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Research Article

### EFFECTS OF CUSCUTA CHINENSIS LAM. VERSUS FLUOXETINE FOR TREATMENT OF MAJOR DEPRESSION: A DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL

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#### Abstract:

*Background: Depression is a common psychiatric disorder and a major worldwide health problem. Although several pharmaceutical agents are available for the treatment of depression, they are sometimes ineffective because patients cannot tolerate the side effects and stop taking their medication. Many herbs can play an important role in the treatment of psychiatric disorders with fewer side effects. Objective: To compare the efficacy of Cuscuta chinensis with fluoxetine in the treatment of major depression. Design and setting: Sixty-eight adult outpatients who met the criteria for major depression based on the structured clinical interview as defined by the Diagnostic and Statistical Manual of Mental Disorders (5<sup>th</sup> edition) participated in a six-week two-armed double-blind randomized controlled trial. Intervention: Patients were randomly assigned to receive C. chinensis or fluoxetine for six weeks. Outcome measures: Both groups filled out the Beck Depression Inventory (BDI-II) and a questionnaire to evaluate side effects at baseline and at 2, 4 and 6 weeks after onset of treatment. Results: The C. chinensis group recorded a significant decrease in BDI-II scores compared to the fluoxetine group ( $p < 0.001$ ). There were no significant differences between groups in terms of observed side effects; however, some complications were significantly lower in the C. chinensis group compared to the fluoxetine group. Conclusion: C. chinensis appears to have antidepressant properties with fewer side effects. This herb is effective and safe in the treatment of major depression and could be administered to depressed patients.*

**Keywords:** *Cuscuta chinensis; Major depressive disorder; Herbal medicine; Fluoxetine; Traditional Persian Medicine.*

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## INTRODUCTION:

### Background

Major depressive disorder (MDD) is a common mental disorder characterized by alterations in mood, cognition, thinking ability, appetite, sleep and psychomotor activity for at least two weeks [1-3]. Depression is a chronic, recurring and debilitating illness that has a significant effect on quality of life, including on the health, work, overall functioning, social and family life of the depressed person [4-6]. It is the fourth highest cause of disability globally, with over 150 million people estimated to be suffering from depression [7,8]. The World Health Organization (WHO) predicts that, by 2020, major depression will be the second most common risk for morbidity after cardiovascular disease [9].

MDD has the highest life time prevalence (almost 17%) of any psychiatric disorder and its prevalence in the general population is 3% to 10% [9,10]. MDD is twice as common among women as men [11]. Depression is a multi-factorial and complex disease, the etiology of which is not well understood. The pathophysiology of MDD includes at least three main categories: peripheral hormone-type factors, pro-inflammatory cytokines and dysregulation of the hypothalamic-pituitary-adrenal axis [10,12-14]. Recently, it has been suggested that an imbalance between the oxidative-anti-oxidative system and a decrease antioxidant status, plays important roles in the pathophysiology of MDD [15-18]. First line treatment choices include selective serotonin reuptake inhibitors (SSRIs) because they are effective, safe and can be tolerated. Among SSRIs, fluoxetine is most frequently prescribed for treatment of depressive disorder [8,19].

Although antidepressants can produce adverse reactions such as anticholinergic effects, orthostatic hypotension, nausea, constipation, sedation, arrhythmia, cardiac toxicity, weight gain or loss, sexual dysfunction and drug interactions [20-22]. Psychiatrists have found that some patients cannot tolerate the complications, do not respond adequately or stop taking their medication [23,24]. This highlights the need for effective, well-tolerated and less harmful agents for the treatment of depression.

Complementary and alternative medicine plays an important role in treatment of psychiatric disorders, including depression [25-27]. Most herbal products are fairly safe with fewer side effects and drug

interactions than chemical drugs such as antidepressants [28, 29]. *Cuscuta chinensis* Lam. (Convolvulaceae) is an important herb in traditional medicine. It has been used to improve liver and kidney function, treat sexual dysfunction, prevent miscarriages, improve vision and treat autoimmune and cardiovascular diseases [30,31]. Modern pharmacological experiments have demonstrated the different biological activities of this plant. These include hepato-protective, anti-cancer, anti-oxidation, anti-inflammatory and anti-aging effects. It has also show immunomodulatory activity and can enhance memory by inducing PC12 cell differentiation [32,33]. In traditional Persian medicine (TPM), *Cuscuta* (koshouth) has been used for neurologic and psychotic disorders, including depression.

