

## EXTRACT OF HERBAL AND THE COMPOSITION CONTAINING THE SAME

### TECHNICAL FIELD

This invention relates to one or more herbal extracts selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* and the composition containing the same for treating and preventing gastrointestinal motility disorder.

### BACKGROUND ART

Functional dyspepsia is not pathological or biochemical organic lesion but functional symptoms accompanied by continuous discomfort or pain in the upper abdominal area. Medically it means various symptoms associated with the continuous and repetitive discomfort or pain confined to the upper abdomen. Specifically non-ulcerative dyspepsia, one of the functional dyspepsia, includes all the symptoms of digestive system including satiety after a meal, anorexia, abdominal distention, an early sense of satiety, belching, discomfort or pain in the upper abdomen, brash, nausea, vomiting, gastric reflux, heartburn and others. Its pathophysiology is not clearly known yet (Panganamamula et al., *Functional(Nonulcer) Dyspepsia*, Current Treatment Options in Gastroenterology, 5, pp.153-160, 2002).

Functional dyspepsia is diagnosed based on various dyspepsia symptoms without apparent organic lesion, so cure is not simple and most symptoms alternate between improvement and deterioration affected severely by diet and stress. These pathological mechanisms act together manifesting one or usually multiple symptoms.

Representative functional dyspepsia treatment includes prokinetic drugs such as domperidone, metoclopramide, levosulpride, mosapride, itopride and erythromycin. As brash and ulcer are the representative symptoms of functional dyspepsia, gastric acid suppressant and antacid are used for the treatment but these including H<sub>2</sub> antagonist drugs usually have temporary efficacy (Vincenzo Stanghellini et al., Delayed Gastric Emptying in Functional Dyspepsia, Current Treatment Options in Gastroenterology, 7, 259-264, 2004).

Recently the development of new prokinetic agent is centered on serotonergic modulating drugs as serotonin(5-hydroxytryptamine, 5-HT) plays a central role in gastrointestinal peristaltic movement, and 80% of serotonin resides in gastrointestinal tract, especially 95% of

which is distributed in intra bowel secretion cells in the small intestine.

Specific agonist and antagonist drugs for 5-HT related receptors are being developed and 5-HT<sub>4</sub> agonist is under development as a cure for functional dyspepsia as well as constipation because it facilitates prokinetic action with increased gastric contractive force and propulsive pressure. 5-HT<sub>3</sub> antagonist is effective for suppressing vomiting and diminishing visceral hypersensitivity, and 5-HT<sub>1p</sub> agonist is being developed as functional dyspepsia cure for its relaxing mechanism in fundus ventriculi (Robin Spiller, *Serotonergic modulating drugs for functional gastrointestinal disease*, J Clin Pharmacol, 54, pp.11-20, 2002).

Specifically 5-HT<sub>3</sub> receptor antagonist, granisetron, reduces rectum sensitivity in irritable bowel syndrome patients, and ondansetron is not effective for irritable bowel syndrome patients but reduces vomiting and gastric sensitivity caused by expansion when fat goes into duodenum in healthy people. Cilansetron improves gastrointestinal sensitivity modulation and the adaptability of digestive duct for gastric expansion, blocks the excitable 5-HT<sub>3</sub> receptor associated with peristaltic movement, and raises jejunal fluid absorption. However tropisetron, ondansetron and most other 5-HT<sub>3</sub> receptor antagonists improve the gastrointestinal fasting delay symptom in rats but the effect is not conclusive in other species including humans.

Cisapride is one of the prokinetic drugs used effectively for cure of functional dyspepsia, is 5-HT<sub>4</sub> receptor agonist and 5-HT<sub>3</sub> receptor antagonist, and is recognized as having a statistically significant effect compared to other drugs. The response rate of cisapride is 50-82%, higher than the rate of placebo which is 27 – 53%, and it is reported to be effective in more than 70% of the cases when administered for 4 to 8 weeks. It is also reported that cisapride has efficacy for the concomitant disease of irritable bowel syndrome and also improves the symptoms of patients who do not respond to the cure using dopamine antagonist of levosulpride and domperidone. After it was approved as a drug for gastro-esophageal reflux disease in 1993, it led the market with an annual revenue of 40 billion (world market: 1.3 billion dollars) but in July 2000 its sales was banned.

On the other hand, another serotonin receptor 5-HT<sub>1 B/D</sub> agonist, triptans, is effective at the dose used for migraine for gastrointestinal movement and sensitive gastro-intestine. Sumatriptan is reported to delay emptying the gastric contents but its effect is known to improve the upper abdominal symptoms as it improves the modulation of fundus ventriculi and lowers the gastrointestinal expansion response in the actual functional dyspepsia patients.

5-HT<sub>4</sub> receptor agonist, which is one of the newly used prokinetic drugs for functional dyspepsia cure, improves the symptoms without increasing the tension at the fundus ventriculi.

Cisapride, one of the 5-HT<sub>4</sub> receptor agonist, is effective to facilitate stomach emptying, and as to the duodenum or intragastric pressure wavelength (>6 cm), the threshold value of recognizing gastric expansion is increased not only in patients but also in healthy humans as well. 5-HT<sub>4</sub> receptor agonist drugs include tegaserod and prucalopride but they are under clinical study and target disorders in the lower digestive system(Fraser RJ, Postprandial antropyloroduodenal motility and gastric emptying in gastroparesis - effects of cisapride, *Gut*, 35(2), p.172-8, 1994 ; Talley NJ., New and emerging treatments for irritable bowel syndrome and functional dyspepsia, *Expert Opin Emerg Drugs*, 7(1), p.91-8, 2002).

Meanwhile, Korean mustard of Sinapis Semen is the ripe seeds of Brassica juncea Cosson of the Cruciferae family, contains Sinalbin, Sinapine and fatty oil, and is effective to discharge phlegm and stimulate skin. (The Korean Pharmacopoeia V Part 2 pp453-454).

Corydalis Tuber is Corydalis ternata Nakai and other tuberous plants of the Papaveraceae family, contains Berberine, 1-Canadine, Protopine and 1-tetrahydrocoptisine, and has analgesic, sedative, antispasmodic, antiemetic and ACTH hyper-secretion actions. (The Korean Pharmacopoeia V Part 2 pp664)

Pharbitidis Seed s are the seeds of Pharbitis nil Choisy of the Convolvulaceae family, contain roughly 11% of fatty oil and 2% of pharbitin which is resinous glucoside, and are known to have easy defecation, diuretic and insecticidal effects. (The Korean Pharmacopoeia V Part 2 pp651).

Strychni Ignatii Semen is the seeds of Strychnos ignatii Bergius of the Loganiaceae family, contains Strychnine, Brucine, Vomicine, α-Colubrine, β-Colubrine and Loganine, and has CNS exciting, stomachic, antifungal, anti-inflammatory and analgesic effects. (Oriental Herb(galenicals) Standard Annotation, pp 175, The Korean Pharmacopoeia V Part 2 pp633-634)

However these galenicals have been used as oriental medicine mixed with other various herbs, so there has been no report on its specific prokinetic mechanism of action.

With the background, to identify the prokinetic herb that have the treatment and preventive effects for functional dyspepsia and irritable bowel syndrome, the inventor performed the activation test for 5-HT<sub>3</sub> and 5-HT<sub>5</sub> receptors which correspond to prokinetic trigger points and identified the candidate herb activating the receptors. Based on this, appropriate herb

extracts have been found through animal model experiments for functional dyspepsia.

Also, the inventor found that the herb extracts of this invention are 5-HT<sub>3</sub> antagonist facilitating antiemetic and gastric emptying, and suppressing visceral hypersensitivity, and are 5-HT<sub>4</sub> receptor agonist showing prokinetic and treatment effects for irritable bowel syndrome accompanied by constipation and chronic colitis. The invention was completed by confirming the fact that the herbs individually or in combination have the cure effect for functional dyspepsia and irritable bowel syndrome.

## DISCLOSURE

### TECHNICAL PROBLEM

The object of the present invention is to provide herbal extracts, and a composition containing the same as an active ingredient, for preventing and treating gastrointestinal motility disorder.

### TECHNICAL SOLUTION

The present invention provides one or more herbal extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*.

In the present, 'a herbal extract' means a herbal extract and/or a mixture of herbal extracts, if the herbal extract is not modified by the other words or phrases.

The present invention is explained in detail below.

The present invention provides a herbal extract of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*.

And, the present invention provides a mixture of two or more herbal extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*.

The present mixture includes a mixture of the herbal extracts of *Sinapis Semen* and *Corydalis Tuber*. Preferably, the mixture has the mixture ratio of the herbal extract of *Sinapis*

*Semen* : the herbal extract of *Corydalis Tuber* from 1: 1 to 10:1 by weight(w/w).

The present mixture includes a mixture of the herbal extracts of *Sinapis Semen* and *Pharbitidis Seed*. Preferably, the mixture has the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Pharbitidis Seed* from 1:1 to 30: 1 by weight(w/w).

The present mixture includes a mixture of the herbal extracts of *Corydalis Tuber* and *Pharbitidis Seed*. Preferably, the mixture has the mixture ratio of the herbal extract of *Corydalis Tuber* : the herbal extract of *Pharbitidis Seed* from 1: 1 to 10: 1 by weight(w/w).

The present mixture includes a mixture of the herbal extracts of *Corydalis Tuber* and *Strychni Ignatii Semen*. Preferably, the mixture has the mixture ratio of the herbal extract of *Corydalis Tuber* : the herbal extract of *Strychni Ignatii Semen* from 3:1 to 1: 3 by weight(w/w).

The present mixture includes a mixture of the herbal extracts of *Pharbitidis Seed* and *Strychni Ignatii Semen*. Preferably, the mixture has the mixture ratio of the herbal extract of *Pharbitidis Seed* : the herbal extract of *Strychni Ignatii Semen* from 1:1 to 1: 10 by weight(w/w).

The present mixture includes a mixture of the herbal extracts of *Sinapis Semen*, *Corydalis Tuber*, and *Pharbitidis Seed*. Preferably, the mixture has the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* : the herbal extract of *Pharbitidis Seed* of (1~30): (1~10): 1 by weight(w/w).

The present mixture includes a mixture of the herbal extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed*, and *Strychni Ignatii Semen*. Preferably, the mixture has the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* : the herbal extract of *Strychni Ignatii Semen* : the herbal extract of *Pharbitidis Seed* of (1~30): (1~10): 1 : (1~10)by weight(w/w).

And, the herbs of the present invention include congener herbs that are known in the art to be useful for preventing and treating the same disorder as specified in the present invention.

Also, the present invention provides a preparation method of the herbal extracts of the present invention, characterized in that a herb selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* is extracted by water, a lower alcohol of C1~C4, or a mixture thereof. Preferably, the selected herb is extracted one to five times at 45~ 75°C for 65~ 80 hours.

The present invention also provides a preparation method of one or more extracts selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*, an extract soluble in polar solvent, and an extract soluble in non-polar solvent, comprising the first step that one or more herbs selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* are extracted by water, a lower alcohol of C1~C4, or a mixture thereof, filtered, and concentrated to obtain a herbal extract; the second step that the herbal extract of the first step is treated sequentially with hexane, chloroform, and ethylacetate to collect extracts soluble in non-polar solvent; and the third step that the extracts soluble in non-polar solvent of the second step are treated with water, methanol, butanol or mixture thereof, to obtain the herbal extracts soluble in polar solvent.

The present extracts include an extract, an extract soluble in polar solvent, or an extract soluble in non-polar solvent. The extract is extracted by a solvent selected from water, a lower alcohol of C1~C4, or a mixture thereof, preferably ethanol. And, the extract soluble in polar solvent is extracted from a solvent selected from water, methanol, butanol or a mixture thereof, preferably butanol. The extract soluble in non-polar solvent is extracted from a solvent selected from hexane, chloroform, and ethylacetate.

