

WHOLESOME DIET AND GUT MICROBIOME, SPECIAL FOCUS ON BUTYRATE; A CRITICAL REVIEW ON ITS MODULATORY EFFECT ON -GUT HOMEOSTASIS IN MALABSORPTION W.S.R TO GRAHANI

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ABSTRACT

Malabsorption is a leading cause for nutritional deficiency disorders. An imbalanced microbiome has been associated with a number of gastrointestinal diseases including irritable bowel syndrome and inflammatory bowel disorder. Dietary fibre is rich source of food for gut bacteria and its reduction can lead to a decreased bacterial production of short chain fatty acid butyrate. This change can lead to dysbiosis and local inflammation in the gut lining, resulting in impaired gut barrier function and the possible leakage of bacterial toxins into the blood stream. Malabsorption refers to impaired nutrients absorbed and maldigestion within the brush border epithelium of gastro intestinal tract. As gastrointestinal tract is the primary organ

provided to diet sections, diet may be regarded as one of the essential factors in the functionality, integrity, and composition of intestinal microbiota. The gut microbiome participates in the absorption of the host's nutrients and metabolism, maintains the microcirculation, and modulates the immune response. By the consumption of *ama*, *virudha* like *aharas* will affect the *agni* and there causes *agnimandya* and leads to diseases there by improper absorption and assimilation will takes place and leads to *grahani*.

KEYWORDS: *Ama, Grahani, Agni.*

INTRODUCTION

Digestion and absorption of nutrients is a complex, highly coordinated and extremely efficient process; normally, less than 5% of ingested carbohydrate, fat and protein is excreted in the faeces.^[1] Malabsorption state is quite common in India and this may result from a number of conditions. The term includes several conditions where intraluminal digestion of food and/or its subsequent absorption are defective. The clinical picture is the total outcome of- (a) no absorption of ingested materials resulting in steatorrhea and creatorrhea, (b) malnutrition manifesting as loss of weight and specific deficiencies, and (c) symptoms of the underlying disease such as tropical sprue, tuberculous enterocolitis or chronic pancreatitis^[2] A healthy diet is one in which macronutrients are consumed in appropriate proportions to support energetic and physiologic needs without excess intake while also providing sufficient micronutrients and hydration to meet the physiologic needs of the body.^[3] The gut immune system continuously communicates with the wide range of microorganisms that colonize the gut and with the different components of foods that are eaten daily. Diet impacts the gut microbiome, of which composition and function differs depending on the intake of fat, sugar, and fibers. *Agni* is responsible for digestion and metabolism in human body. The healthy state of *agni* depends upon nature and quantity of food intake. *Grahani* & *agni* are having *adhara-adheya sambandha*. *Grahani* is described as an *agni adhisthana* by most of the acharyas. *Mandagni* is a root cause of *Ama Dosha* & it is the crucial factor for manifestation of most of the diseases. A wholesome diet is essential for good health and prevention of disease. Malfunction of *agni* occurs due to intake of unwholesome and improper quantity of food intake and other factors which leads to formation of *ama*.^[4]

MATERIALS AND METHODS

All the literature regarding malabsorption, gutmicrobiota, dietary fibers, role of butyrate – interrelation among Nutrition, Immune system & Gut microbiome and ayurvedic view were collected from classical texts, research papers, different articles, journals, authentic websites and different books.

MALABSORPTION

Malabsorption can arise from any defect in the digestion/absorption process. These defects can result from an inherent disease of the mucosa, conditions that lead to acquired damage of the mucosa, congenital defects in the intestinal membrane transport systems, impaired absorption of specific nutrients, impaired GI motility (decreased peristalsis and stasis),

disrupted bacterial flora, infection, or compromised blood flow or compromised lymphatic's.^[5] Coeliac disease is an immunologically mediated inflammatory disorder of the small bowel occurring in genetically susceptible individuals. It can result in malabsorption and responds to a gluten-free diet.^[6] The processes that are impaired may be - (a) intraluminal digestion, (b) transfer across the mucosa lining, or (c) transport from the mucosa to the circulation and to the target organs. In some cases the pathological mechanism is well-defined and evident, e.g. lactase deficiency.

(a) Intraluminal maldigestion occurs when deficiency of bile or pancreatic enzymes results in inadequate solubilisation and hydrolysis of nutrients. This may also occur in the presence of small bowel bacterial overgrowth.

