Efficacy of herbal medicine (Gegen Qinlian Decoction) on ulcerative colitis
A systematic review of randomized controlled trials

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Abstract
Background: This systematic review aims to evaluate the efficacy of Gegen Qinlian Decoction (GQD) for ulcerative colitis (UC).

Methods: PubMed, EMBASE, Springer LINK, Cochrane Library, the China National Knowledge Infrastructure, Chongqing Weipu Database for Chinese Technical Periodicals, Wan-fang Database, and Chinese Biomedicine Database were searched from their inception to December 2018 for randomized controlled trials comparing the use of GQD alone or in combination with western medicine (WM) with that of WM therapies for UC. Outcomes on the therapy’s effectiveness rate, ulcerative colitis endoscopic index of severity (UCEIS), recurrence rate, and adverse events were extracted and analyzed by Review Manager 5.3 software. Meta-analysis was combined with fixed or random-effects model, and risk ratios (RR) and 95% confidence intervals (CI) were calculated for all outcomes. Two researchers independently reviewed each trial to determine its inclusion. The Cochrane risk of bias assessment tool was used for quality assessment.

Results: We included 22 trials involving 2028 patients with UC. When compared with WM therapy, GQD significantly improved the clinical effectiveness (n = 591, RR = 1.21, 95% CI: 1.12–1.31, P < .0001) and recurrence rate (n = 94, RR = 0.23, 95% CI: 0.10–0.54, P = .0006). GQD plus WM was more effective in improving the clinical effectiveness (n = 1337, RR = 1.21, 95% CI: 1.16–1.27, P < .0001), and decreasing UCEIS scores (n = 384, mean difference = −0.63, 95% CI: −1.26 to −0.01, P = .05), recurrence rate (n = 179, RR = 0.18, 95% CI: 0.06–0.61, P = .006). In addition, the adverse events for GQD (n = 238, RR = 0.20, 95% CI: 0.02–1.68, P = .14) and GQD plus WM (n = 427, RR = 0.37, 95% CI: 0.15–0.90, P = .03) was significantly lower than that for WM alone. Noted adverse events primarily included gastrointestinal symptoms, headache, dizziness, and leukocytopenia.

Conclusions: This meta-analysis shows that GQD used alone or in combination with WM might have potential benefits in curing UC. However, there is no sufficient evidence to draw definite conclusion supporting the effect of GQD for UC due to poor methodological quality of the included trials. More rigorously designed investigations and studies with large sample sizes should be conducted to establish clinical evidence further.

Abbreviations: CI = confidence interval, GQD = Gegen Qinlian Decoction, MD = mean differences, RCTs = randomized controlled clinical trials, TCM = traditional Chinese medicine, UC = ulcerative colitis, UCEIS = ulcerative colitis endoscopic index of severity, WM = western medicine.

Keywords: Gegen Qinlian Decoction, inflammatory bowel disease, meta-analysis, ulcerative colitis

1. Introduction
Ulcerative colitis (UC) is a chronic idiopathic intestinal disorder with an unclear etiology, characterized by recurring episodes of mucosal inflammation restricted to the rectum and colon.[1] The typical manifestations of UC include bloody diarrhea, abdominal pain, and rectal urgency.[2] At present, the pathogenesis of UC is regarded as multifactorial, with genetic, environmental, and gut microbiome influences considered to play a role.[3] The incidence and prevalence of UC also differ by region, with a maximal annual incidence of 19.2 to 24.3 per 100,000 in Europe and
North America and only 6.3 per 100,000 in Asia and other developing countries.[14] UC has become a global disease, with an accelerating incidence in western countries and with rates in newly industrialized countries evidencing an even greater increase in incidence.[5]

Current conventional treatment for UC primarily includes amino salicylic acid, steroid hormones, and immune-regulatory medications, and it may help in maintaining partial remission for patients.[6-8] However, these therapies have poor long-term therapeutic efficacy, and even when medicated, patients with UC often remain chronically unwell and suffer from a high short-term recurrence rate.[9,10] In recent years, new biological agents have been shown to be effective in inducing remission in patients with moderate to severe active UC, even preventing the need for a colectomy in some cases.[11,12] However, considering the need for the long-term maintenance of UC treatment, the high financial cost of these biological therapies is a barrier for many patients.[13] Thus, conventional therapies alone may not fully meet the needs of UC patients. A long-term strategy for managing or even slowing the progression of UC with minimal complications remains to be developed.

