



Treating Benign Accumulation Pattern in Young and Middle-Aged Women According to the Theory of Yang Stagnation

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Abstract

Keywords

- ▶ yang stagnation
- ▶ accumulation pattern
- ▶ thyroid nodule
- ▶ nodules and uterus
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- ▶ unblocking yang method
- ▶ six depression

Benign breast nodules, thyroid nodules, and myoma of the uterus are similar in etiology and pathogenesis. These three diseases are classified according to accumulation patterns in traditional Chinese medicine theory and can be treated with the same prescription. Yang stagnation is the basic pathogenesis of benign accumulation patterns in young and middle-aged women. Its treatment principle should be “unblocking yang,” and its treating methods should include diffusing yang, warming yang, dissolving phlegm, and dissipating stasis, which can unblock yang qi and dissolve stasis. Meanwhile, heart-nourishing and mind-calming ingredients should be included in the prescriptions to improve the clinical manifestations.

In recent years, breast nodules, thyroid nodules, and uterine myoma are more commonly encountered in clinical practice. They are commonly seen among women aged 30 to 40 years.^{1–3} Breast nodules and thyroid nodules may turn into cancer. Although uterine myoma is benign, it may cause symptoms like hypermenorrhea, peripheral organ compression, and infertility, two or more of which are often found in one of the patients. Dong et al⁴ confirmed that the incidence of these three diseases was positively correlated, which seriously harmed the physical and mental health of women patients who desire treatment. From the view of modern medicine, these three diseases belong to different departments. In treating them, close follow-up or surgery is often required. However, the efficacy was not satisfactory and patients suffered from heavy mind-load. When they turned to traditional Chinese medicine (TCM) for help, patients mostly hope their diseases to be treated with one prescrip-

tion. How to control or eliminate the nodules with the theory of syndrome differentiation is a problem to be solved in TCM clinical practice.

Breast nodules, thyroid nodules, and uterine myoma belong to “accumulation pattern” in TCM theory. “Accumulation” generally refers to all the masses formed in the human body. According to their characteristics and location, they can be divided into concretion, conglomeration, cord-like mass, lump, tumor, and cancer.⁵ Accumulation in blood level is a tangible mass and is fixed while accumulation in qi level may migrate. According to the historical literature on the etiology, pathogenesis, and clinical characteristics of breast nodules, thyroid nodules, and uterus myoma, these three kinds of diseases can be classified according to benign accumulation patterns. The research team has found in TCM clinical practice that the benign accumulation pattern in young and middle-aged women is closely related to yang stagnation.

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Yang Stagnation Is the Basic Pathogenesis of Benign Accumulation

Historically, TCM focuses on the liver in treating benign accumulation patterns in young and middle-aged women.^{6,7} With “failure of liver to govern the flow of qi” as the main pathogenesis and “soothing the liver to propel qi” as the main treatment principle, certain clinical efficacy can be obtained. However, there are several clinical manifestations, such as irritability, facial acne, thirst, and constipation, which cannot be explained by the theory of “liver fails to govern the flow of qi.”

It can be learned from related literature that Chinese medicine can alleviate patients' symptoms of breast diseases, thyroid nodules, and uterus adenomyosis by using the “six depression” theory.⁸⁻¹⁰ The above-mentioned symptoms which could hardly be explained by “failure of liver to govern the flow of qi” can also be effectively alleviated with the theory of yang stagnation.^{11,12} The six stagnations, however, is part of the yang stagnation theory.¹³ Guided by Prof. Wanlin Wang, the national famous TCM expert, the research team has been working for many years on benign accumulation patterns in young and middle-aged women and has pointed out that yang stagnation is the basic pathogenesis. Andao Wang stated in *Discourse on Tracing Back to the Medical Classics (Yi Jing Su Hui Ji)* that “All diseases occur because of stagnation.” Based on this, he made prescriptions to alleviate the symptoms of many female patients with this pattern. Therefore, the research team believes that most clinical manifestations of benign accumulation patterns in young and middle-aged women are caused by stagnated yang qi which cannot be propelled to the whole body.

