

## Nutraceuticals as Chemopreventive and Therapeutic agents in Gut Associated Pathogenesis

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### Abstract

Nutraceuticals have gained great insights in recent years due to their therapeutic implications. Secondary metabolites like glutamate, flavonoids, polyphenols and terpenoids are widespread in nature and are part of human diet. Polysaccharides of prebiotic nature are used both as therapeutic and prophylactic agents. These nutraceuticals in recent times have been reported to possess great potential to reduce antigenic and oxidative pressure in the human gut. Antioxidant rich diet is a potential therapeutic agent against reactive oxygen species induced pathogenesis. Epigenetic compounds present in antioxidant and prebiotics rich nutraceuticals mitigate and remove the causative factors associated with pathogenesis. Flavonoids and polyphenols exhibit antioxidant properties and have been recognized as potential gastroprotective agents and epigenetic modulators as well. Triterpenoids such as cucurbitacin is reported to possess anticancer activities. Glutamate is an enteric neurotransmitter that is used in improving neonatal gut function. This review comprehensively summarizes the current knowledge of gut modulating nutraceuticals which ultimately can play its role from prophylaxis of gut to its therapeutics by employing various macro and micro molecular pathways.

**Keywords:** Nutraceutical; Gut pathogenesis; Secondary metabolites; Epigenetic modulators

### Introduction

Dietary supplements composed of bioactive components of therapeutic importance are claimed as nutraceutical. The term is the combination of two words “nutrition and pharmaceutical”. This term was coined by Stephen L. De Felice in 1989 [1]. Nutraceuticals have emerged as potential prophylactic/therapeutic modality for prevention and cure of a number of diseases. Epigenetic modulators present in nutraceuticals have been recognized as potential anti-cancer therapeutic agent [2,3]. Secondary metabolites obtained from the dietary plants are the basic source of nutraceuticals epigenetic food. These epigenetic nutraceuticals play an important role in augmenting human health. Nutritional deficiencies can affect our body's immune response, neuroendocrine/exocrine secretions and gastrointestinal (GI) repair system. In their absence health related problems arise that lead to progression of pathogenesis. Plants are basic source of nutraceuticals. Combined intake of fruits and vegetables is found to be associated with improved anti-inflammatory and anti-oxidant status [4]. The World Health Organization (WHO) has found that inadequate intake of fruits and vegetables is one of the leading cause of chronic disease and major cause of mortality around the world [5,6]. These nutraceuticals have direct impacts on gut microflora which plays the most crucial role in GI function. Dietary habits of an individual have been found to be linked with the gut-associated microbial activities. Microbial processing of fruits, vegetables and metabolites in the gut modulate GI functions and therefore maintain good health. Receptors on GI neuronal cell membrane might be capable of recognizing specific molecules present in food that trigger the signals involved in peristalsis and gut motility. This determines functional response of intestine in terms of normal gut motility or abnormal movement of the gut leading to the physiological alterations like vomiting. Dietary nutritional components have capacity to modulate mucosal immunity, neuroendocrine functions, serotonergic metabolism, hypothalamic-pituitary-adrenal-axis and inflammatory cytokines [7]. Anti-inflammatory flavonoids and other polyphenols have been reported to be greatly beneficial in improving enteric and systemic milieu [8,9]. Pharmacological effects of triterpenoids have also been reported in several studies which modulate immune system.

Triterpenoids act through intrinsic mode of apoptotic pathway to prevent tumor progression. Anticancer and anti-inflammatory effects of other secondary metabolites such as cucurbitacins have been extensively studied in targeting cyclin B1, cyclin D1, Mcl-1, cdc25C, STAT3 and p53 [10-15]. Glutamate an important constituent of dietary proteins is reported to improve intestinal barrier function and is also used as therapeutic agent for functional improvement of developing infant gut [16,17]. Dietary epigenetic compounds have been reported to be associated with prevention and treatment of various GI ailments, cardiovascular diseases and cancer [18,19].

Basic sources of epigenetic compounds are fruits, vegetables and probiotics. Probiotics are microbial symbionts which colonize in different ecological niche in the gut and exist predominantly since the birth of an individual. Co-evolution of profound and diverse cellular and metabolic processes of the gut microflora modulates physiology and metabolism of the gut [20]. The genetic composition of enteric microbes helps them to synthesize certain enzymatic profile which is entirely different from the host enzymatic profile. This otherwise helps the host to broaden the nutritional substratum. This symbiotic association between the host gut and microbial flora therefore, has a great significance [21-23].

