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Review article

A Review of Pharmacology and Toxicity of Stomachic Mixture Constituents

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Abstract

Stomachic mixture is used widely for the treatment of gastrointestinal conditions. However, the evidence for its efficacy and safety is scarce. The review of pharmacology and toxicity of stomachic mixture constituents provides information for patients and healthcare providers in making decision to use this drug. Stomachic mixture products registered in Thailand as shown in the Thai Food and Drug Administration database in 2018 contained sodium bicarbonate as the main active ingredient of the stomachic mixture. The herbal components in the stomachic recipe registered to Thai FDA were volatile oils, anthraquinone glycosides, bitter substances, and spicy substances. The amount of each ingredient in the stomachic mixture, when the mixture was used as recommended, was lower than toxic doses of the component. However, the sodium amount in the stomachic mixture could be high for patients requiring sodium restriction. Data regarding the use of stomachic mixture in pregnant and lactating women were insufficient. Therefore, the stomachic mixture should be avoided in patients requiring sodium restriction, pregnant women, and breastfeeding women. Side effects of stomachic mixture on the liver, kidney, heart, gastrointestinal tract, and central nervous system and hypoglycemia are possible.

Keywords: mixture stomachica, stomachic mixture, sodium bicarbonate, thai traditional medicine

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บทความวิชาการ

การทบทวนวรรณกรรมเภสัชวิทยาและพิษวิทยาของส่วนประกอบในยาธาตุน้ำแดง

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บทคัดย่อ

ยาธาตุน้ำแดงเป็นยาที่ใช้อย่างแพร่หลายสำหรับรักษาอาการในระบบทางเดินอาหาร อย่างไรก็ตามไม่มีงานศึกษารองรับประสิทธิภาพและความปลอดภัยของยาธาตุน้ำแดง การทบทวนวรรณกรรมเภสัชวิทยาและพิษวิทยาของส่วนประกอบในยาธาตุน้ำแดงจะช่วยเพิ่มข้อมูลแก่ผู้ป่วยและบุคลากรสาธารณสุขประกอบการตัดสินใจใช้ยา จากสูตรตำรับยาธาตุน้ำแดงที่ขึ้นทะเบียนในประเทศไทยซึ่งแสดงไว้ในฐานข้อมูลของสำนักงานคณะกรรมการอาหารและยาในปี 2561 พบว่า ส่วนประกอบหลักของยาธาตุน้ำแดงคือโซเดียมและไบคาร์บอเนต สำหรับส่วนประกอบสมุนไพรในตำรับยาธาตุน้ำแดงซึ่งได้รับการขึ้นทะเบียนในประเทศไทย ประกอบด้วย น้ำมันหอมระเหย แอนทราควิโนน ไกลโคไซด์ สารที่มีรสขม และสารที่มีรสเผ็ด เมื่อรับประทานยาธาตุน้ำแดงตามขนาดยาที่แนะนำ ร่างกายจะได้รับส่วนประกอบเหล่านี้ในปริมาณต่ำกว่าขนาดที่ทำให้เกิดพิษ อย่างไรก็ตาม ปริมาณโซเดียมในยาธาตุน้ำแดงอาจมากเกินไปสำหรับผู้ป่วยที่ต้องจำกัดโซเดียม อีกทั้งยังมีข้อมูลการใช้ยาธาตุน้ำแดงในสตรีมีครรภ์และให้นมบุตรไม่เพียงพอ จึงไม่ควรใช้ยาธาตุน้ำแดงในผู้ป่วยที่ต้องจำกัดปริมาณโซเดียม สตรีมีครรภ์และให้นมบุตร และยาธาตุน้ำแดงอาจมีผลข้างเคียงต่อตับ ไต หัวใจ ทางเดินอาหาร และระบบประสาทส่วนกลาง รวมถึงอาจก่อให้เกิดภาวะน้ำตาลในเลือดต่ำได้