Many modern practitioners also treat benign accumulation patterns in young and middle-aged women from the point of stagnation. Academician Tong¹⁴ believes that the etiology of the triad is qi stagnation, blood stagnation, and phlegm stagnation, which shall be treated with the main principle of releasing stagnation, dissolving phlegm, dissipating masses, and unblocking the meridians. The main treatment methods shall be dissolving the stagnation and tonifying the deficiency. In treating thyroid nodules, mammary hyperplasia, and uterine myoma, professor Lin¹⁵ believes that it is most important to unblock qi movement and restore its function of ascending, descending, exiting, and entering. Methods that dissolve phlegm, invigorate blood, and dissipate stasis are all effective. It can be observed from the formulas that mostly have unblocking ingredients in them, which implies that benign accumulation patterns shall be treated from the view of yang stagnation.

Yang stagnation means that yang qi is blocked in the body and fails to warm. Although yang qi is blocked, it is not deficient. Young and middle-aged women are in a physiological period when yang qi is exuberant. In the *Yellow Emperor's Inner Classic (Huang Di Nei Jing)*, they are described as “At the age of 28, their muscles and bones are strong and hair grows best; at the age of 35, large intestine meridian and stomach meridian turn weak, their faces start to turn yellow and hairs start to fall.” With improving living conditions and

life expectancy nowadays, the average age of natural menopause for Chinese women is 49 ± 3.7 years old.¹⁶ Therefore, modern women are still in their prime at their thirties, and their yang qi is not deficient. According to clinical observation, yang deficiency manifestations such as cold hands and feet, sore waist and knees, clear and long urine, and loose stools are not common in young and middle-aged women. Therefore, the research team believes that most symptoms that are seen in patients with yang stagnation are not caused by yang deficiency but by too much yang qi blocked inside, which cannot be dispersed.

Discussion on the Theory of Yang Stagnation

Literature Review on Yang Stagnation Theory

“Yang stagnation” originated from *the Yellow Emperor's Inner Classic (Huang Di Nei Jing)*. The book recorded many causes of stagnation of yang qi, like wind being restrained by coldness, coldness stagnating with dampness, pathogen qi invading the body, and coldness remaining in the stomach. Practitioners in later generations discussed yang stagnation from the theory of “dispersing the stagnated fire,” which overrode yang stagnation with fire stagnation, thus hindered the development of yang stagnation.

By the time of Song and Yuan Dynasties, practitioners had understood deeper about yang stagnation theory. In *Key to Diagnosis and Treatment of Children's Diseases (Xiao Er Yao Zheng Zhi Jue)*, Yi Qian noted that the stagnation of lung fire should be treated with White-Draining Powder (Xie Bai San), hidden fire in the stomach by Yellow-Draining Powder (Xie Huang San), and stagnated fire in heart meridian by Red-Guiding Powder (Dao Chi San). Danxi Zhu discussed yang stagnation with the six-stagnation theory.

Practitioners in Ming Dynasty took depression as the primary cause of stagnation. For example, Xianke Zhao mentioned in the treatise of depression syndrome of the *Key Link of Medicine (Yi Guan)* that “Depression causes dampness stagnation, which turns into heat, heat stagnation produces phlegm and blood circulation will be affected, blood stagnation affects food digestion. These six symptoms play as causes and results.” This point of view further restricted the development of the theory of yang stagnation. Since Qing Dynasty, yang stagnation has gradually become mature. For example, Mengyao He said in *A Steppingstone of Medicine (Yi Bian)* that “Stagnation means blockage, which is the cause of many diseases.”

With the continuous development of the yang stagnation theory, the idea of TCM diagnosis and treatment has been expanded and the system of TCM clinical syndrome differentiation has been enriched.

Circulation Is the Key Factor to Yang Qi

Through ascending, descending, exiting, and entering, yang qi plays a dominating role in the growing process of the human body. Yang qi is active, it goes in all directions and enters all organs and collaterals. It moves ceaselessly in the body. Once it is stagnated, diseases may occur.¹⁷ In *Su Wen: Liu Wei Zhi Da Lun (Plain Conversations:Major Discussion on*

the *Abstruseness of the Six Kinds of Qi*) it is stated that “Without exiting and entering, there is no developing process; without ascending and descending, there is no growing circle. Ascending, descending, exiting and entering exist in all living things.”

In qi transformation of human body, qi pertains to yang while essence pertains to yin. Qi keeps moving and consumes energy, which turns into yin essence to nourish organs and meridians. After metabolism, yin essence turns into qi which promotes the human body to growth. Only through this continuous circulation can a status of dynamic balance be kept and a physiological status of calm yin and sound yang be obtained. Therefore, circulation is the key to yang qi.

