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REVIEW

Putative Roles of Aloe vera and Butyrate/Hyaluronan Fermented in Aloe vera for Irritable Bowel Syndrome

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ABSTRACT

The irritable bowel syndrome (IBS) is a fundamental bowel disorder that generates a significant health care burden. The treatment of IBS consists in lifestyle, such as diet and exercise. Butyrate and its supplementation represent potential new IBS therapy. We describe that butyrate may play a beneficial role in treatment of gastrointestinal receptors and aloe vera fermented butyrate is a possible diagnostic biomarker for IBS patients. Furthermore the roles of hyaluronane (HA) from aloe vera endophytic microbiome, for inflammatory bowel disease are discussed.

Key words: *Aloe vera*; Butyrate fermented; Hyaluronan; Irritable bowel syndrome; IBS subgroups; IBS-D; IBS-C; IBS-M

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic-mediated disease characterized by inflammation and ulceration of mucosal and submucosal layers of colon. IBDs include two basic types, namely Crohn's disease (CD) and ulcerative colitis (UC). UC is an idiopathic, chronic inflammation disorder of the colonic mucosa, which starts in the rectum and generally extends proximally in a continuous manner through part or the entire, colon. *Aloe vera* has been claimed to have anti-inflammatory effects and widely used by patients with IBD, despite a lack of evidence of its therapeutic efficacy.

Aloe vera and *A. arborescens* are thought to be useful for treating some of the symptoms associated with irritable bowel symptoms (IBS), such as constipation and diarrhea. The anti-inflammatory properties of *Aloe vera* and *A. arborescens* may be help to reduce gastrointestinal inflammation in which can contribute towards IBS syndromes. Langmead et al^[1] investigated a double-blind, randomized, placebo-controlled trial of the efficacy and safety of aloe vera gel for 44-evaluable hospital out-patients with the mildly to moderately active UC. Oral aloe vera gel taken 4 weeks produced a clinical response more often than placebo; it also reduced the histological disease activity and appeared to be safe. Aloe vera juice ingestion to Iranian IBS-33-patients was treated by Khedmat et al^[2] on 2013. Evidence of the effects of aloe vera extract in the treatment of IBS, is limited, and positively reduced abdominal pain and flatulence in patients with constipation predominated IBS while it is unable to improve urgent and frequency as well as consistency of stool in these patients. A pilot study of the effect of *Aloe vera* extract (AVH200: aloe vera extract 250 mg and ascorbic acid 60 mg, in an

effervescent tablet) in 173 patients with IBS in a randomized, double-blind, placebo controlled study, was investigated by Storsrud *et al.*^[3]. AVH200 (NCT01400048) seems to be a promising treatment option for patients with IBS owing to the positive results seen within the secondary endpoints. To evaluate the efficacy and safety of *Aloe vera* in patients with IBS, Hong *et al.*^[4] searched the Medline, Embase, and Cochrane databases for studies dated between 1st January 1960 and 30th December 2017. Eligible randomized controlled trials compared *Aloe vera* to placebo in patients with IBS. *Aloe vera* is effective and safe for the treatment of patients with IBS compared to placebo.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well-known for exerting numerous adverse effects on the gastrointestinal tract and negatively influence intestinal integrity. Kim *et al.*^[5] investigated the anti-ulcer effects of *Aloe vera* on the small intestine, especially focusing on mucin expression. The authors indicated that processed aloe vera gel (PAG) treatment attenuates not only the severity of intestinal ulcers but also bacterial translocation, by enhancing the mucus layer in the indomethacin-induced small intestinal damage mouse model. Furthermore the authors confirmed that PAG positively regulates the mucin expression in the LS174T human cell line, mainly via the extracellular signal-regulated kinase-dependent pathway.