Contemporary research has suggested that Chinese herbal medicines can be adopted as an auxiliary treatment for UC, with potential benefits including high efficacy and acceptability by patients, safety, and a relatively low associated financial cost.[10] According to the traditional Chinese medicine (TCM) theory, UC, which is a Yangming meridians’ disease, is categorized as Chang Pi (spouting bleeding from the anus).[13] Gegen Qinlian decoction (GQD), which stems from Zhang Zhongjing’s Treatise on febrile diseases, is a well-known Chinese medicinal formula that dates to the Eastern Han dynasty, during which it was used for approximately 2000 years. During this time, GQD was used for the management of the symptoms of infectious diseases such as pyrexia and diarrhea.[16] The Chinese medicine preparation of GQD consists of 4 Chinese medicinal herbs: Radix Puerariae (Gegen in Chinese), Radix Scutellariae (Huangqin in Chinese), Rhizoma Coptidis (Huanglian in Chinese), and Radix Glycyrrhizae (Gancao in Chinese).[17] Many clinical studies have shown that GQD alone or in combination with other therapeutics is widely used to treat UC across the Chinese mainland.[18,19] Experimental trials have further reported that GQD may successfully be used for the management of UC and gastrointestinal function and has anti-inflammatory and antibacterial properties.[20,21] However, only a small number of cases have been included in most clinical trials on this subject. Furthermore, there are no systematic evaluations of the efficacy and safety of GQD for the treatment of UC. Given this background, we conducted the present systematic review, which aimed to investigate the potential benefits of GQD for the management of UC.

2. Methods

2.1. Databases and search strategy

We searched all relevant articles published through December 2018 and available in the following electronic databases: PubMed, EMBASE, Springer LINK, Cochrane Library, the China National Knowledge Infrastructure, Chongqing Weipu Database for Chinese Technical Periodicals, Wan-fang database, and the Chinese Biomedicine Database. The search terms and text words were as follows: (“gegen qinlian” OR “gegen qinlian decoction” OR “gegen qinlian powder”) AND (“ulcerative colitis” OR “colitis” OR “colitis gravis” OR “ulcer colonitis” OR “inflammatory bowel disease”) AND (“randomized controlled trial” OR “random”).

2.2. Inclusion criteria

(1) Type of study: Only RCTs were considered eligible.
(2) Patients: Studies including individuals with UC or chronic UC diagnosed as per appropriate diagnostic criteria[22] and verified via colonoscopy and barium enema examination.
(3) Intervention: The experimental group in included studies comprised recipients of GQD alone or in combination with WM therapies. There was no distinction between an oral or enema-based route of treatment. If modified by the addition of Chinese herbal additives, GQD was determined to be the primary herbal medicine on the basis of TCM syndrome differentiation.
(4) Controls: patients received WM alone.
(5) Outcomes: The primary outcome was the total effectiveness rate of the given treatment, while secondary outcomes included ulcerative colitis endoscopic index of severity (UCEIS),[23] the recurrence rate, and adverse events.

2.3. Exclusion criteria

(1) Irrelevant studies,
(2) Literature reviews,
(3) Case and expert reports,
(4) Animal studies,
(5) Studies related to Crohn disease and other colitis diseases,
(6) GQD combined with other decoction(s), and
(7) Duplicate publications were excluded.

2.4. Literature selection and data extraction

On the basis of inclusion and exclusion criteria, 2 researchers independently reviewed all search results. Differences were resolved by a third party. Both researchers independently extracted data from the included studies. Data included author names, year of publication, study samples, interventional measures from experimental and control groups, efficacy evaluation indicators, treatment course, follow-up duration, and other methods.

2.5. Methodological quality assessment

The methodological quality of included studies was evaluated using the “risk of bias assessment tool” (Cochrane Handbook Version 5.3).[24] Evaluation metrics included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

2.6. Statistical analyses

Review Manager Software (Version 5.3) was used for data analyses. Z-tests and I² tests were applied to assess the overall heterogeneity of included studies. A fixed-effect model or random-effect model was used across all studies. When no statistical heterogeneity was detected among trials (P > .1, I² < 50%), a fixed-effect model was employed. If clinical/methodo-
logical heterogeneity was detected, a random effect model was employed. A pooled relative risk (RR) was assessed with a 95% confidence interval (CI) for dichotomous data. If continuous data were available, a weighted mean difference (MD) or standardized mean difference was calculated. Subgroup analyses were conducted to evaluate the robustness of results when heterogeneity was present. Bias was assessed via a funnel plot.

