

The gastrointestinal tract: safety pharmacology aspects relating to ageing, diet and natural/herbal remedies

Else M. Bartels¹, Adrian P. Harrison²

¹ Copenhagen University Library, and The Parker Institute, Frederiksberg Hospital, Denmark

² Department of Animal and Veterinary Basic Sciences, Faculty of Life Science, Copenhagen University, Frederiksberg, Denmark

Abstract: The gastrointestinal tract (GIT) has always been and remains a major source of interest in terms of both its function, and its malfunction. Our current knowledge of age-related changes in this system, as well as drug-food interactions, however, remains relatively limited. Paradoxically, the GIT is not one of the core battery of tests that pharmaceutical companies are obliged to investigate as part of drug development. This review aims to cover the basics of GIT function before highlighting aspects of relevance for safety pharmacology in terms of age, cancerogenesis, and both drug and diet-related GIT damage and dysfunction. New and novel aspects of drug delivery and drug-dietary supplement interactions are discussed and much needed areas of focus in terms of drug GIT testing are identified.

Key words: animal studies, drug interactions, future methodology, gastrointestinal tract, herbal medicine, humans, natural supplements, safety pharmacology

THE GASTRO-INTESTINAL TRACT (GIT): AN OVERVIEW

Anatomy & Physiology. The GIT consists of several different sections, each with a special anatomy (structure) and physiology (function). Together, these sections coordinate the flow as well as the break-down of many ingested components, and also serves to facilitate the transport of nutrients into enterocytes, their release into the systemic circulation, while at the same time directing the expulsion of left-over undigested waste products. Many of these functions are under hormonal and nervous regulation along the GIT, and this regulation is affected by components passing through the system. Histological sections of the various parts of the GIT are shown in Figure 1.

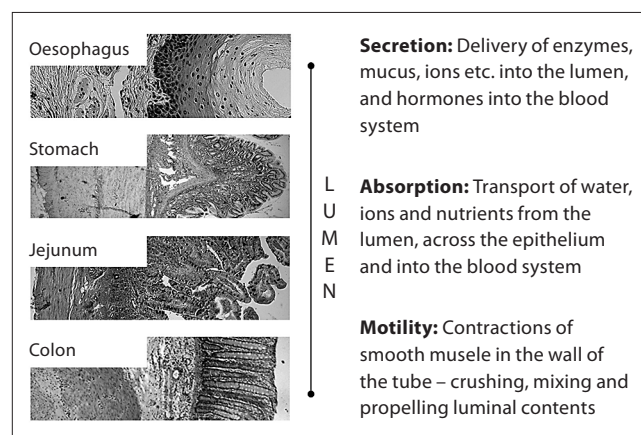


Figure 1 Histologically stained transverse sections revealing gastrointestinal tract (GIT) structure (muscle layers, secretory and absorptive layers) alongside the 3 major functions of the GIT.

Corresponding author: Prof. Adrian P. Harrison, Department of Animal and Veterinary Basic Sciences, Faculty of Life Science, University of Copenhagen, Grønnegaardsvej 7, 1870 Frederiksberg C, Denmark.
E-mail: adh@life.ku.dk

Received: 5 October 2009; accepted: 29 December 2009

From the physical and enzymatic breakdown of ingested material in the mouth, where saliva additionally has some protective effect on the cell surfaces, material travels *via* the oesophagus down into the stomach. Already at this point, there is a regulatory mechanism where an upper and a lower oesophageal sphincter muscle regulate the passage of the ingested items entering (swallowing), as well as leaving (vomiting) the stomach. It is the activation of chemoreceptors, reacting to the presence of poisonous molecules, that initiates vomiting, a reflex that serves to protect an individual from the harm such molecules might cause.

Once in the stomach, both physical grinding and breakdown with the help of the enzymes pepsin and lipase, as well of hydrochloric acid (HCl), occurs. Pepsin is vital for protein breakdown, and this enzyme needs HCl to be activated from the secreted pepsinogen form. Gastric lipase breaks down triglycerides, and the stomach also excretes an intrinsic factor necessary for vitamin B₁₂ absorption in a later section of the GIT. Another sphincter muscle regulates the further transport of partially digested material from the stomach into the proximal small intestine – the duodenum. The stomach regulates the amount of food released at any given time.

In the duodenum, both pancreatic fluid and bile are secreted into the GIT lumen, partly determined by the acidity of the incoming material. More enzymes are added at this point to complete digestion. The result is that all this produces nutrients with a molecular size suitable for absorption. Certain toxins stimulate:

- 1) the secretion of salts into the intestinal lumen, with the result that water, driven by osmotic forces, then follows;
- 2) induce faster peristaltic movements.

In combination, these reactions serve to expel unwanted/harmful components from the GIT, a process referred to as diarrhoea. Otherwise, elimination of waste happens at a far slower rate, with water absorption occurring in the colon. In cases of diarrhoea, this is an overwhelming of the reabsorptive capacity for water *via* the colon that gives rise to a dangerous

risk of dehydration. Transport of both undigested and partly broken down material through the GIT triggers the release of hormones which stimulate enzyme production, facilitating further digestion, and peristalsis. The oral and ab-oral movement of material along the tract occurs through interaction with the local mesenteric and autonomic nervous systems. For a more detailed description of the GIT see: Long & Cheshire [1]. The anatomy of part of the mesenteric system, with a typical functional recording from a ganglion, is shown in Figure 2.

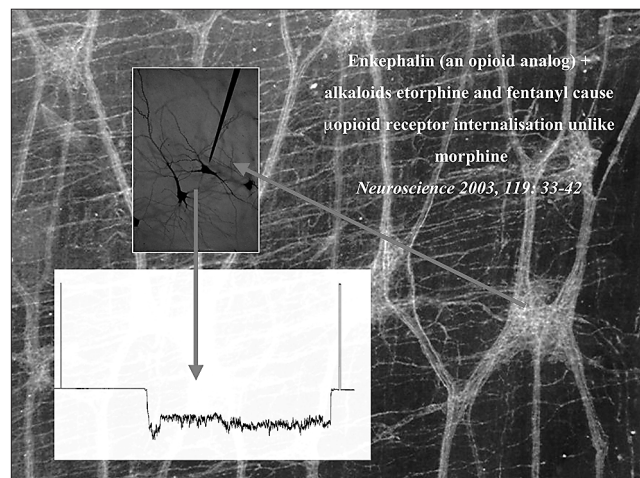


Figure 2 Photograph of the enteric nervous system (jejunal myenteric plexus) of the pig, showing glass micro-electrode placement into a ganglion, the interconnected nerve strands of the myenteric plexus and in the background the outer longitudinal muscle cells. The lower panel shows a typical electrical recording from a microelectrode as it is inserted into a ganglion, and removed a short time afterwards. Magnification $\times 40$.

