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Anti-emetic effects of bioactive natural products

Salman Ahmed[1], Muhammad Mohtasheemul Hasan[1,*], Syed Waseemuddin Ahmed[1], Zafar Alam Mahmood[2], Iqbal Azhar[1], Solomon Habtemariam[3]

[1]Department of Pharmacognosy, Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan.
[2]Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan.
[3]Pharmacognosy Research Laboratories, Medway School of Science, University of Greenwich, Chartham Maritime, Kent ME4 4TB, UK.

[*]Corresponding author: phm.hasan@gmail.com; Tel: (+9221) 99261300-7 Ext. 2400.

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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 antiemtic 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, labyrinthhitis 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 as1-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 *etal.,* 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 sunbstances 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 solitarus 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-HT_3 (serotonin), neurokinin 1 (NK_1), muscarinic acetylcholine (ACh_M), histamine (H_1) and opioid receptors. Upon stimulation by varios endogenous or exogenous chemical insult, 5-HT released from the GIT activates 5-HT_3 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, NK_1, $5HT_3$ and H_1 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.

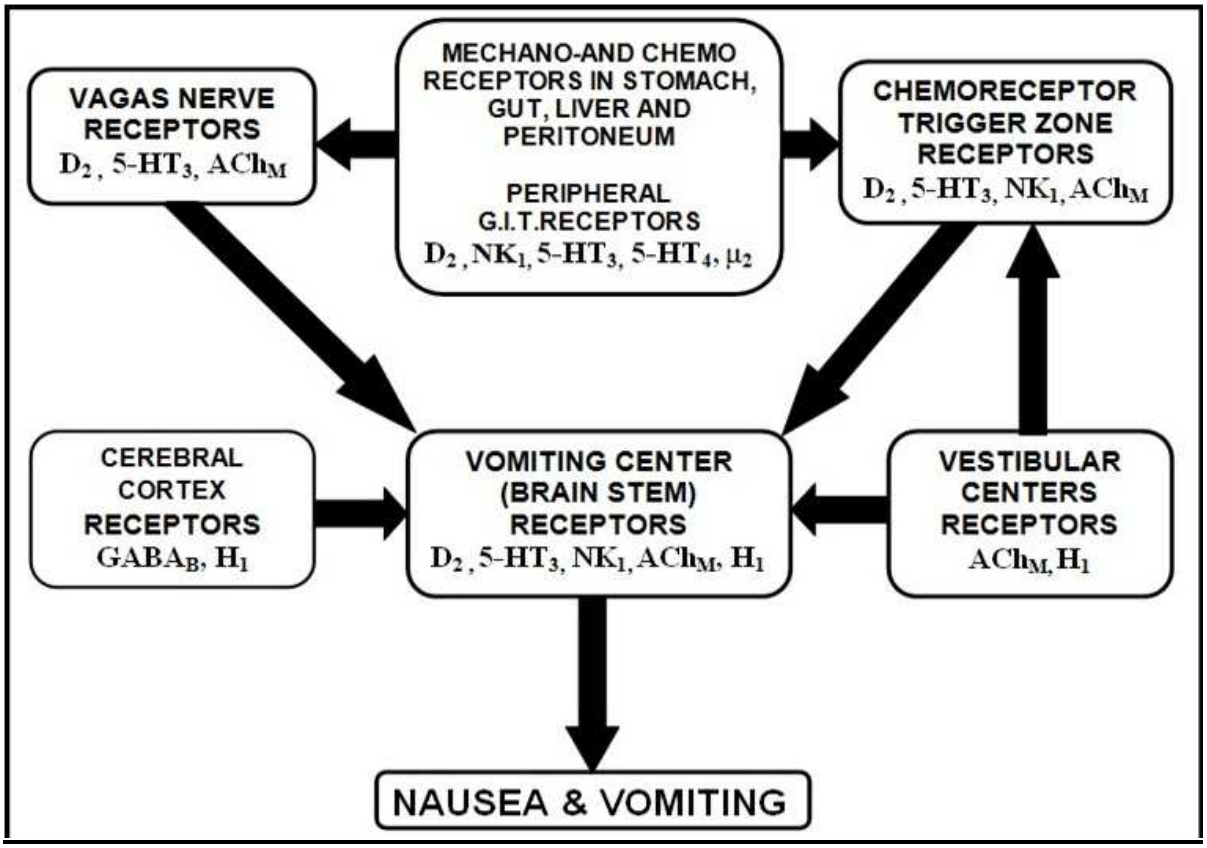


Figure.1. Circuit diagram of emesis pathway.

Exogenous chemicals and endogenous substances that accumulate during inflammation, ischaemia, and irritation excite the mechano, chemo and peripheral G.I.T. receptors. Dopamine (D_2), serotonergic (5-HT_3 & 5-HT_4), ACh_M, neurokinin (NK_1) are highly conesrved for an emetic reflex whereas Gamma amino butyric acid ($GABA_B$), serotonergic (5-HT_{1A}), cannabinoids (CB_1) and opioids (μ_2) have anti-emetic effects (Sanger & Andrews, 2006). The stomach wall also contains D_2, 5-HT_3 & 5-HT_4, ACh_M, NK_1, μ_2 as well as 5-HT_3 receptors that also found in area postrema of the CNS. The 5-HT_4 receptors require ACh as a mediator within the myenteric plexus while substance-P can induces nausea by binding to NK_1 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 also affect the motility of upper gastro intestinal tract. They also have antimuscaranic 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-HT_3 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-HT_3 receptor antagonists with both CNS and peripheral action. They include granisetron, ondansetron, tropisetron and palonosetron. To date, a number of reports suggest that 5-HT_3-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 H_1 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 calss of anti-emetic agentys 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 CB_1 receptors agonists

These agonist anti-emetics include serotonin (5-HT_{1A}), gamma amino butyric acid ($GABA_B$) and cannabinoid (CB_1) receptor agonists. Buspirone (5-HT_{1A} agonist), baclofen ($GABA_B$ agonist) and dronabinol (CB_1 agonist) are good examples (Rheid *et al.,* 1992).

C. *In vivo* and *invitro* 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 amphibions (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-HT_3 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 NK_1 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 NK_1 receptors in the nucleus tractus solitalius and/or area postrema (Ariumi *et al.,* 2000). On the other hand, 5-HT_3 -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 peiod 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-HT_3 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 NK_1 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 (*Macca 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 administratered 1.5 and 3.5 hr after induction of emesis (Fukui *et al.,* 1993c). In this experimental model, vagal afferent terminals and 5-HT_3 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-HT_3 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 peiod were used (Milano *et al.,*1995). In this model of emesis, prostaglandins have also been found to contribute to the cisplatin-induced emetic reponse (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 6°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. Varios studies have indicated the involvement of δ-receptor-mediated mechanism in apomorphine (Harris, 1982), peripheral 5-HT_3 receptors in cisplatin (Fukui *et al.,*1992) and 5-HT_4 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 (D_2) 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-HT_3 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-HT_3 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 lymphsac 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 shrew*s (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 acclamatization 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 regim are shown in Table 1.

