

Anti-emetic effects of bioactive natural products

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Abstract

Emesis, also known as nausea and vomiting, are common symptoms associated with ingestion of toxicants, drug side effects, advanced terminal diseases such as cancer and postoperative procedures. Emesis is mediated through the coordinated action of central and peripheral regulatory centres that involve receptors including dopamine Type 2, serotonin, muscarinic cholinergic, histamine, cannabinoids and NK-1 receptors. Many anti-emetic drugs targeting these receptors are currently in use but they also cause undesirable side effects such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations and extrapyramidal signs. This review highlights the pharmacological mechanism of emesis and current antiemetic drugs together with detailed analysis of *in vitro* and *in vivo* anti-emetic bioassay models. The pharmacology of crude natural products extracts and purified anti-emetic compounds (cannabinoids, chalcones, diarylheptanoids, flavonoids, hydroxycinnamic acids, lignans, phenylpropanoids, polysaccharides, saponins, terpenes and glycosidic derivatives) are also systematically presented with their mechanism of action. The potential of natural products as sources of new clinically proven anti-emetic drugs are discussed

Keywords: Emesis, anti-emetics, natural products, anti-emetic experimental models, drug development.

Introduction

Emesis is a generally unpleasant activity that results in the expulsion of stomach contents through the mouth and clearly associated with gastrointestinal motor activity. It could as such be regarded as the body's response to certain drugs, disease co-morbidities and defenses against food poisoning (Hall & Driscoll, 2005). While vomiting can serve the function of emptying noxious chemicals from the gut, nausea plays a role of conditioned

response to avoid ingestion of offending substances. Emesis can be divided into two broad categories: bilious and non-bilious forms. Bilious emesis occurs when bile is purged along with the gastric contents. Although some small intestinal reflux into the stomach is common with all vomiting, antegrade intestinal flow is preserved in non-bilious vomiting and the majority of the bile drains into the more distal portions of the intestine. Non-bilious emesis is generally caused by infectious and/or inflammatory conditions including acute gastroenteritis, labyrinthitis and pancreatitis. Vomiting may also occur in any neurologic condition that results in increased intracranial pressure (Scorza *et al.*, 2007). Acute ketoacidosis and long-standing diabetes mellitus are other examples of metabolic and endocrinology origin diseases respectively where emesis is prevalent. In cyclic vomiting syndrome, emesis is often associated with increased incidence of migraine headaches. The neurologic conditions associated with vomiting could be a result of structural defect, infections and toxicity. Structural defects include hydrocephalus, congenital malformations, intracranial hemorrhage and intracranial mass lesions while congenital infections including encephalitis and meningitis are major causes of emesis. Kernicterus, acidosis and other metabolic by-products are common examples of toxicity associated with vomiting. Other nonbilious causes of emesis are of psychological origin and obstructive lesion (Murray & Christie, 1998). In children, the common causes of bilious vomiting are intestinal atresia and stenosis, malrotation with or without volvulus, ileus from any cause, intussusception, intestinal duplication, compressing or obstructing mass lesion, incarcerated inguinal hernia, superior mesenteric artery syndrome, appendicitis, peritoneal adhesions and pseudo-obstruction (Murray & Christie, 1998).

Emesis is also the most common side effect of cancer chemotherapy (Griffin *et al.*, 1996). Chemotherapeutic agents are generally classified according to their high, intermediate and low emetic risks. High emetic risk anticancer agents include actinomycin-D, carboplatin, carmustine, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, doxorubicin, epirubicin, hexamethylmelamine, idarubicin, ifosfamide, lomustine, mechlorethamine and streptozotocin. Among the intermediate emetic risk group of chemotherapeutic agents are docetaxel, etoposide, gemcitabine, irinotecan, mitomycin, mitoxantrone, paclitaxel, teniposide and topotecan. Other chemotherapeutic agents such as l-asparaginase, 2-chlorodeoxyadenosine, bleomycin, busulphan, chlorambucil, fludarabine, fluorouracil, hydroxyurea, melphalan, mercaptopurine, methotrexate, tamoxifen, thioguanine, vinblastine, vincristine, vindesine and vinorelbine are regarded as low emetic risk. Emesis is also associated with radiation and its severity is based on the part of the body receiving radiation. High emetic risk is generally associated with whole body irradiation while intermediate emetic risk is associated with the abdominal-pelvic, craniospinal, cranium (radiosurgery), mantle and upper abdomen irradiations. Breast, extremities, head and neck, pelvis and thorax irradiations are known to have low emetic risk (Gralla *et al.*, 1999).

Nausea and vomiting are common features of pregnancy and have adaptive advantage. The first trimester is a period of rapid fetal growth, critically the development of the CNS, which is highly susceptible to toxicosis. The emesis response is thus intended for avoiding potentially harmful substances ingested with food (Flaxman & Sherman, 2000). Age, gender (menses), obesity, previous history of motion sickness or postoperative vomiting, anxiety, gastroparesis, and type and duration of the surgical procedure (e.g., laparoscopy, strabismus, middle ear procedures) are other factors associated with an increased risk of postoperative emesis (Watcha & White, 1992).

Physiological basis of emesis

Various centres including the vomiting centre, chemoreceptor trigger zone, the autonomic, vagal, and spinal nerves emanating from the gastrointestinal (GI) tract and the central nervous system (CNS) (Fig. 1) coordinate nausea and vomiting responses. The Chemoreceptor trigger zone (CTZ) in the CNS is located in the area postrema, closely to the nucleus tractus solitarius and outside of the blood-brain barrier. Hence, emetogenic substances within the blood or the cerebrospinal fluid (CSF) can directly trigger a response at the CTZ. The CTZ, is also implicated in controlling food intake, conditioned taste aversion, and modulating GI tract motility. Among the various receptors within the chemoreceptor trigger zone is dopamine D_2 , 5-HT₃ (serotonin), neurokinin 1 (NK₁), muscarinic acetylcholine (ACh_M), histamine (H₁) and opioid receptors. Upon stimulation by various endogenous or exogenous chemical insult, 5-HT released from the GIT activates 5-HT₃ receptors located on vagal afferent system that innervate the vomiting center. Emesis requires stimulation of a central emetic generator, vomiting centre located within the brain stem and is separated from the blood by the blood-brain barrier. It receives convergent afferent stimulation from several central neurologic pathways. It is anatomically less well defined than the CTZ; the vomiting centre of the third ventricle is the central emetic generator. ACh_M, D_2 , NK₁, 5HT₃ and H₁ receptors are emetogenic receptors present in vomiting center (Goldman *et al.*, 2006). From vestibular centers, signals are transmitted to CTZ and vomiting center whereas the cerebral cortex transmits emesis signals to the vomiting center (Figure 1). Antagonists of receptors involved in the mediation of nausea and vomiting have therefore anti-emetic properties.

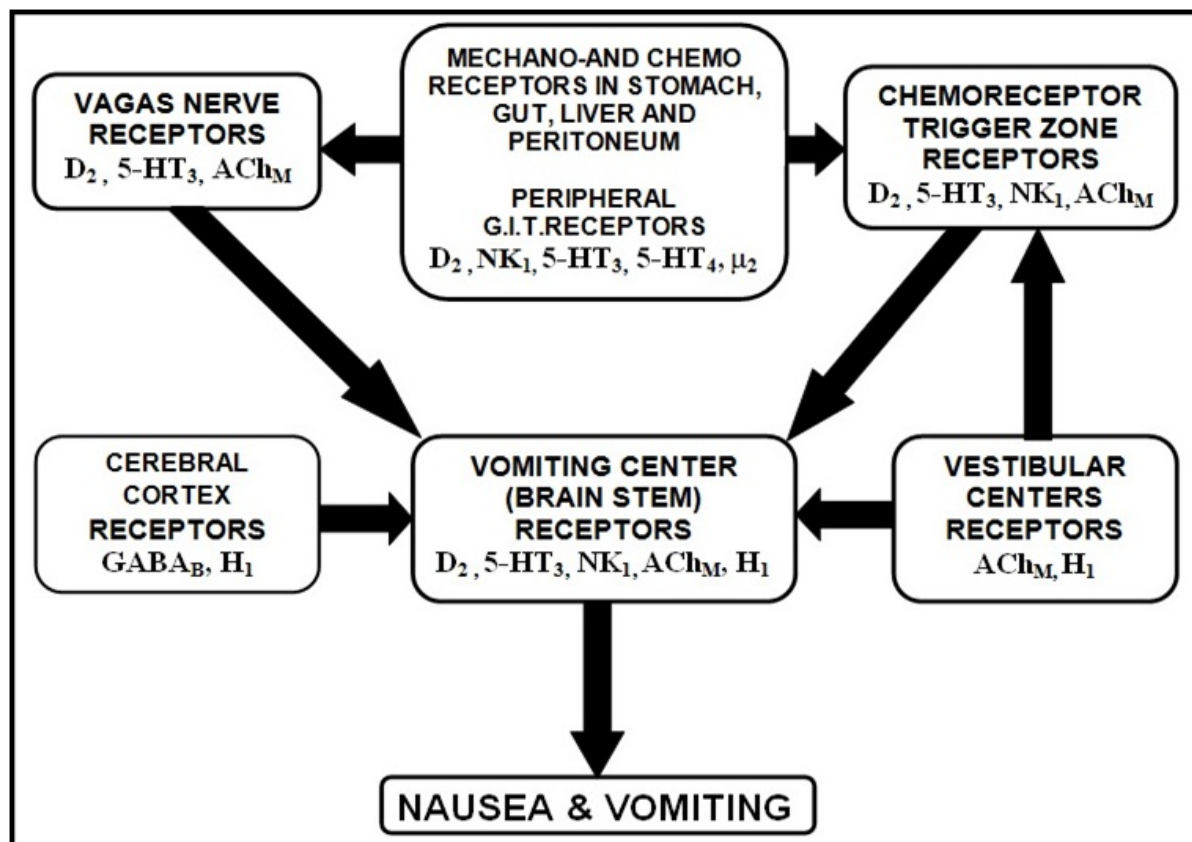


Figure.1. Circuit diagram of emesis pathway.

Exogenous chemicals and endogenous substances that accumulate during inflammation, ischaemia, and irritation excite the mechano, chemo and peripheral G.I.T. receptors. Dopamine (D₂), serotonergic (5-HT₃ & 5-HT₄), ACh_M, neurokinin (NK₁) are highly conserved for an emetic reflex whereas Gamma amino butyric acid (GABA_B), serotonergic (5-HT_{1A}), cannabinoids (CB₁) and opioids (μ₂) have anti-emetic effects (Sanger & Andrews, 2006). The stomach wall also contains D₂, 5-HT₃ & 5-HT₄, ACh_M, NK₁, μ₂ as well as 5-HT₃ receptors that also found in area postrema of the CNS. The 5-HT₄ receptors require ACh as a mediator within the myenteric plexus while substance-P can induce nausea by binding to NK₁ receptors (Figure 1).

The vagal nerve and its neurotransmitter, acetylcholine, play a key role in acute emesis associated with chemotherapy, radiation therapy to the epigastrium, and abdominal distension or obstruction. During emesis, the stomach muscle relaxes and gastric acid secretion is inhibited while a single retrograde giant contraction of small intestine reaches the stomach to cause retching and vomiting (Figure 1).

B. Therapeutic strategies

The current anti-emetic drugs can be classified as follows (Rheid *et al.*, 1992; Sanger & Andrews, 2006):

a. Antidopaminergic drugs

Dopamine receptor antagonists like chlorpromazine, cyclizine, domperidone, droperidol, fluphenazine, haloperidol, metoclopramide, prochlorperazine and thiethylperazine are widely used as anti-emetic agents in many countries. They are effective in blocking the stimuli to the chemoreceptor trigger zone and also affect the motility of upper gastrointestinal tract. They also have antimuscarinic action. These drugs are known to have some adverse effects such as fatigue, drowsiness, and extra pyramidal reactions including dystonia, dyskinesia, and akathisia (Leung & Robson, 2007).

b. Serotonin antagonists

5-HT₃ receptors are located in three sites: gastrointestinal tract, chemoreceptor trigger zone located in the area postrema and nucleus tractus solitarius of the vomiting centre. These are selective 5-HT₃ receptor antagonists with both CNS and peripheral action. They include granisetron, ondansetron, tropisetron and palonosetron. To date, a number of reports suggest that 5-HT₃-RAs do offer a far better result in combating emesis during chemotherapies (Kris *et al.*, 2005).

c. Antihistamines

Comprehensive evidence on the effectiveness of antihistamines for treating nausea and vomiting is still lacking. Numerous reports however suggest that H₁ receptor antagonists have potential for treating motion sickness and related disorders. The lack of evidence and their general sedative effect in general means that they are not first line treatment for emesis

(Patanwala *et al.*, 2010). Anti-emetic agents of this class include cinnarizine, cyclizine, dimenhydrinate, diphenhydramine, hydroxyzine, meclozine and promethazine.

d. Anticholinergic drugs

These agents compete with ACh at muscarinic receptors in the gut and CNS. Scopolamine is one of the examples that induce both anti-emetic and antispasmodic action in the gut wall.

e. Corticosteroids

Steroids are an integral component of almost each anti-emetic therapy and used either by their own or in combination with other anti-emetic agents. The mechanism by which steroids exert their anti-emetic activity are not fully understood, but they may affect prostaglandin activity in the brain, modify the blood–cerebrospinal fluid barrier and inhibit cortical input to the vomiting centre or through interference of serotonin release/effect the gastrointestinal tract (Perwitasari *et al.*, 2011). Dexamethasone and methylprednisolone are classical examples of steroidal antiemesis drugs.

f. NK-1-receptor inhibitors

NK-1-receptors are abundant in the chemoreceptor-trigger-zone (CTZ), nucleus tractus solitarius (NTS) and gastrointestinal tract (GI tract) (Diemunsch & Grelot, 2000). In addition to direct anti-emetic effect, recent studies documented the synergistic anti-emetic interaction between the serotonergic 5-HT₃ and tachykininergic NK1-receptor antagonists (Darmani *et al.*, 2011).

g. Cannabinoids

Cannabinoids (e.g. dronabinol) are another class of anti-emetic agents but their usefulness has been limited by the high incidence of toxic effects such as dizziness, dysphoria and hallucinations. It is likely that their anti-emetic activity is due to effects at the cannabinoid receptor, likely to be located in the brain stem (Jordan *et al.*, 2011).

h. Agonist anti-emetics

5-HT_{1A}, GABA_B and CB₁ receptors agonists

These agonist anti-emetics include serotonin (5-HT_{1A}), gamma amino butyric acid (GABA_B) and cannabinoid (CB₁) receptor agonists. Buspirone (5-HT_{1A} agonist), baclofen (GABA_B agonist) and dronabinol (CB₁ agonist) are good examples (Rheid *et al.*, 1992).