To the best of our knowledge, only one clinical study on the antidepressant effect of *Cuscuta* in combined therapy with conventional antidepressants was conducted in 2014. This clinical study showed that *Cuscuta* could be a potentially effective herb in the treatment of depression [34]. Multiple TPM textbooks refer to the antidepressant effect of *C. chinensis*, but no evidence-based information has been found. The current study was undertaken to evaluate the antidepressant effect of *C. chinensis* Lam. as compared to fluoxetine in a six-week double-blind randomized trial.

## MATERIAL AND METHODS:

### Study design and patients

This study was a two-armed randomized double-blind clinical trial performed over a six-week period. It was conducted from July 2015 to April 2016 at Hafez Psychiatric Clinic at Shiraz University of Medical Sciences in the city of Shiraz in Iran.

Out patients who met the criteria for major depression as assessed by at least two psychiatrists based on Diagnostic and Statistical Manual of mental Disorders (5<sup>th</sup> edition; DSM-V) criteria and the Beck Depression Inventory (BDI-II) were asked to participate in the trial. The Persian translation of the BDI-II has been validated in previous studies.

The inclusion criteria were a diagnosis of MDD according to DSM-V criteria, age range 18-65 years, providing informed consent, no history of heart disease, renal disease, diabetes, hepatic disease, gastrointestinal ulcers, seizures and respiratory disease, no history of clinical disorders

that can simulate depression (i.e. hypothyroidism) and not being pregnant. The exclusion criteria were a current or past history of other psychiatric disorders, the diagnosis of a mental disorder or mental retardation, the use of a psychotropic medications for at least four weeks prior to the onset of intervention, addiction to drugs or alcohol, history of suicide attempts or significant suicidal ideation, history of allergies to any plant in the Convolvulaceae family, an allergy to SSRIs and the individual requiring electroconvulsive therapy.

All participants provided written informed consent forms and the protocol satisfied the Shiraz University of Medical Sciences Ethics Committee requirements (reference number: IR.SUMS.REC.1394.4) and was registered in the Iranian Registry of Clinical Trials (ID: IRCT2015060722584N1).

### Preparation of drugs

The fruits of *C. chinensis* Lam. have been purchased from local medicine herbal market in Tehran. The specimens are identified at the herbarium, department of Pharmacology, Tehran University of Medical Sciences (TUMS), Tehran - Iran, and kept under a voucher number PMP -374. Quality control of *Cuscuta chinensis* Lam., was done via total flavonoid analysis using HPLC in parallel investigation (Routinm, Hyperoside, Isorhamnetin, Kaempferol). As the *C. chinensis* is not heat resistance and its constituents will be destroyed so the formulation was prepared in a crude form. Total parts of the herbs were washed, dried, and then powdered.

*Cuscuta chinensis* capsules were filled up with 500 mg of *C. chinensis* powder and all the pharmaceutical controls were done. In parallel, fluoxetine capsules were filled up with 20 mg fluoxetine as same as the *Cuscuta* capsule in shape, color, size, texture and smell. The capsules were packed in the same container with a specific code number.

### Intervention

The patients were randomly divided in to the intervention group (*C. chinensis* group) and the control group (fluoxetine group) at a 1:1 ratio using computer-generated codes (block randomization). Both groups consumed one capsule per day for five days, which was then increased to two capsules per day. The patients in intervention group were given *C. chinensis* (500 mg BID) and those in the control group were given fluoxetine (20 mg BID) for six

weeks. The capsules were provided by a pharmacist; thus, the physician, patients and other investigators were all blind during the trial. Patients were not allowed to receive any other antidepressant drugs or behaviour therapy during the study. The patients were administered the Beck Depression Rating Scale at baseline and at 2, 4 and 6 weeks after onset of intervention. At the beginning of the study, the phone number of the responsible researcher was given to all patients and they were asked to contact the researcher if they experienced any side effects during the study or after stopping. Any possible side effects were evaluated with a self-report questionnaire completed by the patients. A mean decrease in BDI-II score from baseline was considered to be the main outcome.