In most entiemetic studies using Suncus *murinus,* a 10 mins 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 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 consists 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	• Peripheral action	Chen *et al.,* 1997
Cisplatin	20 mg/kg i.p., & 40 mg/kg i.v.	2hrs	• Direct or indirect stimulation of Serotonergic 5-HT3 receptor of the vagus afferent neurons • Freee radical induced oxidative damage • 5-HT_{1A} receptor antagonism	Mutoh *et al.,* 1992
	30 mg/kg i.p.	72 hrs		Matsuki *et al.,*1988, 1997; Mutoh *et al.,* 1992; Okada *et al.,*1994; Sam *et al.,*2003; Torii *et al.,*1991; Torii *et al.,* 1993a
	40 mg/kg i.p.	90 mins		
Copper sulfate	21.4 mg/kg p.o.	30 mins	• Gastric irritation or direct stimulation of stomach wall • 5-HT_{1A} receptor antagonism • Possibly through effect on 5-HT_4 receptors	Andrews *et al.,* 1990; Nakayama *et al.,*2005; Okada *et al.,*1994; Ueno *et al.,* 1987; Wang & Borison, 1951
Cyclophosphamide	200 mg/kg i.v.	30 mins	• 5-HT_3 receptor-mediated mechanism	Torii *et al.,*1991; Yoshifumi Torii *et al.,*1991
Emetine dihydrochloride	47.6 mg/kg s.c.	2hrs	• Stimulation of CTZ	Ueno *et al.,* 1987
Ethanol	40% v/v i.p.	90 mins	• Peripheral action through acetaldehyde intermediate • Free radicals induced oxidative damage • 5- HT_3 receptor mechanism	Chen *et al.,* 1997
E-capsaicin	25.4 nmol, i.c.v.	90 mins	• Multiple receptor sites	Rudd & Wai, 2001
Naloxone	60 mg/kg, s.c.	30 mins	• Effects via NK_1 and 5-HT_{1A} receptors	Rudd *et al.,* 1999
Nicotine	5,10 mg/kg, s.c. 10 mg/kg, s.c 7.9mg/kg s.c.	30 mins 30 mins 30mins	• Central μ -opioid receptors	Rudd *et al.,* 1999 Torii *et al.,*1991 Ueno *et al.,* 1987
Pyrogallol	128 mg/ kg i.p.	30 mins	• Generation of free radicals causes the release of peripheral 5-HT • Other peripheral action, possible via indirect release of 5-HT and stimulation of 5-HT_3 receptors	Torii *et al.,* 1994
Resininferatoxin	100 µg/kg s.c.	-------	• Multiple targets	Andrews *et al.,* 1996; 2000; Rudd & Wai, 2001
Veratrine sulfate	0.4 &0.5 mg/kg s.c.	30 mins	• Vagal ganglion stimulation • 5-HT_{1A} receptor antagonism	Okada *et al.,*1994; Ueno *et al.,* 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 NK_1 receptors have been shown to be involved in Substance-P-induced emesis (Darmani *et al.,* 2008) whereas stimulation of $5HT_3$ receptors mediate the cisplatin-induced emesis (Darmani, 1998) .

10. Pigeon emesis model

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

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

Ouratea angustifolia (Vahl.) Baillon. (roots)	
Panax quinquefolium. (roots)	
Pavonia ododrata Willd. (whole plant)	
Phragmites australis Trin. (stem)	
Phragmites communis Trin. (rhizome)	Khare, 2007
Phyllostachys nigra (Lodd. ex Lindl.) Munro. (bark)	
Portulaca oleracea L. (leaves)	Asima, 2003; Kirtikar & Basu, 1976
Prunella vulgaris L. (whole plant)	
Pueraria thunbergiana (Sieb. & Zucc.) Benth. (whole plant)	
Pueraria tuberosa (Roxb.ex Willd.) DC. (tuber)	Jain *et al.,*2005
Punica granatum L. (fruits)	Khare, 2007
Sanguinaria canadensis L. (roots)	Asima, 2003; Kirtikar & Basu, 1976
Scirpus kysoor Roxb. (stem)	Khare, 2007
Sida acuta Burm.f. (roots)	Jain *et al.,*2005
Syzygium aromaticum (Linn.) Merr. & Perry. (flowering buds)	Khare, 2007
Zingiber officinale Roscoe. (rhizome)	
Pakistan	
Ajuga bracteosa Wall. (whole plant)	Jan *et al.,*2008
Calendula arvensis L. (flowers and leaves)	Sher *et al.,*2011
Jasminum officinale L. (whole plant)	
Mentha longifolia (L.) Huds. (whole plant)	Shah *et al.,*2012
Mentha spicata L. (leaves)	
Punica granatum L. (flower and bark)	Khan *et al.,*2012
Iran	
Berberis vulgaris L. var. asperma Don (whole plant)	Javadzadeh & Fallah, 2012
Cynodon dactylon (L.) Per. (roots and rhizome)	Miraldi *et al.,* 2001
Mentha longifolia **(**aerial parts)	Hosseinzadeh *et al.,* 2004
Mentha piperata Linn. emend. Huds. **(**aerial parts)	Hossein *et al.,* 2005
Valeriana officinalis L. (roots)	Hosseinzadeh *et al.,* 2011
Africa	
Afzelia africana Sm. ex Pers. (aerial parts)	Odugbemi, 2008
Anethum graveolens L. (whole plant)	Boulos, 1983
Garcinia kola Heckel. (seeds)	Aluka, 1985
Grewia lasiodiscus K. Schum. (root)	Oliver- Bever, 1983
Nymphaea lotus L. (whole plant)	Burkill, 1995
Phragmites australis (Cav.) Trin. ex Stead. (whole plant)	Boulos, 1983
Solanum aethiopicum L. (leaves)	Grubben & Denton, 2004
Vitex iringensis Gürke. (leaves)	Mathias,1982
Arab	
Anethum graveolens L. (seeds)	
Citrus limon (L.) Burm. f. (fruits)	
Citrus limon (L.) Burm. f. (leaves)	
Eugenia caryophyllata Thunb. (seeds)	Saganuwan & Saganuwan, 2010
Heliotropium indicum L. (flower)	
Heliotropium indicum L. (leaves)	
Phragmites australis (Cav.) Trin. ex Stead. (whole plant)	Ghazanfar, 1994
Raphanus Sativus L. (seeds)	Saganuwan & Saganuwan,2010
Vigna unguiculata (L.) Walp. (flower)	
Thailand	
Morinda citrifolia L. (fruits)	Prapaitrakool & Itharat, 2010
New Guinea	
Ageratum conyzoides 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 acitivity are often subjected to analytical studied 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, phenylpopanoids, 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-HT_3 / 5-HT4 receptors antagonism II) tachykinin NK_1 receptors antagonism III) antioxidant action IV) δ (enkephalinergic)-receptor inhibition V) cannabinoid CB_1 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 CB_1 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

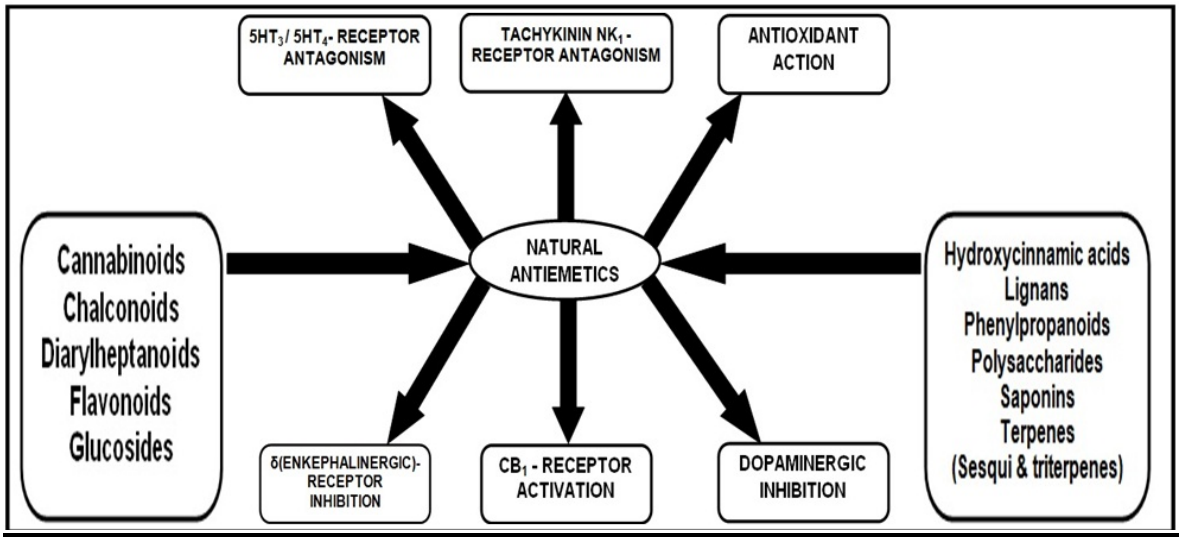


Figure.2. Proposed mechanisms of natural anti-emetics.

