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THE PHARMACOLOGICAL IMPACT OF RESTRICTED OR NON VARIANT DIET

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ABSTRACT

Food is often consumed for its nutritive value but food items also contain chemicals that have pharmacological activities. The pattern of food intake may make the phytochemical constituent of food pharmacologically relevant, especially when food is restricted to one particular type or is varied within a narrow range with similar phytochemical. This review examines this concept and draws attention to the importance of food variation.

Introduction

Traditionally we consider diet as nourishing. Food is taken to replenish energy or meet certain nutritional requirements. However, food items contain chemicals that are pharmacologically active in their own right. When consumed regularly as a mixed or single diet for sufficient time, the pharmacological impact of that food may become a significant factor in the physiology of the individual. Such impact may be predictable and may have important clinical utility. Dietary chemo type (the chemical signature of food) may, therefore, need to be considered in food consumption. Diet variation based on pharmacological effects may be a new outlook in 21st century preventive and therapeutic medicine.

Determinants of the phenotype of health and disease

It is generally accepted that a combination of genetic and environmental factors determine health status. The three components of phenotypic variability are usually identified as gene (G), the environment (E) and the GXE interaction [1]. Genotypic (G) variations may be partitioned into three components: the additive variance, which is associated with average effects of alleles at the same locus, or the variance due to linear regression of genotypic values on gene frequencies in individual genotypes; the dominance variance, which is due to the overbearing effects of alleles at the same locus; and the epistatic variance, which is due to non allelic interaction of two or more loci [1]. On the other hand environmental (E) factors are not usually stratified. The gene environment (GXE) interaction may be taken as the complex and dynamic result of the modifying influence of the environment on genotype or that of genotype on environment, with the potential for vicious circles. Food choice may modify gene expression. On the other hand expressed genes may modify food choices.

Dietary plants as drugs

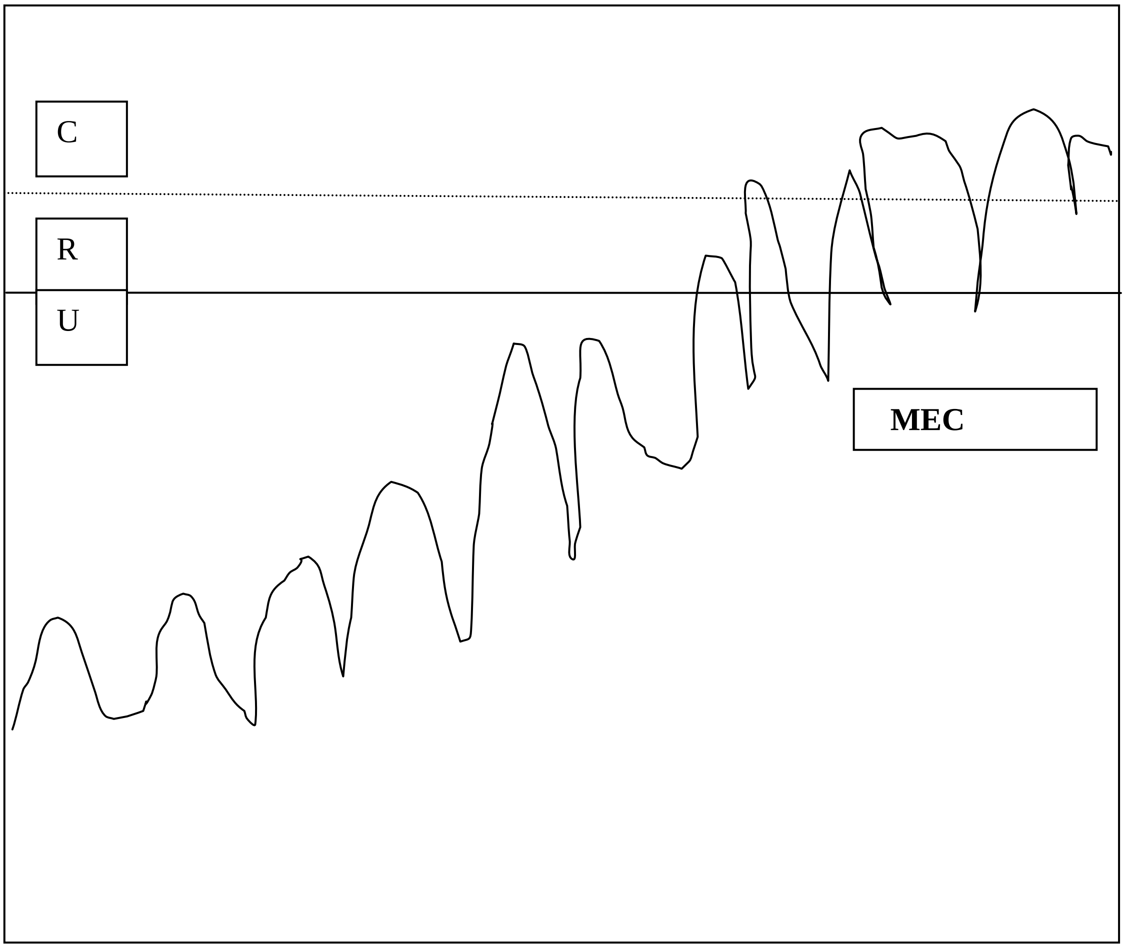
Food contains various compound and chemical structures in varying composition. Dietary plants have been shown to contain many pharmacologically active structures and when taken regularly, it may be argued that this represent quasi dosing of pharmacologically active agents. Such dosing acquires increasing significance depending on the pharmacokinetic and the pharmacodynamic profile of the chemical constituent under consideration.

