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Exploration on Etiopathogenesis and Therapeutic Principles of Ankylosing Spondylitis Guided by Ye Tianshi's Theory of Dredging Collaterals

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Abstract: ***Ankylosing spondylitis (AS) is an immune-mediated chronic inflammatory disease that mainly involves the axial joints and sacroiliac joints. Its pathological characteristics include bone destruction and new bone formation induced by immune inflammatory responses. The collaterals disease theory can be traced back to Huangdi Neijing (Huangdi's Internal Classic). Collaterals function to defend against exogenous pathogens, connect the exterior and interior of the body, and nourish the skin and interstices. Harmonious qi and blood circulation in collaterals maintains normal bodily functions. Abnormal circulation of qi and blood in collaterals impairs its functions such as pathogen resistance and internal-exterior communication, triggering immune inflammatory responses in AS, followed by bone destruction and neo-osteogenesis, resulting in joint swelling and pain, partial spinal fusion and even deformity. Ye Tianshi's collaterals disease theory carries important guiding significance for the treatment of this disease. By sorting out Ye Tianshi's academic thought of "chronic diseases entering collaterals", this paper systematically elaborates three core pathogeneses of AS: the early stage of AS is characterized by "channel heat leading to bi syndrome"; the middle stage manifests as "dampness invasion and intermingling of phlegm and blood stasis"; the late stage is dominated by "deficiency of extraordinary meridians and malnourishment of collaterals". At the therapeutic level, a three-dimensional collateral-unblocking system is proposed: at the defensive aspect, pungent-cool dispersion to expel pathogens outward; at the qi aspect, dispersing sanjiao to resolve phlegm and remove blood stasis; at the nutrient aspect, tonifying liver and kidney and insect medicinals for collateral dredging. It provides new ideas and therapeutic options for the treatment of AS.***

Keywords: Ye Tianshi, Collateral Dredging Method, Ankylosing spondylitis (AS), Huangdi Neijing, Case Records as a Guide to Clinical Practice.

1. Introduction

Ankylosing Spondylitis is an immune-mediated specific inflammation involving the sacroiliac and axial joints, which may lead to joint fibrosis and even ossification. In the advanced stage, it may manifest as vertebral squaring, ligament calcification, "bamboo spine" changes of the spine, etc. [1]. Severe cases develop deformity accompanied by joint pain, and some patients present extra-articular manifestations. Studies have shown that the age of onset of Ankylosing Spondylitis covers a wide range and generally shows a "bimodal" trend: the incidence is relatively high in adolescence and young adulthood, while it decreases in middle and old age [2]. The onset of AS tends to occur at younger ages with a high disability rate, which seriously impairs patients quality of life and increases the social burden. There is no record of AS in ancient Chinese medicine. AS can be categorized into the "Bi disease" in traditional Chinese medicine. Due to spinal ankylosis in the late stage and pathological changes located in the bone, AS is also named "Wang Bi", "Gu Bi", "Tortoise Back Wind" and "Da Lou". The theory of collaterals can be traced back to Huangdi Neijing. Unobstructed collaterals help defend against exogenous pathogens and connect qi and blood in the upper, lower, internal and external parts of the body. If collaterals lose their smoothness and qi-blood circulation is blocked, visceral functions will be impaired. When exogenous pathogens invade the body, Bi syndrome tends to occur.

At present, non-steroidal anti-inflammatory drugs, glucocorticoids and immunosuppressants are commonly adopted in Western medicine to treat AS. Such regimens can control symptoms and suppress disease progression in the short term. However, satisfactory therapeutic effects cannot be achieved in most patients. Long-term administration increases the risk of infection and causes adverse reactions such as hepatorenal damage and gastrointestinal discomfort [3]. Treatment of AS based on the "collateral dredging theory" provides richer diagnostic and therapeutic ideas for AS management.