In the present invention, one or more herbal extracts selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* can be obtained by the following processes.

Firstly, after *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* or *Strychni Ignatii Semen* is washed and dried, the dried herb is milled to make a milled herb by a mill, and the

milled herb is grinded to powder by a grinder. The dried herb or powder is put in water, a lower alcohol such as ethanol or methanol (preferably ethanol), or a mixture thereof, in the amount of 1~25 times the weight of the dried herb or powder (preferably 5~15times). And, they were extracted by hydrothermal extraction, cold precipitated extraction, refluxing-cooling extraction, or ultrasonic extraction [preferably extracted one to five times by using the hydrothermal extraction at 20~100°C (preferably 45~75°C) for about 1~100 hours (preferably 65~80 hours)], filtered under vacuum, and lyophilized to obtain the herbal extract from *Sinapis Semen*, the herbal extract from *Corydalis Tuber*, the herbal extract from *Pharbitidis Seed*, and the herbal extract from *Strychni Ignatii Semen*.

Each of the herbal extract from *Sinapis Semen*, the herbal extract from *Corydalis Tuber*, the herbal extract from *Pharbitidis Seed*, and the herbal extract from *Strychni Ignatii Semen* was suspended in water and extracted by using solvents in the order of chloroform, ethylacetate, and butanol to obtain an extract soluble in polar solvent and an extract soluble in non-polar solvent of the present invention. Particularly, the extract soluble in polar solvent and the extract soluble in non-polar solvent of the present invention were obtained by a method comprising the first step in which each of the herbal extract from *Sinapis Semen*, the herbal extract from *Corydalis Tuber*, the herbal extract from *Pharbitidis Seed*, and the herbal extract from *Strychni Ignatii Semen* (the extracts obtained by hydrothermal extraction) was added to hexane to obtain a hexane-soluble extract and a water-soluble extract; the second step in which the water-soluble extract obtained in the first step was extracted by chloroform to obtain a chloroform-soluble extract and a water-soluble extract; the third step in which the water-soluble extract obtained in the second step was extracted by ethylacetate to obtain an ethylacetate-soluble extract and a water-soluble extract; and the fourth step in which the water-soluble extract obtained in the third step was extracted by butanol to obtain a butanol-soluble extract and a water-soluble extract.

The present invention provides a composition for preventing and treating gastrointestinal motility disorder, comprising the herbal extracts of the present invention as an active ingredient and pharmaceutically acceptable carrier, diluent, or filler.

The composition of the present invention contains the extracts in 0.01 to 80% weight of the total weight of the composition [preferably, 1 to 50%(w/w)].

In preparing the present composition, some elements can be added to, or taken out from, the present herbal extract, and the mixing ratios may be changed.

Here, gastrointestinal motility disorder is characterized as a disease caused by hyperactivity of 5-HT<sub>3</sub> receptor and/or 5-HT<sub>4</sub> receptor antagonism.

The gastrointestinal motility disorder includes functional dyspepsia such as early satiety, pain, epigastric distress, a false sense of satiety, heartburn, nausea and vomiting; ulcerative dyspepsia; non-ulcerative dyspepsia; reflux oesophagitis; paralysis of gastric motility; constipation; irritable bowel syndrome; hypersensitive colitis; diabetic gastrointestinal motility disorder; gastrointestinal motility disorder originated chemotherapy; and intestinal atresia originated motility disorder of digestive tract and myotonic dystrophy originated gastric intestinal motility disorder.

The irritable colitis includes general colitis, irritable colitis accompanied by constipation or diarrhea.

The present composition including the herb extracts may further include appropriate carrier, excipient or diluent.

Carrier, excipient and diluent that can be included in the composition of the present invention include lactose, dextrose, sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia rubber, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinyl pyrrolidone, water, methylhydroxybenzoate, propylhydroxybenzoate, talc, magnesium stearate or mineral oil.

Also, the composition of the present invention can be prepared into oral medicine like powder, granulum, tablet, capsule, suspension, emulsion, syrup and aerosol; external medicine; or suppository or sterile injection solution.

Specifically, when prepared into medicines, diluent or excipient such as generally used priming agents, expanders, bonding agents, humectants, disintegrators or detergents can

be added. Solid products for oral administration include tablets, pills, powder, granulum, capsules and others. The herb composition can be mixed with at least one or more excipients like starch, calcium carbonate, sucrose, lactose or gelatin. Not only the simple excipient but also lubricants like magnesium stearate or talc can be used. For liquid oral products, suspension, contents agent, emulsion and syrup can be used, but commonly used simple diluents like water and liquid paraffin as well as various excipients such as humectants, sweetening agents, odorants or preservatives can also be used. Non-oral administrative products include sterile aqueous suspension, non-aqueous solvent, suspension, emulsion, freeze-dried products, and suppository. For non-aqueous solvent and suspension, propylene glycol, polyethylene glycol, vegetable oil like olive oil, or injectable ester such as ethyl oleate can be used. For the base of suppository, witepsol, macrogol, tween 61, cacao butter, laurin fat, glycerol gelatin and others can be used.

Also, the present invention provides a use of the herb extracts of the present invention for cure and prevention of gastrointestinal motility disorder.

Moreover, the present invention provides a treatment method of gastrointestinal motility disorder by administering the pharmaceutical composition with the herb extracts of the present invention in the effective dosage to mammals including humans.

The administration dose of the composition of the present invention including the herb extracts may vary depending on the age, gender or body weight of a patient. However, generally, the dried powder of the extracts can be administered in single or multiple doses in the amount of 0.01 to 10g/Kg, preferably 5g/Kg a day. The dose can be adjusted depending on administration path, severity of disease, gender, body weight, age, health status, diet, administration time and method, and excretion rate. Therefore the above dose by no means limits the scope of the present invention.

The pharmaceutical composition of the present invention can be administered to mammals like rat, mouse, cattle or humans through a variety of paths. For instance, it can be administered orally, through rectum, or by venous, muscular, subcutaneous, uterine dura mater or intracerebroventricular injection.

The herb extracts of the present invention can be safely used for a long time for the purpose of prevention since they have little toxicity or adverse effect.

To confirm the prokinetic and anti-dyspepsia efficacy of the herb extracts, the present inventor tested their affinity to, antagonism against and agonism to the receptors of 5-HT<sub>3</sub> and 5-HT<sub>4</sub>, and verified their selective and outstanding efficacy. Also, to identify the proper ratio of the herb extracts, various *in vivo* experiments using many functional dyspepsia pathologies on animal models were performed, and the remarkable effects of the extracts have been verified.

To prevent and improve the gastrointestinal motility disorder, the present invention provides health functional foods with one or more extracts selected from the group of Korean mustard, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*, and food additives allowed in sitology.

The health functional foods used in the present invention have the characteristics of health function food ingredients listed in the Korean FDA Notice 2004-12 based on the functions and safety on humans for newly defining the Health Function Food Act of 2002.

The present invention also provides a health care food for preventing and improving gastrointestinal motility disorder containing two or more herbal extracts selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*, and sitologically acceptable addition agents.

The present invention provides a health care food for preventing and improving gastrointestinal motility disorder containing a mixture of the herbal extract of *Sinapis Semen*, the herbal extract of *Corydalis Tuber*, and the herbal extract of *Pharbitidis Seed*, and sitologically acceptable addition agents. Preferably, in the mixture, the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* : the herbal extract of *Pharbitidis Seed* is (1~30): (1~10): 1 by weight(w/w).

The present invention provides a health care food for preventing and improving gastrointestinal motility disorder containing a mixture of the herbal extract of *Sinapis Semen*,

the herbal extract of *Corydalis Tuber*, the herbal extract of *Pharbitidis Seed*, and the herbal extract of *Strychni Ignatii Semen*, and sitologically acceptable addition agents. Preferably, in the mixture, the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* : the herbal extract of *Strychni Ignatii Semen* : the herbal extract of *Pharbitidis Seed* is (1~30): (1~10): 1 : (1~10) by weight(w/w).

The present invention provides a health care food for preventing and improving gastrointestinal motility disorder containing a mixture of the herbal extract of *Sinapis Semen* and the herbal extract of *Corydalis Tuber*, and sitologically acceptable addition agents. Preferably, in the mixture, the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* is 1: 1 to 10:1 by weight(w/w).

The present invention provides a health care food for preventing and improving gastrointestinal motility disorder containing a mixture of the herbal extract of *Sinapis Semen* and the herbal extract of *Pharbitidis Seed*, and sitologically acceptable addition agents. Preferably, in the mixture, the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Pharbitidis Seed* is 1:1 to 30: 1 by weight(w/w).

The present invention provides a health care food for preventing and improving gastrointestinal motility disorder containing a mixture of the herbal extract of *Corydalis Tuber* and the herbal extract of *Pharbitidis Seed*, and sitologically acceptable addition agents. Preferably, in the mixture, the mixture ratio of the herbal extract of *Corydalis Tuber* : the herbal extract of *Pharbitidis Seed* is 1: 1 to 10: 1 by weight(w/w).

The present invention provides a health care food for preventing and improving gastrointestinal motility disorder containing a mixture of the herbal extract of *Corydalis Tuber* and the herbal extract of *Strychni Ignatii Semen*, and sitologically acceptable addition agents. Preferably, in the mixture, the mixture ratio of the herbal extract of *Corydalis Tuber* : the herbal extract of *Strychni Ignatii Semen* is 3:1 to 1: 3 by weight(w/w).

The present invention provides a health care food for preventing and improving gastrointestinal motility disorder containing a mixture of the herbal extract of *Pharbitidis Seed* and the herbal extract of *Strychni Ignatii Semen*, and sitologically acceptable addition agents.

Preferably, in the mixture, the mixture ratio of the herbal extract of *Pharbitidis Seed* : the herbal extract of *Strychni Ignatii Semen* is 1:1 to 1: 10 by weight(w/w).

On the other hand, the composition including the herb extracts of the present invention can be used in various forms of drugs, food, and drinks for prokinetic effect. The herb extracts of the present invention can be added to various foods like drinks, gum, tea, vitamin complex, and health supplementary food, and can be used in the form of pill, powder, granule, infusion, tablet, capsule, or drink.

The dose of the herb extracts in food or drinks for the health food composition of the present invention is generally 0.01 to 15 weight% of the total food weight, preferably 0.1 to 10 weight%. For health drink composition, 0.1 to 30g, preferably 0.2 to 5g, of the herb extracts can be added to 100ml.

For the health drink composition, only the herb extracts are necessary ingredients with specific ratio, and there are no special restrictions on the liquid ingredients. Like common drinks, various kinds of flavors and natural carbohydrate can be added.

The examples of the above mentioned natural carbohydrate would be mono-saccharides, disaccharides such as glucose and fructose, polysaccharides such as maltose and sucrose, general sugar such as dextrin and cyclodextrin, and sugar alcohol such as xylitol, sorbitol, and erythritol. In addition to the above mentioned flavors, natural flavors (thaumatin, stevia extract (i.e. rebaudiosid A, glycyrrhizin)) and synthetic flavors (i.e. saccharides, aspartame) can be used. For the above natural carbohydrate composition, generally 1 to 20g per 100ml, preferably 5 to 12g, is used.

Other than the above, the composition of the present invention may contain various nutrients, vitamins, minerals (electrolyte), synthetic and natural flavoring agents, colorants, extenders(such as cheese, chocolate), pectic acid and pectinate, alginic acid and alginate, organic acid, protective colloid thickening agents, pH modulator, stabilizer, preservatives, glycerin, alcohol, carbonator used in carbonated drinks and others. Additionally, the composition of the present invention can contain the flesh of fruits to produce natural fruit juice, fruit juice drinks, and vegetable drinks. These ingredients can be used alone or in

combination. The ratios of these additives are not crucial, but generally 0 to 20 weight/percent per 100 weight of the composition of the present invention is used.

