TCM, a further modified pilot RCT is suggested to retest the potential clinical effects of DTD in AD therapy. Currently, there is no evidence to support the efficacy of DTD to use as a single treatment for AD.

Declaration

We certify that we have each made a substantial contribution so as to qualify for authorship and that we have approved the contents.

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Availability of Data and Materials

The dataset supporting the conclusions of this article is included within the article and its Additional file 2.

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