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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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ROLE OF GUT MICROBIOME HOMEOSTASIS, INTEGRITY OF THE INTESTINAL EPITHELIAL CELLS, AND THE (ENDOGENOUS) BUTYRATE IN ENDURING A HEALTHY LONG LIFE

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Abstract.

The influence of gut microbiomes on health has been gaining significance lately. More emphasis is their role in neurological illnesses as several of the metabolites and factors produced by the gut affect the brain via the gut-brain axis. Among all the gut microbiome produced metabolites, butyrate has been considered the most significant. Externally supplemented butyrate though has health benefits, when evaluated thoroughly, it is understood that there have been different pathways involved in the production of butyrate by the gut microbiome with the produced butyrate even being detrimental, though majority are beneficial. Importantly maternal butyrate supplementation has resulted in detrimental effects in the offspring. In this background, a black yeast Aureobasidium pullulans produced biological response modifier beta glucans (BRMGs) has shown beneficial outcome (anti-inflammatory: decrease in IL-6, Ferritin, C-reactive protein in COVID-19, D-Dimer; anti-fibrotic in fatty liver disease; improvement of behaviour and sleep with increase in α-synuclein, melatonin in autism) along with its effect on increasing the butyrate producing bacteria in the gut. Since only advantageous outcome has been reported with this BRMG produced butyrate, it is worth being considered as a yardstick for evaluation of exogenously supplemented and endogenous produced butyrate for their differential effects on host and its offspring.

Key words. Gut microbiome, butyrate, exogenous, endogenous, beta-glucans.

Manuscript content.

The gut microbiome is gaining increasing attention as a factor that controls intestinal homeostasis and plays a major role in the pathogenesis of several diseases and disorders. Our focus is on the influence of the gut microbiome on the central nervous system (CNS), the gut-brain axis, which occurs via different mechanisms, viz., through the vagus nerve, ii. modulation of the immune system, and iii. the hypothalamic-pituitary-adrenal (HPA) axis via tryptophan metabolism; and iv. synthesis of neurotransmitters and production of metabolites, such as short-chain fatty acids (SCFAs), which possess neuroactive properties. Among the SCFAs, acetate, propionate, and butyrate are the main metabolites produced by the gut microbiota, especially anaerobic bacteria, through the fermentation of dietary fibers and starch [1]. In addition to anaerobic fermentation, SCFAs can also be produced by amino acid metabolism. SCFAs are absorbed by colonocytes, wherein butyrate is absorbed and utilized within the colon, whereas propionate and acetate enter hepatic circulation [2]. These SCFAs improve gut health through several local effects, including the maintenance of intestinal barrier integrity, mucus production, and protection against inflammation. SCFAs binding to different cells in the body leads to different kinds of functions; for example, binding of SCFAs to their receptors on enteroendocrine cells leads to an increase in insulin secretion. By promoting the acetylation of lysine residues in the nucleosomal histones of various cell populations, SCFAs exhibit systemic effects on different tissue-organ systems [1,3]. The microbiota responsible for the production of these SCFAs are as follows: propionate—*Bacteroidetes* and *Negativicutes* (*Firmicutes* phylum)—which use the succinate pathway, and *Lachnospiraceae* that use the propanediol pathway to produce propionate; for butyrate, the main butyrate-producing bacteria belonging to the phylum *Firmicutes*, in particular *Faecalibacterium prausnitzii* and *Clostridium leptum* of the family *Ruminococcaceae*, *Eubacterium rectale*, and *Roseburia spp*. of the family *Lachnospiraceae, Eubacterium hallii*, and *Anaerostipes spp*. Other bacteria such as *Actinobacteria, Bacteroidetes, Fusobacteria, Proteobacteria, Spirochaetes*, and *Thermotogae* also have potential butyrate-producing abilities [4]. Major producers such as *Faecalibacterium prausnitzii, Eubacterium rectale*, and *Eubacterium hallii* use butyryl CoA:acetate CoA transferase while few taxa such as *Coprococcus* comes and *Coprococcus eutactus* use the butyrate kinase route. These are commensal butyrate producers, while some pathogens such as *Fusobacterium* utilize different pathways such as glutamate (4-aminobutyrate) and lysine to produce butyrate, which may also produce harmful byproducts such as ammonia. Gut environmental factors that stimulate butyrate production include lower PH, presence of iron and oxygen concentrations. Iron deficiency leads to an increase in

the abundance of *Lactobacilli* and *Enterobacteriaceae*, but a significant decrease in butyrate producers such as *Roseburia* species and *Eubacterium rectale* [5].

