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Urgent Demand of the Continual Studies of Drug-Nutrition-Interrelation.

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ABSTRACT

There are many combinations of drug-drug interactions that have been extensively cited in the literature; on the other hand different food-drug interactions exist and can have serious negative effects on health which must not be discarded. During the present review different points were discussed including effect of drug administration on food utilization, nutritional status and appetite such as effect of drug on eating behavior or macronutrient specific dietary selection and nutrients absorption and metabolism. Effect of drug on vitamin needs, nutrient-nutrient incompatibilities, impact of anti-inflammatory drugs on nutritional status and effect of slimming drugs on serum minerals during consumption of different food were reviewed. Also, effect of the food consumed and nutritional status on the efficiency of drugs was dealt with; such as influence of the type of food, malnutrition and obesity on drug absorption, blood levels and efficiency. Nutritional effect on drug-protein binding in plasma, systemic reactions induced by drug-food incompatibilities and effect of different nutrients on drug biotransformation were discussed. Among the important points which were reviewed id to what extent the consumption of food or nutrient may affect the drug dosage. The present review highlighted the various bioactive components of food that possess medicinal effect.

Keywords: Drug, food, mutual interaction, bioactive food components.

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INTRODUCTION

Drug-nutrition interaction is an old and simultaneously new subject that requires continuous investigations and search due to the increased discovery of new drugs and bioactive constituents from food. Studies concerned with nutrition and drug interrelations are very important. This is because drug may be harmless under optimal nutritional circumstances but may be deleterious when nutritional intake is inadequate or imbalanced. The type and timing of food may affect drug absorption and metabolism; consequently affect the therapeutic efficiency of drugs. On the other hand drugs may impair nutrients absorption and utilization thereby may induce some sorts of malnutrition. So, mutual effect of drug and food must not be ignored.

Drugs control eating behavior and micronutrient specific dietary selection

Neural basis of nutrient-specific appetites will remain unknown, however some data are available. d-nor fenfluramine, fluoxetine which stimulate synaptic 5HT reduce food intake specially carbohydrates (dextrin containing diet) and negative feedback loop exists [1]. Chronic dexfenfluramine suppresses fat intake independent of the preferred macronutrient [2]. Phentermine, diethyl propion (amphetamine like drugs acting by catecholamiergic mechanism) and thyroxin reduce food intake specially high fat-low sucrose diet more than low fat-high sucrose diet [3, 4]. Reduction of fat intake during administration of the previously mentioned slimming drugs is certainly very important in obese subjects since fat provides higher calories (9 Calories) than carbohydrate and protein (4 Calories). Cyproheptadine (an appetite stimulant) block serotonin in the hypothalamus thereby increases caloric intake but had no effect on the relative contribution of macronutrients. The number of eating meals increases without change in meal size [5]. On shifting diet from high fat-low carbohydrate to low fat-high carbohydrate, aspirin induces increase in food intake [6, 7]

Effect of drug administration on nutritional status

Drug users were more likely to be exposed to increasingly severe food insufficiency problems. A survey was carried out showed decreased consumption of vegetables, fish, and baked, boiled and steamed food and generally meals with increased consumption of fried food, sweet and desert in drug users. In non drug users, normal consumption of vegetables, fried food, sweet, desert and meals with increased consumption of fish and baked, boiled and steamed food were noticed. Drug users generally maintain poorer nutritional status than non-drug users. So, nutrition interventions as part of drug treatment are needed [8].

Nausea and/or vomiting are adverse side effects of cancer chemotherapeutic drugs in adult as well as pediatric cancer patients. In addition food aversions and immunomodulation are interpreted as conditioned responses [9, 10]. Up to 50 % of patients with cancer suffer from weight loss and undernutrition which when combined with chemotherapy would be worsened, effective nutritional care could improve such condition [11].

Drug administration may affect nutrients' absorption and metabolism and thereby may induce malnutrition. Example of such drugs is cholestyramine which induces malabsorption of Fat and vitamin A, D, K and E. through sequestration with bile salt. It also reduced absorption of Folic acid and B12 by Resin binding or adsorption. Vitamin K deficiency and bleeding could occur after long-term use of cholestyramine [12]. Also, colestipol reduced the absorption of Fat soluble vitamins by sequestration of bile salt [13, 14] The mechanism of action of cholesterol lowering drugs (cholestyramine and colestipol) involves mainly sequestration with bile salts with consequent reduction of fat absorption which is a required effect of such drugs while malabsorption of vitamins is unwanted effect. This unwanted effect may be overcomed by supplementation of fat soluble vitamins after elapsing a considerable time from administration of the cholesterol lowering drugs. Antacid $Al(OH)_3$ produced P, Ca and Vitamin A malnutrition through increased fecal excretion and precipitation of bile salts. The mechanism may also involve minerals sorption on aluminum hydroxides [15]. Mineral oil such as liquid paraffin that used for treatment of constipation induced Vitamin A, D and K malnutrition since the vitamins dissolve in the non absorbable lipid phase and excreted [16]. This may be only mild effect in case of short term administration however severe malnutrition may be manifested only in case of prolonged use. Neomycin and kanamycin (aminoglycosides) induce Fat, nitrogen, cholesterol, sugars, carotene, iron and vitamin B12 malnutrition (Kanamycin has lower effect on fat absorption) through interference with the action of bile salts, decrease pancreatic lipase, toxic effect on intestinal mucosa and inhibition of intestinal

