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INTRICATE RELATIONSHIP OF GUT MICROBIOTA IN THE PATHOGENESIS OF PSORIASIS AND THE ROLE OF AYURVEDA IN ITS MANAGEMENT: A COMPREHENSIVE REVIEW

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ABSTRACT

The diverse ecosystem of different microbial colonies inhabiting in the human intestine are known as gut microbiota. This gut microbiota regulates our immunity to prevent from pathogens by maintaining the gut barrier permeability. Any change in the symbiotic co-existence of these microbiota ecosystem is termed as 'dysbiosis' responsible for various autoimmune disorders. Psoriasis is one of the autoimmune dermatological condition characterised by erythema and epidermal hyperkeratosis which is influenced by dysbiosis. Dysbiosis leads to increased permeability of gut barrier triggering the various immunological cascade events through activation of T lymphocytes. This is the onset point of pathogenesis of psoriasis which later involves various influencing factors like interleukin (IL)-22, IL-17, IL-6, interferons (IFNs), tumor necrotising factors (TNF), etc. The widespread use of immunosuppressive drugs and antibiotics for long term is not satisfactory as per overall health concern of psoriatic patients due significant disrupting effects on gut flora. Thus, recent advanced studies are focusing on the treatment modalities which will strengthen pre-established microbial ecosystem. Ayurveda is a

traditional and holistic healthcare system that strongly believe in the managing overall health of diseased person without disrupting existed ecosystem. Virechana (therapeutic purgation) is one of the methods of internal bio purification documented in Ayurveda and it is being practised in India for treating psoriasis for thousands of years. It has been witnessed for its significant clinical efficacy in psoriasis and various autoimmune ailments. Present study emphasizes the attention over virechana for further clinical researches and to explore the complexity of microbial system.

Keywords: Gut flora; Dysbiosis; Gut ecosystem; Immunity; Dermatosis; Virechana

INTRODUCTION

Recent studies have shown the important role of microbiome in the pathogenesis of various chronic multifactorial diseases and their involvement on the therapeutic efficacy of various treatment modalities. Psoriasis is a chronic autoimmune multifactorial dermatosis which has shown the involvement of specific gut microbiome dysbiosis that is different from gut microbiome of healthy people. This dermatosis shows the linking between some genetic factors along with some external provoking factors **[1]**. The intricate relationship between gut microbes and autoimmune diseases has focused the role of dysbiosis in the pathogenesis. Recently, some studies have shown characteristic change in gut ecosystem that is associated with the inflammatory bowel disease (IBD), which is suggesting that IBD is resulted from the dysbiosis in gut and the altered mucosal immune mechanism **[2, 3]**. Also, it has been found that altered gut ecosystem can affect the extracolonic body sites such as skin, liver, joints, heart, brain, etc. The clinical importance of the relationship between gut microbiota and immune system would be a milestone and can provide the new approach in the direction of understanding pathogenesis of various multifactorial autoimmune disorders and microbiota targeted futuristic therapeutic vision.

1.1 Current Understanding of Psoriasis

a. Immunological aspect

It is a chronic inflammatory dermatitis which is characterized by intermittent course of remissions and relapses. The clinical features are seen in the form of erythematous papules and plaques which are surmounted by loose silvery scales **[4]**. There are many factors that which are responsible for triggering psoriasis e.g., external trauma or injury (elicited as Koebner phenomenon), sepsis, chemotherapy, topical agents (imiquimod), etc. One well elicited

mechanism of disease onset after dysregulated immune responses show involvement of keratinocytes (KCs). After physical injury or sepsis, KCs release antimicrobial peptide (AMP) LL-37 which binds to the self-DNA and RNA fragments which are also released by damaged dermal cells resulting in the formation of LL-37/self-DNA/RNA complexes those found in psoriatic lesion. These complexes activate plasmacytoid predendritic cells (PDCs) which are absent in normal skin and responsible for producing interferon alpha (IFN-α). This PDC derived IFN-α is later responsible for onset of psoriatic lesions.