A fundamental function of the intestinal epithelium is to serve as a barrier between luminal contents and the underlying immune system and the remainder of the body, while simultaneously supporting vector transport of nutrients, water and waste products and ion. Epithelial barrier function requires a contiguous larger of cells as well as the junctions that seal the para-cellular space between epithelial cells. Regulation of tight junctions by extracellular stimuli; nutrients, cytokines and immune cell by tight junctions is composed of a complex network of transmembrane and cytosolic protein accomplished by cytoskeletal and regulatory proteins. Two distinct pathways- termed pore and leak- regulate para-cellular flux in intact epithelial, whereas the unrestricted flux pathway is the dominant route across ulcerated or damaged epithelia. Reduced intestinal epithelial barrier function is associated with a variety of gastrointestinal and systemic diseases including IBS. Odenwald *et al.*^[6] discussed mechanisms of intestinal barrier loss and the role of intestinal epithelial barrier function in IBS. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier. Low-fiber diet consumption was found to trigger the expansion of mucin-degrading bacteria by Desai *et al.*^[7]. Using a gnotobiotic mouse model, in which animals were colonized with a synthetic human gut microbiota composed of fully sequenced commensal bacteria, the authors elucidated the functional interactions between dietary fiber, the gut microbiota, and the colonic mucus barrier, which serves as a primary defense against enteric pathogens. The authors found that during chronic or intermittent dietary fiber deficiency, the gut microbiota resorts to host-secreted mucus glycoproteins as a nutrient source, leading to erosion of the colonic mucus barrier. Dietary fiber deprivation, together with a fiber-deprived, mucus-eroding microbiota, promotes greater epithelial access and lethal colitis by the mucosal pathogen. The intestinal barrier includes surface mucus, epithelial layer and immune defenses. Epithelial permeability results from increased para-cellular transport, apoptosis or transcellular permeability. Camilleri^[8] reviewed on leaky gut for clinicians discussing the components of the intestinal barrier, the diverse measurements of intestinal permeability, their perturbations in non-inflammatory 'stressed states' and the impact of treatment with dietary factors.

Present paper describes how a fiber-deprived gut microbiota

mediates degradation of the colonic mucus barrier and butyrate fermented and hyaluronan enhance as a diagnostic biomarker for the patients with IBS.

FECAL SHORT-CHAIN FATTY ACIDS IN SUBJECTS WITH AND WITHOUT IBS

Butyrate fermented and its therapeutic role in metabolic syndrome

Metabolic syndrome (MetS) and the associated incidence of cardiovascular disease and type 2 diabetes represent significant contributors to morbidity and mortality worldwide. People with IBS syndromes typically manage their symptoms through lifestyle changes including a diet with high levels of fiber, such a type of non-digestive polysaccharide of *Aloe vera* and *A. arborescens*. In our previous paper we described the fermentation of short chain fatty acids by endophytic bacteria in *Aloe* species^[9, 10]. Butyrate produced by the gut microbiome and endophytic bacteria in *Aloe vera* and *A. arborescens* improves MetS parameters including insulin sensitivity and intestinal glucagon-like peptide-1 secretion in in vitro and animal studies^[11].

Fecal short-chain fatty acids: a diagnostic biomarker for irritable bowel syndrome (IBS)

Farup *et al.*^[12] evaluated the properties of fecal short-chain fatty acids (SCFAs) as diagnostic biomarkers for IBS. In the IBS and control group; twenty-five subjects with IBS and 25 controls were included in the explanatory case-control study. Stool samples were analyzed for SCFAs. The study indicated that fecal SCFA could be a non-invasive, valid and reliable biomarker for the differentiation of healthy subjects from subjects with IBS. The difference between propionic and butyric acid (mmol/L) had the best diagnostic properties.

The alteration in fecal short-chain fatty acids in patients with irritable bowel syndrome (IBS)

Sun *et al.*^[13] performed a meta-analysis to explore and clarify alterations in fecal SCFAs in IBS patients. Case-control studies, randomized controlled trials, and self-controlled studies were identified through electronic database search. Concentration of fecal propionate and butyrate in patients with constipation-predominant IBS (IBS-C) was significantly lower than that in healthy control (HCs), and the concentration of fecal butyrate in patients with diarrhea-predominant IBS (IBS-D) was higher than that in HCs. In term of fecal SCFAs there were differences between patients with IBS and healthy controls (HCs). In IBS-C patients, propionate and butyrate were reduced, whereas butyrate was increased in diarrhea-predominant IBS-D patients in comparison to HCs. It was concluded that restricted diets correlated with fecal butyrate reduction in IBS and propionate and butyrate could be used as biomarkers for IBS diagnosis.

