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“Gut-skin” axis: understanding psoriasis from the gut

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Background: The exact pathogenesis of psoriasis is complex, and scholars use the intestinal mucosal immunity as an entry point to analyze the important role of the intestine in the pathogenesis of psoriasis. Traditional Chinese medicine treats psoriasis from the intestine based on the theory that “the lung governs the fur” and “the Interior-Exterior Relationship Between the Lung and Large Intestine”. Based on this understanding, this paper puts forward the idea of understanding psoriasis from the “gut-skin” axis. **Objective:** Based on the “gut-skin” axis to explore the pathogenesis of psoriasis from the intestines, and open up new ideas for research and development of new drugs for psoriasis. **Method:** Collect literature on the treatment of psoriasis from the perspective of the intestine and “gut-skin” axis; then, use Western medicine’s intestinal pathogenesis, Traditional Chinese Medicine (TCM) theory and examples of TCM treatment are demonstrated; finally, the treatment of psoriasis from the “gut-skin” axis is summarized. **Results:** Western medicine has not carried out treatment of psoriasis involving the intestinal tract. In-depth research and clinical applications based on the “gut-skin” axis are still needed. The effective rate of treating psoriasis by TCM has been as high as 90%, but the mechanism research is relatively scarce. **Conclusion:** The construction of the “gut-skin” axis mechanism is consistent with TCM theories, and is consistent with modern scientific connotations as well.

1. Introduction

Psoriasis, known in Chinese medicine as “Bai bi”, “neurodermatitis” and so on, is a chronic, inflammatory, difficult to cure autoimmune disease with high recurrence rate and presents itself as a global medical problems (Zhang et al. 2019; Kuchekar et al. 2011). Because of the main symptom of damaged skin, itching is unbearable, and accompanied by erythema, papules, scales and other clinical characteristics, seriously threatening the physical and mental health of patients (Organization WH 2016). In addition to the negative effects of quality of life, psoriasis is associated with a number of complications, including psoriasis arthritis, depression and anxiety, lymphoma, obesity and metabolic syndrome, which will increase the risk of early death (Elmets et al. 2019).

A growing number of research results shows that the intestines play an important role in the pathogenesis of psoriasis. In the case of human intestinal disorders, the bacteria and their metabolic inflammatory delivery can enter the blood directly, destroying the stability of the skin (Baba et al. 2006). When a large number of intestinal microorganisms translocate, the body’s endogenous infection will further aggravate, leading to the dysfunction of the immune system. At the same time, *Staphylococcus*, *Streptococcus*, *Candida albicans* and *Pityrosporum* metabolites in the skin are produced, which are directly transmitted to T cells as an antigen through human leukocyte DR antigen and activate T cells. Cells migrate into the epidermis and rapidly release inflammatory mediators and epidermal growth factors, which leads to the rapid growth and proliferation of skin keratinocytes and the formation of skin plaques (Kim and Krueger 2015). This is the main pathogenesis of the gut skin axis. Therefore, this paper is based on the new perspective of “gut-skin” axis in the treatment of psoriasis in order to explore a new way for medical treatment of psoriasis.

2. Modern medicine found that the gut plays an important role in the pathogenesis of psoriasis

Psoriasis is an autoimmune disease, so when it occurs, the immune mechanism has “difficulty to escape responsibility”. As the body’s largest immune organ, the intestinal mucosa immunity as the largest and most complex part of the immune system has a “heavy responsibility” (Trivedi and Adams 2016). Therefore, there is no doubt that gut, immunity and skin are closely related, so the theory of “gut mucosal immunity related to psoriasis” came into being (Yegorov et al. 2020).

The essence of the damage to the immune function of the intestinal mucosa is that the exogenous antigen causes the intestinal bacterial disorder through the close connection of cells in the damaged intestinal epithelial, which activates the process of immune response, thus forming an intestinal mucosal immune path disorder consisting of mechanical (closely connected proteins, etc.), microorganisms (intestinal bacteria, etc.) and immune cells (Th17/Treg cells, etc.) (Cani 2017; Shi et al. 2017; Cheng et al. 2019; Groeger et al. 2013). Early in clinical studies, it was found that psoriasis patients with disease-related skin damage and other symptoms are often accompanied by increased permeability of the intestinal mucosa, abnormal tolerance of the intestinal bacteria, intestinal immune CD4+T cells and intestinal immunomarkers sIgA, RANKL levels significantly increased, and so on, all symptoms of intestinal mucosal immune disorders (Codoñer et al. 2018; Tan et al. 2018; Zhu 2016; Su et al. 2010; Eppinga et al. 2016). In addition, the feces of patients with psoriasis showed a decrease in *Fusobacterium prausnitzii*, short chain fatty acids (SCFA) and an increase in *E. coli*, which was similar to the intestinal flora disorders in patients with inflammatory bowel disease (Hidalgo-Cantabrana et al. 2019). Among them,