In this review, we consider diet as 'restricted' when food intake is limited to a narrow range of food type that also contains similar phytochemicals (e.g. a diet table that include Yam for breakfast, rice for lunch and beans for dinner may be considered restricted because all contain phytoestrogens). Alternatively we consider diet as 'non variant' when food is actually restricted to a particular type (e.g. Rice every meal).

Dietary restriction and non variation are important considerations in view of the influence of economy and productivity on available food alternatives especially in the developing world and the availability of prescriptions diets in disease states. The influence of economy on food choices appears obvious but prescription diets are frequently given with considerations focused on the nutritional value while the phytochemical constituents are frequently disregarded.

When food is consumed in a restricted or non variant way either as a forced choice or guided prescription, the net effect would be expected to depend on the serving quantity, the pharmacokinetic profile of the chemicals and the duration.

Figure 1. Concentration –time plot of a hypothetical phytochemical in the body



U= Zone of 'unrestriction', R= Zone of restriction, C= Zone of Commitment, MEC= Minimum effective concentration

Figure 1 is a hypothetical kinetic plot of the concentration (y-axis) of a pharmacologically active food constituent (Pi) in the body. The dose (feeding) interval (x-axis) has been depicted as variable to reflect the loose non regimental pattern of food intake i.e. food is not necessarily taken at the same time every day. The saw-edged pattern of the curve is to reflect the possible influence of temporal and quantitative dose variation (i.e. food consumption).

In this plot, three zones (U, R, C) are particularly important. The Zone 'U' is the zone at which substance pi is present in the body but is below the minimum effective concentration (MEC). If food pattern is such that this zone is never crossed, then pharmacological effect of pi may not occur. However, once the concentration crosses into zone 'R' the patients diet may be described as pharmacologically restricted. Change in dietary habit may return the concentration of substance pi into the U zone. Zone 'Ç' is described only when the half life of substance pi is long e.g. weeks or months. This may cause the concentration of pi to cross into zone 'C' . At this zone the individual is essentially committed to the effect of substance pi because, months to years of absence of pi in diet is required to escape from its pharmacological effect. This may be unlikely without conscious interventions.

