- Kampo-preparation -

TSUMURA Daikenchuto Extract Granules for Ethical Use

<table>
<thead>
<tr>
<th>Storage</th>
<th>Store in light-resistant, air-tight containers.</th>
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<tbody>
<tr>
<td>Expiration date</td>
<td>Use before the expiration date indicated on the container and the outer package.</td>
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### DESCRIPTION

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<tr>
<th>Composition</th>
<th>15.0 g of TSUMURA Daikenchuto extract granules (hereafter TJ-100) contains 1.25 g of a dried extract of the following mixed crude drugs and 10.0 g of JP Koi. JP Processed Ginger .......... 5.0 g JP Ginseng .................................. 3.0 g JP Zanthoxylum Fruit ............ 2.0 g (JP : The Japanese Pharmacopoeia)</th>
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<tr>
<td>Inactive ingredients</td>
<td>JP Magnesium Stearate JP Lactose Hydrate</td>
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<tr>
<th>Description</th>
<th>Dosage form Granules Color Light grayish white Smell Characteristic smell Taste Sweet and pungent ID code TSUMURA/100</th>
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### INDICATIONS
TJ-100 is indicated for the relief of abdominal cold feeling and pain accompanied by abdominal flatulence.

### DOSAGE AND ADMINISTRATION
The usual adult dose is 15.0 g/day orally in 2 or 3 divided doses before or between meals. The dosage may be adjusted according to the patient’s age and body weight, and symptoms.

### PRECAUTIONS
1. **Careful Administration (TJ-100 should be administered with care in the following patients.)**
   Patients with liver dysfunction [Liver dysfunction may be aggravated.]

2. **Important Precautions**
   (1) When TJ-100 is used, the patient’s “SHO” (constitution/symptoms) should be taken into account. The patient’s progress should be carefully monitored, and if no improvement in symptoms/findings is observed, continuous treatment should be avoided.

(2) When TJ-100 is coadministered with other Kampo-preparations (Japanese traditional herbal medicines), etc., attention should be paid to the duplication of the contained crude drugs.

SHO: The term “SHO” refers to a particular pathological status of a patient evaluated by the Kampo diagnosis, and is patterned according to the patient’s constitution, symptoms, etc. Kampo-preparations (Japanese traditional herbal medicines) should be used after confirmation that it is suitable for the identified “SHO” of the patient.

### Adverse Reactions
1) **Clinically significant adverse reactions**
   1. **Interstitial pneumonia** (incidence unknown): If cough, dyspnea, fever, abnormal pulmonary sound, etc. are observed, administration of this product should be discontinued, and examinations such as X-ray or chest CT should be performed immediately and appropriate measures such as administration of adrenocortical hormones taken.
   2. **Hepatic dysfunction and jaundice** (incidence unknown): Hepatic dysfunction, with increased AST (GOT), ALT (GPT), Al-P, and γ-GTP levels, and/or jaundice may occur. The patient should be carefully monitored for abnormal findings. Administration should be discontinued and appropriate therapeutic measures should be taken, if abnormalities are observed.

### Approval No.
(61AM)3299

### Date of listing in the NHI reimbursement price
October 1986

### Date of initial marketing in Japan
October 1986

### Storage
Store in light-resistant, air-tight containers.

###Expiration date
Use before the expiration date indicated on the container and the outer package.
PHARMACOLOGY

1. Enhancement of gastrointestinal motility
   (1) Oral administration of TJ-100 (7.5g) improved the transport ability of ascending colon in healthy American adults (n=19, scintigraphy)\(^3\).
   (2) Intragastric administration of TJ-100 enhanced the force and frequency of contractions of ascending colon, transverse colon and descending colon in dogs (Strain gauge transducer method)\(^4\).
   (3) Oral administration of Daikenchuto improved the chlorpromazine\(^5\)-or morphine\(^6\)-induced decrease in small intestinal and distal colonic transit in mice.
   (4) Daikenchuto induced contraction of the longitudinal muscle\(^7\) and suppressed contraction of the circular muscle\(^8\) in isolated guinea-pig ileum (*in vitro*).

