Clinical Review

Prevention with Probiotics and Treatment with Thalidomide, Celecoxib and Valproic Acid for Fibromyalgia.

Association between microbiota, chronic inflammation, angiogenesis and fibromyalgia

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Abstract

Symptoms of fibromyalgia (FM) are chronic widespread pain that is often last for more than three months. The pain, stiffness, and tenderness of the muscles, tendons, and joints occurs on both sides of the body and above and below the waist. Other various symptoms co-exist: irritable bowel syndrome（IBS）, headaches, temporomandibular joint disorders and multiple other unexplained symptoms such as fatigue, insomnia, anxiety. The criteria for the classification of fibromyalgia are widespread pain in combination with tenderness at 11 or more of the 18 specific tender point sites.

Fibromyalgia is etiologically a multifactorial disease relevant to oxidative stress, diabetes mellitus (DM), advanced glycation end products (AGEs), small intestinal bacterial overgrowth (SIBO) and others. Catechol-O-methyltransferase (COMT) plays the major role in perception of pain in FM. These factors activate nuclear factor-kappa B (NF-κB) that drives the production of pro-inflammatory cytokines and pain. It has been reported that FM is not relevant to inflammatory responses, however inflammation might play an important role in FM.

Thalidomide and celecoxib potently suppress NF-κB activated by oxidative stress and pro-inflammatory cytokines.

Key words： **thalidomide, celecoxib, valproic acid, probiotics, fibromyalgia**

Introduction

FM is a chronic disease with pain, stiffness, and tenderness of the muscles, tendons, and joints without inflammation of each organ. Other various symptoms co-exist: IBS, depression, headaches, temporomandibular joint disorders and multiple other unexplained symptoms such as fatigue, insomnia, anxiety [1] [2]. The criteria for the classification of FM are widespread pain in combination with tenderness at 11 or more

of the 18 specific tender point sites 3 4.

FM is etiologically a multifactorial disease relevant to oxidative stress, DM, AGEs, SIBO, among others.

It is estimated that the symptoms of COVID-19 infection and FM could be caused by a common mechanism through oxidative stress. Oxidation is normal physiological processes, however, oxidative stress, overproduction of reactive oxygen species (ROS), damages cells and tissue 5.

FM is a common disorder in patients with types 1 and 2 diabetes mellitus (T1,2 DM) and is prevented by the control of blood glucose 6.

AGEs are the modified proteins with less solubility and less proteolytic digestion. AGEs stimulate various kinds of cells and activate NF-κB through the receptor for advanced glycation end products (RAGE). Both mechanisms develop and spread the pain of FM 7.

SIBO is the presence of colonic bacteria expanding into small intestine 8. SIBO is associated with a variety of small intestinal motility disorders such as IBS and also FM. The common symptoms are diarrhea, flatulence, abdominal pain and bloating 9.

Oxidative Stress and Cell Damage

Oxidation is associated with molecular signal pathways for normal physiological processes 5. ROS are produced in the plasma membrane through NAD(P)H oxidases, mainly in mitochondria during the process of apoptosis 10. Oxidative stress is overproduction and accumulation of ROS in cells and tissues, and damage cells and tissue.

In equilibrium state ROS work to detoxify these reactive products like in the case of bactericidal activity of white blood cells 11. Superoxide radical is a state in which one extra electron is incorporated into a normal oxygen molecule which is unstable and highly reactive leading to cell and tissue damage. ROS are defined as radicals with unpaired electrons in outer orbitals and potent active chemically 12 including superoxide radicals ($O_2•−$), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and singlet oxygen ($^1O_2$) 13. Although most of ROS are produced as by-product of oxygen metabolism, ROS are also produced by environmental factors such as ultraviolet (UV) radiation, pollutants (cigarette smoking, heavy metals) and xenobiotics 11 14 15. ROS play major roles in initiation and progression of a variety of diseases such as FM, cancer, DM, metabolic disorders, atherosclerosis, and cardiovascular diseases 16. ROS damage membrane of cells and tissues producing end products of membrane such as lipid peroxidation (LP) and carbonylated proteins 17 18.

LP is the end product of ROS and lipid especially with polyunsaturated fatty acids resulting in cell survival or cell death 18.

LP and carbonylated proteins are significantly higher in the plasma with FM 19. Oxidative stress plays an important role in coexistence of various microbes by the production of a variety of protective enzymes leading to reduce the pathogenic biofilm 20. There are a variety of intracellular producing factors of ROS such as nicotinamide adenine dinucleotide phosphate (NADPH) LPS oxidase (NOX), mitochondrial electron transport chain leakage, and cytokine receptors.

Gastrointestinal (GI) disorders and FM are closely related and more common in women 21. Gut microbiota play an active role in pathological factors of various diseases such as metabolic, immunological, and neurological disorders. Recently, the knowledge of cellular mechanisms in chronic pain such as FM has grown exponentially 22.

Gut microbiota consists of a significantly complex microbial flora, however it is clinically important to simplify the community to treat patients with FM .