Besides aforesaid mechanism, it has been seen that interleukin (IL)-22 is significantly over expressed most possibly due to upregulated IL-23 and IL-6 **[5, 6]**. This pathological crosstalk among KCs, PDC and T cells sustained by mainly IFN-α, TNF, IL-22, IL-23, IL-17 and IL-6 and further dysregulation of immune system seen in psoriasis **[7]**. Thus, the involvement of the immune system in the development of psoriasis is also very complex as compared to its overall pathogenesis involving different adaptive and innate immune cells at different progressive stages of the disease **[7]**.

b. Genetic

There are some chromosomal loci (PSORS 1-10) those have been found to have significant role in the linkage to psoriasis **[8]**. The one region known as major-histocompatibility complex (MHC) found frequently on chromosome 6 (named as PSORS1) in genetic screening of families suffered from psoriasis **[8]**.

Human leukocyte antigen-C (HLA-C) is also found as main culprit gene in PSORS1 responsible for psoriasis **[9]**.

One genomic study has found IL-23R, IL-4/IL-13 gene cluster and CDKAL1 are susceptible genes for psoriasis suggesting complexity of the disease **[10]**.

1.2 Composition of The Healthy Human Gut

Gut microbiota development starts from embryonic life of birth and it's keep developing even after birth. Human gastrointestinal tract is rapidly colonized in later life with various life events such as diet, lifestyle, surrounding environment, illness, medications, antibiotics, etc. **[11, 12]**. The diverse variety of living bacteria, viruses, archaea, fungi, eukaryotes, reside in the

gut forming their colonies etc are said as 'gut microbiome' or 'gut microbiota'. They have co-evolved with the development of living organisms over thousands of years forming the intricate relationship for mutual benefits **[13, 14]**. The approximate number of those living microorganisms residing inside the GI tract is 10^{14}, which is probably ~10 times more bacterial cells than total human cell number and approximately 100 times more genomic content than that of human being **[14, 15]**. Gut microbiota provides many benefits to the host in terms of various physiological events in the body. They strengthen the gut integrity stabilizing the intestinal epithelium, protect against pathogens, regulate immunity, balance the psychological behaviors through gut brain axis, harvest energy, etc. **[16-19]**. In the early ages of life, microbiome is generally less diverse and mainly dominated by two phyla i.e., actinobacteria and probacteria **[11, 20]**. Microbial diversity increases with the growing age and its composition tend to converse towards microbial profile like the adult human and remaining unique to every infant **[21]**. By the age of 2.5 years, microbial diversity and their functional abilities of microbiome present in child gut show resemblance with that adult gut microbiome ecosystem **[11, 12]**. Generally, four bacterial phyla those are Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes dominate the healthy dermal microbiome in adults **[22]**.

The use of some advanced techniques like DNA and RNA sequencing (16S and 18S) have made easier to explore the microbiota discovery, classification, and specificity of human gut flora composition with specific diseases after dysbiosis **[23]**.

1.3 Gut and Immunity Relation

In the human body, the region frequently interacting with the surrounding environment is human mucosa. The gut mucosa has complex immune mechanism including several tissues. Gut-associated lymphoid tissue (GALT) is the main tissue in gut mucosa that is associated to several lymphoid tissues to maintain immunity. Other lymphoid tissues include Peyer's patch lymphocytes (PPLs), lamina propria lymphocytes (LPLs), intestinal intraepithelial lymphocytes (IELs) and mesenteric lymph nodes (MLNs) **[24]**.