(b) Mucosal malabsorption results from small bowel resection or conditions which damage the small intestinal epithelium, thereby diminishing the surface area for absorption and depleting brush border enzyme activity.

(c) Post mucosal lymphatic obstruction prevents the uptake and transport of absorbed lipids into lymphatic vessels. Increased pressure in these vessels results in leakage into the intestinal lumen, leading to protein-losing enteropathy.^[1]

Diarrhoea and weight loss in patients with a normal diet should always lead to the suspicion of malabsorption. Occasionally, nutrients are not adequately absorbed from the small intestine even though the food has become well digested. Several diseases can cause decreased absorption by the mucosa; they are often classified together under the general term "sprue." Malabsorption also can occur when large portions of the small intestine have been removed.^[7]

LEADING CAUSES OF MALABSORPTION

1. Abnormalities of the stomach: These are (i) partial or total gastrectomy, (ii) gastrocolic fistula, (iii) hypertrophic gastritis (this leads to excessive protein loss in feces), and (iv) Zollinger-Ellison syndrome.

2. Pancreatic disorders: These include chronic pancreatitis, cystic fibrosis and carcinoma.

3. Biliary disorders (a) Long-standing obstructive jaundice leads to defective digestion and absorption of fat and fat soluble vitamins. (b) Deficiency of bile acids which may occur in two groups of conditions

4. Intestinal diseases: These lead to defective transport across the gut mucosa. The mucosa may show gross pathological lesions or may be histologically normal. Mucosal damage

occurs in intestinal tuberculosis, celiac disease, Crohn's disease, Whipple's disease and intestinal lymphoma

5. Impairment of transport from the small intestine: Blockage of lymphatics draining the small intestine prevents the discharge of absorbed chylomicrons into the systemic circulation.^[2]

GUT MICROBIOTA- A DEFENSIVE SHIELD

The human body and its microbiome constitute a highly delicate system. Human micro biota, often referred to as the “forgotten organ”, comprises 100 times more metagenomes than the human genome. An imbalance in their abundance is closely related to infections, autoimmune diseases, obesity, diabetes, cardiovascular diseases, and cancer. Bacterial metabolites synthesized by the gut microbiome play an important role in the complex interplay between the gut immune system and gut microbiome.

ROLE OF DIETARY FIBERS ON GUT MICROBIOTA

The diversity of microorganisms present in our gut is dependent on and modulated by the molecules we take as food, medicines, etc. Foods rich in high fat and carbonated other chemicals, and environmental toxicants can lead to an imbalance in gut microorganisms. The gut epithelial layer is tightly regulated by tight junction proteins present on the enterocytes and controlled considerably by beneficial bacteria present in the gut. Gut-dysbiosis or microbial imbalance leads to inflammation and inappropriate expression of signal molecules like TNF- α , IFN- γ , etc. These cytokines lead to increased intestinal membrane permeability by regulating the tight junction proteins and give rise to leaky gut syndrome and several diseases like diabetes type 1 and 2, crohn's disease, celiac disease, etc.^[8]

When assuming primary roles for promoting host well-being, this intestinal health environment is presented to the effect of external influences, including dietary patterns. In comparison with a more traditional western diet, healthier alternatives are higher in plant-based foods, including fresh fruits and vegetables, whole grains, legumes, seeds, and nuts and lower in animal-based foods, particularly fatty and processed meats.^[3]

BENEFITS OF HIGH FIBER DIET

- Normalizes bowel movement and bowel health
- Lowers cholesterol levels
- Helps control blood sugar levels

- Aids in achieving healthy weight

IMPORTANCE OF BUTYRATE-A DERIVED FATTY ACID FROM DIETARY FIBERS

Butyrate, a short chain fatty acid (SCFA), is one of the products of the microbial digestion of carbohydrates and dietary fibers in the large bowel, which represents a dominant energy source for the colonocyte. The main metabolites produced by gut microbiome are short-chain fatty acids (SCFAs). Among SCFAs, butyrate is essential for maintaining gut immune homeostasis and exerts a pivotal role in immune tolerance with strong anti-inflammatory effects in allergic diseases.

Dietary Fibers and Short Chain Fatty Acid- Butyrate Production by Gut Micro biome

Dietary fibers are made up of non-digestible carbohydrates derived from plant polysaccharides and oligosaccharides, which are resistant to chemical and enzymatic digestion up to the large intestine. These carbohydrates are the main nutritional source for gut bacteria, and their fermentation leads to the production of SCFAs. Although SCFAs can also be derived from dietary proteins and glycoprotein metabolism, carbohydrates represent the main sources. In gut dysbiosis, butyrate-producing bacteria are reduced, resulting in a reduction in butyrate production.