### Complication and side effects

The patients were requested to advise investigators about any side effects or complaint during the study. Possible side effects were checked and registered at baseline and each visit.

### Randomization, blinding and allocation concealment

Block randomization was done by a statistician with Microsoft Excel. Patients were randomly allocated to 2 groups in parallel design. The allocation was done by the secretary of the clinic who was wanted to use a block randomization list consecutively. The researchers, physicians and the statistician were blind to assignments.

### Statistical analysis

The sample size was estimated by considering a one-side significance level of 0.05 ( $\alpha=0.05$ ), 0.2 ( $\beta=0.2$ ), 0.80 power (power=80%), 30 patients in each group. Results were presented as mean  $\pm$  standard deviation (SD) and the P value less than 0.05 was considered significant. The Chi-square test for statistical comparison of nominal variables in the baseline of the two groups was used. The repeated measure analysis of variance (ANOVA) for time-treatment interaction during the trial was used. The two groups as a between-subject factor (group) and the six weekly measurements during treatment as the within-subject factor (time) were considered. To compare the two groups at baseline and the outcome of two groups at the end of the trial, independent t-test was applied. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was used.

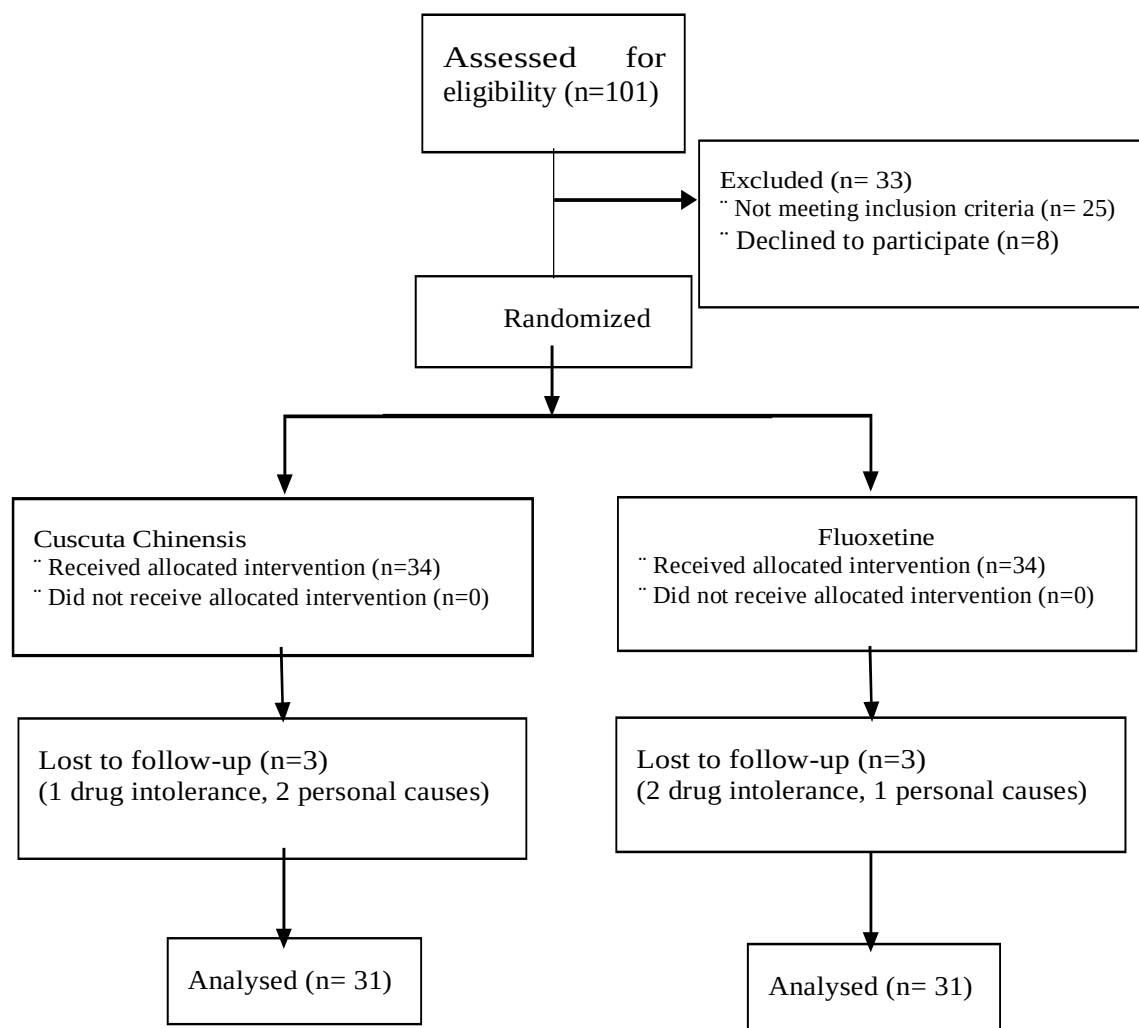
The SPSS software (version 22, IBM Corporation) was performed for data analysis.