GIT: AGEING, ILLNESS & CANCEROGENESIS

Relatively little work has been produced that describes the gastrointestinal changes associated with normal ageing in humans, and in many instances, 'normal' data on which clinical comparisons can be based, are simply not available [2].

In a rare cohort of human subjects with no upper GIT-related disease it was found that in the absence of gastric mucosal atrophy, there was no change in gastric secretion with increasing age [3]. Furthermore, in a rat study undertaken in order to address this particular issue, the most prominent age-related changes of the GIT were found to be a decrease in intestinal motility, an associated compromise in nutritional status, and an increased risk of colon cancer [4]. Recently, however, a review of advances as well as future research directions was published presenting the recommendations of the US National Commission on Digestive Diseases [5]. Five of the Commissions recommendations for new research directions concerned the effect of ageing on the GIT.

Maturation changes pertinent to the upper oesophageal sphincter and oesophageal phases of swallowing are not completely understood [6]. It is known that full-term infants have successful oral feeding skills *cf.* those of preterm infants, presumably due to increased organ growth, greater muscle mass, and improved enteric neuromuscular coordination [6]. Thus, maturity at birth has an important impact on oesophageal function and the risk of damage during the perinatal period. Successful coordination and complete

propagation of primary peristalsis has been found to occur in 99% of all adult swallows, but occurs in only 70-80% of those recorded for neonates [6]. Since the upper oesophageal sphincter and oesophageal body characteristics, as well as the transit times, are faster in full-term infants and adults *cf.* preterm infants, it seems very likely that receptor sensitivity, as well as the function of both afferent and efferent arcs, improve in the oesophagus with maturation and growth. Increasing age, however, has been found to be associated with a loss of enteric neurons in the human oesophagus. The number of neurons decreases after 70 years of age, which is accompanied by an increase in the size of the existing neurons [2]. There is also evidence of a reduction in the amplitude of contractions in the lower oesophagus of the elderly, a finding that is consistent with observations of reduced oesophageal clearance after gastro-oesophageal reflux [2].

Research into the ageing enteric nervous system has shown a phenomenon of age-related neuro-degeneration in 3 rodent species (rat, mouse and guinea pig) [7, 8], which makes these animals potential candidates for safety pharmacology studies into the adverse effects of drugs on the ageing GIT. In a study involving human subjects, however, it was concluded that ageing had no effect on gastric emptying, antral contractions, or the small intestinal transit rate, all of which rely heavily on the enteric nervous system. The motility parameters were not affected by gender or body mass index [2]. In contrast, [9] a delay in gastric emptying when recorded in connection with lipid ingestion reported in the elderly, was an effect shown to be alleviated by the administration of the enzyme lipase. Thus, unlike the oesophagus, the human stomach may not undergo enteric neuro-degeneration with aging; rather, with increasing age, it may just become sensitive to dietary regulators. In a recent review of this field, it was concluded that ageing compromises the sympathetic and parasympathetic efferent innervation in the GIT to different degrees [10]. These authors concluded that, 'age-related neuronal losses occur in both the myenteric plexus and the submucosal plexus' of the GIT, that 'such losses start in adulthood, increase over time, and are specific to cholinergic neurons', with 'parallel losses of enteric glia also occurring', and that the 'distal GIT is more severely affected'. From this, it can be concluded that such changes in the enteric nervous system will affect the functional aspects of the GIT to varying degrees, depending on which region is most adversely affected.

Madsen & Graff [11] have reported a slower colonic transit time in healthy persons aged 80 and above, a process that seems to derive from a reduced propulsive capacity of the colon. If one assumes that this loss is neuronal in origin, then the findings of Roberts *et al.* [12] from rat colon may partly explain this phenomenon. They found an age-dependent reduction in acetylcholinesterase-release in the myenteric plexus, which in part may be associated with a decreased calcium influx *via* membrane calcium channels. Thus, an age-related decline in calcium channels in neurons may well underlie this ageing effect, which must have an impact on the function of the GIT. Indeed, animal studies report an impaired adaptive response of the aged intestine, so that dietary restriction in aged rats results in dramatic weight loss, without a following stabilization when a normal diet is reintroduced. This correlates well with observations showing that, following a period of stress – whether this be illness or injury derived – elderly patients continue to underfeed themselves for 10-15 days, while younger patients increase

their energy intake [13]. One might therefore conclude that elderly patients may simply have a reduced functional reserve of their intestine. For further articles addressing diverse aspects of GIT ageing, see Table 1.

Table 1
Age Related Aspects.



MICE:	Developmental up-regulation of IFN- γ -regulated genes with intestinal maturation – <i>The Journal of Immunology</i> 2005, 175: 1127-1136.
MAN:	Duodenal calcium channel TRPV6 expression decreases with age in women but not men – <i>Journal of Bone & Mineral Research</i> 2006, 21: 1770-1777.
MAN:	Neuron numbers in the ganglia of the myenteric plexus are reduced in old versus young individuals (duodenum > 38% reduction) – <i>Gerontology</i> 1993, 39: 183-188.
MAN:	The activity of gastric mucosal glutathione-S-transferase decreases with age – <i>Italian Journal of Gastroenterology</i> 1996, 28: 477-481.
MAN:	Age related changes in the autonomic system induce a dysrhythmia in gastric slow waves – <i>Folia Medica Cracoviensia</i> 1999, 40: 53-62.
MAN:	Advancing age increases oesophageal acid contact time – <i>Digestive Diseases and Sciences</i> 1989, 34: 372-378.