2. The Theoretical Summary of "Chronic Diseases Entering Collaterals"

The collateral theory was first put forward in Huangdi Neijing. Lingshu·Mai Du (Spiritual Pivot·On the Length of Vessels) records the location of collaterals in detail: "The meridians lie internally; their transverse branches are collaterals, and the further branches of collaterals are minute collaterals." Collaterals branch off from meridians and constitute the transverse branches of meridians. Lingshu·Ben Zang (Spiritual Pivot·On the Viscera) indirectly illustrates the functions of collaterals: "Meridians are responsible for circulating qi and blood, nourishing yin and yang, moistening bones and tendons, and lubricating joints." As an extension of meridian functions, collaterals undertake the roles of permeating qi and blood and nourishing zang-fu organs as well as limbs. The meridian-collateral system mainly transports and distributes qi and blood throughout the body. Qi and blood permeate from meridians into collaterals to nourish the whole body, while metabolic wastes generated by the body flow back into meridians via collaterals and are excreted out of the body. In this way, collaterals remain unobstructed to maintain normal physiological functions of the organism. When collaterals become unsmooth, their defensive function is impaired. Wind-cold-damp pathogens

invade the body and linger in the meridians and collaterals of limbs, giving rise to swelling and pain of axial and sacroiliac joints. Suwen·Sheng Qi Tong Tian Lun (Plain Questions·On the Communication between Qi and Heaven) states: "Yang qi flourishes at midday and becomes deficient in the late afternoon." Yang qi is vigorous and qi-blood circulates rapidly during daytime; at night, yin blood converges inward and qi-blood circulation slows down. Therefore, lumbosacral pain in AS patients is aggravated at night and relieved after physical activity [4]. Blockage of collaterals by metabolic wastes, phlegm-dampness and blood stasis leads to "pain due to obstruction". Long-term stagnation of phlegm-dampness and blood stasis generates abundant pathological products, which ultimately result in deformity of sacroiliac joints and abnormal osteophyte formation.

3. An In-depth Investigation of the Etiology and Pathogenesis of Bi Syndrome

3.1 Pathogenesis of Pathogen Invasion into Collaterals and Immune Response Mechanism of AS

Ankylosing spondylitis is a rheumatic immune-mediated disease, and immune-inflammatory responses run through its pathological process. Affected by multiple factors including immunity, environment and heredity, patients may develop inflammatory reactions in the spinal and sacroiliac joints. When immune responses become abnormal, the recognition or phagocytic function of immune cells is impaired, and a large number of inflammatory factors are released. These immune factors are mainly involved in two types of immune responses: humoral immunity and cellular immunity, with T cells and B cells participating in immune responses [5]. Defective recognition function of T cells in the early stage of immune responses triggers abnormal signals, leading to abnormal proliferation of B cells, other immune cells and immune factors. B cells participate in abnormal immune attacks, encapsulation and phagocytosis occurring in specific tissues of the body in the middle phase of immune processes. Consequently, patients present with swelling and pain of sacroiliac joints, and even deformity.

Ye Tianshi put forward the viewpoint that "heat in meridians leads to bi syndrome, while heat in collaterals leads to wei syndrome". He held that bi syndrome arises from the struggle between healthy qi and pathogenic factors in meridians, which belongs to qi-related disorders, whereas wei syndrome results from such struggle in collaterals, which belongs to blood-related disorders [6]. The defensive function of collaterals is analogous to human immune function, which resists invasion by exogenous microorganisms. From the perspective of traditional Chinese medicine, collaterals regulate the circulation of qi and blood in meridians, maintain normal visceral functions and prevent the invasion of exogenous pathogens. Immunology suggests that the human immune system can defend against pathogenic microorganisms, eliminate senescent and apoptotic cells, and maintain relative stability of immune function.

When the defensive function of collaterals is dysfunctional, exogenous pathogens invade the body's meridians. Collaterals fail to resist pathogens, meridians and collaterals are obstructed by pathogenic factors, immune function is relatively deficient, and immune-inflammatory responses are triggered, resulting in pain in sacroiliac and spinal joints. Studies have shown that epidermal-specific Langerhans cells activate T cells and B cells to exert their specific cellular and humoral immune functions [7]. Impaired defensive function allows exogenous pathogens to easily activate immune responses and promote the activation of inflammatory reactions. The progression of most rheumatic immune diseases is accompanied by infection, or symptoms are aggravated upon infection. This characteristic is highly consistent with the integrity of the defensive function of collaterals.