More than 1000 microbial species reside in human body, and the harmful microbe is F. nucleatum and beneficial one is Bifidobacterium longum. These microbes with other beneficial and harmful microbes alter the microenvironment by producing various factors that influence cells of FM patients 23. Short-chain fatty acids (SCFAs) contribute to anti-inflammatory effects through down regulation of Interleukin -8 (IL-8) 24 and subsequently enhance the tight junction between intestinal epithelial cells resulting in promotion of barrier function of colon 23 25. Butyrate and propionate suppress the genesis and differentiation of dendritic cells that cause immune dysfunction. These two factors also induce the generation and differentiation of anti-inflammatory regulatory T cells, and SCFAs reduce pro-inflammatory cytokine production from LPS-activated neutrophils and macrophages, both of which are induced through HDAC inhibition 26. Inflammation and peripheral injuries (tissue and nerves) induce epigenetic change such as DNA methylation and histone modifications (e.g., acetylation and methylation), and cause chronic pain 27. Gene polymorphisms that may exacerbate FM are the serotonin transporter (5-HTT), the serotonin 2A (5-HT2A) receptor, COMT and the dopamine receptor. COMT degrades neurotransmitters such as norepinephrine and dopamine, therefore, inhibition of COMT increases the sensitivity of pain especially for women with low activity of COMT 28.

Advanced Glycation End Products and Fibromyalgia

AGEs are produced between sugar aldehyde groups and protein amino groups by non-

enzymatic reactions, known as the Maillard reaction, resulting in low solubility and potent resistance to proteolysis in a variety of tissues during aging. AGEs activate NF-κB that promote expressing inflammatory cytokines through RAGE. These mechanisms lead to the development of FM pain 7. Oxidative stress and AGEs promote each other and produce expression of inflammatory cytokines and growth factors.

Skeletal muscle, adipose tissue and liver overexpress insulin receptors, resulting thereby the major targets of insulin, therefore these organs can be the glucose store. In the skeletal muscle, about 75% of insulin-dependent postprandial glucose is there disposed 29. AGEs are produced by intra- and extracellular components such as proteins, lipids, nucleic acids, and those promote various pathological conditions 30. The AGEs accumulate on proteins especially on the large matrix proteins such as collagen, vitronectin, and laminin through AGE-AGE intermolecular covalent bonds in the extracellular matrix (ECM), with increase stiffness of vasculature 31.

Glycation processes play an important pathophysiological role in the development of various disorders such as neurodegenerative diseases, aging, DM, atherosclerosis, and chronic renal failure 32. Increasing levels of AGEs are also observed by the exogenous intake of AGEs that are spontaneously generated in standard diets that are high temperature processed. Exogenous AGEs also contribute organ damage33.

Neuroplasticity, also known as brain plasticity, refers to correspondence ability to "change and experience", and is negatively influenced by AGEs 34. Change of gray matter and white matter displays a high-level neuroplasticity, showing decreased gray matter contribute to various chronic pain conditions in FM, back pain, and IBS 35.

Small intestinal bacterial overgrowth (SIBO)

FM is a disease with a variety of somatic pain and GI disorders, probably it may be associated with dysbiotic GI dysfunction, functionally and slightly organical 36. The gut microbiota in small intestine and colon play a key role in FM and inflammatory bowel disease (IBD), and induce musculoskeletal dysfunction through the gut-musculoskeletal axis 37.

Small intestinal bacterial overgrowth (SIBO) is dysbiosis in small intestine where bacteria in upper GI proliferate more than 10^5–10^6 organisms/mL and cause maldigestion and malabsorption. Symptoms are the same with IBS such as bloating, constipation, diarrhea, incontinence, and psychological disturbances 38. Imbalance of pro-inflammatory cytokines and anti-inflammatory mediators such as IL-6, IL-8, tumor necrosis factor-α (TNF-α), IL-10 leads to SIBO. SIBO and IBD have the same

relationship in cytokine increase and decrease in anti-oxidants resulting in delayed GI motility. It is estimated that the same microbes contribute to the both disorders, different only in immune responses 39.

There is considerable evidence that IBD patients show a depletion of firmicutes and an increase of Proteobacteria 40 41.

The dominant species increased in IBD are Proteobacteria (particularly adherent invasive E coli (AIEC)), Fusobacterium species (Fusobacterium nucleatum), Pasteurellaceae (Haemophilus parainfluenzae), Veillonellaceae（Veillonella parvula, Neisseriaceae (Eikenella corrodens). The dominant species decreased in IBD are Bacteroides (Bacteroides vulgatus, Bacteroides caccae), Bifidobacterium species (Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium adolescentis, Bifidobacterium dentum), and Faecalibacterium prausnitzii 42 43 44.

AIEC belonging to Proteobacteria phyla play an important role in IBD in adhering to and invading intestinal epithelial cells, and survive intracellularly. AIEC strains enhance to express high amounts of TNF-α and IL-17 from macrophages45 46.

Fusobacterium nucleatum (F. nucleatum) is an oral pathogen and known to express pro-inflammatory cytokines and invasive from oral till GI tract epithelium. The strains of Fusobacterium induce the damage to colon epithelium causing IBD 47. F. nucleatum exacerbate colonic inflammation through both with Th1-related cytokines IFN-γ through the AKT2 signaling pathway and with macrophage repolarization 48.