In view of the paucity of human data in this particular area of research, the findings concerning rats showing a decrease in intestinal motility, an associated compromise in nutritional status, and an increased risk of colon cancer with ageing, we feel that pharmaceutical companies should seriously consider conducting safety profiles for novel drug compounds in the aged, as well as young animals. Perhaps an array of species could be adopted including rats, pigs and dogs, and one might even consider repeat testing of compounds in particular animals throughout both the adolescent and elderly phases of their life spans.

An additional consideration, which in many ways remains unresolved, is that of the effects of cancerogenesis on the GIT [14, 15]. There appear to be 2 aspects regarding age-dependent changes in DNA-methylation: one indicating that hyperproliferative tissues, such as the GIT, gradually acquire aberrant promoter hypermethylation [16], while others have shown that at different sites hypomethylation of the DNA can also occur [15], with both of these being associated with development of GIT tumours.

It is widely believed that gastric cancer is a multistage process that includes chronic gastritis, gastric atrophy, intestinal metaplasia and finally, dysplasia [17]. However, in a recent human cohort study based on more than 800 individuals, it was found that intestinal metaplasia represents a risk factor for dysplasia and gastric cancer, but only one type (IM subtype II) in connection, and only in connection with *H. pylori* infection, resulted in gastric carcinogenesis, whilst another type (IM subtype III) did not lead to the development of gastric cancer but was found to be associated with ageing [18].

Also generally significance is the issue of foetal programming, with its wide-ranging consequences. In a recent paper involving adult rats, it was concluded that there was an effect of dietary

protein type during pregnancy on colon tumour multiplicity, as well as colon tissue gene expression in the progeny as later adults [19]. This study raised the possibility that colon cancer of the elderly may be influenced by dietary/metabolic perturbations or programming early in development and, as such, could be seen as a latent ticking bomb with which individuals are born.

GIT: DRUG INTERACTIONS

Drug-induced injury of the GIT is becoming increasingly more common in patients, although it often remains under-recognized. Whilst the number of drugs that affect the GIT are far too numerous to mention in this review, the types of injury that drugs tend to cause have a limited number of characteristics, and once one knows what to look for, the task of screening a new drug becomes easier. Perhaps a more complex problem is the issue of drug-drug interactions, and any effects they may have on the GIT. A classic example is the case of tenofovir disoproxil fumerate taken in connection with didanosine for the management of HIV infection. In individuals receiving 400 mg of tenofovir disoproxil fumerate, such adverse effects as nausea, abdominal pain, diarrhea and flatulence can occur if the dosage of these 2 drugs taken in combination is not regulated, since mean didanosine concentration in plasma may become increased by as much as 40-60% [2].

At the macroscopic level, one typically finds that drugs induce erosions, ulcers, strictures and diaphragms throughout the GIT, while at the microscopic level, changes are mostly typified by cell hypertrophy and hyperplasia, inflammation or erosion of tissue layers, or fibrosis. See Parfitt & Driman [21] for a recent review.

Oral salts (e.g. KCl), taken by elderly patients in connection with heart failure as part of counteractive supplementation for diuretics, will often give rise to local irritation and ulcers, particularly if taken in the slow-release rather than the encapsulated form (22). In another elderly group, namely those suffering from osteoporosis, the drug Alendronate is used in treatment. This drug serves to inhibit osteoclast-mediated bone-resorption, and can potentially cause ulcers in the oesophagus and stomach, as well as give rise to oesophageal strictures [23]. In the younger part of the population, the drug doxycycline taken in pill form against acne and urinary tract infections, may, at times, be associated with oesophageal injury [24].

Other forms of physiological drug interactions include achalasia, irritable bowel syndrome, diarrhoea and vomiting. Achalasia is an oesophageal motility disorder typified by inappropriate contraction of the smooth muscle layer of the oesophagus, resulting in reduced peristalsis (the ability of muscles to move food down the oesophagus) and failure of the lower oesophageal sphincter (LES) to relax properly in response to swallowing.

Irritable bowel syndrome (IBS), or spastic colon, is a functional bowel disorder, which is characterized by abdominal pain and changes in bowel habits, which are not associated with any abnormalities seen during routine clinical testing. IBS is surprisingly common, constituting 20–50% of patient visits to gastroenterologists.

To date, some 700 drugs are implicated in causing diarrhoea in patients, and recent statistics indicate that GIT adverse drug reactions (ADRs) account for approximately 18% of all

adverse drug reactions, with 20-40% of these ADRs being in hospitalised patients. A few examples of drugs that affect the GIT are listed below:

- Metoclopramide (Emperal/Gastro-Timelets) is a motility stimulant that may enhance peristalsis and help acid clearance in the oesophagus [2].
- Alvimopan (ADL 8-2698) is a μ -opioid antagonist, which is specific to the GIT, inducing increased motility. However, adverse effects associated with its use include abdominal pain, flatulence and diarrhoea [25].
- Erythromycin acts as an agonist for neural and muscular motilin receptors with the result that it induces an increase in GIT motility (25). However, the effect of this drug is reduced after 2-3 weeks, presumably through down-regulation of motilin receptors.

These alarming cases of drug-GIT interactions, which occur at a rate of 1 in every 5 adverse drug reaction cases, serve to highlight the need for the inclusion of the GIT as one of the core battery of tests that pharmaceutical companies are obliged to investigate as part of novel drug development.

GIT: DIET INTERACTIONS

The majority of what we eat and drink has some effect on the GIT, even if it is simply mediated through the processes of digestion and absorption. Even something thought to be as innocent as milk contains a number of bioactive factors which are known to interact with opioid receptors in the GIT. Two recent reviews in this field present a number of drug-nutrient interactions and their effects on the GIT when dealing with elderly individuals [26], and hospitalised patients [27]. The point of interest here is that for certain drugs an interaction with dietary nutrients may result in an enhancement of its efficacy without any adverse effects, while for other drugs, interactions with nutrients may prove to be lethal, and in such cases these foods should be avoided, or a nutrient interaction may simply diminish any benefit of the ingested drug.

Table 2 Bioactive factors present in milk and their effect on the GIT.