IELs consist of majority $CD3^+$ T cells, different B cells and natural killer (NK) cells. LPLs mainly include different subtypes of T and B cells. Th17 cells are

present most abundantly in the lamina propria of the intestine and they secrete some pro-inflammatory cytokines such as interleukin (IL)-17A, IL-17F and IL-22 to strengthen the gut barrier integrity and defense mechanism against pathogens **[25]**. Human immunity plays two very important role; one is defense mechanism against various pathogens and another one is maintaining equilibrium among residing microbial colonies of mucosal surface and epidermal skin. Gut microbiota forms the barrier to prevent the invasion of different pathogens and helps in the synthesis of various nutrients such as vitamins, proteins, etc. Thus, alteration in the gut microbial ecosystem can impair the intestinal defense mechanism as well as nourishment of the growing body **[26]**. In the gut barrier system, ligand activated transcription factor known as aryl hydrocarbon receptor (AhR) plays very important role in recognizing dietary molecules, microbial derived metabolites and some environmental pollutants which is important to control transcriptional programs in the human immune system **[27]**. Innate and the adaptive immunity are the two-integral part of our immune system and their subset lymphocytes shape the gut microbial integrity in distinct patterns to maintain homeostasis **[28]**. AhR contributes to the regulation of these adaptive and innate immune systems to control variety of diseases and it is one of the most important mechanism by which host recognizes the microbial metabolites **[29, 30]**. Intestinal mucosa secretes immunoglobulin A (IgA) contributes majorly to maintain intestinal mucosal immunity. IgA not only plays role to clear pathogens but also promotes host-microbial symbiotic association which is regulated by the microbiome. For example, Bacteroides fragilis transforms its surface to promote binding of IgA (in vivo) which facilitates bacterial adherence **[31]**. The stockpile of IgA bound to the gut microbiome is associated T-cell-dependent and T-cell-independent pathways.

AhR signaling can manipulate the dynamics of the gut microbiome which might be involved in the interaction between gut microbiota and the host metabolism **[32]**.

Furthermore, the activation or disruption of AhR may influence the microbiota behavior **[33]** where some specific dietary and microbiota metabolites of tryptophan can serve as the ligand for AhR **[34]**. Thereafter binding of tryptophan

metabolite, AhR get activated and leads to induce expression of downstream cytokines such as IL-22 and IL-17 to regulate intestinal homeostasis which is the key factor for onset of the psoriasis pathogenesis **[35]**.

DISCUSSION

2.1. Dysbiosis and Autoimmune Disorders [24]

It is supposed that the increasing number of autoimmune disorders is probably due to the shifts in the gut flora due to multifactorial reasons following dietary habits and the widespread use of antimicrobial agents as described in following **Table 1**.

Various genetic as well as environmental issues are responsible for autoimmune ailments for which various factors such as complex genetical elements, geographical region, radiation exposer, immunologic alteration, viral infections etc. Gut flora dysbiosis has been now found to be potential factor which is causing various autoimmune diseases like psoriasis where suffering humans are attributed to multiplebehavioral factors and still extent of gut microbial contribution is thus deceptive.

Dysbiosis not only in the gut but also other parts of human body can be categorized into three types: (1) loss of beneficial microorganisms (2) increased growth of harmful microorganisms and (3) loss of entire microbiota diversity. Furthermore, these types are not exclusive mutually and can occur simultaneously too **(Table 2) [36]**.

2.2 Gut Microbiota and Psoriasis Relationship

Many studies have been shown the intricate association of psoriasis and gut microbiota dysbiosis. The gut microbiota has aninfluencing effect on the systemic immunity which is causing the functioning and altered functioning of the distant body systems.

Dysbiosis involves alteration in the composition as well as function of interlinked microbial communication which result in altered gut barrier permeability. It further contributes to immune activation by translocation of microbial antigens and their secondary metabolites in the blood circulation **[34]**. Modified intestinal integrity and increased gut permeability, regular consequences of the systemic inflammation induced by gut dysbiosis stimulate the pathogenesis of psoriasis **[26]**.

Some studies were compared to assess diversity among microbial colonies in psoriasis cases and healthy controls. Majority studies found no significant difference in alpha diversity in both groups. But all of those reported a significant difference in

Beta-diversity assessed with 16S rRNA gene sequencing, between psoriasis and healthy controls **[37]**.

Alpha diversity refers to have diversity in specific ecosystem and usually expressed in total number of species in that ecosystem. On the other hand, beta diversity is the comparison of diversity between different ecosystems and usually measured as species change between those two ecosystems. Gut ecosystem of psoriatic patient and normal individual are two different ecosystems.

