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Metabolomics Mechanistic Exploration of Traditional Chinese Medicine Dietary Intervention for Female Recurrent Urinary Tract Infections Under the Guidance of the "Medicine-Food Homology" Theory

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Abstract: ***This study explores the potential mechanisms of Traditional Chinese Medicine (TCM) dietary therapy in intervening with recurrent urinary tract infections (rUTI) in women, based on the TCM theory of "food as medicine" and metabolomics technology. Starting from the core pathogenesis of "spleen-kidney damp-heat, stasis, and toxic complex," this research analyzes the properties, flavors, and meridian tropism of spleen-strengthening and kidney-tonifying foods such as Chinese yam and Poria, as well as heat-clearing and dampness-reducing foods like Amaranth and mung beans. It combines the principles of flavor balance and meridian targeting in dietary prescriptions to elucidate their scientific connotations in regulating energy metabolism, improving oxidative stress status, controlling the gut-urinary axis microbiota, and estrogen-related metabolism, thereby repairing the urothelial barrier and enhancing mucosal immunity. The study reveals that the dietary therapy with the same origin of food and medicine acts through multi-component and multi-target synergistic effects to reshape the "host-microbiota-metabolism" balance, providing a theoretical basis for the integration of Chinese and Western medicine in the prevention and treatment of female rUTI.***

Keywords: Food as Medicine, Recurrent Urinary Tract Infections in Women, Metabolomics, Traditional Chinese Medicine Dietary Therapy, Mechanism of Action**.**

1. Introduction

Urinary Tract Infection (UTI) refers to infectious diseases caused by the growth and reproduction of various pathogenic microorganisms in the urinary tract, with a significantly higher incidence in females than in males. A variety of pathogens such as bacteria, fungi, mycoplasmas, chlamydiae, viruses, and parasites can lead to UTI, with Gram-negative bacilli being the most common causative bacteria. Among these, *Escherichia coli* is the most frequently encountered, followed by *Klebsiella*, *Proteus*, *Citrobacter*, and others [1]. Recurrent UTI (rUTI), also known as recurrent urinary tract infection, is defined as the recurrence of simple and/or complicated UTI, with at least three episodes of UTI occurring annually, or more than two episodes within six months [2]. Women are at a higher risk for rUTI, primarily due to their anatomical and physiological characteristics, microbiota balance, fluctuations in hormone levels, and immune metabolic status. Postmenopausal women, in particular, experience a decrease in estrogen levels, leading to atrophy of the urethral and vaginal mucosa, an increase in local pH, and urinary incontinence and vesicoureteral reflux caused by pelvic muscle relaxation, creating a vicious cycle of "infection - mucosal damage" [3].

2. Theoretical Understanding of Traditional Chinese Medicine in Female Recurrent Urinary Tract Infections (rUTI)

2.1 Etiology and Pathogenesis in Traditional Chinese Medicine

In Traditional Chinese Medicine (TCM), recurrent urinary tract infections (rUTI) in women are classified under the categories of "*Lao Lin*" (fatigue-induced urinary disorder) and "*Re Lin*" (heat-induced urinary disorder). The core pathogenesis involves kidney deficiency with damp-heat, blood stasis, and toxin accumulation, leading to a complex pathological condition characterized by underlying deficiency and excessive pathogenic factors interwoven [4].

The *Su Wen · Ling Lan Mi Dian Lun* states, "The kidney governs strength and dexterity," implying that when kidney qi is sufficient, the bladder functions properly, ensuring the orderly excretion of turbid fluids. However, when individuals have a constitutional kidney deficiency or suffer chronic illness affecting kidney function, impaired qi transformation results in water retention and damp accumulation. The spleen, being the "foundation of acquired health," governs the metabolism of bodily fluids. A weak spleen fails to transport water efficiently, leading to internal damp accumulation, which ultimately manifests as "kidney deficiency impairing retention, spleen deficiency disrupting fluid transport."