3. Results

3.1. Search results

The workflow followed for study selection is illustrated in Figure 1. A total of 142 articles were retrieved according to the search strategy and data collection methods detailed above. Per our inclusion and exclusion criteria, 22 primary studies with a total of 2028 participants were included in the final systematic review. All included studies were published in China. The basic characteristics of these included studies are shown in Table 1.

3.2. Quality evaluation of included articles

All of the 22 included RCTs reported no significant differences between experimental and control groups at baseline. However, only 5 studies used a randomization technique (e.g., random number table), while 1(33) used randomization based on registration order and 1(27) randomized according to the parity number. The remaining studies simply mentioned the term “random” within the text. Moreover, none of the 22 trials described double-blinding and/or allocation concealment, nor did they provide any information on drop-out or loss to follow-up, incomplete outcome data, selective reporting, or other biases. The risk bias assessment of methodological quality is shown in Figures 2 and 3.
3.3. Results of meta-analysis

3.3.1. Clinical effectiveness rate

3.3.1.1. GQD versus WM. Six trials\cite{30,37–39,43,44} including 591 patients were evaluated for the overall clinical efficacy of GQD for UC treatment. No statistically significant heterogeneity was detected among the 6 trials comparing GQD and WM alone ($P = .75, I^2 = 0\%$; Fig. 4A). The results of fixed effects modeling combined with effect sizes showed that the clinical effectiveness rate was significantly higher for the experimental group than for the control group (RR = 1.21, 95% CI: 1.12–1.31, $P < .00001$).

3.3.1.2. GQD + WM versus WM. In 15 studies\cite{18,19,25,26,28,29,31–36,40–42} comparing GQD plus WM and WM alone, no statistically significant heterogeneity was detected ($P = .99, I^2 = 0\%$; Fig. 4B).

Table 1

| Articles (yr of publication) | Male: Female | Sample size | Intervention | Outcomes measured | Severity of UC | Course of treatment/d |
|-----------------------------|--------------|-------------|--------------|-------------------|----------------|-----------------------|
| He (2013)                   | 34:26        | 32:28       | GQD          | Olsalazine        | Efficacy, Recurrence rate, UCEIS | Active | 30                     |
| Wang (2012)                 | 97:81        | 89:89       | GQD          | Sulfasalazine     | Efficacy, CRR, Adverse events | Not given | 14                     |
| Wang* (2013)                | 33:27        | 30:30       | Gegen Qinlian Wutan Decoction | Sulfasalazine | Efficacy, TSI, TNF-α, IL-6, IL-8 | Moderately to severely active | 40                     |
| Wang (2013)                 | 67:53        | 60:60       | GQD          | Sulfasalazine     | Efficacy        | Not given | 30                     |
| Yuan (2017)                 | 68:45        | 60:53       | GQD          | Sulfasalazine     | Efficacy        | Moderately to severely active | 45                     |
| Zhao (2012)                 | Not given    | 30:30       | GQD          | Sulfasalazine     | Efficacy, Recurrence rate, TSI, Adverse events | Moderately to severely active | 30                     |
| Bian (2015)                 | Not given    | 45:45       | GQD + Con    | Methalazine       | Efficacy, Clinical symptoms | Not given | 21                     |
| Chen (2017)                 | 55:45        | 50:50       | GQD + Con    | Sulfasalazine     | Recurrence rate, TSI, Adverse events, TNF-α, IL-10, IL-8, UCEIS | Not given | 30                     |
| Gao (2017)                  | 50:36        | 101:101     | GQD + Con    | Methalazine       | Efficacy, Adverse events | Not given | 30                     |
| Fang (2015)                 | 28:8         | 18:18       | GQD + Con    | Sulfasalazine     | Efficacy, Adverse events | Not given | 30                     |
| Huang (2015)                | 44:36        | 40:40       | GQD + Con    | Sulfasalazine     | Efficacy, Duration of symptoms | Active | 60                     |
| Li (2010)                   | 65:40        | 58:47       | GQD + Con    | Sulfasalazine     | Efficacy,     | Moderately to severely active | 84                     |
| Nong (2017)                 | Not given    | 39:40       | GQD + Con    | Bacillus subtilis | Efficacy, Recurrence rate, Adverse events | Not given | 30                     |
| Shen (2012)                 | 48:38        | 43:43       | GQD + Con    | Sulfasalazine     | Efficacy, Adverse events | Active | 28                     |
| Tian (2013)                 | 55:39        | 47:47       | GQD + Con    | Sulfasalazine     | Efficacy, Clinical symptoms | Mildly and moderately active | 60                     |
| Wang (2011)                 | Not given    | 45:45       | GQD + Con    | Sulfasalazine + hydrocortisone sodium succinate | Efficacy,     | Mildly and moderately active | 14                     |
| Xie (2007)                  | 28:21        | 29:20       | GQD + Con    | Aminosalicylic acid | Efficacy | Not given | Not given |
| Zeng (2017)                 | 35:25        | 30:30       | GQD + Con    | Sulfasalazine     | Efficacy, TSI | Moderately to severely active | 30                     |
| Wang (2014)                 | 40:22        | 32:30       | GQD + Con    | Sulfasalazine     | Efficacy, Clinical symptoms, UCEIS | Not given | 30                     |
| Xu (2017)                   | 72:54        | 63:63       | Gegen qinlian wutan decoction + Con | Methalazine | Efficacy, UCEIS, TNF-α, IL-6,IL-10, Adverse events, SOD, MDA | Mildly and moderately active | 60                     |
| Xu (2018)                   | 52:44        | 48:48       | GQD + Con    | Sulfasalazine     | Efficacy, UCEIS | Not given | Not given |
| Chai (2018)                 | 55:27        | 41:41       | Gegen qinlian wutan decoction + Con | Sulfasalazine | Efficacy, UCEIS | Not given | B          |