C. *In vivo* and *in vitro* experimental models of emesis

a. Animal emesis models

Several animal emesis models are currently available to evaluate the therapeutic potential of natural and synthetic anti-emetics. Non-mammal models include amphibians (frogs) and birds (pigeons) whereas in mammals, insectivores (house musk shrew and least shrew),

artiodactyls (pig), carnivores (cat, dog and ferret) and non-human primates (monkeys) are used. The emetic responses in these animals are characterized as vomiting, retching and pica (ingestion of a non-nutritive substance such as kaolin). Vomiting (expulsion of gastric content) and retching (an emetic action without emitting gastric material) responses are observed in animals which have ability to vomit: e.g. ferret, house musk shrew, dog and cat. Pica is observed in those animals that lack the emetic reflex such as rats and mice (Takeda *et al.*, 1993; Liu *et al.*, 2005). These animal models have been successfully used for the evaluation of anti-emetic potential of crude extracts and isolated natural compounds. Chemicals, motion and radiation are among the few common emetic stimuli used in these experiments (King, 1990).

1. Ferret emesis model

Albino or Fitch ferrets (*Mustela putorius furo*) of either sex weighing 0.7-2kg are generally used for emesis model. Emesis is characterized by rhythmic abdominal contractions associated with retching and vomiting. Retching is counted as rhythmic abdominal contractions with no expulsion of material and vomiting as a contraction resulting in expulsion of solid or liquid material from the G.I.T. Generally, apomorphine 0.25 mg/kg s.c. (Rudd *et al.*, 1996) and cisplatin 10 mg/kg i.v. are used for induction of acute emesis (Nakayama *et al.*, 2005). For delayed emesis, cisplatin 5 mg/kg i.p., is used (Nakayama *et al.*, 2005). Other chemicals used as emetic challenge are 40 mg/kg p.o. copper sulfate (Nakayama *et al.*, 2005), 200 mg/kg i.p. / p.o. cyclophosphamide (Minami *et al.*, 1997), 2mg/kg p.o. ipecacuanha (Warneck *et al.*, 2008), 0.3 mg/kg s.c. morphine (Wynn *et al.*, 1993), 3mg/kg s.c. / i.p. / p.o. yohimbine (Robichaud *et al.*, 2001), 0.3 mg/kg p.o. zacopride (King, 1990). Emesis is usually observed for 30 mins except for yohimbine (120 mins) and ipecacuanha (180 mins). For cisplatin-induced acute emesis, the observation time is 4 hr while delayed emesis require 72 h of observation. Animal behaviour is recorded remotely using a video camera. Retching or vomiting is observed by a trained observer who is blind to the test, control and treated groups. Cisplatin induces the release of 5-HT from enterochromaffin cells present in intestinal mucosa (Fukui *et al.*, 1993a). 5-HT then activates 5-HT₃ receptors present in peripheral endings of afferent vagal nerves resulting in emetic reflex (Fukui *et al.*, 1993b; Miller & Nonaka, 1992; Kamato *et al.*, 1993;). This mechanism of action is also proposed for cisplatin's-induced emesis in cats, dogs, ferrets and pigs. Stimulation of NK₁ receptors on the emetic peripheral receptor sites is also suggested as a possible mechanism of emesis induction by cisplatin (Minami *et al.*, 1998). The peripheral emetogen copper sulfate activates the vagal afferent nerve projecting to the nucleus tractus solitalius and/or the area postrema, followed by emetic responses through the stimulation of the NK₁ receptors in the nucleus tractus solitalius and/or area postrema (Ariumi *et al.*, 2000). On the other hand, 5-HT₃ -receptors on visceral afferent nerves (abdominal visceral innervations) is known to mediate emetic action by cyclophosphamide (Hawthorn *et al.*, 1988) while morphine-induced emesis in ferrets appeared to be mediated by kappa opioid receptors (Rudd & Naylor 1992). Yohimbine's emetic action is likely to be linked to noradrenergic pathway by mimicking the pharmacological actions of a pre-synaptic α_2 -adrenoceptor inhibition (Robichaud *et al.*, 2001). The emetic response to zacopride has been shown to be mediated in part by 5-HT receptors residing on either enteric neurons or vagal afferents but possible effects via activation of cholinergic and dopaminergic pathways have also been suggested (King, 1990).

2. Mink emesis model

In this animal model, adult male minks (*Mustela vison*) weighing 1.3-1.8 kg are used. Emesis is induced by apomorphine (1.6 mg/kg s.c.), cisplatin (7.5mg/kg i.p.), copper sulfate (40 mg/kg p.o.) or whole-body X-irradiation (18 Gy for 4.5mins). Anti-emetic test drugs (i.p.) are usually administered 30 mins prior to induction of emesis and animals observed for 6 hrs (Zhang *et al.*, 2006). For cisplatin-induced delayed emesis, the observation time is extended to 72 hrs and monitored through closed circuit camera recording (Qian *et al.*, 2010). During vomiting, the mink's head is protruding downwards ahead with open mouth, shrugging shoulder, contracting abdomen and occasional sounds of vomiting. A vomiting cycle starts when vomiting began and ends when a smooth breathing is recovered. The frequency of retching and vomiting during this period is then calculated (Zhang *et al.*, 2006). Acute emesis induced by cisplatin is thought to involve the release of serotonin, and is particularly dependent on the 5-HT₃ receptors on vagal afferent neurones (Cubeddu., 1996; Martin, 1996). During the most intense period of delayed emesis, which occurs during the 48–72 h period, substance-P has been shown to play a vital role. Thus, the tachykinin NK₁ receptor antagonists can improve delayed emesis reactions (Hesketh *et al.*, 2003; Andrews & Rudd, 2004). Other studies indicate that 5-HT released from the enterochromaffin cells of small intestine is involved in vomiting induced by apomorphine, copper sulfate and X-irradiation (Zhang *et al.*, 2006).

3. Monkey emesis model

Cynomolgus monkeys (*Macaca cynomologus*) weighing 2.1-4.0 kg are used in this model. Anti-emesis agents are normally administered 30 mins prior to induction of emesis either by cisplatin (3 mg/kg i.v.) or copper sulfate (20 mg/kg i.v. and 100 mg/kg p.o.). Retching and vomiting episodes are recorded during the first (i.v. route) or 3 h (p.o route) of copper sulfate administration while a 9 hr observation period is used for cisplatin-induced emesis. In some anti-emesis studies using cisplatin, test agents are also administered 1.5 and 3.5 hr after induction of emesis (Fukui *et al.*, 1993c). In this experimental model, vagal afferent terminals and 5-HT₃ receptors have shown to play important role in the emetic response. The role of serotonin in the small intestine, which in turn stimulates vagal afferent fibers through 5-HT₃ receptors, has also been established (Fukui *et al.*, 1993c).

4. Pig emesis model

Young (12-15 weeks-old) domestic pigs (*Sus scrofa domesticus*) of both sexes weighing 28-40 Kg are generally used in this experimental model. Test drugs are given by i.v. 15 mins prior to cisplatin infusion (2 mg/kg i.v.) and acute emesis is observed over a period of 16 hrs (Szelenyi *et al.*, 1994). For delayed emesis study, a higher dose of cisplatin (5.5 mg/kg i.v.) and a 60 hrs observation period were used (Milano *et al.*, 1995). In this model of emesis, prostaglandins have also been found to contribute to the cisplatin-induced emetic response (Girod *et al.*, 2002).

5. Dog (*Canis familiaris*) emesis model

Usually Beagle (6.8-14 kg body weight) or Mongrel dogs (4-13 kg body weight) of both sexes are used for observing emesis. Emesis may be induced by 0.03 mg/kg i.v. apomo-

rphine (Blancquaert *et al.*, 1986), 3.2 mg/kg i.v. cisplatin (Yamakuni *et al.*, 2000), 100 mg/kg p.o. copper sulfate (Fukui *et al.*, 1994), 2.5 mg/kg (i.v.) methotrexate (Yamakuni *et al.*, 2000) or by using radiation (rotaray ^{60}Co therapy unit at 0.2-0.4 Gy/min; Carpenter *et al.*, 1988). The acute emesis observation periods are as follow: apomorphine (30 mins), cisplatin (5 hrs), copper sulfate (1 hr), and radiation (4 hrs). Delayed emesis by methotrexate is commonly studied over a period of 72 hrs. Test samples (i.v.) are normally introduced 10-30 mins before emetic challenge but may also reintroduced by i.v. at 24, 36, 48 and 60 hrs of the delayed methotrexate emesis study (Blancquaert *et al.*, 1986; Carpenter *et al.*, 1988; Fukui *et al.*, 1994; Yamakuni *et al.*, 2000). In delayed emesis, animal behavior is typically recorded using a video camera with an automatic night photographing system. Various studies have indicated the involvement of δ -receptor-mediated mechanism in apomorphine (Harris, 1982), peripheral 5-HT₃ receptors in cisplatin (Fukui *et al.*, 1992) and 5-HT₄ receptors in copper sulfate (Fukui *et al.*, 1994) and methotrexate-induced emesis (Yamakuni *et al.*, 2000). Carpenter *et al.* (1998) have further shown that peripheral dopamine (D₂) receptors and prostaglandins are involved in radiation-induced emesis model of dogs.

6. Rat emesis model

Male Wistar strain rats (*Rattus norvegicus*) weighing between 150 and 300 g are usually used in this study. In these animals which lack emetic reflex, pica (measured as kaolin intake) involves similar mechanisms as vomiting in humans and can be used to test the efficacy of anti-emetic drugs (Takeda *et al.*, 1993). It has been shown that pica is associated with 5-HT release from the enterochromaffin cells, increased c-fos labelling in the area postrema and the nucleus tractus solitarius, and delay in gastric emptying as with emesis in humans (Vera *et al.*, 2006). In this experimental model, apomorphine and cisplatin through i.v. route (10 mg/kg) or oral dose (40mg/kg) of copper sulfate are used for measuring pica in rats. Test samples are administered by i.p. route 10 mins prior to emetic stimuli and pica is observed for a period of 120 hrs (Takeda *et al.*, 1993). Dopaminergic involvement in CTZ has been shown to be evident in apomorphine model while copper sulfate stimulates the terminals of the visceral afferent neurons of the stomach wall (Takeda *et al.*, 1993). Cisplatin has shown to activate GI vagal afferent fibers via 5-HT₃ receptors to emesis (Horna *et al.*, 2004). Some studies also suggest that cisplatin-induced emesis can be attributed to cytotoxicity to the enterochromaffin cells in the small intestine (Cubeddu, 1996). Oxidant injury to these cells could result in 5-HT release, stimulation of 5-HT₃ receptors located on the vagal afferents, and initiation of the emetic reflex in the brain stem (Matsuki *et al.*, 1993). X-ray irradiation (4Gy of 4MV at the dose of 1.5 Gy/min) some 30 mins after administration of test agents (i.p.) has also been used to measure pica (Yamamoto *et al.*, 2002). Such studies revealed that the serotonergic pathway is predominantly involved in x-ray irradiation emesis in rats (Yamamoto *et al.*, 2002).

7. Chick emesis model

Copper sulfate and free radical-induced emesis are studied in chicks (*Gallus gallus domesticus*). Young male chicks, 4 days of age, weighing from 32-52 g are used for anti-emetic activity studies. Each chick sets aside for 10 minutes to stabilize in a large beaker. Test samples are administered orally before 10 minutes of emetic stimuli. Copper sulfate 50 mg/kg p.o. (Akita *et al.*, 1998) or AAPH-liposomal form (2,2'-Azobis(2-amidinopropane)

dihydrochloride dissolved in liposome at a dose of 200 mg/kg i.p. is used (Yang *et al.*, 1999c). The number of retching is then observed during the next 10 minutes (Akita *et al.*, 1998; Yang *et al.*, 1999c). In other studies, copper sulfate (60 mg/kg, p.o.) and ipecac (600 mg/kg, p.o.) were also reported to induce emesis in chick. Test samples are administered i.p. one hour prior to treatment with the emetic agents. The retching frequency recorded for copper sulfate and ipecac were 60 and 20 minutes after treatment period respectively (Moallem *et al.*, 2009).

8. Frog emesis model

Leopard (*Rana nigromaculata*) and ranid (*Rana japonica*) frogs of either sex weighing 6-16 g are used for this study. The frogs are set aside for 30 min to stabilize. Test samples are administered into the lymph sac 30 min before the emetic agent. The emetic action is induced by copper sulfate (15 mg/kg p.o.) and apomorphine (100 mg/kg p.o.). The first emesis (emetic latency) by copper sulfate is recorded during the next 80 min. Anti-emetic potential is judged by the prolongation of the emetic latency. The frequency of retching due to apomorphine is also counted during the next 80 min (Kinoshita *et al.*, 1996).

9. House musk shrew emesis model

6-month-old house musk shrews (*Suncus murinus*) of either sex weighing 50-90 g are used in this model (Ueno *et al.*, 1987; Okada *et al.*, 1994). After a period of 10 min acclimatization in transparent cage, test agents are administered 30 mins prior to induction of emesis (Torii *et al.*, 1994; Ueno *et al.*, 1987). An assessment of 30 min is routinely followed by using close circuit video recording (Ueno *et al.*, 1987; Andrews *et al.*, 1996; 2000). Details of the study regimen are shown in Table 1.

In most antiemetic studies using *Suncus murinus*, a 10 min period of reciprocal shaking (horizontal oscillation/amplitude: 40 mm; frequency: 1.0 Hz) is used to induce vomiting. Test materials (mg/kg i.p.) are given, 10 mins prior to a motion stimulus and the number of the emetic episodes recorded (Ueno *et al.*, 1988; Javid & Naylor, 2002). Antagonism of serotonergic 5HT_{1A} receptors has been suggested as possible mechanism of action in motion induced emesis (Okada *et al.*, 1994). Parasympathetic nervous function has also been suggested to be relevant in the enhancement of motion stimuli-induced emetic response (Uchino *et al.*, 2001).