disaccharidase. Neomycin also reduces the bioavailability of vitamin A [12, 17]. Colchicine, an anti-inflammatory drug that used in gout, induces mal-absorption of Na, K, fat, Nitrogen, sugars and vitamin B12 due to toxic effect on the villi, microvilli, irreversible inhibition of disaccharidase by depression of brush border [12, 18]. P-aminosalicylic (antituberculus) induce mal-absorption of fat, fat soluble vitamins, B12, d-xylose. The prevention of vitamin B12 absorption occurs through interference with illial receptors. Biguanides (metformin, phenformin) reduce vitamin B12, sugar and Na due to decrease jejunal disaccharridase and interference with illial receptors. Administration of K Cl produces vitamin B12 malabsorption by interference with illial receptors. Phenindione an anticoagulant, and mephenamic acid an analgesic drug induce mal-absorption of fat and fat soluble vitamins [19]. Mefenamic acid causes functional impairment of red cell membrane which could be prevented by supplementation of vitamin E that has protective role in maintaining normal red cell functions [20]. Sulfasalazine induces folate malabsorption [21]. Administration of prednisone that converted to prednisolone in the liver, an anti-inflammatory glucocorticoid induced malabsorption of Vitamin C, vitamin B6, vitamin D and folate. Cellulose Phosphate that used in case of hypercalcemia reduces Ca and Mg absorption due to its ion exchange affinity to divalent cation [22], malabsorption of Ca is a required action of the drug.

Drug may not only affect nutrient absorption but may also affect its bioavailability thereby nutrient need arise. Some drugs may induce vitamin needs or reduced their blood levels. Oral contraceptives induce the needs of folacin, vitamin B6, riboflavin and vitamin C [23]. Anticonvulsant increased the needs of folacin, vitamin B12, vitamin D and K [24, 25]. Increased vitamin D needs in children given anticonvulsants may lead to rickets. Spironolactone a potassium sparing diuretics induces needs for vitamin A supplement [26]. Methotrexate an anti-cancer and immunosuppressive drug and pyrimethamine an antifolate anti malarial drug increased the needs of folacin [27, 28]. Altered efficacy of sulfadoxine-pyrimethamine on supplementation of folic acid was not observed and did not contribute to adverse events [29]. Biguanides administration increased the needs of vitamin B12. Isonicotinic hydrazide an anti-tuberculosis, penicillamin used to prevent copper absorption in Wilson's disease, L-dopa used in Parkinson's disease increase the needs of vitamin B6 [30, 19]. Phenylbutazone that used under special supervision to treat ankylosing spondylitis and which have toxic effect on the heart increased the needs of niacin [31]. Aspirin administration increases the needs of vitamin C. Prolonged use of acid-suppressing drugs such as cimetidine, ranitidine and omeprazole can lead to a serious vitamin-B12 deficiency [32].

In many cases nutrients are administered in form of pharmaceutical preparations as dietary supplement, so the dose must be in the recommended level. Megadoses of vitamin E produce reduction in vitamin K level since the metabolite of vitamin E, tocopheryl hydroquinone, works as antimetabolite for vitamin K resulting in prolongation of prothrombin time that induces an increase in coumarin, warfarin Na anticoagulant effect [33]. Vitamin C administration in a dose of 1 g/day reduces the level of serum vitamin B12 [34]. However nutrient-nutrient interaction may lead to beneficial effect. A study in cholestatic infants that are deficient in fat soluble vitamins showed that supplementation of oil rich in medium chain triglycerides concomitantly with vitamin E produced significant improvement in serum level of vitamin E, and vitamin E: total lipid ratio [35].

Administration of some anti-inflammatory drugs may induce changes in nutritional parameters including body weight, food intake, protein efficiency and serum protein. Aspirin and methyl-prednisolon reduce protein efficiency ratio [36, 37]. Methyl-prednisolon reduces body weight gain and food intake in normal and adjuvant arthritic rats [38]. Serum albumin is significantly reduced on administration of prednisolon with diet containing 10% protein while no change on serum albumin is noticed with 20% protein diet [39]. Declofenac administration did not affect body weight or food intake however it reduced serum albumin level [39].

Administration of anorectic drugs may induce changes in serum minerals during consumption of different diets. Administration of phentermine with high sucrose diet produced reduction in serum Ca and Mg while its administration with high butter fat produced no change in serum Ca level with reduction of Mg. Treatment with diethylpropion with feeding high sucrose diet produced reduction in Ca and no change in Mg occurs and P while on feeding high fat diet reduction of Ca and Mg with increased P level [40].

Effects of the type and timing of food and nutritional status on the efficiency of drugs

The study of the effects of drugs comprises two divisions; pharmacokinetics (is what the body does to the drugs) (The absorption, distribution, metabolism and excretion of drugs) and pharmacodynamics which is what drugs do to body (The biological and therapeutic effects of drugs).

Drugs are absorbed after oral administration as a consequence of a complex array of interactions between the drugs, its formulation and the gastrointestinal tract contents. The presence of food within the GIT affects Transit profile, pH and solublizing capacity of drugs. Consequently, food is expected to affect the absorption of the co-administered drugs when their physicochemical properties are sensitive to these changes [41].

The effect of food on drug absorption may involve the water and lipid solubility of the drug, the nature and temperature of the food, formation of drug-food precipitates and the effect of food on the gastrointestinal ph, motility and blood flow. Intestinal absorption of many drugs is slowed by concurrent food intake, either because of delayed gastric emptying or because of dilution of the drug in intestinal content. The absorption of aspirin, barbiturates, penicilins, the antibacterial lincomycin, propanthine bromide that used for treatment of peptic ulcer, tetracycline, and demethyl chlortetracycline increase on fasting state. Although Gastric absorption of acidic drugs such as aspirin is reduced after food but it is preferred to be given after food to minimize its side effect on stomach but the diet must be balanced one. Absorption of Nitrofurantoin (macrocrystalline) that used in urinary tract infection increased in fed state. Absorption of The anti-fungal griseofulvin decreases in fasting state and increases with high fat diet since it is a lipophilic drug. Theophylline (bronchodilator) absorption increases in fasting state and decreases on feeding high fat and high carbohydrate meal. Absorption of Sulpha drug: Sulpha-dimethoxine, Sulpha-methoxypyridazine, sulpha-isoxazole decrease in fed state. Sulpha-salazine absorption decreases when given with iron salts. It is to be noted that sulphasalazine is effective in preventing relapse of ulcerative colitis. The drug splits by colonic microflora into sulphapyridine and 5-amino salicylic acid. The active moiety is 5-amino salicylic acid which is not absorbed. Sulphapyridine is well absorbed and may only supply adverse effect which is RBCs haemolysis. Milk and dairy products can inhibit the absorption of certain blood pressure medications and antibiotics, consequently reducing their effectiveness. So, these products may be taken at least one hour before or two hours after taking the medication [42]. It was suggested that soy can slow thyroid function, and can interfere with thyroid medications. Alcohol soluble components other than the major isoflavones in soy remarkably inhibited iodide uptake in the Fischer rat thyroid cells. Soy isoflavones, particularly genistein, induced the production of P40 a known autoimmunogen, which might be responsible for the higher incidence of autoimmune thyroid disease reported in soy infant formula-fed children [43]. However, Silverstein et al. [44] proved that Dietary soy increases triiodothyronine in preovariectomized monkeys and prevents a decline in thyroxine after surgical menopause. So, soy protein and isoflavone consumption does not adversely affect-and may even preserve-thyroid function in postmenopausal women.

