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CLINICAL STUDY

Use of probiotics for prevention of radiation-induced diarrhea

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Abstract: Probiotics can be applied in therapy and mainly in prevention of many civilization disorders. Experimental studies in animal models and clinical trials of patients with inflammatory bowel disease (IBD) have consistently shown that the use of probiotic organisms may effectively down-modulate the severity of intestinal inflammation by altering the composition and metabolic and functional properties of indigenous flora of the gut. Previous studies showed a protective effect of probiotic administration after radiation therapy, and probiotic may play an important role in the pathogenesis of radiation enteropathy. These studies indicate that probiotics may decrease the risk of accumulated reactive oxygen species (ROS) in host organisms and could potentially be used as probiotic food supplements to reduce oxidative stress *(Tab. 2, Ref. 47)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: probiotics, radiation-therapy, diarrhea.

Exposition to ionizing radiation or neutrons in a dose exceeding 0.7 Gy leads to the development of acute radiation syndrome manifestations. Apart from the non-specific nerve and humoral stress reaction reflected in the activated hypothalamic-pituitary-adrenal axis accompanied by the production of corticoids and release of biogenous amines (serotonin, histamine, heparin, and prostaglandins), the clinical picture is marked with system failures, represented mostly in the so-called radiosensitive cell populations. The generally accepted law is the basic law of radiobiology from the year 1906 (the Law of Bergonie and Tribondeau) saying that it is the less differentiated cells with high mitotic activity (i.e. bone marrow stem cells, reproductive cells of the intestinal and skin epithelium and seminiferous tubules) that are most likely radiosensitive (1).

The intestinal system is extremely complex, consisting of three basic components: host cells, microflora and ingested food. It plays a major role in the immunity of an organism through the mucous membrane barrier, colonisation resistant microflora and GALT *(gut associated lymphoid tissue)* system. Damage caused to any of the said components leads to disease (2). Apart from strengthening the barrier function, the intestinal flora also influences the expression of genes regulating postnatal enterocyte maturation, metabolism, and angiogenesis (3).

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Definition of acute enteritis

Radiation enteritis (being a subunit of acute radiation syndrome) is a summary of inflammatory and degenerative processes affecting all parts of gastrointestinal tract that develop following a radiation dose of 8 Gy and more approximately after 5 to 8 days after exposure. Pathologically and anatomically we deal with enteritis necroheamorrhagica acuta, resp. duodenitis, jejunitis or ileitis (4).

The "deep tissue damage following exposure to X-rays" affecting the gastrointestinal tract was described by Walsh in 1897, two years after radioactivity had been discovered by Becquerel. Walsh came to the conclusion that ionising radiation causes direct inflammation of the intestinal mucous membrane. The "frightening effects" of ionising radiation on the intestine were mentioned by Claude Regaud in 1912 (5). The first systematic study on the effect of radiation on the structure and function of the intestine *in vivo* was published by Waren and Whipple in 1922 (6).

Definition of chronic enteritis

Within the period of 6 weeks to 10 years (with the maximum limits of 6 months up to 5 years) following irradiation with subliminal doses (7), sub-acute or chronic intestinal damage develops gradually. Endothelial proliferation and occlusive vasculitis result in ischemia. Deposits of submucosal collagen foster the development of progressive fibrosis (8, 9), which results in deep ulcerations penetrating the whole intestine wall, necroses, perforations, abscesses and fistules. The ulcerations heal with more fibroses and scarring, and stenoses and obturations develop (9). Clinical picture and X-ray findings are suggestive of the diagnosis of small intestine obstruction, which usually tends to be in-

termittent (7). Chronic changes in the irradiated intestine affect the majority of patients after abdominal-pelvic actinotherapy (15 %), or 0.5–16.9 %, require surgical intervention (5 %) are extremely difficult to manage and often take a fatal course (10).