Yang Qi Functions to Warm and Dissipate

Su Wen:Sheng Qi Tong Tian Lun (Plain Conversations:Discussion on Interrelationship Between Life and Nature) states that only when yin is calm and yang is sound, essence-spirit can be normal, which emphasizes that the dynamic balance of yin and yang is the secret to human health and longevity. The book also states that yang transforms into qi, while yin constitutes form, which stresses that the basis of qi transformation is yang and the basis of formation is yin. Only through warming, scattering, and circulating in the human body can qi be normally transformed. Only in the same way can the nutrient substance go to its proper location. With no stagnation of yin-essence, there will not be the pathogenic status of yang transforming into qi or yin constituting form.

Normal human life activities are indispensable to the warming function of yang qi, which covers the whole body. When yang qi fails to warm the organs, functions that heart governs spirit, lung frees and regulates the waterways, spleen governs transportation and transformation, liver governs the free flow of qi, the kidney stores essence will be affected and all diseases emerge. Therefore, yang qi has to keep warming the organs and meridians, as well as warming qi, blood, and body fluids.

Yang Stagnation May Cause Phlegm and Stasis, Making a Vicious Circle of Yang Stagnation-Phlegm Stasis-Worse Stagnation

There is a saying in *Su Wen:Sheng Qi Tong Tian Lun (Plain Conversations:Discussion on Interrelationship Between Life and Nature)* that “The relation of yang qi and human body is similar to the relation of the sun and the sky. Once yang qi is weakened, human health will be affected.” It emphasizes that yang qi is the basis of human life activities. Once it fails to function properly, human life will be threatened. It is also stated in *Su Wen:Baoming Quanxing Lun (Plain Conversations:Discussion on Preserving Health and Protecting Life)* that “Yang is active and is the source of human energy.” Yang qi is active and circulates around the whole body, propelling the transformation of blood essence and body fluid. It nourishes limbs, bones, and zang-fu organs. Once there is stagnation, blood essence and body fluid will not be dissipated to the whole body to nourish zang-fu organs and meridians. They stagnate in the body and tend to produce phlegm and stasis, which may turn into accumulation. It is stated in *Complete*

Medical Records by Tianshi Ye (Ye Tian Shi Yi An Da Quan) that “Turbid yin coagulates where yang qi fails to reach.” *Introduction to Medicine (Yi Xue Ru Men)* points out that “Qi cannot become a mass. Masses are formed by tangible substances like food accumulation or blood stasis. They coagulate and become conglomerations.”

When phlegm stasis is formed and blocks organs and meridians, it affects the circulation of yang qi. When yang qi is stagnated, yang stagnation will be more serious and phlegm stasis in zang-fu organs will be worse. With time it may turn into a vicious circle of yang stagnation-phlegm stasis-worse stagnation. The imbalance of yin and yang in this vicious circle has exceeded the normal self-healing function of the human body and is difficult to restore.

Chronic Yang Stagnation May Turn into Fire

Yang qi must flow freely. It cannot be stagnated because stagnation is most likely to be transferred into fire and heat. In addition, pathological products like blood stasis and phlegm coagulation may be produced because of yang stagnation. When this kind of qi, phlegm, and stasis are coagulated, it is also easy to turn into pathological status of fire and heat.¹⁸ There may be many clinical manifestations like feeling irritated easily, bitter taste in the mouth, often feeling thirsty, preference for cold food, getting “fire” easily, insomnia, profuse dreaming, red tongue with a yellow greasy coating, and rapid wiry pulse. Shima Li, one of the Masters of Chinese Medicine, stated in *Discussing Febrile Disease by Pulse Checking and Syndrome Differentiation (Ping Mai Bian Zheng Wen Zheng Qiu Suo)* that “Yang qi is the healthy qi of human body, it nourishes organs, limbs and bones by ascending, descending, exiting, entering and ceaselessly circulating...Once qi movement is constrained... the stagnation will turn into fire.”