### ADVANTAGEOUS EFFECTS

The extracts of the present invention or a mixture thereof may be used as a pharmaceutical composition for preventing and treating gastrointestinal motility disorder and a health functional food to facilitate gastrointestinal motility through HT<sub>3</sub> receptor antagonism and/or HT<sub>4</sub> receptor agonism.

### DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic drawing illustrating the analytic results of thin liquid chromatography (TLC) of ethanol extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* using H<sub>2</sub>SO<sub>4</sub>.

Fig. 2 is a schematic drawing illustrating the analytic results of thin liquid chromatography (TLC) of ethanol extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* using KMNO<sub>4</sub>.

Fig. 3 is a schematic drawing illustrating multi activities of agonist for 5-HT<sub>3</sub> receptor.

### MODE FOR INVENTION

The present invention is explained by the following examples and experimental examples in more detail.

The following examples are intended to further illustrate the present invention, and the scope of the present invention cannot be limited thereby in any way.

r.t means a room temperature in the present invention.

Example 1. Preparation of herbal extracts of the present invention

#### 1-1. Preparation of an extract of *Sinapis Semen*

*Sinapis Semen* was bought at a Chinese herb medicine shop of Kyung-dong market,

washed to remove adulterations, and dried to use at the experiment. And, the dried herb was milled by a mill, and 20g of the milled *Sinapis Semen* was put in 0%, 15%, 30%, 50%, 70%, 85% and 96% ethanol-water (160ml) and stirred at room temperature for 72h. Then, the resulting mixture was extracted, filtered, and concentrated at 55~65 °C under a low pressure, and freeze-dried to obtain an extract of *Sinapis Semen* (1.04~3.1g)(Table 1: Yields of extracts of *Sinapis Semen* as a kind of solvent).

[Table 1]

| Amount of a herb | solvent   | Amount of solvent | wash  | Extraction temperature | Extraction time | Obtained amount (g) | Yield (%) |
|------------------|-----------|-------------------|-------|------------------------|-----------------|---------------------|-----------|
| 20g              | 96%EtOH   | 160 ml            | 20 ml | r.t                    | 3days           | 1.24                | 6.2       |
| 20g              | 85%EtOH   | 160 ml            | 20 ml | r.t                    | 3days           | 1.93                | 9.7       |
| 20g              | 70%EtOH   | 160 ml            | 20 ml | r.t                    | 3days           | 1.96                | 9.8       |
| 20g              | 50%EtOH   | 160 ml            | 20 ml | r.t                    | 3days           | 2.28                | 11.4      |
| 20g              | 30%EtOH   | 160 ml            | 20 ml | r.t                    | 3days           | 2.37                | 11.9      |
| 20g              | 15%EtOH   | 160 ml            | 20 ml | r.t                    | 3days           | 3.1                 | 15.5      |
| 20g              | 100%water | 160 ml            | 20 ml | r.t                    | 3days           | 1.04                | 5.2       |

#### 1-2. Preparation of an extract of *Corydalis Tuber*

*Corydalis Tuber* was bought at a Chinese herb medicine shop of Kyung-dong market, washed by using water to remove adulterations, and dried to use in the experiment. And, the dried herb was milled by a mill, and 20g of the milled *Corydalis Tuber* was put in 0%, 15%, 30%, 50%, 70%, 85% and 96% ethanol-water (160ml) and stirred at room temperature for 72h. Then, the resulting mixture was extracted, filtered, and concentrated at 55~65 °C under a low pressure, and freeze-dried by using the same method as Example 1-1 to obtain an extract of *Corydalis Tuber* (0.36~2.94g)(Table 2: Yields of extracts of *Corydalis Tuber* as a kind of solvent).

[Table 2]

| Herb | Solvent | Amount of solvent | Wash  | Extraction Temperature | Extraction Time | Obtained yield(g) | Yield(%) |
|------|---------|-------------------|-------|------------------------|-----------------|-------------------|----------|
| 20g  | 96%EtOH | 160 ml            | 20 ml | r.t                    | 3days           | 0.36              | 1.8      |
| 20g  | 85%EtOH | 160 ml            | 20 ml | r.t                    | 3 days          | 0.84              | 4.2      |
| 20g  | 70%EtOH | 160 ml            | 20 ml | r.t                    | 3 days          | 1.3               | 6.5      |
| 20g  | 50%EtOH | 160 ml            | 20 ml | r.t                    | 3 days          | 1.65              | 8.3      |
| 20g  | 30%EtOH | 160 ml            | 20 ml | r.t                    | 3 days          | 1.92              | 9.6      |
| 20g  | 15%EtOH | 160 ml            | 20 ml | r.t                    | 3 days          | 2.16              | 10.8     |
| 20g  | 100%물   | 160 ml            | 20 ml | r.t                    | 3 days          | 2.94              | 14.7     |

### 1-3. Preparation of an extract of *Pharbitidis Seed*

*Pharbitidis Seed* was bought at a Chinese herb medicine shop of Kyung-dong market, washed by using water to remove adulterations, and dried to use in the experiment. And, the dried herb was milled by a mill, and 20g of the milled *Pharbitidis Seed* was put in 0%, 15%, 30%, 50%, 70%, 85% and 96% ethanol-water (160ml), and stirred at room temperature for 72h. Then, the resulting mixture was extracted, filtered, and concentrated at 55~65 °C under a low pressure, and freeze-dried by using the same method as the Example 1-1 to obtain an extract of *Pharbitidis Seed* (0.92~3.85g)(Table 3: Yields of extracts of *Pharbitidis Seed* as a kind of solvent).

[Table 3]

| Herb | Solvent | Amount of solvent | Wash  | Extraction temperature | Extraction time | Obtained Amount (g) | Yield(%) |
|------|---------|-------------------|-------|------------------------|-----------------|---------------------|----------|
| 20g  | 96%EtOH | 160 ml            | 20 ml | r.t                    | 3 days          | 0.92                | 4.6      |
| 20g  | 85%EtOH | 160 ml            | 20 ml | r.t                    | 3 days          | 1.03                | 5.2      |

|     |           |        |       |     |        |      |      |
|-----|-----------|--------|-------|-----|--------|------|------|
| 20g | 70%EtOH   | 160 ml | 20 ml | r.t | 3 days | 1.27 | 6.4  |
| 20g | 50%EtOH   | 160 ml | 20 ml | r.t | 3 days | 2.13 | 10.7 |
| 20g | 30%EtOH   | 160 ml | 20 ml | r.t | 3 days | 2.14 | 10.7 |
| 20g | 15%EtOH   | 160 ml | 20 ml | r.t | 3 days | 3.85 | 19.3 |
| 20g | 100%water | 160 ml | 20 ml | r.t | 3 days | 3.77 | 18.9 |

#### 1-4. Preparation an extract of *Strychnos ignatii Semen*

*Strychnos ignatii Semen* was bought at a Chinese herb medicine shop of Kyung-dong market, washed by using water to remove adulterations, and dried to use in the experiment. And, the dried herb was milled by a mill, and 20g of the milled *Strychnos ignatii Semen* was put in 0%, 15%, 30%, 50%, 70%, 85% and 96% ethanol-water(160ml) and stirred at room temperature for 72h. Then, the resulting mixture was extracted, filtered, and concentrated at 55~65 °C under a low pressure, and freeze-dried by using the same method as the Example 1-1 to obtain an extract of *Strychnos ignatii Semen* (0.59~5.41g)(Table 3: Yields of extracts of *Strychnos ignatii Semen* as a kind of solvent).

[Table 4]

| Herb | Solvent   | Amount of solvent | Wash  | Extraction temperature | Extraction time | Obtained amount(g) | Yield(%) |
|------|-----------|-------------------|-------|------------------------|-----------------|--------------------|----------|
| 20g  | 96%EtOH   | 160 ml            | 20 ml | r.t                    | 3days           | 0.59               | 3.0      |
| 20g  | 85%EtOH   | 160 ml            | 20 ml | r.t                    | 3 days          | 2.26               | 11.3     |
| 20g  | 70%EtOH   | 160 ml            | 20 ml | r.t                    | 3 days          | 3.69               | 18.5     |
| 20g  | 50%EtOH   | 160 ml            | 20 ml | r.t                    | 3 days          | 3.88               | 19.4     |
| 20g  | 30%EtOH   | 160 ml            | 20 ml | r.t                    | 3 days          | 4.3                | 21.5     |
| 20g  | 15%EtOH   | 160 ml            | 20 ml | r.t                    | 3 days          | 4.96               | 24.8     |
| 20g  | 100%water | 160 ml            | 20 ml | r.t                    | 3 days          | 5.41               | 27.1     |

Example 2. Preparation a soluble extract in polar solvent and a soluble extract in non-polar

solvent

#### 2-1. Preparation of an extract soluble in hexane

10g of 50% ethanol extracts from Example 1 each were dissolved in 100ml of a distilled water and 80ml of methanol, put in a separatory funnel and, and mixed strongly to separate a water layer and a hexane layer. 180ml of hexane was put again in the water-layer, mixed, and separated to obtain a soluble extract in hexane and an insoluble extract in hexane.

#### 2-2. Preparation of an extract soluble in chloroform

The insoluble extract in hexane (water-layer) was mixed with 160ml of chloroform to separate a chloroform layer and a water layer. And, the water layer was added to 160ml of chloroform, and mixed to obtain a soluble extract in chloroform and an insoluble extract in chloroform.

#### 2-3. Preparation of an extract soluble in ethylacetate

The insoluble extract in chloroform (water-layer) was mixed with 140ml of ethylacetate to separate an ethylacetate layer and a water layer. And, the water layer was added to 140ml of ethylacetate, and mixed to obtain a soluble extract in ethylacetate and an insoluble extract in ethylacetate.

#### 2-4. Preparation of an extract soluble in butanol

The insoluble extract in ethylacetate (water-layer) was mixed with 40ml of butanol to separate a butanol layer and a water layer. And, the water layer was added to 20ml of butanol, and mixed to obtain a soluble extract in butanol and an insoluble extract in butanol.

The extracts soluble in hexane, chloroform, ethylacetate and butanol, and the extracts insoluble in hexane, chloroform, ethylacetate and butanol were concentrated under a low pressure, and then freeze-dried to obtain an extract soluble in hexane (0.2~0.4g), an extract soluble in chloroform (0.1~0.3g), an extract soluble in ethylacetate (0.3~0.6g), an extract

soluble in butanol (0.8~1.6g), and an extract soluble in water (1.5~3.0g). The results were shown in Table 5 (The yield of extracts soluble in polar solvent and in non-polar solvent of various herbs)

[Table 5]

| Herb                                            | Sequentially Fractional solvent | Amount of solvent | Extraction temperature | Obtained Amount (g) | Yield(%) |
|-------------------------------------------------|---------------------------------|-------------------|------------------------|---------------------|----------|
| Sinapis Semen<br>(50%EtOH-extract, 10g)         | Hexane                          | 180 ml×2          | r.t*                   | 0.2                 | 2        |
|                                                 | Chloroform                      | 160 ml×2          | r.t                    | 0.24                | 2.4      |
|                                                 | Ethylacetate                    | 160 ml×2          | r.t                    | 1.37                | 14       |
|                                                 | Butanol                         | 40 ml, 20 ml      | r.t                    | 0.22                | 2.2      |
| Corydalis Tuber<br>(50%EtOH extract 10g)        | Hexane                          | 180 ml×2          | r.t                    | 0.08                | 0.38     |
|                                                 | Chloroform                      | 160 ml×2          | r.t                    | 0.86                | 2.9      |
|                                                 | Ethylacetate                    | 160 ml×2          | r.t                    | 1.17                | 12       |
|                                                 | Butanol                         | 40 ml, 20 ml      | r.t                    | 0.02                | 0.07     |
| Pharbitidis Seed<br>(50%EtOH extract 10g)       | Hexane                          | 180 ml×2          | r.t                    | 0.20                | 2.0      |
|                                                 | Chloroform                      | 160 ml×2          | r.t                    | 0.11                | 1.1      |
|                                                 | Ethylacetate                    | 160 ml×2          | r.t                    | 0.32                | 3.2      |
|                                                 | Butanol                         | 40 ml, 20 ml      | r.t                    | 0.81                | 8.1      |
| Strychni Ignatii Semen<br>(50%EtOH extract 10g) | Hexane                          | 180 ml×2          | r.t                    | 0.06                | 0.6      |
|                                                 | Chloroform                      | 160 ml×2          | r.t                    | 0.87                | 8.7      |
|                                                 | Ethylacetate                    | 160 ml×2          | r.t                    | 0.52                | 5.2      |
|                                                 | Butanol                         | 40 ml, 20 ml      | r.t                    | -                   | -        |

\*r.t means room temperature.

