

Advancements in Medication Rule for Pulmonary Nodules: A Review of Current Research Progress

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Abstract

This paper reviewed the literature on medication rule of pulmonary nodules in recent years. It is found that contemporary doctors pay more attention to regulating Qi, clearing heat and detoxifying, eliminating phlegm, dissolving phlegm and dissipating masses. They use mild drugs, cold and warm treatments in parallel, combining the tastes of pungent, bitterness, and sweetness at the same time. The treatment focuses on the five viscera with emphasis on the lung meridian while also considering the spleen and stomach functions as well as soothing liver stagnation. This information aims to provide some reference for clinical treatment of pulmonary nodules.

Keywords

Pulmonary Nodules, Medication Rule, Review

1. Introduction

Pulmonary nodules are focal, circular, dense solid or subsolid pulmonary opacities with a diameter of ≤ 3 cm in the lung. They can occur as isolated lesions or multiple lesions and are typically not associated with atelectasis, hilar lymphadenopathy, or pleural effusion [1]. With the widespread use and increasing utilization of computerized tomography (CT), there has been a significant rise in the global detection rate of pulmonary nodules, which is approximately 20% [2]. There exist variations in the assessment and management of pulmonary nodules across different populations [3]. Typically, follow-up is the primary approach to

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managing detected nodules, leaving patients with a predicament of ‘easy detection but difficult treatment’. In traditional Chinese medicine, there is no direct equivalent term for pulmonary nodules; instead, doctors often refer to them as ‘lung accumulation’, ‘cough’, ‘asthmatic disease’, or other syndromic treatments [1] [4]. The intervention of Traditional Chinese medicine in pulmonary nodules can effectively manage symptoms, enhance physical well-being, and induce local nodule control and shrinkage in certain patients. Additionally, as a complementary alternative therapy unsuitable for surgical procedures, it can also alleviate patient anxiety [4]. Currently, numerous researchers have investigated the rule of medication in the treatment of pulmonary nodules, with each physician exhibiting unique medication characteristics. However, no scholars have yet conducted comprehensive studies or explored their commonalities. Therefore, this review aims to synthesize recent literature on medication rule for pulmonary nodules, providing valuable clinical references for treatment strategies. The subsequent sections present a detailed analysis.

2. Common Treatment

2.1. Pay Attention to Conditioning Qi Machine

2.1.1. Reinforcing Qi to Rectify Qi Deficiency

The results of numerous studies consistently indicate that the average age at which pulmonary nodules are typically detected is approximately 50 [5]-[11], in line with previous research [12] [13]. During this stage, individuals aged over 50 often experience physiological deficiencies and a weakened positive Qi, rendering them susceptible to external pathogens exploiting their vulnerabilities. Furthermore, internal pathogenic factors can easily arise due to the deficiency in positive Qi, leading to the accumulation of pathological substances within the lungs and subsequent formation of nodules. Contemporary doctors believe that the basic pathogenesis of pulmonary nodules involves deficiency-excess complex, and the main treatment should focus on supporting healthy Qi while also incorporating exorcism [1] [4]. Some studies have indicated that Qi deficiency is the primary syndrome elements in pulmonary nodules [14], so contemporary doctors use Qi-supplementing herbs for treating pulmonary nodules, such as astragalus, *atractylodis macrocephalae rhizoma*, *codonopsis pilosula*, *dioscorea opposita*, and *pseudostellaria heterophylla* [5] [15] [16] [17] [18]. The commonly used drug combinations include *Radix pseudostellariae*—Yam [19], *Radix Codonopsis*—Tuckahoe [17], *Radix pseudostellariae*—Tuckahoe [20] [21], *Platycodonopsis platycodonopsis*—Yam [9], *Radix Astragalus*—*Radix pseudostellariae* [18], *Radix Astragalus*—*Radix pseudostellariae* [14], *Radix Astragalus*—*Frangipani* [22] and so on.