BENEFICIAL EFFECTS OF BUTYRATE IN INTESTINAL INJURY

The effect of butyrate on the intestinal barrier

The molecular mechanisms underlying the butyrate regulation of the intestinal barrier was investigated by Peng *et al.*^[14]. The authors determined the effect of butyrate on the intestinal barrier by measuring the trans-epithelial electrical resistance and inulin permeability in a Caco-2 cell monolayer model. The authors further used a calcium switch assay to study the assembly of epithelial tight

junctions and determined the effect of butyrate on the assembly of epithelial tight junction and AMP-activated protein kinase activity (AMPK). The authors concluded that butyrate enhances the intestinal barrier by regulating the assembly of tight junctions. This dynamic process is mediated by the activation of AMPK, and these results suggest an intriguing link between SCFA and the intracellular energy sensor for the development of the intestinal barrier.

Protection of butyrate for the intestinal epithelium developing the disease like necrotizing enterocolitis

It is controversial whether butyrate is protective or destructive for the intestinal epithelium in the development of disease like necrotizing enterocolitis (NEC). Liu *et al.*^[15] determined the effect of butyrate on the intestinal epithelium by studying its effects on intestinal epithelial cells exposed to injury and *in vivo* by investigating the effects on the intestine in an experimental model of NEC. The authors concluded that butyrate can protect cells from H₂O₂-induced injury and can *in vivo* protect the intestine from NEC, and this beneficial effect is because of down-regulation of inflammation and enhancement of intestinal barrier.

Modulation of butyrate mucin secretion in LS174T human colorectal cells

Jung *et al.*^[16] investigated butyrate modulates mucin secretion in LS174T human colorectal cells, thereby influencing the adhesion of probiotics such as *Lactobacillus* and *Bifidobacterium* strains and subsequently inhibiting pathogenic bacteria such as *E.coli*. The authors found that butyrate is an effective regulator of modulation of mucin protein production at the transcriptional and translational levels, resulting in changes in the adherence of gut microbiota. Butyrate potentially stimulates the mitogen-activated protein kinase signaling pathway in intestinal cells, which is positively correlated with gut defense.

Dynamical regulation of butyrate for intestinal homeostasis

Intestinal epithelial barrier dysfunction and dysbiosis are central themes of inflammatory bowel diseases (IBDs). Zheng *et al.*^[17] examined if butyrate promote epithelial barrier through the epithelial anti-inflammatory IL-10 receptor α -submit (IL-10RA)-dependent mechanisms. Using human intestinal epithelial cells (IECs) the authors discovered that butyrate enhanced IEC barrier formation, induced IL-10RA mRNA protein, and transactivation through activated Stat3 and HDAC inhibition. Loss and gain of IL-10RA expression directly correlates with IEC barrier formation and butyrate represses permeability-promoting claudin-2 tight-junction protein expression through an IL-10RA-dependent mechanism. These findings provide a novel mechanism by which microbial derived butyrate promotes barrier through IL-10RA-dependnt expression of claudin-2.

Initial studies by Wang *et al.*^[18] revealed that short chain fatty acid butyrate selectively promotes epithelial wound-healing responses. Using unbiased single-cell RNA sequencing approaches, the authors identified a cluster of actin-associated genes regulated by butyrate. Among these, the authors showed the selective induction of the actin-binding protein synaptopodin (SYNPO) as an intestinal tight junction protein with a central role in epithelial barrier regulation. *In vivo* studies revealed that microbiota depletion abolished SYNPO expression that was rescued with butyrate. These findings exhibited a fundamental contribution of microbial butyrate to homeostatic intestinal mucosal function through selective regulation of SYNPO.

PRE-CLINICAL STUDIES OF SHORT CHAIN FATTY ACID BUTYRATE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Alteration of fecal short-chain fatty acids following fecal microbiota transplantation

In the study of the pathophysiology of irritant bowel syndrome (IBS), El-Salhy *et al.*^[19] examined fecal SCFAs after performing fecal microbiota transplantation (FMT) in the IBS patients. FMT increased the fecal SCFA levels in IBS patients. The increase in the butyric acid level is inversely correlated with symptoms in IBS patients following FMT, suggesting that SCFAs might play a role in the pathophysiology of IBS. (NCT03822299)

The effect of a colonic-delivery formation of butyrate on the fecal microbiota of irritable bowel disease patients

