Food and Therapeutic Product Interactions – A Therapeutic Perspective

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INTRODUCTION

Foods and therapeutic products are both used for well defined purposes. In simple terms food provides energy for sustenance, while therapeutic products are taken for managing ailments (1). However, over the years roles of foods have changed considerably. Now, food no longer is seen as simply the provider of energy, but it is expected to provide physiological benefits for good health and productive lifestyles. Well managed combination of foods and therapeutic products plays important role in the prevention and treatment of many diseases, including a number of chronic diseases such as cancer, diabetes, hypertension, obesity. Most often food is combined with medicine to enhance the benefits of medicine - an additive and/or synergistic effect: food-therapeutic product synergism. At the most basic level, food is a complex mixture of chemicals with many functional groups; hence, they not only confer positive effects, but may also make negative contributions. The later effect is of major concerns among the health practitioners and regulatory officials.

The Canadian Food and Drug Act and Regulations through its definitions restrict health-related claims for therapeutic products, foods, and food ingredients. There is no provision in the legislation to make a therapeutic claim for the use of a regulated food. The term, functional food is not defined in the Act and is generally taken to mean a food that is similar in appearance to, or may be, a conventional food, that is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions. A nutraceutical is a product that has been isolated or purified from foods and is generally sold in medicinal forms not usually associated with food. A nutraceutical would usually be a natural health product (NHP) and encompassed within the NHP regulations (http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/regs_cg2_tc_e.html). Therapeutic products are defined as any substance or mixture of substances manufactured, sold or represented for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, restoring, correcting or modifying organic function. Therapeutic products and NHPs will be collectively referred to here as therapeutic products. A substance will be defined here as any entity not covered above or non-therapeutic product that has distinct chemical, pharmacological or toxicological activity such as, but not limited, to environmental contaminants, and social products such as alcohol, illicit therapeutic products and tobacco smoke.

The general public has the perception that foods, and functional foods are natural, and by extension safe. There are numerous reasons why functional foods are used. Among the concerns for many regulatory and public health care workers is that some consumers may self-medicate with these products or other substances when they develop a serious health problem before seeking medical intervention. Some consumers may have a sense that their condition is not being adequately treated when it's actually getting worse and can also self-medicate after seeking medical intervention to supplement their treatment without informing their medical practitioner, opening the door to even more interactions. This self-medication practice may lead to the development of a serious adverse reaction following the initiation of conventional therapeutic product use.

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The event could be an adverse therapeutic product reaction with a noxious and unintended response including resistance at doses normally used or tested for the diagnosis, treatment or prevention of a disease, or the modification of an organic function, or an adverse event which is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily require a causal relationship with this treatment.

There have been several recent reviews on food-therapeutic product interactions (1-10) and the scope of this review is firstly to supplement these reviews with new information that further demonstrates the potential for foods to affect therapeutic product disposition and secondly to discuss critical criteria for conducting clinical investigations.

INTERACTIONS

Spinella (11) has emphasized the additive and supra-additive effects of a plant's multiple constituents as these interactions underpin the philosophy of herbal medicine (12). *In vitro* screening assays with beverages or foods such as beer, garlic, red wine, herbal tea and tea, fruit, and fruit juices have shown the potential for one or more constituents of these products to inhibit an enzyme-mediated biotransformation or protein-mediated transport (13, 14). Cytochrome P450 (CYP) 2C19 inhibition by 18 berry constituents are shown to exhibit moderate to poor inhibitors in a concentration-dependent fashion with IC_{50} values ranging from 20.2 μM up to >316 μM. In decreasing order, anthocyanidins were more inhibitory than anthocyanidin-monoglycosides and procyanidins; anthocyanidin-diglucosides exhibited weak and biphasic effects (14).