In conclusion, only through circulation can yang qi work properly in the human body. Once it stagnates in the organs and meridians, pathogenic products like phlegm-damp and blood stasis will be produced. These pathogenic products, circulating with qi movement, will not stay fixed. They become breast nodules when stagnated in mammary glands, thyroid nodules when stagnated in the neck area, and uterus tumor when stagnated in the uterus. When yang qi is stagnated for a long time, it may move from the qi level to the blood level and keep qi, phlegm, and stasis in the body. These pathogens, cold or warm, will tangle together and could not be eliminated within a short time. These chronic accumulation disorders may recur after surgery or develop into a malignant tumor.

Discussion on Benign Accumulation Pattern with the Theory of Yang Stagnation

Treating Breast Nodules, Thyroid Nodules, and Uterus Tumor with the Same Method

Breast nodules, thyroid nodule, and uterus tumor are all endocrine diseases. They are affected and regulated by the chain of hypothalamus-hypophysis-gland. Regulating hormones shall be the key to treating these three diseases.

Hormones shall be supplemented, accelerated, or inhibited, to make the disordered endocrine system work properly.

In TCM theory, there is similar pathogenesis in these three diseases. It is stated in *Compiled Case Records of External Syndromes (Wai Zheng Yi An Hui Bian)* that “Breast diseases are all stagnation in the liver and spleen that turn into lumps.” In *Formulas to Aid the Living (Yan Shi Ji Sheng Fang)*, it is stated that “Goiters mainly grow in the necks while tumors are produced in muscles along with qi movement. Tumor may bulge abruptly like a plum and grow bigger with time.” *Orthodox Lineage of External Medicine (Wai Ke Zheng Zong)* recorded that “Goiters or tumors are not produced by healthy qi but are formed because of blood stasis in five organs or turbid qi and phlegm stasis.” In *Secrets to Conception (Yun Yu Xuan Ji)*, it is mentioned that “Most of these diseases are caused by lack of blood and qi in the liver and spleen, or stagnation in these organs.” From these literature studies, we can conclude that these three diseases are located in the liver and spleen. Depression hurts the liver and anxiety hurts the spleen. Both emotions affect the ascending, descending, exiting, and entering of qi. Qi pertains to yang, so the dysfunction of qi movement may produce pathological products like phlegm and stasis, which coagulate and become an accumulation.

The accumulation pattern discussed in this thesis includes different diseases, which, however, not only share the same basis of physiopathology from the view of modern medicine but also share similar pathogenesis from the view of TCM. Therefore, they can be treated with the same method.

Unblocking Yang Is the Key to Treat Yang Stagnation

In *Su Wen:Sheng Qi Tong Tian Lun (Plain Conversations: Discussion on Interrelationship Between Life and Nature)*, it points out that yang dominates the balance of yin and yang. The book emphasizes that only when yang qi functions well can health be maintained. Every step of human growth, people's social life and work, as well as emotion regulation all depends on yang qi to drive. The basic pathogenesis of benign accumulation patterns in young and middle-aged women is yang stagnation. Yang qi shall be active and it dominates ascending, so it cannot be stagnated. Therefore, unblocking yang should be the basis in treating benign accumulation patterns in young and middle-aged women. When yang qi is unblocked, qi and blood can move smoothly, in which circumstance stasis and pathogen toxin are not likely to be formed. Then, the stagnation disease is cured and the symptoms disappear.

Effect of Unblocking Yang

The Primary Purpose Is to Diffuse Yang Qi

In six stagnation in the *Teachings of Danxi (Dan Xi Xin Fa)*, Danxi Zhu stated that “When qi and blood are in harmony, no disease will occur; when a man is down in emotion, diseases take place. That is to say that many diseases are caused by depression.” It stresses that emotion is a common factor of diseases. Depression is a pathological factor of accumulation syndromes, so diffusing yang qi shall be the first step to

eliminate stagnation. Patients with reversal cold in the limbs or pain in stomach and rib-side areas should be treated with modified Frigid Extremities Powder (Si Ni San) to soothe liver, alleviate stagnation, and unblock yang qi; patients with stagnated fire in liver and bladder, whose yang qi is stagnated in bladder meridian, and has symptoms like bitter mouth, constipation, and irritation should be treated with modified Minor Bupleurum Decoction (Xiao Chai Hu Tang) to regulate qi movement, dissipate stagnated fire in liver and bladder, and unblock yang qi. Diffusing ingredients like Sangzhi (Mori Ramulus), Xiakucuo (Prunellae Spica), Guizhi (Cinnamomi Ramulus), Jiegeng (Platycodonis Radix), Xiebai (Allii Macrostemonis Bulbus), Niuxi (Achyranthis Bidentatae Radix), and Zhike (Aurantii Fructus) can also be used.