Pathogenesis of post-radiation enteritis

The generally accepted opinion is that the cause of sub-cellular and cellular pathogenesis of radiation enteritis is unknown. The ionising radiation activates signal pathways induced by impaired intracellular homeostasis based on DNA damage. The decrease in DNA replication and transcription activity is dose dependent, with replication radiosensitivity being (cca 40 times) higher than transcription radiosensitivity – Harrington's experiment (1). The result is a stress reaction leading to cell cycle inhibition in stages G1/S and G2/M. Cell proliferation inhibition gains enough time necessary to repair the damaged DNA sequences. In case the repair is not possible, the process of apoptosis is activated (11). In metazoans the apoptic programme is safeguarded by an anti-oncogene – the tumour suppressor protein TP53 that mediates the inhibition of the cell cycle in the G1-stage (11, 12). The activation of a block that is non-dependent on TP53 requires the presence of two forms of choline kinase marked CHK1 and CHK2 that regulate the transition from the G2/M-stage. Latest research shows that the cellular response to ionising radiation is much more complicated than expected and that apart from the cell cycle inhibition and DNA reparation there also shows the activation of the so-called "quick genes". In case of irradiation, these genes transfer signals that trigger long-term changes in gene expression and make it possible for mammal cells to adapt to radiation stress.

The alteration of the classic signal pathway may show on multiple levels:

1) Activation of the membrane receptor without the presence of a specific ligand (inhibition of receptor dephosphorylation) (13).
2) Increased production of (H)-Ras proto-oncogene (Harvey retrovirus associated sequence) (14).
3) Proteinase C activation (15).
4) Activation of transcription factors – nuclear factor κB (NF-κB) (14).

NF-κB is an important component participating in the regulation of many genes located on the eukaryotic nuclear DNA. Ionising radiation activates NF-κB most probably via the action of reactive oxygen metabolites or via a ceramide released by enzymatic sphingomyelin hydrolysis (14). NF-κB may also be activated by a whole range of other stimuli such as cytokines IL-1, IL-2 a TNF-α, bacterial lipopolysaccharides, virus products and mitogens (phorbol 12-myristate 13-acetate). NF-κB activation is transient and feedback-regulated (16).

Oxygen radicals act via the inhibition of IB phosphorylation of transcription inhibitors, which causes their degradation to single proteins. Protein dimmers give rise to a transcription activator NF-κB, which migrates from the cytoplasm to the nucleus, binds with DNA, and induces gene expression. Proteosynthesis takes place, and adhesive molecules (predominantly E-selectin and ICAM-1) (17) and their ligands or factors on the surface of neutrophils (especially β2-integrines) (16, 18) are expressed on the surface of the irradiated endothelia.

Expression of adhesive molecules following GIT irradiation

The initial step is a weak reversible adhesive interaction that slows down the flowing leukocyte, and changes it into a leukocyte rolling along the endothelial cell. The potent adhesive powers result in adherence, with the rolling leukocyte adhering firmly to the endothelium and turning into a stationary leukocyte. Adherence is safeguarded by adhesive molecules – on the surface of the endothelium it is the expressed intercellular adhesive molecule ICAM-1 (intercellular adhesion molecule-1, CD54), and on the surface of neutrophils the second leukocytary β2-integrin also known as Mac-1 (CD11b/CD18) (16, 17, 18). In GIT organs the expression of endothelial ICAM-1 is significantly increased following the stimulation by TNF-α or a lipopolysaccharide with the maximum of 5 hours and elevated residual levels during the period of 24 hours (16). The space between the two adjoining endothelial cells is used for the migration of leukocytes into the interstice. This phenomenon again is the result of interacting adhesive molecules. Apart from the above-stated ICAM-1 and ββ2-integrin, it is also PECAM-1 (platelet endothelial cell adhesion molecule, CD31) that seems to be decisive in neutrophil extravasation. PECAM-1 plays an active role in the transfer of leukocytes through the basal membrane of the mesenteric endothelium (19).

The role of neutrophils in the reaction to irradiation

Neutrophils activated by interaction with the endothelium and by the effect of cytokines damage the tissue via three mechanisms of action:

1) By generating more free oxygen radicals.
2) By secerning the group of proteases (elastase, collagenase, gelatinase) into the extravascular environment.
3) By producing a whole range of pro-inflammatory cytokines and chemokines.

On the sub-cellular level, both the direct and the indirect impacts of radiation cause damage to the membrane structures, mitochondria and cytoskeleton as well as to nuclear acids macromolecules in enterocyte nucleus. Most frequently occurring changes are observable in cryptal epithelium. Already in the course of the first few hours following irradiation using supraliminal doses it is possible to observe a rapidly progressing pycnosis, karyolysis, karyorexis, and extrusion of cell residues into the lumen. The mitotic activity in the crypts, which is high in normal conditions considering the rapid cell cycle, is extremely decelerated following irradiation. Cylindrical cells decrease progressively. Cell necrosis reaches its maximum within 6 to 8 hours.