คำสำคัญ: ยาธาตุน้ำแดง โซเดียม ไบคาร์บอเนต ยาแผนไทย

Introduction

Traditional medicine is well established in Europe, Asia, Africa, and Arabian countries. In Asia, traditional Chinese medicine and Ayurvedic medicine influence traditional medicine in many countries including Thailand (1). Mixture stomachica or stomachic mixture is a recipe of an over the counter antacid and carminative (2) that was used widely in Thailand. The main active ingredients, except for sodium bicarbonate, are raw herb materials or herbal preparations. Although mixture stomachica is very popular and used frequently in Thailand, the evidence supporting its efficacy and safety is scarce. This review summarizes evidence of pharmacological effects and potential toxicities of the components of mixture stomachica which helps understand the pharmacology and toxicity of this recipe.

Approved products in Thailand

Until 2018, there were 31 formulations of stomachic mixture approved by Thai Food and Drug Administration (Thai FDA) (3). Only 17 approved formulations had information available in the Thai FDA database. The available information for the formulations is demonstrated in Table 1. The amount of peppermint oil in the peppermint spirit and camphor in camphor water was calculated using a 0.1 multiplicative factor

based on the requirement that the peppermint spirit and camphor water must contain not less than 0.9 ml and not more than 11 ml of peppermint oil, and not less than 0.9 mg and not more than 11 mg of camphor, respectively (4). From the review of the Thai FDA database, the common components of mixture stomachica were sodium bicarbonate, rhubarb (either as a powder or extract), peppermint oil, and ethanol. Minor ingredients were cardamom, Tinospora, camphor, gentian, aromatic ammonia, and ginger. All the minor constituents were either hydroalcohol extracted or alcoholic extracted. A trace amount of methanol (1.60± 0.39 µl/ml) could be found in some formulations (5). The suggested dosing of the registered products was a tablespoonful (15 ml) before a meal, three times a day.

Component of approved stomachic mixture

Sodium bicarbonate

Sodium bicarbonate is widely used as a home remedy for indigestion. It reacts with hydrochloric acid in the stomach as followed: $NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$. Sodium bicarbonate is an effective antacid with short action. However, it is not used as the first-line antacid because it has the lowest power in the acid-neutralizing capacity test (7.40 ± 0.12 mEq) among the inorganic antacids (6). Its reaction with hydrochloric acid results in carbon dioxide which can cause belching (7). Gas release induced by the ingestion of one- half teaspoon of sodium bicarbonate could be a major cause of gastric rupture (8). Metabolic alkalosis is also possible from chronic ingestion (9). However, the ingestion of sodium bicarbonate is generally safe. Sodium bicarbonate ingestion up to 150 mg/kg for 10 days was safe (10). Nevertheless, stomachic mixture contains 8.8 mg/ml of sodium and, therefore, should be avoided in those requiring sodium restriction such as stroke patients for which less than 1500 mg/day of sodium is allowed (Table 2) (11). World Health Organization (WHO) recommended sodium consumption of fewer than two grams per day to reduce the risk of hypertension (12). With the average consumption of approximately four grams of sodium per day in Thai people (13), the consumption of any amount of stomachic mixture should be avoided.

Table 1. Compositions of the stomachic mixture formulations as appeared in the Thai FDA database in 2018.

composition	number of formulations (total = 17)	quantity[1]	units
sodium bicarbonate	17	32.0 (18.0, 40.0)	mg/ml
compound rhubarb tincture	14	106.7 (16.7, 106.7)	µl/ml
peppermint oil	8 (6)[2]	2.0 (0.9, 2.0)	µl/ml
compound cardamom tincture	4	33.3 (33.3, 33.3)	µl/ml
camphor	3 (1)[3]	2.0 (0.8, 9.0)	mg/ml
compound tinospora tincture	3	33.3 (33.3, 33.3)	µl/ml
ginger tincture	3	53.3 (13.3, 66.7)	µl/ml
compound gentian tincture	2	38.3 (10.0, 66.7)	µl/ml
aromatic ammonia spirit	1	8.3 (8.3, 8.3)	µl/ml
ipecacuanha tincture	1	0.02 (0.02, 0.02)	ml/ml
rhubarb powder	1	75.0 (75.0, 75.0)	mg

1: Reported as median (minimum, maximum) and calculated from the formulations containing the composition.

