



Review

Herbal medicine (Gan Mai Da Zao decoction) for depression: A systematic review and meta-analysis of randomized controlled trials



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ABSTRACT

The objective of this review was to analyze the trial data on the efficacy and safety of Gan Mai Da Zao (GMDZ) decoction for depression. PubMed, the Cochrane Library, and EMBASE, AMED, Korea Med, DBPIA, OASIS, RISS, KISS, CNKI, Wan Fang Database, and VIP were searched through to May 2014. Randomized controlled trials (RCTs) testing GMDZ decoction for any type of depression were considered. All RCTs of GMDZ decoction or modified GMDZ decoction were included. Data were extracted by 2 independent reviewers. Meta-analysis was used for the pooled data. A total of 298 potentially relevant studies were identified, and 13 RCTs met our inclusion criteria. All of the included RCTs had a high risk of bias across their domains. Three RCTs failed to show favorable effects of GMDZ decoction on response rate or HAMD score in major depression. One RCT showed a beneficial effect of GMDZ decoction on response rate in post-surgical depression, while another failed to do so. Two studies showed favorable effects on response rate in post-stroke depression, while another two failed to do so. A meta-analysis, however, showed that GMDZ decoction produced better response rates than anti-depressants in post-stroke depression (RR: 1.17, $I^2 = 15\%$). One trial failed to show any beneficial effects of GMDZ decoction on response rate or HAMD score in depression in an elderly sample. Two trials tested GMDZ decoction in combination with anti-depressants but failed to show effects on response rate in major depression, while another did show beneficial effects on response rate in post-stroke depression. In summary, our systematic review and meta-analysis failed to provide evidence of the superiority of GMDZ decoction over anti-depressant therapies for major depression, post-surgical depression, or depression in the elderly, although there was evidence of an effect in post-stroke depression. The quality of evidence for this finding was low, however, because of a high risk of bias.

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1. Introduction

Mental disorder is globally recognized as a major public health problem, but one that has been increasing in prevalence in developing countries. This is especially true of depression. Around world, more than 350 million people of both sexes and all ages suffer from depression [1,2]. Depression is defined as a state of depressed mood, loss of interest or pleasure, insomnia, fatigue, loss of energy, feelings of worthlessness or hopelessness [3,4]. According to the World Health Organization (WHO), depression will become the second largest disease burden after heart attack [5]. In addition, it has considerable financial costs for health services and for society [6]. Severe depression is associated with a high risk of suicide.

Anti-depressants are currently the most commonly used treatment for depression, due to their reported effectiveness. They include tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and atypical anti-depressant drugs, such as monoamine oxidase inhibitors (MAOIs). However, dry mouth, nausea, sexual dysfunction, headache, insomnia, daytime somnolence, agitation and weight gain are commonly reported side-effects, and lead some patients to cease treatment [7,8].

The use of complementary and alternative medicine by people with depression has been increasing [9]. Examples of complementary and alternative therapies include acupuncture, Chinese herbal medicine (CHM), aromatherapy, biofeedback, massage, and yoga [10]. There are fewer side-effects with complementary and alternative therapies than with anti-depressants and greater safety, bringing new hope to patients. In particular, CHM is widely used in East Asia. In recent years, several systematic reviews of CHM for the treatment of depression have been published [11–13].

Gan Mai Da Zao (GMDZ) decoction is a CHM that is widely used for depression in East Asia. Known as Ganmckdaecko-tang in Korean and kambakutaisoto in Japanese, GMDZ is known as an effective treatment for depression. It was first documented in the classic Chinese medical book *Jin Gui Yao Lue* (*Synopsis of the Golden Chamber*) by Zhang Zong Jing (AD 152–219) [14]. Zhang Zong Jing used GMDZ decoction to treat Zang Zao syndrome (a form of abnormal spiritual performance) [15]. GMDZ decoction includes extracts of three herbs: *Glycyrrhiza*, *Fructus Tritici*, and *Jujube*. It is a well-known Chinese herbal formula that has long been used for the treatment of depression. Many pharmaceutical companies manufacture GMDZ decoction to treat depression [16].

The mechanisms of GMDZ decoction are believed to include: significant inhibition of spontaneous motor activity and amphetamine-induced activity in mice [17]; reduction of fatal pentylenetetrazol-induced seizures in mice [18]; a lessening of stress-induced depressive-like behaviors associated with reduced glutamate levels; and increased N-methyl-D-aspartate receptor

subunits (NR2A and NR2B) in the frontal cortex and hippocampus [19].

Practitioners and patients have employed GMDZ decoction as an adjuvant therapy to reduce the required doses of anti-depressant drugs and the adverse events related to prolonged usage of anti-depressant and improving depression, as well as simply to improve outcomes. There has been one systematic review of GMDZ decoction [20]. This included 10 randomized clinical trials (RCTs) comparing GMDZ with conventional drug therapies. It suggested that GMDZ might be as beneficial as anti-depressants. However, it did not adopt an explicit search strategy; therefore, it is possible that not all of the relevant studies were located. Furthermore, the information provided on the included studies was incomplete. Thus, this systematic review failed to conduct a comprehensive analysis of the current evidence for GMDZ decoction in treating depression. We registered the protocol of the present systematic review in PROSPERO and published it in a peer-reviewed journal for transparency and consistency [21]. The aim of this article is to update and to evaluate completely and critically the current evidence from RCTs on GMDZ decoction as an anti-depressant.

2. Methods

2.1. Study registration

The protocol for this systematic review was registered in PROSPERO 2013 (registration number: CRD42013005100) [22] and the protocol was published [21].

2.2. Data sources

The following electronic databases were searched from their inception through February 2014: PubMed, the Cochrane Library, and EMBASE, five Korean medical databases (Korea Med, DBPIA, OASIS, the Research Information [RISS], and the Korean Studies Information Service System [KISS]), and three Chinese medical databases (China National Knowledge [CNKI], Wan Fang Database, and Journal integration platform [VIP]). We used following the search terms: (depression OR melancholia OR major depression OR post stroke depression OR postpartum depression OR involuntal depression OR climacteric depression OR senile depression) AND (gan mai da zao OR gan mai da zao tang OR ganmaidazao OR ganmaidazao tang OR ganmai da zao OR modified gan mai da zao OR modified ganmaidazao OR kambakutaisoto OR kambakutaisoto). Various combinations of the terms were used, depending on the database searched. No language restrictions were imposed. Only data available in complete papers were reviewed. A recursive manual search of the cited references in the published papers was conducted to identify other relevant trials. We conducted and

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