Yang Qi Circulates Freely When Phlegm Is Dissolved and Stasis Is Dissipated

Diseases are mostly caused by phlegm. Phlegm and dampness are body fluids not being transformed properly. They share the same origin but have their own characteristics. They are both nonnegligible pathogenic factors in the formation of accumulation pattern. Banxia (Pinelliae Rhizoma), Zaojiaoci (Gleditsiae Spina), Zhebeimu (Fritillariae Thunbergii Bulbus), Baijiezi (Sinapis Semen), Muli (Ostreae Concha), Biejia (Trionycis Carapax), and Haigeqiao (Meretricis Concha Cyclinae Concha) can be used to dissolve phlegm and unblock yang qi; five substances powder with Poria (Wu Ling San) should be used to drain dampness and unblock yang qi. Qi and blood shall be circulating ceaselessly. Its circulation is warmed and propelled by yang qi. If yang qi is stagnated, blood would turn into stasis, which shall be eliminated by herbs that invigorate blood and dissolve stasis to clear the running path of yang qi and restore its function to unblock yang qi and eliminate accumulation. Sanleng (Sparganii Rhizoma), Ezhu (Curcumae Rhizoma), Taoren (Persicae Semen), and Honghua (Carthami Flos) are most commonly used in clinical practice; yang stagnation is likely to turn into fire and heat, and tangible excess pathogen also generates toxic heat.¹⁷ Herbs which can clear heat, resolve toxins, and dissipate stasis, such as Pugongying (Taraxaci Herba), Xiakucuo (Prunellae Spica), Chonglou (Paridis Rhizoma), Zhimu (Anemarrhenae Rhizoma), and Shancigu (Crematae Pseudobulbus Pleiones Pseudobulbus) can be used to drain heat and unblock qi.

After eliminating the tangible excess pathogens like phlegm and stasis, yang qi will move freely around the whole body. It will function to propel, transform qi and warmth, driving the body fluids into their proper path and make it nourish the body. And the vicious circle of yang stagnation–phlegm stasis–worse stagnation will be relieved.

It Is Necessary to Warm Yang While Unblocking Yang Qi

It is stated in *Spiritual Pivot (Ling Shu)* that “Accumulation starts because of coldness. Then it develops into disease.” This sentence suggests that coldness is an important pathogenic factor in forming an accumulation pattern. Furthermore, when there is yang stagnation in the human body, warming herbs shall be used to generate mild fire and

produce qi. Deficiency and stagnation of yang qi interact as both cause and effect; therefore, warming and unblocking yang shall be performed simultaneously. They complement each other and are inseparable.

Yang stagnation, in essence, is not a deficiency in yang qi. Therefore, tonifying medicinal shall not be used, one of the reasons is that strong fire consumes qi and the other is that it may enlarge the stagnated fire which consumes yin essence, which may cause the syndrome of yin deficiency. However, mildly tonifying herbs like Bajitian (*Morindae Officinalis Radix*), Roucongrong (*Cistanches Herba*), Yinyanghuo (*Epimedii Herba*), and Tusizi (*Cuscutae Semen*) can be used, but their dose should not be large.

Heart-Nourishing and Mind-Calming Herbs Can Be Added to Unblock Yang Qi

Li et al⁶ have proved that benign accumulation in young and middle-aged women has related to the disorder of female hormones. Jing et al¹¹ report that the change in female hormones largely affects women's emotion. Female patients are easy to feel sad or angry before and during menstruation. Emotion is the main factor that forms accumulation syndrome; therefore, heart-nourishing and mind-calming herbs, combined with comforting words, are effective and are recognized by patients. Zhizi (*Gardeniae Fructus*), Dandouchi (*Sojate Semen Praeparatum*), Baihe (*Lilii Bulbus*), Zhimu (*Anemarrhenae Rhizoma*), Lianzixin (*Nelumbinis Plumula*), Baiziren (*Platycladi Semen*), Honeyed Yuanzhi (*Polygalae Radix*), and Hehuanhua (*Albiziae Flos*) are most commonly used.