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
Acalypha fimbriata Schumach. & Thonn. Leaves and stems	Kola et al., 2008	Methanol (150)	44.42 for leaves and 35.04 for stems (Quds et al.,2012)
Acalypha ornata Hochst. Leaves and stems	----------	Methanol (150)	94.51 for leaves and 65.64 for stems (Quds et al.,2012)
Acalypha wilkesiana 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)
Adenanthera pavonina L. Leaves	Holdsworth, 1977	Methanol (150)	50.17 (Hasan et al.,2012a)
Alpinia katsumadai Hayata. Seeds	Ching Su New Medicinal College, 1978	Methanol (150)	73.9 (Yang et al., 1999a)
Amomum kravanh Pire ex Gagnep. Fruits		Chloroform (150)	52.6 (Yang et al., 1999a)
Alpinia officinarum Hance. Rhizome		Chloroform (150)	45.6 (Yang et al., 1999a)
Amomum tsao-ko Crevost & Lemarié. Fruits		Methanol (150)	54.5 (Yang et al., 1999a)
Amomum xanthioides 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)
Carissa carandus L. Fruits	Buckle, 2003	Ethanol (150)	68.29 (Hasan et al.,2012b)
Cassia angustifolia Vahl. Leaves	Chopra et al., 1956; Usmanghani et al.,1997.	Methanol (150)	79.31 (Ahmed et al.,2012b)
Cassia holosericea Fresen. Leaves		Methanol (150)	41.99 (Ahmed et al.,2012b)
Cassia italica Miller. Lam. ex F.W. Ander. Leaves		Methanol (150)	96.07 (Ahmed et al.,2012b)
Cassia purpurea Roxb. Leaves		Methanol (150)	94.5 (Ahmed et al.,2012b)
Cassia siamea Lamk. Leaves	Ahn et al., 1978	Methanol (150)	18 (Ahmed et al.,2012a)
Chichorium intybus L. Flowers	Buckle, 2003	Ethanol 150)	73.86 (Hasan et al.,2012b)
Cinnamomum tamala L. Rhizomes		Ethanol (150)	70.64 (Hasan et al., 2012b)
Cleome viscosa L. Seeds (fixed oil)	Mali, 2010	Hexane (125)	91.77 (Ahmed et al.,2011)
Cleome scaposa DC. Leaves	Atiqur et al.,2004; Khan, 2009	Methanol (150)	49.94 (Ahmed et al.,2012a)
Curcuma caesia Roxb. Leaves	Buckle, 2003	Ethanol (150)	89.97 (Hasan et al.,2012b)
Cyamopsis tetragonoloba Taubert. Leaves	Duke, 2002	Methanol (150)	34.39 (Ahmed et al.,2012a)
Delonix regia Rafin. Leaves	Lawal et al.,2010	Methanol (150)	96.74 (Ahmed et al.,2012a)
Eupatorium fortunei Turcz. Leaves and stem	Ching Su New Medicinal	Chloroform (150)	32.1 (Yang et al., 1999a)

	College, 1978		
Garcinia kola Heckel. Seeds	Aluka, 1985	Ethanol (150)	75.47 (Nosiri et al.,2010)
Grewia asiatica L. Leaves	Morton, 1987	Methano (100)	59.69 (Zia-Ul-Haq et al., 2012)
Grewia lasiodiscus K. Schum. Roots	Oliver- Bever, 1983	70% aqueous methanol (200)	71.77(Tijani et al., 2008)
Hypnea pannosa J. Ag. Red algae	----------	Ethanolic (200)	40.38 (Mazhar et al.,2011)
Lallemantia royleana Benth. Leaves	Buckle, 2003	Ethanol (150)	83.61 (Hasan et al.,2012b)
Luffa cylindrica (L.) Roem. Leaves	----------	Ethanol (150)	68.66 (Khan et al.,2013)
Luffa cylindrica (L.) Roem. Flowers	----------	Ethanol (150)	68.46 (Khan et al.,2013)
		Hexane (150)	71.75 (Khan et al.,2013)
Matricaria chamomila L. Flowers	Buckle, 2003	Ethanol (150)	59.92 (Hasan et al.,2012b)
Nelumbo nucifera Gaertn. Seeds	Khare, 2007	Chloroform(150)	27.20 (Yang et al., 1999a)
Peltophorum roxburghii L. Leaves	----------	Methanol (150)	54.89 (Hasan et al.,2012a)
Piper longum L. Fruits	Buckle, 2003	Ethanol (150)	81.65 (Hasan et al.,2012b)
Piper methysticum G. Forst. Fruits		Ethanol (150)	80.03 (Hasan et al.,2012b)
Piper nigrum L. Fruits		Ethanol (150)	89.48 (Hasan et al.,2012b)
Pistacia vera 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)
Prosopis cineraria L. Leaves	---------	Methanol (150)	69.49 (Hasan et al.,2012a)
Prosopis juliflora DC. Leaves	Pasiecznik et al., 2001	Methanol (150)	73.64 (Hasan et al.,2012a)
Samanea saman Merr. Leaves	Ayensu,1981; Perry, 1980	Methanol (150)	76.41 (Ahmed et al.,2012a)
Syzygium aromaticum Linn., Merr. & Perry. Flowering buds	Buckle, 2003	Ethanolic(150)	87.81 (Hasan et al.,2012b)
Tamarindus indica L. Leaves	---------	Methanol (150)	69.48 (Khan et al., 2005)
Thymus transcaspicus Klokov. Aerial parts	Krappand & Longe, 2001	Petroleum ether (1300)	77.30 (Moallem et al.,2009)
Valeriana officinalis L. Roots	----------	Hydroethanol (700)	65.70 (Hosseinzadeh et al.,2011)
Vigna trilobata 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
Citrus unshiu (Swingle) Marcow. Fruit peels	Ching Su New Medicinal College, 1978	Methanolic -500	74.7 (Kinoshita et al.,1996)
Diospyros kaki L. Sepals		Aqueous -500	65.6 (Kinoshita et al.,1996)
Eriobotrya japonica Lindl. Leaves		Methanol -500	115.2 (Kinoshita et al.,1996)
Foeniculum vulgare Mill. Fruits		Chloroform -500	27.7 (Kinoshita et al.,1996)
Forsythia suspensa Vahl. Fruits		Methanolic -500	167.7 (Kinoshita et al.,1996)
Hovenia dulcis Thunb.		Chloroform	119.8

