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Evidence-Based Integrative Medicine

Effect of Zhizhu Kuanzhong Capsules (枳术宽中胶囊) on Treatment of Functional Dyspepsia: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT **Objective**: To evaluate the effect of Zhizhu Kuanzhong Capsules (枳术宽中胶囊, ZKC) for functional dyspepsia (FD) through meta-analysis. **Methods**: Online databases, including PubMed, EM base, China National Knowledge Infrastructure, Wanfang Data, VIP database and Cochrane Library, were searched for randomized controlled trials (RCTs) of ZKC for FD from the inception to April, 2016. Trials were selected according to inclusion criteria and were evaluated with quality assessment standards in the Cochrane Handbook for Systematic Reviews of Interventions and Jadad scale. RevMan 5.3 and GRADEprofiler 3.6 were used for statistical analysis and evidence quality assessment. **Results**: Twenty-three trials with 2,496 patients were included and most of them were of poor methodological quality. ZKC alone or ZKC combined with routine Western medicine (WM) showed a better clinical effect rate compared with the control group of WM [odds ratio (OR)=3.32, 95% confidence interval (2.66, 4.15), *P*<0.00001]. No serious adverse reactions were reported. **Conclusions**: ZKC alone or ZKC combined with routine WM could significantly improve the clinical effective rate in the treatment of FD. The quality of the evidence is low, so it is necessary to design multicenter, strictly randomized and double-blind controlled trials with large samples to validate the conclusions.

KEYWORDS Zhizhu Kuanzhong Capsules, functional dyspepsia, randomized controlled trial, meta-analysis, Chinese medicine

Functional dyspepsia (FD) is a common gastrointestinal disorder and affects as many as 21% of the population worldwide and 2%–24% of the Chinese population.[1] The Rome Ⅲ criteria for FD consist of a sensation of pain or burning in the epigastrium, early satiety, fullness during or after a meal, or a combination of these symptoms. Symptoms must be chronic, occurring at least weekly and over a period of at least 6 months, in the absence of an organic explanation.[2] Although the pathophysiology of FD is still not well identified, gastro-duodenal motility dysfunction, visceral hypersensitivity, psychological distress and *Helicobacter pylori* may play an important role.[3] *Helicobacter pylori* therapy, acid-suppression therapy, prokinetic agents and psychological therapy are used to treat FD, but the results may not be satisfied.[3] Zhizhu Kuanzhong Capsules (枳术宽中胶囊, ZKC) are widely used in the treatment of FD in China for more than 10 years and have favorable curative effects.[4] Therefore, this study was conducted to summarize current evidence and perform a meta-analysis of randomized controlled trials (RCTs) available to evaluate its curative effects and provide evidence for doctors treating FD with Chinese medicine (CM).

METHODS

Search Strategy

Online databases, including PubMed, EM base, China National Knowledge Infrastructure, Wanfang Data, VIP database and Cochrane Library, were searched from the inception to April, 2016 without any language restrictions. Search terms were "zhizhukuanzhong capsules/Zhizhu Kuanzhong capsules" and "functional dyspepsia".

Inclusion Criteria

Studies were considered eligible if they met the

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following criteria. (1) The study type was RCT. (2) Patients included in the study had a clear diagnosis according to the Rome Ⅲ diagnosis standards. (3) For intervention, studies must have an experimental group receiving ZKC alone or ZKC combined with routine Western medicine (WM) and a control group receiving WM. (4) For outcome measures, criteria for successful treatment-effective rate were clearly stated and the effective rate was measured according to the symptom scores. Efficacy index=(symptom scores before treatment–symptom scores after treatment)/symptom scores before treatment. The studies can have different criteria for judging the results effective or invalid according to efficacy index. Effective rate=number of patients with effective results/number of all samples.

Exclusion Criteria

Studies were excluded for the following reasons. (1) Clinical studies have no predefined outcome data. (2) Repeatedly published studies were excluded.

Data Extraction

Two reviewers independently reviewed the full text of the included studies and extracted data including the name of the first author, age of the participants, male-female ratio, adverse reactions, experimental duration, outcome measures and study outcomes. Disagreements were resolved by discussion and if a conclusion could not be reached, the opinion of a senior reviewer was needed.