Damp-heat pathogens can originate from external invasion (such as prolonged exposure to humid environments or excessive heat) or internal formation (spleen deficiency-induced dampness, which transforms into heat). When these pathogenic factors descend into the bladder, they manifest as *Re Lin*, presenting symptoms of frequent urination, urgency, and pain. If left untreated, prolonged damp-heat

evaporates bodily fluids into blood stasis, as noted in the *Xue Zheng Lun · Lin Zhuo*, stating: "Heat-type urinary disorder results in painful and obstructed urination due to heat-induced blood stasis in the bladder." Blood stagnation obstructs meridians, causing bloody urine and lower abdominal pain. Over time, damp-heat-blood stasis-toxin accumulation damages urinary tract mucosa, forming a persistent pathological condition that leads to repeated episodes and difficult recovery. The *Zhu Bing Yuan Hou Lun · Lin Bing Zhu Hou* documented, "Kidney deficiency leads to bladder heat accumulation in the womb, deficiency causes frequent urination, while heat causes painful urination," precisely describing the pathogenesis as spleen-kidney deficiency as the internal foundation and damp-heat-blood stasis as the key pathogenic factor [5].

Due to the unique physiological characteristics of women—such as menstruation, vaginal secretions, pregnancy, and childbirth—qi and blood are more prone to depletion. The *Fu Qingzhu Gynecology* states, "Some women develop illnesses after early menstruation cessation due to blood depletion and stagnation," indicating that qi and blood deficiency can weaken Ren Mai (Conception Vessel) and Chong Mai (Penetrating Vessel), leading to compromised lower abdominal defensive functions. Additionally, women's short and straight urethra (approximately 4 cm), which is anatomically adjacent to the vagina, is highly susceptible to disturbances in vaginal microecology. A decline in lactobacillus, accompanied by an increase in vaginal pH, disrupts the local microenvironment, impairing urinary tract mucosal barrier function. This creates a physiological predisposition for "easy invasion by damp-heat and retention of pathogens," aligning closely with the TCM concept of "insufficient vital qi allows pathogenic factors to accumulate."

2.2 The Guiding Significance of "Preventive Treatment" Philosophy

The concept of "preventive treatment" in Traditional Chinese Medicine(TCM) originates from the "Huangdi Neijing" (Yellow Emperor's Inner Canon), specifically from the chapter "Suwen: The Great Treatise on the Four Qi and the Spirit" which emphasizes "The superior physician prevents diseases before they occur, rather than treating diseases that have already manifested, this is what is meant by it." The core essence of this philosophy encompasses three aspects: preventing disease before it occurs, preventing disease progression once it has occurred, and preventing relapse after recovery [6]. This philosophy holds unique guiding value in the prevention and treatment of recurrent urinary tract infections (rUTI) in women.

Preventing disease before it occurs is based on the identification of one's constitution. For those with insufficiencies in the spleen and kidneys and a predisposition to damp-heat, dietary therapy aims to "strengthen the spleen and kidneys to consolidate the foundation, and clear heat and dampness to cut off the source" to improve the body's susceptibility. For instance, as recorded in "The Compendium of Dietary Therapy," Chinese yam is used for "treating deficiency and replenishing insufficiency," while Poria benefits "urination and breaking qi stagnation." Cooking these two ingredients into porridge can strengthen the spleen, boost energy, and clear dampness and turbidity. Amaranth and mung beans, which are cold in nature and sweet in taste, can clear heat, promote urination, and detoxify, reflecting a "tailored to the individual" preventive strategy.

Preventing disease progression and preventing relapse after recovery focus on the coordination of dietary therapy and syndrome-based rehabilitation: during the acute phase, auxiliary medication is used to clear heat and dampness to alleviate symptoms, while during the convalescent phase, lotus seeds and Euryale ferox are used to benefit the kidneys and consolidate essence, combined with Poria and Atractylodes to strengthen the spleen and clear dampness, improving the "deficient fundamental" state and interrupting the "deficiency - pathogen lingering - relapse" cycle. This model aligns with the "Huangdi Neijing" concept of "grains, meats, fruits, and vegetables, all nourish completely" by regulating the flow of Qi and blood through diet to achieve the prevention goal of "when the right Qi is within, the pathogenic factors cannot invade" [7].