Faecalibacterium prausnitzii is one of the most common microorganisms in the digestive tract. It can inhibit and promote the peripheral activation of Treg by forming butyrate, increase the density and number of cell subsets, inhibit the activity of CD4+ T and CD8+ T cells, and play an important role in maintaining the dynamic balance of the colonic mucosal barrier (Hong et al. 2012; Xu et al. 2021). According to the mean and median of intestinal flora detected in patients with psoriasis, the “core microbiome of psoriasis” can be described at the genus level. Comparing data from more than 300 healthy individuals extracted from the Psoriasis Gut Microbes and the Human Microbiome Project and analyzing the main components, the results showed that the number of *Bacteroides* decreased and the number of *Ackermann Myxobacteria* and *Bifidobacteria* increased in patients with psoriasis. SCFA is the direct energy source of intestinal epithelial cells and plays an important role in maintaining normal intestinal metabolism. For example, it can regulate the number and function of T cell population by promoting the induction and adaptation of T cells in the colon environment. It also plays an irreplaceable role in the regulation of Th1 / Th2, Th17 / Treg immune balance by Treg cells, its deficiency or defect is closely related to immune inflammatory response (Scher et al. 2015; Xu et al. 2020; Dainichi et al. 2018).

Some modern technologies have also created a new world in the field of treating psoriasis based on the “gut-skin” axis. Some studies have shown that when patients with severe psoriasis were evaluated for fecal transplantation technology (FMT), clinical efficacy was significant, the clinical symptoms of irritable bowel syndrome disappeared, and no adverse reactions occurred (Yin et al. 2019). Other studies have explored the intestinal microbiome genomics based on the genetic characteristics of psoriasis, and showed that it is possible to find the DNA sequence related to the disease based on this technology, and use it as a target for monitoring the onset, recurrence and treatment intervention (Dand et al. 2020; Chen et al. 2018). In addition, in the aspect of mental factors inducing the onset of psoriasis, some studies have shown that long-term mental factors such as excessive tension and depression can lead to stress reaction, affect the intestinal flora, especially the ectopic intestinal bacteria are likely to produce superantigen, which is involved in the occurrence and recurrent attacks of psoriasis (Jiang et al. 2014). These studies will make a breakthrough in understanding psoriasis based on the “gut-skin” axis, and prove that there is a close relationship between intestinal mucosal immunity and psoriasis (Sikora et al. 2020).

In the classic psoriasis mouse model induced by imiquimod (IMQ), the corresponding phenomenon was also confirmed (Su et al. 2017). Long term use of antibiotics can reduce the number and diversity of intestinal microflora in neonatal mice, resulting in imbalance of immune homeostasis of CD4+ T cells, and then significantly aggravate the symptoms of psoriasis (Zanvit et al. 2015; Zákostelská et al. 2016; Hu et al. 2016); *E. coli* Nissle 1917 (EcN) can interfere with psoriasis model dermal damage in mice induced by imiquimod, reducing the level of related pro-inflammatory factors and increasing the level of anti-inflammatory factors (Wang et al. 2019). The use of broad-spectrum antibiotics or metronidazole can reduce skin inflammation by reducing the Th17 immune response in newborn mice and increasing microorganisms such as *Lactobacillus* and *Bifidobacteria* in the intestines. Moreover, compared with the control group of a psoriasis mouse model without probiotic treatment, the probiotic-treated mice showed mild erythema, scales and skin thickening (Stehlikova et al. 2019; Chen et al. 2017).

In summary, because of these characteristics, intestinal mucous membrane immunity is not only the “main culprit” on the pathogenesis of psoriasis, but a key for effective treatment (Salem et al. 2018; Mcmillin et al. 2000). Whether from genetic or mental factors, as well as prevention or treatment as the goal, the application of technology based on the “gut-skin” axis has made the understanding of psoriasis more comprehensive and clear, and thus significantly expands the spectrum of treatment (Tsoi et al. 2016).

3. Understanding of psoriasis from the perspective of “gut-skin” axis in Traditional Chinese Medicine

3.1. Theories of “the lung governs the fur” and “the interior-exterior relationship between the lung and large intestine”

Traditional Chinese Medicine believes that human beings are an organic and unified whole. The viscera do not exist independently, but are connected through meridians and collaterals to form the external and internal relationship between the viscera and the viscera. Both physiologically and pathologically, they are interconnected and influence each other (Wang et al. 2019). Psoriasis, although manifested as superficial skin erythema and scales, is closely related to the dysfunction of the viscera. It has long been recorded in the Inner Canon of the Yellow Emperor that those who have all kinds of inner organs must show them to the outside, and the external expression must also be based on the internal dysfunction of the viscera (Gong and Tian 2019). The fur and the large intestine are related to two different organs, which seems to “be totally unrelated”. Among them, skin dominates the whole body, defending against the invasion of external evil. The large intestine is the conduction organ and the main excretion organ of the human body. Both in form and function, the two are far apart. However, after careful study, it has been found that fur is not only related to the large intestine, but also closely related (O’Neill et al. 2016).

Under the guidance of the “holistic view” of Traditional Chinese Medicine, the theory of “lung governs the fur” believes that the lungs spread the essence of qi on the skin, so that the fur can be firm and strong. If the lung qi is insufficient or the lung qi is blocked, it will be abnormal. The essence of mizutani cannot be reached out, and if the skin is dystrophic, the skin will be dry or chapped, and the hair will be dry, such as ichthyosis and psoriasis which are common in dermatology (Luo 2014). Therefore, Chinese medicine believes that the lung has the function of protecting the muscle surface and resisting external evil. The relationship between the lung and the fur is not limited to the connection between the lung and the muscle surface in an anatomical sense, but also shows a physiological and pathological phenomenon of lung qi activity, as well as clinical practice guided by this theory. For example, Mahuang, a traditional Chinese medicine, has the effects of dispersing lung, promoting health and Qi, and dispersing exogenous evil. Based on the theory of “the lung governs the fur”, Mahuang combined with gypsum has a significant effect in the treatment of psoriasis and other erythematous and scaly skin diseases. The representative prescriptions include daqinglong decoction, Xiaoqinglong plus gypsum decoction, Houpu Mahuang Decoction, etc (Zhang et al. 2019).