Assessment of Methodological Quality

Included RCTs were strictly evaluated according to the Cochrane Collaboration's tool for risk of bias, which contains random sequence generation, allocation concealment, blindness, incomplete outcome data, selective outcome reporting, and other bias. Each research result was judged by these criteria using "low risk of bias", "high risk of bias", or "unclear." The modified Jadad scoring system was also used for quality assessment. Furthermore, GRADEprofiler 3.6 was used to access the quality of the evidence as high, medium, low or very low grades.

Statistical Analysis

The statistical package Revman 5.3 provided by the Cochrane Collaboration was used to analyze collected data. Odds ratios (ORs) were used for dichotomous data, with 95% confidence intervals (CIs). Heterogeneity of effects measurements among the selective studies was evaluated by the chi-squared test. Heterogeneity was presented as significant when I^2>50% and P<0.1, and a random effect model was used for meta-analysis. A condition of I^2≤50% and P≥0.1 was taken as evidence of almost no heterogeneity, the fixed effect model would be applied. Publication bias was evaluated by inspecting funnel plot and sensitivity analysis was performed to evaluate whether the statistical result was changed after exclusion of any single study.

RESULTS

Search Results

The study selection process is summarized in Figure 1. A total of 81 studies were retrieved from the above-mentioned electric databases, and finally 21 studies[5-25] met the inclusion criteria. All the 21 trials were only performed in China and were written in Chinese.

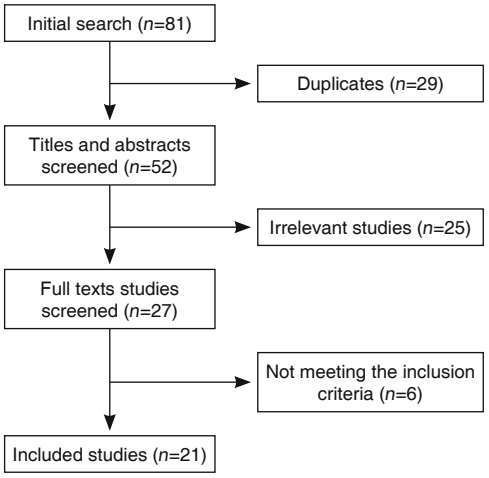

Figure 1. Study Selection Process of Zhizhu Kuanzhong Capsules on Functional Dyspepsia

Characteristics and Quality of Included Studies

According to the interventions of the experimental group, ZKC alone and ZKC combined with routine WM, the articles could be divided into 2 groups. Chang, et al[8] and Guo, et al[12] could go into both of the groups, so we had 23 trials. The characteristics and Jadad scores of the studies are listed in Table 1. The assessments on the quality of the individual study are shown in Figures 2 and 3. Most of the trials were of poor methodological quality and details of the trials were unclear.

Clinical Efficacy

All of the 23 trials reported total effective rates. Nine trials of ZKC compared with routine WM had

Table 1. Characteristics of the Studies

Author	Gender (Male/femal, case)	Age (Year)	Intervention		Duration (Week)	Adverse reaction	Jadad score	Judgment criteria of null efficacy index
			Treatment	Control				
Xu CP[5]	137/164	18–65	ZKC	Cisapride	2	Abdominal pain	3	<30%
Zhang CX[6]	123/102	21–59	ZKC	Domperidone	6	No	0	<25%
An B[7]	53/67	18–70	ZKC	Domperidone	4	No	1	<30%
Chang TM1[8]	30/30	41	ZKC	Pancreatin enteric coated tablets	2	No	1	<30%
Zhu M[9]	22/38	35	ZKC	Domperidone	3	Not mentioned	1	<30%
Deng Q[10]	74-83	18–65	ZKC	Domperidone	4	No	1	<30%
Qin B[11]	37/27	19–75	ZKC	Domperidone	4	No	2	<30%
Guo XH1[12]	34/46	14–77	ZKC	Mosapride	4	Not mentioned	2	<25%
Guan SS[13]	15/31	28–64	ZKC	Domperidone and neurostan	4	No	1	<50%
Feng JA[14]	44/42	15–59	ZKC and esomeprazole	Esomeprazole	2	Thirst and swirl	1	<50%
Zhang LF[15]	30/65	20–68	ZKC, amitriptyline and clebopride malate tablets	Amitriptyline and clebopride malate tablets	2	Stools frequency increased, thirst, sleepy	1	Not mentioned
Chang TM2[8]	30/30	41	ZKC and pancreatin enteric coated tablets	Pancreatin enteric coated tablets	2	No	1	<30%
Yang Y[16]	103/67	20–65	ZKC and amitriptyline	Amitriptyline	2	Not mentioned	1	Not mentioned
Yang JM[17]	25/35	44	ZKC and mosapride	Mosapride	2	Thirst and dizziness	1	Not mentioned
Lei JJ[18]	38/44	22–55	ZKC and omeprazole	Omeprazole	2	Stools frequency increased, abdominal pain	1	<50%
Wang X[19]	43/53	18–65	ZKC, flupentixol and melitrance	Flupentixol and melitrance	2	Diarrhea	1	<30%
Yuan F[20]	40/40	18–79	ZKC and domperidone	Domperidone	3	No	1	<30%
Zhao N[21]	54/48	24–64	ZKC, lansoprazole and alprazolam	Lansoprazole and alprazolam	4	Sleepy and thirst	2	Not mentioned
Lei MZ[22]	55/35	22–60	ZKC and trimebutine maleate tablets	Trimebutine maleate tablets	4	Diarrhea	1	Not mentioned
Men AH[23]	111/89	28–75	ZKC and domperidone	Domperidone	4	No	1	<50%
Zhang K[24]	25/35	41	ZKC and mianserin	Mianserin	4	Diarrhea and dizziness	1	<25%
Guo XH2[12]	30/50	14–77	ZKC and mosapride	Mosapride	4	Not mentioned	2	<25%
Wang YH[25]	59/73	20–70	ZKC and mosapride	Mosapride	4	Thirst	2	<30%