2.1.2. Regulating Qi to Relieve Qi Stagnation

Pulmonary nodules are tangible and pathogenic, making them susceptible to obstructing the flow of Qi in the body’s energy system. Therefore, contemporary medical practitioners often focus on regulating Qi by supplementing it to alle-

viate stagnation in the Qi machinery. Professor Pang Lijian suggests that stagnation of Qi is a precursor to the formation of pulmonary nodules. This stagnant Qi hinders the transportation of body fluids, leading to accumulation and ultimately resulting in nodule formations. The combination of Codonopsis Radix and Bupleurum is commonly used to promote optimal circulation and relaxation of Qi for improved health [23]. Chief physician Zhou Dayong emphasized that in the early stage of pulmonary nodules, they are primarily formed due to the consolidation of Qi, phlegm, and dampness in the lungs. Therefore, it is essential to regulate Qi and eliminate phlegm while ensuring proper correction. This approach helps prevent the accumulation of blood stasis, toxins, and even malignant transformation over time [9]. Professor Lyu Xiaodong utilized costus-curcumae radix medicine for the treatment of pulmonary nodules, as the former plays a pivotal role in enhancing Qi circulation while the latter primarily focuses on promoting blood flow. The synergistic effect of these two medications enables direct regulation of the pathogenesis associated with pulmonary nodules by effectively balancing both Qi and blood [24]. Qi regulation is a common treatment for pulmonary nodules by Professor Shi Suofang, which includes soothing liver Qi using traditional Chinese medicines such as incense, curcumae radix, and Qingpi; conditioning lung Qi using traditional Chinese medicines like platycodon, almonds, and Perilla seeds; and tempering with traditional Chinese medicines like orange peel, fructus aurantii, and wood fragrance [25]. Chief physician Ma Zhanping attaches great importance to the pathogenesis of pulmonary nodules associated with “depression”. He often utilizes bitter almond and Perilla leaves, which can help regulate the Qi mechanism and resolve phlegm and blood stasis by promoting Qi circulation [26].

2.2. Clearing Heat and Detoxifying, Resolving Phlegm and Clearing Knot

Pulmonary nodules are mainly diagnosed by imaging. They are nodules due to the accumulation of evil air in the lungs, such as benign and malignant tumors and inflammatory granulomatosis. Visible turbidity of phlegm obstructing the lungs is an important pathogenesis of pulmonary nodules [15]. Patients with pulmonary nodules tend to have a long disease course, and those with prolonged dampness and heat in the phlegm are common physical types associated with pulmonary nodules [5] [27], while accumulation of heat in the lungs is a common type of pulmonary nodules [8] [17]. Therefore, treatment should focus on clearing heat, detoxifying phlegm, and dissipating it. Professor Luo Xiuli often uses Thunberg Fritillium and oyster to clear heat, resolve phlegm, soften hardness, and dissipate knots. This combination is the core drug pair for eliminating phlegm and dissolving knots [7]. Professor Xu Li pointed out that if spleen dampness does not move, internal obstruction of phlegm dampness occurs along with liver disorder and blocked Qi. This leads to non-coagulation of phlegm dampness and a higher susceptibility to pure glass nodules. Therefore, tangerine peel-pinellia is commonly used in patients with spleen-deficient phlegm damp-

ness to eliminate phlegm and regulate Qi in the middle [28]. Professor Song Kang emphasized that heat toxicity plays a pivotal role as the primary pathogenic factor in the development of pulmonary nodules. Heat toxicity disrupts bodily fluids and depletes Qi, leading to the formation of phlegm, blockage of veins, and accumulation. In clinical practice, silkworm rigid-dilong medicine is commonly employed for detoxification purposes while simultaneously promoting blood circulation, eliminating phlegm, and resolving obstructions [29].

3. Characteristics of Drug Usage

Extensive research has been conducted on the characteristics and preferences of contemporary physicians in the management of pulmonary nodules, revealing their inclination towards prescribing medications classified as cold, warm, flat, pungent, bitter or sweet [6]-[11] [22] [23] [24] [25] [30] [31] [32] [33] [34].

3.1. Utilize both Cold and Warm, Gentle Medication

The majority of physicians employ cold, warm, and neutral pharmacotherapies for the management of pulmonary nodules, whereas only a minority utilize both cooling and heating medications. The pulmonary nodules primarily occur in the lungs, which are delicate and sensitive to temperature changes. Hence, a combination of cold, warm, and neutral drugs is prescribed to harmonize their effects for better therapeutic outcomes without causing harm or irritation to the lung tissues. This strategy aims at regulating Yin and Yang.