3.2 Collateral Obstruction and Abnormal Osteoproliferation

The pathogenesis of AS is accompanied by disordered bone metabolism, which is mainly manifested by local ectopic new-bone formation. New-bone formation involves the participation of osteoblasts. Osteoblasts undergo excessive differentiation during inflammatory responses, generating pathological new bone. Extensive fusion and hyperplasia of bone tissue give rise to abnormal osteophytes, resulting in sacroiliac joint deformity [8]. The abnormal metabolism of osteoblasts is regulated by the immune process of AS, and the occurrence of AS-related immune responses affects the differentiation and functional expression of osteoblasts. Studies have shown that inflammatory responses in AS interfere with the differentiation and proliferation of osteoblasts. The release of chronic inflammatory mediators such as TNF-α, IL-17 and IL-23 at enthesitis sites promotes the over-expression of Wnt agonists, which leads to excessive activation of the Wnt/β-catenin signaling pathway at entheses. Consequently, osteoblasts differentiate and proliferate abnormally, resulting in local ectopic ossification, bone-bridge formation and osteophyte development [9].

When collaterals are obstructed, phlegm-dampness and blood stasis block the collaterals, inflammatory levels rise, and the osteoblast-activating factor Wnt is over-expressed. Abnormal proliferation of osteoblasts leads to the formation of bone bridges and osteophytes. Lingshu·Bai Bing Shi Sheng (Spiritual Pivot·On the Origin of All Diseases) states: "If dampness persists, coagulated blood accumulates and fails to disperse; body fluids stagnate and adhere to tissues, thus forming accumulations." Dampness is sticky and lingering, which may cause blood to stagnate internally and hinder blood circulation, giving rise to pain and accumulations. Ye Tianshi noted that "Recurrent and protracted ailments inevitably injure collaterals. Collaterals are where blood gathers; chronic diseases are invariably accompanied by blood-stasis blockage." Initial diseases locate in the qi aspect. When pathogenic factors linger in the qi aspect and fail to be eliminated, they progress into the nutrient and blood aspects. Collaterals are fine and narrow in physiological structure; pathogenic factors easily invade yet are difficult to dispel, tending to accumulate and stagnate. Damage to collaterals disrupts the circulation of qi, blood and body fluids. Blood stagnates to form stasis, and body fluids stagnate to produce phlegm. The intermingling of phlegm and blood stasis obstructs collaterals [7]. Collateral obstruction disturbs the distribution and circulation of qi, blood and body fluids in the body. Impaired distribution gives rise to pathological products

including phlegm, heat, blood stasis and toxin. These pathological products block meridians and collaterals, resulting in "pain due to obstruction". Accumulation of pathological products triggers bone remodeling or adhesion, causing local abnormal space-occupying changes or bone remodeling, and subsequently forming bone bridges and osteophytes [10].

3.3 This Section Discusses Liver-Kidney Essence-Blood Deficiency and Osteoporosis.

The late-stage pathogenesis of AS is often accompanied by systemic osteoporosis. Abnormal differentiation, activation and proliferation of osteoclasts are enhanced, with bone resorption exceeding bone formation. Combined with factors such as age, these changes jointly result in systemic bone mass loss, manifested as reduced systemic bone mineral density, and fractures may occur in severe cases. The abnormal differentiation of osteoclasts is regulated by immune factors of AS. When immune-inflammatory responses are activated, inflammatory factors accumulate in the body and further affect the function of osteoclasts. Studies have shown that upon the occurrence of immune-inflammation, the local inflammatory microenvironment induces excessive expression of RANKL in synovial and bone cells. RANKL promotes abnormal differentiation of osteoclasts. Driven by core cytokines such as TNF-α, osteoclasts proliferate abnormally, inhibit osteogenesis, and induce osteoblast necrosis, which aggravates bone loss and gives rise to osteoporosis [11].