Con = control group, CRR = complete remission rate, DAI = disease active score, Ex = experiment group, GQD = Gegen Qinlian Decoction, TNF-α = Tumor necrosis factor-α, TSI = TCM symptom integrals, UC = ulcerative colitis, UCEIS = ulcerative colitis endoscopic index of severity.
Furthermore, the results of fixed effects modeling combined with effect sizes demonstrated that the clinical effectiveness rate was significantly higher for the experimental group than for the control group (RR = 1.21, 95% CI: 1.16–1.27, P < .00001).

3.3.3. Recurrence rate
3.3.3.1. GQD versus WM. Two trials compared the recurrence rates between GQD and WM alone,[30,44] with no significant heterogeneity in data (P = .29, I² = 9%; Fig. 6A). The results of fixed effects modeling combined with effect sizes confirmed a significant difference between the experimental and control groups (RR = 0.23, 95% CI: 0.10–0.54, P = .0006), with the experimental group outperforming the control group.

3.3.3.2. GQD + WM versus WM. With regard to studies comparing recurrence rates between GQD plus WM and WM alone, no statistically significant heterogeneity was detected between the 2 included trials[27,33] (P = .63, I² = 0%; Fig. 6B). The results of fixed effects modeling combined with effect sizes indicated a significant difference between the experimental and control groups (RR = 0.18, 95% CI: 0.06–0.61, P = .006), with the experimental group outperforming the control group.

3.3.4. Adverse events
3.3.4.1. GQD versus WM. Among studies[37,44] comparing adverse events between GQD and WM alone, 2 showed no statistically significant heterogeneity in data (P = 1.00, I² = 0%; Fig. 7A). The results of fixed effects modeling showed a significant difference between the experimental and control groups (RR = 0.20, 95% CI: 0.02–1.68, P = .14), with a significantly lower adverse event rate in the experimental group than in the control group.

3.3.4.2. GQD + WM versus WM. Among studies comparing adverse events between GQD plus WM and WM alone, 5[27,28,33,34,42] showed no statistically significant heterogeneity in data (P = .88, I² = 0%; Fig. 7B). When these 5 trials were analyzed, a significant difference was detected between the experimental and control groups (RR = 0.37, 95% CI: 0.15–0.90, P = .03), with the former showing a significantly lower rate than the latter.