Butyrate can improve gut epithelial barrier integrity through increasing the thickness of the mucus layer (enhancing the expression of mucin genes, in particular MUC2) and the expression of tight junctions. One of the molecular mechanisms by which SCFAs including butyrate modulate immune system functions is through binding to specific G protein-coupled receptors (GPR) such as GPR43, GPR41, and GPR109a. These receptors are expressed not only on intestinal epithelial cells (IECs), but also on gut immune cells such as Tregs and dendritic cells. Furthermore, the GPR109a receptor mediates butyrate induction of IL-18 in colonic epithelium, which is responsible for strengthening the tolerance to commensal bacteria and promoting gut homeostasis.

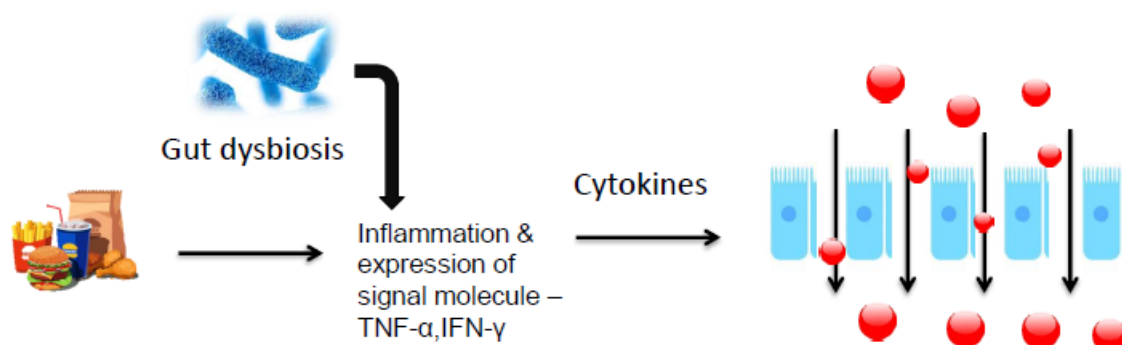


Fig.1 Unhealthy food intake leads to gut dysbiosis and destruction of gut barrier integrity

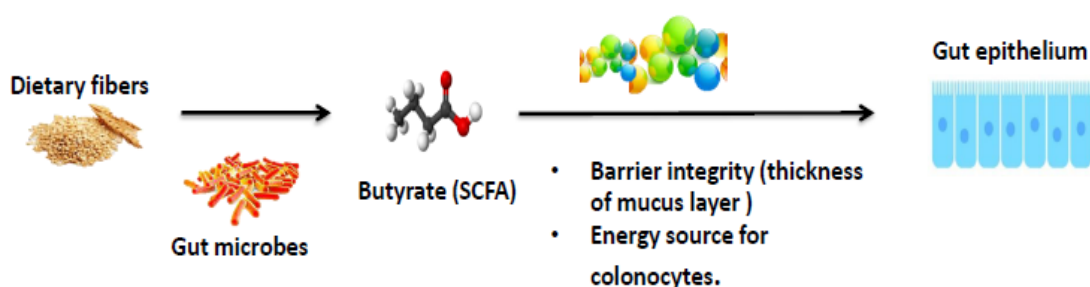


Fig.2 dietary fibers intake balances the gut homeostasis

Role of butyrate –Interrelation among Nutrition, Immune system & Gut microbiome

The gut immune system continuously communicates with the wide range of microorganisms that colonize the gut and with the different components of foods that are eaten daily. Butyrate, a gut-microbiome derived metabolite, has received particular attention for its multiple beneficial effects from the gut to the peripheral tissues. Among the immune mechanisms of action, butyrate acts through different pathways. Butyrate is also able to enhance vitamin A metabolism, which in turn induces the activity of aldehyde dehydrogenases (ALDH) in gut CD103⁺ dendritic cells and increases the percentage of Tregs and IgA production. Moreover, high-fiber diet-induced activation of GPR43 and GPR109A activates the NLRP3 inflammasome, which is essential for gut homeostasis.