Example 3. Preparation of mixtures of herb extracts of the present invention

3-1. Preparation of a mixture of the extracts of *Sinapis Semen*, *Corydalis Tuber*, and

*Pharbitidis Seed*

The 50% ethanol extracts obtained from Example 1 were mixed by the ratios of the extract of *Sinapis Semen* : the extract of *Corydalis Tuber* : the extract of *Pharbitidis Seed* to be 30:10:1, 30:3:1, 10:10:1, 10:3:1, 10:1:1, 3:3:1 and 3:1:1 weight in weight(w/w) to prepare 3-1-A, 3-1-B, 3-1-C, 3-1-D, 3-1-E, 3-1-F and 3-1-G as milled mixtures.

3-2. Preparation of a mixture of the extracts of *Sinapis Semen* and *Corydalis Tuber*

The 50% ethanol extracts obtained from Example 1 were mixed by the ratios of the extract of *Sinapis Semen* and the extract of *Corydalis Tuber* to be 10:1, 3:1 and 1:1 weight in weight(w/w) to prepare 3-2-A, 3-2-B and 3-2-C as milled mixtures.

3-3. Preparation of a mixture of the extracts of *Sinapis Semen* and *Pharbitidis Seed*

The 50% ethanol extracts obtained from Example 1 were mixed by the ratios of the extract of *Sinapis Semen* and the extract of *Pharbitidis Seed* to be 30:1, 10:1 and 3:1 weight in weight(w/w) to prepare 3-3-A, 3-3-B and 3-3-C as milled mixtures.

3-4. Preparation of a mixture of the extracts of *Corydalis Tuber* and *Pharbitidis Seed*

The 50% ethanol extracts obtained from Example 1 were mixed by the ratios of the extract of *Corydalis Tuber* and the extract of *Pharbitidis Seed* to be 10:1, 3:1, and 1:1 weight in weight(w/w) to prepare 3-4-A, 3-4-B and 3-4-C as milled mixtures.

3-5. Preparation of a mixture of the extracts of *Corydalis Tuber* and *Strychni Ignatii Semen*

The 50% ethanol extracts obtained from Example 1 were mixed by the ratios of the extract of *Corydalis Tuber* and the extract of *Strychni Ignatii Semen* to be 3:1, 1:1 and 1:3 weight in weight(w/w) to prepare 3-5-A, 3-5-B and 3-5-C as milled mixtures.

3-6. Preparation of a mixture of the extracts of *Pharbitidis Seed* and *Strychni Ignatii Semen*

The 50% ethanol extracts obtained from Example 1 were mixed by the ratios of the extract of *Pharbitidis Seed* and the extract of *Strychni Ignatii Semen* to be 1:1, 1:3 and 1:10

weight in weight(w/w) to prepare 3-6-A, 3-6-B and 3-6-C as milled mixtures.

3-7. Preparation of a mixture of the extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed*, and *Strychni Ignatii Semen*

The 50% ethanol extracts obtained from Example 1 were mixed by the ratios of the extract of *Sinapis Semen* : the extract of *Corydalis Tuber* : the extract of *Pharbitidis Seed* : the extract of *Strychni Ignatii Semen* to be 30:10:1:10, 30:10:1:3, 30:3:1:10, 30:3:1:3, 10:3:1:3, 10:10:1:10, 10:10:1:3, 10:3:1:10 and 3:3:1:3 weight in weight(w/w) to prepare 3-7-A, 3-7-B, 3-7-C, 3-7-D, 3-7-E, 3-7-F, 3-7-G, 3-7-H and 3-7-I as milled mixtures.

<Experimental Example 1> 5-HT<sub>3</sub> receptor Binding assay on the extracts of Example 1

A binding assay was performed against Human-originated 5-HT<sub>3</sub> receptor for selecting a herbal extract having affinity for 5-HT<sub>3</sub> receptor [Nagakura Y et al., Pharmacology properties of a novel gastrointestinal prokinetics benzamide selective for human-5-HT<sub>4</sub> receptor versus human 5-HT<sub>3</sub> receptor. *Pharma. Research*, 39(5), pp. 375-382, 1999; Miyake et al., Molecular cloning of human 5-hydroxyamine<sub>3</sub> receptor: heterogeneity in distribution and function among species. *Mol. Pharmacology*, pp.407-416, 1995].

1-1. The extract of *Sinapis Semen*

5-HT<sub>3</sub> receptor gene of sequence list No.1 (HTR03A0000, UMR cDNA Resource Center) was transfected into Cos-7 cell to prepare a cell membrane of a developing receptor. The membrane (protein: 20 $\mu$ g) was seeded to 96 well plate, and then an isotope-labeled ligand and the extract of *Sinapis Semen* were added to the plate, and mixed. After the plate was incubated at 25 °C for 40min, the radioactivity of the plate was measured by beta radioactivity measuring instrument (top counter). The inhibition rates were calculated by using the following Math Figure 1.

[Math Figure 1]

Inhibition ratio(%) = 100-[(searching substance CPM – non-specific binding CPM)/(overall CPM – non-specific binding CPM)x100]

(\*CPM : count per minute)

As shown in Table 6, the extract of *Sinapis Semen* from 50~96% ethanol-water showed the strongest affinity for 5-HT<sub>3</sub> receptor. The 50% inhibitive concentration (IC<sub>50</sub>) of the extract of *Sinapis Semen* from 50% ethanol-water is 79.2  $\mu\text{g/ml}$  (Table 7).

[Table 6]

|                                          | Concentration        | Inhibition ratio(%) |
|------------------------------------------|----------------------|---------------------|
| 96%EtOH -extract of <i>Sinapis Semen</i> | 100 $\mu\text{g/ml}$ | 95.5                |
|                                          | 300 $\mu\text{g/ml}$ | 100.6               |
| 85%EtOH-extract of <i>Sinapis Semen</i>  | 100 $\mu\text{g/ml}$ | 88.4                |
|                                          | 300 $\mu\text{g/ml}$ | 94.3                |
| 70%EtOH -extract of <i>Sinapis Semen</i> | 100 $\mu\text{g/ml}$ | 87.6                |
|                                          | 300 $\mu\text{g/ml}$ | 98.3                |
| 50%EtOH -extract of <i>Sinapis Semen</i> | 100 $\mu\text{g/ml}$ | 73.3                |
|                                          | 300 $\mu\text{g/ml}$ | 93.0                |
| 30%EtOH-extract of <i>Sinapis Semen</i>  | 100 $\mu\text{g/ml}$ | 52.3                |
|                                          | 300 $\mu\text{g/ml}$ | 79.3                |
| 15%EtOH-extract of <i>Sinapis Semen</i>  | 100 $\mu\text{g/ml}$ | 33.2                |
|                                          | 300 $\mu\text{g/ml}$ | 57.4                |
| Water-extract of <i>Sinapis Semen</i>    | 100 $\mu\text{g/ml}$ | 41.1                |
|                                          | 300 $\mu\text{g/ml}$ | 54.9                |

[Table 7]

|                 | Concentration ( $\mu\text{g/ml}$ ) | Inhibition ratio(%) |
|-----------------|------------------------------------|---------------------|
| 50%EtOH-extract | 10                                 | 1.0                 |
|                 | 30                                 | 8.0                 |
|                 | 100                                | 60.0                |
|                 | 300                                | 89.7                |

### 1-2. The extract of *Strychni Ignatii Semen*

The affinity of the extract of *Strychni Ignatii Semen* for 5-HT<sub>3</sub> receptor was measured by using the same method as the Experimental Example 1-1. The results were shown in Tables 8 and 9. As shown in Tables 8 and 9, the extracts of *Strychni Ignatii Semen* from 30~85% ethanol-water showed the strongest affinity for 5-HT<sub>3</sub> receptor. The 50% inhibitive concentration (IC<sub>50</sub>) of the extract of *Strychni Ignatii Semen* from 50% ethanol-water is 144.9 ug/ml (Table 9).

[Table 8]

|                                                  | Concentration         | Inhibition ratio(%) |
|--------------------------------------------------|-----------------------|---------------------|
| 96%EtOH-extract of <i>Strychni Ignatii semen</i> | 300 $\mu\text{g/ml}$  | 77.8                |
|                                                  | 1000 $\mu\text{g/ml}$ | 79.8                |
| 85%EtOH-extract of <i>Strychni Ignatii semen</i> | 300 $\mu\text{g/ml}$  | 70.2                |
|                                                  | 1000 $\mu\text{g/ml}$ | 93.6                |
| 70%EtOH-extract of <i>Strychni Ignatii semen</i> | 300 $\mu\text{g/ml}$  | 67.6                |
|                                                  | 1000 $\mu\text{g/ml}$ | 89.0                |
| 50%EtOH-extract of <i>Strychni Ignatii semen</i> | 300 $\mu\text{g/ml}$  | 72.6                |
|                                                  | 1000 $\mu\text{g/ml}$ | 87.6                |
| 30%EtOH-extract of <i>Strychni Ignatii semen</i> | 300 $\mu\text{g/ml}$  | 70.8                |
|                                                  | 1000 $\mu\text{g/ml}$ | 87.5                |
| 15%EtOH-extract of <i>Strychni Ignatii semen</i> | 300 $\mu\text{g/ml}$  | 60.4                |
|                                                  | 1000 $\mu\text{g/ml}$ | 80.0                |
| Water extract of <i>Strychni Ignatii semen</i>   | 300 $\mu\text{g/ml}$  | 66.4                |
|                                                  | 1000 $\mu\text{g/ml}$ | 86.1                |

[Table 9]

|                        | Concentration ( $\mu\text{g/ml}$ ) | Inhibition ratio(%) |
|------------------------|------------------------------------|---------------------|
| 50%-ethanol<br>extract | 30                                 | 20.0                |
|                        | 100                                | 40.0                |
|                        | 300                                | 69.3                |
|                        | 1000                               | 84.3                |

<Experimental Example 2> 5-HT<sub>4</sub> receptor Binding assay of the extracts of Example 1 A binding assay was performed against human-originated 5-HT<sub>4</sub> receptor for selecting a herbal extract having affinity for 5-HT<sub>4</sub> receptor [Nagakura Y et al., Pharmacology properties of a novel gastrointestinal prokinetics benzamide selective for human-5-HT<sub>4</sub> receptor versus human 5-HT<sub>3</sub> receptor. *Pharma. Research*, 39(5), pp.375-382, 1999; Wyngaert IV et al., Cloning and expression of a human serotonin 5-HT<sub>4</sub> receptor cDNA. *J. Neurochemistry*. 69(5), pp.1810-1819, 1997].