Among SCFAs, butyrates are the most studied because of their beneficial properties [6-10]. At the intestinal level, butyrate exerts a powerful pro-absorptive stimulus on intestinal NaCl transport and an anti-secretory effect on Cl- secretion. In a study on the effects of orally administered, nonabsorbed starch (precursor to butyrate) on diarrhea in 48 patients with cholera, with standard oral rehydration therapy showed that this combination reduced the fecal fluid loss and shortened the duration of diarrhea, by improving colonic absorption without altering the osmolality, which in turn reduced the output of stools, thereby contributing to the benefits [11]. Even in patients affected by Congenital Chloride Diarrhea (CLD), butyrate by pro-absorptive effect on Na+, Cl-, and K+ intestinal transport, was able to prevent the severe dehydration episodes as well as helped to avoid the long-term complications [6,12]. Butyrate has anticarcinogenic properties by inhibiting proliferation, induction of apoptosis, or differentiation of tumor cells. In normal intestinal cells, butyrate stimulates the physiological pattern of proliferation while reducing the number and size of aberrant crypt foci, which are the earliest detectable neoplastic lesions in the colon. Butyrate acts as an anti-inflammatory agent, primarily via the inhibition of nuclear factor κB (NF-κB) activation in human colonic epithelial cells. Butyrate helps reinforce the colonic defense barrier by increasing the expression of MUC2 and inducing mucin synthesis. Butyrate strengthens innate immunity via LL-37 gene expression and increases histone acetylation and mitogen-activated protein (MAP) kinase signaling. Butyrate regulates intestinal epithelial permeability through the assembly of tight junctions via AMP-activated protein kinase (AMPK). Owing to its effects on intestinal motility, butyrate is used as a nutritional approach to treat various gastrointestinal motility disorders. Sodium phenylbutyrate 4 (4-PBA), approved by the FDA, acts as an ammonia scavenger in patients with urea cycle enzyme deficiency. Butyrate downregulates the expression of nine key genes involved in intestinal cholesterol biosynthesis and therefore helps regulate lipid levels. Dietary supplementation with butyrate has been shown to prevent and treat diet-induced obesity and insulin resistance. In ischemic stroke, butyrate treatment has been shown to increase the number of cells expressing polysialic acid-neural cell adhesion molecule, nestin, glial fibrillary acidic protein, phospho-cAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF) [6,13].

In the immune system, butyrate can induce Treg differentiation and control inflammation [14]. Another major immune-related function is the regulation of invariant NKT (iNKT) cells, which play critical roles in various immune-related diseases, especially autoimmune diseases, by producing large amounts of IFN-g- and IL-4. Butyrate inhibits cytokine production by iNKT cells by suppressing class I histone deacetylases (HDACs), which have the potential to alleviate autoimmune diseases. Thus, the inhibitory effects of butyrate on inflammation were orchestrated by iNKT cells. It is important to note that iNKT cells promote both anti-inflammatory and pro-inflammatory responses in autoimmune diseases [15]. In addition, iNKT regulates the mobilization of other types of immunomodulatory cells, including regulatory T cells. The dual action suggests that there are at least two types of iNKT cell-activation by SCFAs both favorable for health by production of anti-microbial peptides, stimulation of IgA and IgG secretion, interleukin-13 (IL-13) regulated mucus production and glycosylation and unfavorable by stimulation of secretion of pro-inflammatory cytokines via CD1d-retrograte signaling leading to inflammation such as in joints and as well as contributing to the development of auto-immune diseases [13]. Depending on gut health, the correct type of SCFAs based immune cell activation and therefore the regulatory effects are generated by gut microbiota from food and the environment by which either health is improved or diseases develop. For example, in cancer cells due to the Warburg effect, the metabolic shift to primarily aerobic glycolysis in these cells lead to accumulation of butyrate and propionate leading to decreased HDAC activity and altered histone acetylation. However, if cancer cells are grown in low glucose concentrations, butyrate or propionate are oxidized to acetyl-CoA by increase in oxidative metabolism and histone acetylation is not affected. Thus, the epigenetic effects of butyrate exposure are strongly dependent on glucose metabolism [16]. Also, more research is needed to correlate the effects of dyslipidemia whether the SCFA's effects on different types of iNKT activation is dependent on increase in good cholesterols such as HDL or increase in harmful cholesterols such as LDL [13-15].