Ayurveda aspect of *grahani* in relation with *agni* on gut microbiota – A Birds eye view

In the era of fast food, there is change or irregularity in diet and diet timings and also sedentary lifestyle. In addition to change in diet and lifestyle, one is always under tremendous mental stress. Any disease has two stages: *Amavastha* and *Niramavastha*. If the disease is in *Amavastha*, first line of the treatment is to remove *Ama* and make *Nirama avstha*. In

Ayurveda, the term “*Agni*” is used in the sense of digestion of food and metabolic products. *Agni* converts food in the form of energy, which is responsible for all the vital functions of our body. Therefore, Ayurveda considers that *Dehagni* is the cause of life, complexion, strength, health, nourishment, lusture, *oja*, *teja* (energy) and *prana* (life energy). (Cha. Chi. 15/3.).^[9]

According to modern medicine, metabolic processes, division and multiplication are going on in all cells (*dhatu parinamam*) of our body from birth till death. The cell is the functional unit of the body. In *Shushruta Samhitha*, we can see how the “*Avayavaas*” are formed from “various *dhatu*s” (Su.Sha.4/25- 30). According to Charak, the constituent parts of the body, if further divided into the atoms, are sure to become innumerable, as such cells or atoms are exceedingly numerous, very minute and ultrasensory. In the conjunction and disjunction of cells, the activating factors are *Vata* and the nature of action (Cha. sha.7/17). Thus, based on Susruta and Charaka, the above cells can be considered as “*dhatu paramanus*.” For these constant processes in all iological energy is constantly essential, without which the survival of our body will be quite impossible. The same biological energy is provided by *Agni* in concept of Ayurveda. This *Agni*-provided biological energy in the cells (*dhatu paramanu*) of our body is of two types: potential and kinetic.^[10]

The definition of the term *kala* and the functions ascribed to the seven of them, in the Ayurvedic classics, resemble, for the most part, the protective or epithelial tissues. In addition, descriptions and functions, especially of the *pittadhara* and *pureeshadhara kalas* are reminiscent of those of the covering membrane of the intestine-small and large. The epithelium that lines the entire length of the gastro intestinal tract is of the simple columnar variety. Glandular diverticula form gastric glands of different types in the stomach, Burner's glands in the duodenum and the crypts of Liberkhun in the whole extent of the small and large intestine manufacture the digestive juices; those covering the villi of the intestine are concerned with the absorption of the products of digestion and those that line the serous cavities provide a smooth moist surface. It is of interest to note that blood vessels are absent from epithelia. In most cases, they compose the semipermeable membranes through which materials pass to and from, in the course of secretory and excretory activities of the body.

Epithelial tissues constitute tissues that cover the surface of the body e.g., the skin, or form the delicate linings of the body cavities which open directly or indirectly to the surface; The term epithelium may be used in an elementary sense to cover all the tissues.

According to Susruta, *kala* is the (fine) structure that separates the *dhatus* from their *ashayas*

- *Mamsa dhara kala* is stated to separate and support the *mamsa dhatu*, in which latter, are to be found *siras* (blood vessels), *dhamanis* (arteries), *snayus* (ligaments) and *srotamsi* (capillaries)
- *Pittadhara kala* is stated to cover that part of the *koshtha* (gastro-intestinal tract) described as the *grahani*. Its main function is seen to be to provide *pachakapitta* which is necessary for the digestion of the food brought to this part of the *koshtha* from the *adho-amashaya* (stomach), on its way to the *pakwashaya* (large intestine); the retention of food, in this part, for the duration of its digestion, and the separation of the *sara* (nutrient)-fraction from the *kitta* (residue) fraction.

Agni is the heat to decompose, disintegrate, separate or break-down substances and also to accelerate different kinds of chemical reactions. Likewise, the digestion of food in the *amashaya* and *pachyamanashaya*, corresponding to the stomach and small intestine, involving the splitting of complex food substances into their simpler components that is break-down of complex proteins into amino-acids, fats into fatty acids and glycerol and starches into glucose, so that they may be rendered fit for absorption, is made possible by *kayagni*.^[11]

Disturbance to the digestive system, which results into many diseases, amongst which digestion and absorption disorders constitute an important group. *Grahani* and *Agni* are interdependent. Functionally weak *Agni* i.e., *Mandagni*, causes improper digestion of ingested food, which leads to *Ama Dosha*. This *Ama Dosha* is a root cause of most of the diseases. *Grahani* is considered under eight major diseases, so it is hard to diagnose and difficult to treat.