An examination of soybean, sweet taste and liquorice candies in the above context may further illuminate our hypothesis. The soybean plant is a member of the pea family (family leguminosae) and its ban is rich in protein, vitamins, minerals, and fibres [2]. The term 'soy' is commonly used to refer to products made from whole soybeans, while soy protein is the protein extract of soybeans[3]. Soybean/soy is fast acquiring medical prominence. It has the prospect to be the key source of protein for human consumption in the 21st century. It has been presented as a good and cheap source of protein (an attractive combination in the developing economies) especially an alternative to breast milk for the children of HIV positive mothers [3]. Also, because of soybean's positive health effects, the developed world has given it increasing prominence. Innovative soy foods have been developed in the last decade that are not only considered healthy, but are also satisfactorily to even the most selective palate. Burgers, hot dogs, and soy beverages are available in the developed economies and the tasty soy food is expected to have strong appeal worldwide. In concert with its increasing prominence, a rich amount of research on it is ongoing. A Medline search with the key world 'soybean', time range January 2001 to January 2010, and with no language restriction on 21/02/2010 (revealed over 132460 documents. Furthermore the U.S Food and Drug Administration approved soy products as "heart disease preventive" foods in October 1999. Soybean is therefore a good candidate for consideration on dietary restriction. What is the pharmacological impact?

Soybeans contain the phytoestrogens genistein and daidzain (isoflavones) in amounts of ~1-3mg/g [4]. It also contains phytic acids [5]. Phytoestrogens are plant substances that are structurally or functionally similar to the physiological hormone 17 beta estradiol. They are divided into several classes, but current research focuses on Isoflavones (found in soy). Most isoflavones in plants are inactive glycosides requiring activation by bacterial enzymes to the aglycone form to facilitate absorption and exert physiological effects. The bioavailability of soy isoflavones is highly variable but the consumption of approximately 50mg of soy isoflavones per day (roughly 25g of soy protein daily) has been shown to have pharmacological effects. The plasma half-life of both genistin and diadzein is approximately eight hours, with peak concentrations observed within six to eight hours [6]. With these PK values, an average meal including 25 to 50g of soy protein three times daily enables steady state phytoestrogen concentration in about 40 hours (within 4 days). This has various consequences. On the one hand soy phytoestrogens when consumed in the above quantity will be expected to have hypocholesterolemic effects [7] , raise serum HDL cholesterol concentrations, decrease platelet aggregation

]8] and diminish the tendency of thrombosis [9] . These have been confirmed in several studies. In a randomised, double blind trial, soy protein (56 or 90mg of isoflavones per day) was substituted for animal protein in the diet of 66 postmenopausal women with hyperlipedemia. Non HDL cholesterol was reduced by 7%, a significant change, and HDL cholesterol increased 3-5% [10]. Soybean has also been touted as protective in Alzheimer's [11] and prostatic malignancies [12]. On the other hand, Isoflavones are partial agonists at the estrogen receptor, which means that at normal 17-beta estradiol activity in the female (reproductive age) isoflavones are essentially anti-estrogens but are oestrogen agonists in male and children in whom 17-beta estradiol activity is normally low. Regular intake of soybean may, therefore, promote ovulation in the reproductive age group by causing a Clomiphene like effect on the pituitary ovarian axis but may, at the same time, reduce ongoing pregnancy rate due to its effect on the endometrium. Reviewing figure 1 in the context of soybean, it will expected to promote fertility in the 'R' zone and infertility when consumptions leads to levels in zone 'C'. These have also been confirmed in several studies. Kohama et al [13] showed that consumption of 6g of soybean per day promoted ovulation and improved pregnancy rates. On the other hand, Litvinova and Fedorchenk [14] showed that higher amount of soybean reduced the number of living fetus in the uterus and increased embryonic death in females. Furthermore, both Michell et al [15] and Chavarro et al [16] demonstrated that, in males, long term exposure to dietary soy decreased sperm count and fertility. The feminizing effect of long term consumption of soybean on children has been reported by several authors [17, 18]. Soybean also contains phytates. Phytate in food is composed of a mixture of different phosphorylated forms of inositol phosphate [19]. The phosphate groups can form strong and insoluble complexes with cation such as zinc and iron and as the gastrointestinal tracts of higher species lack any significant phytase activity, phytate-bound minerals will be lost in stool. By using radioisotopes and whole body counting, very low zinc bioavailability has been shown to result from soy based infant formula compared with milk formula and human milk [20]. From several studies in humans to whom various protein sources and amounts had been administered, fractional zinc absorption was found to increase linearly with protein content [21]. Zinc is ubiquitous in sub cellular metabolism. It is an essential component of the catalytic site or sites of at least one enzyme in every enzyme classification [22]. An early sign of zinc deficiency in animals is decreased food intake. Reduce immune function, involving B cell and T cell depletion and/or reduce activity, and skin lesions associated with secondary infection are also common findings. Chronic zinc deficient in human results in reduced growth (Dwarfism) and sexual development and is reversible by increasing zinc intake. There is a parallel between zinc deficiency and protein calorie Malnutrition and this suggests that a restrictive diet might be a trigger or an enhancer.