Whole-body irradiation at a dose of 10 Gy (160 cGy/min) and radiation distance of 50 cm for 6 mins are also used in induction of emesis. Animals are then returned to their home cages and the latency and frequency of emetic episodes are recorded for a up to 1 h. Emetic responses during and after the irradiation could consist of vertical tremors of the trunk and face with or without expulsion of the upper gastrointestinal contents. It has been shown that x-ray irradiation-, motion-, or drug-induced emesis in this animal model involve specific activation of neurons of the reticular formation dorsal and dorsomedial to the nucleus ambiguus in the rostral medulla (Itoa *et al.*, 2003). In addition to the prominent role of 5-HT (Torii *et al.*, 1993a), hydroxyl radical generation have been shown to contribute to the mechanisms of x-irradiation-induced emesis (Torii *et al.*, 1993b).

Table 1. Study regim of House Musk Shrew emesis model.

Emetic agent	Dose & Route of Administration	Period of observation	Proposed mechanism	Reference
Acetaldehyde	6% v/v i.p., & 6% v/v s.c.	90 mins	<ul style="list-style-type: none"> Peripheral action 	Chen <i>et al.</i> , 1997
Cisplatin	20 mg/kg i.p., & 40 mg/kg i.v.	2hrs	<ul style="list-style-type: none"> Direct or indirect stimulation of Serotonergic 5-HT₃ receptor of the vagus afferent neurons 	Mutoh <i>et al.</i> , 1992
	30 mg/kg i.p.	72 hrs	<ul style="list-style-type: none"> Freee radical induced oxidative damage 	Matsuki <i>et al.</i> , 1988, 1997; Mutoh <i>et al.</i> , 1992; Okada <i>et al.</i> , 1994; Sam <i>et al.</i> , 2003; Torii <i>et al.</i> , 1991; Torii <i>et al.</i> , 1993a
	40 mg/kg i.p.	90 mins	<ul style="list-style-type: none"> 5-HT_{1A} receptor antagonism 	
Copper sulfate			<ul style="list-style-type: none"> Gastric irritation or direct stimulation of stomach wall 	Andrews <i>et al.</i> , 1990; Nakayama <i>et al.</i> , 2005; Okada <i>et al.</i> , 1994; Ueno <i>et al.</i> , 1987; Wang & Borison, 1951
	21.4 mg/kg p.o.	30 mins	<ul style="list-style-type: none"> 5-HT_{1A} receptor antagonism Possibly through effect on 5-HT₄ receptors 	
Cyclophosphamide	200 mg/kg i.v.	30 mins	<ul style="list-style-type: none"> 5-HT₃ receptor-mediated mechanism 	Torii <i>et al.</i> , 1991; Yoshifumi Torii <i>et al.</i> , 1991
Emetine dihydrochloride	47.6 mg/kg s.c.	2hrs	<ul style="list-style-type: none"> Stimulation of CTZ 	Ueno <i>et al.</i> , 1987
Ethanol			<ul style="list-style-type: none"> Peripheral action through acetaldehyde intermediate 	
	40% v/v i.p.	90 mins	<ul style="list-style-type: none"> Free radicals induced oxidative damage 5- HT₃ receptor mechanism 	Chen <i>et al.</i> , 1997
E-capsaicin	25.4 nmol, i.c.v.	90 mins	<ul style="list-style-type: none"> Multiple receptor sites 	Rudd & Wai, 2001
Naloxone	60 mg/kg, s.c.	30 mins	<ul style="list-style-type: none"> Effects via NK₁ and 5-HT_{1A} receptors 	Rudd <i>et al.</i> , 1999
Nicotine	5,10 mg/kg, s.c.	30 mins	<ul style="list-style-type: none"> Central μ-opioid receptors 	Rudd <i>et al.</i> , 1999
	10 mg/kg, s.c	30 mins	<ul style="list-style-type: none"> Central μ-opioid receptors 	Torii <i>et al.</i> , 1991
	7.9mg/kg s.c.	30mins	<ul style="list-style-type: none"> Generation of free radicals causes the release of peripheral 5-HT 	Ueno <i>et al.</i> , 1987
Pyrogallol	128 mg/ kg i.p.	30 mins	<ul style="list-style-type: none"> Other peripheral action, possible via indirect release of 5-HT and stimulation of 5-HT₃ receptors 	Torii <i>et al.</i> , 1994
Resiniferatoxin	100 μ g/kg s.c.	-----	<ul style="list-style-type: none"> Multiple targets 	Andrews <i>et al.</i> , 1996; 2000; Rudd & Wai, 2001
Veratrine sulfate			<ul style="list-style-type: none"> Vagal ganglion stimulation 	
	0.4 & 0.5 mg/kg s.c.	30 mins	<ul style="list-style-type: none"> 5-HT_{1A} receptor antagonism 	Okada <i>et al.</i> , 1994; Ueno <i>et al.</i> , 1987

35–60 days old least shrew (*Cryptotis parva*) weighing 4–5 g are also used for anti-emetic studies (Darmani, 1998). Cisplatin (20 mg/kg i.p.) is commonly used as emetic stimuli in a 90 mins observation studies (Darmani, 1998) while a 30 mins period is used for substance-P (50mg/kg i.p.) (Darmani et al., 2008). Peripheral NK₁ receptors have been shown to be involved in Substance-P-induced emesis (Darmani et al., 2008) whereas stimulation of 5HT₃ receptors mediate the cisplatin-induced emesis (Darmani, 1998).

10. Pigeon emesis model

Carneau pigeons (*Columbia livia*) of weight 250-500 g are used in this emesis model. Apomorphine at a dose of 250 µg/kg, i.m. (Dhawan et al., 1961), cisplatin at 4 mg/kg i.v. (Tanihata et al., 2000) or reserpine and yohimbine at 500 µg/kg i.m. (Khandar et al., 1994) are used to induce emesis. The emetic responses are characterized by a bout of emesis (more than an emetic behavior) known as pecking (Tanihata et al., 2000). The emesis observation period is generally 2 hrs (Dhawan et al., 1961; Khandar et al., 1994) but in case of cisplatin, which showed acute and delayed emesis, 3 hrs for early and 72 hrs of observation for delayed emesis are used (Tanihata et al., 2000). Cisplatin-induced early emesis in pigeons is shown to be mediated via the vagal nerve and reserpine-sensitive monoaminergic systems including the serotonergic system while the delayed emesis is associated with monoaminergic systems (Tanihata et al., 2000). In yohimbine and reserpine model of emesis, the release of monoamines are implicated in the emesis response (Khandar et al., 1994).

11. Cat emesis model

Dopamine 3 mg/kg i.c.v. (Jovanović-Mićić et al., 1995) and xylazine 0.66 mg/kg s.c. (Lucot & Crampton, 1986) are used as emetic agent in cats (*Felis catus*) of 2-4 kg of body weight. Emesis was observed for 10 mins in case of dopamine (Jovanović-Mićić et al., 1995) and 30 mins for xylazine (Lucot & Crampton, 1986). Adrenergic mechanisms have been shown to be involved in both types of emesis (Lucot & Crampton, 1986; Jovanović-Mićić et al., 1995).

B. *In vitro* emesis model (*Dictyostelium* Chemotaxis model)

Animals have been used as experimental models for centuries but ethical concerns, legislative changes and the current economic climate encourage researchers to look forward for alternative non-animal models. Animal experiments which can involve a significant level of suffering and distress due to the effects induced emesis e.g. reduced food intake, weight loss and dehydration have also been a major concern (Robinson, 2009). *Dictyostelium discoideum* chemotaxis model is one example of recently developed non-animal models. This *in vitro* chemotaxis model is simple, rapid and inexpensive experimental design that serves as an early indicator of anti-emetic compounds. The emetic response is investigated by observing the *Dictyostelium* cell behaviour (shape, speed and direction of movement) for 10 mins. Usually emetic compounds blocked the motility of *Dictyostelium*. In this assay model, three bitter tasting compounds (denatonium benzoate, quinine hydrochloride and phenylthiourea), the pungent constituent of chili peppers (capsaicin), stomach irritants (copper chloride and copper sulfate) and a phosphodiesterase IV inhibitor have been shown to strongly and rapidly

block the motility of *Dictyostelium* (Robery et al.,2011). Such convenient *in vitro* bioassay models are likely to flourish in the future exploration of anti-emetic agents.

D. Bioactive natural products

1. Anti-emetic plants: Overview of ethnobotanical information

Traditional Chinese Medicine (TCM) consists of number of natural products used in the treatment of emesis. Among these are medicinal plants whose anti-emetic effects have been confirmed by using animal emesis models. For example, Xiao-Ban-Xia-Tang which contain 10g of *Zingiber officinale* Roscoe and 20g of *Pinellia ternata* (Thunb.) Breit., showed anti-emetic activity against cisplatin-induced acute and delayed emesis in minks (Qian et al., 2010). Furthermore, several Indian medicinal plants are also reported for their effective use in the treatment of emesis. Most of the Indian anti-emetic plants are also part of the Pakistani flora and employed for similar medicinal uses. A review of ethnomedicinal information in these regions has shown in Table 2. This table further lists plant from China, Iran, Africa, Arab, Thailand and New Guinea, which are commonly used for treating emesis.

Table 2. Natural products used for treating emesis in various countries and cultures.

Plant name and part(s) used	References
China	
<i>Abrus precatorius</i> L. (seeds)	Huang, 1999 ; Li, 2002
<i>Alisma orientale</i> (rhizomes)	
<i>Alpinia katsumadai</i> Hayata., (seeds)	Ching Su New Medicinal College, 1978
<i>Alpinia officinarum</i> Hance. (rhizomes)	
<i>Amomum cardamomum</i> L. (seeds)	Li, 2002
<i>Amomum globosum</i> Lour. (seeds)	
<i>Amomum kravanh</i> Pire ex Gagnep., (fruits)	Ching Su New Medicinal College, 1978
<i>Amomum tsao-ko</i> Roxb. (fruits & seeds)	Ching Su New Medicinal College, 1978 (fruits) ; Li, 2002
<i>Amomum villosum</i> L. (seeds)	Li, 2002
<i>Amomum xanthioides</i> Wall. ex Baker. (fruits & seeds)	Ching Su New Medicinal College, 1978 (fruits) ; Li, 2002
<i>Aquilaria agallocha</i> Roxb. (stem wood)	Li, 2002
<i>Aquilaria sinensis</i> (Lour.) Gilg. (resinous wood)	Huang, 1999 ; Li, 2002
<i>Arundo donax</i> L., (roots)	Li, 2002
<i>Atractylodes japonica</i> Koidz. (rhizomes)	
<i>Atractylodes lancea</i> DC. (roots)	Ching Su New Medicinal College, 1978
<i>Changium smyrnioides</i> Wolff. (roots)	
<i>Citrus deliciosa</i> Tenore. (fruit peel)	
<i>Citrus nobilis</i> Lour., (fruit peel)	Li, 2002
<i>Citrus reticulata</i> Blanco. (fruit peel)	
<i>Citrus unshiu</i> (Swingle) Marcow. (fruit peel)	
<i>Diospyros kaki</i> Thunb. (sepals)	
<i>Eriobotrya japonica</i> Lindl. (leaves)	Ching Su New Medicinal College, 1978
<i>Eupatorium fortunei</i> Turcz. (aerial parts)	
<i>Evodia rutaecarpa</i> (Juss.) Benth. (fruits)	Huang, 1999; Li, 2002
<i>Foeniculum vulgare</i> Miller. (fruits)	Ching Su New Medicinal College, 1978
<i>Forsythia suspensa</i> (Thunb.) Vahl., (fruits & leaves)	Li, 2002
<i>Glycyrrhiza uralensis</i> (roots)	
<i>Hovenia dulcis</i> Thunb. (fruits)	Ching Su New Medicinal College, 1978
<i>Inula britannica</i> L. (aerial part, including flower head)	
<i>Inula japonica</i> Thunb. (aerial part, including flower head)	Li, 2002
<i>Inula linariaefolia</i> L. (flowers)	Ching Su New Medicinal College, 1978