In total, adverse events in gastrointestinal symptoms were mainly reported in 5 trials.[28,33,34,37,42] primarily including abdominal distention, nausea, emesis. Two trials reported leukocytopenia.[27,44] Headache and dizziness symptoms were also mentioned in 7 trials.[28,33,34,37,42] No serious side effects or abnormal laboratory parameters, including markers of liver and renal function, were reported. Treatment with WM alone was more likely to be associated with adverse side effects such as gastrointestinal symptoms, headache, and leukocytopenia.

3.3.5. Funnel plot analysis. A funnel plot analysis of the clinical efficacy of the assessed treatments including GQD versus WM and GQD + WM versus WM suggested that there was possibility certain publication bias in the literature included here and trials with negative results may not be published (Fig. 8). This result indicates the present analysis of clinical efficacy needs more high-quality literatures to identify.

4. Discussion
The present systematic review provided a quantitative synthesis of the clinical efficacy and safety of GQD for the treatment of UC significantly heterogeneous (P < .00001, I² = 96%; Fig. 5B). Given this, a random-effects model was applied, from which we concluded that changes in UCEIS significantly differed between the experimental and control groups (MD = −0.63, 95% CI: −1.26 to −0.01, P = .05).
Figure 4. Forest plot showing the clinical efficacy for ulcerative colitis. (A: GQD vs WM, B: GQD + WM vs WM). GQD = Gegen Qinlian Decoction, WM, western medicine.

Figure 5. Forest plot showing the effects of Gegen Qinlian Decoction and Gegen Qinlian Decoction plus Western medicine therapy on UCEIS in patients with ulcerative colitis. (A: GQD vs WM, B: GQD + WM vs WM). GQD = Gegen Qinlian Decoction, UCEIS = ulcerative colitis endoscopic index of severity, WM, western medicine.
by integrating outcomes from 22 clinical trials involving 2028 individuals with UC. The results of analyses demonstrated that the therapeutic efficacy of GQD alone or in combination with traditional WM may significantly better than that of conventional WM alone for the treatment of UC. These beneficial effects are evidenced by the facts that GQD had greater beneficial effects than did WM therapy, that GQD plus WM therapy significantly reduced UCEIS scores compared with WM therapy alone, and that GQD alone or in combination with WM therapy was effective in treating UC and maintaining low recurrence and adverse events. Notably, although GQD therapy appears to be more effective than WM therapy alone, only 1 trial[30] used a UCEIS score to define the patient response to treatment. Because there were only 60 patients in this trial, it does not allow us to draw a definitive conclusion. Given the limited number of available studies, the present systematic review attempted to offer an evidence-based approach to confirm that GQD may be a promising adjunct option for patients with UC.

UC, a chronic inflammatory bowel disease, degrades the patient’s quality of life because of its long duration, high recurrence rate, and wide range of associated pathological symptoms and clinical features.[45] However, because of its complexity, the underlying pathogenesis of UC remains unclear. One possibility, indicated by previous studies, is that susceptibility gene variants and environmental changes play a significant role in the pathogenesis of UC.[46,47] Furthermore, a hyperactive
mucosal immune response to intestinal microorganisms in genetically susceptible individuals with microbial dysbiosis and reduced microbial diversity has been shown to impact the development of inflammatory bowel disease. Sustained dysregulation of mucosal immunity, particularly in terms of pro-inflammatory cytokine overproduction and active inflammation, has further been implicated in the damage to intestinal mucosa seen in UC. All the time clinical symptoms and colonoscopy have been the vital diagnostic criteria used by physicians to evaluate the severity and extent of UC. Presently, the goal of UC clinical treatment also tends to mucosal healing. In this context, UCEIS scores were employed as an outcome, which is extremely useful for evaluating the efficacy of GQD for patients with UC. Present study showed that GQD plus WM therapy significantly reduced UCEIS scores may be associated with the pharmacological action of GQD.