β -casomorphin \uparrow (opiate agonist)	\downarrow stomach emptying, \downarrow intestinal motility, \uparrow transit time (>hrs)	\uparrow uptake of electrolytes and amino acids
Lactoferronin \uparrow (opiate antagonist)	\uparrow intestinal motility, \downarrow transit time (<hrs)	\downarrow uptake of electrolytes and amino acids – diarrhoea?
Casoxin \uparrow (opiate antagonist)	\uparrow intestinal motility, \downarrow transit time (<hrs)	\downarrow uptake of electrolytes and amino acids – diarrhoea?
\downarrow symbolises a decrease, whilst \uparrow symbolises an increase		

Interestingly, and perhaps not without some concern, modern dietary habits, particularly in the young, have now begun to include energy-rich chewing gums and drinks in response to our increasingly high-speed life-style. Busy mothers, top executives, students and drivers are among those targeted by leading 'health' product companies, e.g. 'Jolt Energy Gum', 'Buzz Gum – Extra Strength', 'Xtazy Energy 8-Hour Shot Drink' and 'Four Premium Malt Beverage Energy Drink'. Many of these products contain large quantities of such herbal extracts as guarana, wormwood oil, ginseng and

ginkgo biloba, all of which are perceived by the general public as 'natural', and therefore *per definition* as being 'healthy'. Many people certainly perceive 'natural herbal medicines' as being safer than conventional drugs, even though there are ever-increasing reports of the adverse effects of interactions between well-known herbal remedies and conventional drugs, when taken simultaneously [28]. For further studies addressing diverse aspects of GIT diet interactions, see Table 3.

Table 3
Diet Related Aspects.



MAN:	Intoxicating doses of alcohol alters the circadian variation of MMCs in healthy individuals – <i>Digestive Diseases Sciences</i> 1994, 39: 51-58.
MAN:	17% of Americans take herb and dietary supplements – compounds that American physicians, pharmacists and nurses have had little training in – <i>Clinical Toxicology</i> 2006, 44: 1-603.
MAN:	Ingestion of a typical breakfast reduced oral bioavailability of frusemide by 30% – <i>British Journal of Clinical Pharmacology</i> , 1996, 42: 743-746.
MAN:	High-protein and low-carbohydrate diets reduce the bioavailability of warfarin (high protein = \uparrow serum albumin = \downarrow warfarin binding) – <i>The Annals of Pharmacotherapy</i> 2005, 39: 744-747.
DOG:	Intestinal solubility of poorly soluble drugs is higher in the fed ct. the fasted state – <i>Pharmaceutical Research</i> 2005, 12: 2141-2151.
RAT:	Glycine & glycine dipeptides reduce the permeability (70-80%) of antiarrhythmic bi-disomide in the ileum – <i>Pharmaceutical Research</i> 1997, 14: 1030-1038.

Fruits and berries. These contain natural phytochemical compounds, otherwise known as plant secondary metabolites (PSM). This is a diverse group of natural products thought to provide plants with a defence against herbivores. Berries, for example, are particularly rich in flavonoids, a class of plant secondary metabolites that are most commonly known for their antioxidant activity. Flavonoids are also commonly referred to as bioflavonoids, terms that are equivalent and interchangeable, for flavonoids, of course, are biological in origin [29, 30].

Black elderberry (*Sambucus nigra*). Long accredited as being health-promoting, and is often something recalled from childhood days as being administered by parents when we were ill. Recently, it was shown that anthocyanins from elderberries are absorbed unchanged in their glycosylated form in man [29]. In an earlier study, the glucoside quercetin was shown to be capable of interacting with the sodium-dependent glucose-transport receptor of the mucosal epithelium [31]. Thus, anthocyanins and quercetin, which share a similar basic flavonoid structure, may utilise glucose-transport receptors to facilitate intestinal absorption *in vivo*. This is an area of importance, not only in terms of understanding how these compounds cross the intestinal epithelium unchanged, which has implications for drug design, but also in terms of flavonoids being a group of compounds that play a significant role in altering antioxidant status in individuals. *S. nigra* fruits have a higher antioxidant capacity than vitamins C or E, and are

capable of enhancing immune-system responses through elevated production of cytokines, something that supports their use against the ravages of colds, asthma and arthritis for thousands of years [30]. However, the routine administration of NSAIDs in the treatment of conditions such as rheumatoid arthritis, osteoarthritis and inflammatory arthropathies, acting to reduce cyclooxygenase-2 levels, may unwittingly lead to reduced drug efficacy if individuals then self-prescribe plant flavonoids such as those found in elderberries.

Liquorice (*Glycyrrhiza glabra L.*). Contains a chemical called glycyrrhizic acid, which is responsible for many of its reported side effects. In general, prescription drugs should be taken 1 hour before taking liquorice or 2 hours after, since liquorice may affect the absorption of many drugs. Indeed, liquorice and its ingredient, glycyrrhizin, in mice and rats, have been shown to increase the activity of CYP3A4 after repeated dosing over 4-10 days [32, 33]. Likewise, Echinacea has been shown to cause an induction in CYP3A4 activity in human clinical trials [34]. Thus, a liquorice-induced up-regulation of CYP3A4 may be expected to result in a greater degree of drug metabolism at the level of intestinal enterocytes than would otherwise occur. The result would be a lower systemic dose of orally administered drugs. Moreover, by altering the activities of certain hormones, liquorice can cause electrolyte disturbances, among them low potassium levels. Since the toxicity of digoxin is increased when potassium levels are low, people who are prescribed digoxin should be advised not to consume liquorice. Indeed, liquorice may be implicated in the reduced efficacy of birth control pills, hormone replacement therapies, and testosterone therapy [35, 36].

Grapefruit (*Citrus paradisi*). Ingested in juice form (200-300 mL) or in the form of whole segments, has an irreversible inactivation effect on cytochrome P450 CYP3A4, the form found in enterocytes of the GIT. Grapefruit juice affects pre-systemic metabolism so that CYP3A4 activity becomes greatly reduced. In consequence, the bioavailability of drugs is increased. The effect may occur up to 24 hours after consumption, and in association with prescribed felodipine and nifedipine, excessive vasodilatation can occur. In diabetics taking repaglinide, the result may be hypoglycemia, and in patients with angina pectoralis, taking verapamil, grapefruit juice can induce atrio-ventricular conduction disorders (PQ interval). However, perhaps the most serious effect of grapefruit juice consumption is found in patients with congestive heart failure, where a combination of prescribed carvediol and juice can often prove fatal [37].