Bacteroides fragilis works as beneficial flora with the host in the anaerobic gut. Although Bacteroides fragilis is less in number (0.5%) in the colon flora, the bacteria show strong virulence in the extra-gut causing bacteremia and abscess formation 49 50.

Prevotella exacerbates intestinal inflammation by reduction of SCFAs, specifically acetate, and consequently results in a decrease in intestinal IL-18 levels and potentiates systemic autoimmunity 51.

Immune homeostasis especially in the gut is regulated by complicated crosstalk between beneficial and harmful microbes including Bifidobacterium, Lactobacillus, Clostridium coccoides group, F. nucleatum and Escherichia coli 41.

Intriguingly, there has been considerable interest in Helicobacter pylori (H. pylori). H. pylori is a risk factor for gastroduodenal ulcer and gastric cancer, moreover, this bacterium is supposed to have a protective role in IBD 52.

Fermentation of non-digestible plant stuffs by gut microbiota contribute to human health producing bioactive compounds including SCFAs and bioactive phytochemicals 23. Endothelial and immune cells induce inflammatory disease such as IBD with the effects of lipopolysaccharide (LPS) or TNF-α. SCFAs have beneficial effects on both

cell types through NF-κB and MAPK signaling pathways by activating FFA2, FFA3 receptors and GPR109A and by inhibiting HDACs 53.

Immunological mechanisms of gut microbiota have been shown to play an important role in the inflammation of epithelial cells and myeloid cells through NF-κB 54.

The existing evidence demonstrates that probiotics including polyphenols, fibers induce clinical improvement through anti-inflammatory cytokines 41.

SIBO increases gastroduodenal and small bowel permeability and correlated with the severity of FM patients' pain 55. In addition, mediation of pain sensitivity is associated with pro-inflammatory cytokines, prostaglandins and ROS 56. NF-κB is the transcriptional factor playing an important role in inflammation and pain. NF-κB especially initiate inflammatory genes such as TNFα, IL-1β, and cyclooxogenase-2 (COX-2) that is associated with pain 57.

NF-κB Signaling and Fibromyalgia

NF-κB is a ubiquitous complex protein regulating the transcription of more than 200 genes involved in immune and inflammatory response and pain 58 59. NF-κB composed of homo- and heterodimers of five members including P50, P52, P65 (RelA), RelB and c-Rel. The NF-κB family protein is composed of two subfamilies: the NF-κB and the REL subfamily proteins. P50 and P52 proteins are included in NF-κB subfamily and P65 (RelA), RelB and c-Rel are in REL subfamily 59 60. At not active condition, NF-κB1 consists of p105/p50 + RelA (p65) and inhibitor IKKα and NF-κB2 consist of p100/p52+RelB and IKKα. NF-κB pathway has two major sub-pathways canonical (classical) and non-canonical (alternative) pathways 60. The canonical pathway, when stimulated, activates IκB kinase (IKK) complex (IKKα and IKKβ) and in non-canonical pathway IKKα is activated through NF-κB-inducing kinase (NIK) 61.

COMT metabolizes catecholamines into neurotransmitters, and associated with the etiology and pathogenesis of disorders in various central nervous system. TNF-α induced-activated NF-κB modulates the inhibition of COMT expression through IKKβ 62 63. The metabolized catecholamines affect pain sensitivity in FM patients 62 64.

Thalidomide suppresses activated NF-κB through IκBα kinase activation resulting in suppression of proliferation, inflammation, angiogenesis, and the immune system that are caused by TNF-α and H_2O_2 65. Celecoxib inhibit activation of IκBα kinase through TNF-α signal at nuclear translocation 66 67.

Treatment

Currently pharmacological treatment of FM is to suppress each symptom with appropriate medicine. Antidepressants such as low-dose amitriptyline are used for insomnia and pain, and antiepileptic drugs such as pregabalin and gabapentin are used when the target is mainly pain, but the effects are not sufficient with severe side effects 68.

Figure	receptor	signal transduction	transcriptional factor	chromatin	molecular target	ref
thalidomide			NF-κB		VEGF, bFGF COX-2	69 70 71
celecoxib			NF-κB COX-2		COX-2	72
valproic acid				HDACs	bFGF	73

The exciting findings in the past decade are that the gut microbiota may act as a regulator of oxidative stress.

Probiotics

The microorganism that exerts beneficial effects in human health are known as probiotics which are defined as live microbial feed supplements including the genus Lactobacillus and Bifidobacterium. **Probiotics might play an important role in improvement of FM 74.** Oxidative stress induces dysbiosis, lowering levels of Lactobacilli and Bifidobacterium 75 76. At least it is important to maintain the homeostasis of gut microbiota with probiotics, prebiotics and berberine 77.

Prebiotics

The fermentation may lead to the increased production of SCFAs including acetate, propionate, and butyrate. The potential natural products are whole grains, fruits, vegetables, and nuts. SCFAs are known as HDAC inhibitors, especially butyrate possesses significant response and modulate cancer and immunological stability 78.