The capacity of grapefruit to effect CYP3A4 mechanism-based inhibition and cause clinically relevant interactions is well known, but in some cases it may still be underestimated. An example was the report that grapefruit and tonic water was a deadly combination in a patient with long QT interval syndrome (15). Some therapeutic products such as Class 1A, 1C and II anti-arrhythmics, anti-psychotics, tricyclic/tetracyclic anti-depressants, macrolide and quinolone antibiotics, etc. have been reported to cause QT prolongation and are susceptible to these products. Other patient groups may also be at risk of prolonged QTc from their medications. Guo and Yamaoe (16) noted that grapefruit is not the only food that contains furanocoumarins as it is present in foods from at least four different plant families: Fabaceae (legumes), Moraceae (mulberry), Rutaceae (citrus), and Apiaceace (flowering top – umbrella like). Many of the fruits and vegetables from these families are common but others would be considered ethnic, but in a broad multi-cultural environment would be present. Mechanism-based inhibition is also possible in CYPS: 1A1, 1A2, 2A6, 2A13, 2B1, 2B4, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4/5 (17). Sakamaki et al. (18) determined that differing amounts of the furanocoumarins (FCs) bergamottin (BG), bergaptol (BT) and 6',7'-dihydroxybergamottin (DHB) were present in grapefruit juice (n=13), citrus fruit (n=20), and health food (n=16). These results suggest that patients prescribed critical, narrow therapeutic index therapeutic products should be cautious about their intake of grapefruit juice, citrus and health foods with their medications.

Two studies examining various fruits for inhibition of CYP3A-mediated metabolism found similar trends. In the first study inhibition by grapefruit juice (GFJ*) > black mulberry* > wild grape* > pomegranate* > black raspberry* was noted. The second study examined different fruits and found inhibition by star fruit > pomegranate* > papaw ≥ GFJ* >> orange > mango > rambutan > kiwi > dragon fruit ≥ passion fruit (19). The noteworthy observation here is that the relative position of pomegranate differed. This may have broader clinical implications as noted by the case report of a 48-year-old man with myopathy treated with ezetimibe 10 mg/day & rosuvastatin 5 mg every other day for 17 mo. who consumed pomegranate juice (200 ml twice weekly / 3 wks) before presenting urgently with thigh pain and increased serum creatine kinase level (138,030 U/L, normal < 200 U/L) (20). Pomegranate juice consumption in male mice for 4 weeks decreased total hepatic CYP content as well as the expression of CYP1A2 and CYP3A (21). Pomegranate but not apple, peach, orange, pineapple, grapefruit juice potently inhibited the sulfoconjugation of 1-naphthol in Caco-2 cells in both a dose- and culture time-dependent manner (22). The star fruit (*Averrhoa carambola*) juice inhibitory effect towards different CYP isoforms were in the following order: CYP2A6 > CYP1A2 > CYP2D6 >

CYP2E1 > CYP2C8 > CYP2C9 > CYP3A4 (23). Time-dependent inhibition was not observed. Apple, grapefruit and orange juice decreased human organic anion transport polypeptide (OATP) activity resulting in lowered fexofenadine AUC, C_{max} and urinary excretion values (24). Grapefruit and orange juice inhibited human embryonic kidney 293 cell OATP2B1- mediated uptake of estrone-3-sulfate and glibenclamide and also inhibited estrone-3-sulfate uptake (25).

A patient on warfarin ingested 300-600g of fiddleheads containing (170 :g vitamin K1 per 100 g) had a lowered International Normalized Ratio **(**INR) which resulted in hospitalization (26). Griffiths et al. (27) report a case of fatal internal haemorrhage in an elderly man who consumed only cranberry juice for two weeks while maintaining his usual dosage of warfarin. Variegatic acid and xerocomic acid, pulvinic acid derivatives, isolated from edible Chinese mushrooms *Boletus calopus* and *Suillus bovines* had nonspecific inhibitory effects on CYP1A2, 2C9, 2D6 and 3A4, comparable to cimetidine, dicoumarol, erythromycin, safrole, and uniconaole (28). Food products are known to affect phase II UDP-glucuronosyltransferase and PAPS-sulfotransferase pathways (29). Continual exposure to chrysin and quercetin present in fruits and vegetables induces UGT1A1.