2: The number of formulations containing peppermint spirit is shown in parenthesis.

3: The number of formulations containing concentrate camphor water is shown in parenthesis.

Table 2. Therapeutic and toxic doses of stomachic mixture components

composition	GI effect (dose/day)	amount of stomachic mixture required for GI effect	toxic dose in adult human	amount of stomachic mixture required for toxic effect
sodium bicarbonate	acid neutralization	45 ml as labeled	adverse cardiovascular effect (7.3 g/day equivalent to 2 g sodium (12))	183-405 ml*
rhubarb powder	laxative (1.5 g/day (18))	20 bottles*	no data	not estimable
peppermint oil	0.6-1.2 ml/day	300-1200 ml*	no data	no data
compound cardamom tincture	protective effect (0.64 g/day (58, 62))	not estimable	no data	not estimable
camphor	cooling sensation (5% w/w approximate to 50 mg/ml)	6-60 ml	convulsion (5-12 g)	2500-6000 ml*
compound tinospora tincture	bitter tonic (no data)	not estimable	ID_{50} = 1 g/kg	not estimable
ginger tincture	antiemesis (2 ml/day (93))	30-150 ml	mild GI side effects (5-8 ml/day (97))	75-600 ml*
compound gentian tincture	appetite stimulation (3 ml/day (124))	45-300 ml*	no data	no data
aromatic ammonia spirit	not known (no data)	not estimable	irritation dose (30 µg/ml)	not toxic
ipecacuanha tincture	induced emesis (15-30 ml once)	60-120 ml*	fatal dose (100 ml (145))	5000 ml*

*Exceeding the recommended daily consumption amount of stomachic mixture (45 ml)

Rhubarb (Polygonaceae)

Rhubarb (Rhizoma Rhei, Chinese rhubarb, kot-nam-tao) is the root and rhizome of *Rheum officinale* Baill. or *R. palmatum* L. (14). While another species of Rheum, *R. rhabarbarum*, is used as food, Chinese rhubarb has been used primarily as herbal medicine for the treatment of the gastrointestinal (GI) tract (14) and kidney disorders (15). The major constituents of Chinese rhubarb are anthraquinone and its glycoside derivatives e. g. emodin, rhein, sennosides, and rheinosides. Sennosides and rheinosides are irritants, thus stimulating the motility of large intestinal (14, 16). The laxative effects of rhubarb in GI tract are derived from the adrenaline antagonist activity, cholinergic neuron regulation, and aquaporin protein down-regulation (17). The laxative dose of rhubarb was reported as 0.5 g of powdered rhubarb for 3 times/day in critically ill patients (18) (Table 2).

Emodin and rhein help restore the balance of the intestinal flora, reduce injuries to the intestinal mucosa, and protect the liver from injuries during sepsis (19). In addition, *in vitro,* and *in vivo* studies have exhibited the benefits of rhubarb extract in oral cancer (20), hepatocellular carcinoma (21), pancreatitis (22,

23), anti-cariogenic bacteria (24) and anti-hepatitis-B viral infection (25). The potential side effects of Chinese rhubarb include GI discomfort, diarrhea (26), hepatotoxicity, and renal toxicity. A study in aged animals suggested that a high dose (40 g/kg/day) of ethanolic rhubarb extract has profound hepatic and renal toxicities (27, 28). Also, another animal experiment showed that rhubarb ethanolic extract caused liver fibrosis (15, 29). However, Chinese rhubarb demonstrates no serious adverse effects in human patients with chronic kidney disease (30). WHO recommends against the use of Chinese rhubarb in pregnancy and breastfeeding women according to insufficient safety data and possible adverse effects from its stimulant action (14). Furthermore, Chinese rhubarb can activate p-glycoprotein, thus causing a drug-herb interaction by reducing the GI absorption of phenytoin (31). In addition, anthranoids in rhubarb can diminish drug absorption by decreasing GI transit time (32).