<i>Inula salsoloides</i> (Turcz.) Ostenfeld. (flowers)	Li, 2002
<i>Lindera strychnifolia</i> Sieb. et Zucc. (roots)	
<i>Nelumbo nucifera</i> Gaertn. (seeds)	Ching Su New Medicinal College, 1978
<i>Panax ginseng</i> C. A. Meyer. (roots)	
<i>Phragmites communis</i> Trin. (roots)	
<i>Phyllostachys bambusoides</i> Sieb. Et Zucc. (shoot)	
<i>Phyllostachys nigra</i> Munro. var. <i>henonis</i> Mak. (leaves)	Li, 2002
<i>Pinellia ternata</i> (Thunb.) Breit. (tuber)	
<i>Pinellia tuberifera</i> Tenore . (tuber)	
<i>Pogostemon cablin</i> (Blanco) Benth. (aerial parts)	
<i>Polyporus umbellatus</i> Fries. (sclerotia)	Ching Su New Medicinal College, 1978
<i>Poria cocos</i> Wolf. (sclerotia)	
<i>Syzygium aromaticum</i> (L.) Merr. & Perry. (flowering bud)	Li, 2002
<i>Zingiber officinale</i> Roscoe. (rhizomes)	Ching Su New Medicinal College, 1978
India	
<i>Abutilon Indicum</i> (L.) Sweet. (bark)	
<i>Achillea millefolium</i> L. (whole plant)	Asima, 2003; Kirtikar & Basu, 1976
<i>Aconitum heterophyllum</i> Wall. ex Royle. (whole plant)	
<i>Aconitum palmatum</i> D. Don. (roots)	Khare, 2007
<i>Adhatoda zeylanica</i> Medic. (whole plant)	Khare, 2004
<i>Alhagi maurorum</i> Medik. (whole plant)	CSIR, 1985
<i>Alhagi pseudalhagi</i> (Bieb.) Desv. (whole plant)	Khare, 2007
<i>Amomum krervanh</i> Pierre. (fruits)	Asima, 2003; Kirtikar & Basu, 1976
<i>Amorphophallus campanulatus</i> (Roxb.) Blume ex Decne. (tuber)	Khare, 2004
<i>Annona Squamosa</i> L. (fruits)	Asima, 2003; Kirtikar & Basu, 1976
<i>Apium graveolens</i> L. (whole plant)	Khare, 2007
<i>Arundo phragmites</i> L. (stem)	
<i>Averrhoa carambola</i> L. (fruits)	
<i>Ballota nigra</i> L. (whole plant)	
<i>Bixa orellana</i> L. (whole plant)	Asima, 2003; Kirtikar & Basu, 1976
<i>Blighia sapida</i> Konig., (aerial parts)	
<i>Calendula officinalis</i> L. (florets)	
<i>Cannabis sativa</i> L. (whole plant)	Khare, 2007
<i>Cetraria islandica</i> (L.) Ach. (Whole moss)	Asima, 2003; Kirtikar & Basu, 1976
<i>Cinnamomum cassia</i> Blume. (whole plant)	Khare, 2007
<i>Cinnamomum verum</i> J. Presl. (fruits)	
<i>Citrus aurantifolia</i> (L.) Osbeck. (fruits)	
<i>Citrus reticulata</i> Blanco. (fruits)	Asima, 2003; Kirtikar & Basu, 1976
<i>Curcuma petiolata</i> Roxb. (rhizome)	
<i>Cyperus articulatus</i> L. (whole plant)	Khare, 2007
<i>Desmodium gangeticum</i> (L.) DC. (roots)	Thakur et al., 1989
<i>Emblica officinalis</i> Gaertn. (fruits)	Khare, 2007
<i>Eriobotrya japonica</i> Lindl. (fruits)	
<i>Fagonia cretica</i> L. (leaves)	Asima, 2003; Kirtikar & Basu, 1976
<i>Ferronia elephantum</i> Correa. (fruits)	Asima, 2003; Kirtikar & Basu, 1976
<i>Ficus benghalensis</i> L. (roots)	
<i>Ficus racemosa</i> L. (fruits)	
<i>Gentiana kurroo</i> Royle. (roots)	Khare, 2007
<i>Hedychium spicatum</i> Ham. ex Smith. (rhizome)	
<i>Hemerocallis fulva</i> L. (flowers)	Asima, 2003; Kirtikar & Basu, 1976
<i>Ipomoea pes-caprae</i> (L.) Sweet. (whole plant)	
<i>Iris versicolour</i> L. (rhizome)	
<i>Mentha piperata</i> Linn. emend. Huds. (leaves)	Khare, 2007
<i>Mentha spicata</i> Linn. emend. Nathh. (leaves)	
<i>Mesua ferrea</i> L. (leaves)	Asima, 2003; Kirtikar & Basu, 1976
<i>Michelia champaca</i> L. (flowers)	Khare, 2007
<i>Murraya koenigii</i> (L.) Sprengel. (leaves)	Asima, 2003; Kirtikar & Basu, 1976
<i>Nardostachys grandiflora</i> DC (leaves)	ICMR, 1976 ; Kapoor, 1990
<i>Nelumbo nucifera</i> Gaertn. (roots)	Khare, 2007
<i>Ocimum gratissimum</i> L. (whole plant)	Asima, 2003; Kirtikar & Basu, 1976

<i>Ouratea angustifolia</i> (Vahl.) Baillon. (roots)	
<i>Panax quinquefolium</i> . (roots)	
<i>Pavonia odorata</i> Willd. (whole plant)	
<i>Phragmites australis</i> Trin. (stem)	
<i>Phragmites communis</i> Trin. (rhizome)	Khare, 2007
<i>Phyllostachys nigra</i> (Lodd. ex Lindl.) Munro. (bark)	
<i>Portulaca oleracea</i> L. (leaves)	
<i>Prunella vulgaris</i> L. (whole plant)	Asima, 2003; Kirtikar & Basu, 1976
<i>Pueraria thunbergiana</i> (Sieb. & Zucc.) Benth. (whole plant)	
<i>Pueraria tuberosa</i> (Roxb.ex Willd.) DC. (tuber)	Jain et al.,2005
<i>Punica granatum</i> L. (fruits)	Khare, 2007
<i>Sanguinaria canadensis</i> L. (roots)	Asima, 2003; Kirtikar & Basu, 1976
<i>Scirpus kysoor</i> Roxb. (stem)	Khare, 2007
<i>Sida acuta</i> Burm.f. (roots)	Jain et al.,2005
<i>Syzygium aromaticum</i> (Linn.) Merr. & Perry. (flowering buds)	Khare, 2007
<i>Zingiber officinale</i> Roscoe. (rhizome)	
Pakistan	
<i>Ajuga bracteosa</i> Wall. (whole plant)	Jan et al.,2008
<i>Calendula arvensis</i> L. (flowers and leaves)	Sher et al.,2011
<i>Jasminum officinale</i> L. (whole plant)	
<i>Mentha longifolia</i> (L.) Huds. (whole plant)	Shah et al.,2012
<i>Mentha spicata</i> L. (leaves)	
<i>Punica granatum</i> L. (flower and bark)	Khan et al.,2012
Iran	
<i>Berberis vulgaris</i> L. var. <i>asperma</i> Don (whole plant)	Javadzadeh & Fallah, 2012
<i>Cynodon dactylon</i> (L.) Per. (roots and rhizome)	Miraldi et al., 2001
<i>Mentha longifolia</i> (aerial parts)	Hosseinzadeh et al., 2004
<i>Mentha piperata</i> Linn. emend. Huds. (aerial parts)	Hossein et al., 2005
<i>Valeriana officinalis</i> L. (roots)	Hosseinzadeh et al., 2011
Africa	
<i>Afzelia africana</i> Sm. ex Pers. (aerial parts)	Odugbemi, 2008
<i>Anethum graveolens</i> L. (whole plant)	Boulos, 1983
Garcinia kola Heckel. (seeds)	Aluka, 1985
<i>Grewia lasiodiscus</i> K. Schum. (root)	Oliver- Bever, 1983
<i>Nymphaea lotus</i> L. (whole plant)	Burkill, 1995
<i>Phragmites australis</i> (Cav.) Trin. ex Stead. (whole plant)	Boulos, 1983
<i>Solanum aethiopicum</i> L. (leaves)	Grubben & Denton, 2004
<i>Vitex iringensis</i> Gürke. (leaves)	Mathias,1982
Arab	
<i>Anethum graveolens</i> L. (seeds)	
<i>Citrus limon</i> (L.) Burm. f. (fruits)	
<i>Citrus limon</i> (L.) Burm. f. (leaves)	
<i>Eugenia caryophyllata</i> Thunb. (seeds)	Saganuwan & Saganuwan, 2010
<i>Heliotropium indicum</i> L. (flower)	
<i>Heliotropium indicum</i> L. (leaves)	
<i>Phragmites australis</i> (Cav.) Trin. ex Stead. (whole plant)	Ghazanfar, 1994
<i>Raphanus Sativus</i> L. (seeds)	
<i>Vigna unguiculata</i> (L.) Walp. (flower)	Saganuwan & Saganuwan,2010
Thailand	
<i>Morinda citrifolia</i> L. (fruits)	Prapairakool & Itharat, 2010
New Guinea	
<i>Ageratum conyzoides</i> L. (leaves)	WHO, 2009

In the U.K. and U.S.A., Asian herbs such as *Agastache rugosa* (Fischer & C. Meyer) Kuntze., (Mills, 1997); leaves of *Mentha piperita* (Aslam, 1997); flowers of *Eriobotrya japonica* Lindley., and *Eugenia caryophyllata* Thunberg., (Mills, 1997); fruits of *Cocos nucifera* L., (Aslam, 1997) and *Amomum cardamomum* L., (Mills, 1997); roots of *Cyperus rotundus* L., (Aslam, 1997); rhizome of *Zingiber officinale* Roscoe (Mills, 1997) are generally used to treat emesis.

2. Crude natural products with reported anti-emetic properties

To date, a number of plants identified through ethnomedicinal information have been shown to display anti-emetic potential in different animal models. A systematic review of plants with validated anti-emetic potential are listed in Table 3. Included in the list are also mushrooms *Ganoderma lucidum* (Curtis) P. Karst., (Ganodermataceae) and *Poria cocos* Wolf., (Pleurotaceae) and red algae *Hypnea pannosa* J. Ag., (Rhodophyceae) that showed anti-emetic behavior in rat, frog and chick emesis models respectively (Table 3).

3. Purified natural products with anti-emetic effect

Secondary metabolites of natural origin, often with complex structural diversity, are used as reliable sources of new drugs (Harvey, 2008). Hence crude natural products showing anti-emetic activity are often subjected to analytical studies to reveal the active constituents. The class of compounds identified with anti-emetic activities so far include cannabinoids, chalcones, diarylheptanoids, flavonoids, glucosides, hydroxycinnamic acids, lignans, phenylpropanoids, polysaccharides, saponins and terpenes (sesqui & triterpenes) (Table 4). As shown in Fig 2, the proposed mechanisms of action for these natural products are I) 5-HT₃ / 5-HT₄ receptors antagonism II) tachykinin NK₁ receptors antagonism III) antioxidant action IV) δ (enkephalinergetic)-receptor inhibition V) cannabinoid CB₁ receptor activation, and VI) inhibition of dopaminergic stimulation of the visceral afferent innervations.

Cannabinoids

Δ^9 -THC (delta-9 tetrahydrocannabinol) is a cannabinoid isolated from *Cannabis sativa* flowers and buds (Gaoni & Mechoulam, 1964). Δ^9 -THC (Table 3, Entry No. 68-70) selectively acts at CB₁ receptors to reduce neuronal activation in response to emetic stimuli in specific regions of the dorsal vagal complex (Van Sickle *et al.*, 2001 & 2003). It has been shown that Δ^9 -THC prevents serotonergically mediated vomiting *via* central and peripheral

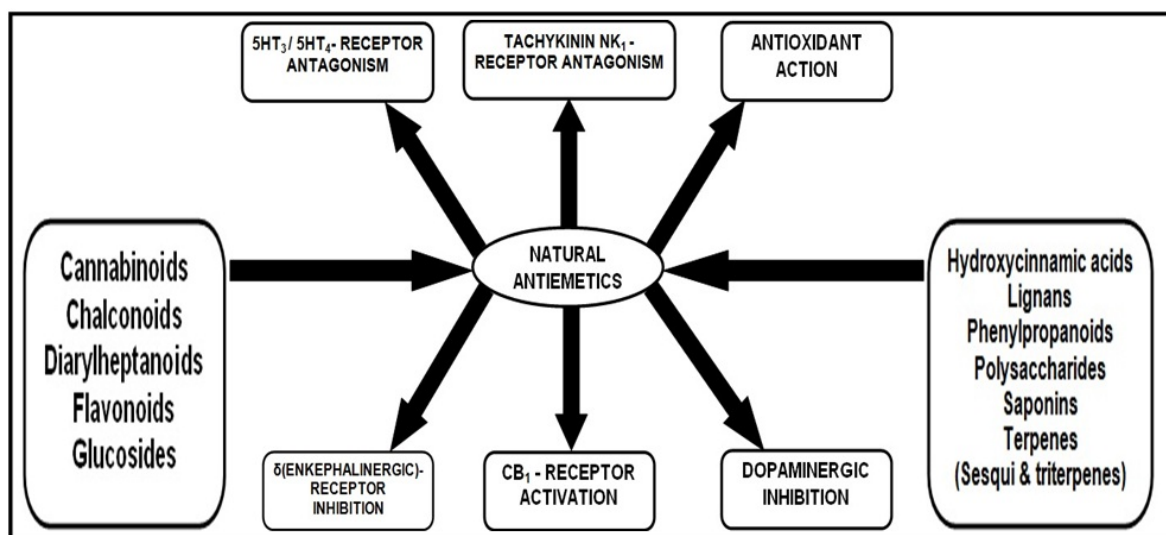


Figure.2. Proposed mechanisms of natural anti-emetics.

Table 3. Medicinal plants with reported anti-emetic effects.

Copper sulfate-induced emesis model in chicks			
Plants and part(s)	Traditional uses (references)	Extract and Dose (mg/kg p.o.)	% inhibition of retches
<i>Acalypha fimbriata</i> Schumach. & Thonn. Leaves and stems	Kola et al., 2008	Methanol (150)	44.42 for leaves and 35.04 for stems (Quds et al.,2012)
<i>Acalypha ornata</i> Hochst. Leaves and stems	-----	Methanol (150)	94.51 for leaves and 65.64 for stems (Quds et al.,2012)
<i>Acalypha wilkesiana</i> cv. godseffiana Muell Arg. Leaves and stems	Akinyemi et al., 2005	Methanol (150)	68.96 for leaves and 77.91 for stems (Quds et al.,2012)
<i>Adenanthera pavonina</i> L. Leaves	Holdsworth, 1977	Methanol (150)	50.17 (Hasan et al.,2012a)
<i>Alpinia katsumadai</i> Hayata. Seeds	Ching Su New Medicinal College, 1978	Methanol (150)	73.9 (Yang et al., 1999a)
<i>Amomum kravanh</i> Pire ex Gagnep. Fruits		Chloroform (150)	52.6 (Yang et al., 1999a)
<i>Alpinia officinarum</i> Hance. Rhizome		Chloroform (150)	45.6 (Yang et al., 1999a)
<i>Amomum tsao-ko</i> Crevost & Lemarié. Fruits		Methanol (150)	54.5 (Yang et al., 1999a)
<i>Amomum xanthioides</i> Wall. ex Baker. Fruits		Chloroform (150)	53.8 (Yang et al., 1999a)
Brazilian propolis (Bee glue collected by honeybees)		Methanol (100)	44.9 (Eda et al., 2005)
<i>Carissa carandus</i> L. Fruits	Buckle, 2003	Ethanol (150)	68.29 (Hasan et al.,2012b)
<i>Cassia angustifolia</i> Vahl. Leaves	Chopra et al., 1956; Usmanghani et al.,1997.	Methanol (150)	79.31 (Ahmed et al.,2012b)
<i>Cassia holosericea</i> Fresen. Leaves		Methanol (150)	41.99 (Ahmed et al.,2012b)
<i>Cassia italica</i> Miller. Lam. ex F.W. Ander. Leaves		Methanol (150)	96.07 (Ahmed et al.,2012b)
<i>Cassia purpurea</i> Roxb. Leaves		Methanol (150)	94.5 (Ahmed et al.,2012b)
<i>Cassia siamea</i> Lamk. Leaves	Ahn et al., 1978	Methanol (150)	18 (Ahmed et al.,2012a)
<i>Chichorium intybus</i> L. Flowers	Buckle, 2003	Ethanol 150)	73.86 (Hasan et al.,2012b)
<i>Cinnamomum tamala</i> L. Rhizomes		Ethanol (150)	70.64 (Hasan et al., 2012b)
<i>Cleome viscosa</i> L. Seeds (fixed oil)	Mali, 2010	Hexane (125)	91.77 (Ahmed et al.,2011)
<i>Cleome scaposa</i> DC. Leaves	Atiqur et al.,2004; Khan, 2009	Methanol (150)	49.94 (Ahmed et al.,2012a)
<i>Curcuma caesia</i> Roxb. Leaves	Buckle, 2003	Ethanol (150)	89.97 (Hasan et al.,2012b)
<i>Cyamopsis tetragonoloba</i> Taubert. Leaves	Duke, 2002	Methanol (150)	34.39 (Ahmed et al.,2012a)
<i>Delonix regia</i> Rafin. Leaves	Lawal et al.,2010	Methanol (150)	96.74 (Ahmed et al.,2012a)
<i>Eupatorium fortunei</i> Turcz. Leaves and stem	Ching Su New Medicinal	Chloroform (150)	32.1 (Yang et al., 1999a)