At the same time, Traditional Chinese Medicine believes in an “interior-exterior relationship between the lung and large intestine”, which means that the lung and the large intestine are inter-related in meridians and influence each other in physiology and pathology. If one of the lesions can cause the other side dysfunction, the diseases of the lung and intestines will affect each other, transmit and involve each other (Ni and Gao 2012; Zheng et al. 2018; Gray et al. 2017; Zhang et al. 2016). Current studies have also shown that intestinal and respiratory bacteria can affect each other, that the intestinal and respiratory mucosa immune systems have synchronization patterns in the immune response, and that cytokines are also interrelated (He et al. 2017; Mjösberg and Rao 2018; Marsland et al. 2015). Therefore, the lung is the bridge between the skin and the large intestine. Then, according to logical reasoning, there must be direct and indirect connections between the two parts, so fur and large intestine are connected (Coates et al. 2019). This view is applied to the clinical treatment of psoriasis to obtain optimum efficacy. For example, the cure rate of 312 cases of psoriasis is over 95% by Xuanfei and intestine therapy, and all the cured cases were followed up for more than 2 years and no recurrence was found. Therefore, colorectal lesions are closely related to skin pathological changes, so the clinical treatment of psoriasis, acne, eczema, chloasma and other skin diseases with TongFuXieXia can often achieve satisfactory results (Peng et al. 2013).

It is worth noting that although the large intestine in the field of Chinese medicine is different from the intestine in modern medicine, the essence is the same when it comes to the root. Modern medicine holds that the intestines include the large intestine and the small intestine, so the large intestine is part of the intestines (Gasbarrini et al. 2008). In addition, TCM's understanding of modern medical intestinal tract also fully confirmed this conclusion; "The small intestine is filled with the preliminarily digested food that is moved down from the stomach and intestines. At the same time as it is further digested, the process of separating the fine grains and metabolites follows", "large intestine conduction, change cross" and so on are all based on TCM's understanding of modern medical intestinal function (Li et al. 2019). Therefore, the large intestine, lung and skin transmit each other, and then the three are related. Therefore, the understanding of the mechanism of "gut-skin" axis in Traditional Chinese Medicine is that the lung is the medium to organically link the skin and intestine (Wang et al. 2021; Duan and Yuan 2017), as shown in the Fig.

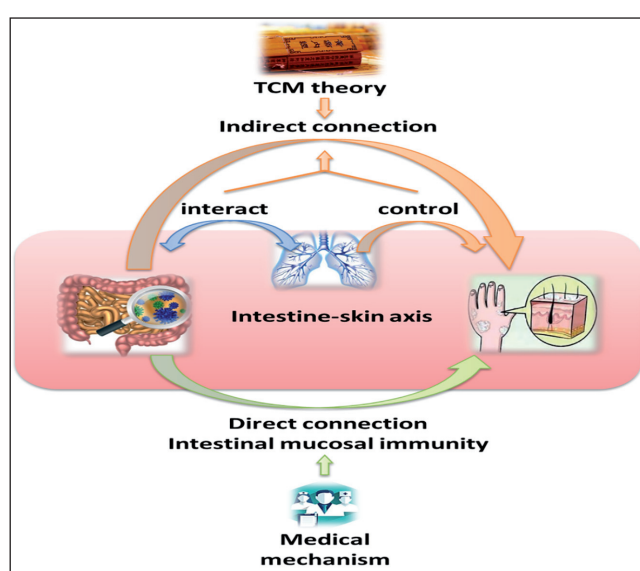


Fig.: Understanding of modern medicine and traditional Chinese medicine on the treatment of psoriasis with "gut-skin" axis

Traditional Chinese Medicine is based on the theory of "the lung governs the fur" and "the interior-exterior relationship between the lung and large intestine". When the lungs are weak, the function of governing the fur is dereliction of duty, and the essence of Mizutani cannot be supplied on the fur, causing psoriasis. At the same time, the interior-exterior relationship between the lung and large intestine, interact with each other. When the conduction of large intestine is abnormal and the Qi mechanism is blocked, the Lung Qi will descend abnormally, the lung will lose its function of dispersing and eliminating, and the function of the lung governs the fur will be disordered (Wang et al. 2008; Ji et al. 2019; Cervantes and Hong 2017). Therefore, when intestinal disorder occurs, the intestine indirectly affects the occurrence of psoriasis through the lung (Zhang 2010; Duan et al. 2020).

Modern medicine believes that the gut directly acts on the skin through intestinal mucosal immunity (Zheng et al. 2013). Along with the intestinal mucosal immune disorder, psoriasis easily develops.

