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Standard Commodity Classification No. of Japan
875200

■100■

- Kampo-preparation -

TSUMURA Daikenchuto Extract Granules for Ethical Use

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

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

Approval No.	(61AM)3299
Date of listing in the NHI reimbursement price	October 1986
Date of initial marketing in Japan	October 1986

DESCRIPTION

Composition	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)	
	Inactive ingredients	JP Magnesium Stearate JP Lactose Hydrate
Description	Dosage form	Granules
	Color	Light grayish white
	Smell	Characteristic smell
	Taste	Sweet and pungent
	ID code	TSUMURA/100

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.

3. Adverse Reactions[1)]

In a clinical survey of adverse reactions of 3,269 patients treated with TJ-100 (April 2010 - March 2012), 72 adverse reactions including abnormal laboratory values were reported for 64 patients (2.0%).

(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.

(2) Other adverse reactions

	Incidence unknown	5% > ≥0.1%	<0.1%
Hypersensitivity Note 1)			Rash, Urticaria, etc.
Hepatic		Abnormality of hepatic function [containing increased AST (GOT), ALT (GPT), Al-P and γ-GTP levels, etc.]	
Gstrointestinal	Abdominal pain	Nausea, Diarrhea	Enlarged abdomen, Epigastric distress, Vomiting

Note 1) If such symptoms are observed, administration should be discontinued.

4. Use in the Elderly

Because elderly patients often have reduced physiological function, careful supervision and measures such as reducing the dose are recommended.

5. Use during Pregnancy, Delivery or Lactation

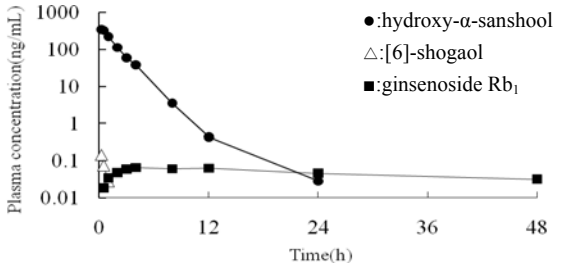
The safety of TJ-100 in pregnant women has not been established. Therefore, TJ-100 should be used in pregnant women, women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

6. Pediatric Use

The safety of TJ-100 in children has not been established. [Insufficient clinical data]

PHARMACOKINETICS

The plasma concentrations and pharmacokinetic parameters in healthy subjects after a single oral administration of 5 g of TJ-100 in the fasting state are shown below (n=16) [2].



	hydroxy-α-sanshool	[6]-shogaol	ginsenoside Rb_1
AUC(0-last)* (ng•h/mL)	658±223	0.0751±0.0571	2.27±0.839
C_{max}* (ng/mL)	391±136	0.142±0.109	0.0744±0.0229
$t_{1/2}$# (h)	1.71 (1.04-3.26)	0.312 (0.286-0.793)	41.0 (21.3-330)
t_{max}# (h)	0.258 (0.233-0.633)	0.242 (0.233-0.500)	4.02 (1.98-12.0)

n=16, *: average ± S.D., #: median (range)

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[8].

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 (CCKA)-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)*[7]. Daikenchuto also enhanced release of acetylcholine, and its contractile effect was suppressed by atropine[7] or the concomitant application of atropine and a substance P receptor antagonist, spantide[11], 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[4].

(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 $CaCl_2$ (*in vitro)*[8]**.**

(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-Cl-DPhe6, Leu17]-VIP, and atropine, but was not suppressed by spantide[16].

-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[17].

(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)[18].
- Daikenchuto inhibited the production of inflammatory cytokines (TNF-a、IFN-g) in colon of TNBS-induced inflammatory mouse model[18].
- Daikenchuto inhibited the cyclooxygenase (COX-2) activity (COX enzymatic activity assay kit, in vitro)[10].

PACKAGING

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

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Consumer Information Services Center
Tsumura & Co.
2-17-11 Akasaka, Minato-ku, Tokyo 107-8521, Japan
TEL:0120-329970 FAX:03-5574-6610

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