High vitamin intake may affect blood levels of drugs and drug response. The blood level of diphenyl hydantoin (DPH) and phenobarbital (PB) decreases when given with Folic acid (therapeutic dose), thereby fit frequency and severity increased in epileptics. DPH and PB blood level also decreases when administered with vitamin B6 (400mg/day) which could be explained by the increased activity of pyridoxal phosphate-dependent enzymes which might be involved in the metabolism of these drugs [42, 45]. Isonicotinic acid hydrazide when given with vitamin B6 megadose, its anti-tuberculosis activity decreases in mice [46]. Also, L-Dopa when administered with vitamin B6, increased Parkinsonian rigidity occurs [47]. These effects could be due to formation of a Schiff base with the drugs. Administration of high doses of vitamin K with Coumarin anticoagulant produced reduction of Hypo-prothrombinemia [48].

Drug Receptors and Pharmacodynamic Responses

Pharmacodynamic alterations can occur in the presence of disease without altered drug concentration if drug receptors in the target organ are changed in number or sensitivity. The therapeutic requirement of a drug may be quantitatively different in malnutrition due to tissue receptor changes. Studies in experimental animals indicate that steroid receptors increased in undernutrition [49].

Nutritional Effect on Drug-Protein Binding

Many drugs are present in the blood in the form of a complex with plasma proteins. Albumin is the main transport vehicle for drugs. Binding is important because it influences the pharmacologic potency, metabolism, and excretion of a drug. Some of the drugs that bind to plasma protein are frusemide (diuretic), acetyl salicylic acid, declofenac, digitoxin, the beta-blocker propranolol that used for treatment of arrhythmia and hypertension, diphenyl hydantoin, penicillin, phenobarbital, the anti gout probenecid, phenylbutazone, sulphonamide, tetracycline and the potassium sparing diuretic triamterene [50-56]. Both hydrophobic and electrostatic interactions played important roles in the protein-metformin complex formation [57]. The presence of elevated glucose concentrations in diabetes is a metabolic change that leads to an increase in the amount of non-enzymatic glycation that occurs for serum proteins such as human serum albumin (HSA), which is an important carrier agent for many drugs and fatty acids in the circulatory system. Sulfonylureas drugs, used to treat type 2 diabetes, are known to have significant binding to HSA. Ultrafiltration and high-performance affinity chromatography were employed to examine the effects of HSA glycation on the interactions of several sulfonylurea drugs (i.e., acetohexamide, tolbutamide and gliclazide) with fatty acids, whose concentrations in serum are also affected by diabetes. Similar overall changes in binding were noted for these drugs with normal HSA or glycated HSA and in the presence of the fatty acids. For most of the tested drugs, the addition of physiological levels of the fatty acids to normal HSA and glycated HSA produced weaker binding. At low fatty acid concentrations, many of these systems followed a direct competition model while others involved a mixed-mode interaction. In some cases, there was a change in the interaction mechanism between normal HSA and glycated HSA, as seen with linoleic acid. Systems with only direct competition also gave notable changes in the affinities of fatty acids at their sites of drug competition when comparing normal HSA and glycated HSA. This demonstrated the importance of considering how changes in the concentrations and types of metabolites (e.g., in this case, glucose and fatty acids) can alter the function of a protein such as HSA and its ability to interact with drugs or other agents [58].

Nutrition can influence drug binding in two ways; to reduce the amount of available albumin as in severe PCM and by producing variations in the concentration of metabolites that are transported by albumin such as non polar amino acids (tryptophan) and free fatty acids. If these substances increase it will compete with the drug to bind plasma albumin. Displacement of drugs will occur when the FFA-albumin molar ratio exceeds 2 [59].

Systemic reactions induced by drug-food incompatibilities

Monoamine oxidase inhibitor used for treatment of acute depression when administered during feeding Cheese specially those allowed to mature and undergo bacterial putrefaction such as cheddar, or eating broad beans or chickens' liver; hypertensive crisis occur due to presence of tyramine in the cheese and the presence of Dopamine (dopamine changed to noradrenalin by Dopamine oxidase) in broad beans or chickens' liver. This interaction may be utilized to treat patients with severe postural hypotension (drug as 70 mg/day +cheddar 90 mg/day (26 mg tyramine/ day). Chocolate, smoked meats, and wine also contain tyramine and may exhibit the same reaction [60-64]. When alcohol or alcohol containing food is consumed with metronidazole or oral hypoglycemic of sulphonylurea group; disulfiram-like reaction occurs. Alcohol produces a hypoglycemic reaction in patients on chlorpropamide. Alcohol can interact with a wide range of medications, typically decreasing the effectiveness of antibiotics and blood pressure medications, and intensifying the potency of pain relievers and sleep aids to potentially harmful levels. Combining alcohol with the pain reliever acetaminophen can be toxic to the liver, and alcohol with anti-inflammatory medications like ibuprofen and naproxen can increase the risk of stomach bleeding. The use of alcohol with pain medicines (e.g. codeine, oxycodone, morphine) can have serious consequences, including coma or even death [65-67].