## RESULTS:

### Demographic characteristics of participants

Among the 101 participants initially assessed for the

study, 33 were excluded because they did not meet the inclusion criteria. The remaining 68 patients were randomized in two groups. Six patients were unable to complete the trial; 62 patients successfully finished the study (Fig. 1).



**Fig.1: Consort flowchart of the trial.**

Baseline demographic and clinical characteristics are shown in Table 1. Among the 62 patients who completed the study, 43 (69.35%) were female and 19 (30.65%) were male. The mean age of the patients was  $39.78 \pm 11.64$  years. Of these, 16 patients (26%) were single and 46 (74%) were married, 37 (60%) were unemployed and 13 (21%)

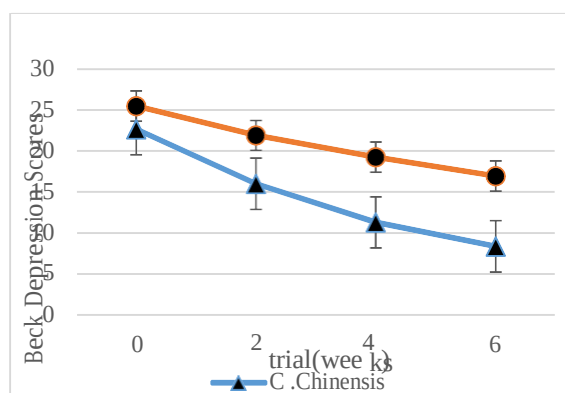
had not completed high school. There were no significant differences in the demographic characteristics of the patients between groups (Table 1).

Table1: Baseline demographic data of the patients in both study groups.

| Variable                | C.Chinensis % (n) | Fluoxetine % (n) | P    |
|-------------------------|-------------------|------------------|------|
| Age in years, mean ± SD | 39.35 ±11.38      | 40.22 ±11.89     | 0.61 |
| Weight ± SD             | 71.17 ±11.34      | 72.06±14.48      | 0.8  |
| Height ± SD             | 1.66 ±0. 09       | 1.66 ± 0. 09     | 1    |
| BMI ± SD                | 25.42 ± 4.06      | 24.16 ± 3.46     | 0.9  |
| Gender                  |                   |                  |      |
| Female                  | 67.70 (21)        | 70.09 (22)       | 0.9  |
| Male                    | 32.20 (10)        | 29.03 (9)        |      |
| Material status         |                   |                  |      |
| Single                  | 19.35 (6)         | 32.25 (10)       | 0.66 |
| Married                 | 80.64 (25)        | 67.74 (21)       |      |
| Job                     |                   |                  |      |
| Unemployed              | 67.74 (21)        | 51.61 (16)       | 0.39 |
| Employed                | 32.25 (10)        | 48.38 (15)       |      |
| Education               |                   |                  |      |
| Under diploma           | 22.50 (7)         | 19.30 (6)        | 0.86 |
| Diploma                 | 38.74 (12)        | 41.94 (13)       |      |

**Efficacy: chinensis versus fluoxetine**

The mean  $\pm$  standard deviation scores of the Beck Depression Inventory questionnaire of two groups of patients are shown in Fig. 2.