<i>Garcinia kola</i> Heckel. Seeds	College, 1978 Aluka, 1985	Ethanol (150)	75.47 (Nosiri et al.,2010)
<i>Grewia asiatica</i> L. Leaves	Morton, 1987	Methano (100)	59.69 (Zia-Ul-Haq et al., 2012)
<i>Grewia lasiodiscus</i> K. Schum. Roots	Oliver- Bever, 1983	70% aqueous methanol (200)	71.77(Tijani et al., 2008)
<i>Hypnea pannosa</i> J. Ag. Red algae	-----	Ethanol (200)	40.38 (Mazhar et al.,2011)
<i>Lallemantia royleana</i> Benth. Leaves	Buckle, 2003	Ethanol (150)	83.61 (Hasan et al.,2012b)
<i>Luffa cylindrica</i> (L.) Roem. Leaves	-----	Ethanol (150)	68.66 (Khan et al.,2013)
<i>Luffa cylindrica</i> (L.) Roem. Flowers	-----	Ethanol (150) Hexane (150)	68.46 (Khan et al.,2013) 71.75 (Khan et al.,2013)
<i>Matricaria chamomila</i> L. Flowers	Buckle, 2003	Ethanol (150)	59.92 (Hasan et al.,2012b)
<i>Nelumbo nucifera</i> Gaertn. Seeds	Khare, 2007	Chloroform(150)	27.20 (Yang et al., 1999a)
<i>Peltophorum roxburghii</i> L. Leaves	-----	Methanol (150)	54.89 (Hasan et al.,2012a)
<i>Piper longum</i> L. Fruits	Buckle, 2003	Ethanol (150)	81.65 (Hasan et al.,2012b)
<i>Piper methysticum</i> G. Forst. Fruits		Ethanol (150)	80.03 (Hasan et al.,2012b)
<i>Piper nigrum</i> L. Fruits		Ethanol (150)	89.48 (Hasan et al.,2012b)
<i>Pistacia vera</i> L. Leaves and nuts	Hameed, 1998	Aqueous (100) for leaves (150) for nuts	71.00 for leaves 68.90 for nuts (Hosseinzadeh et al.,2008)
<i>Prosopis cineraria</i> L. Leaves	-----	Methanol (150)	69.49 (Hasan et al.,2012a)
<i>Prosopis juliflora</i> DC. Leaves	Pasiecznik et al., 2001	Methanol (150)	73.64 (Hasan et al.,2012a)
<i>Samanea saman</i> Merr. Leaves	Ayensu,1981; Perry, 1980	Methanol (150)	76.41 (Ahmed et al.,2012a)
<i>Syzygium aromaticum</i> Linn., Merr. & Perry. Flowering buds	Buckle, 2003	Ethanol(150)	87.81 (Hasan et al.,2012b)
<i>Tamarindus indica</i> L. Leaves	-----	Methanol (150)	69.48 (Khan et al., 2005)
<i>Thymus transcaspicus</i> Klokov. Aerial parts	Krappand & Longe, 2001	Petroleum ether (1300)	77.30 (Moallem et al.,2009)
<i>Valeriana officinalis</i> L. Roots	-----	Hydroethanol (700)	65.70 (Hosseinzadeh et al.,2011)
<i>Vigna trilobata</i> Verdc. Leaves	Joshi, 2000	Methanol (150)	36.32 (Ahmed et al.,2012a)

Copper sulfate-induced emesis model in frogs

Plants and part(s)	Traditional uses (references)	Extract and Dose (mg/kg p.o.)	% prolongation of emetic latency
<i>Citrus unshiu</i> (Swingle) Marcow. Fruit peels	Ching Su New Medicinal College, 1978	Methanolic -500	74.7 (Kinoshita et al.,1996)
<i>Diospyros kaki</i> L. Sepals		Aqueous -500	65.6 (Kinoshita et al.,1996)
<i>Eriobotrya japonica</i> Lindl. Leaves		Methanol -500	115.2 (Kinoshita et al.,1996)
<i>Foeniculum vulgare</i> Mill. Fruits		Chloroform -500	27.7 (Kinoshita et al.,1996)
<i>Forsythia suspensa</i> Vahl. Fruits		Methanolic -500	167.7 (Kinoshita et al.,1996)
<i>Hovenia dulcis</i> Thunb.		Chloroform	119.8

Fruits		-500	(Kinoshita et al.,1996)
<i>Inula linariaefolia</i> L.		Chloroform	52.8
Fruits		-500	(Kinoshita et al.,1996)
<i>Lindera strychnifolia</i> Sieb. et Zucc.		Aqueous	132.6
Roots		-500	(Kinoshita et al.,1996)
<i>Pinellia ternata</i> (Thunb.) Breit.		Methanol	125.9
Tubers		-500	(Kinoshita et al.,1996)
<i>Pogostemon cablin</i> (Blanco) Benth.		Aqueous	37.7
Leaves		-500	(Kinoshita et al.,1996)
<i>Poria cocos</i> Wolf.		Aqueous	161.8
Sclerotium		-500	(Kinoshita et al.,1996)
Apomorphine -induced emesis model in frogs			
Plants and part(s)	Traditional uses (references)	Extract and Dose (mg/kg p.o.)	% inhibition of retches
<i>Diospyros kaki</i> L.	Ching Su New Medicinal College, 1978	Methanol	17.5
Sepals		-500	(Kinoshita et al.,1996)
<i>Forsythia suspensa</i> Vahl.		Methanol	63.6
Fruits		-500	(Kinoshita et al.,1996)
<i>Hovenia dulcis</i> Thunb.		Chloroform	10.71
Fruits		-500	(Kinoshita et al.,1996)
<i>Inula linariaefolia</i> L.		Chloroform	51.3
Fruits		-500	(Kinoshita et al.,1996)
<i>Lindera strychnifolia</i> Sieb. et Zucc.		Methanol	21.3
Roots		-500	(Kinoshita et al.,1996)
Ipecac-induced emesis model in chicks			
Plants and part(s)	Traditional uses (references)	Extract and Dose (mg/kg p.o.)	% inhibition of retches
<i>Pistacia vera</i> L.	Hameed,1998	Aqueous	55.40 for leaves
Leaves and nuts		(100) for leaves	48.00 for nuts
		(150) for nuts	(Hosseinzadeh et al., 2008)
<i>Thymus transcaspicus</i> Klokov	Krappand & Longe, 2001	Petroleum ether	(Moallem et al.,2009)
Aerial parts		-1300	
<i>Valeriana officinalis</i> L.	-----	Hydroethanolic	79.88
Roots		-700	(Hosseinzadeh et al.,2011)
Apomorphine-induced emesis model in dogs			
Plants and part(s)	Traditional uses (references)	Extract and Dose (mg/kg p.o.)	Time of emesis inhibition (mins)
<i>Emblica officinalis</i> Gaertn.	Khare, 2007	Aqueous (500)	180 (Yaqeenddin et al., 1990)
Fruits			
<i>Grewia asiatica</i> L.	Morton, 1987	Alcohol (120)	180 (Yaqeen et al., 2008)
Fruits			
<i>Nelumbium speciosum</i> Wild.	Kirikar et al., 1933	Alcohol 90	180 (Yaqeen et al., 1998)
Seeds			
<i>Prunus domestica</i> L.	Said, 1969	Ethanol (125)	45 (Qureshi et al., 1988)
Fruits			
Cisplatin-induced pica model in rats			
Plants and part(s)	Traditional uses (references)	Extract and Dose(mg/kg i.p.)	Time of significant reduction in pica (hrs)
<i>Ganoderma lucidum</i> (Curtis) P.Karst.		-10	120
Whole mushroom			(Wang et al., 2005)
<i>Panax quinquefolius</i> L.	-----	Aqueous (100)	120
Berry			(Mehendale et al., 2005)
<i>Scutellaria baicalensis</i> Georgi.	Huang, 1999	Aqueous (3)	120
Roots			(Aung et al., 2003)
Cisplatin-induced emesis model in dogs			
Plants and part(s)	Traditional uses (references)	Extract and Dose (mg/kg p.o.)	Complete inhibition of

<i>Zingiber officinale</i> Roscoe. Rhizome	Chopra et al., 1956a	Acetone and ethanol (200)	emesis (hrs) 6.0 (Sharma et al., 1997)
Cisplatin-induced emesis model in ferrets			
Plants and part(s)	Traditional uses (references)	Extract and Dose(mg/kg p.o.)	Complete inhibition of emesis(hrs)
<i>Panax ginseng</i> C. A. Meyer. Roots	Ching Su New Medicinal College, 1978	Aqueous -3000	3.0(Kim et al., 2005)
Cyclophosphamide-induced emesis model in house musk shrew			
Plants and part(s)	Traditional uses (references)	Extract and Dose (mg/kg p.o.)	Complete inhibition of emesis
<i>Zingiber officinale</i> Roscoe. Rhizome	Chopra et al., 1956a	Acetone -150	(Yamahara et al., 1989)

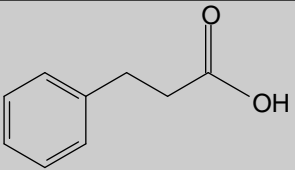
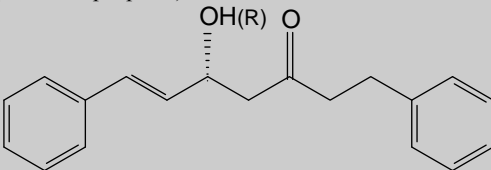
as well as pre- and post-synaptic neuronal mechanisms (Darmani and Johnson, 2004). CB₁ receptor activation is also suggested to be involved in the anti-emetic behavior of Δ^9 -THC (Darmani et al., 2007).

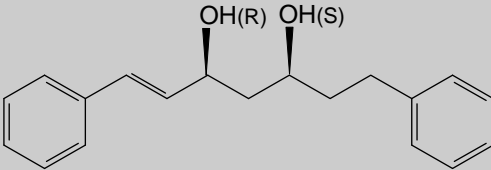
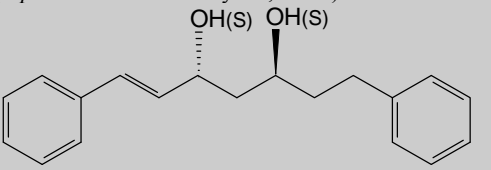
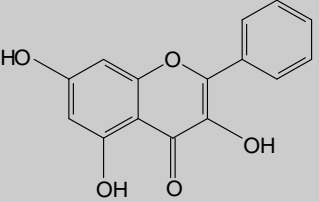
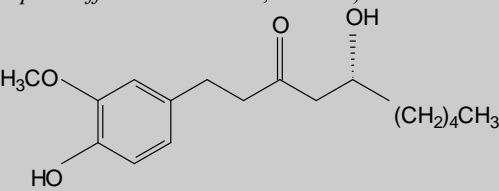
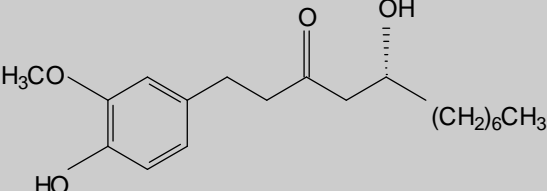
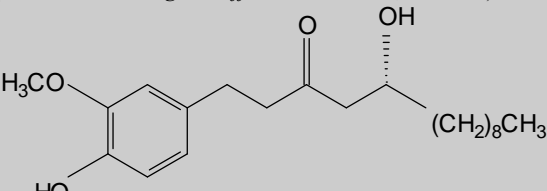

Chalcones

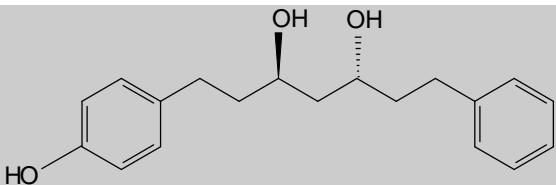
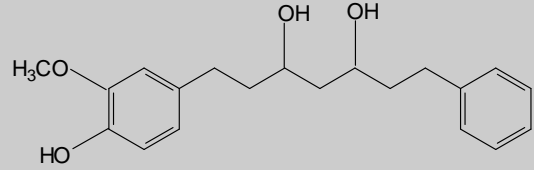
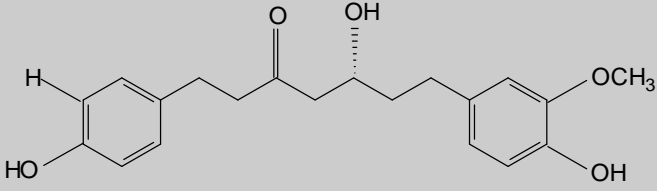
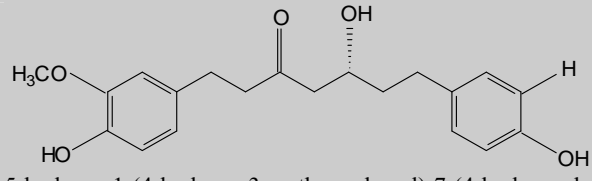
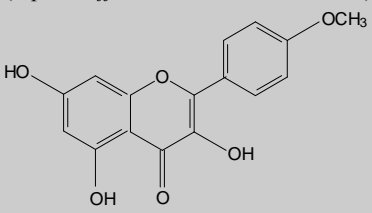
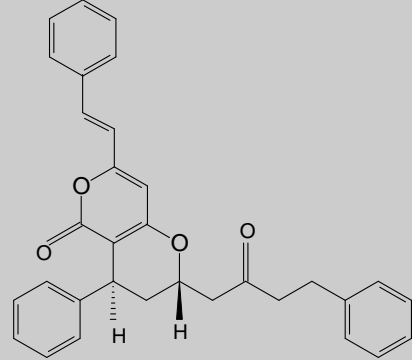
Cardamomin (Table 3, Entry No. 58) isolated from *Alpinia katsumadai* Hayata. seeds (Yang et al., 1999c) has been shown to inhibit emesis in free radical (AAPH in liposome)-induced chick emesis (Yang et al., 1999c). As a polyphenolic compound, cardamomin is expected to act through antioxidant mechanism (Yang et al., 1999c).