Nutrient in Drug Detoxication Reaction (biotransformation)

The metabolic Reactions of Drugs:

Drugs are usually metabolized in three phases whereby non polar are converted into polar excretory products. In Phase I, drug exposed to Oxidation, reduction and hydrolysis while in phase II Synthetic or conjugation products are produced. Most of these reactions occur in the endoplasmic reticulum of the cells of various organs especially the liver. Both phase I and II reactions are usually catalyzed by enzymes which are

proteins. Therefore proteins are required for the synthesis of these enzymes and therefore any nutritional state which reduces the availability of amino acids could be expected to reduce the amounts of drug metabolizing enzymes. This can also occur when the calorie intake is low, that is of carbohydrate and fat; since under these conditions protein will be catabolized and used as source of energy thereby reducing the availability of amino acids for enzyme synthesis.In phase III, further drug modification and excretion occur. Conjugates and their metabolites can be excreted from cells in phase III of their metabolism [68-72].

Nutrients required in phase I reactions.

Nutrients such as Nicotinic acid, glycine, pantothenic acid, iron and protein are needed for the components of oxidizing system; NADPH, heme (in Cyt-P-450), CoA(delta-aminolevulenic acid synthesis), heme, and apo-enzymes of cytochrome P450, respectively. Riboflavin is required for FMN and FAD in NADPH-cytochrome P450 reductase. Cupper is needed for Ferrochelatase in heme synthesis. Calcium, zinc, and magnesium are required for maintenance of membranes on which the oxidizing system is bound. Lipid specially phosphatidyl choline has an important role in microsomal oxidation. Reduced availability of essential elements can affect drug efficiency, since they have specific metabolic roles both as integral parts of metallo enzymes and cofactors for metal ion activated enzymes [73, 74].

Nutrients required in phase II Reactions or Congugations:

In this phase, phase I metabolites conjugated with metabolites of the body (conjugating agent) thereby the drug is detoxicated and its biological activity diminished or abolished. The sources of conjugating agents such as glycine, cysteine, glutamine, glutathione, methionine, sulphate and sulphur are amino acids while that of glucouronic is carbohydrate and that of acetyl radical is fat, carbohydrate or protein.

Conjugations are synthetic reactions and need a source of energy for their accomplishment. This is supplied through ATP which is formed from the energy yielding nutrients of the body. Conjugations are characterized by the formation of an active intermediate which in most cases is a nucleotide. A transferring enzyme is also necessary to catalyze the reaction between the activated intermediate and the conjugating agent or drug.

For producing conjugated drug two types of reactions may be adopted; type A where the conjugated agent is activated by energy and in the presence of drug and transferase enzyme; conjugated drug is produced. In type B reaction, the drug is first activated by energy then in the presence of transferase and conjugating agent, the drug is converted to conjugated drug [75, 76].

Some Drug-Vitamin Interrelations: Effect of Vitamin status on Drug utilization (Drug metabolism):

Dietary deficiencies of various vitamins such as ascorbic acid, retinol, thiamin, riboflavin and tocopherol can affect the hepatic drug-metabolizing enzymes system [77, 78]. Vitamin E deficiency can result in enhanced transport of passively absorbed drugs from the intestine. Deficiency of vitamin E also decreased the rate of drug degradation represented by hydroxylation and demethylation of drug substrate (microsomal metabolism). These two effects on drug utilization may result in an increased residence time of the drug in the body, therefore a possible increase of this drug action may occur and may not have been accorded adequate attention. Marginal deficiencies for vitamin A, E and C resulted in reduced drug metabolism before there were any clinical signs of vitamin deficiency. In vitamin C deficiency state a prolongation of sleeping time during phenobarbital administration occurs. Elevated dose of vitamin C increased Cytochrome p-450, increased demethylation reaction and drug metabolism thereby reduce drug effect. On the other hand deficiency of vitamin B1 produces increased microsomal metabolism of drugs, reduces their presence in the body thereby reduces their effect. Elevated dose of vitamin B1 reduces microsomal metabolism of drugs and increase their action [79-81]. Deficiency of vitamin B2 reduce microsomal metabolism of drugs and increase their effect.

The effect of various Dietary Modifications on microsomal Drug Metabolizing Enzymes in Small intestine

Starvation for more than 48 hr results in reduction in the activity of 3-Methyl-4 ethylamino azobenzene-N-demethylase, Benzpyrene Hydroxylase, UDP-Glucuronyl transferase and elevation of ß-Glucuronidase. Consumption of cholesterol rich diet induces elevation in the activity of Benzpyrene

Hydroxylase, UDP-Glucuronyl transferase and NADPH-cytochrom C reductase while fat free diet produced reduction in the activity of Benzpyrene Hydroxylase. Diet of low iron content results in reduction in Cytochrome P-450 and Benzpyrene hydroxylase. Eating Cabbage, turnips or spinach produces elevation in the activity of Benzpyrene Hydroxylase [82-90] highlighted the vital role of diet in maintaining adequate expression of major drug-metabolizing P450s and their associated drug-metabolizing activities in the digestive tract and suggest potential involvement of bile acid signaling in the regulatory mechanisms.