Berberine

Berberine is an isoquinoline alkaloid purified from Japanese herb, Phellodendron

amurense (KIHADA in Japanese), for a treatment of microbial diarrhea.

Berberine has a variety of biological and pharmacological activities, effective for multiple disorders such as cancers and FM. Especially, berberine exerts its functions through anti-angiogenic effect inhibiting various pro-inflammatory and pro-angiogenic factors [79]. This activity is induced via AMP-activated protein kinase (AMPK) activation, NF-κB inhibition and AP-1 pathway inhibition resulting in down-regulating the expression of cytokines, including TNF-α, IL-1β, IL-6, monocyte chemo-attractant protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), and COX-2 [80] [81].

Superoxide dismutase (SOD) and catalase (CAT) degradate superoxide anion radical ($O_2 \cdot -$) into H_2O and O_2 through less harmful hydrogen peroxide(H_2O_2).

Berberine may induce the activity of SOD and CAT leading to the reduction of ROS including H_2O_2. Berberine may significantly suppress the activity of oxidative stress [82].

Berberine is poor water-soluble and poor absorbable from intestinal epithelial cells, therefore its bioavailability is low [83] [84]. However, oral administration effectively improves various diseases such as DM. Berberine is converted into 5-fold absorbable dihydroberberine (dhBBR) by gut microbiota. dhBBR is unstable in the intestine and the blood, reverted to BBR after absorption into intestinal tissue and the blood through non-enzymatic oxidation [84].

Thalidomide

Thalidomide is an immunomodulatory agent with strong antiangiogenic properties with COX-2 inhibitor celecoxib. Thalidomide inhibits the mRNA encoding such as TNF-α and vascular endothelial growth factor (VEGF) [85]. In addition, thalidomide modulates activated or irregulated NF-κB, resulting in suppressing malignant cell proliferation and angiogenesis as well as invasion and metastasis [86]. VEGFR-1 has a high affinity to VEGF. Serum level of VEGFR-1, a negative regulator of angiogenesis, are elevated in the patients with FM that leads to pathological angiogenesis. Thalidomide may mediate this pathological angiogenesis [87].

Celecoxib

COX-2 is constitutively overexpressed in chronic inflammation including FM (with slight inflammation) premalignant, malignant, and metastatic tumors induced by oxidative stress. Chronic inflammation induced by pathogens and metabolic state such as FM leads to express COX-2 [88] [89]. Produced prostaglandin and pro-inflammatory cytokines by COX-2 cause pathological angiogenesis in FM especially through NF-κB [72]. Celecoxib, along with glycyrrhizin (injection) [90], effectively suppresses the side

effects of the new corona vaccine, mainly fever and general malaise. This effect is thought to be due to the same molecular mechanism of FM onset.

Valproic acid (VPA)

VPA is a short fatty acid and has been used as an anti-convulsant agent. In recent years, VPA is used as HDAC inhibitor alone or in combination with other anticancer agents 91.

The induction of cell cycle arrest and apoptosis by VPA are associated with increased expression of E-cadherin and decreased expression of VEGF and MMP-9.

VPA inhibits endothelial function and angiogenesis 92.

Thalidomide and valproic acid are contraindicated in pre- pregnancy and during pregnancy. Valproic acid sometimes induce serious side effects, therefore, intensive observation is important.

Conclusion

The ultimate goal of Prevention and Treatment of fibromyalgia is to mediate pathogens binding to Receptors and to select the agents that act on transcriptional factors such as NF-κB.

Every Patient have to select regimen (1).

(1) Probiotics + prebiotics +berberine (100-300mg/day p.o) every day

Bifidobacterium + lactobacillus preparation（higher than normal dose）

Select the regimen according to the symptoms.

a) (1) + (2) Celecoxib(200mg/day) every day

b) (1) + (3) Celecoxib(200mg/day) + Valproic acid (600mg/day) every day

c) (1) + (4) Thalidomide(200mg/day) + Celecoxib(200mg/day) every day

The amount of thalidomide should be lessen day by day according the symptoms to prevent side effects.

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References

1. F. Jahan, K. Nanji, W. Qidwai, et al
Fibromyalgia Syndrome: An Overview of Pathophysiology, Diagnosis and Management
Oman Med J. 2012 May; 27(3): 192–195.
PubMed PMC free article

2. Gracely RH, Ceko M, Bushnell MC.
Fibromyalgia and depression.
Pain Res Treat. 2012;2012:486590.
PMC free article

3. Wolfe F, Smythe HA, Yunus MB, et al
The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee.
Arthritis Rheum. 1990 Feb;33(2):160-72.
PubMed PDF

4. F. WOLFE,D. J. CLAUW, MARY-ANN FITZCHARLES, et al
The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity
Arthritis Care & Research Vol. 62, No. 5, May 2010, pp 600 – 610
PDF

5. Auten RL, Davis JM.
Oxygen toxicity and reactive oxygen species: the devil is in the details.
Pediatr Res. 2009 Aug;66(2):121-7.
PubMed Abstract/FullText

