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## Effect of corosolic acid on postchallenge plasma glucose levels

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### Abstract

Corosolic acid (CRA) is a substance extracted from *Lagerstroemia speciosa* L. and has been reported to have biological activities in in vitro and experimental animal studies. In this study, 31 subjects were orally administered 10 mg CRA or a placebo, on different occasions, in a capsule 5 min before the 75-g oral glucose tolerance test (OGTT) in a double-blind and cross-over design. Nineteen subjects had diabetes, seven had impaired glucose tolerance, one had impaired fasting glucose, and four had normal glucose tolerance according to the 1998 WHO criteria. There were no significant differences in plasma glucose levels before and 30 min after the administration. CRA treatment subjects showed lower glucose levels from 60 min until 120 min and reached statistical significance at 90 min. In this study, we have shown for the first time that CRA has a lowering effect on postchallenge plasma glucose levels in vivo in humans.

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**Keywords:** Corosolic acid; Hypoglycemic effect; Double-blind study; Postchallenge; *Lagerstroemia*

### 1. Introduction

Corosolic acid (CRA) is a substance extracted from *Lagerstroemia speciosa* L. (Banaba) and has been reported to have biological activities in in vitro and experimental animal studies (Fig. 1A). In a study using KK-A<sup>y</sup> mice (a model of type 2 diabetes), elevation of

plasma glucose levels in the group fed with a diet containing the extract from the leaf of *L. speciosa* was significantly suppressed compared to the control group [1]. In studies using Ehrlich ascites tumour cells and 3T3-L1 cells, glucose uptake was stimulated by the extract from the leaf of *L. speciosa* [2,3]. Recently, Judy et al. described the anti-diabetic activity of the leaf extract (including 1% CRA) in humans in a dose-dependent manner [4]. It is known that the main content of the plant leaf extract is polyphenol, which has a blood glucose lowering effect. Screening of the compounds with blood glucose lowering activities

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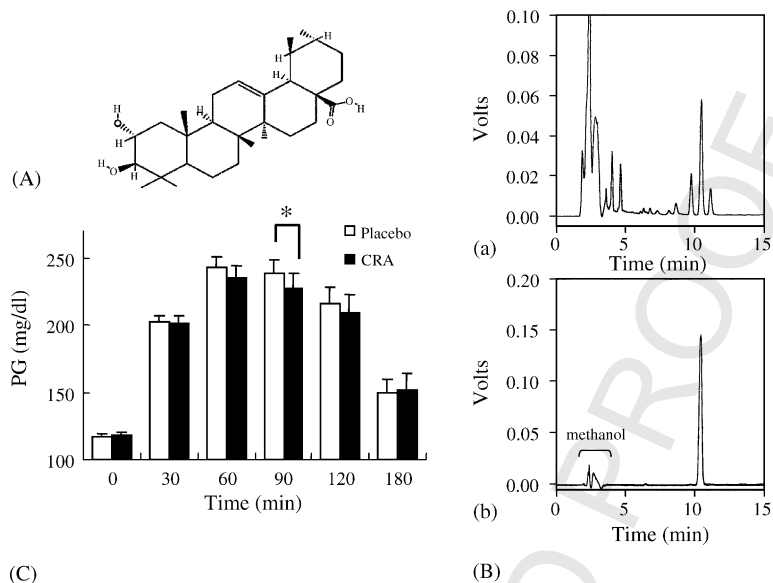


Fig. 1. (A) Structure of corosolic acid. (B) Purification of corosolic acid from *Lagerstroemia speciosa* leaf extract (HPLC chart). Before the purification, there were several peaks near the peak of corosolic acid (a). Single peak of corosolic acid was obtained after the repeated purification of HPLC (b). (C) Effect of corosolic acid on postchallenge plasma glucose levels. Open column represents placebo treatment and closed column CRA treatment. \*  $p < 0.05$ .

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from the crude extract of *L. speciosa* leaf elucidated lagerstroemin (a kind of polyphenol) as the fraction with glucose lowering activity, but it was not enough to explain the glucose lowering effect of the total leaf extract in vivo [5]. CRA is contained in the leaf of *L. speciosa*, but it is still unclear whether CRA per se has an effect on a glucose challenge in humans. In this study, we have clarified the effect of CRA on postchallenge plasma glucose levels in vivo in humans.

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## 2. Subjects and methods

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We examined the fasting plasma glucose (FPG) levels of 80 volunteers 2 weeks prior to the main study. The subjects who had hypertension, hepatic or renal disease, engaged in heavy exercise, or took any medication were excluded. Among them, 31 subjects (16 men and 15 women) had FPG levels between 110 and 140 mg/dl and were enrolled in this study. Thirty-one subjects were orally administered 10 mg CRA or a placebo, on different occasions, in a capsule 5 min before the 75-g oral glucose tolerance test (OGTT) in a double-blind and cross-over design. The interval between the CRA and placebo treatments was 7 days. CRA was extracted from the leaf of *L. speciosa* and was concentrated to a level of more than 99% after repeated high performance liquid chromatography (HPLC), as reported previously (Fig. 1B) [2]. Each 75-g OGTT was performed according to the National Diabetes Data Group recommendations, which require the subjects to fast overnight for 10–16 h [6].