Effect of the type of food on the drug efficiency:

Dietary substitution of sucrose and its constituent monosaccharides affects the activity of aromatic hydroxylase and the level of cytochrome P-450 in hepatic microsomes. When morphine administered with nutririve sweet solutions, morphine' analgesia is enhanced while no change of analgesic response is noticed in the absence of such solutions. The increase in morphine-induced analgesia on consuming a sucrose solution is not due to alterations in either protein or micronutrient intake [91]. Dietary restriction in either quantity or quality of protein results in a decrease of liver microsomal drug metabolism that can modify the pharmacologic and toxicologic effect of drugs. Absorption and C max of **t**he anticonvulsant, Gabapentin, increased on feeding high protein and decreased on protein free diet [92]. Shifting diet from balanced to high protein-low carbohydrate (HP-LC) on administration of theophyllin or antipyrine produced reduction of half life by 36% and 41%, respectively while shifting diet from (HP-LC) to low protein-high carbohydrate induced increased half life by 46% and 63%, respectively [93]. Therapeutic effect of Levodopa decreased on consumption of high protein diet and increased with low protein diet. Concerning drug-fat interaction; drug oxidative enzymes are associated with lipoprotein membrane of hepatic endoplasmic reticulum where 30-55% of hepatic endoplasmic reticulum is composed of lipid. So, quantity and quality of dietary lipid showed to have important effect on drug metabolizing enzymes. Unsaturated lipids are essential in maintaining drug-metabolizing enzymes activities. Fat absorption decreases in such adverse state as kwashiorkor, lactase deficiency and worm infestation. When a drug is given, decreased fat intake may be important in the therapeutic management of patients. Consumption of High fat meal and/or amino acids mixture (Gly, gly-gly and gly-protein) during administration of the antiarrhytmic drugs, bidisomide, decrease systemic availability of the drug due to low permeability and inhibition of absorption in the presence of these nutrients while on administration of Disopyramide with the same meal produce no change in systemic availability of the drug [94, 95]. Cholesterol rich diet increases drug biotransformation by modifying the properties of subcellular membranes thus regulating the activities of metabolizing enzymes [96, 97]. Consumption of Cholesterol rich diet shortened the hypnotic pentobarbital sleeping times. High-fat diet-induced changes in energy metabolism, which eventually result in obesity, modulate the hepatic expression profile of cytochrome P450s, particularly CYP3As. Alternatively, the accumulation of a certain component in a high-fat diet may directly attenuate the CYP3A expression, suggesting a clinically important drug-diet interaction [98]. Food restriction on administration of amphetamin, phencyclidine (anaesthetic) and dizocilipine but not nicotine increases the sensitivity of neural substrates for the effects of the drugs and enhances the central response to these drugs. Food deprivation and restriction increase the rewarding potency of food, drugs of abuse, and electrical brain stimulation. Possible mechanisms of reward sensitization, include sustained decreases in circulating insulin and leptin and increases in corticosterone [99, 100].

Grapefruit and its juice can interact with more than 80 medications, including cholesterol-lowering statin drugs, blood pressure medications, and antihistamines. Depending on how the medication is metabolized, grapefruit can reduce the effectiveness, or worse, result in potentially dangerous drug levels in the body. Organic compounds in grapefruit that are furanocoumarin derivatives interfere with the hepatic and intestinal enzyme cytochrome P450 isoform CYP3A4 and are believed to be primarily responsible for the effects of grapefruit on the enzyme. Bioactive compounds in grapefruit juice may also interfere with P-glycoprotein and organic anion transporting polypeptides, either increasing or decreasing the bioavailability of a number of drugs. Pomelo (the Asian fruit which was crossed with an orange to produce grapefruit) also contains high amounts of furanocoumarin derivatives Seville oranges and tangelos (a cross between tangerines and grapefruit) also contain furanocoumarins [101-105]. In vitro and animal pharmacokinetic data support the possibility of CYP3A4/CYP2C9 inhibition by pomegranate juice; however, the human relevance for drug-food interaction was not established based on the limited case studies [106].

Leafy green vegetables like kale, spinach, broccoli, Brussels sprouts, and cabbage are rich in vitamin K, which plays a role in clot formation and, as a result, can decrease the effectiveness of anti-coagulant like

Coumarin and warfarin. This could be controlled by the timing of administrated drug and eating such food [107, 108].

Food-Drug formulation Interaction

Food interaction of different drug products containing the same active ingredient can be various depending on the pharmaceutical formulation technology, the food/ formulation interaction can play an important role in the development of food interaction. Comparing Nifedipine (used for angina and hypertension) in Hydrophilic matrix extended release tablet with that in osmotic pump tablet when administered with food, Cmax was twice that of osmotic pump tablet which is released to increased erosion rate of the extended release tablets leading to more rapid drug release [109]. Comparing the Administration of Oxybutynin (an anticholinergic used to relief urinary and bladder difficulties) in controlled release tablet, 2 hours after breakfast showed C max significantly higher than in the fasting state in addition of decreased saliva secretion rate after food. Ingestion of the tablet ½-1hr before food may well improve tolerability in patients suffering from adverse reaction. These effects are due to the type of formulation but not the drug itself [110]. New technologies for drug formulations such as nano-technology may need extensive study in relation to nutritional status and type of food consumed.

Drug metabolism in infantile undernutrition.

Drug metabolism is affected in infantile undernutrition. In protein calorie malnutrition (PCM) disease diverse alterations occur; alterations in hepatic function as well as histological changes have been described specially in endoplasmic reticulum in which most enzymes involved in drug biotransformation. Alterations in intestinal absorption as well as alterations in intestinal mucosa were also described in PCM. Alteration in renal plasma flux, glomerular filtration and renal excretion also occur in PCM. These previous factors affect drug efficiency in PCM patients; chloramphenicol peak plasma levels were attained in 4 hours in marasmic infants in contrast to 2 hours in the normal, this is due to slower absorption. The peak plasma levels are higher than the control. The drug takes much longer time to clear from plasma of marasmic children due to decreased biotransformation and to lesser extent to slower renal clearance. So the dose level must be reduced in those patients. The net result was that the comparative bioavailability of the drug was higher in PCM as compared to the control. Observations were similar in the case of sulphadiazine.