#### 2-1. The extract of *Corydalis Tuber*

5-HT<sub>4</sub> receptor gene of sequence list No.2 (HTR0400000, UMR cDNA Resource Center) was transfected into Cos-7 cell to prepare a cell membrane as a developing receptor. The membrane (protein: 20 $\mu\text{g}$ ) was seeded to 96 well plate, and then an isotope-labeled ligand and the extract of *Corydalis Tuber* were added into the plate, and mixed. After the plate was incubated at 25 °C for 40min, the radioactivity of the plate was measured by beta radioactivity measuring instrument (top counter). The inhibition rates were calculated by using the following Math Figure 2.

[Math Figure 2]

Inhibition ratio(%) = 100-[(searching substance CPM – non-specific binding CPM)/(overall CPM – non-specific binding CPM)x100] (\*CPM:Count per minute)

As shown in Tables 10 and 11, the extract of *Corydalis Tuber* from 50~96% ethanol-water showed the strongest affinity for 5-HT<sub>4</sub> receptor. The 50% inhibitive concentration (IC<sub>50</sub>) of the extract of *Corydalis Tuber* from 50% ethanol-water is 43.4  $\mu\text{g/ml}$ .

[Table 10]

|                                       | Concentration        | Inhibition ratio(%) |
|---------------------------------------|----------------------|---------------------|
| 96%EtOH-extract of Corydalis<br>Tuber | 100 $\mu\text{g/ml}$ | 86.2                |
|                                       | 300 $\mu\text{g/ml}$ | 99.5                |
| 85%EtOH-extract of Corydalis<br>Tuber | 100 $\mu\text{g/ml}$ | 86.8                |
|                                       | 300 $\mu\text{g/ml}$ | 99.6                |
| 70%EtOH-extract of Corydalis<br>Tuber | 100 $\mu\text{g/ml}$ | 81.1                |
|                                       | 300 $\mu\text{g/ml}$ | 99.3                |
| 50%EtOH-extract of Corydalis<br>Tuber | 100 $\mu\text{g/ml}$ | 70.5                |
|                                       | 300 $\mu\text{g/ml}$ | 99.7                |
| 30%EtOH-extract of Corydalis<br>Tuber | 100 $\mu\text{g/ml}$ | 60.0                |
|                                       | 300 $\mu\text{g/ml}$ | 85.9                |
| 15%EtOH-extract of Corydalis<br>Tuber | 100 $\mu\text{g/ml}$ | 53.3                |
|                                       | 300 $\mu\text{g/ml}$ | 80.2                |
| Water-extract of Corydalis Tuber      | 100 $\mu\text{g/ml}$ | 27.3                |
|                                       | 300 $\mu\text{g/ml}$ | 77.2                |

[Table 11]

|                     | Concentration ( $\mu\text{g/ml}$ ) | Inhibition ratio(%) |
|---------------------|------------------------------------|---------------------|
| 50%-ethanol extract | 10                                 | 22.3                |
|                     | 30                                 | 37.7                |
|                     | 100                                | 65.1                |
|                     | 300                                | 94.9                |

## 2-2. The extract of *Pharbitidis Seed*

The affinity of the extract of *Pharbitidis Seed* for 5-HT<sub>3</sub> receptor was measured by using the same method as the Experimental Example 2-1. The results were shown in Tables 12 and 13. As shown in Tables 12 and 13, the extracts of *Pharbitidis Seed* from 50~96% ethanol-

water showed the strongest affinity for 5-HT<sub>4</sub> receptor. The 50% inhibitive concentration (IC<sub>50</sub>) of the extract of *Pharbitidis Seed* from 50% ethanol-water is 65.6 ug/ml.

[Table 12]

|                                     | Concentration        | Inhibition ratio(%) |
|-------------------------------------|----------------------|---------------------|
| 96%EtOH extract of Pharbitidis Seed | 100 $\mu\text{g/ml}$ | 61.2                |
|                                     | 300 $\mu\text{g/ml}$ | 90.2                |
| 85%EtOH extract of Pharbitidis Seed | 100 $\mu\text{g/ml}$ | 53.7                |
|                                     | 300 $\mu\text{g/ml}$ | 90.3                |
| 70%EtOH extract of Pharbitidis Seed | 100 $\mu\text{g/ml}$ | 67.1                |
|                                     | 300 $\mu\text{g/ml}$ | 89.8                |
| 50%EtOH extract of Pharbitidis Seed | 100 $\mu\text{g/ml}$ | 53.2                |
|                                     | 300 $\mu\text{g/ml}$ | 87.4                |
| 30%EtOH extract of Pharbitidis Seed | 100 $\mu\text{g/ml}$ | 47.5                |
|                                     | 300 $\mu\text{g/ml}$ | 52.9                |
| 15%EtOH extract of Pharbitidis Seed | 100 $\mu\text{g/ml}$ | 23.2                |
|                                     | 300 $\mu\text{g/ml}$ | 48.5                |
| Water extract of Pharbitidis Seed   | 100 $\mu\text{g/ml}$ | 25.3                |
|                                     | 300 $\mu\text{g/ml}$ | 44.7                |

[Table 13]

|                     | Concentration ( $\mu\text{g/ml}$ ) | Inhibition ratio(%) |
|---------------------|------------------------------------|---------------------|
| 50% ethanol-extract | 10                                 | 11.4                |
|                     | 30                                 | 20.7                |
|                     | 100                                | 66.0                |
|                     | 300                                | 84.9                |

<Experimental Example 3> 5-HT<sub>3</sub> receptor and 5-HT<sub>4</sub> receptor Binding assay of soluble extracts in polar solvent and in non-polar solvent of Example 2

### 3-1. *Sinapis Semen* and *Strychni Ignatii Semen*

The affinities for 5-HT<sub>3</sub> receptor of the extracts extracted from hexane, chloroform, ethylacetate, and water of Example 2 were measured by a binding assay against human-originated 5-HT<sub>3</sub> receptor. The method of experiment was the same as the Experimental Example 1-1, and the extracts from polar solvent and from non-polar solvent had the concentrations shown in Table 14. As shown in Table 14, the extract (fraction) from chloroform was the most effective.

[Table 14]

|                                                           | Concentration        | Inhibition ratio(%) |
|-----------------------------------------------------------|----------------------|---------------------|
| Hexane-fraction of<br><i>Sinapis Semen</i>                | 100 $\mu\text{g/ml}$ | 1.3                 |
|                                                           | 300 $\mu\text{g/ml}$ | 4.6                 |
| Chloroform-fraction of<br><i>Sinapis Semen</i>            | 100 $\mu\text{g/ml}$ | 63.9                |
|                                                           | 300 $\mu\text{g/ml}$ | 87.3                |
| Ethylacetate-fraction of<br><i>Sinapis Semen</i>          | 100 $\mu\text{g/ml}$ | 59.3                |
|                                                           | 300 $\mu\text{g/ml}$ | 79.0                |
| Water -fraction of<br><i>Sinapis Semen</i>                | 100 $\mu\text{g/ml}$ | 22.8                |
|                                                           | 300 $\mu\text{g/ml}$ | 69.6                |
| Hexane-fraction of<br><i>Strychni Ignatii Semen</i>       | 100 $\mu\text{g/ml}$ | 1.9                 |
|                                                           | 300 $\mu\text{g/ml}$ | 1.8                 |
| Chloroform-fraction of<br><i>Strychni Ignatii Semen</i>   | 100 $\mu\text{g/ml}$ | 70.5                |
|                                                           | 300 $\mu\text{g/ml}$ | 90.6                |
| Ethylacetate-fraction of<br><i>Strychni Ignatii Semen</i> | 100 $\mu\text{g/ml}$ | 19.0                |
|                                                           | 300 $\mu\text{g/ml}$ | 45.6                |
| Water-fraction of                                         | 100 $\mu\text{g/ml}$ | 6.0                 |

|                               |                                |      |
|-------------------------------|--------------------------------|------|
| <i>Strychni Ignatii Semen</i> | 300 $\mu\text{g}/\text{m}\ell$ | 27.5 |
|-------------------------------|--------------------------------|------|

### 3-2. *Corydalis Tuber* and *Pharbitidis Seed*

The affinities for 5-HT<sub>4</sub> receptor of the extracts extracted from hexane, chloroform, ethylacetate and water of Example 2 were compared. The method of experiment was the same as the Experimental Example 1-1. As shown in Table 15, the extract (fraction) from chloroform was the most effective.

[Table 15]

|                                                  | Concentration                  | Inhibition ratio(%) |
|--------------------------------------------------|--------------------------------|---------------------|
| Hexane-fraction of<br><i>Corydalis Tuber</i>     | 100 $\mu\text{g}/\text{m}\ell$ | 0.3                 |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 21.0                |
| Chloroform-fraction of <i>Corydalis Tuber</i>    | 100 $\mu\text{g}/\text{m}\ell$ | 86.8                |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 99.6                |
| Ethylacetate-fraction of <i>Corydalis Tuber</i>  | 100 $\mu\text{g}/\text{m}\ell$ | 44.9                |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 79.7                |
| Water-fraction of<br><i>Corydalis Tuber</i>      | 100 $\mu\text{g}/\text{m}\ell$ | 34.5                |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 45.4                |
| Hexane-fraction of<br><i>Pharbitidis Seed</i>    | 100 $\mu\text{g}/\text{m}\ell$ | 41.9                |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 53.8                |
| Chloroform-fraction of <i>Pharbitidis Seed</i>   | 100 $\mu\text{g}/\text{m}\ell$ | 68.9                |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 74.1                |
| Ethylacetate-fraction of <i>Pharbitidis Seed</i> | 100 $\mu\text{g}/\text{m}\ell$ | 52.6                |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 34.2                |
| Water-fraction of<br><i>Pharbitidis Seed</i>     | 100 $\mu\text{g}/\text{m}\ell$ | 48.0                |
|                                                  | 300 $\mu\text{g}/\text{m}\ell$ | 57.1                |

<Experimental Example 4> Antagonistic effect of the extracts of Example 1 on 5-HT<sub>3</sub>

receptors using the colon of guinea pig

An organ bath experiment was performed by using the colon of guinea pig and the extracts from 50% ethanol of the Example 1 to measure the antagonistic effects of the extracts on 5-HT<sub>3</sub> receptor (Briejer M et al., The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound. *European Journal of Pharmacology* 423, pp.71-83, 2001).

Laparotomy was performed to extirpate the colon of guinea pig after CO<sub>2</sub> asphyxiation. And, the extirpated colon with a parallel two stirrup was fixed.

The colon was stabilized at least for 30 min before treated with the extracts, and gradually the tension of the colon became 1g (the tension before loading the sample is 0.0g). For response of the extracts, methacholine (3  $\mu$ M) was added to the colon to induce contraction of the colon. And, the colon was stabilized for 15min, treated with the extracts to make each sample to have the same concentration, and cultured for 15min. After 0.1 $\mu$ M of serotonin(5-HT) was treated thereto, the contraction of the colon was checked, and then the colon was washed out, and treated with the extracts repeatedly to prepare a sample and 0.3 $\mu$ M of serotonin(5-HT). The inhibitive effects of the sample after treated with 0.1, 0.3, 1, 3, 10 and 30 $\mu$ M of serotonin(5-HT<sub>3</sub>) by repeatedly using the method are shown in the following Table 16. The value of IC<sub>50</sub> of the extract of *Pharbitidis seed* from 50% ethanol-water was 27.8 ug/ml, and that of the extract of *Corydalis Tuber* from an 50% ethanol-water was 76.5 ug/ml, and that of the extract of *Strychni Ignatii Semen* from an 50% ethanol-water was 138.7 ug/ml.