The effect of microencapsulated sodium butyrate (MSB) was assessed by Banasiewicz *et al.*^[20] on the severity of symptoms in patients with irritable bowel diseases (IBD). Sixty-six patients treated with one of the standard pharmacological therapies for at least 3 months were excluded in the study. After 4 weeks there was a significant decrease of pain during defecation in the MSB group which extended to improvement of urgency and bowel habits at 12 weeks. Reduction of abdominal pain, flatulence and disordered defecation was not statistically significant. MSB as a supplemental therapy can reduce the frequency of selected clinical symptoms in patients with IBD, without significant influence on reducing symptoms severity. The double-blind, placebo-controlled pilot study by Facchin *et al.*^[21] was randomized to oral administration of microencapsulated-sodium-butyrate or placebo to 49 IBD patients for 2 months, in addition to conventional therapy. Sodium butyrate is important for intestinal health showing anti-inflammatory and regenerative properties. Butyrate administration seems to promote the growth of bacteria able to increase the production of butyrate. Exogenous butyrate can modulate the gut bacteria, stimulating the growth of butyrogenic and short chain fatty acid genera, which in turn may produce more endogenous butyrate for the restoration of intestinal homeostasis. Pre-clinical impact of this finding provides further clinical investigation.

The alteration of short chain fatty acids in patients with diarrhea-predominant IBS (IBS-D)

IBS subgroups are based on stool consistently as measured by the Bristol Stool Form Scale: Those with hard or lumpy stool more than 25% of time have IBS with constipation, or IBS-C. Those with loose or watery stool more than 25% of the time have IBS with diarrhea, or IBS-D. Those with a mixture of hard or lumpy stools and loose or watery stools have IBS with a mixed bowel pattern, or IBS-M.

Tian *et al.*^[22] reported the alteration of short chain fatty acids (SCFAs) in patients with diarrhea-predominant IBS (IBS-D) and their potential role in the occurrence and development of IBS. Compared with healthy controls, the levels of the serum propionate and butyrate were significantly higher in patients with IBS-D group. Metabolites of gut microbiota, the propionic and butyric acid, are increased in patients with IBS-D in serum but not in feces. It was suggested that propionic and butyric acid might be associated with the occurrence and development of IBS.

Compositions of fecal microbiota and short chain fatty acids in oat-using subjects with celiac disease or gluten sensitivity

A gluten-free diet may result in high fat and low fiber intake and

thus lead to unbalanced microbiota. Nylund *et al*^[23] investigated fecal microbiota profiles by 16S MiSeq sequencing among oat-using healthy adult subjects or adult subjects with celiac disease (CeD) or non-celiac gluten sensitivity. The proportion of fecal acetate was higher in healthy when compared to adult subjects with non-celiac gluten sensitivity (NCGS), which may be linked to a higher abundance of *Bifidobacterium* in the control group compared to NCGS and CeD subjects. Propionate, butyrate and ammonia production and β -glucuronidase activity were comparable among the study groups. The results suggested that pure oats have great potential as the basis of a gluten-free diet.

Significant association between butyric acid and celiac disease

Altered circulating levels of free fatty acids (FFAs), namely short chain fatty acids (SCFAs), medium chain fatty acids (MCFAs), and long chain fatty acids (LCFAs), are associated with metabolic, gastrointestinal and malignant diseases. Baldi *et al*^[24] compared the serum FFA profile of patients with celiac disease (CD), adenomatous polyposis, and colorectal cancer to healthy controls. The data supported GC-MS as a suitable method for the concurrent analysis of circulating SCFAs, MCFAs, and LCFAs in different gastrointestinal diseases. Furthermore the authors suggested that butyric acid could represent a potential biomarker for CD screening.

Reduction of butyrate- and methane-producing microorganisms in patients with IBS

Pozuelo *et al*^[25] investigated the microbiome of a large cohort of patients to identify specific signatures for IBS subtypes. The authors examined the microbiome of 113 patients with IBS and 66 healthy controls. In patients with IBS, a significantly lower microbial diversity was associated with a lower relative abundance of butyrate-producing bacteria, in particular in patients with IBS-D and IBS-M. The authors found that IBS-M and IBS-D patients are characterized by a reduction of butyrate producing bacteria, known to improve intestinal barrier function, and a reduction of methane producing microorganisms, known to have a major mechanism of hydrogen disposal in the human colon, which could explain excess of abdominal gas in IBS.