3.2. Pungent Dispersing and Bitter Descending, Willing to Soft Lung

Professor Hu Guojun posits that the development of pulmonary nodules is attributed to the prolonged interaction between phlegm and Qi, coagulation of blood, as well as astringency [6]. Professor Lyu Xiaodong posits that the pathogenesis of this condition is primarily attributed to liver depression and Qi stagnation, which ultimately culminate in the development of phlegm and blood stasis over an extended duration. Moreover, a prolonged period of time will also result in deficiency of Yang Qi and the inability to resolve knots. Wang Hui, a nationally renowned TCM practitioner, believed that pulmonary sarcoidosis initially presented with no obvious clinical symptoms, which he referred to as “ju”. However, in the later stages of lesion progression, the symptoms became significant and diverse, a phenomenon he called “ji” [30]. Director Wang Sheng believed that the deficiency of healthy Qi was the basis for pulmonary nodules, and that spittoon and coagulation of Qi stagnation, blood stasis, and poison knot were its basic pathogenesis [32]. Professor Zhang Nianzhi pointed out that the pathological basis of pulmonary nodules is the imbalance of Qi and blood, and the main pathological factors are phlegm turbidity and blood stasis [17]. Professor Gong Hongwei believes that the basic pathogenesis of pulmonary nodules involves a deficiency in positive Qi and an excess of evil, as well as deficiencies in

positive Qi, stagnation of Qi, interwoven phlegm and blood stasis leading to accumulation [8]. Professor Zheng Weiqin proposed the theory of “qi imbalance”, which suggests that prolonged imbalances in Qi can lead to abnormal activity in essence, blood, and body fluids, resulting in the formation of pathological substances such as phlegm, stasis, dampness, and toxicity. Over time, these substances accumulate and aggregate into nodules [18]. It can be seen that most doctors believe that the basic pathogenesis of pulmonary nodules is the deficiency of healthy Qi, which leads to the accumulation of sputum, dampness, blood stasis, and other evil Qi in the form of nodules. Pungent can open the lungs, bitterness can clear the lungs, Gan can moisturize the lungs. Pungent medicinals have a drying effect, while bitter medicinals promote the descent of Qi. This is also in line with the physiological characteristics of the lung, which prefers moistening and dislikes dryness. The herb pungent possesses the ability to enhance the movement of Qi and blood, alleviate Qi stagnation within the body, and prevent blood stasis in the lungs. Bitterness exhibits properties that can effectively eliminate dampness, strengthen lung function, counteract dryness caused by pathogenic factors, and when combined with sweetness, it can also mitigate potential harm from excessive bitter and warm attributes on pulmonary health. Consequently, a majority of medical practitioners employ pungent in conjunction with sweet and bitter herbs for treating pulmonary nodules.

4. Five Viscera Differentiation Focuses on the Middle and Upper Jiao

Numerous studies investigating the medication rule for pulmonary nodules have shown that practitioners primarily target the lung meridian while also regulating the spleen, stomach, and liver meridians, with consideration for the heart meridian as well [7] [8] [9] [10] [20] [21] [22] [23] [34]. Moreover, some practitioners also address the lower jiao in conjunction with the treatment of the upper and middle jiaos [18] [33] [35].

4.1. Balance the Five Organs, with Emphasis on the Lung

Professor Yan Guizhen of our team has noted that pulmonary nodules fall within the Traditional Chinese Medicine categories of “phlegm nodules” or “cough” or “asthma” and so on [36]. Who suggesting that the etiology and pathogenesis of pulmonary nodules involve inherent deficiency of vital energy, external invasion by toxic and evil Qi, and the internal brewing of phlegm turbidity, stasis of blood, and damp full of toxics, all converging in the lungs. This condition is associated with dysfunction across multiple organs, with the primary disease location in the lungs, yet not confined solely to them [37]. Professor Yan’s understanding aligns with that of other medical practitioners: the formation of pulmonary nodules is related to imbalances in multiple organ functions, and while nodules primarily reside in the lungs, clinical treatment should aim for balace all five organs, often employing medications that enter the Taiyin lung meridian to

directly address the root of the disease.

4.2. Protect the Middle Jiao and Facilitating the Transformation and Function of the Spleen and Stomach

In addition to targeting the lung meridian, contemporary medical practitioners treating pulmonary nodules also choose medications that affect the spleen and stomach meridians. Modern diets, often greasy and surfeit flavour, typically result in a phlegm-damp constitution in clinical observations. Damage from dietary habits first affects the middle jiao; once the spleen and stomach are impaired, their transport and transformation functions fail, failing to metabolize fluids, leading to dampness coalescing into phlegm and accumulating in the lung lobes, hence presenting as lung accumulations. Therefore, practitioners frequently protect the spleen and stomach to facilitate their transport and transformation functions. Professor Shi Suofang believes that while pulmonary nodules are primarily located in the lungs and involve the liver and spleen, protecting the spleen and stomach is crucial for maintaining balance among the five organs. For patients with liver Qi stagnation and spleen deficiency or dual deficiency of lung and spleen, Liu Jun Zi Tang is often used as a base formula for treatment [25]. Professor Zhang Fuli holds that “Once the spleen and stomach are deficient, lung Qi fails first”, often employing methods to cultivating earth to control dampness, such as using ginger to warm and nourish the spleen and stomach, Fu Shen to soothe the mind and lighten the spleen, and Bai Zhu to invigorate the spleen and dry dampness to benefit the spleen and stomach [38]. Professor Zhu Jia advocates for cautious use of bitter and cold herbs to prevent damage to the spleen and stomach, opting for Si Jun Zi decoction or Shen Ling Bai Zhu San with modifications to reinforcing earth to generate metal, ensuring proper transformation and resolution of phlegm accumulations [15].