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Plasma glucose and serum insulin levels were measured at baseline and 30, 60, 90, 120, and 180 min after the administration. Plasma glucose level was measured by the glucose oxidase method using a Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan) and the serum insulin level was measured by enzyme immunoassay (E test Tosoh 2, Tokyo, Japan) [7,8]. Statistical analysis was performed using the Stat-View 5 system (Abacus Concepts, Berkeley, CA) [9,10]. For comparison between the two treatments, paired *t*-test was performed, and  $P < 0.05$  was considered statistically significant. The data from OGTT was expressed as mean  $\pm$  S.E.M. The study was approved by the Ethics Committee of Soiken Inc. and was conducted in compliance with the Helsinki Declaration [11]. All subjects gave written informed consent.

## 3. Results

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The clinical characteristics of the subjects were as follows. Age: 51.6 (years)  $\pm$  5.8 (mean  $\pm$  S.D.), BMI: 24.7  $\pm$  5.3 ( $\text{kg}/\text{m}^2$ ), systolic blood pressure: 130.5  $\pm$  17.0 (mmHg), diastolic blood pressure: 77.5  $\pm$  11.0 (mmHg), total cholesterol: 215.7  $\pm$  36.3 (mg/dl), HDL cholesterol 55.1  $\pm$  14.0 (mg/dl), triglycerides: 125.3  $\pm$  64.2 (mg/dl), and HbA<sub>1c</sub>: 5.9  $\pm$  0.7 (%). Nineteen subjects had diabetes, seven subjects had impaired glucose tolerance, one had impaired fasting glucose, and four had normal glucose tolerance according to the 1998 WHO criteria [12].

As shown in Fig. 1C, there were no significant differences in plasma glucose levels before and 30 min

107 after the administration between the two treatments.  
 108 CRA treatment subjects showed lower glucose levels  
 109 from 60 min until 120 min and reached statistical  
 110 significance at 90 min (Fig. 1C). Area under the curve of  
 111 glucose (G-AUC) during the CRA treatment was lower  
 112 than the placebo treatment, but there was no significant  
 113 difference ( $25482 \pm 828.1$  versus  $24795 \pm 911.0$ ;  
 114 mean  $\pm$  S.E.M.). Serum insulin levels were signifi-  
 115 cantly higher at 30 min in CRA treatment subjects  
 116 compared with the control subjects ( $32.9 \pm 4.2$   $\mu$ U/ml  
 117 versus  $27.5 \pm 3.6$   $\mu$ U/ml), but there were no significant  
 118 differences in serum insulin levels at other time points.  
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#### 4. Discussion

120 In the present study, the CRA treatment subjects had  
 121 lower postchallenge plasma glucose levels at 90 min  
 122 than the placebo treatment subjects. Sixty minutes after  
 123 the challenge, plasma glucose levels began to show a  
 124 difference, and reached statistical significance at 90 min  
 125 (Fig. 1C). At 180 min, plasma glucose levels in CRA  
 126 treatment subjects returned to the levels of the control.  
 127 The mechanism by which CRA reduces postchallenge  
 128 plasma glucose levels is not known at present. The main  
 129 regulators of plasma glucose levels in humans are  
 130 insulin, glucagon, and somatostatin [13–15]. Gut  
 131 hormones such as GIP and GLP-1 also modulate  
 132 plasma glucose levels in response to glucose challenge.  
 133 It is well described that intake of polyphenols shows  
 134 glucose lowering effects by the inhibition of carbohy-  
 135 drate absorption. In a previous report, a negative  
 136 correlation was observed between glycemic index and  
 137 the concentration or total intake of polyphenols in both  
 138 normal and diabetic individuals [16]. Using human  
 139 intestinal cells, polyphenols were shown to decrease  
 140 glucose uptake [17]. We have examined the content of  
 141 an extract from the leaf of *L. speciosa* and detected a  
 142 large amount of polyphenols (water: 5.3%, protein:  
 143 1.2%, lipid: 6.3%, carbohydrate: 73.1%, dietary fiber:  
 144 2.1%, and polyphenols: 10.3%). Thus, it was considered  
 145 that the hypoglycemic effect of the crude extract from  
 146 the leaf was an additive result of polyphenols and other  
 147 factors [16–18]. In this study, we have focused on the  
 148 effect of CRA per se on postchallenge glucose levels.  
 149 The structure of CRA is very different from polyphenols  
 150 and other hypoglycemic agents as shown in Fig. 1A.  
 151 Further studies are necessary to elucidate the mechan-  
 152 ism of the hypoglycemic activities of CRA.  
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154 We have described the importance of postchallenge  
 155 hyperglycemia in the mechanism of developing glucose  
 156 intolerance in previous studies [19,20]. In a postchal-  
 157 lenge state, numerous factors regulate plasma glucose

157 levels positively and negatively with the combination of  
 158 these factors determining the plasma glucose levels. At  
 159 30 min after the glucose challenge, the CRA group had  
 160 higher insulin levels than the control group, a finding that  
 161 may explain the lower glucose levels at 90 min. To fully  
 162 elucidate the mechanism by which CRA lowers plasma  
 163 glucose, further analysis of discrete organs such as liver,  
 164 muscle, pancreas, and adipose tissue as well as dispersed  
 165 cultured cells will be necessary. We administered CRA  
 166 just before the glucose administration in the present  
 167 study, as for many of the hypoglycemic agents in clinical  
 168 use. It is of interest whether prolonged administration of  
 169 CRA controls blood glucose levels more effectively.  
 170 Pharmacological dynamics and strict dose dependence  
 171 between CRA and biological responses are also to be  
 172 clarified. In this study, we have shown for the first time  
 173 that CRA has a lowering effect on postchallenge plasma  
 174 glucose levels in vivo in humans.  
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