Butyrate-producing gut bacteria are reduced in patients with active inflammatory bowel disease

Butyrate-producing gut bacteria are reduced in patients with active inflammatory bowel disease (IBD). Ferrer-Picon *et al*^[26] recruited non-IBD controls and IBD patients for the study. Colonic biopsies and *ex vivo* differentiated epithelial organoids treated with butyrate and/or TNF α were used for analyzing the expression of transfers MCT1 and ABCG2, metabolic enzyme ACADS, and butyrate receptor GPR43, and for butyrate metabolism and consumption assays. The results confirmed using patient-derived organoids, the potent effects of butyrate on the intestinal epithelium and the impact that inflammation, at least in part mediated by the presence of TNF α , has on the ability of epithelial cells to uptake, metabolize, and respond to this bacterial metabolite. Moreover, the authors provide evidence that response to butyrate is not intrinsically altered in IBD patients under quiescent conditions, which thus supports the beneficial effects of butyrate in the absence of inflammation. Nonetheless, as the down regulation of butyrate transporters and enzyme is associated with both active UC and CD patients, supplementation of active patients with butyrate or SCFA extracts may not provide any beneficial effects as long as inflammation persists. The authors proposed that inflammation may decrease epithelial butyrate consumption.

THERAPEUTIC EFFECT OF ALOE VERA GEL ON ULCERATIVE COLITIS INDUCED BY ACETIC ACID IN RATS

Ulcerative colitis (UC) is a chronic intestinal inflammation. Bahrami *et al*^[27] investigated the protective and therapeutic effects of aloe vera gel on 4% acetic acid-induced UC into the rectum in rats. The results of the macroscopic and microscopic examination showed protective and therapeutic effects of 50 mg/kg dose of aloe vera gel extract on acetic acid-induced colitis in rats which reduces the inflammation, ulcers and tissue damage compared with negative control. Based on the results aloe vera gel could be used to improve the symptoms of UC as well as prevent people who are susceptible to the UC.

A NOVEL TREATMENT FOR CONSTIPATION-PREDOMINANT IRRITABLE BOWEL SYNDROME USING TIBETAN HERBAL FORMULA

Padma Lax, a complex Tibetan herbal formula, containing *Zingiber officinalis*, *Rheum officinale*

Aloe barbadensis, *etc.*, for constipation was evaluated for safety and effectiveness in treating constipation-predominant IBS in a 3-month double-blind randomized pilot study. In 61 patients (34 Padma Lax, 27 placebo), significant improvement was demonstrated after 3 months in the Padma Lax group compared to placebo in constipation, severity of abdominal pain, and its effect on daily activities^[28].

THE ROLE OF GUT MICROBIAL AND HOST METABOLIC CHANGES IN DIARRHEA-PREDOMINANT IRRITABLE BOWEL SYMPTOMS (IBS-D) PATIENTS

Microbial and metabolomics profiles in correlation with depression and anxiety co-morbidities in IBS-D

The first randomized controlled trial of *Aloe vera* as a treatment for IBS took place by Davis *et al*^[29] in 2006. The 58 IBS patients were either given aloe vera supplements or a placebo for 3 months. The authors found that improvement occurred in patients with diarrhea or alternating IBS whilst taking aloe vera supplement. Liu *et al*^[30] investigated psychological co-morbidities in IBS, regarding the role of gut microbial and host metabolic changes in clinical and psychological symptoms in IBS. A total of 70 IBS-D patients and 46 healthy controls were enrolled in this study. The results showed that fecal microbiota in IBS-D depleted *Facalibacterium*, *Eubacterium rectale* group, *Subdoligranulum* and increased *Prevotella*. O-Ureido-L-serine, *etc.* demonstrated lower urinary concentration in IBS-D patients. The finding demonstrated that altered microbial and metabolic profiles associated with clinically and psychological symptoms in IBS-D patients.

The effects of *Bifidobacterium longum* NCC3001 on anxiety and depression in IBS patients

Pinto-Sanchez *et al*^[31] performed a prospective study to evaluate the effects of *Bifidobacterium longum* NCC3001 (BL) on anxiety and depression in IBS patients. A randomized, double-blind, placebo-controlled study of 44 adults with IBS-D or IBS-M and mild to moderate anxiety and/or depression was performed from March 2011 to May 2014. The authors found that the probiotic BL reduces

depression but not anxiety scores and increases quality of life in IBS patients. These improvements were associated with changes in brain activation patterns that indicate this probiotic reduces limbic reactivity.