Though the anti-inflammatory effects of butyrate are beneficial, it can be detrimental as well [17]. For instance, in the case of the intestinal epithelium which needs to maintain a low grade of inflammation for it to defend itself against constant immunologic challenges. Butyrate at low concentrations promotes intestinal barrier function but may induce apoptosis and disrupt the at high concentrations [17]. Also, colorectal tumourigenesis has been linked to butyrate-induced senescence [17]. The effect of butyrate on glycolipid metabolism is paradoxical. While many studies suggest that butyrate alleviates high-fat diet induced obesity and insulin resistance, it has been shown to produce the opposite effects of inducing obesity by providing specific substrates for lipid biosynthesis [18-21].

The butyrate comes from two sources, exogenous supplementation, and endogenous generation by the action of gut microbiota on dietary fibers. Exogenous butyrate supplementation is being used, especially for the treatment of gastrointestinal diseases, with several clinical trials showing efficacy. Butyrate-producing microbes have been identified as potential next-generation probiotics. e.g., *Clostridium butyricum* strains and *Clostridium cluster* IV/XIVa [22]. Butyrate whether endogenous or exogenous exerts its paradoxical beneficial and detrimental actions which is regulated in a complex manner and further studies are needed to identify what is the dose or the parameters that influence the action. Perhaps the detrimental effects could be due to the exogeneous butyrate not being able to correct the gut dysbiosis or the intestinal environment. In the case of exogeneous butyrate supplements and probiotics non-standardization [22] of the optimal therapeutic dose required, whether the effect is long-lasting to treat the disease or

condition, extremely poor palatability of the products available on the market, including the unpleasant taste and odor [6] and unwanted effects of the additional biogenetic material including toxins have been postulated as the potential hurdles. Even maternal dietary supplementation with butyrate has been shown to induce insulin resistance and impaired glucose tolerance in the offspring [23]. Therefore, a safer source of butyrate which exerts the right function for optimizing health is needed.

In our studies of the gut microbiome, we reported the effects of two strains of *Aureobasidium pullulans*, AFO-202 and N-163 strain produced biological response modifier beta-glucans (BRMGs) manufactured in a GMP facility and available as a food supplement for several decades with safety and efficacy proven in several clinical studies [24-33], on the regulation of gut dysbiosis, enhancement of butyrate producers, and metabolites, including endogenous butyrate production and amino acids. The glycosidic linkage ratios lead to significant structural differences in β-glucans and these ratios are dependent on both the source and method of isolation [34]. The AFO-202 and N-163 strains of *A.pullulans* produced beta-glucans are manufactured using "screening and fermentation method". The beta-glucans are secreted as an exopolysaccharide. There is no need for cumbersome extraction compared to other beta-glucans which must be extracted from their respective source such as cell wall and then further purified. Therefore, the AFO-202 and N-163 strains of *A.pullulans* produced beta-glucans have higher purity and water-solubility which contributes to their higher biological functionality [35].