3.2. Curative effects of Traditional Chinese Medicine in the intestinal treatment of psoriasis

Skin is closely related to viscera, meridians, Qi and blood, body fluid, especially lung, with the lung governing diffusion, governing the fur, governing Sujiang, governing regulation of water passages (Wang and Jin 2018). If the lung qi is normal, the Qi, blood and body fluid can spread all over the body, the defensive Qi is

abundant, and the external evil cannot invade. However, when dispersing lung qi for lowering adverse qi dysfunction, weakened defensive Qi. It is easy to be invaded by external pathogens, Qi, blood and body fluid cannot be normally distributed, and can generate phlegm dampness and blood stasis, which can accumulate in Couli or aggravate psoriasis. At the same time, if the interior-exterior relationship between the lung and large intestine, and the large intestine function is normal, then the lung function is normal. If the large intestine has pathological changes, it will affect the lung function. The expelling of pathogenic toxin in the body can be solved by sweating and diarrhea. According to the pathogenesis of psoriasis, the treatment should expel pathogenic toxin such as rheumatic fever, regulate the function of viscera, and the lung and large intestine are the key points (Ye and Chen 2019). The function of viscera can be adjusted, the symptoms and roots can be treated simultaneously, and the exterior and interior can be taken into account, so as to achieve better curative effect, and it is not easy to relapse. For example, the application of "Xuan fei Li chang", "Intestinal therapy", "Tong dao san", and "Runchang soup" is effective in treating psoriasis from within 90% (Qian et al. 2009; Zhang and Zhang 1999). Some traditional Chinese medicine prescriptions, such as Sijunzi decoction, Kouyanqing granule, Runzaozhiyang capsule and so on, have also been proved to regulate the intestinal flora (Tang et al. 2016; Yao et al. 2012; Hu et al. 2020). At the same time, there is a high correlation between TCM "intestinal therapy" and intestinal mucosal immune imbalance, thus forming the characteristics of a close dependence of intestinal mucosal immunity, intestinal therapy and psoriasis. It is worth mentioning that Traditional Chinese Medicine has used umbilical application combined with retention enema in the treatment of psoriasis, which is not only efficient and safe, but also reflects the individuality and richness of "intestinal therapy" (Li et al. 2008). At present, although the Traditional Chinese Medicine "intestinal therapy" has a definite effect on psoriasis, however, research on the intestinal mucosal immune mechanism of Chinese medicine for psoriasis has not been reported, and the mechanism, advantages and characteristics of Chinese medicine in treating psoriasis could not be scientifically clarified.

In addition, based on the idea of "skin is closely related to the intestinal tract, so it is also closely related to the intestinal microecology", some scholars believe that the therapeutic principles and methods of "regulating the spleen and stomach" and "calming the nerves" adopted by Traditional Chinese Medicine in the treatment of psoriasis are likely to play a therapeutic role by regulating the intestinal flora (Liu et al. 2014). These two theories provide a strong basis for the correlation between skin and intestine from the perspective of Traditional Chinese Medicine. In addition, the idea of dialectical analysis of intestinal flora has gradually developed, some scholars infer that the intestinal flora of psoriasis with blood heat, blood dryness and blood stasis have their own characteristics (Xuan et al. 2015). It also shows that the three syndromes can be clearly distinguished according to the characteristics of intestinal flora. In the future, we can start with the correlation between intestinal microecology and TCM syndromes, and carry out in-depth TCM research on psoriasis (Liu et al. 2019). Although the characteristics of intestinal flora of different syndrome types, the relationship between intestinal flora and syndrome types, and the mechanism of TCM syndrome differentiation and treatment on intestinal flora disorder of different syndrome types are still unclear, the authors are believing that this inference can more comprehensively study the intestinal mucosal immune mechanism of psoriasis, and make the research idea clearer from the dialectical point of view, so as to expand the "intestinal therapy" of psoriasis new direction.

4. Discussion

More and more studies have shown that the gut plays an important role in the pathogenesis of psoriasis, but Western medicine does not carry out treatment of psoriasis for the gut, but often uses targeted treatment for skin and peripheral blood, such as ultraviolet light therapy, ferulic acid A and amino-polypeptide tablets, and a variety

of specific antibody treatment for TNF, IL-17 and so on (Kauf et al. 2015; Greaves and Weinstein 1995; Krueger and James 2002). Although it also has its unique curative effect, its application is greatly limited due to potential adverse reactions (Lebwohl et al. 2005). However, Traditional Chinese Medicine pays more attention to “treating both the symptoms and the root causes”. Based on the theories of “the lung governing skin and hair” and “the lung and the large intestine are interior-exterior”, its treatment is not only limited to external treatment to alleviate skin damage (Guan et al. 2017), also includes, from different dialectical point of view, internal treatment (Meng et al. 2018). By adjusting the balance of Yin and Yang and improving the viscera Qi mechanism, we can achieve the purpose of “treating the disease and seeking the root cause” (Tse 2003; Yan et al. 2015). For thousands of years, the effectivity rate of Traditional Chinese Medicine in the treatment of psoriasis through the intestinal tract has been as high as 90% (Cai and Wu 2015). The advantages of “remarkable curative effect, low recurrence rate and high safety” in the treatment of psoriasis are demonstrated by examples (Zhai et al. 2015). In addition, TCM has unique advantages in individualized, comprehensive and reasonable selection and development of individualized treatment scheme, which contains the wisdom of TCM “treatment from intestine”.