With the improvement in the living standard, the diet of modern people has changed greatly. Many people nowadays prefer oily and salty food, some of which cannot be digested by the spleen and stomach and leads to accumulated phlegm and food remaining. Therefore, ingredients to fortify the spleen, like Maiya (*Hordei Fructus Germinatus*), Shanzha (*Crataegi Fructus*), Shenqu (*Medicata Fermentata*) can be added to strengthen the function of transportation and transformation. Benign accumulation syndrome may become cancer. Guided by the principle of preventing the existing disease from developing, toxin-resolving or anticancer herbs like Shancigu (*Cremastrae Pseudobulbus Pleiones Pseudobulbus*), Banzhilian (*Scutellariae Barbatae Herba*), and Shijianchuan (*Salviae Chinensis Herba*) can be added.

Recognition of the Method of Unblocking Yang Qi by Modern Medicine and Pharmacology

Yang stagnation is the basic pathology of benign accumulation syndrome in young and middle-aged women. Unblock yang is its key treatment method. In treating breast nodules, thyroid nodules and uterine myoma, Tang¹⁹ and Xia²⁰ use a single or combination of ingredients which can unblock yang qi, soothe the liver, promote urination, dissolve phlegm, dissipate stasis, warm yang, and clear heat. From databases like CNKI, ChinaInfo, VIP, and PubMed, Zhang et al²¹ have retrieved totally 567 Chinese herbal compounds which treat hyperplasia of mammary glands, thyroid nodule, and uterine myoma. All these formulas' ingredients have the functions of heat-clearing, tonifying, phlegm dissolving,

cough-alleviating, blood invigorating, and stasis dissolving. All the compounds include warming ingredients to help yang qi circulate. There are also ingredients to drain stagnated heat. All these methods are applied to alleviate clinical symptoms and improve the patients' living quality.

Modern pharmacology also showed that herbs which unblock yang qi, soothe the liver, dissolve phlegm, dissipate stasis, warm yang, dissipate masses, and clear heat can alone or together improve the inner environment of the human body. For example, the combination of Guizhi (*Cinnamomi Ramulus*)-Fuling (*Poria*) can increase urine volume in mice and has a long-lasting diuretic effect, which proves that five substances powder with Poria (*Wu Ling San*) is effective in unblocking yang and promoting urination²²; the combination of Guizhi (*Cinnamomi Ramulus*) and Taoren (*Persicae Semen*) has an anticoagulate effect and is more effective than a single ingredient, which shows that the function of unblocking yang qi of *Ramulus Cinnamomi* promoted the function of dissipating stagnation of *Semen Persicae*²³; the combination of Gualou (*Trichosanthis Fructus*) and Xiebai (*Allii Macrostemonis Bulbus*) has the function of reducing phlegm and relieving cough, antiatherosclerosis, antiplatelet aggregation, and antitumor, which shows that herbs to unblock yang qi, propel qi, and dissolving phlegm combined can eliminate the pathogenic products like phlegm and stasis²⁴; warming ingredients like Bajitian (*Morindae Officinalis Radix*), Yinyanghuo (*Epimedii Herba*), and Tusizi (*Cuscutae Semen*) all have the function of antitumor and regulating sex hormone²⁵; costunolide (*Cos*) and dehydrocodeno lactone (*Dehy*) which are contained in Pugongying (*Taraxaci Herba*), Gualou (*Trichosanthis Fructus*), Chaihu (*Bupleuri Radix*), and Muxiang (*Aucklandiae Radix*) are anti-breast cancer active ingredient. They can prevent the existing disease from developing.²⁶

Conclusion

Benign accumulation pattern is becoming a kind of commonly encountered disease in young and middle-aged women. It is urgent to study its pathogenesis and to discuss its treatment method. Yang stagnation is the basic pathogenesis of this pattern. Unblock yang is its basic treatment method, which embodies the theoretical characteristics of syndrome differentiation of TCM. Considering the physical characteristics of the patients in this age, the evolving rule of yang stagnation-phlegm stasis-worse stagnation is precisely applied. It has important practical guiding significance for preventing and treating benign accumulation patterns in young and middle-aged women.

CRedit Authorship Contribution Statement

W.Z. and Z.L. were responsible for writing—original draft, investigation, conceptualization. X.C., B.W. and H.Z. were responsible for supervision, funding acquisition, and writing—review and editing.

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Conflict of Interest

The authors declare no conflict of interest.

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