3. Application Basis of the "Food as Medicine" Theory in the Intervention of rUTI

The "food as medicine" theory has clear support from Traditional Chinese Medicine (TCM) theory and modern scientific connotations. By using spleen-strengthening and kidney-tonifying ingredients to cultivate the body's vital energy (Qi) and heat-clearing and dampness-reducing ingredients to purge pathogenic factors, combined with the principles of flavor balance and meridian targeting in formulating dietary plans, the dietary therapy can regulate the body's metabolism and microecological environment at the holistic level, providing a practical basis for subsequent mechanism studies based on metabolomics.

3.1 Analysis of the TCM Properties of Food as Medicine Ingredients

The "food as medicine" theory originates from the "Huangdi Neijing" (Yellow Emperor's Inner Canon), which records, "For diseases treated with strong toxins, six-tenths of the toxicity should be eliminated; for those treated with moderate toxins, seven-tenths; for those treated with mild toxins, eight-tenths; and for those treated with non-toxic substances, nine-tenths, with grains, meats, fruits, and vegetables used for nourishment to complete the cure." This emphasizes the natural synergistic and complementary properties of food and medicine in the prevention and treatment of diseases [8]. Focusing on the core pathogenesis of "kidney deficiency and damp-heat" in women with rUTI, the application of food as medicine ingredients can be divided into two major categories: strengthening the spleen and kidneys to consolidate the foundation and clearing heat and dampness to treat the symptoms, with their flavors, meridian tropism, and efficacy characteristics aligning with the TCM treatment principle of "supporting the healthy Qi and dispelling the pathogenic factors."

3.1.1 Spleen-Strengthening and Kidney-Tonifying Ingredients

These ingredients are mostly neutral or warm in nature, sweet or astringent in taste, and are associated with the spleen and kidney meridians. They can improve the body's "deficient" state by tonifying the Qi of the spleen and kidneys and consolidating the lower energy, enhancing the body's resistance to pathogens. Dioscorea opposita Thunb. (Chinese yam): First recorded in the "Shennong Bencao Jing" (Divine Farmer's Materia Medica), it is neutral in nature, sweet in taste, and associated with the spleen, lung, and kidney meridians, mainly used for "supplementing deficiency and dispelling cold and heat pathogenic factors" ("Ming Yi Bie Lu"). It is rich in components such as Dioscorea polysaccharides and diosgenin, which can regulate the intestinal flora to promote the production of short-chain fatty acids (such as butyric acid), enhancing the intestinal mucosal immune barrier [9]. Modern research has confirmed that extracts of Chinese yam can significantly increase the levels of IL-2 and IgG in the serum of spleen-deficient rat models, improving the state of immune suppression. Poria Cocos (Poria): Neutral in nature, sweet and bland in taste, associated with the spleen, heart, and kidney meridians, "Compendium of Materia Medica" states that it "promotes diuresis and reduces dampness, strengthens the spleen, and calms the heart." Triterpenoid compounds from Poria (such as poric acid, dehydroplicatic acid) can inhibit the NF-κB inflammatory pathway in renal tubular epithelial cells, reducing the secretion of IL-6 and TNF-α; its polysaccharide components can promote the proliferation of splenic lymphocytes and enhance the phagocytic function of macrophages [10], reflecting the characteristic of "strengthening the spleen and reducing dampness without harming the healthy Qi."

Nelumbo Nucifera Gaertn. (Lotus seed): Neutral in nature, sweet and astringent in taste, associated with the spleen, kidney, and heart meridians, it has the effect of "benefiting the kidneys and consolidating essence, strengthening the spleen and stopping diarrhea" ("Ben Cao Shi Yi"). Alkaloids such as lotus seed heart alkaloids and lotus leaf alkaloids can regulate autonomic nervous function, alleviating the anxiety state of rUTI patients; its special starch granule structure can act as a prebiotic to promote the proliferation of intestinal lactobacilli, indirectly improving vaginal microecology [11].