Figure 2: The possible consequences of phytates in food

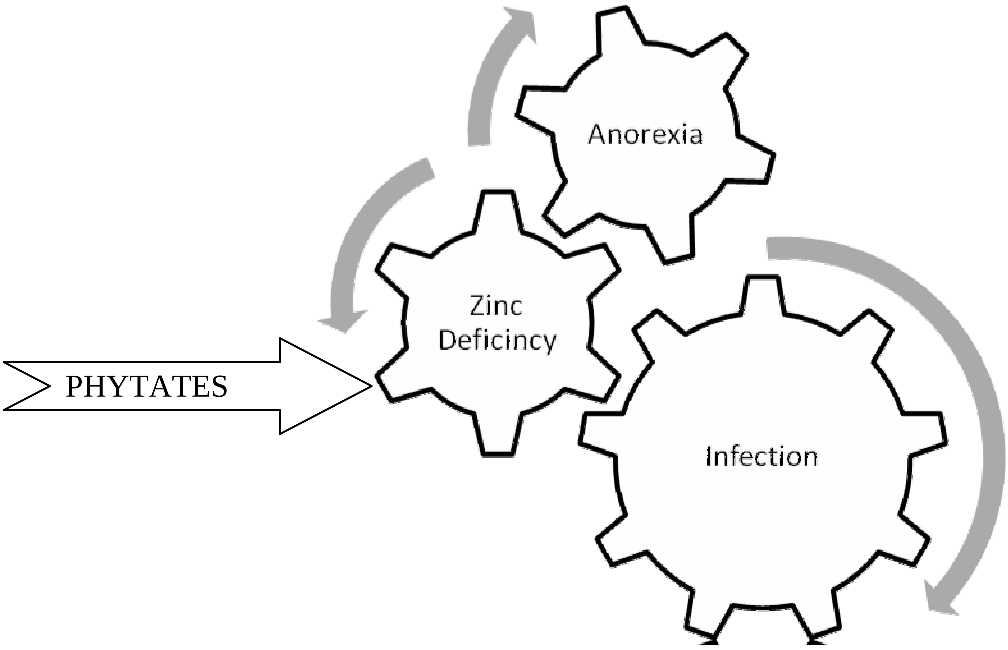


Figure 2 traces the possible consequences of soybean phytates reaching the 'c' zone described in figure 1. Phytates may trigger zinc deficiency which promotes anorexia and further zinc deficiency. Both zinc deficiency and anorexia promote immune compromise, allowing infections which in turn cause anorexia.

Restrictive and non variant consumption of soybean is of similar implication pharmacologically to ingestions of multiple drugs at the same time while only one or so has the targeted benefit. Similar arguments may be presented for Rice (*Oryza sativa* L.), corn (*Zea Mays* L.) and lettuce (*Lactuca sativa* L.).