The effects of grapefruit juice appear to be due to both flavanoid and non-flavanoid interaction with enterocyte CYP3A4 activity. Naringin, which is present in grapefruit juice at a level of 450 µg/mL (approx. 10% of the dry wt of juice), is a potent *in vitro* inhibitor of the CYP3A isozyme, yet it is less effective *in vivo*. Another constituent of grapefruit juice, the furanocoumarin bergamottin, is a prominent inhibitor of CYP3A4 found in GIT enterocytes. However, sadly, this is far from the whole story as bergamottin is also found in lime juice, which has little effect on CYP3A4 activity.

Natural/herbal remedies and drug interactions. Today we live in a therapeutic revolution, with a worldwide interest in natural remedies, many of which are taken alongside prescription medication and very often without

the knowledge or consent of the prescribing physician [38]. A recent paper reported that 17% of Americans take herb and dietary supplements, more often than not compounds for which American physicians, pharmacists and nurses have had little training in [39]. Among the most commonly used natural/herbal remedies taken by individuals are garlic, ginger, ginko and ginseng [40].

Garlic (*Allium sativum L.*). Generally taken by individuals with cardiovascular problems, high blood pressure and serum lipids (LDL & cholesterol), although it also has an effect as a blood-thinner [35, 36].

Numerous controlled trials have examined the effects of oral garlic on serum lipids. Most studies report a modest reduction in total cholesterol *versus* a placebo in the short term (4-12 weeks), and unclear effects after 20 weeks. Small reductions in blood pressure (<10 mm Hg) and inhibition of platelet aggregation have been reported, although evidence is doubtful in these areas. Moreover, numerous case-control and population-based studies suggest that regular consumption of garlic may reduce the risk of gastric and colorectal cancer, although once again carefully designed and controlled studies are much needed.

Garlic has been implicated in the decrease of the plasma protease inhibitor called Saquinavir, following 3 weeks of oral administration to healthy volunteers [41]. The induction of the gut cytochrome P450 enzyme system CYP3A4 by garlic (see Figure 3), has been thought to be the reason for the reduction in bioavailability of this drug, although a contribution from P-glycoproteins (a Saquinavir substrate) cannot be ruled out. Also of importance are the findings of limited laboratory studies in animals. These studies suggest that garlic may interfere with the liver's cytochrome P450 enzyme system. This is based on results showing that blood levels of some drugs may be elevated, causing increased effects or potentially serious adverse reactions with intake of garlic [35, 36].

Garlic should be taken with care by people with bleeding disorders, or those taking drugs that may increase the risk of bleeding, or indeed by those about to undertake any form of surgical procedure. In particular, care should be exercised when taking such prescription medications as, warfarin (Coumadin), anti-platelet drugs such as clopidogrel (Plavix), and NSAIDs, for example, ibuprofen (Motrin, Advil).

In terms of its pharmacology, garlic comprises enzymes (e.g. allinase, peroxidase, myrosinase) a range of amino acids (e.g. arginine, glutamic acid, methionine), minerals, vitamins etc., but also a range of sulphur-containing compounds (0.45% of dried powder; e.g. alliin, allicin) and their secondary products. After an oral administration of alliin and allicin (8 mg/kg) to rats, absorption was completed after 10 and 30-60 minutes, respectively, and mean total urinary and faecal excretion after 72 hours was 85.5% of the ingested dose [35]. Peak plasma concentrations of garlic compounds have been recorded after one hour, and a half-life of 2.33 hours has been measured [35]. Typically, garlic powder taken as part of clinical trials, has been administered orally at a dose of 600-900 mg per day, while the European Scientific Co-operative on Phytotherapy recommends a dose of 0.5-1.0g of dried garlic per day (6-10 mg alliin; 3-5 mg allicin) [35].

Ginger (*Zingiber officinale R.*). Generally taken by individuals suffering from nausea and vomiting, anorexia, cardiovascular problems, bronchitis and arthritis.

Supportive evidence from one randomized controlled trial indicates that ginger reduces the severity and duration of chemotherapy-induced nausea/emesis. The anti-emetic activity of ginger extracts has also been assessed in dogs [42]. Acetone and ethanolic extracts of ginger, administered intragastrically at doses of 25, 50, 100 and 200 mg/kg, protected against cisplatin-induced emesis. Furthermore, in mice, administration of an acetone extract of ginger (75 mg/kg) enhanced the transportation of a charcoal meal, indicating enhancement of gastrointestinal motility [43]. However, people with ulcers or inflammatory bowel disease are not advised to ingest ginger supplements as there is some evidence to suggest that ginger increases acid production in the stomach. Thus, based on its effects, we may suggest that ginger acts against the effects of antacids such as sucralfate (Carafate), anti-reflux H₂ blockers such as ranitidine (Zantac) and proton pump inhibitors, for example lansoprazole (Prevacid) [35, 36].

Finally, although clear evidence is sadly lacking, ginger may:

- 1) increase the risk of bleeding when taken in connection with blood-thinning medications, eg. the anticoagulant warfarin (Coumadin), anti-platelet drugs such as clopidogrel (Plavix), and NSAIDs, such as ibuprofen (Motrin, Advil);
- 2) at high doses, also interfere with medications that alter heart contractions, including beta-blockers and digoxin.

Pharmacologically, ginger comprises carbohydrates (e.g. starch), a range of lipids (e.g. palmitic, oleic, linoleic, capric; 6-8%), oleo-resin (e.g. gingerol, zingerone), volatile oils (e.g. zingiberene, zingiberol; 1-3%), amino acids, vitamins and minerals.

Gingerol administration for the treatment of ulcers, atherosclerosis, inflammation and cancer, has been shown to be beneficial, with a plasma clearance rate of 7.23 minutes *t*-half, and a total body clearance of 16.8 ml/min/kg – serum protein binding being 92.4% [35]. Typically, ginger powder taken orally at a dose of 1-2 g 30 minutes prior to travel prevents motion sickness, most likely through a local gastrointestinal tract action, rather than by a centrally-mediated mechanism [35].

Ginko (*Ginkgo biloba* L.). Generally taken by individuals suffering from the early stages of dementia or impotency. It is also effective in cases of claudication, and is a vasorelaxant, anti-oxidant and anti-inflammatory.