Peppermint oil (Lamiaceae)

Peppermint oil is extracted from leaves of *Mentha piperita* L. It contains menthol as a major component and contains rosmarinic acid, terpenes, and flavonoids, primarily eriocitrin, luteolin, and hesperidin (33). The major constituents are menthol (30-55%) and menthone (14-32%). Other monoterpenes present are limonene (1-5%), cineole (3, 5-14%), menthofuran (1-9%), isomenthone (1.5-10%), menthyl acetate (2.8-10%), pulegone (up to 4%), carvone (up to 1%) with a ratio of cineole content to limonene content greater than 2 (34).

The use of peppermint oil for therapeutic purposes has been well established. Scientific evidence supports the use of peppermint oil in irritable bowel syndrome (35, 36), colonic spasm in patients undergoing barium enema, and non-ulcer dyspepsia (37). The antispasmodic effect might be the result of smooth muscle relaxation from the calcium channel antagonist activity of the peppermint oil (38). Other uses of peppermint oil include the topical application for treating headache (37), pruritus, dermatitis (39), and promoting hair growth (40). In the stomachic mixture, peppermint oil is used as an antispasmodic and a flavoring agent. The therapeutic use of oral peppermint oil is 0.3 ml/day in children whose weight is lower than 45 kg and 0.6-1.2 ml/day in adults (35) which are equivalent to 300 ml - 1200 ml of the stomachic mixture (Table 2). It is therefore prudent to assume that peppermint oil from the stomachic mixture is unlikely to be toxic. However, the ingestion of high doses of peppermint oil is toxic to the liver and kidney and can also cause shock (41). Other common side effects include heartburn, perianal burning, blurred vision, nausea, and vomiting (37).

Allergy (42-46) or anaphylaxis (47, 48) caused by peppermint is not uncommon. Peppermint oil is safe for short-term use (4-7 days) as aromatherapy in pregnancy (49, 50). However, the safety data on oral use of peppermint oil in pregnant women are conflicting since one study showed that having two spoons of menthol leaves a day did not cause immediate danger in pregnant women (51), while another study showed that the oil can trigger menstruation (37). A study suggested that peppermint tea should be used cautiously in patients with GI reflux, hiatal hernia, or kidney stones (33). Peppermint oil has several potential interactions with drugs. It can inhibit glucose uptake in rats (52) and can also inhibit *CYP450 1A2* (53) which leads to interaction with several medications such as cyclosporin (54). A case report demonstrated that peppermint oil increases the oral bioavailability of felodipine and simvastatin (55). *In vitro* study showed an anticholinesterase inhibitor activity of peppermint oil (56), thus it might interfere with cholinergic agonists or antagonists. In addition, the in *vivo* research found the competitive antagonism at calcium channels and increased the potentiality of calcium-channel blockers interaction (34).

Cardamom (Zingiberaceae)

Two cardamom species are available in Thailand. True cardamom (cardamom) is the fruits of *Elettaria cardamomum* L. Fruits of plants in genus Amomum (*Amomum krervanh* or Thai kravanh) are also called cardamom (57). The major chemical constituents in cardamom oil include monoterpene volatile oils (e.g. pinene, limonene, terpinyl acetate) and other minor components (e.g. hydrocarbons, carboxylic acids, aldehydes, and alcohols). Cardamom is used for culinary purposes while its volatile oils are mainly used as flavoring agents and perfume.

