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# Beneficial Role of Histone Deacetylase Inhibitor, Butyrate, to Multiple Myeloma: Case Reports

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## Abstract

Multiple myeloma (MM) belongs to hematological malignancy that derives pro-survival/ proliferative signals from the bone marrow niche. Butyrate, a class I histone deacetylase inhibitor in MM, reduces the viability of MM cells, induces MM cell apoptosis via transcriptional activation of p21. The author discussed fermented butyrate in aloe vera juice (AVJ) as a potential adjuvant for MM, and in case reports of MM patient we expressed how autologous peripheral blood stem cell (APBST) transplantation therapy, and daratumab, velcade and dexamethasone (Dvd) and thalidomide administration recovered MM and how butyrate fermented in AVJ as an adjuvant prevented MM patient receiving paraneoplastic cerebella degeneration (PCD) treatment.

***Keywords:*** *Remission of Multiple Myeloma; APBST-Treatment; Drug Admission; Aloe Vera Gel; Fermented Butyrate; Case Reports*

## Introduction

Histone deacetylases (HDAC) control gene expression through their ability to acetylate proteins, thereby influencing a diverse range of cellular functions. Class I HDAC (HDAC1-3 and 8) and HDAC6 are predominantly upregulated in malignancies and their altered expression in some cancer has a significant prognostic implication. Mithraprabhu., *et al*. [1] investigated that HDACs are dysregulated in multiple myeloma (MM) and patients with high expression have significantly poor prognostic outcomes. The author indicated that overexpression of class I HDAC, particularly HDAC1, butyrate, is associated with poor prognosis in MM. MM belongs to hematological malignancy that derives pro-survival/proliferative signals from the bone marrow niche, and its incidence is increasing worldwide. Yao., *et al*. [2] reported that butyrate decreased survival of several human MM cell lines in a dose- and time-dependent manner. Butyrate: a well-known epigenetic histone deacetylase inhibitor reduces the viability of MM cells, induces MM cell apoptosis via transcriptional activation of p21 (cyclin-dependent kinase-inhibitor) suggesting that butyrate as a potential therapeutic drug for MM.

In previous paper we described that butyrate as a possible potential therapeutic drug-like substance for MM and case reports of MM, acute leukemia, malignant lymphoma and glioma patients [3]. Gut microbiome alterations are closely related to human health and link to a variety of diseases. Patients with MM who achieve minimal residual disease (MRD) negativity after upfront treatment have superior outcomes compared with those who remain $MRD^{+}$. The associations have shown between specific commensal microbes and development

of plasma cell disorders. Pianko., *et al*. [4] reported the association between intestinal microbiota composition and treatment outcomes in MM. Microbiota composition of fecal samples collected from 34 MM patients after induction therapy and at the time of flow cytometry-based bone marrow MRD testing was determined by 16S ribosomal RNA sequencing. The author found a high relative abundance of *Eubacterium hallii* in the 16 $MRD^+$ patients relative to the 18 $MRD^-$ patients. *E. hallii* and *Faecalibacterium prausnitzii* were identified in LeFac analysis and present in ≤ 10 patients. The research has correlated that short chain fatty acids, mainly butyrate, produced by *E. hallii* and *F. prausnitzii*, are associated with minimal residual disease negativity and the end of induction therapy for MM. Intestinal microbiota containing several butyrate-producing anaerobes appear to be associated with $MRD^-$ in patients with myeloma, with higher relative abundance of *Eubacterium hallii* and *Faecalibacterium prausnitzii* in $MRD^-$ patients compared with $MRD^+$ patient. Butyrate and other short chain-fatty acids are biologically active metabolites formed during microbial fermentation of dietary or host-derived carbohydrates, which supply the host with energy and also modulate immunity, including exerting anti-inflammatory functions [5]. The potential association of microbiota composition with treatment response in MM patients is an important parameter for additional correlative and clinical investigation. The role of the gut microbiome and alterations of its metabolic functions in the development of MM patients was demonstrated by Jian., *et al* [6]. The author collected from a cohort of 19 newly diagnosed patients with MM and 18 gender- and age-matched healthy controls (HCs), fresh fecal samples and fasting serum samples, respectively, for metagenomics sequencing and metabolomics detection. The results validated that the increase of *Klebsiella pneumoniae* abundance accelerated MM progression *in vivo*, while *Clostridium butyrate* had an opposite effect. The author showed that the gut microbiome in MM patients played an active role in malignant progression and that the microbe-host interactions were predominantly involved in nitrogen recycling and utilization in MM, which open new avenue for MM treatment via monitoring and manipulation of intestinal flora. And the findings lead us to propose a broad mechanism, in which the increasing urea or $NH_4^+$ alters the gut bacterial composition, leading to preferential accumulation of nitrogen-recycling bacteria and suppression of the bacteria producing short chain fatty acids. The gut microbiome should be conductive to nitrogen recycling and utilization by the host-microbe superorganism. In our previous paper, we described case report of useful aloe vera ingestion for the intestinal environment: In 61-years old frail female who had hay fever ingested aloe vera juice during ten-years, increased 3.4 hold higher in the comparative fecal content of butyrogenic prebiotic *Faecalibacterium* spp. Since then she had no hay fever and well-being of QOL [7].