Fruits		-500	(Kinoshita et al.,1996)
Inula linariaefolia L.		Chloroform	52.8
Fruits		-500	(Kinoshita et al.,1996)
Lindera strychnifolia Sieb. et Zucc.		Aqueous	132.6
Roots		-500	(Kinoshita et al.,1996)
Pinellia ternata (Thunb.) Breit.		Methanol	125.9
Tubers		-500	(Kinoshita et al.,1996)
Pogostemon cablin (Blanco) Benth.		Aqueous	37.7
Leaves		-500	(Kinoshita et al.,1996)
Poria cocos 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
Diospyros kaki L.	Ching Su New	Methanol	17.5
Sepals	Medicinal College, 1978	-500	(Kinoshita et al.,1996)
Forsythia suspensa Vahl.		Methanol	63.6
Fruits		-500	(Kinoshita et al.,1996)
Hovenia dulcis Thunb.		Chloroform	10.71
Fruits		-500	(Kinoshita et al.,1996)
Inula linariaefolia L.		Chloroform	51.3
Fruits		-500	(Kinoshita et al.,1996)
Lindera strychnifolia 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
Pistacia vera 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)
Thymus transcaspicus Klokov Aerial parts	Krappand & Longe, 2001	Petroleum ether -1300	(Moallem et al.,2009)
Valeriana officinalis 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)
Emblica officinalis Gaertn. Fruits	Khare, 2007	Aqueous (500)	180 (Yaqeenddin et al., 1990)
Grewia asiatica L. Fruits	Morton, 1987	Alcohol (120)	180 (Yaqeen et al., 2008)
Nelumbium speciosum Wild. Seeds	Kirikar et al., 1933	Alcohol 90)	180 (Yaqeen et al., 1998)
Prunus domestica L. Fruits	Said, 1969	Ethanol (125)	45 (Qureshi et al., 1988)
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)
Ganoderma lucidum (Curtis) P.Karst. Whole mushroom		-10	120 (Wang et al., 2005)
Panax quinquefolius L. Berry	---------	Aqueous (100)	120 (Mehendale et al., 2005)
Scutellaria baicalensis Georgi. Roots	Huang, 1999	Aqueous (3)	120 (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

Zingiber officinale 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)
Panax ginseng 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
Zingiber officinale Roscoe. Rhizome	Chopra et al., 1956a	Acetone -150	(Yamahara et al., 1989)

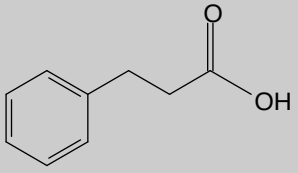
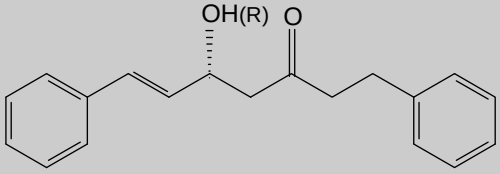
as well as pre- and post-synaptic neuronal mechanisms (Darmani and Johnson, 2004). CB_1 receptor activation is also suggested to be involved in the anti-emetic behavior of Δ^9 -THC (Darmani *et al.,* 2007).

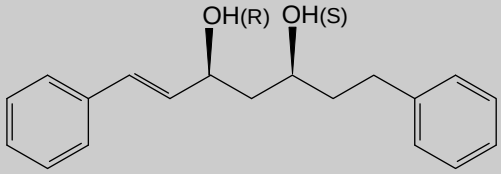
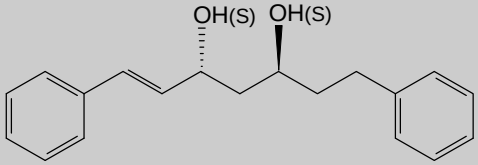
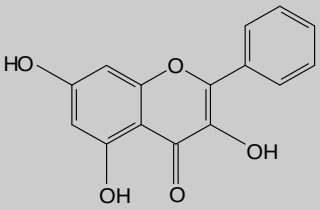
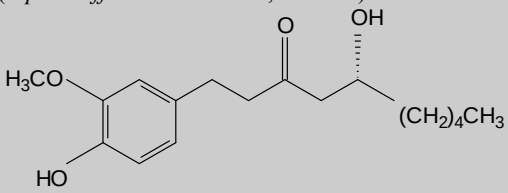
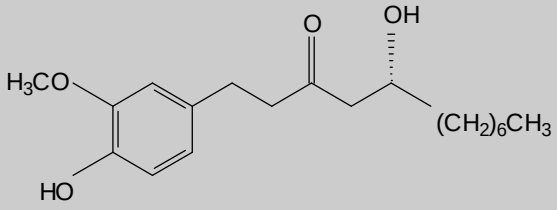
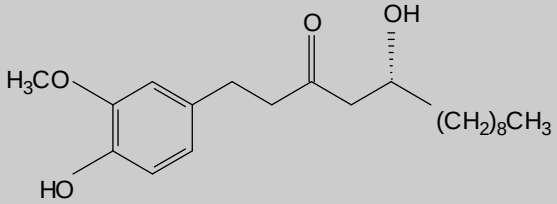
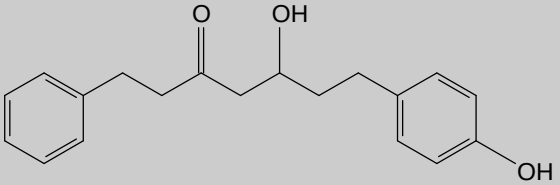
Chalcones

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).

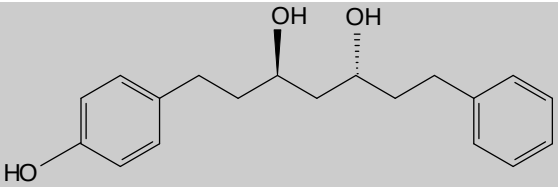
Diarylheptanoids

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	 Dihydrocinnamic acid (100mg/kg p.o.) (*Brazilian propolis*)	59.30 (Eda *et al.*,2005)
2	 Dihydroyashabushiketol (50mg/kg p.o.) (*Alpinia katsumadai* Hayata., seeds)	46.90 (Yang *et al.,* 2002)

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

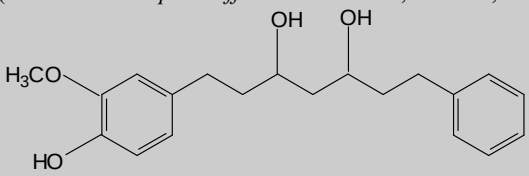
10



(3*R*,5*R*)-1-(4-hydroxyphenyl)-7-phenyl-3,5-heptanediol (50mg/kg p.o.)
(isolated from *Alpinia officinarum* Hance., rhizome, Shin *et al.,* 2002).