Omega-3 polyunsaturated fatty acids present in fish oil, flax seed and hemp have been advocated for use in hyperlipidemia, coronary heart disease, hypertension, and other conditions. In a case report, a patient developed a subdural haematoma after a minor fall requiring craniotomy that likely was precipitated by concomitant use of high-dose omega-3 fatty acids 6 g/d with both aspirin and warfarin (30). In a second report, a 67-year-old white woman had been taking 1.5 mg/d warfarin for 1.5 yr due to recurrent transient ischemic attacks. The patient doubled the fish oil dose from 1 to 2 g/d, and the INR increased from 2.8 to 4.3 within 1 month (31). The INR decreased to 1.6 one week after subsequent fish oil reduction, and she was returned to the original warfarin dosing regimen. There have been concerns for using omega-3 fatty acids in fish or flax seed oil with therapeutic products such as warfarin (32). Here, authors postulate the inhibition of CYP2C9 by omega-3 fatty acids decreased warfarin metabolism, allowing higher amounts (toxic) of warfarin in plasma.

Currently, there is great emphasis on the use of products derived from barley, flax, pulses, oat, soy as part of diet because they all contain non-nutritive components with added physiological benefits. For example, flax, pulses and soy contain phytoestrogenic compounds such as isoflavones, lignans, proteins, and omega 3-PU fatty acids.

Similarly, it has been reported that regular consumption of soy in diet has been responsible for lower incidences of cancer in Asian countries, and that genistein, one of the major isoflavones may be the source of this reduced incidence (33). Several soybean varieties have been shown to have modest potential to inhibit CYP3A4-mediated metabolism (13). The aglycone, genistein but not the glycone genistin inhibited CYP3A4/5/7-mediated metabolism (13). However there are reported cases of interactions of genistein with therapeutic products such as tamoxifen; and practitioners are cautioning post-menopausal women consuming dietary genistein while on tamoxifen (34). Similar examples may be found for other highly touted agri-foods. The mechanisms for interaction are not known in most cases, however. These results suggest that the concurrent use of some foods with other substances that are handled by the same enzyme and transport systems can have important safety and efficacy implications. Such *in vitro* findings should not be overly extrapolated. The results suggest that acute exposure may have an inhibitory *in vivo* effect. The caveat is that a bioactive in an *in vitro* system, where there is constant exposure, may not be bioavailable in an *in vivo* system, or that the pharmacokinetic characteristics of the bioactive would restrict it from having a pronounced pharmacodynamic effect.

There is some confusion in the literature where an attempt at such a correlation of *in vitro* results appears contradictory to the clinical findings, particularly when there has been chronic or repeated exposure to the food or therapeutic product where there may be up-regulation or induction of these mechanisms. This form of classic biphasic response is well known where initial inhibition or blockage by a substance can lead to up-regulation (induction) with constant exposure.

The US Food and Drug Administration guidance on therapeutic product interaction studies does not include a specific section on contributions

of metabolites to observed inhibitory therapeutic product-therapeutic product interactions (35). A literature analysis identified 129 inhibitors, 106 of which had circulating plasma metabolites. Among the 21 potent inhibitors with a 5-fold or greater increase in area-under-the time concentration curve (AUC), 17 had circulating metabolites, and the remaining four were all extensively metabolized. It is noteworthy that *in vitro* evaluation of inhibition potential was conducted for only 32% of these circulating metabolites suggesting a need for increased effort to characterize the inhibitory potency of metabolites of new therapeutic products.

RISK DETERMINATION

As with therapeutic products, an adequate pre-marketing investigation of the safety and efficacy of a food or nutraceutical that may be taken in the presence of a therapeutic product should include characterization of the metabolism of the major active component(s) and exploration of its interactions with other substances and therapeutic products that may affect the safety and efficacy of the product (Table 1).