Continuous repair and renewal of intestinal epithelium is required for maintenance of the homeostasis of mucosal epithelial layer of the villi and its integrity which depends on the production of new cells or by apoptosis [24,25]. To maintain a healthy as well as functionally efficient

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Nutraceuticals	Effects
1. Prebiotics	Modulation of enteric microbiome by concurrently improving population of enteric symbionts and suppression of opportunistic pathogens.
2. Polyphenols	Gastroprotection, antioxidation, immunomodulation, antitumor, anti-diabetic, anti-malarial, antimicrobials and anti-helminthic agents [34,51,54].
3. Flavonoids	Anti-microbial, anti-viral, anti-inflammatory, hepatoprotection, cardioprotection, antioxidant, anti-cancer and anti-thrombogenic [55,34].
4. Triterpenoids	Target inflammatory pathways and inhibition of tumorigenesis [56].

Table 1: Therapeutic effect of some important nutraceuticals.

GI tract, factors that regulate various metabolic and physiological process should be balanced [26]. The main player among that factors are enteric microbiota, gastrointestinal mucosa, mucosal immunity, gut-brain axis, digestive enzymes and gastrointestinal neurosecretory hormones. Under the present article we therefore, have attempted to review the biomedical application of gut modulating nutraceuticals.

### Modulation of GI function by interactive action of symbionts and nutraceuticals

Gut-associated microbiome modulates enteric functions in various ways. Neonates have a sterile guts. It normally acquire microorganisms through the environment of birth canal. Breast fed babies are known to have better health than the formula fed infant. This happens mainly due to healthy and balanced microbial colonization among the breast fed individuals. Nutraceuticals augment health among the individuals in all age groups from infant to adults. The dietary component of nutraceuticals are established to improve the microbial biota of the gut, thereby, ensuring a healthy gut. During the course of microbial degradation of undigested food molecules/particles by the microbes, multiple by-products are generated which ultimately upgrade the host nutritional status.

Mucosal development is linked with a balanced microbial population of symbiotic nature in the gut. Gut-associated symbionts are known to have co-existed and co-evolved that compete for adherence with GI epithelial surface [27,28]. Neonatal gut however is more susceptible to the pathogenic challenges. Host-microbe interactions are essential for the development of mucosal immunity and enteric neurohormonal function. Germ free (GF) animals have impaired and undeveloped gut. GF animals have hypoplastic Peyer's patches, reduced number of plasma cells, abnormal spleen and lymph nodes, and impaired capillaries in intestinal villi. Restoration of these deficiencies is achieved by colonization of a single *Bacteroides* species [29-31]. These facts support the therapeutic use of probiotic bacteria. Probiotic-based metabolite like short chain fatty acids have been recognized as an energy source for gut mucosa its immune immunity and associated epigenetic modulations [32].

Probiotics have co-evolved their metabolic or biochemical pathways to utilize available undigested gut nutrients for their own benefit and extend additional nutritional pool for the host as their by-product. These probiotics are capable of fermenting non-digestible polysaccharides into digestible carbohydrates, SCFAs (short chain fatty acids), amino acids and vitamins [21]. This can be achieved by taking the example of germ free animals which are not capable of synthesizing vitamin K and certain species of vitamin B, while the conventionally colonized animals synthesize these components by employing different symbiotic microbial genus like *Bacteroides* and *Eubacterium* [33,34]. A healthy microbiome in the gut augments good health. Therefore, gut-associated normal flora needs to be protected by balanced dietary habits.