Morphological changes occurring in intestinal mucosa

In 24 hours following irradiation, characteristic changes start developing as a result of the disturbed balance between enterocyte

proliferation and depletion. The decrease in the number of effector cells leads to denudation of the basal membrane, crypts and villi in the course of 3 to 4 days. Microulcerations occurs in various segments. Numerous foci of microhaemorrhages cause the presence of bloody liquid the intestinal lumen. More extensive ulcerations may result in the perforation of the intestinal wall. The alteration of structure of crypts and villi leads to their gradual atrophy (7). Some authors refer to the separation of villous epithelium from lamina basalis and intraepithelial oedema. Morphological changes in the epithelium are accompanied by subepithelial protein and fibrin precipitation, leukocytic infiltration and intestinal wall oedema (20). Leukocytic accumulation (neutrophils, lymphocytes, macrophages) in the tissue diagnosed by histology is the main cause of inflammation. The joint action of leukocytic activation and infiltration of the tissue followed by the release of proteases and secondary oxygen radicals is responsible for the radiation-induced and neutrophils-mediated tissue damage (16).

Within five to seven days following irradiation the present villi are significantly atrophic and partially covered with small amounts of residual epithelium, or they are denudated – "naked" (7, 21). During actinotherapy, the duodenum, proximal jejunum and terminal ileum are reached and affected by higher doses (7). The post radiation inflammatory changes are non-specific and difficult to distinguish from inflammation resulting from other diseases (such as m. Crohn) by means of histological examination. Acute inflammatory changes develop in up to 50–75 % patients treated with radiotherapy (19, 22).

Functional changes of the intestinal mucosa

Functional changes occur within hours following irradiation. The said changes affect intestinal motility and play an important role in the process of timely reaction to symptoms in the prodromal stage. The physiological character of peristalsis is severely damaged. Shortly after irradiation the contractile waves become significantly irregular with dramatically strengthened "shifting" contractions and the activity of aberrant pacemakers in the distal parts of the intestine initiates the retrograde propagation causing nausea, vomiting etc. (23, 24). The deepithelization of the intestinal mucosa that culminates on the day 5 to 7 after irradiation results in functional failure of the intestine. The secretion, absorption, as well as immune function of the intestines is impaired. Extensive areas of superficial ulcerations are the sites through which electrolytes, proteins and water pass (7, 23). For several days up to weeks following exposure to ionising radiation the Na^+-K^+-ATP-ase activity is decreased in the small intestine mucosa, its absorption capacity is decreased and results in malabsorption diarrhoea (25). Under physiological conditions, bile acids are nearly completely reabsorbed in the small intestine. Due to the loss of epithelium following irradiation the reabsorption of conjugated bile acids decreases by 50–85 %, since the said acids undergo deconjugation by intestinal bacteria, bind with water and cause diarrhoea (20). The malabsorption of bile acids and lactose and the misbalance in the composition of local intestinal flora as well as the changes in the structure of intestinal motility lead to profusion diarrhoea. The devastated epithelium causes the important barrier function against intestinal microorganisms, especially bacteria (microbial lift) and their toxins to fade. The normal intestinal flora turns into a pool of virulent pathogens. Apart from gram-negative *Enterobacteriaceae* there also is *Clostridium difficile. Clostridium difficile*, an anaerobic spore-forming gram-positive bacillus, is part of a normal intestinal flora, and is present in 3 % of healthy adults, in 15–30 % of hospitalised patients, and 50 % of newborns. Infections, septicaemia, and toxaemia develop (26). Apart from the damage of mucous membrane barrier, this is preconditioned by coinciding pancytopoenia and loss of immunity. It is leucopoenia combined with maximal epithelium denudation that is the cause of fatal sepsis (7). Doses of 6–10 Gy and more give rise to a mixed form of acute irradiation syndrome, which is a combination of marrow depression and gastrointestinal syndrome. During the local irradiation of the abdominal cavity, intestinal dysfunction shows a character similar to cases of whole body irradiation, however with substantially less bone marrow damage expression.