Interactions with foods are confounded by their complex nature and in many instances difficult to ascribe to the product and may enhance the known adverse events of a therapeutic product after one or many doses. In addition, products can demonstrate toxicity that are pharmacologically predictable and dose dependent. Idiosyncratic toxicity is also possible with reactions which cannot be predicted on the basis of pharmacological properties, and are generally not dose dependent but are often serious and fatal. Some products can have both types of toxicity.

Pharmacokinetic interactions can occur at various levels such as changes in activity of the metabolic enzymes (Table 2) and transport proteins. Of the metabolic enzymes, the cytochrome P450 (CYP450) isozyme-mediated metabolism is the most important to the disposition of bioactives. P-glycoprotein-mediated transport is the major efflux transport mechanism but there are many other Phase 0 and II transporters that should be considered in the determination of risk interactions. CYP1-3 are directly associated with the metabolism of therapeutic products and other substances, with CYP3 being the most important and/or active for disposition. However, these are just 3 of the 18 human CYPs that occur in 57 genes and 58 pseudogenes. It is highly likely that other CYPs may also be involved in adverse events. Variations in enzyme and transport protein expression can occur as a result of polymorphisms and this can affect clinical outcome.

Risk identification and assessment require that hazards are identified and stratified in terms of evidence, probability and significance. There are a number of problems and challenges in interpreting the NHP safety literature, such as the poor documentation or characterization of the NHP in case reports and clinical studies; an adverse event may be based on only one report and studies may have been reported with pure compound rather than whole extract or botanical. The situation is further confounded by the question of phytoequivalence where the results of one study with one product are extrapolated to all similar products, even though they may be significantly different (36). Much of the clinical literature is based on proprietary extracts with known chemistry and clinical pharmacology. Data from such trials may not be relevant to other botanical preparations as many proprietary products are chemically distinct and defined. Hence, findings of one study with one product cannot be extrapolated to all similar products. Evaluation then requires structured risk assessment of interactions of the information available or required by examining the quality of evidence and clinical relevance.

Table 1. Interactions: risk versus harm. Key questions to ask regarding food interactions.

- Is the potential interaction real or theoretical?
- Are clinically noticeable interactions mild or serious?
- Will a substance alter exposure to other therapeutic products?
- Will other therapeutic products alter exposure to the substance?

Table 2. Metabolic enzymes that may play a role in therapeutic product-food interaction

Phase I

- Cytochrome P450 isozymes (1A1/2, 2B6, 2C9/19, 2D6, 2E1, 2J2, 3A4/5/7, 4A, 19)
- Dehydrogenases (alcohol, aldehyde)
- Epoxide hydrolases
- Esterases (serum cholinesterase, paraoxonase)
- Flavin-containing mono-oxygenease
- Monoamine oxidase
- S-oxidases (aldehyde and xanthine)

Phase II

- Glutathione S-transferases
- N-acetyltransferases
- N-acyltransferases (amino acids)
- N-, O-, S-methyltransferases
- Sulfotransferases
- UDP-**glucuronosyl** transferases

There are many intrinsic factors such as age, gender, health status, weight, ethnic group and/or race and extrinsic factors including diet and nutrient intake, duration of use, response on re-challenge and social products (alcohol, illicit therapeutic products, tobacco) which may make one person or a population at risk of an interaction leading to the development of an adverse event. Stress, such as family or work related, holidays, travel, or out of the ordinary events or disease may change the safety and efficacy of these products.