Note: ZKC: Zhizhu Kuanzhong Capsules

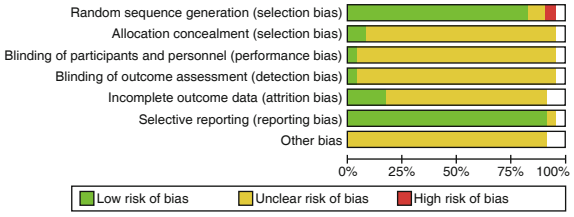

Figure 2. Risk of Included Studies

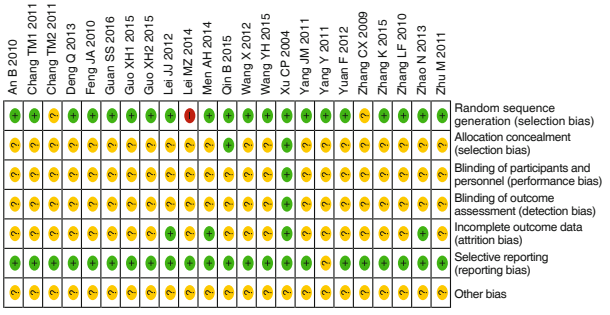

Figure 3. Risk Bias of Included Studies on Zhizhu Kuanzhong Capsules

moderate heterogeneity (P=0.08, I^2=43%). The fixed effect model was adopted for meta-analysis. Merged OR value was 2.56 [95% CI (1.84, 3.55), P<0.00001]. There was no heterogeneity of 15 trials of ZKC combined with WM compared with routine WM (P=0.92, I^2=0%), and therefore, the fixed effect model was used. Merged OR value was 4.16 [95% CI (3.09, 5.60), P<0.00001]. ZKC therapy was better than routine WM and there was a statistical significance in effective rate [OR=3.37, 95% CI (2.71, 4.20), P<0.00001, I^2=12%], no matter ZKC used alone or combined with WM. Figure 4 is the forest plot.

Sensitivity Analyses and Publication Bias

The result was not changed after exclusion of any single study. The meta-analysis is reliable.