When Bi syndrome persists for a long time, it consumes liver blood and kidney essence, impairs the lower jiao, and leads to failure of consolidation of the eight extraordinary meridians. Ye Tianshi stated: "Heat invades the yin aspect and blood, predominantly affecting the lower jiao; the upper jiao pertains to qi, while the lower jiao pertains to blood." Liver-kidney essence-blood deficiency renders the body vulnerable to invasion by exogenous pathogens or obstruction of collaterals by phlegm-dampness and blood stasis. Elevated inflammatory markers activate osteoclast-activating factors, triggering abnormal differentiation of osteoclasts and increased bone resorption, which makes patients more prone to reduced bone mineral density. Linzheng Zhinan Yi'an (Case Records as a Guide to Clinical Practice) records: "Numbness of limbs, with twitching and stabbing pain in the knee." After middle age, human essence-blood becomes half-depleted, giving rise to internal stirring of deficient wind. Liver-kidney blood deficiency causes water failing to nourish wood, resulting in hyperactivity of wood and generation of wind. Malnourishment of meridians leads to spasmodic pain; in severe cases, joint deformity and dysfunction occur. Sufficient kidney essence nourishes bones; ample essence-blood ensures adequate generation of bone marrow, thereby maintaining strong tendons and bones. In the advanced stage of Bi syndrome, pathogenic factors sink inward. The lingering illness invades yin collaterals and resides in zang-fu organs, which may cause organic visceral lesions such as renal failure and pulmonary interstitial fibrosis [12]. This is highly consistent with Ye Tianshi's pathogenic transmission rule of "chronic diseases entering collaterals and prolonged pain entering collaterals". It reflects that if the condition of ankylosing spondylitis cannot be effectively controlled, it will progress from functional disorders of viscera to organic damage.

4. Therapeutic Methods of Bi Syndrome

4.1 Pungent Dispersion to Release the Exterior, Expel Pathogens and Unblock Collaterals

The early onset of AS is closely related to the invasion of exogenous pathogens. Invasion of exogenous pathogens obstructs qi and blood circulation in collaterals, leading to collateral stagnation. Obstruction causes pain. In Clinical Guide to Medical Cases, Ye Tianshi stated, "Pungent dispersing medicinals move freely and reach every corner within collaterals; only pungent and aromatic medicinals can enter collaterals." He pointed out that medicinals with pungent, aromatic and moving properties can unblock collaterals for the treatment of Bi Syndrome.

Suwen · Treatise on Cough records: "The skin and hair are associated with the lung. When pathogenic factors first invade the skin and hair, pathogens follow this connection inward." Pathogens attacking the skin first invade the lung. Insufficient consolidation of lung defense qi renders the body vulnerable to pathogenic invasion. The lung governs the skin in the body. The skin acts as the unique immune barrier of the organism. Epidermal Langerhans cells activate T cells and B cells to exert specific cellular and humoral immune functions. The proportion of CD4+T cells, CD4+/CD8+ ratio, levels of IL-6 and TNF-α are closely correlated with the severity of ankylosing spondylitis [13]. Diffusing and releasing the exterior restores the defensive qi's function of governing the body surface, regulates the immune disorder of T and B cells to alleviate limb pain, inhibits the activation of immune cells, and eliminates immune inflammation at its early stage [14].

Ye Tianshi said: "Defensive qi is followed by qi (qi phase)." If pathogens stagnate in the lung-defense system without being resolved, they transmit into the qi phase. Synopsis of Prescriptions of the Golden Chamber · Chapter 4: Pulse Manifestations and Treatise on Malaria Diseases states: "Warm malaria manifests with nearly normal pulse, fever without chills, severe aching pain of bones and joints, and occasional vomiting, which should be treated with White Tiger Decoction plus Ramulus Cinnamomi." When pathogenic heat invades the qi phase, the pivot of the middle jiao becomes dysfunctional. The qi phase mainly refers to the stomach and intestines. All limbs of the human body receive qi from the stomach. When the stomach is attacked by fiery pathogens, food essences cannot be distributed to the limbs, resulting in limb pain and stiffness. Once pathogenic heat is dispersed outward, body fluid regenerates and qi movement becomes smooth, and Bi Syndrome is cured.