DISCUSSION

Malabsorption can arise from any defect in the digestion/absorption due to malfunctioning of *agni*. This will lead to impaired absorption of specific nutrients. *Pitta* is stated to be located in an area between the *pakwashaya* and *amashaya*; in its constitution, it is *pancha-bhouthika*. It is *drava* or liquid in consistency, in spite of which it performs actions similar to *anala* (fire), largely due to the accension of its *tejas* component over the rest. This fact is inferred from the way in which it performs *pakadikarmas* (chemical actions) viz., it digests the food, and separates the *sara* (the nutrient fraction) from the *kitta* (the residue fraction). The microbiota

participates in key functions related to human health, including physiological activities such as nutrition absorption, vitamin synthesis, exogenous substance metabolism, and immune regulation. Gut dysbiosis can predispose to the onset of immune-mediated diseases including allergic diseases. Evidence shows that gut microbiota plays a vital role in pathogen resistance, host immunity and metabolism. SCFAs have been long known to be key nutrients generated in the gut, contributing to GI tract physiology. In the gut, bacterial fermentation results in generation of short chain fatty acids (SCFAs), a class of nutrients, which are sensed by specific membrane, bound receptors, FFA2, FFA3, GPR109a, and Olfr78. These receptors are expressed uniquely throughout the gut and signal through distinct mechanisms.

Butyrate, a bacterial product from fermentation of dietary fiber in the colon. GPR109A (encoded by *Niacr1*) is a receptor for butyrate in the colon. GPR109A is also a receptor for niacin, which is also produced by gut microbiota and suppresses intestinal inflammation. Butyrate, one of the SCFA, is known to take part in the development and maintenance of the intestinal barrier. SCFAs, which result from the bacterial fermentation of dietary fibers in the colon, have multiple beneficial effects in autoimmune and inflammatory diseases because of their impact on the immune system.

The term *kala* means membrane internal organs are lined internally and covered externally with membranes. These membranes are termed as *kala*. *Pureesha dhara kala* which is situated in the GI tract, separates *kitta* of digested part. *Pitta dhara kala* holds four types of food and drinks. According to Dalhana, *pitta* means the internal fire which means that position of *pitta dhara kala* is the seat of *pitta*, the place of *pachaka pitta* is mentioned to be in between *amashaya* and *pakwasaya*. This is for executing digestion. *Ashtanga sangraha* has mentioned the holding of food by *pitta dhara kala* clearly. So these *kala* can be correlated to intestinal barrier which helps in the transfer of nutrients to and fro. *Sakrut* will be mixed with *ama* and food; cardinal symptom of *grahani*, eliminated either when the food is undigested, during digestion or after it. *Samanya lakshna* like *karshya*, *jwara*, *moorcha* etc can be seen as same as malabsorption.

CONCLUSION

Dietary adjustments affect small intestinal epithelial cells and can be used to modulate the mucosal immune system. The overall function of the receptors is to regulate aspects of intestinal motility, hormone secretion, maintenance of the epithelial barrier, and immune cell function. Prominent role of the receptors has emerged in modulation of inflammatory and

immune responses during pathological conditions. Moreover, these receptors are being revealed to interact with the gut microbiota. The SCFAs are sensed by the receptors, and through this interaction, modulate a variety of physiological and hormonal processes that contribute to whole body energy sensing. After being produced in colonic lumen, SCFAs are transported across the epithelium by diffusion. Once transported into colonic tissue, most of SCFAs are metabolized into lipids or ketone bodies such as β -hydroxybutyrate or acetoacetate by colonic epithelium, resulting in significant drop in SCFAs exiting the colonic tissue into portal circulation. SCFAs reaching the liver are metabolized into lipids.

It may be concluded that, *Mithya Aahara Vihara* is the main cause of the *Agni Dushti*, which leads to *Ama Dosha* and finally it results into *Grahani Roga*. If we consume *Guru vidahi ahara*; will causes *mandagni* and improper digestion leads to improper absorption of *ahara rasa* and leads to various drastic diseases. Dietary fibres probably best known for its ability to prevent or relive constipation, also maintain healthy, lowering the risk of diabetes, heart diseases etc. Butyrate, a gut-microbiome derived metabolite, has received particular attention for its multiple beneficial effects from the gut to the peripheral tissues. It's essential to maintain the gut flora and gut homeostasis. Healthy life is always an essential factor for building a future healthy society.

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