It was noted that many antimicrobials are taken with food to reduce gastro-intestinal adverse events and that the food may not be reflective of that used in clinical trials. Currently, most therapeutic products undergoing clinical testing for approval would include a food effect study using the FDA-mandated high-calorie (1000 calories) and high-fat (50% of total caloric meal content) nutrient poor diet to determine if "food" affects the pharmacokinetic parameters. However, this diet may be markedly different from standard diets for many patient groups and those who follow a culturally distinct non-western diet (37). Many of the foods taken may now be fortified with dairy, fruits and vegetables high in anti-oxidants (flavanoid botanicals, etc), fibre, various minerals, or vitamins that would not necessarily be observed in the standard clinical trial diet. Fluroquinolones are known to interact with products containing multivalent ions (37, 38). In a three-way randomized cross over study in 15 healthy volunteers, oral ciprofloxacin (500 mg) was administered with 12 ounces of water, orange juice or with calcium-fortified orange juice. Orange juice and calcium-fortified orange juice significantly decreased the Cmax by 23% and 41% relative to the control, respectively. The 24 hr AUC values were decreased by 22% and 38% for both forms of juice. The ciprofloxacin dose between the two juice arms was not bioequivalent. The calcium fortified juice contained more calcium than an equivalent serving of whole milk. The authors postulated that despite good compliance, this decrease in plasma concentration may have no clinical effect or result in pathogens being sub-inhibited that may result in therapeutic failure and the possible development of therapeutic product resistance.

Fortification of foods with multivalent cationic minerals such as aluminum, calcium, iron, magnesium and zinc may result in chelation and adsorption interactions that may cause decreased absorption (39). The polyvalent ions may also result in changes in gastric and urinary pH, and non-specific absorption effects that can change therapeutic product plasma levels. The quinolone, tetracycline and cephalosporin classes of antibiotics are affected by multivalent ion chelation and food-tetracycline interactions that are well known (39). Renal clearance will be altered with changes in

urinary pH. The ionization and dissolution of organic acids is increased with a corresponding increase in gastric pH, resulting in an inverse reduction in absorption due to decreased passive mucosal membrane diffusion. Weakly basic therapeutic products are affected in the opposite direction. Antacids may increase the absorption of some non-steroidal anti-inflammatory therapeutic products (NSAIDs) but the literature is confounded suggesting that the interactions may be product and cation specific, precluding a simple encompassing concept**.**

The high fat FDA breakfast diet used to determine if there are food effects on the pharmacokinetics and efficacy of a therapeutic product may not be clinically relevant for all patient groups. A typical cardiovascular disease or irritable bowel disease patient community breakfast may consist of fresh fruit, cereal (such as muesli supplemented with wheat bran and ground flax seed) with 1% or less milk fat milk or yoghurt. Food studies need to take into consideration the medications, both conventional and alternative, that may be used by the target population to determine if there are real or potential interactions.

PRODUCT CHARACTERIZATION

There is a large number of foods available in multiple formulations ranging from capsules, cereals, creams, juices, oils, tablets, teas to tinctures. The differing physico-chemical properties of these substances require diligence during examination (Table 3). Each manufacturing process may affect the chemical composition of each product making the number of products available for consideration prohibitive. The pharmacodynamic active substance or substances may not be the same substance or substances which can affect pharmacokinetic or disposition; they are effecter compounds but with different activities. There may be competing antagonistic and synergistic interactions occurring simultaneously within the food.

Foods are highly complex products that cannot be standardized to the extent found in conventional therapeutic products. At best, some products can be characterized for a limited portion of their content. This is partly due to many botanical constituents existing as free (aglycone) and conjugated (glycone) compounds that may be acidic, basic, and neutral substances. Some will be hydrophilic or hydrophobic and have different extraction coefficients or boiling points so that multiple extraction protocols may be required to determine the true activity of the product. Many of these constituents will have different stabilities and solubilities**;** some will be labile to heat, light, heavy metals, solid surfaces, pH, and oxygen. In addition, the active constituent may be present in low concentrations that will vary with varietal differences and chemotypes, climate (humidity, rain, and temperature), regional and seasonal effects, and whether the product is used fresh or processed and stored under differing conditions.

For single ingredient botanical preparations, information on the raw material and final preparation is needed. For multiple ingredient botanical preparations identification and quality information is needed for each individual ingredient, as well as for the mixture as a whole. In many cases the bioactive component is the glycone (pro-therapeutic product) that is metabolized/hydrolyzed to the active metabolite.