3.1.2 Heat-Clearing and Dampness-Reducing Ingredients

These types of ingredients are typically characterized by their cold or cool nature and sweet or bitter flavors, and they are associated with the Bladder, Kidney, and Small Intestine meridians. They are capable of directly reaching the site of disease, clearing heat and dampness, promoting the unblocking of urinary flow, and detoxifying, targeting the "excess" pathogenic factors characterized by damp-heat and stasis-toxicity. Portulaca Oleracea L. (Amaranth): With a cold nature and sour taste, it is associated with the Large Intestine, Liver, and Bladder meridians. The "New Compilation of Materia Medica" records its use for "treating various swellings, fistulas, and warts of the eyes, applied by mashing; the juice is used for vomiting and various types of strangury." Modern pharmacological studies have shown that flavonoid compounds in Amaranth, such as quercetin and kaempferol, have significant inhibitory effects on Escherichia coli and Staphylococcus aureus. The mechanism may be related to the disruption of bacterial cell membrane integrity and the inhibition of biofilm formation. Additionally, polysaccharides from Amaranth can downregulate the TLR4/NF-κB pathway, reducing inflammatory damage to the urinary tract mucosa [12]. Vigna Radiata (Mung Bean): With a cold nature and sweet taste, it is associated with the Heart and Stomach meridians, and its effects are described as "clearing heat and detoxifying, relieving summer heat and promoting diuresis" in the "Supplement to the Compendium of Materia Medica." Trypsin inhibitors in mung bean protein can inhibit the binding of bacterial adhesion factors (such as Escherichia coli P pili) to the receptors on urothelial cells, reducing bacterial colonization [13]. The oligosaccharides it contains can promote the proliferation of beneficial intestinal bacteria, indirectly inhibiting the migration of pathogenic bacteria through the "gut-urinary axis." Zea Mays L. Stigma (Corn Silk): With a neutral nature and sweet taste, it is associated with the Bladder, Liver, and Gallbladder meridians. The "Mi Nan Ben Cao" records its use for "relieving intestinal gas, treating women's milk stasis, and lactation issues." Flavonoid compounds in corn silk, such as luteolin, can promote urine excretion by regulating aquaporin (AQP2), reducing the positive rate of residual urine bacterial culture. The organic acids it contains, such as malic acid and citric acid, can acidify the urine, inhibiting the growth of Proteus and Klebsiella, which thrive in alkaline environments [14].

3.1.3 Modern Pharmacological Evidence

Vaccinium Macrocarpon Ait. (Cranberry): Although not a traditional Chinese medicine, its mechanism for preventing and treating UTI is highly consistent with the TCM concept of "detoxifying and promoting urination." Research has confirmed that proanthocyanidins (PACs) in cranberry can inhibit the binding of Escherichia coli P pili to the glycoprotein receptors (such as α-D-galactose) on the surface of urothelial cells, reducing bacterial adhesion by more than 70% [15], which aligns with the TCM efficacy of "expelling pathogenic factors and promoting the smooth flow of waterways."

Lycium Barbarum L. (Goji berry): Neutral in nature, sweet in taste, associated with the liver and kidney meridians, "Ben Cao Hui Yan" states that it "can replenish Qi and blood." Goji berry polysaccharides (LBP) can enhance the mitochondrial function of urothelial cells by activating the AMPK pathway, improving energy metabolism levels [16]; at the same time, LBP can promote the maturation of dendritic cells, enhance antigen presentation ability, and regulate the balance of Th1/Th2 immunity [17], reflecting the modern immune regulatory mechanism of "tonifying the kidneys to consolidate the foundation and resist pathogenic factors."

3.2 Principles of Formulating Dietary Therapy Plans

Based on the pathogenesis of "deficiency at the root and excess at the branch" in women with recurrent urinary tract infections (rUTI), dietary therapy plans must adhere to the TCM principle of "syndrome-based diet therapy," focusing on the balance of flavors and targeting the affected areas to achieve a dual approach of "attacking and supplementing, treating both the root and the branch."

3.2.1 Balance of Flavors: Aiming at the physical characteristics of women being "prone to deficiency and stasis," the formulation of dietary therapy emphasizes the rational combination of cold and warm ingredients to avoid excessive flavors that could harm the vital energy (Qi).

Warming Supplementation and Clearing Dampness: Ingredients such as Chinese yam and lotus seeds, which are neutral and sweet, are used to strengthen the spleen and kidneys, while ingredients like amaranth and mung beans, which are cold and sour, are used to clear heat and dampness. For example, in the "Chinese Yam, Poria, and Amaranth Porridge," Chinese yam and Poria strengthen the spleen and supplement deficiency, while amaranth clears heat and promotes urination. The combination of warm and cold ingredients prevents the warming ingredients from generating heat and dampness and avoids the cold ingredients from damaging the spleen and stomach.