The use of cardamom for medicinal purposes is not well established. *In vitro* and *in vivo* studies showed antimicrobial (58), cytotoxic, anticarcinogenic properties (59, 60), and gastroprotective effect (61) of cardamom. In addition, a human study showed that cardamom at the dose of 3 g/day reduced fatty liver (62). Since crude cardamom (58) yields 8% cardamom oil, the therapeutic dose of cardamom oil can be speculated as 0.64 g per day (Table 2).

A study in mice found that the ethanol extract of *E. cardamomum* was safe at the dose of 30 µg/g body weight and was toxic at the dose of 300 µg/g (58). The toxicity includes weight loss and increasing creatine phosphokinase. This study also showed that the extract at the dose of 3 mg/g was lethal while another mice study showed that essential oils in cardamom at the dose of 0.75 mL/kg were not lethal (63). Allergic reaction to cardamom in humans has been reported (64) but rare (65). Haematuria from the ingestion of cardamom is also possible (64). Moreover, information on cardamom use in pregnancy and lactation is scarce. There is a study demonstrating the negative effects of cardamom on breastfed mice (66). Therefore, the use of cardamom in breastfeeding women should be discouraged. Also, there are studies that cardamom seeds oil can interfere with medications, such as liver inflammatory and gall-stones drugs (67, 68).

Tinospora (Menispermaceae)

Tinospora is a genus of medicinal plants used widely in ethnomedicine. In Thailand, the major species used is *T. crispa* (L.) Hook. f. & Thomson (69). The stem of Tinospora contains alkaloids, the main component, and the others e.g. terpenoids, phenolics, steroids, aliphatic compounds, and polysaccharides (70). The alkaloids in Tinospora is a bitter tonic and can be used as a substitution for gentian in the stomachic mixture. Tinospora has been used in Ayurvedic and Chinese medicine as immunomodulatory (71, 72) and hypoglycemic medicine (73).

Other pharmacological effects of Tinospora include anticancer (74), analgesics, anti-inflammatory, antipyretics (75), and positive bone effects (76). Although the information on the GI pharmacology of Tinospora is insufficient, studies demonstrate that Tinospora is safe. The LD_{50} of Tinospora in human extrapolated from animals is higher than 1 g/kg orally (77). A human study indicated that an aqueous extract of Tinospora at a dose of 500 mg was safe in humans (78). It is safe to assume that the usual dose of the stomachic mixture contains a nontoxic amount of Tinospora (Table 2). However, Tinospora contains furanoditerpenoids (79) and is hepatotoxic in humans (80, 81). Drug interactions with Tinospora via pharmacokinetic or pharmacodynamic mechanisms are possible. Tinospora should be used with caution in diabetes patients since it has hypoglycemic effects and can interact with glibenclamide in vivo (82). An in vitro experiment showed that *Tinospora* methanolic extract (0.5mg/ml) inhibited CYP3A4 (83). Tinospora might have pharmacodynamic interactions with diuretics (84), cholinergic (85), and dopaminergic (86) drugs. Tinospora shows a positive effect on lactation in a study in cows (87) and does not show teratogenicity in a mice study (88). However, the information on the use of Tinospora in lactating and pregnant women is unavailable.

Ginger (Zingiberaceae)