37.70
(Shin *et al.,* 2002)

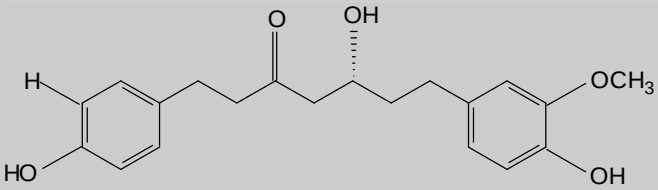
11



1-(4-hydroxy-3-methoxyphenyl)-7-phenyl-3,5-heptanediol (50mg/kg p.o.)
(*Alpinia officinarum* Hance)

45.70
(Shin *et al.,* 2002)

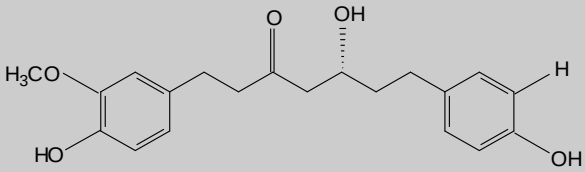
12



5-Hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-3-heptanone
(50mg/kg p.o.)
(*Alpinia officinarum* Hance., rhizome)

38.30
(Shin *et al.,* 2002)

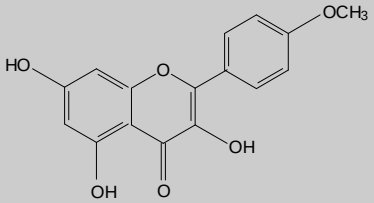
13



5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-3-heptanone
(50mg/kg p.o.)
(*Alpinia officinarum* Hance., rhizome)

12.40
(Shin *et al.,* 2002)

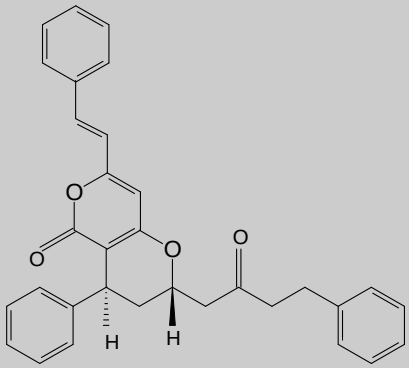
14



Kaempferide (20mg/kg p.o.)
(*Alpinia officinarum* Hance., rhizome)

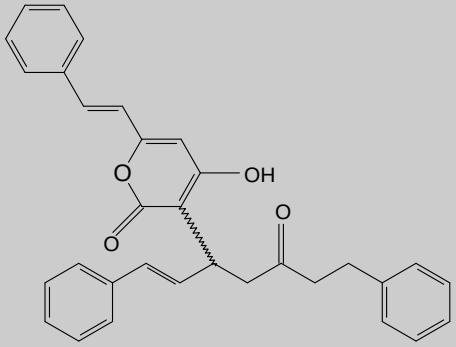
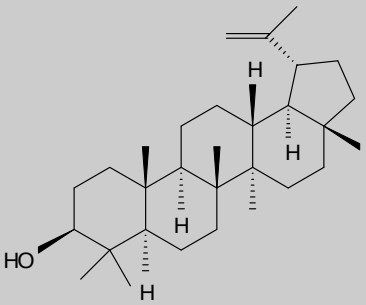
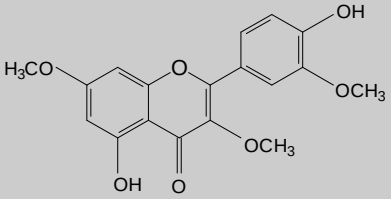
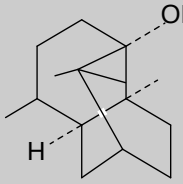
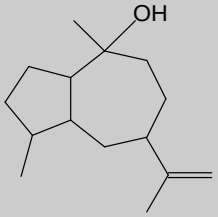
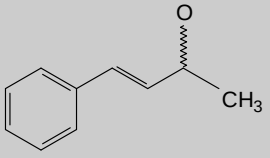
63.30
(Shin *et al.,* 2002)

15

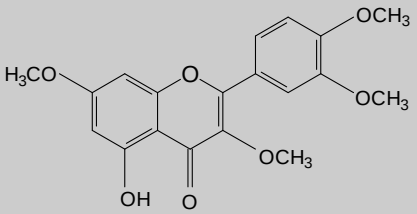


Katsumadains A (50mg/kg p.o.)
(*Alpinia katsumadai* Hayata., seeds)

50.20
(Yang *et al.,* 1999b)

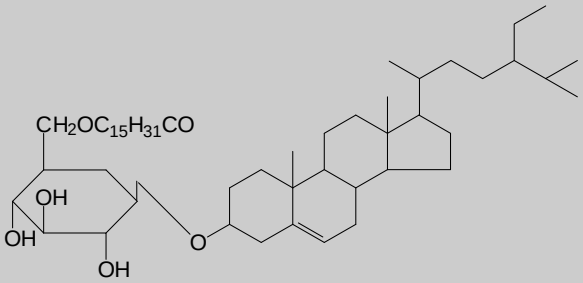
16	 Katsumadain B (50mg/kg p.o.) (*Alpinia katsumadai* Hayata., seeds)	41.40 (Yang *et al.,* 1999b)
17	 Lupeol (10mg/kg p.o.) (*Brazilian Propolis*)	49.90 (Eda *et al.,*2005)
18	 Pachypodol (50mg/kg p.o.) (*Pogostemon cablin,* leaves)	50.50 (Yang *et al.,* 1999a)
19	 Patchouli alcohol (70mg/kg p.o.)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

(*Alpinia katsumadai* Hayata., seeds)

22 

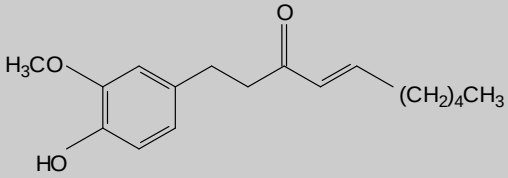
45.60
(Yang *et al.,* 1999a)

Retusin (50mg/kg p.o.)
(isolated from *Pogostemon cablin* leaves, Yang *et al.,* 1999a).

23 

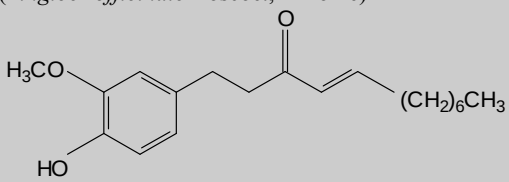
50.90
(Shin *et al.,* 2002)

β-sitosterol 3-*O*-*β*-D-6-palmitoylglucoside (50mg/kg p.o.)
(*Alpinia officinarum* Hance., rhizome)

24 

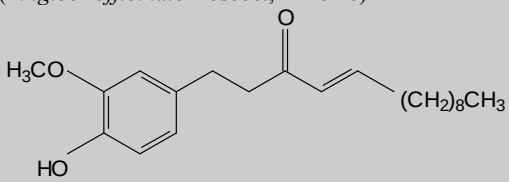
49.20
(Akita *et al.,* 1998)

[6]-shogaol (50mg/kg p.o.)
(*Zingiber officinale* Roscoe., rhizome)

25 

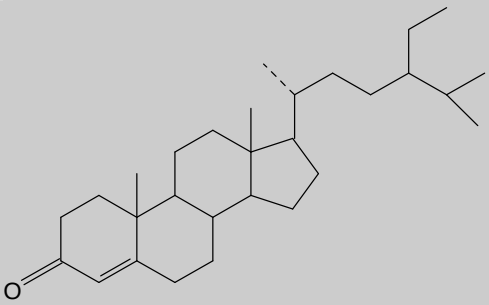
53.70
(Akita *et al.,* 1998; Kawai *et al.,* 1994)

[8]-shogaol (50mg/kg p.o.)
(*Zingiber officinale* Roscoe., rhizome)