Diarylheptanoids

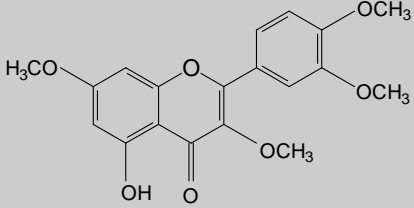
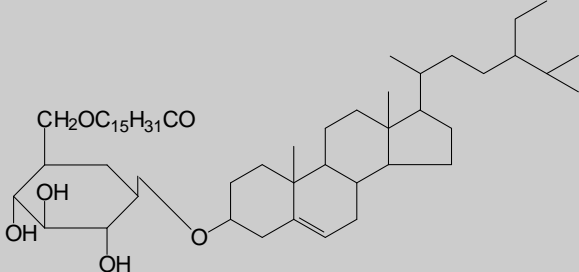
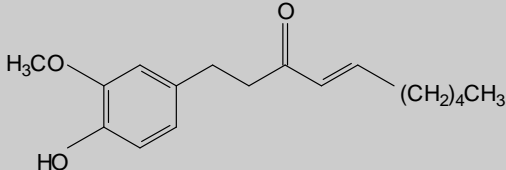
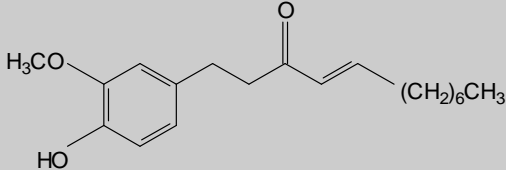
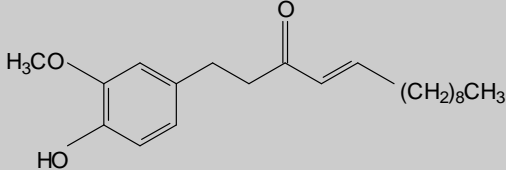
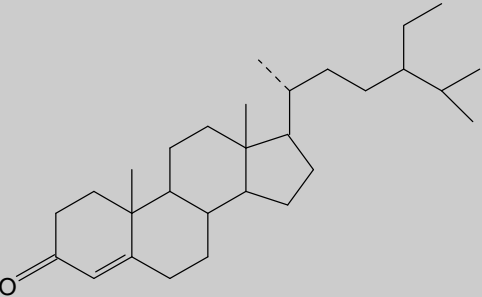
A number of diarylheptanoids (Table 3, Entry No. 2-4, 9-13, 15, 16, 21, 28-35, 65) isolated from *Alpinia katsumadai* Hayata. seeds (Yang et al., 2002) and *Alpinia officinarum*

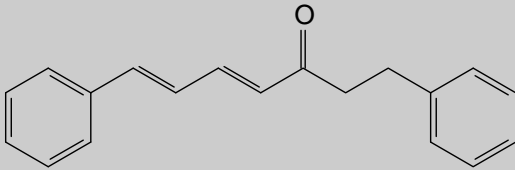
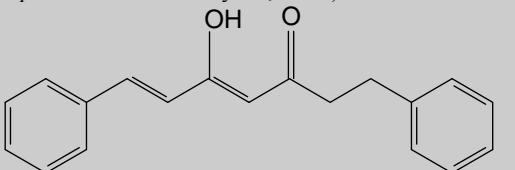
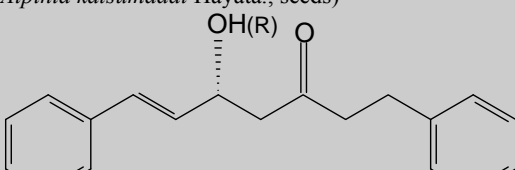
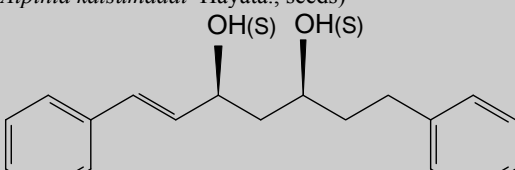
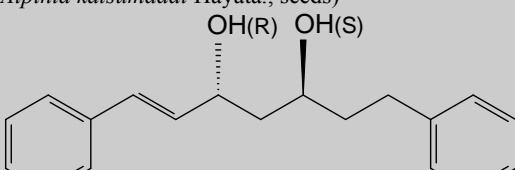
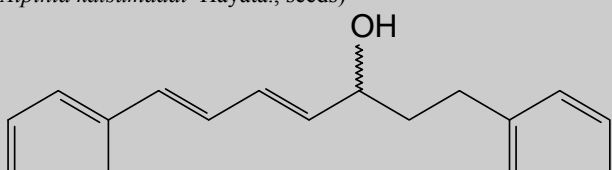
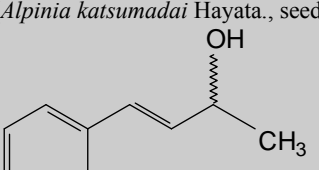
Entry	Compound, sources and doses used	% Inhibition of Retches (References)
Copper sulfate-induced emesis model in chicks		
1	 <p>Dihydrocinnamic acid (100mg/kg p.o.) (Brazilian propolis)</p>	59.30 (Eda et al., 2005)
2	 <p>Dihydroyashabushiketol (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)</p>	46.90 (Yang et al., 2002)

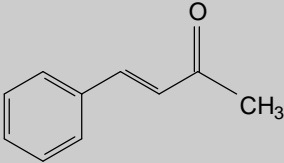
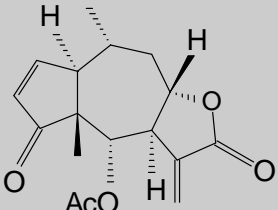
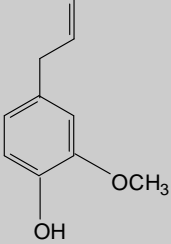
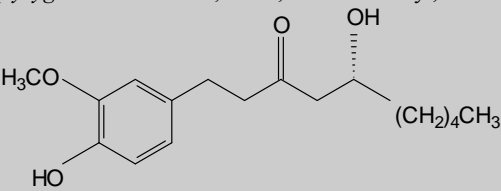
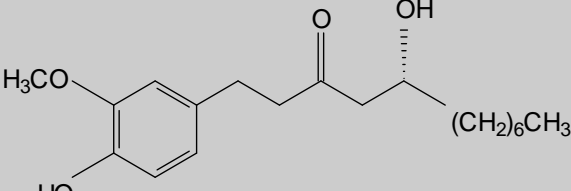
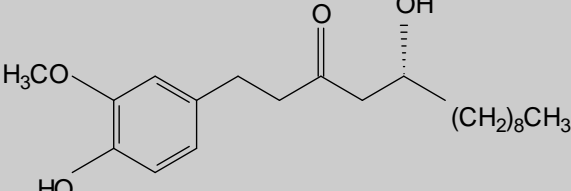
3	 <p>(3<i>S</i>,5<i>R</i>)-3,5-dihydroxy-1,7-diphenyl-heptane (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)</p>	47.80 (Yang et al., 2002)
4	 <p>(3<i>S</i>,5<i>S</i>)-3,5-dihydroxy-1,7-diphenylheptane (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)</p>	47.10 (Yang et al., 2002)
5	 <p>Galangin(20mg/kg p.o.) (<i>Alpinia officinarum</i> Hance., rhizome)</p>	25.40 (Shin et al., 2002)
6	 <p>[6]-gingerol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	58.00 (Akita et al., 1998; Kawai et al., 1994; Yamahara et al., 1989)
7	 <p>[8]-gingerol (50mg/kg p.o.) (isolated from <i>Zingiber officinale</i> Roscoe., rhizome)</p>	58.00 (Akita et al., 1998; Kawai et al., 1994)
8	 <p>[10]-gingerol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	46.30 (Akita et al., 1998; Kawai et al., 1994; Yang et al., 1999c)
9	 <p>5-hydroxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanone (20mg/kg p.o.) (<i>Alpinia officinarum</i> Hance., rhizome)</p>	71.00 (Shin et al., 2002)

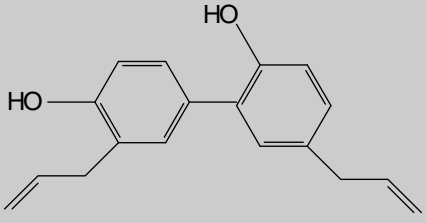
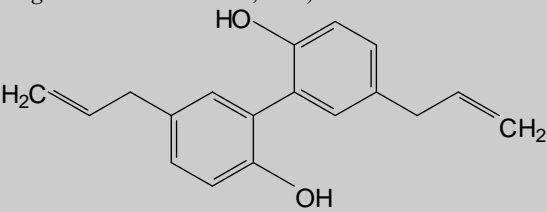
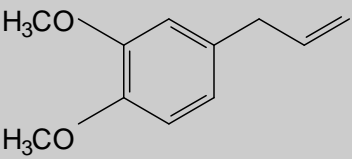
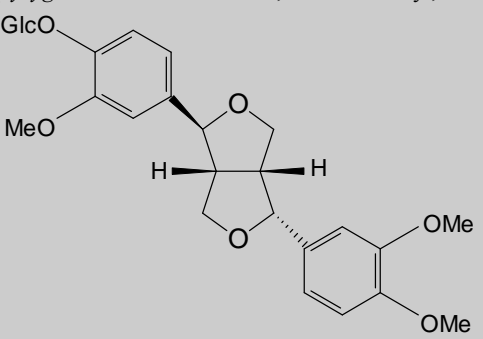
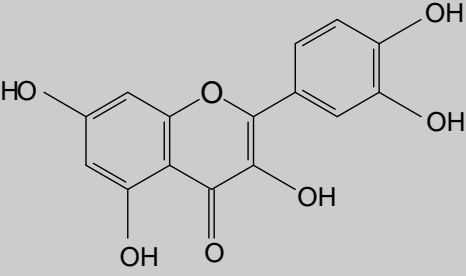
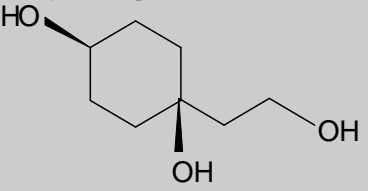
- 10  37.70
(Shin et al., 2002)
(3R,5R)-1-(4-hydroxyphenyl)-7-phenyl-3,5-heptanediol (50mg/kg p.o.)
(isolated from *Alpinia officinarum* Hance., rhizome, Shin et al., 2002).
- 11  45.70
(Shin et al., 2002)
1-(4-hydroxy-3-methoxyphenyl)-7-phenyl-3,5-heptanediol (50mg/kg p.o.)
(*Alpinia officinarum* Hance)
- 12  38.30
(Shin et al., 2002)
5-Hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-3-heptanone
(50mg/kg p.o.)
(*Alpinia officinarum* Hance., rhizome)
- 13  12.40
(Shin et al., 2002)
5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-3-heptanone
(50mg/kg p.o.)
(*Alpinia officinarum* Hance., rhizome)
- 14  63.30
(Shin et al., 2002)
Kaempferide (20mg/kg p.o.)
(*Alpinia officinarum* Hance., rhizome)
- 15  50.20
(Yang et al., 1999b)
Katsumadains A (50mg/kg p.o.)
(*Alpinia katsumadai* Hayata., seeds)