Sweet and Bland with Sour and Astringent: Ingredients like Poria and corn silk, which are sweet and bland, are used to drain dampness and promote urination, while lotus seeds and Euryale ferox, which are sour and astringent, are used to consolidate kidney essence. For instance, the "Lotus Seed, Euryale Ferox, and Corn Silk Tea" regulates the transformation function of the bladder through a combination of "draining and astringing," suitable for patients in the convalescent stage with both spleen and kidney deficiency and damp-heat, reflecting the formulating idea from "Jingyue Quanshu" (Complete Works of Jingyue) that "in the treatment of strangury, heat should be cleared, stasis should be dredged, sinking should be lifted, and deficiency should be supplemented."

3.2.2 Targeting the Affected Areas: The selection of ingredients is guided by the theory of meridian tropism.

Ingredients for the Spleen Meridian: Ingredients such as Poria, Chinese yam, and lotus seeds, which are associated with the spleen meridian, strengthen the spleen and stomach and promote the transformation of substances, reducing the internal production of dampness from the source. Modern research indicates that spleen-strengthening ingredients can regulate the intestinal flora - short-chain fatty acid axis, improving the function of the intestinal mucosal barrier and interrupting the pathological chain of "spleen deficiency leading to dampness - dampness flowing downward."

Ingredients for the Kidney Meridian: Ingredients such as lotus seeds, Euryale ferox, and goji berries, which are associated with the kidney meridian, tonify the kidneys and consolidate essence to strengthen the congenital foundation. Experiments have shown that polysaccharides in kidney-tonifying ingredients can increase the activity of SOD in the renal tissue and reduce the content of MDA, mitigating the damage to renal tubular epithelial cells caused by oxidative stress [16].

Ingredients for the Bladder Meridian: Ingredients such as amaranth, corn silk, and mung beans, which are associated with the bladder meridian, directly address the damp-heat in the lower burner. The phenolic and flavonoid components contained in these ingredients can inhibit the activation of the NLRP3 inflammasome, reducing the release of pro-inflammatory factors such as IL-1β and IL-18, and improving the inflammatory state of the bladder mucosa [14].

4. Pathological Metabolic Characteristics of rUTI from a Metabolomics Perspective

As a core technology for analyzing the dynamic changes in small molecule metabolism within an organism, metabolomics can reveal the biological essence of the "kidney deficiency and damp-heat" mechanism in rUTI from aspects such as energy metabolism, oxidative stress, and microbiota interactions. Through the metabolite profiling analysis of biological samples such as urine and blood, significant metabolic pathway abnormalities and gender-specific metabolic characteristics in rUTI patients have been identified, providing precise molecular targets for the intervention of "food as medicine" dietary therapy.

4.1 Key Metabolic Pathway Abnormalities Associated with rUTI

4.1.1 Disruption of Energy Metabolism: Mitochondrial Dysfunction and Defective Urothelial Defense

The homeostasis of energy metabolism in urothelial cells is a crucial foundation for resisting bacterial adhesion. Patients with rUTI commonly exhibit mitochondrial dysfunction, characterized by decreased levels of key metabolites in the tricarboxylic acid (TCA) cycle such as succinate and α-ketoglutarate, and reduced ATP production. Succinate, as an important intermediate product of the mitochondrial respiratory chain, its reduced concentration directly leads to decreased efficiency of oxidative phosphorylation, insufficient energy supply to urothelial cells, and subsequently affects the synthesis and secretion of antimicrobial peptides (such as defensin β-2). Additionally, the disruption of energy metabolism can activate the AMPK signaling pathway, inhibiting mTORC1 and reducing the formation of autophagosomes, weakening the cell's ability to clear intracellular pathogens (such as Escherichia coli). This "energy-defense" coupling disorder is highly consistent with the TCM theory of "kidney deficiency leading to impaired qi transformation" and the resulting decline in bladder function, suggesting that kidney-tonifying ingredients (such as Chinese yam and goji berry) may enhance urothelial defense by improving mitochondrial function [17].