Present review focused on butyrate as a beneficial fermented metabolite in aloe vera gel to multiple myeloma and case reports showing that how APBST therapy and Dvd and thalidomide administration recovered MM and how butyrate fermented in AVJ ingestion as an adjuvant prevented MM patients receiving PCD treatment without any side effect.

## The correlation of multiple myeloma (MM) with histone deacetylase inhibitors

Cea., *et al*. [8] presented new sights into the treatment of multiple myeloma with histone deacetylase inhibitors. MM is a common hematologic malignancy of plasma cells representing an excellent model of epi-genomics dysregulation in human disease. Histone deacetylase inhibitors (HDACIs) represent a novel class of drugs targeting enzymes involving in epigenetic regulation of gene expression, which have been evaluated for the treatment of MM. HDACIs appear to be synergistic both *in vitro* and *in vivo*. Mechanisms of action of HDACIs have a great potential as anti-cancer agents. Classically HDACIs act as repressors of gene expression, tethered to sequence-specific transcription factors. A recent high-throughput screening in cancer cell lines revealed 3600 lysine acetylation sites on 1750 proteins, associated with various intracellular functions; cell growth, chromatin remodeling, DNA replication and repair, cytoskeletal reorganization, autophagy, angiogenesis and protein chaperone activity. Importantly, acetylation changes as well as a gene expression profile in response to the deacetylase inhibitors are individuated. The author reviewed molecular events underlining antitumor effects of HDACIs and the most recent results of clinical trials in relapsed and refractory MM.

While HDACI by gut commensals has long been attributed to the short chain fatty acid (SCFA) butyric acid, the potent metabolic reservoir provided by the gut microbiota and its rate in host physiology was warranted by Yuille., *et al*. [9] in variety of diseases. Cell free

supernatant (CFS) of 79 phylogenetically diverse gut commensals isolated from healthy human donors were screened for their SCFA profile and their total HDAC inhibitory properties. The three most potent HDAC inhibiting strains were evaluated and subjected to additional analysis of specific class I and class II HDAC inhibition. All three HDAC inhibitors are butyrate producing strains, and one of these also produced substantial levels of valeric acid and hexanoic acid. The author showed that single bacteria strain (*Megasphaera massiliensis* MR0029) from the human gut microbiota have potential as novel HDAC inhibition therapeutics for disease areas involving host epigenetic aberration.

### Drugs with immune-stimulating activity in multiple myeloma

Multiple myeloma (MM) is a monoclonal plasma cell malignancy. Adoptive immunotherapy of MM using cytokine-induced killer cells is yielding promising results in clinical trials. The efficacy of cytokine-induced killer cells in targeting this tumor, using selective small-molecule inhibitors which increase and stabilize surface expression of the natural killer group 2, member D ligand, major histocompatibility complex class I polypeptide-related sequence A (MICA) on myeloma cells was investigated by Nwangwu., *et al* [10]. The author demonstrated that cytokine-induced killer cells have increased cytotoxicity against MM cells after combined drug treatment than without drug pre-treatment. The author demonstrated that sodium butyrate upregulates MICA in MM cell lines, when combined with a matrix metalloproteinase inhibitor III and phenylarsine oxide, a drug that hinders surface ligand internalization.