In a study conducted using AFO-202 β-glucan in children with autism spectrum disorders (ASD), there was an increase in beneficial bacteria, especially butyrate producers such as *Faecalibacterium prausnitzii* and *Roseburia* [24]. In another study conducted in the Stellic Animal model (STAM) of non-alcoholic steatohepatosis (NASH), there was an increase in the abundance of butyrate producers such as *Firmicutes*, an increase in the abundance of precursors of butyrate, and an increase in amino acids such as tryptophan, which exert a positive influence on the CNS after the administration of the combination of AFO-202 and N-163 beta-glucans [25]. These A. pullulans food supplements AFO-202 and N-163 are thus more useful for clinical use, as they are easily consumable and do not alter the taste or flavor of any food substance; they are added with and have been consumed by the pediatric population [26, 28]. The beta-glucans produced by the two strains AFO-202 and N-163 vary in their structure and their effects also differ. Standalone, AFO-202 strain produced beta-glucan are immune-enhancers apart from producing more metabolic regulation effects [31]. The N-163 strain produced beta-glucan is a broad spectrum immunomodulator. Their combination complements each other by metabolic and immune regulation leading to cumulative benefits, as proven in pre-clinical studies of NASH and clinical studies in COVID-19 [29-31]. The metabolic regulation of glucose and lipids [29,31] by these β-glucans, along with a decrease in inflammatory cytokines such as IL-6, D-dimer, and C-reactive protein (CRP) in COVID-19 patients [29,30], apart from the decrease in inflammatory factors and liver fibrosis in NASH models [31], can now be attributed partly to the effects of endogenous butyrate, which is enhanced by the consumption of these β-glucans. These *A.pullulans* BRMG produced endogenous butyrate seems to have produced only beneficial actions evident from the improvement of clinical parameters such as behaviour, sleep, alpha-synuclein and melatonin in the study on children with autism [32,33], which to our knowledge has not been so clearly outlined by other butyrate supplements. Therefore, these BRMGs which are produced in a GMP facility [35,36], whose active ingredient quantity can be standardized in a drug like manner and whose effects span the entire system's health as well correction of gut dysbiosis can actually be considered as a scale of assessment for comparison of the activities of other exogenous butyrate supplements and also the endogenous butyrate by evaluating the characteristics of the butyrate produced by the gut microbiomes in a controlled in vitro environment. Such validation will throw more light on the approaches to enhance the right kind of butyrate for exerting its beneficial actions alone. A similar paradoxical yet highly significant glycoprotein is the Fetuin-A (FetA) secreted by liver and adipose tissue [37], which has been shown to have inconsistent effects in obesity and metabolic syndrome [38]. There have been studies that have explored the complex relationship between gut microbiota, butyrate, and FetA [39] but results have not been able to provide clarity. Assessment of the parameters such as Fet A and butyrate modulation by gut microbiota deserves further exploration in the context of BRMGs.

The intestine-gut-human health maintenance by these BRMGs can be compared to a plant in the soil whose health and the environment relies upon the correct delivery of nutrients, management of proper metabolism, removal of weeds, and maintenance of the soil crust integrity. This situation is analogous to the metabolic regulation by AFO-202 and immune-regulation by N-163 beta-glucan, the combination of both through endogenous butyrate maintains the intestinal health and the integrity of its environment (Figure 1).

A recent study on the association between the gut microbiome and longevity between subjects in urban and rural areas has shown that the main difference between subjects with increased longevity and those with lesser longevity was the increased abundance of butyrate-producing microbiota in individuals with increased longevity who also had lesser inflammation [39]. Long-term chronic microinflammation, cancer and longevity are influenced by this key metabolite, butyrate. Its endogenous production and further studies on this novel approach of using AFO-202 and N-163 strain produced beta-glucan food supplements to increase endogenous butyrate production in a safe manner are worth being considered for long-term clinical studies in different populations for validation and potential application as a routine food supplement across age groups.

Conclusion.

Therefore, it looks like papaverine after additional research can be added to the list of pharmaceuticals that prevent sugar absorption in intestine for blood sugar control and/or weight loss.

Dietary herbal supplement with papaverine (D-28) has proven to be quite effective in reducing body weight in dogs. For a month, dogs with initial overweight lost on average more than 1 kg (10+%), that is a very good result for their size.

