Ⅱ-36

Analgesic and anti-inflammatory effects of the leaf of *Ilex latifolia*

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Objectives

The aim of the present study is to investigate analgesic and anti-inflammatory effects of *I. latifolia* in *in vivo* and *in vitro.* Although inflammation is a kind of host defense mechanism against infection or injury, increased blood flow to the tissue by inflammation causes fever, redness, swelling and pain. In inflammatory responses, arachidonic acid is catalyzed to prostaglandins (PG) by cyclooxygenase (COX). COX exists in two isoforms of COX-1 and COX-2. COX-1 is responsible for maintaining normal physiological functions. In contrast, COX-2 induced by pro-inflammatory cytokines, which are synthesized in macrophages in response to injury or bacterial infection, is related with inflammation. PG itself does not produce pain but strongly enhance pain-producing effect of 5-hydroxytryptamine or bradykinin. *I. latifolia* has been used to treat various kinds of inflammatory diseases. Previously ethanol extract of *I. latifolia* showed neuroprotective effect through anti-oxidative and anti-inflammatory action in stroke and AD models. Thus it was hypothesized that *I. latifolia* may possess analgesic and anti-inflammatory effect which might be related to its neuroprotection on ischemic brain injury and memory impairment. The purpose of the present study is to investigate analgesic and anti-inflammatory effects of ethanol extract of the leaf of *I. latifolia*.

Materials and Methods

In the present study, chemical and thermal-stimuli, formalin-induced algesia test and acetic acid-induced writhing syndromes test, and tail flick test and hot plate test, respectively, were used to produce algesia and inflammation in mice. In addition, to elucidate the underlying mechanism, inhibitory effect of *I. latifolia* on LPS-induced NO production and expressions of pro-inflammatory mediators and cytokines were studied using RAW264.7 cell line, a mouse leukaemic monocyte macrophage cell line.

Results

Single administration of *I. latifolia* (50-200 mg/kg, p.o.) significantly inhibited delayed phase of formalin-induced pain and acetic acid-induced pain, but not immediate phase of formalin-induced pain and thermal stimuli-induced pain. The analgesic effect of ibuprofen, a COX inhibitor, was shown in the same way. These results suggest that *I .latifolia* could peripherally, but not centrally, inhibit PG-induced algesia.

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Pretreatment with *I. latifolia* (50 and 100 μg/ml) significantly inhibited LPS-induced nitric oxide production and mRNA expression of pro-inflammatory mediators, iNOS and COX-2, and pro-inflammatory cytokines, interleukin-1-beta and interleukin 6, in RAW 264.7 cell line. 3,5-Di-caffeoyl quinic acid methyl ester (5 μM), isolated from *I. latifolia* as an active compound, also significantly reduced the increase of the mRNA expression of pro-inflammatory mediators and cytokines induced by LPS in RAW 264.7 cell line. These results suggest that *I. latifolia* could produce analgesic effect via anti-inflammatory activity and this anti-inflammatory effect may be associated the neuroprotective activity.

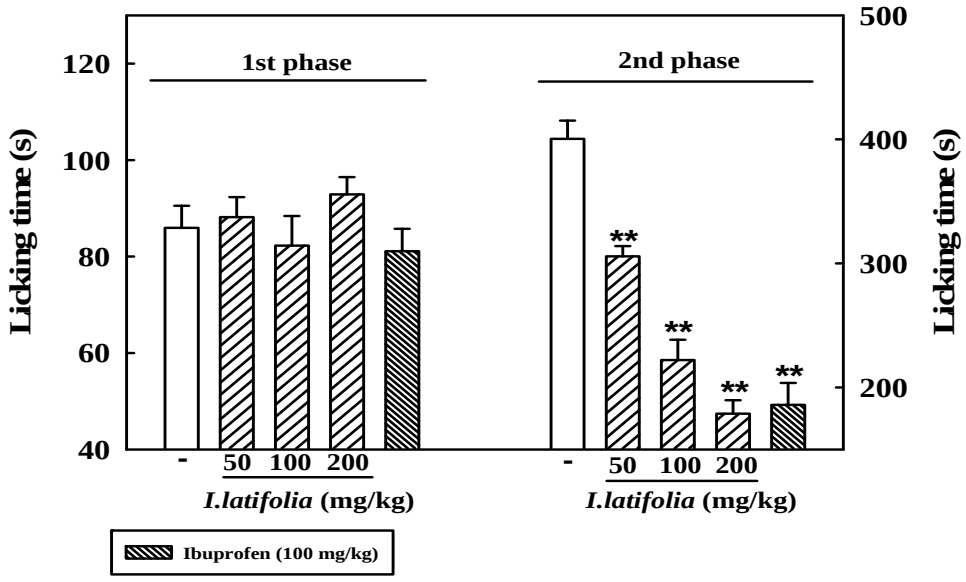

Fig. 1. Inhibitory effect of *I. latifolia* on formalin-induced paw licking in mice.