Probiotics in Human Health and Disease: A New Avenue of Understanding between Diet, Disease and Metabolic Disorders

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As our understanding of the human genome evolves, so does the metabolic significance of the intestinal microflora whose cellular population outnumber the host by approximately ten-fold [1].

These organisms are diverse and have multi-faceted roles in human health and disease: accumulating evidence links them to the interface between diet, metabolism, long term health outcomes and various disease states. Diet-disease relationships are potentially significantly mediated by the intestinal microflora, and therefore, potentially amenable to therapy by probiotics [2] and prebiotics.

A more established example is the literature relating inter-country differences in hormone-dependent disease to habitual diet and effects on sex-hormone metabolism [3]. Differential selection of gut flora by intake of macronutrients, prebiotics and antibiotic agents have been proposed as mechanisms contributing to these observations.

Probiotics and Phytochemical Metabolism—The Role of Gut Flora in Determining Biological Effects of Ingested Phytochemicals

Aside from the effects of diet and intestinal flora on endogenous hormones, the microflora may influence the bioavailability, metabolism and effects of ingested phytochemicals.

Phytoestrogens first came to prominence in Western Australia in the 1940s with the outbreak in sheep, of "Clover Disease", an economically catastrophic infertility syndrome [4]. Attributed to ingestion of isoflavone phytoestrogens, greatly enhanced oestrogenic potency by ruminal microbial demethylation of formononetin to equol was later established. In 1982, equol was reported in human urine [5], and subsequently, found to increase in response to soy ingestion in some, but not all human subjects [6,7], but abolished by antibiotic ingestion [8].

Subsequent interest in the potential role of dietary phytoestrogens in menopausal health eclipsed the likely pivotal role of the gut flora in the metabolism and biological activity of these compounds. Clinical studies on the oestrogenic properties of phytoestrogens in post-menopausal women as foods or as supplements at non-pharmacological levels have been characterised by highly variable and inconsistent findings [9,10]; equol-producing status, the role of microflora, and potentially, its manipulation to modify the bio-availability and potency of these compounds remains an on-going avenue of research. Equol ingestion or production by intestinal flora may be associated with greater consistency, and/or magnitude of biological effects [11].

Interestingly, previous rodent studies have documented highest blood concentrations of certain dietary phytochemicals in the portal circulation [12], hence, the greatest potency of such compounds might be seen in the liver.

Besides endocrine effects, intestinal flora may influence intermediary metabolism by various mechanisms, including micronutrient status [13]. Gut flora synthesize vitamins K and biotin, with broad spectrum antibiotic therapy increasing the risk of deficiency; generation of short chain fatty acids by colonic flora may directly enhance colonic absorption of calcium and magnesium. This is aside from phytate-degradation by probiotic organisms, which may enhance bioavailability of iron and zinc from plant based foods [14].

Probiotics as a Potential Therapeutic Avenue in the Treatment of Inherited Metabolic Disorders Currently Managed By Diet

Inherited metabolic disorders are characterised by the lack of an enzyme or cofactor coded in the host genome, resulting in deficiency of the product downstream from the enzymatic block, an excess of substrate upstream from the block and potentially activation, and/or inhibition of other metabolic pathways which can result in widespread metabolic disturbance [15].

Disorders of host intermediary metabolism, either inherited or acquired, may be aggravated or potentially ameliorated by the metabolic activity of the indigenous intestinal flora.

Microbial ammonia generation is problematic in liver failure [16], and in rare inherited metabolic disorders of the urea cycle (UCD), where endogenous detoxification pathways are compromised; beyond suppression by broad spectrum antibiotic therapy and accelerated gut transit, selection for non-ammonia generating probiotic organisms [17], e.g. lactobacilli could be advantageous.

Intestinal flora may also burden genetically compromised host metabolic pathways in propionic acidaemia (PA) and methyl malonic acidemia (MMA), due to microbial propionic acid production and trimethylaminuria (TMAU or "Fish Odour Disease"), where hepatic metabolism of trimethylamine, microbially derived from choline, is impaired [18]. While broad spectrum antibiotic therapy may help manage both conditions, in TMAU, probiotic organisms may be a therapeutic avenue to modify the indigent gut flora in favour of species which do not produce TMA and suppress those that do [19].

Propionic acid, however, is a short chain fatty acid, produced by many probiotic microflora. In PA and MMA, elevated levels of propionic acid are associated with poor appetite and food intake [20], potentially a marked exaggeration of effects suggested in healthy subjects, where mild appetite suppression may protect against obesity and insulin resistance [21].

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Where the problematic substrate is solely of dietary origin, such as in phenylketonuria (PKU), dietary manipulation, though effective, may be nutritionally restrictive and socially isolating. Modified probiotic organisms, capable of metabolizing dietary phenylalanine, may lessen the need for dietary restriction in the future.

Thus, the genomic contribution of intestinal microflora and its potential modification may represent a therapeutic avenue for genetic disorders of human metabolism, amongst the most challenging conditions in clinical medicine.

References