Human diet that can protect enteric normal flora is considered to be mandatory for good health. Under certain specific circumstances like chemotherapy and radiotherapy microbial homeostasis is disrupted

which can normally be reverted through therapeutic intervention of prebiotic-rich nutraceuticals. Gut modulating nutraceuticals have broad spectrum activities to augment enteric and systemic health (Table 1). Dietary cucurbits are the nutraceuticals that have been reported to contain adequate amounts of nutraceuticals of antioxidant and have prebiotic nature including sitotherapeutic potentials [26,35,36]. Prebiotic polysaccharides in the diet get hydrolyzed by probiotics. Mammals are capable of hydrolyzing disaccharides and absorb monosaccharides, such as glucose and galactose, but they cannot break-down complex carbohydrates such as cellulose, inulin and inulin like polysaccharides. Certain enteric bacteria have potential to synthesize enzymes for the digestion of these polysaccharides. According to the recently evolved functional genomics of "*Bacteroides thetaiotaomicron*" 400 different enzymes are encoded play a crucial role in various cellular activities including digestion of complex sugars [20], and well-understood starch utilization system [37,38]. Gut-associated microbiome regulates fat storage in the host. It also promotes the absorption of monosaccharides from the gut lumen and induce hepatic lipogenesis [39]. Studies on animals and humans are highlighted the important roles for bacterial signals in promoting the digestion of food, modulation of fat metabolism, epithelial homeostasis, angiogenesis, enteric nervous system, resistance to infection and regulation of gut associated immunity [37,39,40-44]. Recent investigations on animal models and *in vitro* studies have revealed that enteric microbiome regulates host cell metabolic pathways to maintain health and nutritional outcomes of the host [45-47]. Butyrate along with some species of probiotic *Lactobacilli* improve GI epithelial barrier integrity by modulating the expression of certain tight junction proteins [48-50]. Many species of probiotic *Lactobacilli* and *Bifidobacteria* are capable of secreting broad spectrum bacteriocins (natural antibiotics) which inhibit or attenuate pathogenic microbes and therefore, modulate innate immunity. Other mechanisms through which *Lactobacilli* assist its functions include immune stimulation, competition for nutrients and blocking of pathogen adhesion on the gut surface.

Many intestinal pathogens like type 1 fimbriated *Escherichia coli*, *Salmonella* and *Campylobacters* utilize oligosaccharide receptor sites in the gut. After recognition of these oligosaccharide receptor sites in gut, these bacteria activate a cascade of pathogenesis and cause gastroenteritis through invasion as well as toxin production. *H. pylori* infection of the gastric mucosa induces a colitogenic condition which further transform into ulcerative colitis, adenocarcinomas and gastric B-cell lymphomas. Dietary polyphenols (DPs) act against various strains of *H. pylori* [51]. DPs protect the gut by modulating gut physiology and metabolisms and by inhibiting the growth or killing the pathogens. Curcumin is one of the most studied DPs having broad spectrum antimicrobial and anti-malarial activities [52,53]. The ability of gut microbiota to communicate with the brain has emerged as an exciting field in modern health sciences [54-56]. The intestinal microbiota influences the gastrointestinal physiology, including its development and enteric nervous system [54]. Nutraceuticals have great impact on enteric as well as systemic metabolisms and association with the enteric microbiomes to ensure better health. Extensive research on diet-microbiome-gut interactions and their influence on enteric as well as systemic functions are still needed.

Function	Target
1. Growth modulator	Increase jejunal villus height, mucosal thickness and intestinal epithelial cell proliferation [68].
2. Energy source	Gut-associated lymphoid tissues (GALTs) and intestinal epithelial cells (IECs) [69].
3. Immunoglobulins enhancer	Purified B-cells and peripheral mononuclear cells were found to produce more IgG and IgE when cultured with glutamate <i>in vitro</i> [70].
4. Precursor	L-alanine, L-aspartate, L-ornithine, L-proline and glutathione (GSH) production [71].

Table 2: Effect of glutamate in gastrointestinal tract.

### Augmentation of gut development by dietary glutamate

The inherited genetic and epigenetic blue prints associated with GI stem cells are capable of maintaining cellular proliferation dynamics in the gut. The diet of the mother can have long-term impacts on the health of her offspring, possibly through inherited diet-induced chromatin alterations. Intestinal mucosa exhibits high rates of proliferation and rapid cell migration. Intestinal crypt stem cells proliferated through mitosis survive only two to four days before their migration to the tip of the villi which are ultimately extruded [57]. Glutamic acid is one of the most abundant amino acids normally present in many proteins and peptides. Glutamate, a derivative of glutamic acid is the major oxidative fuel for the gut. Glutamate is also a potent enteric neurotransmitter; important precursor for synthesis of bioactive molecules and a potential therapeutic agent for improving neonatal gut function [58-61]. The premature neonatal gut exhibits a high rate of cellular proliferation and replacement in gut epithelia. Ill functioning gut limits the ability to provide critically important enteric nutrition [62,63].