DISPOSITION STUDIES

The principle routes of absorption, metabolism, distribution, and excretion of a substance play an important role in the potential for a therapeutic product – food interaction. The relative pharmacodynamic activity of the parent compound and its metabolites that may impact the clinical significance of this interaction can be mediated by a multitude of intrinsic and extrinsic factors. Additional factors that can increase the likelihood of a therapeutic product interaction include disposition via a single pathway, acute or chronic administration having inducing or inhibitory effects, steep dose-response curves or narrow therapeutic ranges, and if the constituent or substance or a metabolite of the compound has non-linear pharmacokinetics. For example grapefruit furanocoumarins (psoralens) are inhibitors of multiple CYP450 isozymes and as a result shunting can increase the risk of toxicity from a newly created or previously insignificant metabolite.

Table 3. Summary of guidelines for examining food and functional foods for interactions modified from the US National Centre for Complementary and Alternative Medicines Guidelines. (http://nccam.nih.gov/research/policies/clinical-considerations.htm)

1. Label information; include product name (scientific taxonomic nomenclature (e.g., genus, species, variety-if applicable) and author citation), product size and use/dosing information, Natural Product Number or Therapeutic product Identification Number. List any other ingredients and excipients.
2. Manufacturer and distributor (if different).
3. Archive information
4. Macroscopic parts (organ, tissue, or fluid).
5. Geographic source of the material, time of harvest, credentials of the person who collected and/or identified the material (if possible).
6. If an extract is being used for testing, provide details on the extraction procedure (e.g., solvent(s) used, ratio of starting material to finished extract, time and temperature employed, type of extraction, whether fresh or dried material was used, whether any excipient (non-medicinal) materials were added, what percentage of the extract is native extract, and what percentage is composed of excipients).
7. Active and/or other relevant marker compound(s) used for standardization.
8. Characterization (e.g., chemical profile or fingerprint) of the product and detailed analytical method(s) used.
9. Any other standardization information (including process control, as well as chemical and/or biological standardization of ingredients).
10. Analysis for contaminants, such as pesticide residues, heavy metals, toxic elements, mycotoxins, microorganisms, and adulterants.
11. Specifications and Certificate of Analysis to show compliance to specifications for purity and content from the supplier/manufacturer or other supporting manufacturer information, relating to the batches to be used in the study.
12. Stability (short- and long-term), following pharmacopoeial methods.
13. Storage conditions appropriate for assuring stability during the life of the study and how you plan to store the test agent.

Substances which act as inhibitors can decrease the activity of protherapeutic products (including botanical glycones or other conjugates) that are converted to an active form. Inhibitors can also enhance the pharmacodynamic activity where there would otherwise be metabolic deactivation. Conversely, inducers can increase the activity of pro-therapeutic product metabolites and decrease the activity of constituents and substances inactivated by metabolism, which could lead to therapeutic failure. When multiple compounds are found within a single product, complex interactions may occur and may be difficult to isolate.

Pharmacodynamic and Pharmacokinetic Interactions

As foods are a complex mixture of different constituents, the potential exists to alter the pharmacodynamic, pharmacokinetic and clinical response obtained with a therapeutic product. Interactions can be attributed to changes in the pharmacodynamic and/or pharmacokinetic profiles of the individuals' compound and metabolites. In the case of pharmacodynamic interactions, the response to the compound is altered without effecting the plasma concentration, while in pharmacokinetic interactions altered levels of exposure affect the absorption, distribution,

excretion or transport of the compound and/or its metabolites. Inhibition and induction can affect both pharmacodynamic and pharmacokinetic based therapeutic product interactions and it is noteworthy that some compounds which are initially inhibitory can become inductive after repeated administration.