4.1.2 Imbalance of Oxidative Stress: The Vicious Cycle of Lipid Peroxidation and Mucosal Injury

Patients with rUTI have an imbalance in the oxidative and antioxidant systems, characterized by significantly increased levels of oxidative products like malondialdehyde (MDA) and decreased activity of antioxidants such as glutathione (GSH) and superoxide dismutase (SOD). MDA, as the end product of lipid peroxidation, can covalently modify membrane proteins of urothelial cells, destroy the integrity of the membrane structure, and increase bacterial adhesion sites; the decrease in GSH levels leads to the suppression of the thioredoxin system's function, failing to effectively eliminate hydroxyl radicals (•OH), exacerbating DNA and mitochondrial damage. Oxidative stress can also activate the NF-κB inflammatory pathway, promoting the release of pro-inflammatory factors

such as IL-6 and TNF-α, forming a cascade amplification effect of "oxidative damage - inflammatory response" [18]. Heat-clearing and dampness-reducing ingredients (such as amaranth and mung beans), rich in flavonoid compounds (quercetin, luteolin), can inhibit the activity of NADPH oxidase, reduce the generation of reactive oxygen species (ROS), and interrupt this pathological chain [14, 19].

4.1.3 Abnormalities in Microbiota-Related Metabolites: The Remote Regulation of Intestinal Dysbiosis

The metabolic products of the gut microbiota participate in the occurrence and development of rUTI through the "gut-urinary axis." Studies have shown that the levels of microbiota-dependent metabolites such as phenylacetylglutamic acid (PAGln) and p-cresol sulfate in the feces of rUTI patients are significantly increased [20]. PAGln, a metabolic product of intestinal Gram-negative bacteria (such as Escherichia coli), can promote the generation of thrombin by activating protease-activated receptor 1 (PAR1), exacerbating the formation of microthrombi in the urinary tract and inflammatory exudate [18]; p-cresol sulfate has direct nephrotoxicity and can damage the mitochondria of renal tubular epithelial cells, reducing their phagocytic ability against bacteria. Additionally, the decrease in short-chain fatty acids (SCFAs) such as acetate and butyrate in the gut leads to decreased expression of tight junction proteins (ZO-1, occludin) in the intestinal mucosa, weakening the intestinal barrier function and increasing the risk of pathogen translocation. This is consistent with the TCM pathogenesis that "spleen deficiency with excessive dampness leads to internal dampness, and dampness flows downward to the bladder," suggesting that spleen-strengthening ingredients (such as Poria and Chinese yam) may reduce the production of toxic metabolites by regulating gut microbiota metabolism.

4.2 Specific Metabolic Characteristics of rUTI in Women

4.2.1 Postmenopausal Estrogen Metabolic Abnormalities: Cascade Effects from Hormone Levels to Microbiota

In postmenopausal women, there is a significant decrease in the levels of estrone sulfate (E1S), the primary circulating form of estrogen. The reduction of this metabolite directly leads to impaired glycogen synthesis in vaginal epithelial cells, insufficient metabolic substrates for lactobacilli, and consequently, an increase in vaginal pH (>5.0) and dysbiosis. Metabolomic studies have shown a positive correlation between E1S levels and the abundance of vaginal lactobacilli, and a negative correlation with the metabolic products of pathogenic bacteria (such as enterococci), such as putrescine and cadaverine. Furthermore, estrogen deficiency can downregulate the expression of estrogen receptor α (ERα) in urothelial cells, inhibiting the transcription and secretion of β-defensin-2 (hBD-2), and weakening the mucosal antibacterial capacity [21]. This imbalance in the "hormone-microbiota-immunity" axis forms the core metabolic basis for the high incidence of rUTI in postmenopausal women, and soy products rich in phytoestrogens (such as soy milk and black beans) may indirectly improve the vaginal microbiota environment by regulating E1S metabolism.

4.2.2 Imbalance of Short-Chain Fatty Acids (SCFAs): Metabolic Regulation of Mucosal Barrier Function

Women with rUTI have significantly lower levels of SCFAs (especially acetate and butyrate) in urine and vaginal secretions compared to healthy individuals, and these levels are negatively correlated with the frequency of recurrence. The deficiency of SCFAs in patients with rUTI essentially reflects the dysfunction of the "lactobacilli-metabolite-host immunity" axis, which is consistent with the TCM understanding that "internal dampness-heat leads to microbiota imbalance," providing a target basis for the use of food as medicine ingredients (such as Chinese yam and corn silk, which are rich in dietary fiber) to improve mucosal barriers by promoting the generation of SCFAs.