**Fig.2. Mean depression scores in 0, 2, 4 and 6 weeks of intervention in C. chinensis and fluoxetine group**

There were no significant differences between the two groups at the baseline on the BDI-II scores. Both groups showed a significant difference in the BDI-II scores during the study (groups-by-time interaction, Greenhouse–Geisser correction;  $F=6.90$ ,  $d.f.=3$ ,  $p<0.001$ ) (Table 2). The difference between the two groups was significant as indicated by the

effect of group as the between-subject factor (Greenhouse–Geisser correction;  $F=15.72$ ,  $d.f.=1$ ,  $p<0.001$ ) (Table 2, Fig.2).

In addition, a one-way repeated measures analysis of variance (ANOVA) showed a significant difference in the BDI- II scores during the study period in each group ( $p<0.001$ ) (Table 2)

**Table2: Mean depression scores in 0, 2, 4 and 6 weeks of intervention in C. chinensis and fluoxetine groups.**

| Time                            | C .Chinensis | Fluoxetin   | P value from ANOVA* |
|---------------------------------|--------------|-------------|---------------------|
| Base line (Mean ±SD)            | 22.67±7.11   | 25.48±9.56  | <0.001              |
| 2 <sup>nd</sup> Week (Mean ±SD) | 16.03±9.10   | 21.90±11.07 |                     |
| 4 <sup>th</sup> Week (Mean ±SD) | 11.32±9.54   | 19.25±10.61 |                     |
| 6 <sup>th</sup> Week (Mean ±SD) | 8.46±8.87    | 16.96±11.18 |                     |
| P value from ANOVA**            | <0.001       | <0.001      |                     |

\*P value of treatment-group interaction between two groups.

\*\*P value of treatment-time interaction in each group

Clinical complications and side effects No serious side effects was reported in the trial. There were no significant differences between groups in terms of observed side effects; however, some complications were significantly lower in the C. chinensis group

compared to the fluoxetine group. These complications included sexual dysfunction, palpitation, dry mouth, abdominal discomfort and decrease appetite (Table 3)

**Table3: Clinical complications and side effects were reported as number per group.**

| Side effects          | C. Chinensis | Fluoxetine | P       |
|-----------------------|--------------|------------|---------|
| drowsiness            | 4            | 9          | 0.076   |
| insomnia              | 1            | 1          | 1       |
| Headache              | 1            | 4          | 0.155   |
| sedation              | 1            | 0          | 0.312   |
| decrease appetite     | 0            | 4          | 0.032*  |
| Increase weight       | 2            | 3          | 0.857   |
| constipation          | 1            | 3          | 0.298   |
| Abdominal discomfort  | 1            | 6          | 0.038*  |
| diarrhea              | 2            | 1          | 0.554   |
| Sexual dysfunction    | 0            | 9          | <0.001* |
| Palpitation           | 0            | 7          | 0.002*  |
| respiratory complaint | 0            | 1          | 0.312   |
| Dry mouth             | 0            | 6          | 0.006*  |
| thirst                | 4            | 2          | 0.147   |

\*P ≤0.05 considered significant

**DISCUSSION:**

The aim of the study was to compare the effect of *C. chinensis* and fluoxetine for the treatment of depression. The experimental results showed that both drugs decreased BDI-II scores after six weeks of treatment, but the *C. chinensis* group recorded significantly lower BDI-II scores than the control group.

The findings indicate that oral administration of *C. chinensis* significantly improved depressive symptoms over that of fluoxetine treatment. The data showed that *C. chinensis* caused no serious adverse effects at therapeutic doses. No significant difference was observed between groups for the frequency of adverse effects; however, some side effects were significantly lower for the *C. chinensis* group. These included sexual dysfunction, palpitations, dry mouth, abdominal discomfort and decreased appetite.

To our knowledge, this is the first study examining the efficacy of *C. chinensis* versus a conventional antidepressant drug (fluoxetine) for the treatment of patients with major depressive disorder. In previous study we evaluated the effect of *C. planiflora* as an adjuvant therapy along with conventional antidepressant drugs for major depression. The results showed that *C. planiflora* was a potentially effective agent with which to treat 43 patients with depression [34]. In the current study, larger sample sizes of outpatients (62 subjects) were tested for six weeks. In previous study used *C. planiflora* (another species of *Cuscuta*) as adjuvant therapy versus conventional treatment with an unknown Pharmacological category. While *C. chinensis* is the main species which has commonly use in Persian medicine and there was no clinical investigation for this species. In the current study, participants were required to be free of all psychotropic medications for at least four weeks before the onset of the study.