Whether in modern medicine or in Traditional Chinese Medicine, it has been proved that the intestine is an important mechanism for the incidence of psoriasis, and after thousands of years of clinical practice, the connection between the intestine and skin has been solidly demonstrated in ancient books of Traditional Chinese Medicine and even in clinical practice. There is also the view that the intestines and the skin are mutually affecting each other, but the specific mechanism has not been clarified so far. Also, the intestinal mucosal immune mechanism according to TCM in the treatment of psoriasis is still unclear, while modern medical research only stays at the level of theoretical and basic research, and has not carried out relevant clinical research. Based on current research results, the construction of a “gut-skin” axis model is in line with the modern scientific connotation of the treatment of psoriasis and other autoimmune skin diseases, and has unlimited development potential (Chen et al. 2021). Moreover, it has important guiding significance to treat psoriasis from the perspective of the “gut-skin” axis, which can provide important reference for drug research and development. More importantly, the construction of a key technology system and research demonstration model based on the intestinal treatment of psoriasis on the “gut-skin” axis meets the needs of the innovative development of the pharmaceutical industry, and for the future multi-aspect, multi-angle prevention, monitoring, treatment of psoriasis, as well as daily life diet conditioning, nursing, psychological intervention, have a major breakthrough significance.

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References

Baba H, Masuyama A, Takano T (2006) Short communication: effects of Lactobacillus helveticus-fermented milk on the differentiation of cultured normal human epidermal keratinocytes. *J Dairy Sci* 89: 2072–2075.
 Cai LH, Wu YH (2015) Research progress on traditional Chinese medicine treatment of psoriasis. *Diagn Ther J Derm-Venerol* 22: 86–88.
 Cani PD (2017) Gut cell metabolism shapes the microbiome. *Science* 357: 548–549.
 Cervantes J, Hong BY (2017) The gut-lung axis in tuberculosis. *Pathogens Dis* 75: ftx097.