Available evidence suggests that ginkgo is efficacious in the management of intermittent claudication (pain in the legs arising from clogged arteries), although additional evidence is needed from well-designed studies comparing or combining ginkgo with drug and exercise therapy. However, while well-designed studies are lacking, animal and human studies suggest that 120-240 mg of ginkgo taken daily, benefits people with early stage Alzheimer's disease and multi-infarct dementia. However, bleeding is sometimes associated with oral administration of ginkgo, and caution should be taken for people with bleeding disorders, or those taking drugs that may increase the risk of bleeding [35, 36]. Care should therefore be taken by people with bleeding disorders, those taking drugs that may increase the risk of bleeding, and also by those about to undergo any form of surgical procedure. In particular, care should be exercised when taking such prescription medication as warfarin (Coumadin), ticlopidine (Ticlid), anti-platelet drugs such as clopidogrel (Plavix), and NSAIDs, e.g. ibuprofen (Motrin, Advil).

In terms of its pharmacology, ginkgo comprises flavonoids (e.g. amentoflavone, ginkgetin, quercetin, kaempferol), a range of terpenoids (e.g. ginkgolides A,B,C,J,M), oleo-resin (e.g. gingerol, zingerone), volatile oils (e.g. zingiberene, zingiberol; 1-3%), amino acids (tryptophan), sugars and waxes. Ginkgo administration for the treatment of cognitive deficiency, with a dose of 120-240 mg daily for a period of 8-12 weeks, has been shown to be beneficial [35]. Mean bioavailabilities of ginkgolide A and B following an oral dose of 120 mg to fasting volunteers was 80% and 88%, respectively, and peak plasma concentrations range from 16.5-33.3 ng/ml for these 2 ginkgolides, with urinary excretion around 50-70% of an oral 120 mg dose [35].

Ginseng (*Panax ginseng*; *Panax quinquefolius*). Taken intentionally by individuals wishing to improve their immune system, stamina, and mental performance, as well as to control type II diabetes.

Several studies report that ginseng can modestly improve mental performance at doses of 200-400 mg per day for up to 12 weeks. Moreover, with respect to type II diabetes mellitus (adult-onset), several studies in humans suggest that ginseng may lower blood glucose levels both in the fasted and post-prandial state. However, although available scientific evidence suggests some effectiveness of the short-term use of ginseng, better quality research is needed before any strong recommendations can be made [35, 36].

Ginseng has been well tolerated in most scientific studies when used at recommended doses, and serious adverse effects appear to be rare. However, long-term use may be associated with diarrhoea, loss of appetite and lowered blood sugar levels. There is also some evidence that ginseng at doses of 200 mg daily may increase the QTc interval of individuals, as seen on an ECG, thus increasing the risk of abnormal heart rhythms.

Care should therefore be exercised by people taking drugs for diabetes, anti-depressants (e.g. Marplan, Nardil, Parnate), or drugs that act as calcium channel blockers – (e.g. nifedipine -Procardia) and diuretics such as furosemide (Lasix).

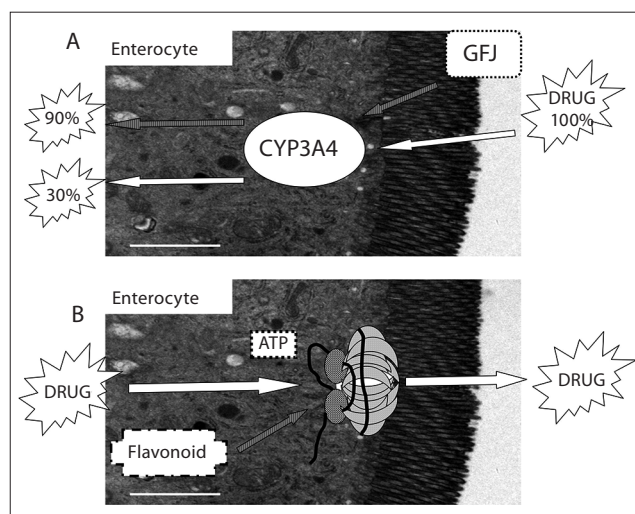


Figure 3 Cytochrome P450 (CYP) and P-glycoprotein systems in GIT enterocytes. A) Grapefruit juice inhibition of a stylised enterocyte CYP3A4 system, resulting in an increase in drug bioavailability, and B) Flavonoid (e.g. kaempferol, galangin, quercetin, genistein) modulated drug efflux via a stylised membrane spanning P-glycoprotein using ATP hydrolysis as the energy source.

GFJ – Grapefruit juice.
ATP – Adenosine triphosphate.
White scale line – 2 µm.

Pharmacologically, ginseng comprises terpenoids (e.g. ginsenosides otherwise termed ginsenosides), a range of volatile oils (e.g. panacene, limonene, terpineol, eucalyptol), polysaccharides (e.g. pectins, glucans), free sugars, vitamins (e.g. B₁, B₂, B₁₂, pantothenic acid, biotin), fats and minerals. Administration of ginseng, as a short-term phytotherapeutic, range in dose from 0.5-1.0g of root extract per day, while more long-term administration is usually at a dose of 0.4-0.8 g per day [35]. A number of *in vitro* studies suggest that ginseng acts as a corticosteroid-like compound, has a hypoglycaemic effect and serves as a cardiovascular performance enhancer, having an average plasma clearance rate of 18.5 minutes *t*-half and a faecal loss of 0.97-1.15% [35].

CONCLUSIONS

Whilst the GIT in many ways still remains a 'black box' in terms of our understanding of the interactions between structure and function, as well as their regulation, it is hopefully apparent that it is particularly susceptible to drug and diet-related damage and dysfunction.

Of particular importance for safety pharmacology is the fact that the metabolism of orally administered drugs may be altered at the level of the enterocyte. This may happen through cytochrome P450 enzyme interactions with other drugs, chemicals and foods [44]. The job of safety pharmacologists, however, has been made a great deal more complex in recent years as the general population perceives herbal remedies as being natural and therefore healthy. Indeed, such 'natural' remedies have been shown to give rise to serious clinical interactions when co-administered with prescription medicines, and this in itself raises the problem of disclosure, since many health professionals are often not informed by their patients of the natural substances they have recommended by family and friends, and consequently take in good faith, in addition to their prescribed medication.