Mother milk is a rich source of glutamate. Infant's formula milk also contain adequate amount of glutamate. Glutamate has the capacity to enhance food intake in old aged individual. Diet free from glutamate evokes visceral sensation from the stomach, intestine and portal vein. The concentration of glutamate in blood is reported to be lowest because most of the glutamate is absorbed and consumed by GI epithelium during transcellular transport from the gut lumen [64]. Large number of transporter molecules are expressed in epithelial cells of gastric lining but only few of them are involved in glutamate transport system [65,66]. Glutamate activates contractile action in the gastric fundus possibly via cholinergic neurons [58,59,67].

Glutamate is also found to be linked with immunomodulatory effect on gut-associated lymphoid tissues (GALT) to optimize the immune function (Table 2). It is oxidative substrate for immune cells and intestinal epithelial cells [68-71]. Therefore, adequate amount of glutamate in the diet influence metabolic and physiological outcome to augment GI health.

### Impact on the gut-brain-axis or enteric nervous system

Gastrointestinal function is controlled and coordinated by enteric neuroendocrine and exocrine components in association with central nervous system (CNS). Efficient digestion of food, absorption and excretion are primary function of the gut which is facilitated through enteric exocrine, endocrine secretions and entero-neuro-endocrine sponsored gut motility. The signal for appetite originate from the gut-brain axis and received by central nervous system (CNS) which in turn regulates the intake of food to maintain food-energy input and expenditure. The most crucial role of gut-brain axis is to connect the brain with neuroendocrine centre and, enteric nervous system leading to multicomponent bidirectional communication network [72]. Amount and nature of the diet also influence GI cellular proliferation.

Deficiency of essential nutrients including dietary polyphenols is associated with enteric neurohormon dysregulation, immunodeficiencies as well as disbalanced microbial composition in the

gut leading to alteration in individual's natural ability to resist against gut-associated pathogenesis [73-76]. Gut pathogenesis such as irritable bowel syndrome, neoplastic development, diabetes, obesity, and cardiovascular diseases are normally initiated due to the nutritional deficiencies of certain bioactive components like modulator of enteric neurohormones and innate/adaptive immunity. Accumulation of exogenous and endogenous oxidants at the surface of the gut wall induce degenerative signal resulting into neuronal damages of enteric nervous system. These degenerative signals trigger leading to gut pathogenesis. Antioxidant rich nutraceuticals play a protective role against oxidative damage of enteric neurons. Nutraceuticals like flavonoids and polyphenols mitigate reactive oxygen species [36]. There is a great scope for investigations on the nutraceuticals and their implications in gut-associated functions.

### Antioxidant defense system

Antioxidant defence mechanism scavenge reactive oxygen species (ROS) to protect the host against oxidative stress. Intake of antioxidant deficient diet may lead to pathogenesis due to accumulation of intrinsic and extrinsic oxidative burden in enteric as well as systemic parts of the body. The consumption of an adequate amount of fruits and vegetables are linked with ROS scavenging potential and improvement of antioxidant defense status [4,72]. Antioxidants defence system acts against oxidative stress at different levels through diverse mechanisms [77].