It has been shown that 'taste' reign supreme in determining food selection [23, 24, 25]. In the strict sense, 'taste' is used to refer only to those sensations arising from the taste system, which includes basic tastes of sweet, salt, sour and bitter. It has been shown that the ingestion of sweet sugars leads to endogenous opioid release [26]. Further corroborating evidence on this point comes from Blass and colleagues' research indicating that during circumcision, the presentation of sweet taste reduces infants' crying and distress [27, 28, 29]. A diet restricted to 'sweetness' may start a circuitry of reinforcement of 'sweet' consumption by the increased endogenous opioids and therefore lead to 'obesegenic' food preference. If the 'C' zone in figure 1 has been reached before an attempt at dieting is started, dieting may be tolerated until levels fall below the 'R' zone. At this point endogenous opioids triggered by the 'sweat' diets would have fallen sufficiently low to trigger either a 'withdrawal type' craving for sweat food plus increased sensation of body pain. Indeed , studies have shown that obesity that developed form indulgence on high sugar diet are more difficult to control by dieting[29] and that patients tend to regain weight after 6 months[30].

Figure 3: The obesegenic circuit of sweet food preference

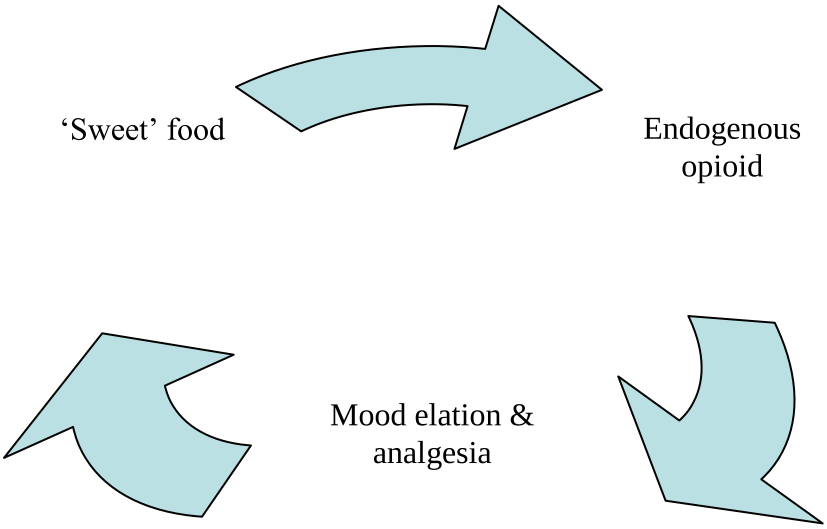


Figure 3 suggests that opioid antagonists may be used in the drug management of obesity and food craving. Indeed opioid antagonists like naloxone, naltrexone, diprenorphine, nalorphine and naloxonazine have all been shown to induce weight loss in mouse [31] and human [32] and some have been shown to have strong anorectant activity [33]. Also, from Figure 3, opioid agonists with good analgesic activity will be expected to promote dieting because it will reduce the opioid withdrawal pain. Indeed, Bungo et al [34] demonstrated that a range of such opioid agonists reduced feeding behaviour in chicks.

Another example of the impact of dietary restriction is the recent findings on black liquorice candies. Glycyrrhizin is the primary chemical component of black liquorice candies and is also found in herbs and tea [35]. Glycyrrhizin could boost prostaglandin production. liquorice candies are a favourite of many pregnant finish women and in one study 2% of the study subjects reported daily consumption and 50% reported weekly consumption of liquorice [36]. In the same study, it was found that women who consumed at last 25 packages (containing 100 grams of black licorice candy each) weekly were more than twice as likely to deliver before 38 weeks than women who consumed little or no liquorice. Studies have also demonstrated that dietary consumption of liquorice roots can deliver medically effective doses of glycyrrhizin [37]. Not considering this fact has proved costly to some patients [38]

In conclusion dietary substances contain pharmacologically active chemicals, which acquire increasing significance as dietary intake become restricted or non-variant. This may be one missing links in the phenotype of various illnesses. Perhaps what we take as food should be considered as drugs on their own recognition and need to be re-evaluated and classified in this regard. Such steps may include dietary chemo-profiling and broad pharmacological evaluations. Perhaps the key to satisfactory food ingestion is chemo type variation. Food chemo typing (the grouping of dietary substances on the basis of chemical constituent) may acquire increasing significance in the 21st century and will also allow guided food intake in health and disease.

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