While there is a clear down-side to natural herbal remedies in connection with prescribed drugs, some of the plant secondary metabolites that do interact with the GIT may prove to be of use to safety pharmacologists. Flavonoids, for example, constitute a new class of bifunctional modulators, interacting with both the ATP binding- and steroid sites of the cytosolic domain of P-glycoproteins. This important finding opens exciting perspectives for studying the molecular mechanism of interactions with flavonoid modulators through structural and functional approaches, giving rise to a new generation of specific inhibitors of P-glycoprotein activity. For sure, anything that might reduce the required dosage of certain drugs by reducing their efflux to the intestinal lumen, and in so doing perhaps reduce the risk of drug-induced GIT damage, must surely be desirable. Furthermore, a recent Italian study of the incidence of colorectal cancer in 1,225 human subjects with cancer of the colon, and a control cohort of 4154 individuals recruited from the same area, revealed a significant decrease in the risk of colorectal cancer for those individuals regularly consuming such classes of flavonoids as isoflavones, anthocyanidins, flavones and flavonols [45].

A better understanding of P-glycoprotein regulation would also prove beneficial in another context, namely that of multi-drug resistance. In cancer cells, multi-drug resistance is often associated with over-expression of P-glycoproteins. Therefore, perhaps the effect of PSM's might be used for the benefit of

mankind. One way of achieving this may be through the use of another plant compound, namely the protease and basic glycoprotein, bromelain, which is to be found in the central 'woody' part of pineapples. Permeation studies with fresh guinea pig intestinal mucosa mounted in Ussing-type chambers has recently shown that bromelain can induce a significant permeation across the GIT of a high-molecular weight marker (FITC-dextran) compound. There may perhaps be a future for bromelain in modern medicine as a new promising strategy capable of raising the *in vivo* efficacy of non-invasive hydrophilic macromolecular drugs.

Other strategies that might prove advantageous in terms of safety pharmacology and the GIT with respect to drugs, ageing, diet and natural/herbal remedies are:

- 1) increased use of pharmacokinetic-pharmacodynamic modelling as a tool for evaluating the clinical relevance of a drug-food or drug/herbal interaction, as typified by a study of nisoldipine administration for the treatment of hypertension and angina pectoris in relation to food consumption [46];
 - 2) more detailed analysis of dietary restrictions and drug interactions, as in the case of monoamine oxidase inhibitors, administered as antidepressants, which have been shown to result in serious hypertensive reactions when taken with as many as 70 different types of food, among them cheese containing high concentrations of tyramine [47].
- It is perhaps essential, more so now than at any other time in history, that the general public should be re-educated in the fact that natural and herbal remedies are very effective forms of medication, and should therefore be treated with a great deal of respect.

DISCLOSURE

The authors are independent government-funded researchers and are not aware of any conflicts of interest.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Vibeke Sødring Elbrønd, IBHV, Faculty of Life Sciences, Copenhagen University, for kindly providing the EM image used in Figure 3. Dr Bartels was supported by The OAK foundation.

REFERENCES

1. Long MS, Cheshire E: Crash Course: Gastrointestinal System (2nd edn), Horton-Szar, Mosby (USA) 2002.
2. Salles N: Basic mechanisms of the aging gastrointestinal tract. *Dig Dis* 2007, **25**, 112-117.
3. Nakamura K, Ogoshi K, Makuuchi H: Influence of aging, gastric mucosal atrophy and dietary habits on gastric secretion. *Hepato Gastroenterol* 2006, **53**, 624-628.
4. Lee HM, Greeley GH, Englander EW: Age-associated changes in gene expression patterns in the duodenum and colon of rats. *Mech Ageing Dev* 2001, **122**, 355-371.
5. Owyang C: Recent advances and future research directions in neurogastroenterology and endocrinology recommendations of the National Commission on Digestive Diseases. *Neurogastroenterol Motil* 2008, **20**, 1189-1203.
6. Jadcherla SR, Duong HQ, Hofmann C, Hoffmann R, Shaker R: Characteristics of upper oesophageal sphincter and oesophageal body during maturation in healthy human neonates compared with adults. *Neurogastroenterol Motil* 2005, **17**, 663-670.