Some foods can affect pharmacokinetic and pharmacodynamic therapeutic product interactions by modulating gene expression at a molecular level by affecting transcription, mRNA processing, export from the nucleus, rate of translation, and half life of mRNA and polypeptide products (40). Epigallocatechin gallate has been shown to be an inhibitor of the proteolytic activity of the proteasome; this inhibition has a significant implication for cell proliferation and the stability of transcription factors in the nucleus. Zinc-containing nuclear receptors have been shown to interact with steroids, hydrophobic hormone molecules, and xenobiotics and potentially result in PXR and CAR effects. Epigenetic changes are now being identified that can also alter gene expression (41). To avoid food-mediated therapeutic product interactions, concentrations of substances in food products should be considered.

Choice of Substance Range

Clinically relevant amounts of the potential interactant may not occur naturally in a food product and an interaction may not occur unless there are increases in the exposure as well as the length and frequency that the interactant is consumed. In some instances, the interactant may reach significant amounts through consumption from several sources**.** Nabekura et al. (42) reported on the *in vitro* effects of the dietary phytochemicals capsaicin, found in chilli peppers, curcumin in turmeric, 6-gingerol in ginger, resveratrol in grapes, sulforaphane in broccoli, 6-methylsulfinyl hexyl isothiocyanate (6-HITC) in Japanese horseradish wasabi, indole-3-carbinol (I3C) in cabbage, and diallyl sulfide and diallyl trisulfide in garlic, on P-glycoprotein function in human multitherapeutic product-resistant carcinoma KB-C2 cells, using the P-glycoprotein substrates daunorubicin and rhodamine 123. Capsaicin, curcumin, 6-gingerol, and resveratrol (in a concentration-dependent manner) increased daunorubicin and rhodamine 123 accumulation in KB-C2 cells. Sulforaphane, 6-HITC, I3C, and diallyl sulfide and diallyl trisulfide had no effect. Alone, these constituents may not have a clinical effect, but when consumed together in a meal such as a curry served with a glass of red wine, the effect is not known.

Many food-therapeutic product interactions occur as a result of concentration-dependant effects on metabolic pathways. *In vitro* interactions may provide mechanistic information which requires confirmation by an *in vivo* study. Conversely, *in vitro* studies may produce interactions that are not observed *in vivo* due to concentration-dependant metabolic pathways. In order to determine if a specific food-therapeutic product interaction is possible, the food component and therapeutic product should be given at their highest recommended doses for a period of time consistent with their intended use by the consumer or patient. A negative study may mean there is no real or perceived potential for an interaction; or it may simply mean no interaction was observed within the parameters of the study (36). The limitations of the study and the applicability of the results to realistic levels of substances found in foods should be considered. Clinically relevant concentrations may be identified for many therapeutic products but dose-ranging studies will be required for extracts from food. Some studies have examined the relative amounts of these but it is also clear that some consumers may eat more than one serving of a bioactive containing food at a sitting (39).

Role of Animal Studies

Caution is advised in extrapolating results from animal studies as results may not be applicable to human systems. Differences in metabolizing enzymes and transport proteins may result in different reactions between and among species. Studies in animal sub-cellular fractions and cell lines and studies with transgenic animals for heterologous expression may provide preliminary data but the applicability of such findings to humans may be problematic.

Clinical Studies

In addition to the points mentioned above, there are many factors to consider when designing human clinical studies. A trial must reproduce the conditions that produce the effect, be it an interaction or health promoting benefit to be

studied. *In vitro* studies and many animal studies have extended contact periods so that the pharmacological level does not fall below the threshold required for a response. Hence, in the case of interactions with food and therapeutic products, reproducing conditions that can produce the interaction can be a challenge and require different test strategies from those normally used in therapeutic product interaction studies.

In addition, consumers and patients may not be compliant if a product needs to be taken in larger amounts over an extended period of time. The Canada Food Guide provides details on recommended amounts of foods in different products and should be consulted in the development of testing protocols. If the active pharmacological constituent is present in more than one food, consideration should be given to alternate dietary supplementation to retain interest and promote compliance in the supplements in order to promote higher compliance.