Ginger is the rhizome of *Zingiber officinale* Roscoe which has been used as spices and herbs in Asia. It has various medicinal uses including anti-inflammatory (89), antimigraine, antidiabetes (90), and anticancer (91). The most studied property of ginger is its antinausea and vomiting properties, especially during pregnancy (92) and chemotherapy (93, 94). The pharmacological properties of ginger derive from its muscarinic agonist and serotonergic agonist activity (95) which leads to the relaxation of the lower esophageal sphincter and the decrease of esophageal contraction velocity (93). Ginger can be consumed at the amount as high as 4 g of ginger rhizome per day (93). However, a recommended safe effective daily dose of ginger in human studies is 1,000 mg of ginger rhizome which is equivalent to 2 ml of the liquid ginger extract (93) or 30-150 ml of the stomachic mixture (Table 2). Side effects of ginger include a mild headache, fever, sweating, thirst, blenching, diarrhea, and somnolence (96). Mild GI side effects e.g. belching, bad taste in the mouth, stomach upset, and heartburn were reported in patients using 2,500–4,000 mg of dried ginger rhizomes (97). A case report showed that chronic use of ginger caused dysuria (98) and subacute thyroiditis (99). Allergy to ginger has been reported in several case reports (100-102). In addition, ginger can be used safely as an antiemetic in pregnant women (103) and a galactagogue in breastfeeding mothers without side effects (104). Ginger might potentiate anticoagulant and antiarrhythmic effects of the medicine. Therefore, it should be used with caution in patients treated with anticoagulants and antiarrhythmics (105).

Camphor (Lauraceae)

Camphor (1,7,7- Trimethylbicyclo[2. 2. 1] - 2-heptanone) is a ubiquitous chemical found in herbs e.g. basil, coriander, and sage; food and beverages; over the counter topical medications e.g. topical analgesic balm, topical nasal decongestant balm, and household products e.g. moth repellant (106, 107). Camphor can be extracted from the old stem and root of *Cinnamomum camphora* (L.) J. Presl or synthesized from α-pinene. Traditional medicine uses camphor as the central nervous system, heart, and sex- drive stimulants (108). Camphor was also used as a contraceptive, abortive agent, and lactation suppressant (108-110). These indications of camphor are usually abused and lead to camphor poisoning (111). Camphor is also used in cold remedies and liniments for musculoskeletal pain (108). The reason for the use of camphor in the stomachic mixture is not known but its cooling sensation stimulating effect via transient receptor potential melastatin 8 (112) and transient receptor potential vanilloid subtype 1 channel (113) may be the reason. The cooling effect occurs at a dose of 5% w/w (114). The approximate amount of camphor in the stomachic mixture is 2 mg/ml which is lower than reported fatal doses which in infants is approximately 6 g; in unborn infants is approximately 10 g (115) and in adults is 50-100 mg/kg (Table 2) (109). At the dose of 100 mg, camphor can lead to hospitalization from nausea, vomiting, and altered mental status (116). Other side-effects of camphor include delusion (117), seizure (118-121), and myocarditis (122). A case report showed that seizure occurred at a dose of 68 mg/kg (123). Therefore, the camphor-containing stomachic mixture should be avoided in patients with a history of seizure or status epilepticus. It should be also avoided in pregnant women because camphor has an abortive effect and fetal deaths were reported in pregnant mothers who ingested 30 grams of camphor (108). Camphor can suppress milk production; therefore, the use of breastfeeding women should be discouraged.

Gentian (Gentianaceae)

Gentian tincture is an alcoholic extract of the root of *Gentiana lutea* L., yellow gentian (124). It should not be confused with gentian violet which is a triphenylmethane dye with antiseptic properties (125).

The major constituents of gentian root include secoiridoid glycosides (bitter substances), xanthones, carbohydrates, volatile oils, phytosterols, and triterpenes. The proposed mechanism of digestion stimulating effect of these substances in gentian was via the cephalic-response pathway, i.e. by acting in the cerebral cortex, and local-response pathway, i.e. by binding to bitter receptors in the upper GI tract (126). Because of the digestion stimulating activities, the medicinal use of gentian tincture is to stimulate appetites and relieve flatulence. Because the daily dose of gentian is one ml of tincture every eight hours (127), the approximate amount of gentian tincture in the stomachic mixture should not have therapeutic or side-effects (Table 2). Side-effects of gentian are uncommon and include flatulence, nausea, stomach cramps or spasms, soft feces, and headache (127). Most of the case reports of the toxicity of gentian occur with the adulteration of gentian with *Veratrum album* (128, 129). *Gentiana* should not be used in pregnant women since it can cause spontaneous abortion (126).