[Table 16]

|                | Inhibition ratio for a 5-HT induced contract(%) |                        |                         |                               |
|----------------|-------------------------------------------------|------------------------|-------------------------|-------------------------------|
| Concentration  | <i>Sinapis Semen</i>                            | <i>Corydalis Tuber</i> | <i>Pharbitidis Seed</i> | <i>Strychni Ignatii Semen</i> |
| 30 $\mu$ g/ml  | 4.4                                             | 30.4                   | 73.3                    | -13.6                         |
| 100 $\mu$ g/ml | 20.5                                            | 59.0                   | 90.0                    | 34.8                          |
| 300 $\mu$ g/ml | 32.5                                            | 84.0                   | 93.0                    | 93.0                          |

<Experimental Example 5> Agonistic effect of the extracts of Example 1 on 5-HT<sub>4</sub> receptors using the oesophagus segment of Wister male rats

An organ bath experiment was performed to the oesophagus segment of Wister male rats, and the extracts from 50% ethanol of Example 1 to measure the agonistic effect of the extracts on 5-HT<sub>4</sub> receptors. The measuring method was disclosed in the document of Briejer M et al. (The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound. *European Journal of Pharmacology*, 423, pp.71-83, 2001; Sonda S et al., Synthesis and pharmacological properties of benzamide derivatives as selective serotonin 4 receptor agonists. *Bioorganic & Medicinal Chemistry*, 12, pp.2737-2747, 2004).

Laparotomy was performed to extirpate the oesophagus of SD rat after CO<sub>2</sub> asphyxiation. The extirpated colon with a parallel two stirrup was fixed.

The colon was stabilized at least for 60 min before treated with the extracts, and gradually the tension of the oesophagus became 1g (the tension before loading the sample is 0.0 g) for early 30min. For response of the extracts, carbachol(3  $\mu$ M) was added to the oesophagus to induce contraction, and the oesophagus was stabilized, and then treated with 0.1, 0.3, 1, 3, 10, 30 $\mu$ M of serotonin(5-HT) to set the maximum relaxation strength 100% at this time. After the oesophagus was washed out, the solution was changed for stabilization for 1hour at 15min interval. Then, the oesophagus was treated with carbachol (3  $\mu$ M) to induce contraction, and stabilized. And, the contractive effects of the oesophagus were measured after treated with 3, 10, 30, 100, 300  $\mu$ g/ml of the extracts. At this time, only the extracts showing the contractive effect to the oesophagus were treated after they were treated with GR13808(30 nM), and the agonistic effects of the extracts on a 5-HT<sub>4</sub> receptor were measured. The results are shown in the following Table 17.

The values of EC<sub>50</sub> (median effective concentration) of the extract of *Corydalis Tuber* from 50% ethanol-water was 12.1 ug/ml, and that of the extract of *Pharitidis seed* from 50% ethanol-water was 67.4 ug/ml, and that of the extract of *Strychni Ignatii Semen* from 50% ethanol-water was 38.8 ug/ml.

[Table 17]

|  | Reactivity by the change of a concentration (%) |
|--|-------------------------------------------------|
|--|-------------------------------------------------|

| Concentration        | <i>Sinapis Semen</i> | <i>Corydalis Tuber</i> | <i>Pharbitidis Seed</i> | <i>Strychni Ignatii Semen</i> |
|----------------------|----------------------|------------------------|-------------------------|-------------------------------|
| 3 $\mu\text{g/ml}$   | 11.0                 | 23.9                   | 5.9                     | 12.3                          |
| 10 $\mu\text{g/ml}$  | 16.8                 | 37.9                   | -14.2                   | 21.9                          |
| 30 $\mu\text{g/ml}$  | 26.6                 | 55.3                   | 24.2                    | 34.1                          |
| 100 $\mu\text{g/ml}$ | 38.0                 | 76.3                   | 55.1                    | 50.8                          |
| 300 $\mu\text{g/ml}$ | 74.0                 | 129.3                  | 95.0                    | 101.6                         |

<Experimental Example 6> Confirmation of delayed gastric emptying effect of the extracts of the present invention

The delayed gastric emptying effects of the extracts from 50% ethanol-water in Example 1 and the mixtures of Example 3 were measured by using delayed gastric emptying model (Ozaki A and Sukamoto et al., Improvement of cisplatin-induced emesis and delayed gastric emptying by KB-R6933, a novel 5-HT<sub>3</sub> receptor antagonist. *General pharmacology*, 33, pp.283-288, 1999).

200~250g of male SD rats were bred with supplying standard food and water at 22-24 °C and 60~80RH% (relative humidity %) for 1 week. And, the rats were divided by the weight, and starved for 24 hours. Each of the extracts were dissolved in physiological salt solution fixed dosage or Hydroxypropylmethylcellulose (HPMC, 3%), and the solution was administrated orally to the rats. After 60 min, 10mg/kg of cisplatin (dissolved in physiological salt solution at 50°C and cooled at 37 °C at the administration) was administered to an abdominal cavity of the rats. And, 1.5ml of semisolid test meal (0.05 % phenol red solution containing 1.5 % MC) were orally administered to each rat. After 15~30 min, the rats were killed to remove the stomach, and the amount of the remained phenol red in the stomach was measured. The stomach and contents were dissolved in 100ml of 0.1N NaOH solution for 20 seconds, and were left at room temperature for 1hour. And, 5ml of the homogenate was moved to tube. Then, 0.5ml of trichloroacetic acid (20%) was added to the tube for protein precipitation, and the tube was centrifuged at 2500× g for 20 min. And, 2ml of 0.5N NaOH solution was added thereto as equivalent liquid, and the absorbance was measured at 560nm (ABS<sub>560nm</sub>). The gastric emptying rate was calculated by the following Math Figure 3.

[Math Figure 3]

$$\text{Gastric emptying (\%)} = [1 - (B/A)] \times 100$$

A: The whole amount of phenol red recovered from the stomach immediately after the phenol red administration

B: The amount of phenol red remaining in the stomach after the phenol red administration

The results about delayed gastric emptying effects of the extracts and mixtures thereof were shown in the following Tables 18 and 19. Each extract showed the delayed gastric emptying effect (Table 18), and the mixtures of the extracts showed the delayed gastric emptying effect (Table 19). Particularly, the mixture of the extracts of *Corydalis Tuber* and *Pharitidis seed*, and the mixture of the extracts of *Corydalis Tuber* and *Strychni Ignatii Semen* were the most effective.

#### 1) The delayed gastric emptying effect of the extracts

[Table 18]

|                        | Dosage (mg/kg) | Gastric emptying ratio(%) |
|------------------------|----------------|---------------------------|
| Normal                 | -              | 84.4                      |
| Control                | -              | 54.6                      |
| <i>Sinapis Semen</i>   | 1              | 50.7                      |
|                        | 10             | 67.9                      |
|                        | 30             | 81.7                      |
|                        | 100            | 81.5                      |
|                        | Dosage(mg/kg)  | Gastric emptying ratio(%) |
| Normal                 | -              | 68.4                      |
| Control                | -              | 43.2                      |
| <i>Corydalis Tuber</i> | 1              | 38.6                      |

|                               |               |                           |
|-------------------------------|---------------|---------------------------|
|                               | 10            | 64.7                      |
|                               | 30            | 64.5                      |
|                               | 100           | 63.7                      |
|                               | Dosage(mg/kg) | Gastric emptying ratio(%) |
| Normal                        | -             | 79.3                      |
| Control                       | -             | 43.0                      |
| <i>Pharbitidis Seed</i>       | 1             | 40.6                      |
|                               | 3             | 73.2                      |
|                               | 10            | 72.8                      |
|                               | 30            | 70.3                      |
|                               | Dosage(mg/kg) | Gastric emptying ratio(%) |
| Normal                        | -             | 85.2                      |
| Control                       | -             | 68.8                      |
| <i>Strychni Ignatii Semen</i> | 3             | 72.3                      |
|                               | 10            | 85.9                      |
|                               | 30            | 85.4                      |

In the above table, 'normal' represents a normal group without cisplatin and the extract of the present invention, and 'control' represents a positive control group with a physiological salt solution.

## 2) The delayed gastric emptying effect of the mixtures of the extracts

[Table 19]

|                                | Mixed ratio | Dosage(mg/kg) | Gastric emptying ratio(%) |
|--------------------------------|-------------|---------------|---------------------------|
| Normal                         |             |               | 90.2                      |
| Control                        |             |               | 69.0                      |
| <i>Sinapis Semen+Corydalis</i> | 30:10:1:10  | 40            | 69.0                      |

|                                                                 |            |    |      |
|-----------------------------------------------------------------|------------|----|------|
| <i>Tuber+Pharbitidis Seed</i><br><i>+Strychni Ignatii Semen</i> | 30:10:1:3  | 40 | 86.7 |
|                                                                 | 30:3:1:10  | 40 | 88.0 |
|                                                                 | 30:3:1:3   | 40 | 89.0 |
|                                                                 | 10:3:1:3   | 40 | 88.7 |
|                                                                 | 10:10:1:10 | 40 | 85.2 |
|                                                                 | 10:10:1:3  | 40 | 85.9 |
|                                                                 | 10:3:1:10  | 40 | 87.1 |
|                                                                 | 3:3:1:3    | 40 | 87.8 |
| <i>Sinapis Semen+Corydalis</i><br><i>Tuber+Pharbitidis Seed</i> | 30:10:1    | 30 | 77.7 |
|                                                                 | 30:3:1     | 30 | 89.1 |
|                                                                 | 10:10:1    | 30 | 78.2 |
|                                                                 | 10:3:1     | 30 | 89.0 |
|                                                                 | 10:1:1     | 30 | 76.9 |
|                                                                 | 3:3:1      | 30 | 85.6 |
|                                                                 | 3:1:1      | 30 | 79.8 |
| <i>Sinapis Semen+Corydalis</i><br><i>Tuber</i>                  | 10:1       | 10 | 77.2 |
|                                                                 | 3:1        | 10 | 84.1 |
|                                                                 | 1:1        | 10 | 76.9 |
| <i>Sinapis Semen+Pharbitidis</i><br><i>Seed</i>                 | 30:1       | 10 | 78.2 |
|                                                                 | 10:1       | 10 | 89.3 |
|                                                                 | 3:1        | 10 | 77.9 |
| <i>Corydalis Tuber+Pharbitidis</i><br><i>Seed</i>               | 10:1       | 10 | 89.1 |
|                                                                 | 3:1        | 10 | 95.4 |
|                                                                 | 1:1        | 10 | 92.5 |
| <i>Corydalis Tuber+Strychni</i><br><i>Ignatii Semen</i>         | 3:1        | 10 | 89.4 |
|                                                                 | 1:1        | 10 | 90.1 |
|                                                                 | 1:3        | 10 | 89.9 |
| <i>Pharbitidis Seed +Strychni</i>                               | 1:1        | 10 | 88.5 |

|                      |      |    |      |
|----------------------|------|----|------|
| <i>Ignatii Semen</i> | 1:3  | 10 | 89.0 |
|                      | 1:10 | 10 | 87.2 |

In the above table, 'normal' represents a normal group without cisplatin and an extract of the present invention, and 'control' represents a positive control group with a physiological salt solution.

<Experimental Example 7> Confirmation of the semi-solid gastric emptying delaying effect of the extracts of the present invention

The semi-solid gastric emptying effects of the extracts from 50% ethanol-water in Example 1 and the mixtures of Example 3 were measured by using semi-solid gastric emptying model (Calatayud S, Garcia-Zaragoza E, Hernandez C, Quintana E, Felipe V, Esplugues JV, Barrachina MD. Downregulation of nNOS and synthesis of PGs associated with endotoxin-induced delay in gastric emptying. Am J Physiol Gastrointest Liver Physiol. 2002 Dec;283(6):G1360-7).