Almost all regimens of radiation therapy may disturb the colonisation resistance of the indigenous gut flora. This is the main mechanism underlying the pathophysiology of acute radiation-induced enteritis and colitis, which are a common and potentially severe complication among cancer patients treated with radiation therapy. Attempts to treat this complication with antibiotics, sucralfate, anti-inflammatory drugs such as mesalazine and balsalazide, glutamine, octreotide, proteolytic enzymes and hyperbaric oxygen have so far provided inconclusive clinical results with failure of treatment occuring in a substantial proportion of patients (27, 28). Futhermore, prophylactic use of sucralfate does not reduce the burden of radiation-induced bowel toxicity, but rather is aasociated with more severe gastrointestinal symptoms including bleeding and fecal incontinence (29).

Usage of probiotics in biomedicine

What seems very beneficial in this context is the therapeutic use of probiotics. The term *probiotic* was for the first time used by Parker in 1974 to describe organisms and substances that improve microbial balance in the intestines (30). Despite varying opinions, the term probiotics has been used worldwide universally to name substances or products containing a sufficient amount of viable microorganisms capable of changing the microflora of their host after implantation or colonisation and showing their salubrious effects. Probiotic action is not limited to the gastrointestinal tract (GIT), but may show in the urogenital or respiratory tract as well. For practical reasons, the method that seems to be the most advantageous is increasing the efficacy of probiotic agents by combining the same with indigestible food components that show synergistic action – *prebiotics* (31). These are combined with preparations called potentiated probiotics. Table 1 gives an overview of the potential clinical indications in the therapeutic use of probiotics (32, 33).

As regards probiotics, the salubrious and medicinally safe microorganisms include especially lactic acid bacteria (*Lacto-*

Tab. 1. Potential clinical application of probiotics.

– Prevention and therapy of ATB induced infectious and postradiation diarrhoea
– Eradication of H. pylori
– Primary and secondary prevention of tumours (colorectal carcinoma, prostate carcinoma and breast carcinoma)
– Prevention of gastrointestinal and urogenital infections as well as surgical infections
– Immunomodulatory effect in rheumatic and allergic diseases
– Autoimmunity
– Hepatic encephalopathy therapy (as an alternative to lactulose)
– Maintenance therapy in idiopathic intestinal inflammations, irritable bowel syndrome, constipation
– Lactose intolerance
– Lower cholesterol levels and improvecd arterial hypertension
– Prevention of osteoporosis

bacillus), bifidobacteria, some cocci *(Enterococcus)*, *Saccharomyces, E. coli,* yeasts or spore-forming bacteria *(Bacillus, Sporolactobacillus, Brevibacillus)* (Tab. 1, 2) (34).

Mechanisms of action in probiotic agents

Despite the amount of knowledge gained, the mechanism of action of probiotic agents remains unknown. Competition takes place in the gastrointestinal tract, in the course of which the physiologically beneficial probiotic microorganisms outplay microorganisms that show pathogenic action. Probiotics participate in the processes of immunity regulation, especially by maintaining the balance between pro-inflammatory and anti-inflammatory cytokines.

The mechanism of inhibition action of probiotics against pathogens may be based on:

– competition for adhesive spots on the intestinal mucosa,
– competition for substrate,
– production of bactericides and antibiotics inactivating other bacteria or signaling molecules that regulate the growth of pathogens,
– inhibiting the inflammatory process in atopic diseases,
– immunomodulatory effect (induced oral tolerance, supported anti-infectious immunity, stimulated IgA antibody production, activated complement, supported phagocytises),
– reducing pro-carcinogenic substances produced by the pathological intestinal flora,
– a combination with probiotics through improved absorption of minerals (Ca, Mg, Fe, Zn) in the large intestine, a change of microenvironment by lowering the pH.

Probiotics and the immune system

In normal circumstances, the intestinal flora stimulates not only the development of local but also of systemic immunity (35), with the immunomodulatory effect of probiotics showing both after oral and subcutaneous administration (3, 36). The employment of probiotic bacteria leads to the stimulation of non-specific immunity – especially phagocytosis but also humoral immunity – and to increased production and secretion of IgA, cytokines TNF-α, IL-6, IL-2, IL-5 and IL-1. Decrease in reversion of age-related cytokine level, activation of T-lymphocytes, and modulation of the ratio between Th1 and Th2 lymphocyte subpopulation were observed. Following a targeted colonisation of premature babies by a non-pathogenic strain of *E. coli 083* a stimulation of the immune system was observed resulting in the eradication of intestinal pathogens, significant decrease in the presence of nosocomial infections and decreased necessity to commence a therapy employing antibiotics (37). The study by Fooks *et al* recorded a significant increase in gamma-interferon levels in instances of oral administration of probiotic agent (38). The positive effect of probiotics is also observable in allergic diseases, where the application of the said agents is followed by melioration of symptoms in patients suffering from atopic dermatitis, asthma, rhinitis or food allergies.