Chen G, Chen ZM, Fan XY, Jin YL, Li X, Wu SR, Ge WW, Lv CH, Wang YK, Chen JG (2021) Gut–brain–skin axis in asoriasis: a review.” *Dermatol Ther* 11: 25–38.
 Chen YH, Wu CS, Chao YH, Lin CC, Tsai HY, Li YR, Chen YZ, Tsai WH, Chen YK (2017) Lactobacillus pentosus GMNL-77 inhibits skin lesions in imiquimod-induced psoriasis-like mice. *J Food Drug Anal* 25: 559–566.
 Chen YJ, Ho HJ, Tseng CH, Lai ZL, Shieh JJ, Wu CY (2018) Intestinal microbiota profiling and predicted metabolic dysregulation in psoriasis patients. *Exp Dermatol* 27: 1336–1343.
 Cheng H, Guan X, Chen D, Ma W (2019) The Th17/Treg cell balance: a gut microbiota-modulated story. *Microorganisms* 7: 583.
 Coates M, Lee MJ, Norton D, MacLeod AS (2019) The skin and intestinal microbiota and their specific innate immune systems. *Front Immunol* 10: 2950.
 Codoñer FM, Ramírez-Bosca A, Climent E, Carrión-Gutierrez M, Guerrero M, Pérez-Orquín JM (2018) Gut microbial composition in patients with psoriasis. *Sci Rep* 8: 1–7.
 Dainichi T, Kitoh A, Otsuka A, Nakajima S, Nomura T, Kaplan DH, Kabashima K (2018) The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. *Nature Immunol* 19: 1286–1298.
 Dand N, Mahil SK, Capon F, Smith CH, Simpson MA, Barker JN (2020) Psoriasis and genetics. *Acta Derm Venereol* 100: 55–64.
 Duan YF, Yuan JF (2017) Gut microbes and skin disease, gut-brain-skin axis: a review. *Chin Sci Bull* 62: 360–371.
 Duan YJ, Zhu XX, Zhai XX (2020) Theoretical basis and clinical application of treating psoriasis from lung. *Tianjin J Trad Chin Med* 37: 1023–1026.
 Elmets CA, Leonardi CL, Davis DMR, Gelfand JM, Lichten J, Mehta NN, Armstrong AW, Connor C, Cordoro KM, Elewski BE, Gordon KB, Gottlieb AB, Kaplan DH, Kavanaugh A, Kivelevitch D, Kiselica M, Korman NJ, Kroshinsky D, Lebwohl M, Lim HW, Paller AS, Parra SL, Pathy AL, Prater EF, Rupani R, Siegel M, Stoff B, Strober BE, Wong EB, Wu JJ, Hariharan V, Menter A (2019) Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol* 80: 1073–1113.
 Eppinga H, Sperna Weiland CJ, Thio HB, van der Woude CJ, Nijsten TE, Peppelenbosch MP, Konstantinov SR (2016) Similar depletion of protective Faecalibacterium prausnitzii in psoriasis and inflammatory bowel disease, but not in Hidradenitis suppurativa. *J Crohn’s Colitis* 10: 1067–1075.
 Gasbarrini G, Montalto M, Santoro L, Curigliano V, D’Onofrio F, Gallo A, Visca D, Gasbarrini A (2008) Intestine: organ or apparatus? *Dig Dis* 26: 92–95.
 Gong M, Tian BK (2019) Thought discussion on treating skin diseases from lung based on the theory of Huang di’s Canon of Medicine. *Acta Chin MedPharmacol* 47: 94–96.
 Gray J, Oehrle K, Worthen G, Alenghat T, Whittsett J, Deshmukh H (2017) Intestinal commensal bacteria mediate lung mucosal immunity and promote resistance of newborn mice to infection. *Sci Transl Med* 9: eaf9412.
 Greaves MW, Weinstein GD (1995) Treatment of psoriasis. *New Engl J Med* 332: 581–589.
 Groeger D, O’Mahony L, Murphy EF, Bourke JF (2013) Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes* 4: 325–339.
 Guan J, Yuan S, Wu H, Na R, Wu X, Wang X, Bao S (2017) Effectiveness and safety of traditional Chinese medical bath therapy combined with ultraviolet irradiation in the treatment of psoriasis: A systematic review and meta-analysis of randomized controlled trials. *PLoS one* 12: e0173276.
 He Y, Wen Q, Yao F, Xu D, Huang Y, Wang J (2017) Gut-lung axis: The microbial contributions and clinical implications. *Crit Rev Microbiol* 43: 81–95.
 Hidalgo-Cantabrana C, Gómez J, Delgado S, Requena-López S, Queiro-Silva R, Margolles A, Coto E, Sánchez B, Coto-Segura P (2019) Gut microbiota dysbiosis in a cohort of patients with psoriasis. *Br J Dermatol* 181: 1287–1295.
 Hong N, Qiu XY, Zhang MM, Yang XT, Yu C (2012) Study of the prevention and therapeutic effects of Faecalibacterium prausnitzii on colitis of experimental rats. *Chin J Digest* 32: 459–465.
 Hu HY, Hu YX, Liu CS, Su XT, Dai H (2020) Effects of Runzao Zhiyang capsule on gut microbiota and inflammatory response in rats with psoriatic lesions. *Chin J Clin Anat* 5: 574–577.
 Hu WJ, Yan YH, Chen HM, Lu CJ (2016) Study on Th17 cells and related cytokines in the intestine of psoriatic mice. *Guangdong Med J* 37: 1925–1928.
 Ji XS, Li YW, Zhou FS, Hou LY (2019) Study on theory of lung and large intestine being interiorly and exteriorly related based on differentially-expressed proteins in mouse model of constipation. *J Guangzhou Univ Trad Chin Med* 39: 269–272.
 Jiang WC, Jian Q, Ma T, Li B (2014) Psoriasis and Intestinal Flora. *Chin Arch Trad Chin Med* 9: 2079–2081.
 Kauf TL, Yang JC, Kimball AB, Sundaram M, Bao Y, Okun M, Mulani P, Hauber AB, Johnson FR (2015) Psoriasis patients’ willingness to accept side-effect risks for improved treatment efficacy. *J Dermatol Treatm* 26: 507–513.
 Kim J, Krueger JG (2015) The immunopathogenesis of psoriasis. *Dermatol Clin* 33: 13–23.
 Krueger JG (2002) The immunologic basis for the treatment of psoriasis with new biologic agents. *J Am Acad Dermatol* 46: 1–26.
 Kuchekar AB, Pujari RR, Kuchekar SB, Dhole SN, Mule PM (2011) Psoriasis: a comprehensive review. *Int J Pharm Life Sci* 2: 857–877.
 Lebwohl, M., P. T. Ting, and J. Y. M. Koo (2005) Psoriasis treatment: traditional therapy. *Ann Rheum Dis* 64 (Suppl 2): ii83–ii86.
 Li PF, Xi Lu, Wang Y, Lu X, Hu SM (2019) View on intestinal functions in modern medicine by traditional Chinese medicine. *Global Trad Chin Med* 12: 871–874.
 Li WH, Huang S, Tan XY, Dong JL, He ZW, Ye P, Cai M (2008) Therapeutic effect observation of psoriasis treated with Chinese drug Hilum application and preservation enema. *J Zhejiang Univ Trad Chin Med* 32: 454–456+437.
 Liu WW, Zhang TY, Gong SQ, Chen H, Cheng Y, Wang H, Wang MN, Li S (2014) Research on regulating lungs-spleen-large intestine axis by “strengthening earth to generate metal” to intervene the spleen and lung Qi deficiency pattern of RRTI