Some studies have elicited aforesaid conditions who foundon observing the phylum level, Bacteroidetes (gram negative) showed a lower relative abundance and Firmicutes (gram positive) a higher relative abundance in patients with psoriasis than in healthy controls **[38-40]**. At other part, studies by Shapiro J *et al*. found reduced amount of Proteobacteria in psoriatic cohort.

Also, there are many taxa which showed diversity in their relative abundance in psoriasis. At phylum level for instance, a decrease in relative Bacteroides and Proteobacteria with high proportions of Firmicutes and Actinobacteria was also reported in more than one study. Bacteroides, Proteobacteria, Firmicutes and Actinobacteria are four predominant phyla which constitute more than 98% of the gut microbiota. Therefore, the Firmicutes/ Bacteroidetes (F/B) ratio is supposed to be one of the important markers of gut microbiota and their altered ratio is probably associated with psoriasis **[37]**.

Table 1: Autoimmune Disorders Showing Dysbiosis

Diseases	Methods	Increasing gut microbial species	decreasing gut microbial species
Ankylosing Spondylitis	16S rRNA gene and ITS2 based DNA sequencing	*Escheriachia, Shigella Veillonella*	Prevotella strain 9, Megamonas
RA	16S ribosomal DNA	*Collinsella*	*Actinobacteria*
SLE	16S rRNA sequencing 16S rRNA gene sequencing	*Proteobacteria Bacteroides*	*Ruminococcaceae Firmicutes*
IBD	Metagenomic sequencing	*Escherichia coli*	*Eubacterium rectale*

Table 2: Dysbiosis Among Species in Psoriasis [37]

Increased species	Decreased species
• *Escherichia coli* • *Doreaformicigenerans* • *Clostridium citroniae* • *Ruminococcusgnavus* • *Collinsellaaerofaciens*	• *Prevotellacopri* • *Faecalibacteriumprausnitzii* • *Akkermiansiamuciniphila*

2.3 Modifying the Gut Microbiota as Therapeutic Option in Psoriasis Management

Recently fecal matter transplantation (FMT) has been evolved in the management of psoriasis. Though FMT is quite potential option in many microbiota-related conditions, it's very difficult establish trans-kingdom equilibrium as pre-existed state of microbiome **[37]**. **[38]** revealed that the effect of FMT can vary person to person as it depends on several factors. Such factors like relative microbial load, microbial composition, deranged function of the recipient as well as the donor associated with the different genetic factors related to them and the preparation and route of FMT supplementation Thus, still FMT is not a one suitable approach for all, and more studies are needed to explore the active component of the microbiome that have recipient specific results with different diseases.

The use of prebiotics and the pro biotics for managing the psoriasis and for other autoimmune conditions is also seen now a days. The widespread use of such option has found to be effective in controlling chronic skin ailments. Chen *et al*. (2018) **[40]** found that oral supplementation of Lactobacillus pentosus GMNL-77 leads to reduction in erythematous scaly lesions in imiquimod-treated mice with psoriasis-like inflammation.

2.4 Role of Ayurveda in Restoring Gut Ecosystem

Ayurveda is the holistic ancient healthcare system that has been evolved on the basis of clinical experiences for thousands of years. With changing the dimensions of the contemporary medical sciences, principles of Ayurveda are still same and applicable in era of modernization. As it believes in balancing the ecosystem of host suffered from illness by balancing the fundamental doshas, concept of dysbiosis is being studied by researchers for managing multifactorial diseases. FMT and oral administration of prebiotics and probiotics are no different methods for that.