If the disease persists for long or is improperly treated, pathogenic heat enters the nutrient phase. Ye Tianshi noted: "Pungent-cool medicinals dispel wind, sweet-mild medicinals eliminate dampness. If the disease remains unresolved, pathogens are gradually entering the nutrient phase." When the nutrient phase is invaded by pathogens, persistent heat scorches body fluid, leading to intermingling of phlegm and blood stasis. Combined with consumption of nutrient yin and loss of moistening nourishment, limb joints fail to flex and

extend freely, resulting in Bi Syndrome. If pathogenic heat in the nutrient phase is not eliminated and invades blood collaterals, prolonged blood heat accumulates and transforms into toxin, or generates phlegm and stasis to block collaterals. Poor blood circulation further fuels pathogenic heat, forming a local vicious cycle [15].

Treatise on Febrile Diseases states: "Once pathogens enter the blood phase, blood consumption and blood movement disturbance are likely to occur. It is necessary to cool blood and dispel blood stasis, such as using Radix Rehmanniae, Cortex Moutan, Colla Corii Asini and other medicinals." For pathogens in the blood phase, Ye Tianshi advocated primarily cooling blood and dispersing blood stasis, supplemented by nourishing blood to unblock collaterals. Bitter-cold medicinals such as Radix Rehmanniae and Cortex Moutan are applied to cool blood and dispel stasis; Semen Persicae and Scolopendra are used to break blood and expel stasis. Blood phase syndrome is often accompanied by blood deficiency, so Radix Angelicae Sinensis and Radix Paeoniae Alba are added to nourish and tonify blood. Once deficient heat recedes, nutrient blood regenerates spontaneously.

4.2 Diffuse and Unblock Sanjiao, Resolve Phlegm and Eliminate Blood Stasis

When pathogenic factors remain unresolved in the defensive phase, they transmit into the qi phase. The qi phase is mainly invaded by damp-heat pathogens that attack the spleen and stomach. Failure of the spleen and stomach to transport and transform nutrients leads to endogenous generation of damp turbidity. Clinical Guide to Medical Cases states: "Excessive dampness generates heat and produces phlegm, gradually bringing on manifestations of flaccidity and Bi Syndrome… Pain appears here, so treatment targets the qi phase." Lingering damp pathogens accumulate for a long time and transform into heat, forming accumulated damp-heat that generates phlegm. The intermingling of damp-heat and phlegm-heat obstructs the qi phase and causes collateral stagnation in the qi phase, resulting in Bi Syndrome.

Suwen · Treatise on Vital Qi and Communication with Heaven records: "When attacked by dampness, the head feels wrapped. If damp-heat is not eliminated, large tendons contract and shorten while small tendons relax and lengthen; contracted tendons cause spasm, and relaxed tendons lead to flaccidity." Regarding damp-heat pathogens, Ye Tianshi proposed that lingering dampness in Sanjiao belongs to qi-phase disease, and Sanjiao pertains to Shaoyang. Dampness obstructs Shaoyang, disrupting the ascent, descent, exit and entry of qi movement, and fluid, phlegm and dampness accumulate within Sanjiao. Therefore, treatment aims to diffuse and smooth qi movement of Sanjiao and eliminate phlegm-dampness. Ye Tianshi put forward the therapeutic method of diffusing and unblocking Sanjiao, dispersion and drainage: diffusing the upper jiao, regulating the middle jiao and smoothing the lower jiao [16]. The representative prescription is Sanren Decoction. To diffuse and unblock the upper jiao, treating the lung is primary; Semen Armeniacae Amarum is used to diffuse lung qi in the upper jiao. The lung governs qi movement of the whole body, and when qi transforms, dampness is also resolved. Endogenous dampness mostly arises from impaired transportation and transformation of the spleen and stomach. Fructus Amomi Rotundus and Rhizoma Pinelliae are warm in nature, capable of transforming qi and draining dampness to promote qi movement and regulate the middle jiao. Semen Coicis is bland and slightly cold, combined with Talc to drain dampness by bland percolation so that damp-heat can leak out [17].