One question remains unanswered, namely into what extent the stimulation of immunity may be employed in an oncological patient immunosuppressed by the underlying disease as well as the applied chemo- and radiotherapy.

The usage of probiotics in prophylaxis and therapy of radiation enteritis is based not only on theoretical presumptions, but also on the results obtained by carrying out multiple clinical trials.

The aim of the **study of Delia and colleagues** was to investigate the efficacy of high-potency probiotic preparation on prevention of radiation-induced diarrhea in cancer patients. This was a double-blind, parallel-group, placebo-controlled trial. Four

Tab. 2. Medicinal effects of probiotic bacteria (31).

Known medicinal effects	Probiotic strains
Modification of the immune system	L. acidophilus, L. casei, L. plantarum, L. delbrueckii, L. rhamnosus
Harmonisation of the intestinal flora	L. acidophilus, L. casei, B. bifidum
Lower carcinogenicity	L. acidophilus, L. casei, L. gaserri, L. delbrueckii
Anticancerous effect	L. acidophilus, L. casei, L. gaserri, l. delbrueckii, L. plantarum, B. infantis, B. adolescentis, B. bifidum, B. longum
Prevention of traveller's	Saccharomyces spp., zmes L. diarrhoea acidophilus, B. bifidum, Streptococcus thermophilus, L. bulgaricus
Prevention of rotavirus-induced diarrhoea	L. rhamnosus, B. bifidum
Prevention of C. difficile-induced	L. rhamnosus, S. diarrhoea spp.
Prevention of other diarrhoea types	L. acidophilus, L. rhamnosus, B. bifidum

hundred and ninety (490) consecutive patients attending the outpatient clinics of the Cancer X-Ray Unit of the University of Messina, Italy, from May 1999 to December 2005, who had received adjuvant postoperative radiation therapy after surgery for sigmoid, rectal, or cervical cancers were randomly assigned either to treatment with VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, MD), or to VSL#3-identical appearing placebo starting from the first day of radiation therapy until the end of the scheduled cycles of radiation therapy.

Each sachet of VSL#3 contained 450 bilions/g of viable lyophilized bacteria, including four strains of lactobacilli (*L. casei, L. plantarum, L. acidophilus and L. delbruekii subsp.* Bulgaricus), three strains of bifidobacteria (*B. longum, B. breve and B. infantis*) and one strain of *Streptococcus salivarius subsp. thermophilus.* Patients were eligible for inclusion if they had no contraindication for probiotic, antibiotic or radiation therapies. The study subjects were followed up weekly during the scheduled cycle of radiation therapy and then 1 month after the completion of radiation therapy. Efficacy endpoints were incidence and severity of radiation-induced diarrhea, number of patients who discontinued radiotherapy because of diarrhea, daily number of bowel movements, and the time from the start of the study to the use of loperamide as rescue medication for diarrhea. The randomisation was balanced between treatment groups in terms of sex, age, nodal involvement, tumor grade and size, local invasion at operation, invasion of contigous structures at histology, and postoperative complications. The total X-ray dose the patients were given was between 60 and 70 Gy [28].

Results

More placebo patients had radiation-induced diarrhea than VSL#3 patients (124 of 239 patients, 51.8 %, and 77 of 243 patients, 31.6 %; $p<0.001$) and more patients given suffered grade 3 or 4 diarrhea compared with VSL#3 recipients (55.4 % and 1.4 %; $p<0.001$). Daily bowel movements were 14.7 ± 6 and 5.1 ± 3 among placebo and VSL#3 recipients ($p<0.05$), and the mean time to the use of loperamide was 86 ± 6 h for placebo patients and 122 ± 8 h for VSL#3 patients ($p<0.001$). $p<0.05$ was taken as significant.