- to probe the sIgA saliva immune mechanism. *Chin J Basic Med Trad Chin Med* 20: 948–950.
- Liu X, Zhang GZ, Jiang CY, Xiao SJ, Tan Y, Qu JH, Chen YF (2019) The traditional Chinese medicine in the treatment of gut microbiota and psoriasis. *J Capital Med Univ* 40: 363–368.
- Luo YH (2014) Discussion on the clinical application of the theory of lung dominating skin and hair. *J New Chin Med* 46: 220–222.
- Marsland BJ, Trompette A, Gollwitzer ES (2015) The gut-lung axis in respiratory disease. *Ann Am Thorac Soc* 12 Suppl 2: S150–156.
- McMillin DL, Richards DG, Mein EA, Nelson CD (2000) Systemic aspects of psoriasis: an integrative model based on intestinal etiology. *Integr Med* 2: 105–113.
- Meng S, Lin Z, Wang Y, Wang Z, Li P, Zheng Y (2018) Psoriasis therapy by Chinese medicine and modern agents. *Chin Med* 13: 16.
- Mjösberg J, Rao A (2018) Lung inflammation originating in the gut. *Science* 359: 36–37.
- Ni JX, Gao SH (2012) Understanding the viscera-related theory that the lung and large intestine are exterior-interiorly related. *J Tradit Chin Med* 32: 293–298.
- O'Neill CA, Monteleone G, McLaughlin JT, R Paus (2016) The gut-skin axis in health and disease: A paradigm with therapeutic implications. *Bioessays* 38: 1167–1176.
- Organization WH. Global report on psoriasis (2016) WHO Library Cataloguing-in-Publication Data 2016.
- Peng Y, Zhang C, Zhang LJ, Tian DZ, Guo L, Wang P (2013) Effects of Zengyechengqitang on skin morphology and the content of hyaluronic acid in the constipated aged mice model with syndrome of fluid-deficiency. *Lishizhen Med Materia Medica Res* 24: 1573–1575.
- Qian F, Yang YF, Guo DJ (2009) Treatment of 30 cases of psoriasis of blood stasis type with Tongdaosan. *Jiangxi J Trad Chin Med* 40: 51–52.
- Salem I, Ramser A, Isham N, Ghannoum MA (2018) The gut microbiome as a major regulator of the gut-skin axis. *Front Microbiol* 9: 1459.
- Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, Marmon S, Neimann A, Brusca S, Patel T, Manasson J, Pamer EG, Littman DR, Abramson SB (2015) Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis Rheumatol* 67: 128–139.
- Shi N, Li N, Duan X, Niu H (2017) Interaction between the gut microbiome and mucosal immune system. *Mil Med Res* 4: 1–7.
- Sikora M, Stec A, Chrabaszcz M, Knot A, Waskiel-Burnat A, Rakowska A, Olszewska M, Rudnicka L (2020) Gut microbiome in psoriasis: an updated review. *Pathogens* 9: 463.
- Stehlikova Z, Kostovcikova K, Kverka M, Rossmann P, Dvorak J, Novosadova I, Kostovcik M, Coufal S, Srutkova D, Prochazkova P, Hudcovic T, Kozakova H, Stepankova R, Rob F, Juzlova K, Hercogova J, Tlaskalova-Hogenova H, Jiraskova Zakostelska Z (2019) Crucial role of microbiota in experimental psoriasis revealed by a gnotobiotic mouse model. *Front Microbiol* 10: 236.
- Su XC, Zhao ZH, Du H, He XY, Wang R, Ju Y, Luo Y, Zhang YL, Zhao QL, Yang GL (2010) Changes of intestinal mucosal permeability in patients with psoriasis. *China J Leprosy Skin Dis* 5: 325–327.
- Su Y, Wang Q, Yang B, Wu L, Cheng G, Kuang H (2017) Withasteroid B from *D. metel* L. regulates immune responses by modulating the JAK/STAT pathway and the IL-17+RORγt+/IL-10+FoxP3+ ratio. *Clin Exp Immunol* 190: 40–53.
- Tan L, Zhao S, Zhu W, Wu L, Li J, Shen M, Lei L, Chen X, Peng C (2018) The Akkermansia-muciniphila is a gut microbiota signature in psoriasis. *Exp Dermatol* 27: 144–149.
- Tang HY, Li YZ, Li CD (2016) Effect of total polysaccharides of Sijunzi decoction on intestinal flora and immune function in mice. *Shaanxi J Trad Chin Med* 37: 1688–1691.
- Trivedi PJ, Adams DH (2016) Gut-liver immunity. *J Hepatol* 64: 1187–1189.
- Tse TW (2003) Use of common Chinese herbs in the treatment of psoriasis. *Clin Exp Dermatol Clin Dermatol* 28: 469–475.
- Tsoi LC, Stuart PE, Tian C, Gudjonsson JE, Das S, Zawistowski M, Ellinghaus E, Barker JN, Chandran V, Dand N, Duffin KC, Enerbäck C, Esko T, Franke A, Gladman DD, Hoffmann P, Kingo K, Köks S, Krueger GG, Lim HW, Metspalu A, Mrowietz U, Mucha S, Rahman P, Reis A, Tejasvi T, Trembath R, Voorhees JJ, Weidinger S, Weichenthal M, Wen X, Eriksson N, Kang HM, Hinds DA, Nair RP, Abecasis GR, Elder JT (2016) Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. *Nature Comm* 136: S64–S64.
- Wang L, Xu MD, He YL, Li MY, Xu NG (2019) Explanation of theory of exterior and interior relationship between lung and large intestine from the immunological view. *Liaoning J Trad Chin Med* 46: 2309–2311.
- Wang WM, Jin HZ (2018) Skin microbiome: an actor in the pathogenesis of psoriasis. *Chin Med J (Engl)* 131: 95–98.