6. Tishler M, Smorodin T, Vazina-Amit M,et al
Fibromyalgia in diabetes mellitus.
Rheumatol Int. 2003 Jul;23(4):171-3.
PubMed

7. Hein G, Franke S.
Are advanced glycation end-product-modified proteins of pathogenetic importance in fibromyalgia?
Rheumatology (Oxford). 2002 Oct;41(10):1163-7.
PubMed Abstract/FullText

8. Pimentel M, Wallace D, Hallegua D, et al
.A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing.

Ann Rheum Dis. 2004 Apr;63(4):450-2.
PubMed PMC free article
9. Sachdev AH, Pimentel M.
Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance.
Ther Adv Chronic Dis. 2013 Sep;4(5):223-31.
PubMed PMC free article
10. Merkhofer, E., Cogswell, P. Baldwin, A.
Her2 activates NF-κB and induces invasion through the canonical pathway involving IKKα.
Oncogene 29, 1238–1248 (2010).
Abstract/FullText
11. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A.
Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev. 2017;2017:8416763.
PubMed PMC free article
12. Southorn PA, Powis G.
Free radicals in medicine. I. Chemical nature and biologic reactions.
Mayo Clin Proc. 1988 Apr;63(4):381-9.
PubMed Abstract/FullText
13. Sharifi-Rad M, Anil Kumar NV, Zucca P, et al.
Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases.
Front Physiol. 2020;11:694. Published 2020 Jul 2.
PMC free article
14. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE.
Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases.
Physiol Rev. 2014;94(2):329-354.
PMC free article
15. Atashgahi S, Shetty SA, Smidt H, de Vos WM.
Flux, Impact, and Fate of Halogenated Xenobiotic Compounds in the Gut.
Front Physiol. 2018 Jul 10;9:888.
PubMed PMC free article
16. Taniyama Y, Griendling KK.
Reactive oxygen species in the vasculature: molecular and cellular mechanisms.

Hypertension. 2003;42(6):1075-1081.
PubMed Abstract/FullText
17. Cordero MD.
Oxidative Stress in Fibromyalgia: Pathophysiology and Clinical Implications
Reumatol Clin. 2011.
Abstract/FullText
18. Ayala A, Muñoz MF, Argüelles S.
Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal.
Oxid Med Cell Longev. 2014;2014:360438.
PubMed PMC free article
19. Juan José García, Julián Carvajal-Gil, Aurora Herrero-Olea, et al
Altered Inflammatory Mediators in Fibromyalgia
Rheumatology (Sunnyvale) 2017, 7:2
PDF
20. Marquis RE.
Oxygen metabolism, oxidative stress and acid-base physiology of dental plaque biofilms.
J Ind Microbiol. 1995 Sep;15(3):198-207.
PubMed
21. Erdrich S, Hawrelak JA, Myers SP, Harnett JE.
A systematic review of the association between fibromyalgia and functional gastrointestinal disorders.
Therap Adv Gastroenterol. 2020 Dec 8;13:1756284820977402.
PubMed PMC free article
22. Minerbi A, Fitzcharles MA.
Gut microbiome: pertinence in fibromyalgia.
Clin Exp Rheumatol. 2020 Jan-Feb;38 Suppl 123(1):99-104. Epub 2020 Feb 12. PMID: 32116215.
PubMed Abstract/FullText
23. Whisner CM, Athena Aktipis C.
The Role of the Microbiome in Cancer Initiation and Progression: How Microbes and Cancer Cells Utilize Excess Energy and Promote One Another's Growth.
Curr Nutr Rep. 2019 Mar;8(1):42-51.
PubMed PMC free article
24. Asarat M, Vasiljevic T, Apostolopoulos V,et al.
Short-Chain Fatty Acids Regulate Secretion of IL-8 from Human Intestinal Epithelial

Cell Lines in vitro.
Immunol Invest. 2015;44(7):678-93.
PubMed
25. Francisqueti-Ferron FV, Ferron AJT, Garcia JL, et al
Basic Concepts on the Role of Nuclear Factor Erythroid-Derived 2-Like 2 (Nrf2) in Age-Related Diseases.
Int J Mol Sci. 2019 Jun 29;20(13):3208.
PubMed PMC free article
26. Li S, Hua D, Wang Q, et al
The Role of Bacteria and Its Derived Metabolites in Chronic Pain and Depression: Recent Findings and Research Progress.
Int J Neuropsychopharmacol. 2020 Mar 10;23(1):26-41.
PubMed PMC free article
27. Liang L, Lutz BM, Bekker A,et al
Epigenetic regulation of chronic pain.
Epigenomics. 2015;7(2):235-45.
PubMed PMC free article
28. Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D.
Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update.
Int J Mol Sci. 2021 Apr 9;22(8):3891.
PubMed PMC free article
29. DeFronzo RA, Tripathy D.
Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009 Nov;32 Suppl 2(Suppl 2):S157-63.
PubMed PMC free article
30. Ahmed N.
Advanced glycation endproducts--role in pathology of diabetic complications. Diabetes Res Clin Pract. 2005 Jan;67(1):3-21.
PubMed
31. Singh VP, Bali A, Singh N, et al.
Advanced glycation end products and diabetic complications.
Korean J Physiol Pharmacol. 2014 Feb;18(1):1-14.
PubMed PMC free article
32. Younus H, Anwar S.
Prevention of non-enzymatic glycosylation (glycation): Implication in the treatment of diabetic complication.