7. Phillips RJ, Powley TL: As the gut ages: time tables for aging of innervation vary by organ in the Fisher 344 rat. *J Comp Neurol* 2001, **434**, 358-377.
8. El-Salhy M, Sandstrom O, Holmlund F: Age-induced changes in the enteric nervous system in the mouse. *Mech Ageing Dev* 1999, **107**, 93-103.
9. Nakae Y, Onouchi H, Kagaya M, Kondo T: Effects of aging and gastric lipolysis on gastric emptying of lipid in liquid meal. *J Gastroenterol* 1999, **34**, 445-449.
10. Phillips RJ, Powley TL: Innervation of the gastrointestinal tract: Patterns of aging. *Auton Neurosci* 2008, **136**, 1-19.
11. Madsen JL, Graff J: Effects of aging on gastrointestinal motor function. *Age Ageing* 2004, **33**, 154-159.
12. Roberts D, Gelperin D, Wiley JW: Evidence for age-associated reduction in acetylcholine release and smooth muscle response in the rat colon. *Am J Physiol* 1994, **267**, G515-G522.
13. Woudstra T, Thomson ABR: Nutrient absorption and intestinal adaptation with aging. *Best Pract Res Clin Gastroenterol* 2002, **16**, 1-15.
14. Shames DS, Minna JD, Gazdar AF: DNA methylation in health, disease, and cancer. *Curr Mol Med* 2007, **7**, 85-102.
15. Suzuki K, Suzuki I, Leodolter A, Alonso S, Horiuchi S, Yamashita K, Perucho M: Global DNA demethylation in gastrointestinal cancer is age dependent and precedes genomic damage. *Cancer Cell* 2006, **9**, 199-207.
16. Kim SK, Jang HR, Kim JH, Kim M, Noh SM, Song KS, Kang GH, Kim HJ, Kim SY, Yoo HS, Kim YS: CpG methylation in exon 1 of *transcription factor 4* increases with age in normal gastric mucosa and is associated with gene silencing in intestinal-type gastric cancer. *Carcinogenesis* 2008, **29**(8), 1623-1631.
17. Correa P: A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**(13), 3554-3560.
18. Kang KP, Lee HS, Kim N, Kang HM, Park YS, Lee DH, Choe G, Kim JS, Jung HC, Song IS: Role of intestinal metaplasia subtyping in the risk of gastric cancer in Korea. *J Gastroenterol Hepatol* 2008; doi: 10.1111/j.1440-1746.2008.05546.x.
19. Xiao R, Hennings LJ, Badger TM, Simmen FA: Fetal programming of colon cancer in adult rats: correlations with altered neonatal growth trajectory, circulating IGF-I and IGF binding proteins, and testosterone. *J Endocrin* 2007, **195**, 79-87.
20. Kearney BP, Sayre JR, Flaherty JF, Chen SS, Kaul S, Cheng AK: Drug-drug interactions between Tenofovir Disoproxil Fumarate and Didanosine. *J Clin Pharmacol* 2005, **45**, 1360-1370.
21. Parfitt JR, Driman DK: Pathological effects of drugs on the gastrointestinal tract: a review. *Human Pathol* 2007, **38**, 527-526.
22. Sherman A, Bini EJ: Pill-induced gastric injury. *Am J Gastroenterol* 1999, **94**, 511-513.
23. Abraham SC, Cruz-Correa M, Lee LA, Yardley JH, Wu TT: Alendronate-associated esophageal injury: pathologic and endoscopic features. *Mod Pathol* 1999, **12**, 1152-1157.
24. Boyce HW Jr: Drug-induced esophageal damage: diseases of medical progress. *Gastrointest Endosc* 1998, **47**, 547-550.
25. Brunton LL, Lazo JS, Parker KL, Goodman LS, Gilman A: Goodman and Gilman's The pharmacological basis of therapeutics (11th edn), McGraw-Hill, New York 2006.
26. Akamine D, Filho MK, Pere sCM: Drug-nutrient interactions in elderly people. *Curr Opin Clin Nutr Met Care* 2007, **10**, 304-310.
27. Gauthier I, Malone M: Drug-food interactions in hospitalised patients. *Drug Safety* 1998; **18**(6), 383-393.
28. Lis-Balchin M: Current Topics: Serious adverse effects between herbal remedies and conventional drugs taken simultaneously. *J Royal Soc Prom Health* 2002, **122**, 210.
29. Milbury PE, Cao G, Prior RL, Blumberg J: Bioavailability of elderberry anthocyanins. *Mech Ageing Dev* 2002, **123**, 997-1006.
30. Thole JM, Burns Kraft TF, Sueiro LA, Kang YH, Gills JJ, Cuendet M, Pezzuto JM, Seigler DS, Lila MA: A comparative evaluation of the anticancer properties of European and American elderberry fruits. *J Med Food* 2006, **9**, 498-504.
31. Gee JM, DuPont MS, Rhodes MJC, Johnson IT: Quercetin glucosides interact with the intestinal glucose transport pathway. *Free Radic Biol Med* 1998, **25**, 19-25.
32. Paolini M, Pozzetti L, Sapone A, Cantelli-Forti G: Effect of liquorice and glycyrrhizin on murine liver CYP-dependent monooxygenases. *Life Sci* 1998, **62** 571-582.
33. Paolini M, Narillari J, Broccoli M, Pozzetti L, Perocco P, Cantelli-Forti G: Effect of liquorice and glycyrrhizin on rat liver carcinogen metabolizing enzymes. *Cancer Lett* 1999, **145**, 35-42.
34. Gorski J, Huang S, Pinto A, Hamman MA, Hilligoss JK, Zaheer NA, Desai M, Miller M, Hall SD: The effect of Echinacea (*Echinacea purpurea* root) on cytochrome P450 activity in vivo. *Clin Pharmacol Ther* 2004, **5**, 89-100.
35. Barnes J, Andersen LA, Phillipson JD: Herbal medicines (2nd edn), Pharmaceutical Press (UK) 2002.
36. Basch EM, Ulbricht CE: Natural Standard. Herb and supplement handbook – the clinical bottom line. Mosby Inc (USA).2005.
37. Kane GC, Lipsky JJ: Drug-grapefruit juice interactions. *Mayo Clin Proc* 2000, **75**, 933-942.
38. Dollery C: Medicine and the pharmacological revolution. *J Royal Coll Phys* 1994, **28**, 59-69.
39. Kang-Yum E, Kurt TL, Smolinske S: Toxicity and drug interactions of herbs and dietary supplements. *Clin Toxicol* 2006, **44**, 603.
40. Aggarwal A, Ades PA: Interactions of herbal remedies with prescription cardiovascular medications. *Coronary Artery Disease* 2001, **12**, 581-584.
41. Piscitelli S, Burstein A, Weldon N, Gallicano KD, Falloon J: The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis* 2002, **34**, 234-238.
42. Sharma SS, Kochupillai V, Gupta SK, Seth SD, Gupta YK: Antiemetic activity of ginger (*Zingiber officinale*) against cisplatin-induced emesis in dogs. *J Ethnopharmacol* 1997, **57**, 93-96.
43. Yamahara J, Huang QR, Li YH, Xu L, Fujimura H: Gastrointestinal motility enhancing effect of ginger and its active constituents. *Chem Pharm Bull* 1990; **38**, 430-431.
44. Delgoda R, Westlake ACG: Herbal interactions involving cytochrome P450 enzymes: A mini review. *Toxicol Rev* 2004, **23**, 239-249.
45. Rossi M, Negri E, Talamini R, Bosetti C, Parpinel M, Gnagnarella P, Franceschi S, Dal Maso L, Montella M, Giacosa A, La Vecchia C: Flavonoids and colorectal cancer in Italy. *Cancer Epidemiol Biomark Prev* 2006, **15**, 1555-1558.
46. Schaefer HG, Heinig R, Ahr G, Adelman H, Tetzloff W, Kuhlmann J: Pharmacokinetic-pharmacodynamic modelling as a tool to evaluate the clinical relevance of a drug-food interaction for a nisoldipine controlled-release dosage form. *Eur J Clin Pharmacol* 1997, **51**, 473-480.
47. Rapaport MH: Dietary restrictions and drug interactions with monoamine oxidase inhibitors: The state of the art. *J Clin Psychiatry* 2007, **68**, 42-46.