26 

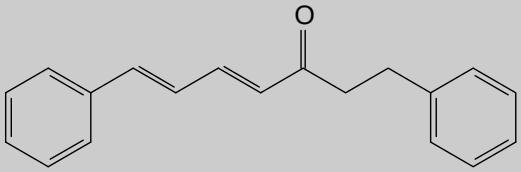
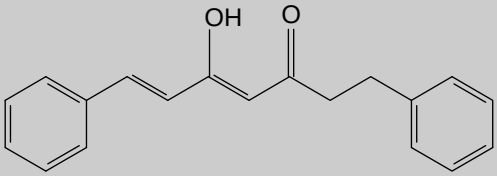
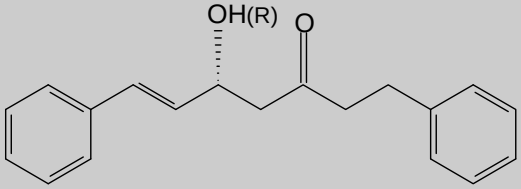
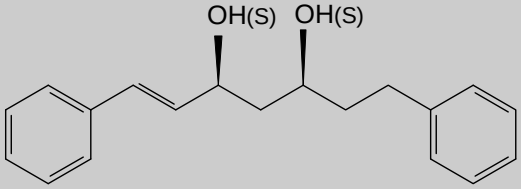
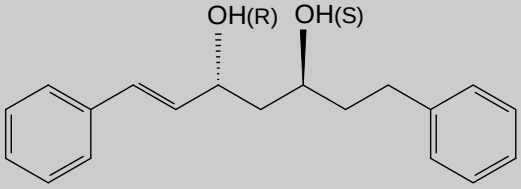
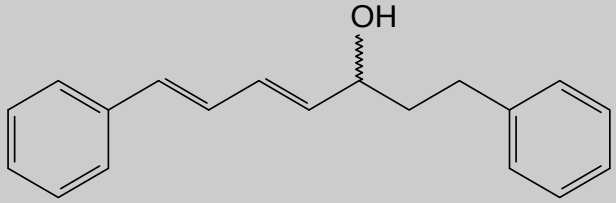
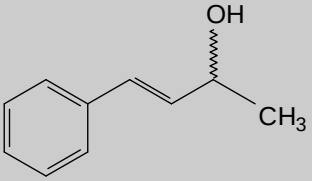
69.00
(Akita *et al.,* 1998; Kawai *et al.,* 1994; Yang *et al.,* 1999c)

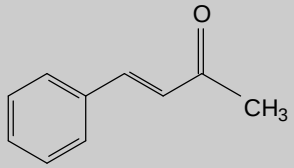
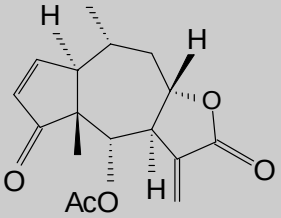
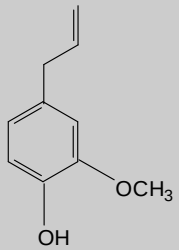
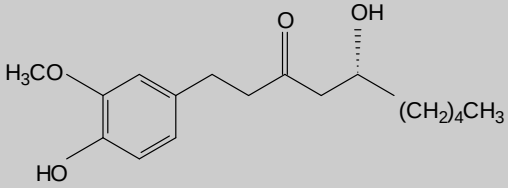
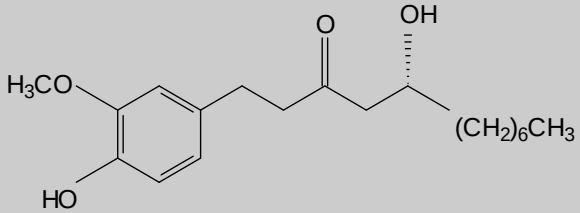
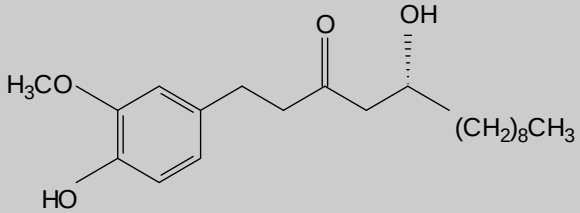
[10]-shogaol (50mg/kg p.o.)
(*Zingiber officinale* Roscoe., rhizome)

27 

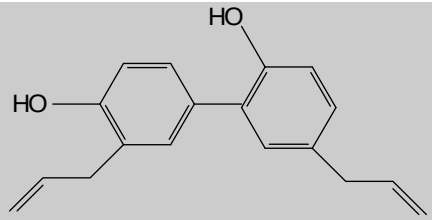
55.70
(Yang *et al.,* 1999a)

Stigmast-4-en-3-one (50mg/kg p.o.)
(*Pogostemon cablin* leaves)

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

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

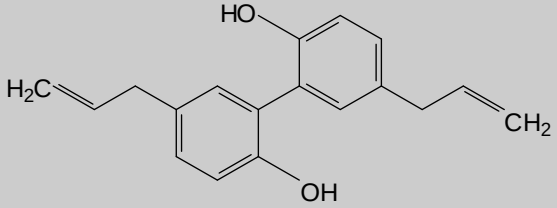
41



Honokiol (100mg/kg p.o.)
(*Magnolia obovata* Thunb., bark)

74.70
(Kawai *et al.,* 1994)

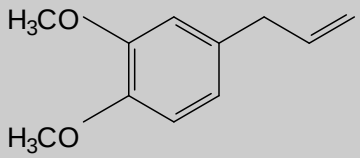
42



Magnolol (100mg/kg p.o.)
(*Magnolia obovata* Thunb., bark)

104.10
(Kawai *et al.,* 1994; Yang *et al.,* 1999c)

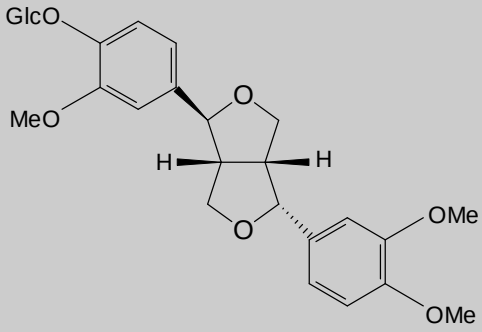
43



Methyleugenol (20mg/kg p.o.)
(*Syzygium aromaticum,* Linn., Merr. & Perry., flower buds)

166.90
(Kawai *et al.,* 1994)

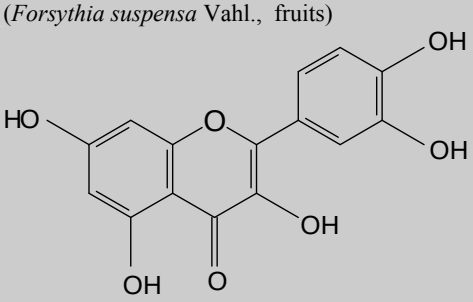
44



Phillyrin (100mg/kg p.o.)
(*Forsythia suspensa* Vahl., fruits)

53.60
(Kinoshita *et al.,*1996)

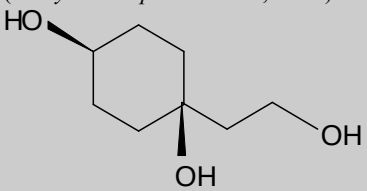
45



Quercetin (30mg/kg p.o.)
(*Forsythia suspensa* Vahl., fruits)

45.70
(Kinoshita *et al.,*1996)

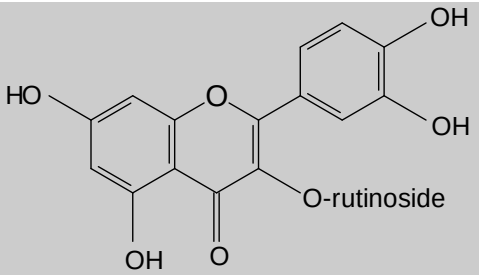
46



Rengyol (10mg/kg p.o.)
(*Forsythia suspensa* Vahl., fruits)