4.3. Focus on Emotional Well-Being and Regulate Liver Qi

The gender statistics for pulmonary nodules reveal that the detection rate in women surpasses that in men [9] [10] [11] [38]. Considering the age of detection is often in the fifties, when many women in the period of perimenopause, emotional fluctuations markedly. Discovering pulmonary nodules during this time can lead to negative emotional responses, subsequently causing a series of psychosomatic changes. Clinically, it is common for patients with pulmonary nodules to experience anxiety and depression [39]. Since the primary approach to pulmonary nodules is “follow-up and monitoring” the fear of nodules progressing to malignancy or causing other adverse effects can impose a psychological burden greater than the nodules themselves. If this state persists, prolonged liver Qi stagnation can lead to complications, hence contemporary medical practitioners place significant emphasis on regulating the liver, employing strategies to disperse liver Qi and alleviate depression. Professor Gong Hongwei believes that pulmonary nodules are closely related to the liver and the spleen-stomach system. Beyond pulmonary symptoms like coughing and chest tightness, the psy-

chological stress from concerns about nodules transforming into lung cancer can also manifest as symptoms of liver Qi stagnation, such as chest tightness and pain. Therefore, it is appropriate to select liver meridian drugs in prescription [8]. Professor Hu Kaiwen ingeniously applies the Five Elements Theory in treating pulmonary nodules, often using Yue Ju Wan to promote Qi movement and relieve depression, while also addressing stagnation in the lungs [34]. Professor Zhang Nianzhi adheres to the principle of “vent the wood constraint” frequently using bupleuri radix and aurantii fructus to disperse and soothe liver Qi, relieving the liver’s stagnation [17]. Professor Qu Niuni, in her clinical observations, found that some patients exhibit extreme anxiety about their pulmonary nodules, hence often uses bupleuri radix and aurantii fructus to soothe the liver and relieve depression, while also regulating the spleen and stomach Qi, restoring the pivotal ascending and descending functions [40].

5. Summary

In this paper, we have summarized the literature on the medication rule of pulmonary nodules in recent years and further explored common treatment protocols for managing them. It is found that contemporary doctors pay more attention to regulating Qi, clearing heat and detoxifying, eliminating phlegm, dissolving phlegm and dissipating masses. They use mild drugs, cold and warm treatments in parallel, combining the tastes of pungent, bitterness, and sweetness at the same time. The treatment focuses on the five viscera with emphasis on the lung meridian while also considering the spleen and stomach functions as well as soothing liver stagnation. It is anticipated that this study will offer additional references for clinical treatment by Chinese medicine practitioners and provide essential data support for the development of novel drugs in the management of pulmonary nodules. While several researchers have employed cluster analysis to uncover patterns in pulmonary nodule administration and derived new prescriptions, only a few have validated their efficacy through clinical application [14]. Therefore, further clinical investigations of this nature are warranted. At the same time, network pharmacology and molecular docking studies can be used to further explore the mechanism of pulmonary nodule core prescription. However, this body of research has its limitations: 1) The number of prescriptions included in most literature is limited, often only amounting to a hundred and more, which may affect the accuracy of the results. 2) Few studies explore the relationship between different syndrome types of pulmonary nodules and medication, which is not conducive to differential diagnosis and treatment in clinical practice. 3) The safety profile of traditional Chinese medicine in the treatment of pulmonary nodules is relatively favorable; however, it is important to acknowledge the presence of potential side effects. Nevertheless, limited research has been conducted to evaluate the safety aspects associated with traditional Chinese medicine prescriptions for this particular condition. 4) The literature analyzed in this study indicates that the detection rate of pulmonary nodules in females is significantly higher than in males, yet other reports suggest a

higher incidence rate of pulmonary nodules in males [5] [41]. This discrepancy could be due to women's higher health consciousness and greater willingness to seek medical advice. Currently, there is a lack of authoritative epidemiological studies on pulmonary nodules, and whether there is a gender difference in the detection rate of pulmonary nodules still requires support from studies with larger sample sizes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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