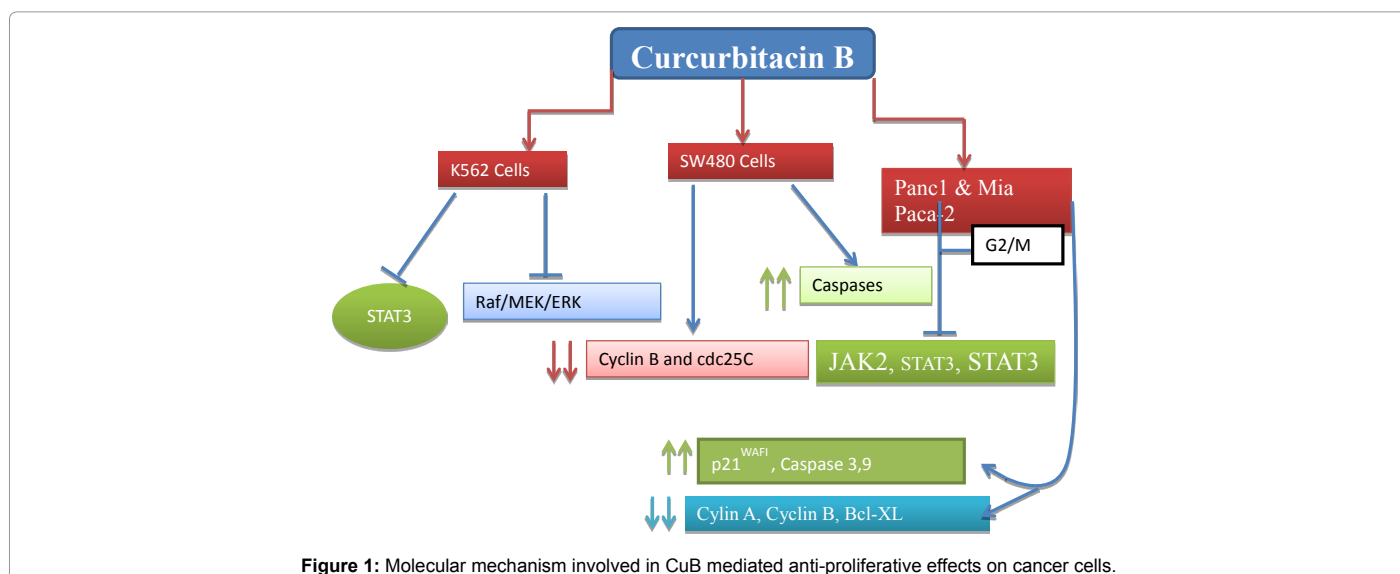
Free radical scavenging occurs by two methods- (i) non-enzymatic action (chemical method) and (ii) enzymatic action. Nutraceuticals like polyphenols and flavonoids are the players under the non-enzymatic action. Endogeneously synthesized enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx or GSH-Px) are the players under enzymatic action. SOD and CAT act primarily in the cytoplasm and form the first line of defense against oxidants [78]. A growing line of evidence suggests that imbalances in the ratio of oxidant/antioxidant induces lipid peroxidation. Enhanced levels of thiobarbituric acid reactive substances (TBARS) with simultaneous depletion of various antioxidant enzymes are found in several cancer types of like cervical, oral, breast, prostate and Hodgkin's lymphoma [79-84]. Balanced food containing antioxidant rich nutrients modulate antioxidant defense mechanisms and display better health. The concept of developing biomedicine/epigenetic diet to prevent gut-associated pathogenesis requires identification of broad spectrum gastroprotective epigenetic nutraceuticals. Plant derived dietary extracts have been found to show their broad spectrum activities such as antioxidant properties, prebiotic action and modulation of proton pumping ATPase [35,85]. Extracts of green tea, broccoli sprouts, turmeric and soybean have been reported for their broad spectrum biological activities including antioxidant properties and epigenetic regulators in gut associated cancers [2,3,86]. These have been recognized as epigenetic diet (Table 3).

### Nutraceuticals Employed in Cancer Therapeutics

In recent years, an array of experimental evidence has underlined the importance of traditional medicines which have been served through ages for prevention and treatment of various types of chronic

Epigenetic modulators	Activity at the target
1. Curcumin	Reactivation of epigenetically silenced gene (demethylation of DNA), inhibits HDAC1, HDAC3, p300 and p300 HAT activity [98,106-108].
2. Genistein (Phytoestrogens)	Inhibition of DNMT, reactivation of epigenetically silenced genes (p16INK4a, RAR beta, and MGMT) [100,109].
3. Epigallocatechin (EGCG)	Inhibition DNMTs, modulate expression of 16-miRNA and inhibit HDAC
4. Apple polyphenols	Inhibition DNMT and reactivate epigenetically silenced TSGs [112].
5. Resveratrol	Activation class III HDACs [113].
6. SCFAs	Histone deacetylase inhibitors (HDACi) [114-116,15].
7. Butyrate	Epigenetic remodeling and the expression of pluripotency-associated genes of stem cell derived from human adult or fetal fibroblasts [117].
8. Sodium butyrate	Modulate expression of cathelicidin gene by regulating activator protein 1 (AP-1) and histone acetylation of cathelicidin promoter [118].