42.00
(Kinoshita *et al.,* 1996; Yang *et al.,* 1999c)

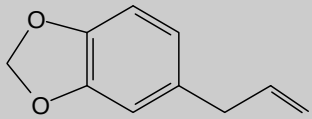
47



Rutin (100mg/kg p.o.)
(*Forsythia suspensa* Vahl., fruits)

222.60
(Kinoshita *et al.,*1996; Yang *et al.,* 1999c)

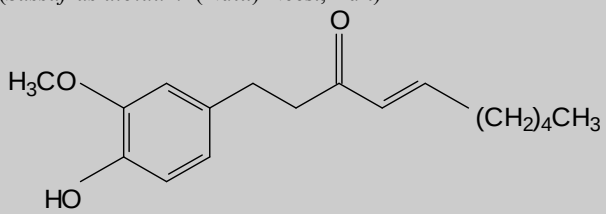
48



Safrole (20mg/kg p.o.)
(*Sassafras albidum* (Nutt.) Nees., fruit)

30.40
(Kawai *et al.,* 1994)

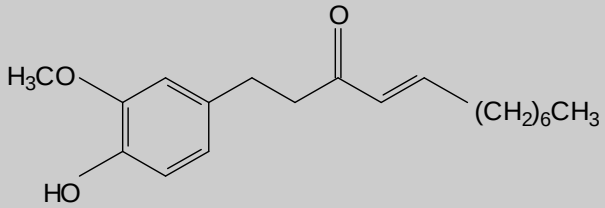
49



[6]-shogaol (50mg/kg p.o.)
(*Zingiber officinale* Roscoe., rhizome)

66.00
(Akita *et al.,* 1998; Kawai *et al.,* 1994)

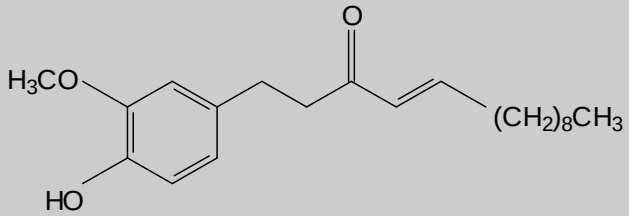
50



[8]-shogaol (20mg/kg p.o.)
(*Zingiber officinale* Roscoe., rhizome)

58.00
(Akita *et al.,* 1998; Kawai *et al.,* 1994)

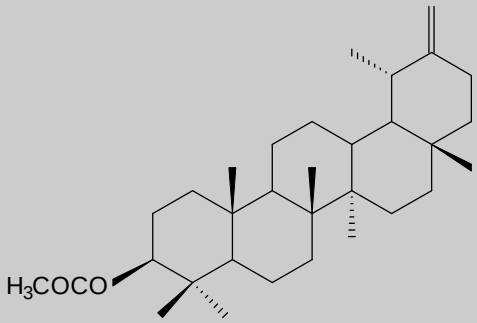
51



[10]-shogaol(20mg/kg p.o.,)
(*Zingiber officinale* Roscoe., rhizome)

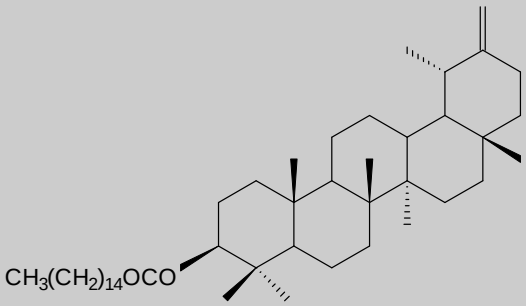
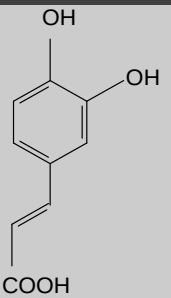
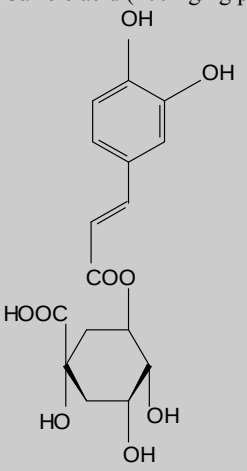
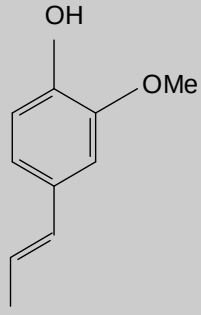
146.80
(Akita *et al.,* 1998; Kawai *et al.,* 1994; Yang *et al.,* 1999c)

52

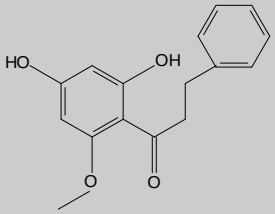
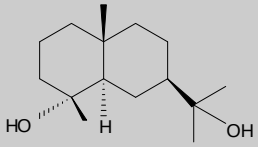
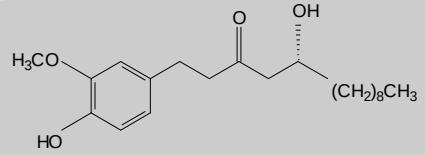
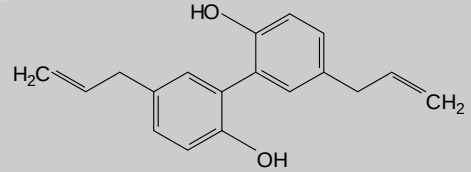


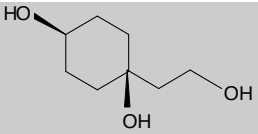
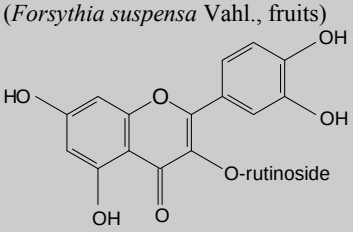
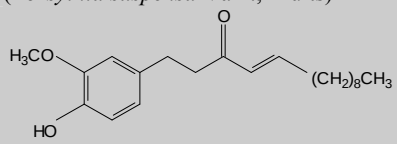
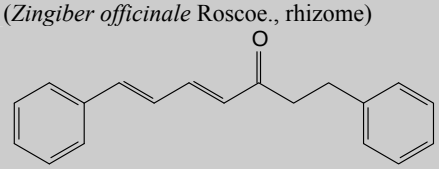
Traxasteryl acetate (100mg/kg p.o.)
(*Inula linariaefolia* L., flowers)

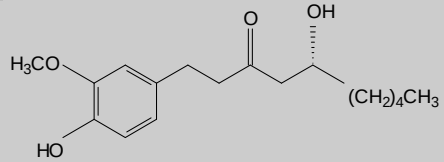
53.40
(Kinoshita *et al.,*1996)

53	 Taraxasteryl palmitate (100mg/kg p.o.) (*Inula linariaefolia* L.,flowers)	120 (Kinoshita *et al.,*1996)
Apomorphine induced emesis in frogs Anti-emetic activity by using this model proposed δ(enkephalinergic)-receptor antagonism (Harris, 1982) or dopamine inhibition (Takeda *et al.,*1993)		
Entry	Compound sources and doses used	% inhibition of Retches (References)
54	 Caffeic acid (100mg/kg p.o.) (*Inula linariaefolia* L.,flowers)	56.10 (Kinoshita *et al.,*1996)
55	 Chlorogenic acid (200mg/kg p.o.) (*Inula linariaefolia* L.,flowers)	39.20 (Kinoshita *et al.,*1996)
56	 Ferulic acid (500mg/kg p.o.,) (*Inula linariaefolia* L., flowers)	25.00 (Kinoshita *et al.,*1996)