## Case Reports

### Case report 1: Mitigation of multiple myeloma (MM) patient administrated DVd (daratumab, velcade, dexamethasone) with AVJ ingestion

A 54-years old male Hungarian diagnosed MM was operated on the autologous peripheral blood stem cell transplantation (APBST) therapy and daratumab, velcade and dexamethasone (DVd) administration on January, 2019. After the intervention he recovered with revlimid (a so-called immune modulating drug of thalidomide derivative). Unfortunately the disease had recurred in June, 2020, and he started DVd treatment in December 2020, because the disease has recurred for the third time. On December, 2021, a new treatment started due to diplopia at the moment and he received PCD (paraneoplastic cerebella degeneration) treatment. On March 2022, he had the examination of magnetic resonance imaging and got the negative and the double vision had ceased. Then he administrated PCD-treatment in administration of endoxan, imnovid and dexamethasone with AVJ 200 ml/day ingestion on April 15, 2022. He had well-being QOL, but some trouble about fatigue with PCD administration on May 18, 2022. Then he is constantly taking PCD treatment with AVJ as an adjuvant and *Lycium* fruits reported for so-called-nourishment herb. He had a well-being QOL in July 1, 2022.

### Case report 2: Remission of MM patient operated on APBST and administered thalidomide with AVJ ingestion

A 51-years old Japanese male having weak body temperature and lack of sleep, was diagnosed MM with back bone fracture on September, 2014. Then, he was administered thalidomide with Aloe vera juice ingestion. Furthermore, he started APBST therapy on September, 2015. After two years-medical treatment with AVJ ingestion as an adjuvant, he was remitted without any drug, showing normal range in blood inspection and bone density and had a well-being QOL in 2019 [3].

## Discussion on Case Reports 1 and 2

MM, which is derived from immunoglobulin-producing plasma cells, was treated using novel cancer drug and APBST therapy. An inhibitor butyrate of histone deacetylases (HDAC) has potential as next-generation therapeutics because HDAC isoform-selective inhibition is effective in MM cells. Butyrate (HDAC specificity: Class I, II-a) has the potential to be incorporated into cancer prevention and treatment

regimens. Alkharabsheh., *et al*. [11] reviewed that microbe-host communication is actively maintained across physiological barriers of various body sites and is mediated by a range of bidirectional secreted proteins and small molecules. Plasma cells in MM have the potential to survive in the gastrointestinal tract for long periods of time. The nature of the gut microbiota impacts the degree of antigen stimulation of these cells and may play a role in mutation development and clonal evolution. HDAC inhibition has emerged as a potential approach for the treatment of MM. Specially, combination treatment with HDAC inhibitors and proteasome inhibitors or immunomodulatory drugs shows remarkable anti-MM activity in both preclinical and clinical settings. Harada., *et al*. [12] investigated that HDAC inhibitors showed unfavorable side effects which can be avoided by isoform and/or class selective HDAC inhibitor, which preserve significant antitumor activity and may improve patients outcomes in MM. In 2015, the FDA approved panobinostat (HDAC specificity; Class I, II-a) in combination with bortezomib and dexamethasone to treat patients with refractory/relapsed MM. Lu., *et al*. [13] discussed the association between the dynamic community of microbiota and the host they colonize appears to be vital for ensuring host health. Microbe-host communication is actually maintained across physiological barriers of various body sites and is mediated by a range of bidirectional secreted proteins and small molecules.

## Summary

Histone deacetylases are crucial regulators of gene expression that function through histone modification, and HDAC inhibitor sodium butyrate functions in various physiologic processes to MM cells; reducing the viability of MM cells and inducing MM cell apoptosis via transcriptional activation of p21. The case report 1 and 2 showed how APBST therapy, and DVd and thalidomide administration recovered MM and how butyrate fermented in AVJ ingestion as an adjuvant prevented MM patient receiving PCD treatment without any side effect. There are no boundaries in human medical care.

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