2. Suppression of excess gastrointestinal motility
   Oral administration of Daikenchuto suppressed enhancement of small intestinal transit induced by carbachol in mice\(^9\).

3. Inhibitory effect on the development of ileus
   (1) Oral administration of Daikenchuto inhibited the delay of gastrointestinal transit in post-operative ileus in rats\(^9\).
   (2) Oral administration of Daikenchuto prevented intestinal adhesion induced by sprinkling talc on the small intestine in rats\(^10\).
   (3) Oral administration of Daikenchuto prevented the delay of intestinal transit induced by intraperitoneal injection of acetic acid in mice\(^11\).

4. Increase in intestinal blood flow
   Oral administration of TJ-100 (5.0g) increased the blood flow in superior mesenteric artery in healthy adults (n=14)\(^12\).

5. Secretion of gastrointestinal hormone
   (1) Oral administration of TJ-100 (7.5g) increased the plasma motilin concentrations in healthy adults (n=24) at 60 and 90 min. post-administration\(^13\).
   (2) Oral administration of TJ-100 (7.5g) increased the plasma concentrations of VIP and serotonin in healthy adult (n=6)\(^14\).
   (3) Oral administration of TJ-100 (7.5g) increased the plasma concentrations of calcitonin gene-related peptide (CGRP) and substance P in healthy adult (n=5)\(^15\).

6. Mechanisms of action
   Daikenchuto shows pharmacological effects via the following actions:
   (1) Enhancement of gastrointestinal motility
      - The improving effect of Daikenchuto on the decrease in small intestinal transit induced by chlorpromazine was suppressed by concomitant administration of atropine and a cholecystokinin-A (CCK-A)-receptor antagonist, lorglumide, to mice. The improving effect on distal colonic transit was also suppressed by atropine\(^5\).
      - Contractile effect of Daikenchuto on longitudinal muscle was suppressed by a 5HT\(_4\) receptor antagonist, high concentration of ICS205-930, but not by ondansetron (a 5HT\(_3\) receptor antagonist) in isolated guinea-pig ileum (*in vitro*).
Daikenchuto also enhanced the release of acetylcholine, and its contractile effect was suppressed by atropine or the concomitant application of atropine and a substance P receptor antagonist, spantide, in isolated guinea-pig ileum in vitro.

- Colonic motility induced by the intragastric administration of Daikenchuto in dogs was inhibited by the TRPV1 inhibitor, capsazepine.

(2) Suppression of gastrointestinal motility

Daikenchuto at low concentrations inhibited electrically-induced contraction but did not inhibit acetylcholine-induced contraction in the longitudinal muscle of a mucosa-free preparation of isolated guinea-pig ileum. It also inhibited contractions induced by KCl at high concentrations, and the inhibitory effect was reduced by pretreatment with CaCl2.

(3) Increase of gastrointestinal blood flow

- The increase of intestinal blood flow by Daikenchuto in rat was suppressed by a CGRP receptor antagonist, CGRP (8-37), and partially suppressed by a VIP receptor antagonist, [4-CI-DPhe6, Leu17]-VIP, and atropine, but was not suppressed by spantide.

- The increase in the small intestinal blood flow in rats occurred by intraduodenal administration of Daikenchuto performed under anesthesia was inhibited by the antagonist of TRPA1 receptor and anti-adrenomedullin antibody.

(4) Anti-inflammatory effect

- Daikenchuto increased in the production of ADM in IEC-6, rat small intestinal epithelial cell lines in the concentration-dependent manner (in vitro).
- Daikenchuto inhibited the production of inflammatory cytokines (TNF-α, IFN-γ) in colon of TNBS-induced inflammatory mouse model.
- Daikenchuto inhibited the cyclooxygenase (COX-2) activity (COX enzymatic activity assay kit, in vitro).

PACKAGING

Bottles of 500 g and boxes of 5 kg (500 g x 10 bottles)
2.5 g x 84 packets
2.5 g x 189 packets

REFERENCES