Pharmacokinetic studies on antipyrine and acetaminophen have been carried out in infants and children suffering from PCM. Increased antipyrine plasma half-life in PCM indicated altered mixed oxidative microsomal enzyme activity in hepatocytes. The rate of absorption (ka) of acetaminophen was not affected in children with PCM, but the elimination rate constant was slower and plasma half-life prolonged. Noticeable improvement was observed within 6-8 weeks of nutritional rehabilitation with respect to chloramphenicol, antipyrine, and acetaminophen pharmacokinetics. [111]. Elimination kinetics determined by a timed plasma concentration curve on chloramphenicol, antipyrine, acetaminophen and sulphadiazine showed that plasma half-life was increased and elimination rate constant was diminished in malnourished children compared to those with normal nutrition. Area under the curve (AUC) was increased. Decreased urinary excretion of metabolites of chloramphenicol and sulphadiazine in malnourished children suggested an alteration in biotransformation. These findings were supported by a significant increase in steady-state levels of chloramphenicol and phenobarbitone in malnourished patients receiving drugs for therapy. In a subhuman primate animal model (young rhesus monkey) which was akin to the human situation both for protein energy malnutrition and for drug pharmacokinetics it was observed that hepatic aminopyrine demethylase and chloramphenicol glucuronyl transferase activity was diminished. Thus drugs metabolised by the liver apparently clear at a slower pace in malnourished children. Therapy needs to be modified appropriately to achieve therapeutic response and avoid toxicity. Hepatotoxicity monitoring of antitubercular therapy with isoniazid and rifampicin was found to be 3 times higher in malnourished children. The acetylator status of the child did not correlate with hepatotoxicity. The majority of the children were slow acetylators. AUC of isoniazid was higher in malnourished children [112].

Tetracyclines half life and absorption are lower in undernourished than in well nourished [113, 114]. Generally, protein nutrition may exert a major influence in the responsiveness to pharmaceutical preparations.

Obesity-drug interaction

Although grossly overweight patients receive different dosages than lean persons, the relationship between clinical obesity and drug biotransformation has not been well studied.

A few drugs such as digoxin and aminoglyoside antibiotics are not well distributed in adipose tissue. Other drugs with low therapeutic indices are also capable of causing toxicity in obese patients if these drugs are distributed only in the lean compartment. The calculation of volume of distribution on the basis of the patient's lean body weight rather than total body weight was an important factor that contributed to the accuracy of the predicted level of gentamycin, an aminoglyoside antibiotic [115]. An increased serum concentration of fluorine after administration of fluorinated anaesthetics to obese subjects was reported [116].

The plasma half life of antipyrine and tolbutamide metabolized by the the microsomal mixed function oxidation pathway, sulfisoxazole and isoniazid metabolized by acetylation and procainamide metabolized by the pseudo-cholinesterase hydrolysis pathway are normal in obese but otherwise healthy subjects when allowance is made for body weight [117].

In severely obese subjects, antipyrine apparent volume of distribution (V) is mildly increased but V corrected for total body weight is significantly decreased. In addition, obesity is associated with a slight prolongation of antipyrine elimination half life whereas its clearance rate is unaltered. These findings may indicate that obesity, even in its extreme form, has a negligible effect on the oxidative metabolic capacity of the liver [118].

How the consumption of food or nutrients may affect drug dosage

Plasma ascorbic acid concentration and ascorbic acid intake was inversely correlated to systolic and diastolic blood pressures and pulse rate. Regular consumption of dietary fish and omega 3 fatty acids of marine origin reduce blood pressure (BP) and cardiovascular risk. Weight reduction reduces BP and cardiovascular risks. Combining a daily fish meal with a weight reducing regimen led to additive effects on ambulatory BP and decreased heart rate. The effect is large suggesting dose reduction of antihypertensive drugs. Dietary fish involves a cardiac autonomic component as well as vascular effect. BP is positively associated with Na Cl. K, Ca and Mg may be protective electrolytes against hypertension Habitual coffee consumption, large doses of liquorice are positively correlated with BP. Drug dose of anti-hypertensive drugs can be reduced if the previously mentioned points are taken into consideration [119-121].

Drug-food interaction of beneficial effect:

Administration of fish oil together with gentamicin (aminoglycoside antibiotic) partially protected from nephrotoxicity induced by gentamicin i.e reduces gentamicin side effect without compromising its antibiotic effect [122]. Vitamin C, Vitamin E, and grape seed extract decreased aspirin, and ethanol-induced ulcers and malondialdehyde (the indicator of lipid peroxidation) values [123]

Medicinal Effect of bioactive constituents of food

Long time ago Cabbage and other members of brassica family that contain thiourea and thiouracil were used for treatment of Grave'disease, they act by blocking the formation of thyroid hormone by interfering with the binding of circulating iodine into its organic form in the thyroid gland [124, 125]. Also, nutmeg and parsley contain Myristicin that culd be used as Narcotic (Psychotropic drugs) [126].

Oxidative stress and inflammation are involved as risk factors of different chronic non communicable diseases [127-130]. The consumption of dietary fibers, phytochemicals and specific micronutrients such as carotenoids, polyphenols, phytosteroles, toccopherols, omega-3 fatty acids from fruits, vegetables, nuts, cereals, and marine products has been associated with decreased incidence of various inflammation and oxidative stress related chronic diseases. Nutraceutical is an emerging era in the prevention and treatment of chronic diseases. Nutraceuticals are bioactive extracts or products prepared from foods, and have a physiological benefit or provide protection or treatment from chronic disease. Nutraceuticals are assuming a

middle ground between food and drugs due to growing body of evidence that supports their role in maintaining health and contributing to treatment of disease.

Recent researches in the last two decades have focused on different bioactive constituents (nutraceuticals) from food that possess medicinal effects. Fenugreek seeds contain Sapogenins (natural steroids) that possess Anti-inflammatory activity through inhibition of prostaglandin [38]. Coriander fruits contain Quercetin of Anti-inflammatory activity [131, 132]. Liquorice root contains Glycerrhizin, O-acetylsalicylic and Flavonoides as anti-inflammatory agent [133]. However licorice due to presence of glycyrrhizin can reduce the effectiveness of blood pressure drugs and diuretics. It can also increase the potency of certain steroids, potentially causing negative side effects.