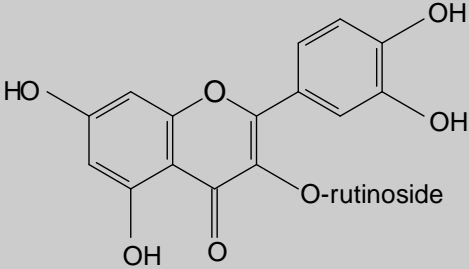
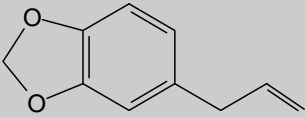
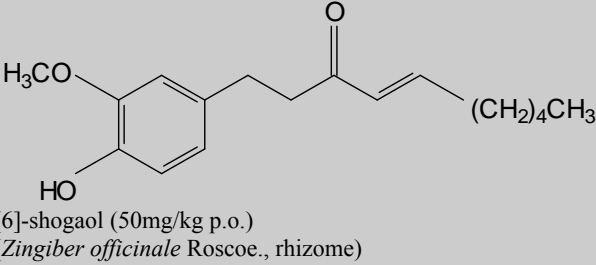
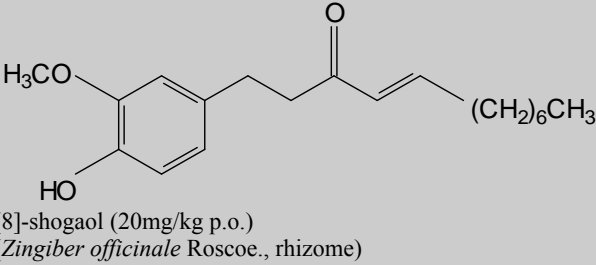
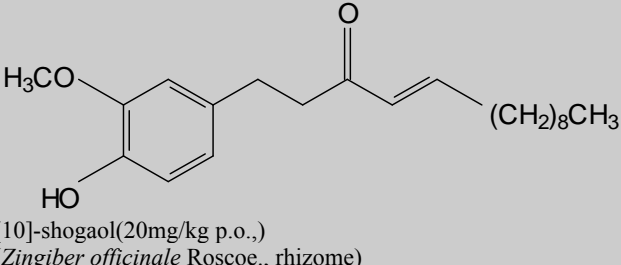
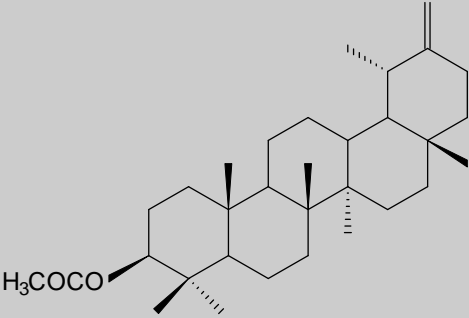
16		41.40 (Yang et al., 1999b)
<p>Katsumadain B (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)</p>		
17		49.90 (Eda et al., 2005)
<p>Lupeol (10mg/kg p.o.) (Brazilian Propolis)</p>		
18		50.50 (Yang et al., 1999a)
<p>Pachypodol (50mg/kg p.o.) (<i>Pogostemon cablin</i>, leaves)</p>		
19		57.70 (Yang et al., 1999a)
<p>Patchouli alcohol (70mg/kg p.o.) (<i>Pogostemon cablin</i> Blanco., leaves)</p>		
20		43.20 (Yang et al., 1999a)
<p>Pogostol (50mg/kg p.o.) (<i>Pogostemon cablin</i> leaves)</p>		
21		21.30 (Yang et al., 2002)
<p>4-Phenylbutan-2-one (50mg/kg p.o.)</p>		

22	<p>(<i>Alpinia katsumadai</i> Hayata., seeds)</p> 	45.60 (Yang et al., 1999a)
	<p>Retusin (50mg/kg p.o.) (isolated from <i>Pogostemon cablin</i> leaves, Yang et al., 1999a).</p>	50.90 (Shin et al., 2002)
23		50.90 (Shin et al., 2002)
	<p>β-sitosterol 3-O-β-D-6-palmitoylglucoside (50mg/kg p.o.) (<i>Alpinia officinarum</i> Hance., rhizome)</p>	49.20 (Akita et al., 1998)
24		49.20 (Akita et al., 1998)
	<p>[6]-shogaol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	53.70 (Akita et al., 1998; Kawai et al., 1994)
25		53.70 (Akita et al., 1998; Kawai et al., 1994)
	<p>[8]-shogaol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	69.00 (Akita et al., 1998; Kawai et al., 1994; Yang et al., 1999c)
26		69.00 (Akita et al., 1998; Kawai et al., 1994; Yang et al., 1999c)
	<p>[10]-shogaol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	55.70 (Yang et al., 1999a)
27		55.70 (Yang et al., 1999a)
	<p>Stigmast-4-en-3-one (50mg/kg p.o.) (<i>Pogostemon cablin</i> leaves)</p>	

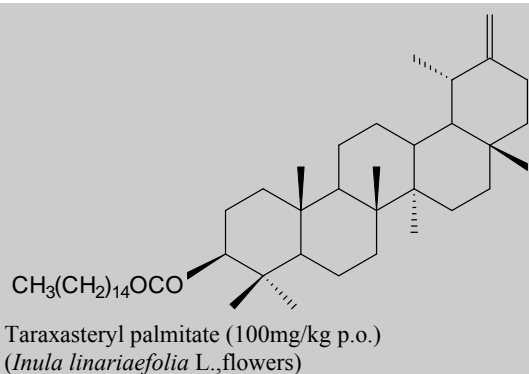
28		36.60 (Yang et al., 1999c ; 2002)
	<i>trans, trans</i> -1,7-diphenyl-4,6-heptadiene-3-one (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)	
29		17.30 (Yang et al., 2002)
	<i>trans, trans</i> -1,7-diphenyl-5-hydroxy-4,6-heptadien-3-one (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)	
30		55.60 (Yang et al., 2002)
	(5 <i>R</i>)- <i>trans</i> -1,7-diphenyl-5-hydroxy-6-hepten-3-one (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)	
31		55.60 (Yang et al., 2002)
	(3 <i>S</i> , 5 <i>S</i>)- <i>trans</i> -3,5-dihydroxy-1,7-diphenyl-1-heptene (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)	
32		70.80 (Yang et al., 2002)
	(3 <i>R</i> ,5 <i>S</i>)- <i>trans</i> -3,5-dihydroxy-1,7-diphenyl-1-heptene (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)	
33		47.40 (Yang et al., 2002)
	<i>trans,trans</i> -1,7-Diphenyl-1,3-heptadien-5-ol (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)	
34		13.80 (Yang et al., 2002)
	<i>trans</i> -4-phenyl-3-buten-2-ol (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)	

35		19.70 (Yang et al., 2002)
<p><i>trans</i>-4-Phenyl-3-buten-2-one (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)</p>		
Copper sulfate-induced emesis model in frogs		
Entry	Compound sources and doses used	% Prolongation of emetic latency (References)
36	 <p>Bigelovin (30mg/kg p.o.) (<i>Inula linariaefolia</i> L., flowers)</p>	86.60 (Kinoshita et al., 1996)
37	 <p>Eugenol (20mg/kg p.o.) (<i>Syzygium aromaticum</i>, Linn., Merr. & Perry., flower buds)</p>	147.40 (Kawai et al., 1994)
38	 <p>[6]-gingerol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	57.20 (Akita et al., 1998; Kawai et al., 1994; Yamahara et al., 1989)
39	 <p>[8]-gingerol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	68.50 (Akita et al., 1998; Kawai et al., 1994)
40	 <p>[10]-gingerol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	49.70 (Akita et al., 1998; Kawai et al., 1994; Yang et al., 1999c)

41	 <p>Honokiol (100mg/kg p.o.) (<i>Magnolia obovata</i> Thunb., bark)</p>	74.70 (Kawai et al., 1994)
42	 <p>Magnolol (100mg/kg p.o.) (<i>Magnolia obovata</i> Thunb., bark)</p>	104.10 (Kawai et al., 1994; Yang et al., 1999c)
43	 <p>Methyleugenol (20mg/kg p.o.) (<i>Syzygium aromaticum</i>, Linn., Merr. & Perry., flower buds)</p>	166.90 (Kawai et al., 1994)
44	 <p>Phillyrin (100mg/kg p.o.) (<i>Forsythia suspensa</i> Vahl., fruits)</p>	53.60 (Kinoshita et al., 1996)
45	 <p>Quercetin (30mg/kg p.o.) (<i>Forsythia suspensa</i> Vahl., fruits)</p>	45.70 (Kinoshita et al., 1996)
46	 <p>Rengyol (10mg/kg p.o.) (<i>Forsythia suspensa</i> Vahl., fruits)</p>	42.00 (Kinoshita et al., 1996; Yang et al., 1999c)

47	 <p>Rutin (100mg/kg p.o.) (<i>Forsythia suspensa</i> Vahl., fruits)</p>	222.60 (Kinoshita et al., 1996; Yang et al., 1999c)
48	 <p>Safrole (20mg/kg p.o.) (<i>Sassafras albidum</i> (Nutt.) Nees., fruit)</p>	30.40 (Kawai et al., 1994)
49	 <p>[6]-shogaol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	66.00 (Akita et al., 1998; Kawai et al., 1994)
50	 <p>[8]-shogaol (20mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	58.00 (Akita et al., 1998; Kawai et al., 1994)
51	 <p>[10]-shogaol (20mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	146.80 (Akita et al., 1998; Kawai et al., 1994; Yang et al., 1999c)
52	 <p>Traxasteryl acetate (100mg/kg p.o.) (<i>Inula linariaefolia</i> L., flowers)</p>	53.40 (Kinoshita et al., 1996)

53



120
(Kinoshita *et al.*,1996)

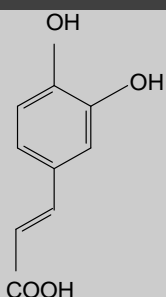
Apomorphine induced emesis in frogs
Anti-emetic activity by using this model proposed δ(enkephalinergetic)-receptor antagonism (Harris, 1982) or dopamine inhibition (Takeda *et al.*,1993)

Entry

Compound sources and doses used

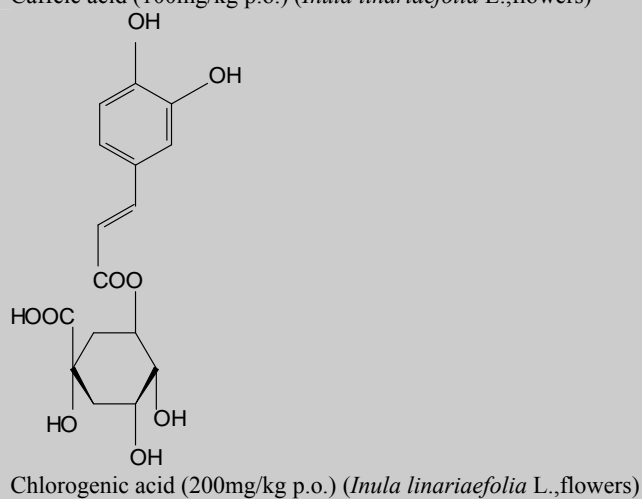
% inhibition of Retches
(References)

54



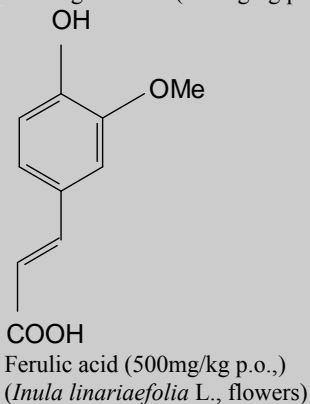
56.10
(Kinoshita *et al.*,1996)

55

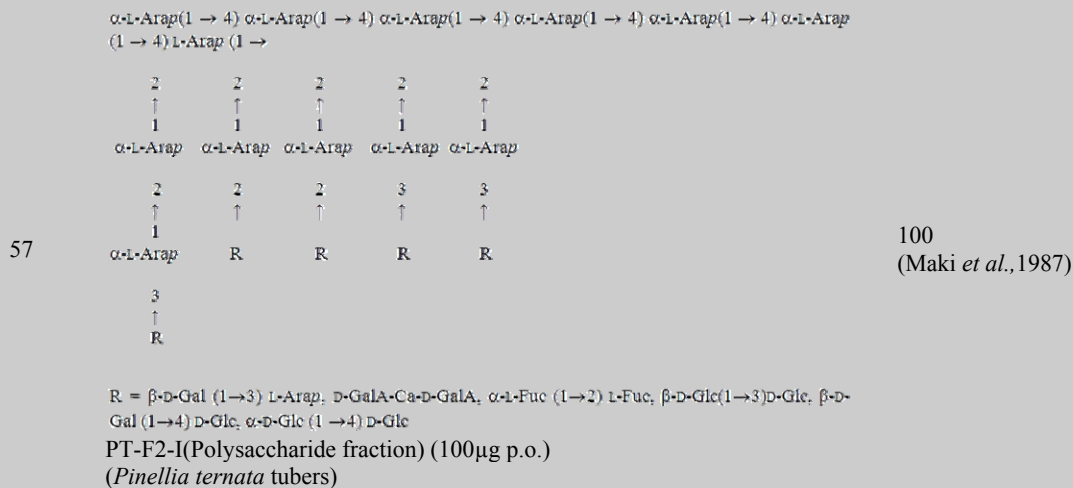


39.20
(Kinoshita *et al.*,1996)

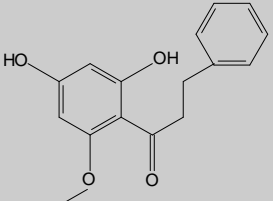
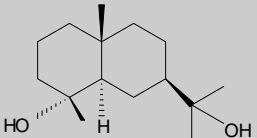
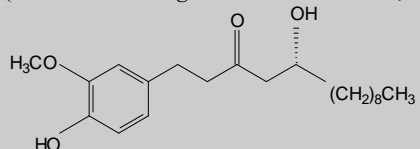
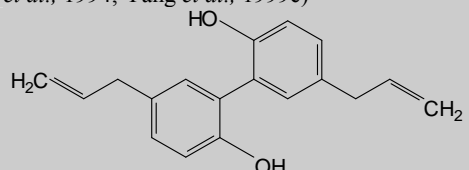
56

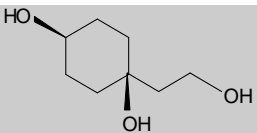
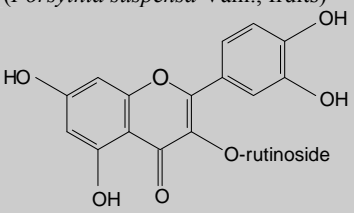
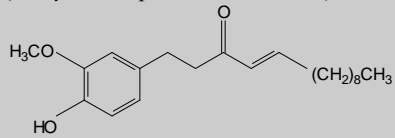
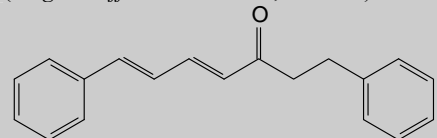


25.00
(Kinoshita *et al.*,1996)

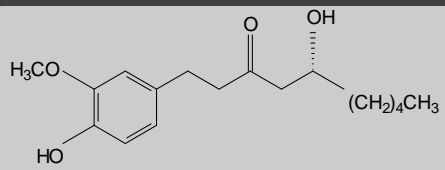


Free radical (AAPH in liposome)-induced emesis model in chicks

Entry	Compound sources and doses used	% inhibition of Retches (References)
58	 <p>Cardamomin (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)</p>	63.50 (Yang et al., 1999c)
59	 <p>Cryptomeridiol (50mg/kg p.o.) (Isolated from <i>Magnolia obovata</i> Thunb., bark, Yang et al., 1999c)</p>	66.30 (Yang et al., 1999c)
60	 <p>[10]-gingerol(50mg/kg p.o.) (isolated from <i>Zingiber officinale</i> Roscoe., rhizome, Akita et al., 1998; Kawai et al., 1994; Yang et al., 1999c)</p>	84.90 (Yang et al., 1999c)
61	 <p>Magnolol (50mg/kg p.o.) (isolated from <i>Magnolia obovata</i> Thunb., bark, Kawai et al., 1994; Yang et al., 1999c)</p>	69.90 (Yang et al., 1999c)