Effects of *Aloe barbadensis* extract on symptoms, fecal microbiota and fecal metabolite profiles in patients with IBS: RCT study

Aloe barbadensis (*Aloe*) with potential prebiotic effects has been suggested to reduce symptoms in patients with IBS^[3]. Ahluwalia *et al.*^[32] investigated the effects of an aloe extract on symptoms of IBS, and evaluated whether effects may be mediated by fecal microbiota and metabolites in a randomized, double-blind, controlled trial. IBS patients (160 IBS patients in total) received *Aloe* or control treatment (inulin) for 4 weeks. IBS symptom severity score (IBS-SSS) was assessed, and fecal samples collected before and at end of treatment. The overall severity of IBS symptoms was reduced in both *Aloe* and control treatment groups (comparing baseline vs end of treatment), without difference between groups. The frequency of responders (IBS-SSS reduction ≥ 50) did not differ between *Aloe* treatment and control. Fecal microbiota and metabolite profiles differed between *Aloe* but not control treatment responders and non-responders both before and after treatment. In a mixed group of IBS patients, *Aloe* was not superior to control treatment, although it showed potential to reduce IBS symptom severity in subsets of IBS patients which could be predicted by fecal microbiota and metabolite profiles. (ClinicalTrials.gov no: NCT01400048)

ROLE OF HYALURONAN IN INFLAMMATORY BOWEL DISEASE: PROMOTING DEFENSE OF THE INTESTINAL EPITHELIUM

Hyaluronan (Hyaluronic acid; HA) is a major extracellular matrix component and an important component of active pharmaceutical ingredients for treatment of arthritis and osteoarthritis^[33]. HA is an active participant in many disease states, including inflammatory bowel disease (IBD). IBD consists of two closely related disorders: Crohn's disease and ulcerative colitis, whose overall prevalence is increasing in both industrialized and developing countries worldwide. Intestinal epithelium plays a critical role in host defense against orally acquired pathogens. Dysregulation of this protective barrier is a primary driver of inflammatory bowel diseases (Crohn's and ulcerative colitis) and also infant gastrointestinal infections. HA has the potential to be a novel dietary supplement for formula fed infants and children at risk for enteric bacterial infection, as well as patients who suffer from bacterial dysbiosis, for example, individuals with IBD^[34]. Kessler *et al.*^[35] reported that HA isolated from human milk induces the expression of the antimicrobial peptide defensin in vivo and protects against *Salmonella typhimurium* infection of epithelial cells in vitro. And the authors demonstrated that a dual role for HA in host innate immune defense at the epithelial cell surface, acting to induce antimicrobial peptide production and block pathogen-induced leaky gut. Low molecular weight HA has signaling property, and fragments ~35kDa size (HA35) have biological activity in eliciting epithelial β -defensins and tight junction protein, notably zonula occludens; ZO1, important components of innate host defense arsenal of the gut barrier in preclinical models. HA35 is a promising therapeutic in defense against bacterially induced colitis in compromised adults and vulnerable newborns. Safety of HA35 (140mg in water once daily for seven days) in healthy human 20-subjects (30.7 \pm 5.6 years) was measured in demographical, clinical, biochemical laboratory tests. Bellar *et al.*^[36] showed that oral HA35 administration does not affect metabolic,

inflammatory or microbiome parameters.

Petrey and de la Motte^[37] discussed the functional significance of HA in the cells and tissues involved in inflammatory bowel disease pathobiology, and reviewed that regulation of HA-degrading enzymes is disrupted in IBD and HA regulates megakaryocyte and platelet maturation. The authors reported that HA is a novel regulator of the immune response in IBD.

THE EFFICACY OF HYALURONAN IN THE INDUCTION OF CLINICAL REMISSION IN SUBJECTS WITH DISTAL ULCERATIVE COLITIS AND IN ANIMAL FOR INFLAMMATORY BOWEL DISEASES

Fiorino *et al.*^[38] investigated the safety and efficacy of sodium hyaluronate enema (IBD98E) in distal active ulcerative colitis in a prospective, uncontrolled, open-labeled pilot trial. Subjects with active distal ulcerative colitis (UCDAI ≥ 4 and sigmoidoscopy score ≥ 1) received IBD98E 60 ml enema once a day. Twenty-one subjects were enrolled. Eight subjects achieved clinical remission and subjects had an endoscopic response. The mean average UCDAI score decreased from 6.10 to 3.81 at day 28, and average endoscopic score decreased from 1.57 to 1.10.