57	α-L-Ara*p*(1 → 4) α-L-Ara*p*(1 → 4) α-L-Ara*p*(1 → 4) α-L-Ara*p*(1 → 4) α-L-Ara*p*(1 → 4) α-L-Ara*p* (1 → 4) L-Ara*p* (1 → 2 2 2 2 2 ↑ ↑ ↑ ↑ ↑ 1 1 1 1 1 α-L-Ara*p* α-L-Ara*p* α-L-Ara*p* α-L-Ara*p* α-L-Ara*p* 2 2 2 3 3 ↑ ↑ ↑ ↑ ↑ 1 α-L-Ara*p* R R R R 3 ↑ R R = β-D-Gal (1→3) L-Ara*p*, D-GalA-Ca-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 PT-F2-I(Polysaccharide fraction) (100µg p.o.) (*Pinellia ternata* tubers)	100 (Maki *et al.,*1987)

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

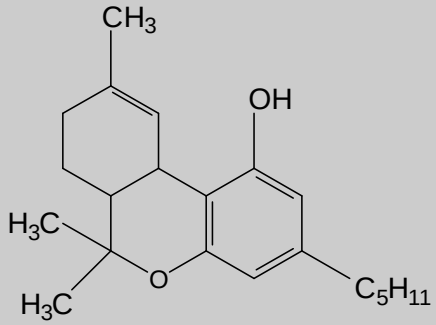
62	 Rengyol (20mg/kg p.o.,) (*Forsythia suspensa* Vahl., fruits)	60.00 (Kinoshita *et al.,* 1996; Yang *et al.,* 1999c)
63	 Rutin (50mg/kg p.o.,) (*Forsythia suspensa* Vahl., fruits)	80.50 (Kinoshita *et al.,*1996; Yang *et al.,* 1999c)
64	 [10]-shogaol (50mg/kg p.o.) (*Zingiber officinale* Roscoe., rhizome)	65.50 (Akita *et al.,* 1998; Kawai *et al.,* 1994; Yang *et al.,* 1999c; Yang *et al.,* 1999c)
65	 *trans, trans*-1,7-diphenyl-4,6-heptadiene-3-one (50mg/kg p.o.) (*Alpinia katsumadai* Hayata., seeds)	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	 [6]-gingerol (25mg/kg p.o.) (*Zingiber officinale* Roscoe., rhizome)	30 (Akita *et al.,* 1998; Kawai *et al.,* 1994; Yamahara *et al*., 1989)

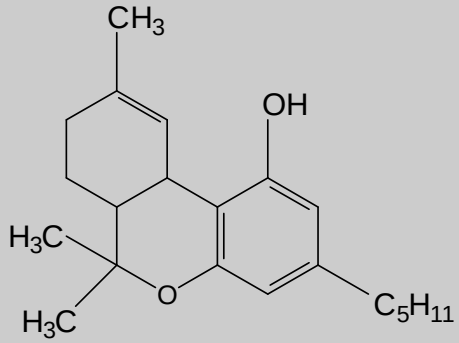
Apomorphine-induced emesis model in cats		
Entry	Compound sources and doses used	% inhibition of emesis (References)
67	α-L-Araf(1 → 4) α-L-Araf(1 → 4) α-L-Araf(1 → 4) α-L-Araf(1 → 4) α-L-Araf(1 → 4) α-L-Araf (1 → 4) L-Araf (1 → 3 2 2 2 2 ↑ ↑ ↑ ↑ ↑ 1 1 1 1 1 α-L-Araf α-L-Araf α-L-Araf α-L-Araf α-L-Araf 2 2 2 3 3 ↑ ↑ ↑ ↑ ↑ 1 α-L-Araf R R R R 3 ↑ R R = β-D-Gal (1→3) L-Araf, D-GalA-Ca-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	100 (Maki *et al.,*1987)

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

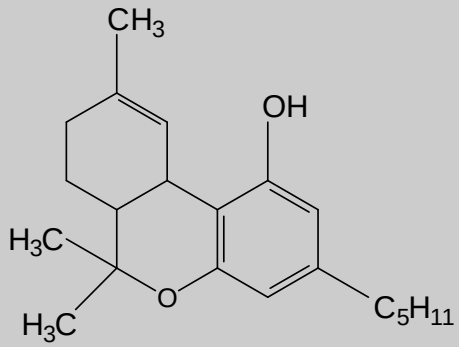
Cisplatin-induced acute emesis model in least shrews

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

Radiation-induced emesis in least shrews

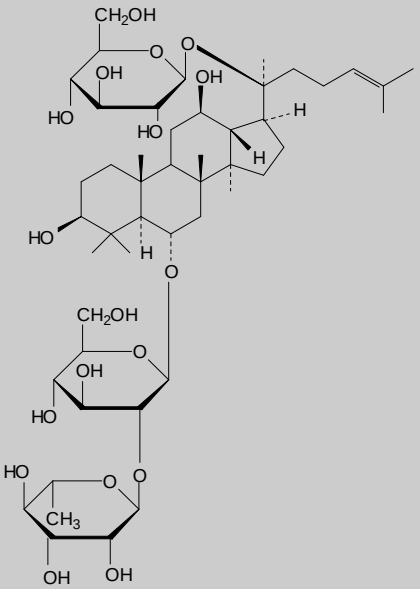
Entry	Compound sources and doses used	Time (min) of complete inhibition of emesis (References)
69	 Δ^9-tetrahydrocannabinol (20 mg/kg i.p.) (*Cannabis sativa* flowers and buds)	30 (Gaoni & Mechoulam, 1964; Darmani *et al.,*2007)

Motion-induced emesis model in house musk shrews

Entry	Compound sources and doses used	Time (min) of complete inhibition of emesis (References)
70		45 (Gaoni & Mechoulam, 1964; Cluny *et al.,* 2008)

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	 Ginsenoside Re (5 mg/kg i.p.,) (*Panax quinquefolius* L., berry)	Decreased kaolin intake and significant recovery of food intake (Mehendale *et al*., 2005)

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-HT_3 (Fukui *et al.,*1993c), 5-HT_4 (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 $5HT_3$ but not $5HT_4$ (Heba *et al.,* 2006 ; Pertz *et al.,*2011) or NK_1 receptor antagonism (Tsuchiya *et al.,* 2002).

Flavonoids

Galangin and kaempferide (Table 3, Entry No.5, 19) from *Alpinia officinarum* Hence., 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-HT_3 (Fukui *et al.,* 1993c), 5-HT_4 (Fukui *et al.,*1994) an/or NK_1 (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-HT_3 (Fukui *et al.,*1993c), 5-HT_4 (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-HT_3 (Fukui *et al.,* 1993c), 5-HT_4 (Fukui *et al.,*1994) and/or NK_1 (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-HT_3 (Fukui *et al.,*1993c), 5-HT_4 (Fukui *et al.,*1994) and/or NK_1 (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 safrole (Table 3, Entry No.48) from *Sassafras albidum* (Nutt.) Nees., fruit (Kawai *et al.,* 1994) have shown to induce anti-emetic effect through 5-HT_3 (Fukui *et al.,*1993c), 5-HT_4 (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-HT_3 antagonism (Cubeddu, 1996; Matsuki *et al*., 1993; Endo *et al.,* 2000; Mehendale *et al.*, 2005) and NK_1 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-HT_3 (Fukui *et al.,*1993c), 5-HT_4 (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-HT_3 (Fukui *et al.,* 1993c), 5-HT_4 (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 casis, 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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