If Bi Syndrome persists for a long time without relief, pathogens enter collaterals and blood. Blood stasis in the blood phase produces pathological products such as phlegm turbidity and blood stasis, manifesting as stabbing pain, stiffness and even deformity of joints. As recorded in Clinical Guide to Medical Cases: "The classics state that Bi Syndrome arises from the combination of wind, cold and dampness. When pathogens linger for years, qi and blood are both injured. Morbid blood and coagulated phlegm mix within the meridians, which commonly occurs." Ye Tianshi held that searching and dispelling to unblock collaterals, resolving phlegm and eliminating blood stasis constitute important therapeutic methods for Bi Syndrome with chronic disease entering collaterals. He also stated, "When pathogens linger in meridians and collaterals, searching and dynamic medicinals must be adopted; medicinals without swift and mobile properties cannot achieve efficacy." Ye Tianshi believed that simple methods of dispelling wind, cold and dampness often fail to work, so unblocking collaterals should be prioritized. Insect medicinals are applied to search and dispel pathogenic factors lodged in collaterals; these medicinals reach zang-fu organs and collaterals all over the body to expel collaterals pathogens [18].

Thus, medicinals for Bi Syndrome treatment are mainly insect medicinals. They are flexible and swift in action: flying insect medicinals tend to ascend, diffuse and disperse; crawling ones tend to descend, drain and break stagnation. Long-standing Bi Syndrome is characterized by intermingled phlegm and blood stasis in vessels with mixed primary and secondary pathogens, which requires slow treatment by medicinals that search and dispel pathogens in collaterals. Medicinals such as Scolopendra, Scorpio, Bombyx Batryticatus, Carapax Trionycis and Eupolyphaga Seu Steleophaga can enter collaterals to break blood and expel stasis, diffuse and unblock collaterals, unblock collaterals to relieve pain. Studies also show that insect medicinals such as Bombyx Batryticatus can effectively prolong activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) in rat plasma. This fully demonstrates that Bombyx Batryticatus inhibits both extrinsic and intrinsic coagulation systems, reduces platelet aggregation rate and ameliorates hypercoagulable state. It can improve hemorheology, dilate local small blood vessels and improve peripheral tissue circulation [19]. Drying dampness to resolve [20].

4.3 Tonify the Liver and Kidney, Regulate and Consolidate the Extraordinary Meridians

When pathogenic factors of Bi Syndrome linger unresolved for a long time, they impair essence and blood of the five zang-organs. The depletion of essence and blood involves the extraordinary meridians, leading to failure of consolidation of the extraordinary vessels. Ye held that tonifying the liver and

kidney as well as regulating and consolidating the extraordinary meridians constitutes the therapeutic principle and method for Bi Syndrome. The treatment should follow the principle that "chronic diseases require unblocking the Conception and Governor Vessels, combining unblocking with consolidation".

For patients with deficiency-cold of the Governor Vessel and declined genuine yang, only medicinals of flesh and blood nature can tonify the deficiency. Suwen · Treatise on the Essential Truth and the Great Theories states: "Essence insufficiency should be tonified with flavors; form insufficiency should be warmed with qi." Colla Cornus Cervi is selected to warm and unblock the Governor Vessel and tonify yang qi, supplemented with Fructus Psoraleae, Fructus Foeniculi, and Rhizoma Cibotii; Fructus Toosendan, Rhizoma Corydalis, and Radix Aucklandiae are used to promote qi movement and unblock collaterals, for "when the Governor Vessel is unblocked, all diseases subside".