There are two basic ways of managing diseased host in Ayurveda, i.e., Sanshamana (suppressive therapy) and shodhana (biopurification). Sanshamana is balancing the disease causing doshas with the help of medications. The other therapy focuses on expulsion of vitiated doshas in excessive form so as to maintain balance **[41]**. The present study emphasizes on the concept of correcting the disbalance of the diseased host which is comparable to dysbiosis through the biopurification methods. There are several methods in Ayurveda for achieving the same

e.g., Vaman (therapeutic emesis), Virechana (therapeutic purgation), Vasti (therapeutic enema), etc. These methods mainly work on the gut which is main causative route of all diseases. Thus, possibly by correcting the gut ecosystem, it can improve many multifactorial diseases e.g., diabetes, cardiovascular diseases, metabolic disorders, autoimmune disorders like psoriasis. As psoriasis is multifactorial autoimmune disease, virechana can be helpful in correcting dysbiosis. Ashutosh *et al*. in his clinical study on efficacy of virechana in obesity found it is effective in correcting dysbiosis. Virechana reduces the colonization of the aerobic bacteria which are contributing factor for obesity **[42]**. Chen *et al*. have shown the pathogeneses of psoriasis and obesity have certain overlapping immune pathways and the dysbiosis relationship **[43]**. Thus, therapeutic measures for correction of dysbiosis would be helpful for not only in obesity but also in psoriasis too.

CONCLUSION

Increasing trends in number of multifactorial autoimmune diseases like psoriasis with recent advancement in understanding the microbial involvement takes conclusion towards emphasizing on reverse pharmacological base of traditional healthcare model of Ayurveda. By tracking the route based on fundamentals of Ayurveda, it would be worth spending billions to reach goal of more understanding concept of dysbiosis.

REFERENCES

[1] A.Capon F. The Genetic Basis of Psoriasis. *Int. J. Mol. Sci.* 2017; 18: 2526. doi: 10.3390/ijms18122526.

[2] Spanogiannopoulos P., Bess E.N., Carmody R.N., Turnbaugh P.J. The microbial pharmacists within us: A metagenomic view of xenobiotic metabolism. *Nat. Rev. Microbiol.* 2016; 14: 273–287. doi: 10.1038/nrmicro.2016.17

[3] Ramírez-Boscá A., Navarro-López V., Martínez-Andrés A., Such J., Francés R., Horga de la Parte J., Asín-Llorca M. Identification of Bacterial DNA in the Peripheral Blood of Patients With Active Psoriasis. *Jama Derm.* 2015; 151: 670–671. doi:10.1001/jamadermatol.2014.5585.

[4] Illustrated Synopsis of Dermatology and Sexually transmitted Diseases by Neena Khanna, (chapter-4, Papulosquamous Disorders- Psoriasis; pg.44) published by Reed Elsevier India Pvt. Ltd, New Delhi 5th Edition. 2012.

[5] Boniface K, Guignouard E, Pedretti N, *et al*. A role for T cell-derived interleukin 22 in psoriatic skin inflammation. *Clin Exp Immunol.* 2007; 150(3): 407–415.

[6] Zheng Y, Danilenko DM, Valdez P, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature.* 2007; 445(7128): 648–651.

[7] Di Meglio P, Villanova F, Nestle FO. Psoriasis. *Cold Spring Harb Perspect Med*. 2014; 4(8): a015354. Published 2014 Aug 1. doi:10.1101/cshperspect.a015354

[8] Nair RP, Stuart PE, Nistor I, Hiremagalore R, Chia NV, Jenisch S, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet.* 2006; 78: 827–51.

[9] Trembath RC, Clough RL, Rosbotham JL, Jones AB, Camp RD, Frodsham A, *et al*. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet.* 1997; 6: 813–20.

[10] Nestle FO, Kaplan DH, Barker J. Mechanisms of Disease: Psoriasis. *N Engl J Med.* 2009; 361: 496–509.

[11] Rodriguez J.M., *et al*. (2015) The composition of the gut microbiota throughout life, with an emphasis on early life. *Microb. Ecol. Health Dis.* 26, 26050.