The study must be for an appropriate length of time to produce the reaction to be studied and repeated if the duration was short or if maximal conditions were not employed. The study must consider the end use of the product in question and be relevant with respect to the recommended use of the product in the Canada Food Guide (http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php).

The specific parameters for safety monitoring, including when to take blood samples and which systems to monitor for adverse events, must be considered. For example, immunological reactions can occur with mechanism-based inhibition of CYP450.

The study design should have the required precision and power to detect the desired effect using established, validated, markers and it must be appropriate for the type of study being conducted as study design and data analysis are key to determining the exposure response and other important information for proper labelling. Appropriate pharmacokinetic parameters must be determined for the putative active substance in the food and, where possible, should include the pharmacokinetic of the parent therapeutic product and its major metabolites. The selection of pharmacokinetic parameters is also dependant on the intended route of administration and proposed dose of the test therapeutic product. These should correspond to the final recommended dose and route of administration and dose ranging studies may be required to fully characterize the dose-dependency of an interaction.

Due to the difficulty in isolating active substances in food and the numerous confounding factors in this type of interaction study, exclusion criteria need to be re-evaluated. Studies need to consider the dietary habits of the targeted consumer or patient population. The selection of food products to consider for interactions is broad, since in theory, all foods have the potential to interact if taken in sufficient amounts. To establish baseline dietary intakes and reduce the risk of interactions, healthy study volunteers should not use prescription or over-the-counter products, or consume any food or beverage that may affect therapeutic product disposition from at least two weeks prior to the start of the study until its conclusion. This would include alcoholic beverages, any food or therapeutic product containing the ingredient under examination, grapefruit, most fruit juices, vegetables such as the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats. Foods known to contain mechanism-based inhibitors of CYP450 enzymes such as ginger, liquorice and peppers are clear choices for exclusion. Other fruits and vegetables such as legumes (beans, peas), breadfruit, fig, jackfruit, lime, orange (Seville orange & juice variety), prickly ash, carrot, celery, dill, fennel, parsnip, Baihi (*Angelica dahurica* root), Hamaudo (*A. japonica*), Qianghuo (*Notopterygium incisum*), Fangfeng (*Saposhnikovia divaricata*) should also be excluded (43).

Clinical studies for products intended for specific patient populations should consider diets that are normal within the patient population and not impose a presumed diet that may not be relevant. Clinical studies with healthy subjects may identify the potential for an interaction but as inflammation and hormonal changes can affect disposition, safety and efficacy studies are required in the intended patient population to fully characterize this potential.

Social factors such as the cultural cuisine of a patient population and the most commonly consumed foods on a national basis may also be useful criteria for selection. If the food product is

already selected, the study population may be the group for whom the product is intended.

Analysis of the patient population, their health status, food consumption patterns, and genotype is important in development of a study design though it should be remembered that findings from studies in homogenic populations cannot necessarily be extrapolated to the population as a whole. International Conference on Harmonisation (ICH) Guidelines on General Considerations for Clinical Trials (E8), Good Clinical Practice (E6(R1)), and, if appropriate, studies in the elderly (E7) and paediatric populations (E11) should be consulted (http://www.ich.org).

CONCLUSION

The risk of serious adverse events from food interactions with therapeutic products is real; the risk for most subjects will be low and dependent upon the number of products used and the state of health. In general those at most risk are those who are least able to handle the extra stress. The pharmacokinetics of a bioactive will greatly depend on the age, genetics/metabolic capacity, nutrient-gene interaction, body mass index, health condition and food matrix. International travel may require changes in medication regimens to maintain efficacy and safety. Interactions from a large amount of a single polyvalent ion or food constituent or small amounts of multiple polyvalent ions or food constituents may have the same serious consequence, including therapeutic failure, therapeutic product resistance, necessity for frequent dose changes, or increased morbidity and mortality (39).

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