5. Exploring the Metabolomics Mechanisms of Food as Medicine Dietary Intervention in rUTI

Based on the intersection of Traditional Chinese Medicine (TCM) "food as medicine" theory and modern metabolomics, the intervention mechanism of dietary therapy for women with rUTI can be summarized as a multi-component, multi-target, and multi-pathway synergistic regulation. It restores energy metabolism, regulates the microbiota axis, inhibits oxidative stress, and improves estrogen-related metabolism, reshaping the "host-microbiota-metabolism" balance at the molecular level to achieve the therapeutic goal of "strengthening the spleen and kidneys to support health, and clearing heat and dampness to dispel pathogens."

5.1 Regulating Energy Metabolism and Repairing Mucosal Barriers

5.1.1 Activation of Mitochondrial Function and Reshaping Energy Metabolism

Yam polysaccharides (YPS) and Poria triterpenoids (PTs) are the core active substances for regulating energy metabolism. YPS can activate the AMP-activated protein kinase (AMPK) pathway, promoting the expression of mitochondrial DNA-encoded cytochrome C oxidase (COX) subunits, enhancing oxidative phosphorylation efficiency, and increasing ATP production in urothelial cells by 30% to 50%. PTs, on the other hand, maintain mitochondrial membrane potential stability by inhibiting the opening of the mitochondrial permeability transition pore(mPTP), reducing the release of succinate to the extracellular environment, thereby blocking succinate-mediated HIF-1α/NF-κB inflammatory signal activation [22]. This precise regulation of the succinate-fumarate metabolic axis can significantly reduce the levels of pro-inflammatory factors such as IL-6 and TNF-α, improving mucosal inflammatory damage.

5.1.2 Energy-Dependent Enhancement of Mucosal Defense Function

Adequate energy supply is the basis for the synthesis of antimicrobial peptides (such as hBD-2, cathelicidin) in urothelial cells. Dietary components enhance the activity of mitochondrial complex IV, promoting the transcription of ribosome biogenesis-related genes (RPS19, RPL23),

increasing the secretion of antimicrobial peptides by 2 to 3 times. At the same time, the activation of the AMPK pathway can enhance the expression of autophagy-related proteins (ATG5, ATG7), promoting the autophagic clearance of intracellular pathogens, forming a positive cycle of "energy supplementation - defense enhancement - pathogen clearance" [22]. This corresponds to the TCM theory of "tonifying the kidneys and Qi to consolidate the bladder," providing metabolomics evidence for the improvement of "kidney deficiency and impaired Qi transformation" by ingredients such as Chinese yam and Poria.

5.2 Regulating the Gut-Urinary Axis Microbiota Metabolism

5.2.1 Dietary Fiber-Mediated Optimization of Intestinal Flora

Ingredients such as Chinese yam and corn silk, rich in soluble dietary fiber (pectin, β-glucan), act as prebiotics that specifically promote the proliferation of intestinal lactobacilli (such as Lactobacillus rhamnosus, Lactobacillus reuteri), increasing the abundance of intestinal lactobacilli by 40% to 60%. These beneficial bacteria ferment dietary fiber to produce short-chain fatty acids (SCFAs), with acetate and butyrate concentrations increased by 50% and 30%, respectively. SCFAs, entering the circulatory system through the portal vein, on one hand, acidify the urine (pH value decreased by 0.5 to 1.0 units), inhibiting the adhesion of Escherichia coli and Klebsiella, which depend on an alkaline environment; on the other hand, they inhibit the expression of virulence genes of pathogens (such as fimH, papC), reducing pilus synthesis and lowering bacterial adhesion to urothelial cells [23].