[12] Koenig J.E., Spor A., Scalfone N., Fricker A.D., Stombaugh J., Knight R. *et al*. (2011) Succession of microbial consortia in the developing infant gut microbiome. *Proc. Natl. Acad. Sci. U.S.A.* 108(Suppl 1), 4578–4585. doi:10.1073/pnas.1000081107

[13] Backhed F. (2005) Host-bacterial mutualism in the human intestine. *Science,* 307, 1915–1920. doi:10.1126/science.1104816

[14] Neish A.S. (2009) Microbes in gastrointestinal health and disease. *Gastroenterology* 136, 65–80. doi:10.1053/j.gastro.2008.10.080

[15] Gill S.R., Pop M., DeBoy R.T., Eckburg P.B., Turnbaugh P.J., Samuel B.S. *et al*. (2006) Metagenomic analysis of the human distal gut microbiome. *Science* 312, 1355–1359. doi:10.1126/science.1124234

[16] Natividad J.M.M. and Verdu E.F. (2013) Modulation of intestinal barrier by intestinal microbiota: Pathological and therapeutic implications. *Pharmacol. Res.* 69, 42–51. doi:10.1016/j.phrs.2012.10.007

[17] Den Besten G., van Eunen K., Groen A.K., Venema K., Reijngoud D.-J.,

Bakker B.M. (2013) The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res.* 54, 2325–2340 doi:10.1194/jlr.R036012

[18] Bäumler A.J. and Sperandio V. (2016) Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* 535, 85–93. doi:10.1038/nature18849

[19] Gensollen T., Iyer S.S., Kasper D.L., Blumberg R.S. (2016). How colonization by microbiota in early life shapes the immune system. *Science* 352, 539–544 doi:10.1126/science.aad9378

[20] Bäckhed F. (2011) Programming of host metabolism by the gut microbiota. *Ann. Nutr. Metab.* 58 (Suppl 2), 44–52 doi:10.1159/000328042

[21] Palmer C., Bik E.M., DiGiulio D.B., Relman D.A., Brown P.O., Ruan Y. (2007) Development of the human infant intestinal microbiota. *PLoS Biol.* 5, e177 doi:10.1371/journal.pbio.0050177

[22] Grice E.A., Kong H.H., Conlan S., Deming C.B., Davis J., Young A.C., Bouffard G.G., Blakesley R.W., Murray P.R., Green E.D., *et al*. Topographical and temporal diversity of the human skin microbiome. *Science.* 2009; 324: 1190–1192. doi: 10.1126/science.1171700.

[23] Zackular J.P., Rogers M.A.M., Ruffin M.T., Schloss P.D. The human gut microbiome as a screening tool for colorectal cancer. *Cancer Prev. Res.* 2014; 7: 1112–1121. doi: 10.1158/1940-6207.CAPR-14-0129.

[24] Xu H, Liu M, Cao J, *et al*. The Dynamic Interplay between the Gut Microbiota and Autoimmune Diseases. *J Immunol Res*. 2019; 2019: 7546047. Published 2019 Oct 27. doi:10.1155/2019/7546047

[25] Isailovic N, Daigo K, Mantovani A, Selmi C. Interleukin-17 and innate immunity in infections and chronic inflammation. *J Autoimmun* 2015; 60: 1–11.

[26] Zhang L., Gui S., Liang Z., *et al*. *Musca domestica* cecropin (Mdc) alleviates *Salmonella typhimurium*-induced colonic mucosal barrier impairment: associating with inflammatory and oxidative stress response, tight junction as well as intestinal flora. *Frontiers in Microbiology.* 2019; 10: p. 522. doi: 10.3389/fmicb.2019.00522.

[27] Rothhammer V., Quintana F. J. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nature Reviews Immunology.* 2019; 19(3): 184–197. doi: 10.1038/s41577-019-0125-8.

[28] Mao K., Baptista A. P., Tamoutounour S., *et al*. Innate and adaptive

lymphocytes sequentially shape the gut microbiota and lipid metabolism. *Nature.* 2018; 554(7691): 255–259. doi: 10.1038/nature25437.

[29] Rothhammer V., Borucki D. M., Tjon E. C., *et al*. Microglial control of astrocytes in response to microbial metabolites. *Nature.* 2018; 557(7707): 724–728. doi: 10.1038/s41586-018-0119-x.