**Table 3:** Chemopreventive epigenetic modulators from dietary plants and probiotics.



**Figure 1:** Molecular mechanism involved in CuB mediated anti-proliferative effects on cancer cells.

ailments. Gastroprotective nutraceuticals such as triterpenoids, flavonoids and polyphenols have also been reported to be meaningful in the treatment of various types of cancer.

### Triterpenoids

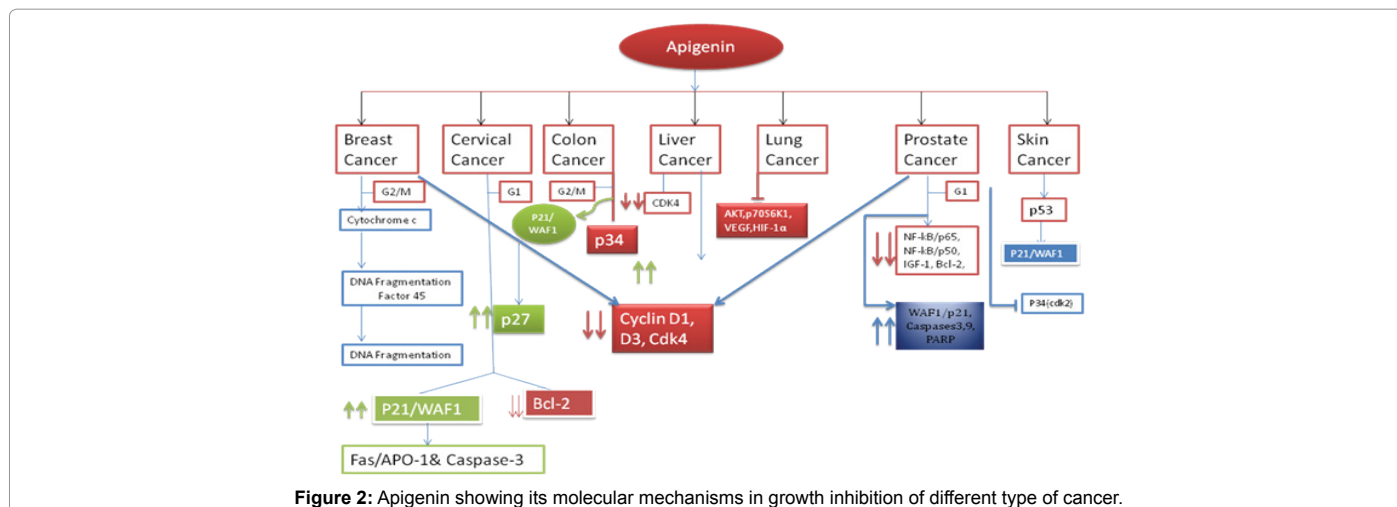
Fruits and vegetables are rich source of triterpenoids. Cucurbitaceous plants contain adequate amount of cucurbitacins which act as microbicidal, anti-inflammatory and anticancer. CucurbitacinB (CuB) is one of the most studied member of triterpenoids. Its anticancer effect has been seen on different leukemia cell lines. Role of CuB as antiproliferative agent on K562 cells through STAT3 activation and the regulation of Raf/MEK/ERK pathway have been reported [10]. Further, study on the K562 cell line demonstrated that cucurbitacin B act as regulator of STAT3 activation and RAf/MEK/ERK pathway. Type of Cucurbitacine B isolated from Thai herb *Trichosanthes cucumerina L.* is reported to be growth inhibitor of breast cancer through supression of hTERT and cMy-c expression). Meixia et al. have demonstrated its (CuB) anticancer effect in pancreatic cancer cells by inhibition of STAT3 phosphorylation, activation of caspase3, up-regulation of p21, p53 and down regulation of both survivin as well as Bcl-2 [87]. The *in vivo* study has revealed the anticancer effect of this compound through by mechanism associated with inhibitory effect on JAK2/STAT3 and decreased expression of Bcl-XL whereas, the expression of caspase3 and caspase 9 was found to be upregulated [14]. Cucurbitacin B, isolated from *Trichosanthes cucumerima L.* has been found to act as immunomodulatory which effectively inhibits the expression of CD69+CD3+, and CD25+CD3+ on PHA-stimulated human peripheral blood mononuclear cells (PBMCs). Molecular mechanisms of CuB has been summarized shown in the figure (Figure 1).