It has been shown that the local application of hyaluronan (HA) improves endoscopic and clinical outcomes in subjects with active distal ulcerative colitis. Sammarco *et al.*^[39] demonstrated that HA treatment in vitro and in vivo improved mucosal healing by accelerating intestinal epithelial regeneration. The authors showed that histological analysis revealed less ulcerated mucosa in mice treated with HA, characterized by re-epithelialized areas. The secreted product of TNF-stimulated gene-6 (TSG-6) is an HA-binding protein shown to have tissue-protective properties and promote wound healing. Mucosal levels of TSG-6 increased in UC patients compared to the healthy controls and also after wounding in mice. TSG-6 deletion prevented the beneficial properties of HA in mucosal wound repair, suggesting that the interaction of HA with TSG-6 is crucial for intestinal epithelial regeneration. The authors demonstrated that these results are consistent with HA having a therapeutic effect via the promotion of mucosal healing in patients with ulcerative colitis.

Safety and efficacy of dermal fillers in patients with connective tissue disease (CTD), such as hyaluronic acid and poly-L-lactic acid, were conducted through PubMed, Ovid MEDLINE, and Ovid Embase to identify articles discussing the treatment of cutaneous defects secondary to CTD. The dermal fillers seem to be safe as an adjunctive treatment for cutaneous defects in patients with CTD^[40]

THE ROLE OF HYALURONIC ACID IN ANGIOGENESIS OF WOUND

Angiogenesis is an essential part of the proliferation phase of the wound healing process. During this process, endothelial cells (EC) migrate from established vessels into surrounding tissues where they proliferate and create new cell-to-cell attachments. Interaction between EC and EC matrix (ECM) components are crucial in the regulation of new vessel formation. Hyaluronic acid (HA) is a basic ECM component with some unique properties that make it a key player in tissue regeneration. ECM components play an important role in regulation of all phases of tissue repair, including cellular migration, inflammation, angiogenesis, remodeling, and scar formation. Litwiniuk

et al^[41] concluded that HA is present through all steps of the wound healing process not only as a component of the wound environment, but also as a factor that actively modulates tissue regeneration.

PREPARATION OF CALCIUM PHOSPHATE-HYALURONIC ACID BONE CEMENT AND THE BIO-MATRIX FORMED OF HYALURONIC ACID AND Mg^{2+} / Ca^{2+} -PHOSPHATE

Ahmadzadeh-Asl et al^[42] investigated calcium phosphate cements (CPCs) prepared by using hyaluronic acid (HA) solutions with two different molecular weights. The results revealed that the long setting time and the low compressive strength of the CPC could be improved drastically by using HA in the cement composition, in molecular weight dependent manner, suggesting that calcium phosphate nano-composite cement obtained by HA solution can be successively used as injectable bone filler material.

In a biomimetic approach, to enhance cartilage synthesis and regeneration, Wang et al^[43] prepared amorphous inorganic polyphosphate (polyP) micro-particles with Mg^{2+} as a counter-ion. Similar particles were obtained addition of Mg^{2+} ions to a solution containing HA, as a major component of the synovial fluid and soluble Na^+ -polyP and Ca^{2+} polyP. The authors proposed a strategy for treatment of joint dysfunction caused by osteoarthritis based on the application of amorphous Mg^{2+} -polyP micro-particles that prevent calcium crystal formation in the synovial fluid using scavenging Ca^{2+} polyP ions (Mg^{2+}/Ca^{2+} exchange) and enhance chondrocyte function after binding of the Ca^{2+} -polyP to HA at the cartridge surface. In complex polyP, HA might be protected against enzymatic degradation by hyaluronidase.

Walker et al^[44] published several preparations of HA being available for many United State, FDA Labelled indication, for cosmetics and intraarticular uses.

SUMMARY

Irritable bowel syndrome (IBS) is a functional disorder of the intestinal tract, which induces abdominal discomfort concomitant with a change in bowel habit including defecation disorders. The efficacy of *Aloe vera* in the treatment of IBS was discussed on regulation of tight junction and it could be suggested that short chain fatty acids, butyrate fermented reduce abdominal discomfort in patients. Hyaluronic acid (HA) in aloe vera gel may play promising a therapeutic effect via the promotion of mucosal healing to patients with ulcerative colitis and bone regeneration.

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