Int J Health Sci (Qassim). 2016 Apr;10(2):261-77.
PubMed PMC free article
33. Aragno M, Mastrocola R.
Dietary Sugars and Endogenous Formation of Advanced Glycation Endproducts: Emerging Mechanisms of Disease.
Nutrients. 2017;9(4):385. Published 2017 Apr 14.
PMC free article
34. Bennmann D, Horstkorte R, Hofmann B,et al.
Advanced glycation endproducts interfere with adhesion and neurite outgrowth. PLoS One. 2014 Nov 11;9(11):e112115.
PubMed PMC free article
35. Ceko M, Bushnell MC, Fitzcharles MA,et al.
Fibromyalgia interacts with age to change the brain.
Neuroimage Clin. 2013 Sep 6;3:249-60.
PubMed PMC free article
36. Dane A, Gurbuz T.
Clinical Comparative Study of the Effects of Helicobacter Pylori Colonization on Oral Health in Children.
Pak J Med Sci. 2016 Jul-Aug;32(4):969-73.
PubMed PMC free article
37. Minerbi A, Gonzalez E, Brereton NJB, et al.
Altered microbiome composition in individuals with fibromyalgia.
Pain. 2019 Nov;160(11):2589-2602.
PubMed Abstract/FullText
38. Andrew C Dukowicz 1, Brian E Lacy, Gary M Levine
Small Intestinal Bacterial Overgrowth: A Comprehensive Review
Gastroenterol Hepatol (N Y), 3 (2), 112-22 Feb 2007
PubMed PMC free article
39. Rana SV, Sharma S, Kaur J, et al.
Relationship of cytokines, oxidative stress and GI motility with bacterial overgrowth in ulcerative colitis patients.
J Crohns Colitis. 2014;8(8):859-865.
PubMed Abstract/FullText
40. Stojanov S, Berlec A, Štrukelj B.
The Influence of Probiotics on the Firmicutes/Bacteroidetes Ratio in the Treatment of Obesity and Inflammatory Bowel disease.

Microorganisms. 2020 Nov 1;8(11):1715.
PubMed PMC free article
41. Malinowski B, Wiciński M, Sokołowska MM, Hill NA, Szambelan M.
The Rundown of Dietary Supplements and Their Effects on Inflammatory Bowel Disease-A Review. Nutrients. 2020 May 14;12(5):1423.
PubMed PMC free article
42. Glassner KL, Abraham BP, Quigley EMM.
The microbiome and inflammatory bowel disease.
J Allergy Clin Immunol. 2020 Jan;145(1):16-27.
PubMed Abstract/FullText
43. Vester-Andersen MK, Mirsepasi-Lauridsen HC, Prosberg MV, et al.
Increased abundance of proteobacteria in aggressive Crohn's disease seven years after diagnosis.
Sci Rep. 2019 Sep 17;9(1):13473.
PubMed PMC free article
44. Gevers D, Kugathasan S, Denson LA, et al.
The treatment-naive microbiome in new-onset Crohn's disease.
Cell Host Microbe. 2014 Mar 12;15(3):382-392.
PubMed PMC free article
45. Lee JG, Han DS, Jo SV, Lee AR, Park CH, Eun CS, Lee Y.
Characteristics and pathogenic role of adherent-invasive Escherichia coli in inflammatory bowel disease: Potential impact on clinical outcomes.
PLoS One. 2019 Apr 29;14(4):e0216165.
PubMed PMC free article
46. Darfeuille-Michaud A.
Adherent-invasive Escherichia coli: a putative new E. coli pathotype associated with Crohn's disease.
Int J Med Microbiol. 2002 Sep;292(3-4):185-93.
PubMed
47. Strauss J, Kaplan GG, Beck PL, Rioux K, Panaccione R, Devinney R, Lynch T, Allen-Vercoe E.
Invasive potential of gut mucosa-derived Fusobacterium nucleatum positively correlates with IBD status of the host. Inflamm Bowel Dis. 2011 Sep;17(9):1971-8.
PubMed
48. Liu L, Liang L, Liang H, Wang M, Lu B, Xue M, Deng J, Chen Y.
Fusobacterium nucleatum Aggravates the Progression of Colitis by Regulating M1