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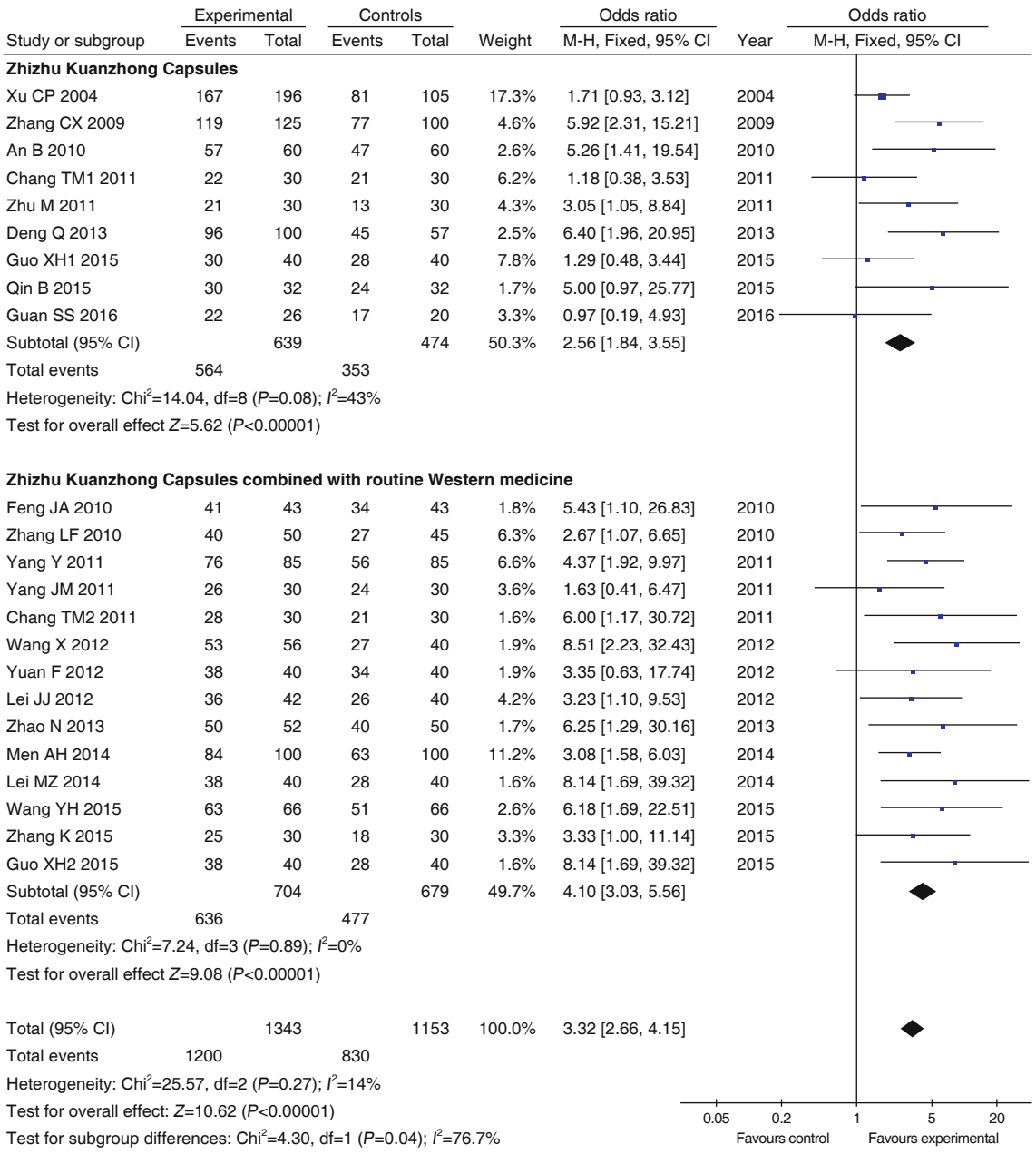

Figure 4. Meta-Analysis for Comparison of Effective Rate between Zhizhu Kuanzhong Capsules and Western Medicine

Publication bias was identified by the funnel plot (Figure 5). The results showed that included studies had little publication bias.

Quality of Evidence

The quality of evidence was low (Appendix 1). We had weak recommendation of ZKC for the treatment of FD.

DISCUSSION

FD includes the presence of symptoms originating in the gastroduodenal region with no evidence of structural disease explaining the

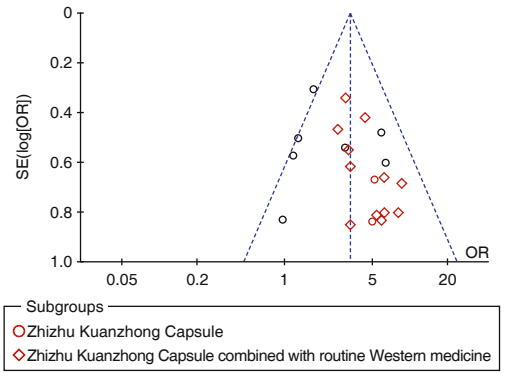

Figure 5. Funnel Plot of Effective Rate of Zhizhu Kuanzhong Capsules

symptoms, according to the Rome Ⅲ criteria.[2] FD reduces patients' quality of life and imparts a significant economic burden to families and the state.[26] However, the pathogenesis of FD is not fully understood, and prokinetic agents are still the most common medication, despite their unsatisfactory results. Nevertheless, ZKC could provide a new method for treating FD. This is a meta-analysis of ZKC RCTs for treatment of FD. The efficacy of ZKC on FD was measured by the total effective rate and symptom scores.