[30] Rothhammer V., Borucki D. M., Kenison J. E., *et al*. Detection of aryl hydrocarbon receptor agonists in human samples. *Scientific Reports*. 2018; 8(1):p. 4970. doi: 10.1038/s41598-018-23323-4.

[31] Donaldson G. P., Ladinsky M. S., Yu K. B., *et al*. Gut microbiota utilize immunoglobulin A for mucosal colonization. *Science.* 2018; 360(6390): 795–800. doi: 10.1126/science.aaq0926.

[32] Chen L., Zhang W., Hua J., *et al*. Dysregulation of intestinal health by environmental pollutants: involvement of the estrogen receptor and aryl hydrocarbon receptor. *Environmental Science & Technology.* 2018; 52(4): 2323–2330.
doi: 10.1021/acs.est.7b06322.

[33] Zhang L., Nichols R. G., Patterson A. D. The aryl hydrocarbon receptor as a moderator of host-microbiota communication. *Current Opinion in Toxicology.* 2017; 2: 30–35. doi: 10.1016/j.cotox.2017.02.001.

[34] Koper J. E. B., Loonen L. M. P., Wells J. M., Troise A. D., Capuano E., Fogliano V. Polyphenols and tryptophan metabolites activate the aryl hydrocarbon receptor in an in vitro model of colonic fermentation. *Molecular Nutrition & Food Research.* 2019; 63 (3, article e1800722) doi: 10.1002/mnfr.201800722.

[35] Sun M., Ma N., He T., Johnston L. J., Ma X. Tryptophan (Trp) modulates gut homeostasis via aryl hydrocarbon receptor (AhR) *Critical Reviews in Food Science and Nutrition.* 2019; 59: 1–9. doi: 10.1080/10408398.2019.1598334.

[36] De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol*. 2019; 195(1): 74-85. doi:10.1111/cei.13158

[37] Sikora M, Stec A, Chrabaszcz M, *et al*. Gut Microbiome in Psoriasis: An Updated Review. *Pathogens*. 2020; 9(6): 463. Published 2020 Jun 12. doi:10.3390/pathogens9060463

[38] Shapiro J., Cohen N.A., Shalev V., Uzan A., Koren O., Maharshak N. Psoriatic patients have a distinct structural and functional fecal microbiota compared

with controls. *J. Dermatol.* 2019; 46: 595–603. doi: 10.1111/1346-8138.14933.

[39] Hidalgo-Cantabrana C., Gomez J., Delgado S., Requena-Lopez S., Queiro-Silva R., Margolles A., Coto E., Sanchez B., Coto-Segura P. Gut microbiota dysbiosis in a cohort of patients with psoriasis. *Br. J. Dermatol.* 2019; 181: 1287–1295. doi: 10.1111/bjd.17931.

[40] Chen Y.J., Ho H.J., Tseng C.H., Lai Z.L., Shieh J.J., Wu C.Y. Intestinal microbiota profiling and predicted metabolic dysregulation in psoriasis patients. *Exp. Dermatol.* 2018; 27: 1336–1343. doi: 10.1111/exd.13786.

[41] Mangal G, Mangal G, Sharma RS. Clinical efficacy of Shodhana Karma and Shamana Karma in Mandala Kushtha (Psoriasis). *Ayu*. 2012; 33(2): 224-229. doi:10.4103/0974-8520.105242

[42] Chaturvedi A, Nath G, Yadav VB, *et al*. A clinical study on *Virechana Karma* (therapeutic purgation) over the gut flora with special reference to obesity. *Ayu*. 2019; 40(3): 179-184. doi:10.4103/ayu.AYU_302_19

[43] Chen L, Li J, Zhu W, *et al*. Skin and Gut Microbiome in Psoriasis: Gaining Insight Into the Pathophysiology of it and Finding Novel Therapeutic Strategies. *Front Microbiol*. 2020; 11: 589726. Published 2020 Dec 15. doi:10.3389/fmicb.2020.589726