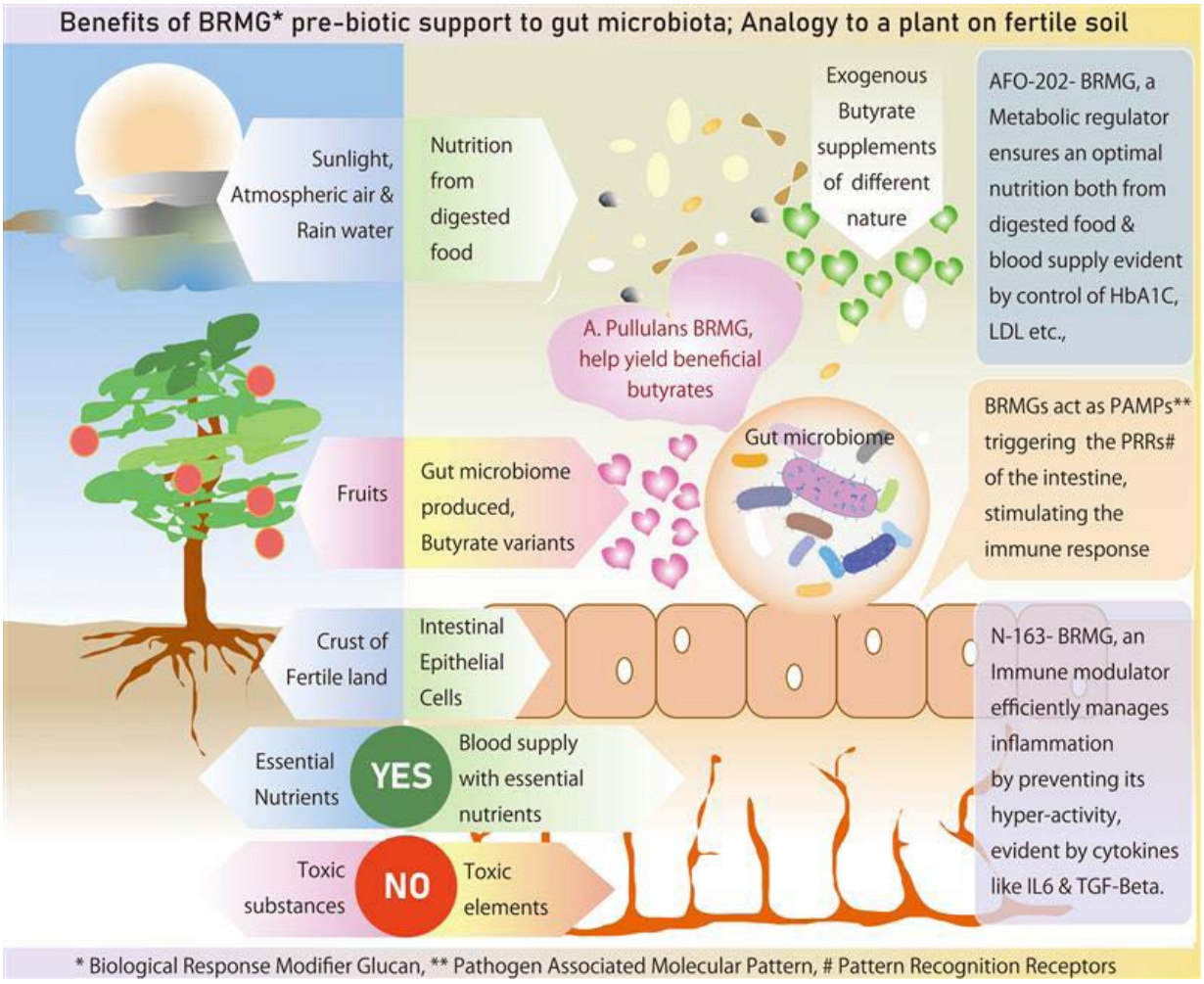

Figure 1. *An illustration explaining the analogy of a plant supported by the fertile soil insisting its similarity to the significance of intestinal epithelial cell (IEC) integrity to maintain a homeostasis of gut microbiome, enable them produce butyrate, an important metabolite to healthy long life and prevention of many illnesses. The source of the butyrate may be exogeneous or endogenous with varying actions, some beneficial while others detrimental. The Aureobasidium pullulans strain AFO-202 produced beta glucan produced beneficial effects only by playing the role of a metabolic regulator managing the delivery of optimal nutrients through blood circulation and digested food in the intestine and the immune modulating N-163 strain produced beta glucan manages the immune system thereby keeping the environment of intestinal epithelial cells, free from pathogens. These two beta glucans act as Pathogen Associated Molecular patterns (PAMPs) stimulating the pathogen recognition receptors (PRR) for immune surveillance maintaining overall intestinal health, especially that of the IECs.*

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Author Contributions.

N.Y and S.A. contributed to conception and design of the study. S.A, and S.P. drafted the manuscript. N.L, S.I and S.S performed critical revision of the manuscript. All the authors read and approved the submitted version.