200~250g of male SD rats were bred with supplying standard food and water at 22-24 °C and 60~80RH% (relative humidity %) for 1 week. And, the rats were divided by the weight, and starved for 24 hours. During the starving time, drinking water was supplied, but the supplying was stopped 3 hours before the experiment. Each extract was dissolved in physiological salt solution fixed dosage or Hydroxypropylmethylcellulose (HPMC, 3%), and the solution was administrated orally to the rat. After 45 min, 2ml of semisolid test meal (0.05 % phenol red solution containing 1.5 % MC) made by crushing down an animal food dissolved in water was orally administered to each rat. After 35 min, the rats were killed to remove the stomach, and the stomach having semisolid test meal weighed. The gastric emptying rates were calculated by the following Math Figure 4.

[Math Figure 4]

Gastric emptying(%) =  $[1 - (\text{weight of semisolid meal remained in stomach} / \text{weight of semisolid meal remained in 0 hour's stomach})] \times 100$

("Weight of semisolid meal remained in 0 hour's stomach" is measured from remained semisolid meal obtained from the stomach immediately after it's administration)

The results about the gastric emptying delaying effects of the extracts and their mixtures were shown in the following Tables 20 and 21. Each extract showed the gastric emptying delaying effect (Table 20), and the mixture of extracts showed the more effective gastric emptying delaying effect (Table 21) than the extracts. Particularly, the mixture of the extracts of *Corydalis Tuber* and *Pharbitidis seed*, and the mixture of the extracts of *Corydalis Tuber* and *Strychni Ignatii Semen* were the most effective.

1) The semi-solid gastric emptying effect of the extracts

[Table 20]

|                         | Dosage(mg/kg) | Gastric emptying ratio(%) |
|-------------------------|---------------|---------------------------|
| Control                 | -             | 31.5                      |
| <i>Sinapis Semen</i>    | 1             | 36.0                      |
|                         | 10            | 36.2                      |
|                         | 30            | 47.3                      |
|                         | 100           | 44.4                      |
| Control                 | -             | 34.1                      |
| <i>Corydalis Tuber</i>  | 1             | 38.7                      |
|                         | 10            | 55.6                      |
|                         | 30            | 47.4                      |
|                         | 100           | 48.6                      |
| Control                 | -             | 33.0                      |
| <i>Pharbitidis Seed</i> | 0.3           | 35.6                      |
|                         | 1             | 45.6                      |
|                         | 3             | 53.2                      |
|                         | 10            | 37.5                      |
| Control                 | -             | 35.4                      |

36

|                               |    |      |
|-------------------------------|----|------|
| <i>Strychni Ignatii Semen</i> | 1  | 38.4 |
|                               | 3  | 42.7 |
|                               | 10 | 53.0 |

In the above table, 'control' means control group to which a physiological salt solution instead of the extract is administered.

## 2) The semi-solid gastric emptying effect of the mixtures of extracts

[Table 21]

|                                                                               | Mixed ratio | dosage(mg/kg) | Gastric emptying ratio (%) |
|-------------------------------------------------------------------------------|-------------|---------------|----------------------------|
| Control                                                                       |             |               | 20.4                       |
| <i>Sinapis Semen+Corydalis Tuber+Pharbitidis Seed +Strychni Ignatii Semen</i> | 30:10:1:10  | 40            | 48.9                       |
|                                                                               | 30:10:1:3   | 40            | 49.0                       |
|                                                                               | 30:3:1:10   | 40            | 50.8                       |
|                                                                               | 30:3:1:3    | 40            | 53.2                       |
|                                                                               | 10:3:1:3    | 40            | 52.8                       |
|                                                                               | 10:10:1:10  | 40            | 44.4                       |
|                                                                               | 10:10:1:3   | 40            | 47.6                       |
|                                                                               | 10:3:1:10   | 40            | 48.5                       |
|                                                                               | 3:3:1:3     | 40            | 52.1                       |
| <i>Sinapis Semen+Corydalis Tuber+Pharbitidis Seed</i>                         | 30:10:1     | 30            | 47.3                       |
|                                                                               | 30:3:1      | 30            | 51.2                       |
|                                                                               | 10:10:1     | 30            | 48.0                       |
|                                                                               | 10:3:1      | 30            | 49.4                       |
|                                                                               | 10:1:1      | 30            | 45.7                       |
|                                                                               | 3:3:1       | 30            | 50.5                       |
|                                                                               | 3:1:1       | 30            | 44.5                       |

|                                                     |      |    |      |
|-----------------------------------------------------|------|----|------|
| <i>Sinapis Semen+Corydalis<br/>Tuber</i>            | 10:1 | 10 | 45.6 |
|                                                     | 3:1  | 10 | 42.7 |
|                                                     | 1:1  | 10 | 48.5 |
| <i>Sinapis Semen+Pharbitidis<br/>Seed</i>           | 30:1 | 10 | 48.2 |
|                                                     | 10:1 | 10 | 47.5 |
|                                                     | 3:1  | 10 | 43.0 |
| <i>Corydalis Tuber+Pharbitidis<br/>Seed</i>         | 10:1 | 10 | 54.5 |
|                                                     | 3:1  | 10 | 57.8 |
|                                                     | 1:1  | 10 | 44.5 |
| <i>Corydalis Tuber+Strychni<br/>Ignatii Semen</i>   | 3:1  | 10 | 48.3 |
|                                                     | 1:1  | 10 | 50.3 |
|                                                     | 1:3  | 10 | 40.2 |
| <i>Pharbitidis Seed +Strychni<br/>Ignatii Semen</i> | 1:1  | 10 | 45.8 |
|                                                     | 1:3  | 10 | 49.8 |
|                                                     | 1:10 | 10 | 42.9 |

In the above table, 'control' means control group to which a physiological salt solution instead of the extract is administered.

<Experimental Example 8> Confirmation of the upper gastrointestinal motility effect of the extracts of the present invention

The upper gastrointestinal motility effect of the extracts from 50% ethanol-water in Example 1 and the mixtures of Example 3 were measured.

220~230g of male SD rats were bred with supplying standard food and water at 22-24 °C and 60~80RH% (relative humidity %) for 1 week. And, the rats were divided by the weight, and the rats were starved for 24 hours. For inhibiting the upper gastrointestinal motility effect, 1mg/kg of atropine (dissolved in physiological salt solution at 50°C and cooled at 37 °C at the administration) was administrated to the rat's abdominal cavity. Then, each extract's fixed dosage was dissolved in physiological salt solution or

Hydroxypropylmethylcellulose (HPMC, 3%), and the solution was administrated orally to the rats. After 1 hour, 1ml of fluorescein isocyanate-labeled dextran (FITC)(used 5mM of FITC solution diluted up to 10 times in physiological salt solution) was administered to each rat. After 15min, autopsy was done to the rats. And, a small intestine from the portio pyorica ventriculi to the appendix was cut equally to 10 pieces. The tissues were soaked in 1ml of physiological salt solution, and left in a refrigerator. After 1 day, the fluorescence of each equivalent liquid was detected. The distribution ratio of fluorescein isocyanate-labeled dextran in the small intestine was obtained by using the Math Figure 5 from the detected values, and the motility of a gastrointestinal tract represented to a geometric center to the distribution of fluorescein isocyanate-labeled dextran. And, the stomach was separated, and weighed to measure the gastric emptying.

[Math Figure 5]

- 1) Fraction of fluorescence per segment = (fluorescence of each segment / overall)x100
- 2) Geometric center =  $[\sum (\text{fraction of fluorescence per segment} \times \text{segment number})]/100$

The effects of the gastrointestinal motility to each herbal extract and mixtures thereof were shown in the following Table 22 (The delayed effect of gastrointestinal motility effect of extracts of the present invention) and Table 23 (The gastric emptying effect in the delayed model of gastrointestinal motility effect of extracts of the present invention). It was confirmed that the mixtures of herbal extracts are more effective than the herbal extracts.

[Table 22]

|                  | Herb                    | Dosage<br>(Mixed ratio) | Geometric center |
|------------------|-------------------------|-------------------------|------------------|
| Control          | -                       | -                       | 3.46             |
| A herbal extract | <i>Sinapis Semen</i>    | 30                      | 3.62             |
|                  | <i>Corydalis Tuber</i>  | 30                      | 4.25             |
|                  | <i>Pharbitidis Seed</i> | 3                       | 3.54             |
|                  | Strychni Ignatii Semen  | 10                      | 3.96             |

|                            |                                                                                    |               |      |
|----------------------------|------------------------------------------------------------------------------------|---------------|------|
| Control                    | -                                                                                  | -             | 3.32 |
| A mixture of herb extracts | <i>Sinapis Semen + Corydalis Tuber + Pharbitidis Seed + Strychni Ignatii Semen</i> | 40 (30:3:1:3) | 4.04 |
|                            | <i>Sinapis Semen + Corydalis Tuber + Pharbitidis Seed</i>                          | 30 (30:3:1)   | 3.66 |
|                            | <i>Sinapis Semen + Corydalis Tuber</i>                                             | 10 (10:1)     | 3.66 |
|                            | <i>Sinapis Semen + Pharbitidis Seed</i>                                            | 10 (30:1)     | 3.58 |
|                            | <i>Corydalis Tuber + Pharbitidis Seed</i>                                          | 10 (3:1)      | 4.09 |
|                            | <i>Corydalis Tuber + Strychni Ignatii Semen</i>                                    | 10 (1:1)      | 3.66 |
|                            | <i>Pharbitidis Seed + Strychni Ignatii Semen</i>                                   | 10 (1:3)      | 3.58 |
| Control                    | -                                                                                  | -             | 3.32 |
| A mixture of herb extracts | <i>Corydalis Tuber + Pharbitidis Seed</i>                                          | 0.3 (3:1)     | 3.50 |
|                            |                                                                                    | 1 (3:1)       | 4.09 |
|                            |                                                                                    | 3 (3:1)       | 3.66 |
|                            |                                                                                    | 10 (3:1)      | 3.66 |
|                            |                                                                                    | 30 (3:1)      | 3.58 |

At the above table, “control” means a positive control group treated with a physiological salt solution instead of the extract.

[Table 23]

|  | Herb | Dosage<br>(mixed ratio) | Gastric emptying<br>ratio (%) |
|--|------|-------------------------|-------------------------------|
|--|------|-------------------------|-------------------------------|

|                                 |                                                                                             |               |       |
|---------------------------------|---------------------------------------------------------------------------------------------|---------------|-------|
| Control                         | -                                                                                           | -             | 52.8  |
| A herbal extract                | <i>Sinapis Semen</i>                                                                        | 30            | 64.94 |
|                                 | <i>Corydalis Tuber</i>                                                                      | 30            | 75.89 |
|                                 | <i>Pharbitidis Seed</i>                                                                     | 3             | 59.48 |
|                                 | <i>Strychni Ignatii Semen</i>                                                               | 10            | 65.17 |
| Control                         | -                                                                                           | -             | 48.28 |
| A mixture of<br>herbal extracts | <i>Sinapis Semen + Corydalis<br/>Tuber + Pharbitidis Seed +<br/>Strychni Ignatii Semen.</i> | 40 (30:3:1:3) | 70.52 |
|                                 | <i>Sinapis Semen + Corydalis<br/>Tuber + Pharbitidis Seed</i>                               | 30 (30:3:1)   | 73.63 |
|                                 | <i>Sinapis Semen + Corydalis<br/>Tuber</i>                                                  | 10 (10:1)     | 68.51 |
|                                 | <i>Sinapis Semen + Pharbitidis<br/>Seed</i>                                                 | 10 (30:1)     | 63.58 |
|                                 | <i>Corydalis Tuber + Pharbitidis<br/>Seed</i>                                               | 10 (3:1)      | 81.72 |
|                                 | <i>Corydalis Tuber + Strychni<br/>Ignatii Semen</i>                                         | 10 (1:1)      | 73.66 |
|                                 | <i>Pharbitidis Seed + Strychni<br/>Ignatii Semen</i>                                        | 10 (1:3)      | 73.58 |
| Control                         | -                                                                                           | -             | 48.28 |
| A mixture of<br>herbal extracts | <i>Corydalis Tuber + Pharbitidis<br/>Seed</i>                                               | 0.3 (3:1)     | 71.60 |
|                                 |                                                                                             | 1 (3:1)       | 82.73 |
|                                 |                                                                                             | 3 (3:1)       | 80.51 |
|                                 |                                                                                             | 10 (3:1)      | 73.18 |
|                                 |                                                                                             | 30 (3:1)      | 64.80 |

At the above table, “control” means a positive control group treated with a physiological salt solution instead of the extract.