5.2.2 Metabolic Linkage Effect of "Gut Immunity - Urinary Tract Defense"

SCFAs, as important signaling molecules, promote the differentiation of regulatory T cells (Treg) in mesenteric lymph nodes by binding to the GPR43 receptor on the surface of immune cells, increasing IL-10 secretion by more than 2 times, while inhibiting the IL-17 inflammatory response mediated by Th17 cells. Locally in the urinary tract, SCFAs enhance the secretion of IgA by plasma cells in the mucosal lamina propria, forming an antibacterial antibody barrier, increasing the concentration of secretory IgA (sIgA) in urine by 35%. In addition, butyrate upregulates the expression of tight junction proteins ZO-1 and occludin in urothelial cells through the inhibition of histone deacetylases (HDAC), repairing the mucosal mechanical barrier and reducing the translocation of pathogens. This cross-organ metabolic - immunity regulation is a modern biological manifestation of the TCM treatment method of "nourishing the soil to generate metal, strengthening the spleen and promoting dampness elimination."

5.3 Inhibiting Oxidative Stress and Inflammatory Response

5.3.1 Free Radical Scavenging and Antioxidant Enzyme Activation

Amaranth flavonoids (such as quercetin, luteolin) and goji berry polysaccharides (LBP) have broad-spectrum antioxidant activity, capable of scavenging toxic oxygen free radicals such as superoxide anions (O_2^- ·) and hydroxyl radicals (· OH), reducing MDA content in urine by 25% to 30%, while enhancing the activity of antioxidant enzymes such as SOD and GSH-Px by 15% to 20%. LBP can also activate the Nrf2/ARE pathway, promoting the expression of phase II detoxification enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H: quinone oxidoreductase 1 (NQO1), enhancing cellular antioxidant defense capabilities.

5.3.2 Multi-Node Blockade of Inflammatory Cascade Reactions

Dietary components inhibit the activation of the NLRP3 inflammasome, blocking the "oxidative damage - inflammation" vicious cycle. Quercetin can target the PYD domain of the NLRP3 protein, inhibiting its interaction with ASC, reducing the activation of Caspase-1 by 60%; LBP, on the other hand, reduces mitochondrial ROS production, inhibiting the translocation of NLRP3 to the mitochondria, suppressing the assembly of the inflammasome from the source. In addition, luteolin can competitively bind to the DNA-binding domain of the NF-κB p65 subunit, inhibiting its migration to the nucleus, reducing the transcription of pro-inflammatory cytokines such as IL-1β and IL-18 by 40% to 50% [24]. These effects are highly consistent with the TCM effects of "clearing heat and detoxifying, cooling blood and promoting urination," providing molecular targets for the treatment of "damp-heat stasis-toxicity" by ingredients such as amaranth and mung beans.

5.4 Regulating Estrogen-Related Metabolism and Improving Vaginal Microecology

5.4.1 Bilateral Regulation of the Hormone Metabolic Axis by Plant Estrogens

Soy isoflavones (such as genistein, daidzein), as plant estrogens, can bind to estrogen receptors α (ERα) and β (ERβ), regulating the metabolism of estrone sulfate (E1S) in postmenopausal women. Clinical studies have shown that after 3 months of consuming a dietary plan containing soy isoflavones, E1S levels can increase by 20% to 30%, glycogen content in vaginal epithelial cells can increase by 15%, and the abundance of lactobacilli can return to the level of reproductive age. The increase in E1S not only maintains the acidic environment of the vagina (pH≤4.5) but also directly inhibits the adhesion of Escherichia coli by inducing the secretion of antimicrobial peptides (such as hBD-2) in vaginal epithelial cells.

5.4.2 Synergistic Antibacterial Effect of Dietary Components and Probiotics

Plant estrogens in dietary therapy can have a synergistic effect with the metabolic products of vaginal probiotics (such as lactic acid, hydrogen peroxide). Lactic acid enhances the antibacterial activity of soy isoflavones by lowering the pH value of the vagina; hydrogen peroxide can destroy the matrix of bacterial biofilms, reducing the formation of Escherichia coli biofilms by more than 50%. In addition, genistein can

inhibit the synthesis of bacterial quorum sensing signal molecules (such as AI-2), blocking the adhesion and colonization signals of pathogens, inhibiting infection from three dimensions of “environmental acidification - biofilm destruction - signal interference” [14]. This dual mechanism of “endogenous hormone regulation + exogenous microbiota intervention” provides an innovative path for the prevention and treatment of rUTI in postmenopausal women.

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