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Competing interests.

Author Samuel Abraham is a shareholder in GN Corporation, Japan which in turn is a shareholder in the manufacturing company of novel beta glucans using different strains of Aureobasidium pullulans and an applicant to several patents of relevance to these beta glucans.

Data Share statement.

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES

1. Silva YP, Bernardi A, Frozza RL. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. Front Endocrinol (Lausanne). 2020;11:25.

2. Wang RX, Lee JS, Campbell EL, et al. Microbiota-derived butyrate dynamically regulates intestinal homeostasis through regulation of actin-associated protein synaptopodin. Proc Natl Acad Sci U S A. 2020;117:11648-11657.
3. Takewaki D, Suda W, Sato W, et al. Alterations of the gut ecological and functional microenvironment in different stages of multiple sclerosis. Proc Natl Acad Sci U S A. 2020;117:22402-22412.
4. Parada Venegas D, De la Fuente MK, Landskron G, et al. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. Front Immunol. 2019;10:277.
5. Deleu S, Machiels K, Raes J, et al. Short chain fatty acids and its producing organisms: An overlooked therapy for IBD? EBioMedicine. 2021;66:103293.
6. Canani RB, Costanzo MD, Leone L, et al. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol. 2011;17:1519-1528.
7. Guilloteau P, Martin L, Eeckhaut V, et al. From the gut to the peripheral tissues: the multiple effects of butyrate. Nutr Res Rev. 2010;23:366-384.
8. Louis P, Flint HJ. Diversity, metabolism, and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS Microbiol Lett. 2009;294:1-8.
9. Hamer HM, Jonkers D, Venema K, et al. Review article: the role of butyrate on colonic function. Aliment Pharmacol Ther. 2008;27:104-119.
10. Liu J, Zhu H, Li B, et al. Beneficial effects of butyrate in intestinal injury. J Pediatr Surg. 2020;55:1088-1093.
11. Ramakrishna BS, Venkataraman S, Srinivasan P, et al. Amylase-resistant starch plus oral rehydration solution for cholera. N Engl J Med. 2000;342:308-313.
12. Canani RB, Terrin G, Cirillo P, et al. Butyrate as an effective treatment of congenital chloride diarrhea. Gastroenterology. 2004;127:630-634.
13. Lee S, Koh J, Chang Y, et al. Invariant NKT Cells Functionally Link Microbiota-Induced Butyrate Production and Joint Inflammation. J Immunol. 2019;203:3199-3208.
14. Liu H, Wang J, He T, et al. Butyrate: A Double-Edged Sword for Health? Adv Nutr. 2018;9:21-29.
15. He L, Han M, Farrar S, et al. Impacts and regulation of dietary nutrients on gut microbiome and immunity. Protein Pept Lett. 2017;24:380-381.
16. Berni Canani R, Di Costanzo M, Leone L. The epigenetic effects of butyrate: potential therapeutic implications for clinical practice. Clin Epigenetics. 2012;4:4.
17. Okumura S, Konishi Y, Narukawa M, et al. Gut bacteria identified in colorectal cancer patients promote tumourigenesis via butyrate secretion. Nat Commun. 2021;12:5674.
18. Gao ZG, Yin J, Zhang J, et al. Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 2009;58:1509-1517.
19. Schwiertz A, Taras D, Schafer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity 2010;18:190-195.
20. Cleophas MCP, Ratter JM, Bekkering S, et al. Effects of oral butyrate supplementation on inflammatory potential of circulating peripheral blood mononuclear cells in healthy and obese males. Sci Rep. 2019;9:775.
21. Vernia P, Monteleone G, Grandinetti G, et al. Combined oral sodium butyrate and mesalazine treatment compared to oral mesalazine alone in ulcerative colitis: randomized, double-blind, placebo-controlled pilot study. Dig Dis Sci. 2000;45:976-981.
22. Boesmans L, Valles-Colomer M, Wang J, et al. Butyrate Producers as Potential Next-Generation Probiotics: Safety Assessment of the Administration of Butyricicoccus pullicaecorum to Healthy Volunteers. mSystems. 2018;3:e00094-18.
23. Huang Y, Gao S, Chen J, et al. Maternal butyrate supplementation induces insulin resistance associated with enhanced intramuscular fat deposition in the offspring. Oncotarget. 2017;8:13073-13084.
24. Raghavan K, Dedeepiya VD, Yamamoto N, et al. Benefits of gut microbiota reconstitution by beta 1,3-1,6 glucans in subjects with autism spectrum disorder and other neurodegenerative diseases. Journal of Alzheimer's Disease. 2022:1-12.
25. Preethy S, Ikewaki N, Levy GA, et al. Two unique biological response-modifier glucans beneficially regulating gut microbiota and faecal metabolome in a non-alcoholic steatohepatitis animal model, with potential for applications in human health and disease. BMJ Gastroenterology Open. 2022.
26. Raghavan K, Dedeepiya VD, Srinivasan S, et al. Disease-modifying immune-modulatory effects of the N-163 strain of Aureobasidium pullulans-produced 1,3-1,6 Beta glucans in young boys with Duchenne muscular dystrophy: Results of an open-label, prospective, randomized, comparative clinical study. medRxiv. 2021;21267706.
27. Ganesh JS, Rao YY, Ravikumar R, et al. Beneficial effects of Black yeast derived 1-3, 1-6 beta glucan- Nichi Glucan in a dyslipidemic individual of Indian origin - A case report. J Diet Suppl. 2014;11:1-6.
28. Dedeepiya V, Sivaraman G, Venkatesh A, et al. Potential Effects of Nichi Glucan as a Food Supplement for Diabetes Mellitus and Hyperlipidemia; Preliminary Findings from the Study on Three Patients from India. Case Reports in Medicine. 2012.
29. Raghavan K, Dedeepiya VD, Suryaprakash V, et al. Beneficial Effects of novel aureobasidium pullulans strains produced beta-1,3-1,6 glucans on interleukin-6 and D-Dimer levels in COVID-19 patients; results of a randomized multiple-arm pilot clinical study. Biomedicine and Pharmacotherapy. 2021.
30. Pushkala S, Seshayyan S, Theranirajan E, et al. Efficient control of IL-6, CRP, and Ferritin in Covid-19 patients with two variants of Beta-1,3-1,6 glucans in combination, within 15 days in an open-label prospective clinical trial. medRxiv. 2021.
31. Ikewaki N, Kurosawa G, Iwasaki M, et al. Hepatoprotective effects of Aureobasidium pullulans derived Beta 1,3-1,6 biological response modifier glucans in a STAM- animal model of non-alcoholic steatohepatitis. Journal of Clinical and Experimental Hepatology. 2022.
32. Raghavan K, Dedeepiya VD, Kandaswamy RS, et al. Improvement of sleep and melatonin in children with autism spectrum disorder after β-1,3/1,6-glucan consumption: An open-label prospective pilot clinical study. Brain Behav. 2022;12:e2750.