Indeed, several studies have sought to shed light on the pharmacological aspects GQD’s role in UC treatment. Li et al reported that GQD relieved UC symptoms and repaired of intestinal epithelial barrier via the inhibition of Toll-like receptor 4/ Nuclear factor-κB signaling, which serves to suppress the production of pro-inflammatory cytokines (Interleukin IL-6, Tumor necrosis factor-α, IL-1β). And active components of GQD, such as puerarin, baicalin, glycyrrhizic acid, and berberine, exert broad antipyretic, antiviral, and anti diarrheal effects, which may further ameliorate the clinical symptoms of UC. In addition, the combination of pueraria, rhizoma coptis, and glycyrrhiza in GQD may drive the reconstruction and repair of colonic mucosa, according to endoscopic assessments.

Certainly, WM is still the mainstream drug for the treatment of UC, such as mesalazine, sulfasalazine, and adalimumab, which also play a vital role in anti-inflammation and regulation of immune apparatus. In this study, the combination of WM and GQD provided substantial benefit beyond that of WM alone, including low recurrence rate and adverse event. But unfortunately, a definite mechanism by which GQD and WM synergistically impact the progression of UC has not yet been described. Thus, we can only guess that, owing to the powerful pharmacological effects of GQD, it may alleviate these adverse events produced by long-term WM treatment and help patient tolerate the prolonged therapy to reduce recurrence rate.

Meanwhile, GQD, in TCM theory, is designed to regulate dampness-heat and its associated syndromes by restoring the conductive function of the large intestine. TCM has a long history of clinical application in Asian countries. In terms of TCM theory, “dampness-heat” serves as a main pathogenic factor underlying UC. Accumulation of dampness-heat in the gut may thus provoke qi stagnation and blood stasis, which in turn generates damage to intestinal mucosa, diarrhea, and purulent bloody stool. Theoretically, eliminating damp-heat and activating blood circulation using TCM techniques may thus heal diseased intestinal mucosa. And, GQD has served as a useful medicine for the treatment of UC for a long time. GQD is often modified with Chinese herbal additions based on the TCM syndromes a patient presents with. Given this, the exact mechanism by which GQD treats UC may involve multiple herbal formulations with various, integrative and synergistic effects.

Collectively, evidence from the present systematic review supports the use of GQD alone or in conjunction with WM therapies for the treatment of UC. However, the RCTs included in this systematic review do have several significant limitations. First, all were conducted in China, and no negative results were reported. Second, the included studies were of low methodological quality. The lack of practitioner and assessor blinding to the participant status likely affected the outcomes, which may have resulted in selection bias. Third, we were unable to assess variations in the composition or dosage of TCM or its route of administration among the included RCTs. These factors contribute to increased heterogeneity and further decrease the reliability.

5. Conclusion
The present systematic review suggests that the Chinese herbal medicine GQD and its use in conjunction with standard WM therapies may benefit in correcting clinical symptoms and promote endoscopic healing in patients with UC. In addition, GQD is associated with a low incidence of adverse reactions and UC recurrence rates. Despite these benefits, limitations exist. Before it was admitted as an evidence-based treatment option in clinical practice, there need more data to determine the pros and cons.

6. Implication on clinical practice
The result in this analysis suggest that the herbal compounds of GQD have a positive, therapeutic effect on UC. And GQD, as
complementary and alternative medicine treatment option, may serve as viable alternatives for the prevention and treatment of UC or as add-on approaches to existing conventional WM. Thus, in clinical practice, the development of a more integrative, individualized treatment approach should be widely promoted to improve the effectiveness of clinical treatment.

7. Implication on future research

The included studies in this system review were of low methodological quality, which reduced the recommendation level and the strength of evidence for systematic evaluation. Therefore, the future clinical research should note as follows.

(1) Randomization should be described in detail specific schemes (including methods for generating random sequences, etc).
(2) Concealment of allocation and blinding should be described in detail.
(3) Further methodological standardization of RCTs assessing TCM therapies, particularly with regard to the composition and dosage, is required.
(4) Future well-designed, large-scale, high-quality, multicenter RCTs are necessary for more reliable assessment of the research.

Author contributions
Conceptualization: Zhigang Mei. Data curation: Yuling Fan, Wen Yi, Han Huang. Formal analysis: Zhitao Feng. Investigation: Yuling Fan. Methodology: Zhigang Mei, Zhitao Feng. Writing – original draft: Yuling Fan, Wen Yi. Writing – review and editing: Zhigang Mei, Zhitao Feng. Zhigang Mei orcid: 0000-0002-9099-7099.

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