Flavonoids that present abundantly in plant foods such as quercetin, quercetrin and rutin were shown to possess anti diabetic effect [134]. Nutrients may also have therapeutic activity; fish oil in conjunction with vitamin E have been shown to have anti-inflammatory activity [135].

Oral administration of polar and non polar extracts (nutraceuticals) of celery leaves, celery seeds, rosemary, cinnamon and turmeric produced significant anti-gout activity in animal model of gout. The anti-gout activity was associated with both antioxidant and anti-inflammatory effects which was ascribed to the presence of phenolic compounds, unsaturated fatty acids, long chain fatty acids and phytosterols. Theses extracts were shown also to be xanthine oxidase inhibitors. So, these extracts could be helpful in inhibiting the severity of the disease and alleviating inflammation and pains in gouty patients [136, 137].

The beneficial effect of three nutraceuticals (plant food extract mixtures) and *Bifidobacterium bifidum* (Probiotic) was studied in adjuvant arthritis in rats that resemble rheumatoid arthritis in human. The nutraceuticals were prepared from green tea, wheat germ, tomato, rosemary, walnuts, sweet potato, broccoli, hazelnuts and carrot. The results showed that nutraceuticals and probiotic could reduce the size of inflammation and disease severity significantly. The mechanism of action seems to involve a reduction in oxidative stress, inhibition of inflammatory biomarkers and an effect on colonic microflora profile that showed increase in colonic *Bifidobacteria*. DNA fragmentation, apoptosis and genotoxic effects that induced by adjuvant arthritis were prevented by the nutraceuticals. The health benefits of nutraceuticals were attributed to the presence of carotenoids, toccopherols and phenolic compounds [138].

Two nutraceuticals prepared from thyme herb, wheat germ, carrot, celery seeds, rice bran and tomato showed promising prevention of atherosclerosis and cardiovascular diseases through improvements in plasma lipid profile [total lipids, total cholesterol (T-Ch), triglycerides (TGs), low density lipoprotein cholesterol (LDLCh), T-Ch/HDL-Ch, TGs/HDL-Ch and high density lipoprotein cholesterol (HDL-Ch)], reduction in oxidative stress (reduction of malondialdehyde and elevation of vitamin E and beta-carotene) and elevation of plasma testosterone in rats. The antiatherogenic effect of the extract mixtures was attributed to the presence of phenolic compounds, phytosterols, tocopherols and unsaturated fatty acids [139].

Pumpkin seed oil was shown to have great impact in protection from cardiovascular risk. It showed an improvement in the plasma lipid profile, a significant increase in adiponectin and a decrease in oxidative stress with promising prevention of atherosclerosis and cardiovascular diseases in experimental rats. Pumpkin seed oil also showed beneficial effect towards fatty liver. These effects of pumpkin seed oil were ascribed to the presence of unsaturated fatty acids, phytosterols, tocopherols and phenolic compounds [140, 141].

Ceratonia siliqua (Carob pods) methanol extract, petroleum ether extract and extracted polyphenol and seed powders were prepared and tested for their reduction of hyperglycemia in rats. Polyphenol and seed powders showed promising anti hyperglycemic effect pointing to their possible therapeutic effect in diabetic patients [142].

Nigella sativa crude oil was tested and showed promising prevention of steatohepatitis (fatty liver with inflammation) in rats reflected in the significant improvement in dyslipidemia, tumor necrosis factor-alpha, malondialdehyde and liver function along with significant reduction of liver triglycerides and cholesterol. This heath benefit was attributed to the presence of p-cymene and thymoquinone [143].

Stabilized rice bran oil showed beneficial effect towards fatty liver. The effect of rice bran oil was ascribed to the presence of the antioxidant and antiiflammatory constituents such as Policosanol, gamma oryzanol, phytosterols, unsaturated fatty acids, phenolic compounds and dietary fibers [141, 144].

Reno-protective effect of nutraceuticals prepared from grape, coriander, roselle and fennel extracts was reported in rat model of renal dysfunction. A mixture of ethanol and petroleum ether extracts was prepared as the ratio of its presence in the parent plant. Administration of extract mixtures produced improvements in biochemical (plasma urea, creatinine, malondialdehyde, plasma albumin, total protein, catalase activity, total antioxidant level, creatinine clearance), histopathological and cytogenetic (Chromosomal aberration and sperm-shape abnormalities) changes. The nutraceuticals offered renal protection *via* antioxidant and possibly anti-inflammatory actions which might be due to presence of phenolic compounds, unsaturated fatty acids including omega-3 and phytosterols that was verified from analysis of the extracts [145].

Ipomoea batatas (L.) Lam, also known as sweet potato, a valuable medicinal plant which is a valuable source of unique natural products having anti-cancer, antidiabetic, and anti-inflammatory activities [146].

Onion and garlic have diverse medicinal purposes. The pungent fractions are mostly sulfur containing moieties Constituents such as flavonoids and ALK (EN)-based cysteine sulphoxides were shown to possess marked effect on human health. Compounds in onions have been reported with a range of health benefits, including anti-cancer properties, anti-platelet activity, antithrombotic activity, antiasthmatic and antibiotic effects [147].

Tea (*Camellia sinensis*) has a long history of medicinal use. The bioactive components of tea are polyphenols, catechins, proteins, polysaccharides, chlorophyll and alkaloids [148]. Green tea have health benefits against array of maladies e.g. obesity, diabetes mellitus, cardiovascular disorders, cancer and anti-mutagenic. The major bioactive molecules are epigallocatechin-3-gallate (EGCG), epicatechin, epicatechin-3-gallate, epigallocatechin. the mechanisms of green tea to control cancer involve induction of apoptosis to control cell growth arrest, altered expression of cell cycle regulatory proteins, activation of killer caspases, and suppression of nuclear factor kappa-B activation. It acts as carcinoma blocker by modulating the signal transduction pathways involved in cell proliferation, transformation, inflammation, and metastasis. Green tea and its components have medicinal effect especially against colon, skin, lung, prostate, and breast cancer [149]. The health benefits of tea consumption in preventing cancers and cardiovascular diseases have been intensively investigated [150].