33. Raghavan K, Dedeepiya VD, Ikewaki N, et al. Improvement of behavioural pattern and alpha-synuclein levels in autism spectrum disorder after consumption of a beta-glucan food supplement in a randomized, parallel-group pilot clinical study. BMJ Neurol Open. 2022;4:e000203.
34. De Oliva-Neto P, Oliveira SS, Zilioli E, et al. Yeasts as Potential Source for Prebiotic β-Glucan: Role in Human Nutrition and Health. Probiotics and Prebiotics in Human Nutrition and Health. 2016.
35. https://sophy-inc.co.jp/pages/sophy_bglucan
36. Ikewaki N, Ikeue Y, Nagataki M, et al. Beneficial effects of 1,3–1,6 β-glucans produced by Aureobasidium pullulans on non-esterified fatty acid levels in diabetic KKAy mice and their potential implications in metabolic dysregulation. Jou Diabetes Metab Disord. 2022.
37. Trepanowski JF, Mey J, Varady KA. Fetuin-A: a novel link between obesity and related complications. Int J Obes. 2015;39:734-741.
38. Saad MJ, Santos A, Prada PO. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. Physiology (Bethesda). 2016;31:283-293.
39. Naito Y, Takagi T, Inoue R, et al. Gut microbiota differences in elderly subjects between rural city Kyotango and urban city Kyoto: an age-gender-matched study. J Clin Biochem Nutr. 2019;65:125-131.