The need for more effective and well-tolerated therapeutic agents for the treatment of depression has prompted researchers to study herbal medicines that have traditionally been used to treat mental disorders [35, 36]. In ancient Persian medical manuscripts, *C. chinensis* has been recommended by scholars such as Avicenna (980-1037 CE) and Rhazes (865-925 CE) for the treatment of psychiatric disorders, including depression [37,38]. Although a number of Persian medicinal plant textbooks refer to its antidepressant effects, no evidence-based document has been uncovered thus far.

The mechanisms of action for herbal medicines

used for treatment of psychiatric disorders involve modulation of neuronal communication by specific plant metabolites that bind to the neurotransmitter/neuromodulator receptors and stimulate or sedate CNS activity, regulating or supporting the healthy function of the expression of antioxidant system [28,39,40]. The active constituents in *C. chinensis* include flavonoids, lignans, cinnamic acid and polysaccharides [39,40]. These compounds have been suggested to be responsible for the pharmacological activity of the plant. Flavonoids are the main biologically-active constituents in *C. chinensis* [41]. Polyphenols and flavonoids have shown multiple pharmacological activities, including antioxidant, antineoplastic and antidepressant effects [42]. The polyphenolic and flavonoid contents of *C. chinensis* may be responsible for the antidepressant effect recorded in the current study. Although the role of *C. chinensis* in the treatment of depression has not been determined, some studies have suggested that oxidative stress may play an important role in the pathogenesis of neurological and psychiatric diseases such as depression [43,44]. Several studies have demonstrated that oxidative stress increases in depressed patients and have indicated a relation between a decrease oxidative stress and antidepressant treatment [15,17,45,46]. Onset of the therapeutic effect of the fluoxetine is known to be 4 to 6 weeks after onset of treatment. In the current study, the effect of *C. chinensis* manifested quickly, at two weeks. This is promising for treatment of depressed patients and further study is suggested to determine the efficacy of *C. chinensis*.

No serious adverse effects were observed in the current study. Sexual dysfunction (delayed ejaculation, reduced libido and lack of orgasm) is an important adverse effect of fluoxetine and has been reported to cause many patients to discontinue use of this medication [47]. There are no records of similar adverse effects for *C. chinensis*. In fact, it has been used to treat impotence and delayed ejaculation and to prevent miscarriages in China for thousands of years [48,49]. Improvement of sexual impairment also has been demonstrated in animal models [50,51]. The current study showed reduction of sexual dysfunction, palpitation, dry mouth, decreased appetite and abdominal discomfort in the *C. chinensis* group as compared to the fluoxetine group. These findings indicate a significant decrease in unwanted adverse reactions in the *C. chinensis* group. As stated, adverse reactions are known for current antidepressant drugs, such that patients may discontinue their use [52,53]. The use

of this natural, effective, less toxic and well-tolerated agent is suggested to avoid such unwanted adverse effects.

The current study was for a short period of time, but the experimental findings showed a decrease in depressive symptoms in patients and in the multiple side effects which have drawn researchers to investigate natural effective antidepressant agents.

Although the results of current study showed the efficacy of *C. chinensis* Lam. as an effective natural antidepressant, the study also had limitations that should be considered. The small sample size was one limitation. Sampling was restricted to a particular outpatient psychiatric clinic and did not have the large sample size that would be possible in some multi-centre studies. The short duration of follow-up was another limitation. Because MDD is a chronic and recurring disorder, it is also important to collect data about its long-term tolerability. The use of a fixed dose of the test drug could be considered another limitation of this study. The lack of a placebo control group was another limitation which means the possibility of spontaneous remission of depression cannot be excluded from the results.

### CONCLUSION:

The findings of this study indicate that *C. chinensis* may have antidepressant properties with fewer side effects over the short term. We recommend further studies conducted with larger sample sizes, longer trial periods and higher doses. Future trials also are required to determine the active components responsible for the antidepressant effect of *chinensis* and clarify the mechanisms of action of this effect.

### Conflict of interest

Authors of this manuscript have no conflicts of interest.

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