62	 <p>Rengyol (20mg/kg p.o.) (<i>Forsythia suspensa</i> Vahl., fruits)</p>	60.00 (Kinoshita et al., 1996; Yang et al., 1999c)
63	 <p>Rutin (50mg/kg p.o.) (<i>Forsythia suspensa</i> Vahl., fruits)</p>	80.50 (Kinoshita et al., 1996; Yang et al., 1999c)
64	 <p>[10]-shogaol (50mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	65.50 (Akita et al., 1998; Kawai et al., 1994; Yang et al., 1999c; Yang et al., 1999c)
65	 <p>trans, trans-1,7-diphenyl-4,6-heptadiene-3-one (50mg/kg p.o.) (<i>Alpinia katsumadai</i> Hayata., seeds)</p>	67.30 (Yang et al., 1999c)

Cyclophosphamide induced emesis in house musk shrews

Entry	Compound sources and doses used	Time (min) of complete inhibition of emesis (References)
66	 <p>[6]-gingerol (25mg/kg p.o.) (<i>Zingiber officinale</i> Roscoe., rhizome)</p>	30 (Akita et al., 1998; Kawai et al., 1994; Yamahara et al., 1989)

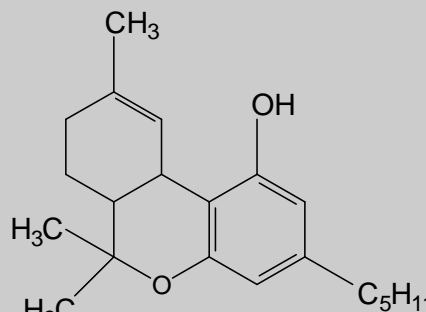
Apomorphine-induced emesis model in cats

Entry	Compound sources and doses used	% inhibition of emesis (References)
67	<p> α-L-Arap(1 → 4) α-L-Arap(1 → 4) α-L-Arap(1 → 4) α-L-Arap(1 → 4) α-L-Arap(1 → 4) α-L-Arap(1 → 4) L-Arap (1 → 4) L-Arap (1 → 4)</p> <p> $\begin{matrix} 2 & 2 & 2 & 2 & 2 \\ \uparrow & \uparrow & \uparrow & \uparrow & \uparrow \\ 1 & 1 & 1 & 1 & 1 \end{matrix}$ </p> <p>α-L-Arap α-L-Arap α-L-Arap α-L-Arap α-L-Arap</p> <p> $\begin{matrix} 2 & 2 & 2 & 3 & 3 \\ \uparrow & \uparrow & \uparrow & \uparrow & \uparrow \\ 1 & 1 & 1 & 1 & 1 \end{matrix}$ </p> <p>α-L-Arap R R R R</p> <p> $\begin{matrix} 3 \\ \uparrow \\ R \end{matrix}$ </p> <p>R = β-D-Gal (1→3) L-Arap, D-GalA-Cu-D-GalA, α-L-Fuc (1→2) L-Fuc, β-D-Glc(1→3)D-Glc, β-D-Gal (1→4) D-Glc, α-D-Glc (1 →4) D-Glc</p>	100 (Maki et al., 1987)

PT-F2-I(Polysaccharide fraction) (25mg/kg p.o.) (*Pinellia ternate*, tubers)

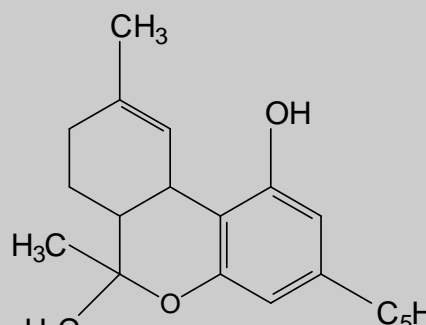
Cisplatin-induced acute emesis model in least shrews

Entry	Compound sources and doses used	% inhibition of emesis (References)
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68	 <p>Δ^9-tetrahydrocannabinol (10 mg/kg i.p.) (<i>Cannabis sativa</i> flowers and buds)</p>	97 (Gaoni & Mechoulam, 1964; Wang <i>et al.</i> , 2009)
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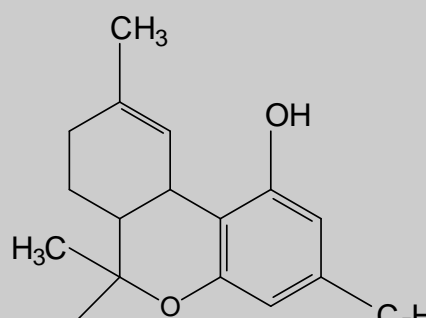
Radiation-induced emesis in least shrews

Entry	Compound sources and doses used	Time (min) of complete inhibition of emesis (References)
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69	 <p>Δ^9-tetrahydrocannabinol (20 mg/kg i.p.) (<i>Cannabis sativa</i> flowers and buds)</p>	30 (Gaoni & Mechoulam, 1964; Darmani <i>et al.</i> ,2007)
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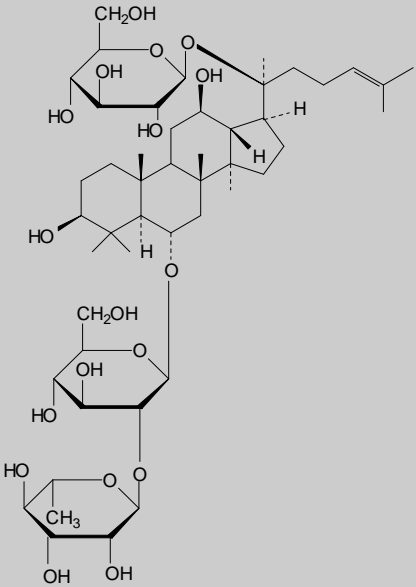
Motion-induced emesis model in house musk shrews

Entry	Compound sources and doses used	Time (min) of complete inhibition of emesis (References)
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70		45 (Gaoni & Mechoulam, 1964; Cluny <i>et al.</i> , 2008)
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Δ^9 -tetrahydrocannabinol (10 mg/kg i.p.) (*Cannabis sativa* flowers and buds)

Cisplatin-induced pica emesis model in rats

Entry	Compound sources and doses used	Antiemetic behaviour (Reference)
71	 <p data-bbox="321 1186 734 1247">Ginsenoside Re (5 mg/kg i.p.) (<i>Panax quinquefolius</i> L., berry)</p>	<p data-bbox="1105 625 1390 737">Decreased kaolin intake and significant recovery of food intake (Mehendale <i>et al.</i>, 2005)</p>

Hance. rhizome (Shin *et al.*, 2002) have been shown to display potent anti-emetic activity. The proposed anti-emetic actions of these compounds include 5-HT₃ (Fukui *et al.*, 1993c), 5-HT₄ (Fukui *et al.*, 1994) and/or NK-1 (Ariumi *et al.*, 2000) receptors antagonism. [6], [8], [10]-gingerol and [6], [8],[10]-shogaol (Entry No. 6-8, 24-26, 38-40, 49-51, 60, 64, 66) isolated from *Zingiber officinale* Roscoe., rhizome (Kawai *et al.*, 1994) have been suggested to act through 5HT₃ but not 5HT₄ (Heba *et al.*, 2006 ; Pertz *et al.*, 2011) or NK₁ receptor antagonism (Tsuchiya *et al.*, 2002).

Flavonoids

Galangin and kaempferide (Table 3, Entry No.5, 19) from *Alpinia officinarum* Hance., rhizome, (Shin *et al.*, 2002) have been shown to display anti-emetic behavior. Pachypodol and retusin (Entry No.18, 22) isolated from *Progesterone cablin* leaves, (Yang *et al.*, 1999a) showed anti-emetic activity possibly through 5-HT₃ (Fukui *et al.*, 1993c), 5-HT₄ (Fukui *et al.*, 1994) an/or NK₁ (Ariumi *et al.*, 2000) receptors antagonism. Quercetin and rutin (Entry No.45, 47, 63) from *Forsythia suspensa* Vahl., fruits (Kinoshita *et al.*, 1996) similarly

revealed anti-emetic activity possibly through their known potent antioxidant effects (Yang *et al.*, 1999c).

Glucosides

Phillyrin (Table 3, Entry No. 44) and rengyol (Table 3, Entry No. 46, 62) isolated from *Forsythia suspensa* Vahl., fruits, (Kinoshita *et al.*, 1996; Yang *et al.*, 1999c) have been shown to display anti-emetic effects. While phillyrin is suggested to act through 5-HT₃ (Fukui *et al.*, 1993c), 5-HT₄ (Fukui *et al.*, 1994) and/or NK₁ (Ariumi *et al.*, 2000) receptors antagonism, rengyol could have additional antioxidant mechanism of action (Yang *et al.*, 1999c). The serotonin 5-HT₃ (Fukui *et al.*, 1993c), 5-HT₄ (Fukui *et al.*, 1994) and/or NK₁ (Ariumi *et al.*, 2000) receptors antagonism could also account for the anti-emetic activity of β -sitosterol 3-O- β -D-6-palmitoylglucoside (Entry No.23) from *Alpinia officinarum* Hance., rhizome, (Shin *et al.*, 2002).

Hydroxycinnamic acids

Caffeic acid, chlorogenic acid, ferulic acid (Table 3, Entry No.54-56) from *Inula linariaefolia* L., flowers (Kinoshita *et al.*, 1996) dihydrocinnamic acid (Entry No.1) from *Brazilian Propolis*, bee glue a natural product collected by honey bees (Eda *et al.*, 2005), showed anti-emetic behavior through possible δ (enkephalinergic)-receptor antagonism (Harris, 1982) and/or dopamine inhibition (Takeda *et al.*, 1993).

Lignans

Honokiol and magnolol (Table 3, Entry No.41,42, 61) from *Magnolia obovata* Thunb., bark, (Kawai *et al.*, 1994) have been shown to possess anti-emetic behavior through 5-HT₃ (Fukui *et al.*, 1993c), 5-HT₄ (Fukui *et al.*, 1994) and/or NK₁ (Ariumi *et al.*, 2000) receptors antagonism.

Phenylpropanoids

Eugenol (Table 3, Entry No.37), methyleugenol (Entry No.43), from *Syzygium aromaticum* (L.) Merr. & Perry., (Kawai *et al.*, 1994) and saffrole (Table 3, Entry No.48) from *Sassafras albidum* (Nutt.) Nees., fruit (Kawai *et al.*, 1994) have shown to induce anti-emetic effect through 5-HT₃ (Fukui *et al.*, 1993c), 5-HT₄ (Fukui *et al.*, 1994) and/or NK₁ (Ariumi *et al.*, 2000) receptors antagonism.

Polysaccharides

Polysaccharide fraction (PT-F2-I) (Table 3, Entry No.57,67) isolated from *Pinellia ternata* tubers, (Maki *et al.*, 1987) has been suggested to act through δ (enkephalinergic)-receptor antagonism (Harris, 1982) or dopamine inhibition (Takeda *et al.*, 1993) taken part against emesis.

Saponins

Ginsenoside Re (Table 3, Entry No.71) a saponin which is isolated from *Panax quinquefolius* berry, (Mehendale et al., 2005) showed action against emesis. An antioxidant action (Horna et al., 2004), 5-HT₃ antagonism (Cubeddu, 1996; Matsuki et al., 1993; Endo et al., 2000; Mehendale et al., 2005) and NK₁ receptor antagonism (Tsuchiya et al., 2002) have been suggested as possible mechanisms of action.

Terpenes (sesquiterpenes & triterpenes)

Sesquiterpene such as bigelovin (Table 3, Entry No.36) isolated from *Inula linariaefolia* L., flowers, (Kinoshita et al., 1996), Pogostol (Entry No.20) and patchouli alcohol (Entry No.19) isolated from *Pogostemon cablin* leaves, (Yang et al., 1999a) showed anti-emetic behavior through possible 5-HT₃ (Fukui et al., 1993c), 5-HT₄ (Fukui et al., 1994) and/or NK₁ (Ariumi et al., 2000) receptors antagonism whereas cryptomeridiol (Entry No.59) isolated from *Magnolia obovata* Thunb. bark (Yang et al., 1999c) could act through antioxidant effect (Yang et al., 1999c). Triterpenes such as lupeol (Entry No.17) isolated from *Brazilian Propolis* (Eda et al., 2005), traxa steryl acetate (Entry No.52) and palmitate (Entry No.53) isolated from *Inula linariaefolia* L. flowers (Kinoshita et al., 1996) showed anti-emetic behavior. Among the suggested mechanisms of action for these compounds are 5-HT₃ (Fukui et al., 1993c), 5-HT₄ (Fukui et al., 1994) and NK₁ (Ariumi et al., 2000) receptors antagonism.

Conclusion

Understanding the physiology and pharmacology of emesis are paramount to developing efficacious anti-emetics with no toxicity and lesser side effects. This review outlined the anti-emetic effect of crude natural products and isolated secondary metabolites studied through a variety of animal models of emesis. In many cases, the crude natural products (for example, herbal drugs) are already used in traditional medicine for treating emesis and the studies simply provided the scientific background to the reported ethnobotanical uses. The demonstration of activity in an experimental model can not be however taken as an absolute proof of efficacy in humans and further clinical trials are necessary to validate the therapeutic potential of the identified anti-emetic natural products. While the mechanisms of actions have elucidated for some promising natural products, further studies are required for the great majority of natural anti-emetic agents. The review revealed that a number of secondary metabolites including polyphenolic (flavonoids, phenyl propanoids and lignans), terpenoids and their glycosides possess anti-emetic effect through multiple mechanisms. These studies may help in the identification of promising single chemical entity compounds that may be used as a potential leads for developing future anti-emetic agents.

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