It was demostrated in a large sample of patients that the probiotic therapy with VSL#3 was beneficial for the prevention and/or reduction of both the incidence and severity of enteritis and colitis associated with adjuvant radiation treatment after surgery for abdominal and pelvic cancer. VSL#3 was also a high-potency preparation with unique characteristics compared with traditional probiotics, in particular, because of the enormously high bacterial concentration and the presence of a consortium of different bacterial species with potential synergistic relations between different strains that may greatly enhance the suppression of potential pathogens. The composite mixture of VSL#3 possessing very different and specialized metabolic and immunoregulatory activities (39). VSL#3 lactobacilli lower the production of proinflammatory cytokines and several other effectors of inflammation and tissue injury, such a nitric oxide and metalloproteinases, interfere with the pro-inflammatory signal transduced by toll-like receptors, exert a significant protection upon the integrity of the intestinal epithelial barrier, and down-modulate the process of apoptosis. This latter mechanism is of utmost importance because the triggering of an unregulated process of apoptosis is regarded as the main factor ultimately responsible for the radiation-induced injury of the intestinal epithelium (40). Furthermore, probiotic bacteria up-regulate the innate immune response in the gut and are thus part of a protective mechanism against invasive organisms, which is important when ileal and colonic protection against invading organisms is severely impaired as a result of exposure to radiation.

Probiotic lactic acid-producing bacteria are an easy, cheap, safe and feasible approach to effectively protect cancer patients against the risk of radiation-induced diarrhea, which is a severe and potentially lethal complication of radiation therapy for cancer (41). Medline search yielded indeed only one other study with probiotics, i.e. the double-blind and randomized trial by *Urbancsek and colleagues* who reported results with *Lactobacillus GG* treatment. *Lactobacillus GG* treatment for IBD patients have provided conflicting results and the true clinical efficacy of this probiotic strain is still substantially unclear (42).

The experience with the administration of probiotic bacteria in neutropoenic patients suffering from oncological diseases is very limited due to the fear of triggering an iatrogenic infection in immunocompromised individuals. The literature offers a number of cases where lactic acid bacteria have caused local infections of the thorax, gastrointestinal and urogenital tract as well as meningitis (43). What results from this experience is the very natural requirement regarding the sensitivity of probiotic strains to antimicrobial substances used in everyday clinical practice. On the other hand, competitive inhibition of colonisation of the intestine by pathogenic organisms via lactic acid bacteria could possibly be one of the possibilities to prevent febrile neutropenia in oncologic patients. Compared with the existing selective decontamination of the intestine using quinolones and/or trimethoprim-sulfamethoxazole, it is possible to expect a decreasing incidence of fungal and gram-positive infections based on the influence exerted on intestinal microflora.

Discussion

Many oncologic patients are being treated with radiotherapy, and the effects of radiation are especially profound in the tissues undergoing rapid cell turnover. The intestinal mucosa is particularly susceptible to damage (44). Radiotherapy may damage intestinal barrier function, change bacterial flora, alter vascular permeability and intestinal motility. Some patients undergoing abdomino-pelvic radiotherapy will develop radiation-induced intestinal injury. Radiation-induced enteritis is characterized by severe intestinal dysfunction and intestinal complications associated with significant morbidity and mortality.

Although the pathogenesis of radiation enteritis is not clear, reactive oxygen species (ROS) have been proposed to act as mediators of cell injury in the digestive system after radiotherapy.

Excessive ROS production may lead to oxidative stress, loss of cell function, and cell death by apoptosis or necrosis. Oxidative stress such as ionizing radiation produces a variety of highly reactive free radicals that damage cells, initiate signal transduction pathways, and alter gene expression. Cells are capable of countering the effects of oxidative stress by virtue of a complex redox buffering system (45).

Some earlier studies suggested that the use of certain bacterial preparations or artificial nutritional support may decrease acute symptoms of radiation-induced acute intestinal injury. Probiotics may modulate mucosal and systematic immunity by altering the composition and the metabolic and functional properties of enteric flora (46). Probiotic substrates such as yoghurt and other dairy products can be given to patients receiving radiotherapy by oral-enteral route to prevent radiation-induced enteritis and related malnutrition. The health benefit of lactic acid bacteria have been attributed to their production of EPS (exoplolysaccharides), which has antitumoral, antiulcer, immunomodulating, or cholesterol-lowering activity (47).

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