The following preparation examples contain one or more extracts selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* of the present invention. But, the preparation examples intended only to explain the present invention in the concrete manner, and are not intended to limit the scope of the present invention in any way.

<Preparation Example 1> Preparation of an injectable dosage form

The extracts of Example 1..... 100mg  
Sodium metabisulphite ..... 3.0mg  
Methylparaben ..... 0.8mg  
Propylparaben..... 0.1mg  
Injectable distilled water..... Proper quantity

The ingredients were mixed and made to 2ml of total volume by a method known in the art. And, the mixture was filled into an ampule of 2ml dose, and sterilized to prepare an injectable dosage form

<Preparation Example 2> Preparation of an injectable dosage form

The extracts of Example 2..... 10~30mg  
Sodium metabisulphite ..... 3.0mg  
Methylparaben ..... 0.8mg  
Propylparaben..... 0.1mg  
Injectable distilled water.....Proper quantity

The ingredients were mixed and made to 2ml of total volume by a method known in the art. And, the mixture was filled into an ampule of 2ml dose, and sterilized to prepare an injectable dosage form.

<Preparation Example 3> Preparation of an injectable dosage form

The extracts of Example 3..... 100~300mg

|                                 |                 |
|---------------------------------|-----------------|
| Sodium metabisulphite .....     | 3.0mg           |
| Methylparaben .....             | 0.8mg           |
| Propylparaben.....              | 0.1mg           |
| Injectable distilled water..... | Proper quantity |

The ingredients were mixed and made to 2ml of total volume by a method known in the art. And, the mixture was filled into an ampule of 2ml dose, and sterilized to prepare an injectable dosage form.

<Preparation Example 4> Preparation of a tablet

|                                |                 |
|--------------------------------|-----------------|
| The extracts of Example 1..... | 100~300mg       |
| Lactose .....                  | 100mg           |
| Starch.....                    | 100mg           |
| Magnesium stearate .....       | Proper quantity |

The ingredients were mixed and made to a tablet by a tablet preparation method known in the art.

<Preparation Example 5> Preparation of a tablet

|                                |                 |
|--------------------------------|-----------------|
| The extracts of Example 2..... | 10~30mg         |
| Lactose .....                  | 100mg           |
| Starch.....                    | 100mg           |
| Magnesium stearate .....       | Proper quantity |

The ingredients were mixed and made to a tablet by a tablet preparation method known in the art.

<Preparation Example 6> Preparation of a tablet

|                                |            |
|--------------------------------|------------|
| The extracts of Example 3..... | 100~1000mg |
|--------------------------------|------------|

Lactose ..... 100mg  
Starch..... 100mg  
Magnesium stearate ..... Proper quantity

The ingredients were mixed and made to a tablet by a tablet preparation method known in the art.

<Preparative Example 7> Preparation of a capsule

The extracts of Example 1..... 100~300mg  
Lactose ..... 50mg  
Starch..... 50mg  
talc..... 2mg  
Magnesium stearate ..... Proper quantity

The ingredients were mixed and filled into a gelatin capsule by a capsule preparation method known in the art to prepare the capsule.

<Preparative Example 8> Preparation of a capsule

The extracts of Example 2..... 10~30mg  
Lactose ..... 50mg  
Starch..... 50mg  
talc..... 2mg  
Magnesium stearate ..... Proper quantity

The ingredients were mixed and filled into a gelatin capsule by a capsule preparation method known in the art to prepare the capsule.

<Preparative Example 9> Preparation of a capsule

The extracts of Example 3..... 100~1000mg  
Lactose ..... 50mg

|                          |                 |
|--------------------------|-----------------|
| Starch.....              | 50mg            |
| talc.....                | 2mg             |
| Magnesium stearate ..... | Proper quantity |

The ingredients were mixed and filled into a gelatin capsule by a capsule preparation method known in the art to prepare the capsule.

<Preparation Example 10> Preparation of liquid formulation

|                                                 |                      |
|-------------------------------------------------|----------------------|
| The extracts of Example 1.....                  | 100~300mg            |
| Sugar.....                                      | 20 g                 |
| Isomerized sugar.....                           | 20 g                 |
| Lemon spices.....                               | Proper quantity      |
| Purified water.....                             | Quantity to make the |
| total volume of the liquid formulation to 100ml |                      |

The ingredients were mixed by a preparing method for liquid formulation known in the art, filled into a brown bottle of 100ml, and sterilized to prepare a liquid formulation.

<Preparation Example 11> Preparation of liquid formulation

|                                             |                      |
|---------------------------------------------|----------------------|
| The extracts of Example 2.....              | 10~30mg              |
| Sugar.....                                  | 20 g                 |
| Isomerized sugar.....                       | 20 g                 |
| Lemon spices.....                           | Proper quantity      |
| Purified water.....                         | Quantity to make the |
| total volume of liquid formulation to 100ml |                      |

The ingredients were mixed by a preparing method for liquid formulation known in the art, filled into a brown bottle of 100ml, and sterilized to prepare a liquid formulation.

<Preparation Example 12> Preparation of liquid formulation

|                                |            |
|--------------------------------|------------|
| The extracts of Example 3..... | 100~1000mg |
| Sugar.....                     | 20 g       |
| Isomerized sugar.....          | 20 g       |

Lemon spices..... Proper quantity

Purified water..... Quantity to make the

total volume of liquid formulation to 100ml

The ingredients were mixed by a preparing method for liquid formulation known in the art, filled into a brown bottle of 100ml, and sterilized to prepare a liquid formulation.

### INDUSTRIAL APPLICABILITY

The extracts of the present invention or mixtures thereof may be used as a pharmaceutical composition for preventing and treating gastrointestinal motility disorder, and a health functional food since it can facilitate gastrointestinal motility as their HT<sub>3</sub> receptor antagonism and/or HT<sub>4</sub> receptor agonism.

### SEQUENCE LIST TEXT

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**WHAT IS CLAIMED IS:**

1. Herbal extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*.
2. The herbal extracts of claim 1, wherein the herbal extract is extracted from water, a lower alcohol of C1~C4, or a mixed solvent thereof.
3. The herbal extracts of claim 1, wherein the herbal extract is extracted from non-polar solvent selected from hexane, chloroform, ethylacetate, and water.
4. The herbal extracts of claim 1, wherein the herbal extract is a mixture of the herbal extracts of *Sinapis Semen* and *Corydalis Tuber*.
5. The herbal extracts of claim 4, wherein the mixture has the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* from 1: 1 to 10:1 weight in weight(w/w).
6. The herbal extracts of claim 1, wherein the herbal extract is the mixture of the herbal extracts of *Sinapis Semen* and *Pharbitidis Seed*.
7. The herbal extracts of claim 6, wherein the mixture has the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Pharbitidis Seed* from 1: 1 to 30:1(w/w).
8. The herbal extracts of claim 1, wherein the herbal extract is the mixture of the herbal extracts of *Corydalis Tuber* and *Pharbitidis Seed*.
9. The herbal extracts of claim 8, wherein the mixture has the mixture ratio of the herbal extract of *Corydalis Tuber* : the herbal extract of *Pharbitidis Seed* from 1: 1 to 10:1 (w/w).
10. The herbal extracts of claim 1, wherein the herbal extract is the mixture of the herbal extracts of *Corydalis Tuber* and *Strychni Ignatii Semen*.

11. The herbal extracts of claim 10, wherein the mixture has the mixture ratio of the herbal extract of *Corydalis Tuber*: the herbal extract of *Strychni Ignatii Semen* from 3: 1 to 1:3 (w/w).

12. The herbal extracts of claim 1, wherein the herbal extract is the mixture of the herbal extracts of *Pharbitidis Seed* and *Strychni Ignatii Semen*.

13. The herbal extracts of claim 12, wherein the mixture has the mixture ratio of the herbal extract of *Pharbitidis Seed* : the herbal extract of *Strychni Ignatii Semen* from 1: 1 to 1:10 (w/w).

14. The herbal extracts of claim 1, wherein the herbal extract is the mixture of the herbal extracts of *Sinapis Semen*, *Corydalis Tuber*, and *Pharbitidis Seed*.

15. The herbal extracts of claim 14, wherein the mixture has the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* : the herbal extract of *Pharbitidis Seed* of (1~30): (1~10): 1 (w/w).

16. The herbal extracts of claim 1, wherein the herbal extract is the mixture of the herbal extracts of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed*, and *Strychni Ignatii Semen*.

17. The herbal extracts of claim 16, wherein the mixture has the mixture ratio of the herbal extract of *Sinapis Semen* : the herbal extract of *Corydalis Tuber* : the herbal extract of *Strychni Ignatii Semen* : the herbal extract of *Pharbitidis Seed* of (1~30): (1~10): 1 : (1~10) (w/w).

18. A composition for preventing and treating gastrointestinal motility disorder, wherein the composition contains the herbal extract of any one of claim 1 to claim 17 as active ingredient.

19. The composition of claim 18, wherein the gastrointestinal motility disorder is a disorder originated from hyperactivity of 5-HT<sub>3</sub> receptor and/or 5-HT<sub>4</sub> receptor antagonism.

20. The composition of claim 19, wherein the gastrointestinal motility disorder is a disorder selected functional dyspepsia such as early satiety, pain, epigastric distress, a false sense of satiety, heartburn, nausea and vomiting; ulcerative dyspepsia, non-ulcerative dyspepsia; reflux oesophagitis, paralysis of gastric motility; constipation; irritable bowel syndrome; hypersensitive colitis; diabetic gastrointestinal motility disorder; gastrointestinal motility disorder originated chemotherapy; and intestinal atresia originated motility disorder of digestive tract and myotonic dystrophy originated gastric intestinal disorder.

21. A health care food for preventing and improving gastrointestinal motility disorder containing a herbal extract of claim 1 to claim 17 as an activity ingredient.

22. The health care food of claim 21, wherein the food is powder, granule, tablet, capsule, syrup or beverage.

23. A method for preparing the herbal extracts of claim 1 comprising extracting one or more herbs selected from the group consisting of dried *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* by using water, a lower alcohol of C1~C4, or mixtures thereof from one to five times at 45~ 75°C for 65~ 80 hours.

24. A method for preparing one or more herbal extracts, polar solvent soluble extracts and non-polar solvent soluble extracts selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen*, comprising the first step that one or more herbs selected from the group consisting of *Sinapis Semen*, *Corydalis Tuber*, *Pharbitidis Seed* and *Strychni Ignatii Semen* are extracted by water, a lower alcohol or a mixture thereof, filtered and concentrated to obtain herbal extracts; the second step that the herbal extracts of the first step are treated sequentially by hexane, chloroform and ethylacetate to collect extracts soluble in non-polar solvent; and the third step that the extracts soluble in non-polar solvent of the second step are treated with water, methanol, butanol or a mixture thereof to obtain the herbal extracts soluble in polar solvent.