Macrophage Polarization via AKT2 Pathway.
Front Immunol. 2019 Jun 12;10:1324.
PubMed PMC free article
49. Wexler HM.
Bacteroides: the good, the bad, and the nitty-gritty. Clin Microbiol Rev. 2007;20(4):593-621.
PubMed PMC free article
50. Mootien S, Kaplan PM.
Monoclonal antibodies specific for Bacteroides fragilis enterotoxins BFT1 and BFT2 and their use in immunoassays.
PLoS One. 2017 Mar 3;12(3):e0173128.
PubMed PMC free article
51. Iljazovic A, Roy U, Gálvez EJC, Lesker TR, Zhao B, Gronow A, Amend L, Will SE, Hofmann JD, Pils MC, Schmidt-Hohagen K, Neumann-Schaal M, Strowig T. Perturbation of the gut microbiome by Prevotella spp. enhances host susceptibility to mucosal inflammation. Mucosal Immunol. 2020 May 20.
PubMed Abstract/FullText
52. Santos MLC, de Brito BB, da Silva FAF, et al.
Helicobacter pylori infection: Beyond gastric manifestations.
World J Gastroenterol. 2020 Jul 28;26(28):4076-4093.
PubMed PMC free article
53. Li M, van Esch BCAM, Wagenaar GTM, Garssen J, Folkerts G, Henricks PAJ. Pro- and anti-inflammatory effects of short chain fatty acids on immune and endothelial cells.
Eur J Pharmacol. 2018 Jul 15;831:52-59.
PubMed Abstract/FullText
54. Wu S, Rhee KJ, Albesiano E,et al
A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses.
Nat Med. 2009 Sep;15(9):1016-22.
PubMed PMC free article
55. Goebel A, Buhner S, Schedel R, et al
Altered intestinal permeability in patients with primary fibromyalgia and in patients with complex regional pain syndrome
Rheumatology (Oxford). 2008 Aug;47(8):1223-7.
PubMed Abstract/FullText

56. Nackley AG, Tan KS, Fecho K, Flood P, et al
Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors.
Pain. 2007 Apr;128(3):199-208. Epub 2006 Nov 7.
PubMed PMC free article
57. Hartung JE, Eskew O, Wong T, et al
Nuclear factor-kappa B regulates pain and COMT expression in a rodent model of inflammation.
Brain Behav Immun. 2015 Nov;50:196-202.
PubMed PMC free article
58. Panday A, Inda ME, Bagam P, et al
Transcription Factor NF-κB: An Update on Intervention Strategies
Arch Immunol Ther Exp (Warsz). 2016 Dec;64(6):463-483.
Abstract
59. Ting Liu, Lingyun Zhang, Donghyun Joo, et al
NF-κB signaling in inflammation
Signal Transduct Target Ther. 2017; 2: 17023.
Abstract/FullText
60. Lingappan K.
NF-κB in Oxidative Stress.
Curr Opin Toxicol. 2018;7:81-86.
PMC free article
61. Hayden MS, Ghosh S.
Signaling to NF-kappaB.
Genes Dev. 2004 Sep 15;18(18):2195-224.
PubMed Abstract/FullText
62. Martínez-Jauand M, Sitges C, Rodríguez V, et al
Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene.
Eur J Pain. 2013 Jan;17(1):16-27.
PubMed
63. Tchivileva IE, Nackley AG, Qian L, et al
Characterization of NF-kB-mediated inhibition of catechol-O-methyltransferase. Mol Pain. 2009 Mar 16;5:13.
PubMed PMC free article
64. Karin M.

How NF-kappaB is activated: the role of the IkappaB kinase (IKK) complex. Oncogene. 1999 Nov 22;18(49):6867-74.
PubMed Abstract/FullText
65. Sekhar Majumdar, Betty Lamothe, Bharat B Aggarwal
Thalidomide Suppresses NF-κB Activation Induced by TNF and H2O2, But Not That Activated by Ceramide, Lipopolysaccharides, or Phorbol Ester
J Immunol, 168 (6), 2644-51
PubMed Abstract/FullText
66. Shishodia S, Koul D, Aggarwal BB.
Cyclooxygenase (COX)-2 inhibitor celecoxib abrogates TNF-induced NF-kappa B activation through inhibition of activation of I kappa B alpha kinase and Akt in human non-small cell lung carcinoma: correlation with suppression of COX-2 synthesis.
J Immunol. 2004 Aug 1;173(3):2011-22.
PubMed Abstract/FullText
67. Funakoshi-Tago.M, Shimizu.T, Tago. T
Celecoxib potently inhibits TNFα-induced nuclear translocation and activation of NF-κB
Biochemical Pharmacology, 76(5),662-671
Abstract
68. Kwiatek R.
Treatment of fibromyalgia.
Aust Prescr. 2017;40(5):179-183.
PMC free article
69. von Haehling S, Anker SD.
Treatment of cachexia: an overview of recent developments.
J Am Med Dir Assoc. 2014 Dec;15(12):866-72.
PubMed Abstract/FullText
70. Ali S, Garcia JM.
Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - a mini-review.
Gerontology. 2014;60(4):294-305.
PubMed PMC free article
71. Dhillon RJ, Hasni S.
Pathogenesis and Management of Sarcopenia.
Clin Geriatr Med. 2017;33(1):17-26.
PubMed PMC free article