ZKC are based on the Zhizhu Decoction (枳术汤) from *Synopsis of the Golden Chamber* (Jin Kui Yao Lue). The frequently-used herbs were *Fructus Aurantii Immaturus*, *Rhizoma Atractylodis Macrocephalae*, *Radix Bupleuri*, *Crataegus pinnatifida* Bunge, of which the major effects are smoothing Gan (Liver) and regulating qi. This treatment aims to treat the syndrome of qi stagnation due to depression of Gan. Modern pharmacological studies have confirmed that *Rhizoma Atractylodis Macrocephalae* has a remarkable effect on enhancing gastric emptying and small intestinal transit speed in patients with FD.[27] *Fructus Aurantii Immaturus* can strengthen the time and intensity of smooth muscles contraction in rats.[28] In addition to enhancing gastric fluid emptying and small intestinal transit speed, *Radix Bupleuri* also have anti-anxiety and antidepressant effect.[29] *Crataegus pinnatifida* Bunge can increase the secretion of digestive enzymes and can enhance the activity of the enzymes.[30] Wang's study[25] showed that ZKC could elevate the level of gastric motility and substance P in plasma. ZKC has an anti-depressant effect and the mechanism may be related to that it inhibits the elimination of 5-hydroxytryptamine (5-HT) in hippocampus, increases the 5-HT content, and relieves the disorder of hypothalamic-pituitary-adrenal axis induced by stress.[31] A clinical study showed that the patients' Hamilton Depression Scales were reduced after the treatment of ZKC.[11] The subgroup analyses showed that ZKC alone or ZKC combined with routine WM showed a better clinical effective rate compared with the control group of WM. In addition to ZKC, alternative therapies such as acid-suppression, prokinetics, psychotherapy, and anxiolytics should also be considered after an individualized assessment for some patients. The combination of the medicine may have a better effect than ZKC alone and this need further studies to confirm. There were no obvious adverse reactions in both groups during the treatment period except light degree of abdominal pain, thirst, dizziness, stools frequency increased and diarrhea in few numbers of patients. These adverse reactions can disappear in few days without any medical intervention and have no difference between the experimental and control groups.

There were several limitations to our meta-analysis, which needed to be taken seriously when interpreting the results from this study. First, all trials were conducted from single center, which all influenced the reliability of this systematic review. And all studies investigating the efficacy of ZKC have been conducted in China. More studies from other parts of the world could help to confirm the efficacy of ZKC in other populations. Second, every study regarded symptom scores as a leading indicator of therapeutic effect. Although a symptom score scale was scientifically designed, it was still subjective and the scores might easily have been affected by the patients and researchers to some extents. And the judgment criteria of null were not consistent. Third, the duration of the studies was less than 6 weeks. According to the diagnostic criteria for FD, it is a chronic condition with symptoms that recur frequently over time. A shortened therapeutic period could impact the treatment and make it difficult to detect adverse reactions. The last limitation of our review is the low methodological quality. The reason for this may be because all of the studies were conducted in China. Some authors refuse to publish negative results, which also causes bias.

Future research should be conducted in multiple centers and more countries and be blinded to increase the quality of RCTs. For scientific research, the main outcome measures should be carefully considered to make the research more objective and conceivable. Future researches are also needed to investigate the long-lasting beneficial effects of ZKC to prevent the relapse of FD and long-term safety and tolerability profiles in large-scale, high-quality clinical trials. In summary, the results of this meta-analysis suggest that ZKC has therapeutic benefits for FD patients in terms of effective rate, with fewer adverse reactions. The evidence grade is low.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Wen MY, Zhang FC and Wang YJ conceived and designed this study. Wen MY performed the data extraction, analysis and

interpretation and wrote the initial draft. Zhang FC assisted with data interpretation. Wang YJ assisted with subsequent manuscript. All authors have read and approved the final manuscript.

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