Camellia oleifera seed is an important source of edible oil in China. Sasanqua saponin is a major active compound in the defatted seeds of Camellia oleifera. The sapogenin from hydrolysis of sasanqua saponin was purified and its amination derivative was prepared. It was proven that the sapogenin improve Parkinson disease where it can protect dopamine neurons through anti-neuroinflammation and activation of dopamine receptor rather than adenosine receptor. Its amination product has superior improvement effect [151].

Smilax china root, which is rich in resveratrol and oxyresveratrol, has been used as emergency foods as well as folk medicine due to their free-radical scavenging activity. The bioactive components were highly extracted during fermentation by Aspergillus usami and Saccharomyces cerevisiae resulting in enhanced antioxidant activity [152].

Tomato (*Solanum lycopersicum*) is an important source of vitamin C, potassium, folic acid and carotenoids such as lycopene. Lycopene is chemically acyclic carotene with 11 conjugated double bonds, normally in trans configuration while isomerization occur in blood plasma for its better absorption. It has ability for adenosine deaminase inhibition that plays important role in the regression of tumor. Tomato also contain other active compounds namely, neoxanthin, lutein, a-cryptoxanthin, α-carotene, β-carotene, cyclolycopene and β carotene 5, 6-epoxide. Both in vitro and in vivo studies have elucidated the potential of tomato against variety of metabolic syndromes. Consuming tomato and its products induced reduced risk of obesity, hyperglycemia, hypercholesterolemia, cardiovascular disorders and cancer [153]

Dietary fibre is a group of food components which is resistant to digestive enzymes and found mainly in cereals, fruits and vegetables. Dietary fibers are classified into water-soluble and water insoluble fibers.

Dietary fibers include arabinoxylan, inulin, pectin, bran, cellulose, β-glucan and resistant starch. Dietary fibres organise functions of large intestine and have important physiological effects on glucose and lipid metabolism. Dietary fibers have protective effect against certain gastrointestinal diseases, constipation, hemorrhoids, colon cancer, gastroesophageal reflux disease, duodenal ulcer, diverticulitis, obesity, diabetes, stroke, hypertension and cardiovascular diseases [154].

Hydrolyzed and unhydrolyzed citrus residues exhibited similar antioxidant activity, which was positively correlated to the contents of total phenols, flavonoids and total carotenoid. Some flavonoids (naringin, naringenin, hesperetin and neohesperidin) and two high value co-products (D-limonene and galacturonic acid) were detected only in hydrolyzed residues. In addition, hydrolyzed residues showed antiproliferative activity and sub-G1 arrest in human melanoma A375 and colon cancer HCT116 cells [155].

Anthocyanins in elderberry species is an antioxidant and antiinflammatory bioactive constituent [156].

Extract from T. mongolicum has hypolipidemic potentials in HepG2 cells and a significant reduction in body weight and levels of serum triglyceride LDL-C and total cholesterol in rats. The mechanism involved decrease in the expression of fatty acid synthase and inhibition of the activity of acetyl-coenzyme A carboxylase through the phosphorylation of AMP-activated protein kinase. Linoleic acid, phytol and tetracosanol are bioactive compounds identified from the extract [157].

Plums (*Prunus domestica, Prunus salicina, Prunus mume)* are rich in unique phytochemicals called neochlorogenic and chlorogenic acids which are classified *as phenols,* and their function as antioxidants has been well-documented. Plum also contains selenium, total sugars, polyphenol, carotenoids, and vitamin C that contribute to its antioxidant effect [158].

The antioxidant effect of three different extract of *Morus nigra* (black mulberry) showed a protective action against peroxidative damage to biomemranes and biomolecules [159]. The plant extract at the dose of 20 mg/kg body mass produced a significant increase in the concentration of glutathione in the liver of diabetic mice with a decrease in MDA concentration [160, 161]. Morus nigra has also been reported for in the treatment of renal stones [162].

CONCLUSION

Nutritional deficiencies either micro or macronutrients'deficiency can affect drug efficiency. So, on prescribing a drug, the patients must not suffer from any form of nutritional deficiencies either micro or macronutrients deficiency. If any deficiency is present, it must be corrected as far as possible during the drug administration.

Some drugs produce malnutrition. So, if the prescribed drug produced any form of malnutrition it must not be ignored and a nutrient supplement or a perfect diet must be prescribed.

Best drug action can be verified by controlling the timing and the suitable type of diet. The best condition of drug administration (Type of diet consumed, fasting, fed state, …etc.) must be mentioned in the prescription to verify best drug action and simultaneously to minimize the side effect whenever possible.

Large doses of vitamins may affect the efficiency of drugs. Vitamins must only be prescribed in deficiency state since large doses may produce adverse reactions.

The patient should be maintained on a balanced diet (Containing RDA of nutrients specially macro-nutrients, protein, fat and carbohydrate) during the period of treatment with any drug to avoid any variations in drug biotransformation.

Protein malnutrition can modify drug potency. So, in infantile protein malnutrition; the drug dose should be reduced than that in normal healthy state.

In obese subject dose level of some drugs should be corrected to verify the best drug action.

Some type of food or nutrients may reduce side effects of certain drugs; so such food could be used to minimize the adverse effect of the drug

Biologically active constituents isolated from food can be used as therapeutic agents. Such food could permit reduction of dose level of the drugs (of the same therapeutic effect), thereby reducing its side effect, on the other hand, ignoring reduction of the dose may result in enhancement of drug response that may lead to worse effect.

Recommendation

Continuous study of drug-nutrition or drug-food interaction is very important to cover all interactions of newly discovered drugs, drug formulations and newly searched nutraceuticals or biocative constituents from food.

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