72. Rogers ES, MacLeod RD, Stewart J, et al.
A randomised feasibility study of EPA and Cox-2 inhibitor (Celebrex) versus EPA, Cox-2 inhibitor (Celebrex), resistance training followed by ingestion of essential amino acids high in leucine in NSCLC cachectic patients--ACCeRT study.
BMC Cancer. 2011 Nov 23;11:493.
PubMed PMC free article
73. Sun R, Zhang S, Hu W, Lu X, Lou N, Yang Z, Chen S, Zhang X, Yang H. Valproic acid attenuates skeletal muscle wasting by inhibiting C/EBPβ-regulated atrogin1 expression in cancer cachexia.
Am J Physiol Cell Physiol. 2016 Jul 1;311(1):C101-15.
PubMed Abstract/FullText
74. Roman P, Carrillo-Trabalón F, Sánchez-Labraca N, et al.
Are probiotic treatments useful on fibromyalgia syndrome or chronic fatigue syndrome patients? A systematic review.
Benef Microbes. 2018 Jun 15;9(4):603-611.
PubMed
75. Cardona D, Roman P, Cañadas F, et al.
The Effect of Multiprobiotics on Memory and Attention in Fibromyalgia: A Pilot Randomized Controlled Trial.
Int J Environ Res Public Health. 2021 Mar 29;18(7):3543.
PubMed PMC free article
76. Logan A.C., Katzman M.
Major depressive disorder: Probiotics may be an adjuvant therapy.
Med. Hypotheses. 2005;64:533–538.
PubMed
77. Geller LT, Barzily-Rokni M, Danino T, et al
Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine.
Science. 2017 Sep 15;357(6356):1156-1160.
PubMed PMC free article
78. Markowiak P, Śliżewska K.
Effects of Probiotics, Prebiotics, and Synbiotics on Human Health.
Nutrients. 2017 Sep 15;9(9). pii: E1021.
PubMed PMC free article
79. Guo P, Cai C, Wu X, et al.
An Insight Into the Molecular Mechanism of Berberine Towards Multiple Cancer Types

Through Systems Pharmacology.
Front Pharmacol. 2019;10:857. Published 2019 Aug 6.
PMC free article
80. Zou K, Li Z1, Zhang Y, et al
Advances in the study of berberine and its derivatives: a focus on anti-inflammatory and anti-tumor effects in the digestive system.
Acta Pharmacol Sin. 2017 Feb;38(2):157-167.
PubMed PMC free article
81. Wang H, Zhu C, Ying Y, et al
Metformin and berberine, two versatile drugs in treatment of common metabolic diseases.
Oncotarget. 2017 Sep 11;9(11):10135-10146.
PubMed PMC free article
82. Ma X, Deng J, Cui X, et al.
Berberine exhibits antioxidative effects and reduces apoptosis of the vaginal epithelium in bacterial vaginosis.
Exp Ther Med. 2019;18(3):2122-2130.
PMC free article
83. Fan J, Zhang K, Jin Y, Li B, et al.
Pharmacological effects of berberine on mood disorders.
J Cell Mol Med. 2019 Jan;23(1):21-28.
PubMed PMC free article
84. Feng, R., Shou, JW., Zhao, ZX. et al.
Transforming berberine into its intestine-absorbable form by the gut microbiota. Sci Rep 5, 12155 (2015).
Abstract/FullText
85. Kim HJ, Yim GW, Nam EJ, et al
Synergistic Effect of COX-2 Inhibitor on Paclitaxel-Induced Apoptosis in the Human Ovarian Cancer Cell Line OVCAR-3.
Cancer Res Treat. 2014 Jan;46(1):81-92.
PubMed PMC free article
86. Tempfer CB, Schultheis B, Hilal Z,et al
Thalidomide and lenalidomide for recurrent ovarian cancer: A systematic review of the literature.
Oncol Lett. 2017 Sep;14(3):3327-3336.
PubMed PMC free article

87. Karadağ A, Hayta E, Çelik VK, et al.
Serum Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor-1 Levels in Patients With Fibromyalgia Syndrome.
Arch Rheumatol. 2019 Apr 22;34(4):414-418.
PubMed PMC free article
88. Pridgen WL, Duffy C, Gendreau JF, et al.
A famciclovir + celecoxib combination treatment is safe and efficacious in the treatment of fibromyalgia.
J Pain Res. 2017 Feb 22;10:451-460.
PubMed PMC free article
89. Hada M.
Chemotherapeutic Strategy with Synbiotics, Thalido-mide and Celecoxib for severe COVID-19 Pneumonia. Associa-tion between microbiota, chronic inflammation and pneumonia. 2020.
PDF
90. Qiang Liu, Yuan-hong Zhou, Zhan-qiu Yang
The cytokine storm of severe influenza and development of immunomodulatory therapy
Cellular & Molecular Immunology volume 13, pages3–10(2016)
Abstract/FullText
91.Lipska K, Gumieniczek A, Filip AA.
Anticonvulsant valproic acid and other short-chain fatty acids as novel anticancer therapeutics: Possibilities and challenges.
Acta Pharm. 2020 Sep 1;70(3):291-301.
PubMed
92. Murugavel S, Bugyei-Twum A, Matkar PN et al
Valproic Acid Induces Endothelial-to-Mesenchymal Transition-Like Phenotypic Switching.
Front Pharmacol. 2018 Jul 11;9:737
PubMed PMC free article