Ipecacuanha (Rubiaceae)

Roots of *Cephaelis ipecacuanha* (Brot.) A. Rich. (ipecacuanha) have two major alkaloids, emetine, and cephaeline, which cause vomiting and diarrhea (130). Emetine and cephaeline bind to several receptors including 5-HT1A, 5-HT3, 5-HT4, dopamine, nicotinic, muscarinic-3, and β_1-adrenergic receptors (131); therefore, ipecac has potentials for drug interactions. Ipecacuanha has been formulated as ipecac syrup which was mainly used for GI decontamination after the ingestion of toxic substances (132, 133). The use of ipecac syrup to induce emesis in patients with drug overdose or toxin exposure has been drastically reduced since the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists have released their guidelines in 2004. The dose of ipecac syrup for emesis induction is 15-30 ml once (134). The amount of total alkaloids in the tincture of ipecac and ipecac syrup is 2 mg/ml (135) and 1.57 mg/ml (4), respectively. Therefore, 12-24 ml of ipecac tincture or 60-120 ml of the ipecac-containing stomachic mixture are adequate to induce emesis (Table 2). Poisoning of ipecac, accidentally or intentionally in bulimia patients, is frequently reported (136, 137) and results in death (138, 139). Ipecac related mortality results from cardiomyopathy including arrhythmias and myositis (140). Cephaeline and emetine can also cause gastroesophageal tears, diarrhea, alkalosis, hypokalemia, and dehydration (139). As a result, warning on the label of the stomachic mixture states that it should be avoided in patients with cardiac conditions (2).

Aromatic ammonia spirit

Aromatic ammonia spirit is a hydroalcoholic solution containing, per 100 ml, 1.7-2.1 g of NH_3 and 3.5-4.5 g of $(NH_4)_2CO_3$ (4). The amount of aromatic ammonia spirit in the stomachic mixture is 8 µl/ml. Therefore, the stomachic mixture contains 1.36-1.68 µg of NH_3 and 2.8-3.6 µg of $(NH_4)_2CO_3$ per ml. Inhalation of ammonia from stomachic mixture does not cause health concerns because the amount is lower than the lowest amount of ammonia that can be detected by the human (5 ppm or 5 µl/ml; 1 ppm equals 1 µg/ml) and the lowest irritation dose (30 ppm for 10 minutes) (Table 2) (141). Ingestion of ammonia causes GI irritation (142) but rarely causes systemic side effects (143). Consumption of a high amount of ammonia that increases the serum concentration of ammonia can be toxic to the brain (144). However, with an insignificant amount of ammonia in the stomachic mixture, it is less likely to cause any side effects from the ingestion.

Conclusions

The stomachic mixture, an antacid, contains sodium bicarbonate as an active ingredient. Sodium content in stomachic mixture is high and should be

monitored in patients requiring sodium restriction. Other components in stomachic mixture are usually at the concentration lower than effective doses. However, some of them demonstrate similar toxicity profiles. For example, rhubarb and peppermint oil are renal and hepatotoxic. Rhubarb, ginger, gentian, and ipecac can cause diarrhea. Cardiotoxicity can occur from using gentian, ipecac, and camphor. Camphor and ammonia spirit can cause CNS side effects. The hypoglycemic effect is caused by peppermint oil and Tinospora. Since the safety data on the combined use of these components or on the use of stomachic mixture is not available, it is prudent to avoid the use in patients with the aforementioned conditions. In addition, there is no safety data regarding the use of stomachic mixture in pregnant and breastfeeding women. The use of stomachic mixture in pregnant women should be avoided since rhubarb, peppermint oil, camphor, gentian, and ipecac have negative effects on pregnancy. Stomachic mixture should not be used in patients who are allergic to its components since several components e. g. peppermint oil can cause severe allergic reactions.

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