As for yang-tonifying medicinals such as Fructus Psoraleae, Treatise on Medicinal Properties records: "It tastes bitter and pungent. It can treat lumbago, cold knees and scrotal dampness in men, expel stubborn cold Bi, control frequent urination, and relieve abdominal cold." It exerts remarkable effects on Bi pain of kidney-yang deficiency pattern. Pharmacological studies show that active ingredients of Fructus Psoraleae can promote proliferation and differentiation of osteocytes and ameliorate osteoporosis [21].

On the other hand, long-standing Bi Syndrome consumes liver-kidney essence and blood and leads to nutrient blood deficiency. Ordinary herbal medicinals without sentience often fail to achieve satisfactory effects. As stated in Clinical Guide to Medical Cases: "Essence and blood are endowed with sentience. Tonification with insentient herbs cannot match their properties. Cinnamon and Aconitum are forceful and fierce in nature. Essence and blood are stored in zang-organs, and the substance of zang-organs pertains to yin… Medicinals of flesh and blood nature cultivate the body's essence and blood. Yet gentle therapies yield no immediate effects; persistent use will bring benefits."

Ye Tianshi adopted medicinals of flesh and blood nature such as Carapax Testudinis and Carapax Trionycis to replenish liver blood and kidney essence. Regarding yin-tonifying medicinals like Carapax Testudinis, Compendium of Materia Medica records: "Both turtle and deer are spiritual… The turtle can unblock the Conception Vessel, so its shell is used to tonify the heart, kidney and blood, all for nourishing yin." Modern pharmacological research demonstrates that Carapax Testudinis can boost immunity, strengthen bones, resist aging and alleviate osteoporosis [22].

Ye Tianshi attached great importance to the mode of tonification. He advocated the principle: "Use shell medicinals to subdue yang, sour medicinals to astringe, and medicinals with thick flavors to calm." He was adept at using thick-flavored medicinals including Carapax Testudinis, Carapax Trionycis and Colla Corii Asini to replenish essence and blood in the lower origin; sour astringent medicinals such as Fructus Mume, Fructus Chaenomelis and Fructus Schisandrae to restrain floating liver yang; heavy medicinals such as Magnetitum and Os Draconis to subdue yang. These medicinals can not only tonify the liver and kidney, but also unblock the extraordinary meridians, targeting the pathogenesis precisely.

As Li Shizhen wrote in Study on the Eight Extraordinary Meridians: "Physicians ignorant of this cannot explore pathogenesis; alchemists ignorant of this cannot stabilize the furnace tripod." Tonifying the liver and kidney, nourishing blood and unblocking collaterals can delay or indirectly inhibit the occurrence of immune inflammation, improve the local inflammatory microenvironment, suppress osteoclast differentiation and ameliorate osteoporosis. Meanwhile, tonifying the liver and kidney can promote the differentiation of bone marrow mesenchymal stem cells into osteoblasts and accelerate bone formation [23].

5. Summary

The effects of collaterals disease on the onset of ankylosing spondylitis are summarized as follows: Malnourishment of qi and blood and disharmony of collaterals constitute the pathogenic basis of ankylosing spondylitis, which generate substantial excess pathogens including phlegm, blood stasis and toxin. These substantial excess pathogens in turn further aggravate the obstruction of collaterals. Therefore, understanding the interaction between malnourished collaterals and pathogenesis induced by excess pathogens can provide better ideas for the etiological exploration and clinical treatment of ankylosing spondylitis in traditional Chinese medicine. Applying the innovative collaterals disease theory to guide clinical practice is of great significance for promoting disciplinary development.

Collateral-unblocking therapies such as pungent-cool diffusion and venting, diffusing and unblocking Sanjiao, tonifying the liver and kidney, and searching and expelling pathogens with insect medicinals offer novel therapeutic approaches for ankylosing spondylitis. However, clinical patients present highly variable symptoms and signs with numerous accompanying symptoms. Hence, extreme caution must be taken in clinical practice. Accurate syndrome differentiation will definitely achieve superior clinical efficacy.

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