### Flavonoids

Studies made on flavonoids have revealed that have certain anticancer effect. Apigenin is a well studied dietary flavonoid available in fruits band vegetables and been reported to act as a therapeutic agent in various types of diseases including cancer [88]. It has been repoted that apigenin have also demonstrated the growth inhibitory effect on different cancers like leukemia, colon, prostate, thyroid, skin, breast as well as lung cancer [89-95]. It is also reported that apigenin inhibits the lung cancer growth via supression of expression of vascular endothelial growth factor (VEGF), trnscription activation of the hypoxia-inducible factor-1 (HIF-1) binding site through p70S6K1 activation and AKT inhibition [95]. HIF-1 and VEGF have been reported as inducers of angiogenesis. Apigenin acts as anti-angiogenesis in mice by inhibition of expression of HIF-1 and VEGF in lung cancer [95] (). Apigenin has also been reported as apoptosis inducer through the up regulation of FADD expression through the induction of phosphorylation in colorectal cancer cells and plays an anticancer role against colon cancer by direct binding and inhibitionof RSP9 (identified ribosomal protein S9) which leads to the activation of CDK1 [96,97]. In addition , epigenin acts as anti-inflammatory and antioxidant agents [98]. the above studies establish the importance of these nutraceuticals and now these doesnt seem to any dout that these nutraceutical compounds may be given to the cancer patient as dietary supplement to reduce progression of tumor. Disease-specific formulation of nutraceuticals might emerge as new therapeutic suppliment in future (Figure 2).

### Polyphenols Act as Potent Epigenetic Modulators

Epigenetic alterations in pathogenesis like cancer have evolved as



possible target for therapeutic intervention. Epigenetically silenced gene due to either DNA methylation (promoter hypermethylation of cytosines at CpG islands) and histone modifications (acetylation, phosphorylation and methylation) may be reactivated because these alterations are reversible. Hypermethylations within CpG islands of tumor suppressor genes (TSGs) have recently been reported to be associated with pathogenesis of various cancer types [99-101]. Out of various polyphenols, curcumin is one of the most widely studied DPs for its therapeutic use as an epigenetic drug for the treatment and prevention of different types of cancer including colorectal [102]. DPs like 2-epigallocatechin-3-gallate (EGCG) isolated from green tea and genistein isolated from soybean have been found to inhibit DNMT activity against cancer cell lines [103,104]. DNMT inhibitory activity is associated with reactivation of epigenetically silenced genes such as p16, RARb, MGMT, MLH1, BTG3 and GSTP1 in human cancer cells, suggesting a possible alternate phytotherapeutic modality by targeting epigenetically silenced tumor suppressor genes through dietary polyphenols [104,105]. Curcumin has also been reported to exhibit epigenetic modulation in cancer cells by histone acetyltransferase (HAT) and DNMT1 inhibition activities [106-109]. Intake of polyphenols rich nutraceuticals, therefore, protects human gut from malignant transformation.

## Conclusion and Future Prospects

The studies on gut-nutrient-microbiome interactions and their consequences have thrown light towards better understanding of metabolic and physiological modulation of GI functions. Human health largely depends on a healthy enteric system which may be maintained by regular intake of fruits and vegetables [110-115]. Dietary nutrients, probiotics and metabolites derived from enteric symbionts are now established for their utility in improving, gut physiology, immunity, and ultimately a better health. Nutraceuticals such as glutamate, polyphenols, flavonoids, prebiotics, probiotics and SCFAs have now been recognized as potential therapeutic and prophylactic agents to cure various gut-associated ailments. Epigenetic nutraceuticals have recently been implicated for prevention and therapy of a number of diseases and cancers. Disruption of either balanced gut-brain axis or the gut microbiome interactions by inappropriate dietary habits and chemotherapeutic intervention caused dysregulation of GI function resulting into the progression of gut pathogenesis. A balanced combination of diet containing epigenetic nutraceuticals and food based probiotics not only can save from various gut pathogenesis

rather it can act as prophylactic. The role of epigenetic nutraceuticals in the alterations of epigenetic composition of human genome leaves a great future for the researchers in the field [116-122]. Further understanding of molecular cross talk of epigenetic nutraceuticals with the microbiome epigenome and cellular milieu of gut can lead to the development of disease specific formulations of natural medicine. This will open new vistas in therapeutics.

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