- Wang WX, Hui Y, Zhu J (2021) Discussion of “treatment of skin diseases through gut” based on “co-diseases of skin and gut” and gut-skin axis theory. *Chin J Integr Trad West Med* 41: 234–237.
- Wang XK, Zhou SY, Yu F, Su X, Zhao S, Zhu XF (2019) Effects of *Escherichia coli* Nissle 1917 (EcN) on psoriasis mouse model. *Int J Biomed Engin* 33: 875–880.
- Wang YL, Long D, He L, Wu ZJ, Wang KM, Cai RL, Liu J, Hu L, Zhou YP (2008) Establishment of an animal model of the exterior interior relationship between lung and large intestine. *Inner Mongolia J Trad Chin Med* 27: 40–41.
- Xu WY, Guo F, Liu HX (2021) Research progress in TCM and Western medicine for intestinal flora of psoriasis. *Chin J Inform Trad Chin Med* 28: 139–141.
- Xu XR, Gong J, Wang J, Wu JM, Liu Q (2020) Research progress of the relationship between gut microbiota and psoriasis. *J Pract Med* 36: 1153–1156.
- Xuan ML, Lu CJ, Han L, Xiang Y (2015) Circulating levels of inflammatory cytokines in patients with psoriasis vulgaris of different Chinese medicine syndromes. *Chin J Integr Med* 21: 108–114.
- Yan Y, Liu W, Andres P, Perner C, Chantalat L, Briantais P, Lin A, Feng L (2015) Exploratory clinical trial to evaluate the efficacy of a topical traditional Chinese herbal medicine in psoriasis vulgaris. *Evid-Based Complement Altern Med* 2015: 719641.
- Yao XH, Tang L, Lin Q, Li WH, Huang YH, Zhang GB, Gao F, Liu YH, Li HJ, Yuan JL, Wen S (2012) Effects of Kouyuanqing granules on the intestinal dysbiosis of mice. *Chin J Microecol* 201: 324–326.
- Ye SZ, Chen ML (2019) The treatment of skin diseases from the lung. *Clin JChin Med* 11: 139–140.
- Yegorov S, Babenko D, Kozhakhmetov S, Akhmaltdinova L, Kadyrova I, Nurgozhina A, Nurgazyev M, Good SV, Hortelano GH, Yermekbayeva B, Kushugulova A (2020) Psoriasis is associated with elevated gut IL-1α and intestinal microbiome alterations. *Front Immunol* 11:2431.
- Yin G, Li JF, Sun YF, Ding X, Zeng JQ, Zhang T, Peng LH, Yang YS, Zhao H (2019) Fecal microbiota transplantation as a novel therapy for severe psoriasis. *Chin J Int Med* 58: 782–785.
- Zákostelská Z, Málková J, Klimešová K, Rossmann P, Hornová M, Novosádová I, Stehliková Z, Kostovčík M, Hudcovic T, Štěpánková R, Jůzlová K, Hercogová J, Tlaskalová-Hogenová H, Kverka M (2016) Intestinal microbiota promotes psoriasis-like skin inflammation by enhancing Th17 response. *PLoS One* 11: e0159539.
- Zanvit P, Konkel JE, Jiao X, Kasagi S, Zhang D, Wu R, Chia C, Ajami NJ, Smith DP, Petrosino JF, Abbatiello B, Nakatsukasa H, Chen Q, Belkaid Y, Chen ZL, Chen W (2015) Antibiotics in neonatal life increase murine susceptibility to experimental psoriasis. *Nature Comm* 6: 8424.
- Zhai L, Shi J, Xu W, Heinrich M, Wang J, Deng W (2015) Ex vivo and in situ evaluation of ‘dispelling-wind’ Chinese medicine herb—drugs on intestinal absorption of chlorogenic acid. *Phytother Res* 29: 1974–1981.
- Zhang BX, Zhang JC (1999) 312 cases of psoriasis treated by the method of dispersing lung and regulating intestine. *China's Naturopathy* 3(3): 6–7.
- Zhang CF, Liu WZ, Pei LY, He YS, Wang L (2016) Enlightenment of modern research on the theory lung and large intestine form an external-internal relationship. *Shandong J Trad Chin Med* 35: 673–677.
- Zhang JB (2010) Lung, colon, skin theories on the significance of prevention and treatment of psoriasis. *Shandong University of Traditional Chinese Medicine*.
- Zhang JF, Zhang LX, Yang SX, Wang Q, Chen W (2019) Analyse the application of ephedra in the treatment of dermatosis based on the theory of “lung lord fur. *Asia-Pac Trad Med* 15: 209–210.
- Zhang WS, Guo XW, Li GR, Liu JL, Sun LY (2019) Interpretation of psoriasis (Baibi) in ancient literature of Traditional Chinese Medicine. *Guiding J Trad Chin Med Pharmacol* 1: 103–106.
- Zheng HT, Fan YM, Yuan HX, Yuan B (2018) Effects of intestinal flora on immune function based on the theory of “superficies-interior relationship between lung and large intestine” of Traditional Chinese Medicine. *Lishizhen Med Materia Medica Res* 29: 1170–1172.
- Zheng XL, Yang Y, Zheng XR, Ye JH, Zhou XY, Ding WJ, Liu WH (2013) Discuss the relevance of “lung and large intestine being interior-exterior” from the perspective of flora changes. *China J Trad Chin Med Pharm* 8: 2294–2296.
- Zhu S (2016) Intestinal flora disorder, chronic systemic inflammation and the development of psoriasis. *The 11th International Congress of Immunology Bulletin Exchange Collection* 11-14.