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REVIEW

Role of Macrophage Polarization in Chronic Rhinosinusitis Based on the Yin-Yang Theory: A Review

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Background: Chronic rhinosinusitis (CRS) is a prevalent otolaryngologic condition that markedly impacts patients' quality of life; however its pathogenesis is intricate and the clinical efficacy of known treatments remains limited.

Methods: In recent years, there has been a growing focus on the role of immune function in the pathogenesis of CRS. Recent studies have revealed a correlation between macrophage polarization and CRS development. Macrophage polarization denotes distinct phenotypes of macrophages in diverse microenvironments, with the M1 and M2 phenotypes sharing similarities with the Yin-Yang concept of traditional Chinese medicine, encompassing mutual support and utilization, a balance between growth and elimination, and self-healing and equilibrium.

Results: This study briefly reviews the latest research on traditional Chinese medicine compound prescriptions and the regulation of macrophage polarization by traditional Chinese medicine monomers, aligned with the main treatment principles of CRS, with the aim of offering novel directions and strategies for the clinical management of this condition.

Conclusion: This study investigated the role of macrophage polarization in CRS from the perspective of the Yin-Yang Theory of traditional Chinese medicine.

Keywords: chronic rhinosinusitis, the Yin–yang theory, macrophage polarization

Introduction

Chronic rhinosinusitis (CRS) is a prevalent condition in otorhinolaryngology characterized by symptoms such as nasal congestion, runny nose, headache, and diminished sense of smell that persists for over 12 weeks. The primary pathological feature of this condition is chronic mucosal inflammation of the nasal cavity and sinuses. In Europe and the United States, the prevalence of CRS among adults exceeds 10%,[1] whereas in China, it surpasses 8%.[2] CRS has emerged as a significant health concern affecting people's daily life and work, with ongoing challenges in both understanding its pathogenesis and conducting clinical research.

To understand the variability of clinically observed manifestations and outcomes, many chronic diseases have been classified into genotypes, phenotypes, and/or endosyms. CRS is no exception. The phenotypic classification of CRS has been determined based on endoscopically observed features, the presence of systemic diseases, and the time of onset. The endoscopic presence (CRSwNP) or absence (CRSsNP) of nasal polyps has been the most widely used phenotype of CRS.[2] However, a precise treatment that relies solely on phenotypic classification remains elusive, driving research on CRS endotype.[3] Endotypic classifications subdivide CRS based on pathobiologic mechanisms. For CRS, this was based on histologic features such as the presence of fibrosis, glandular hypertrophy, and epithelial dysmorphosis. Recent efforts attempt to define CRS endotypes based upon specific molecular mechanisms with biomarkers, which appear to be

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strongly correlated with phenotype, histological features, and treatment response. The endotypic classification of CRS ultimately shifts the focus to molecules produced by T lymphocytes of types 1, 2, and 3 (also known as type 17), which lead to different inflammatory patterns observed in tissues. EPOS 2020 recommends evaluating and treating CRS based on its endogenous correlation with type 2 or non-2 inflammatory diseases, focusing therapeutic choices on specific disease mechanisms and facilitating individualized treatment.[4]

In recent years, research into the involvement of macrophages in the CRS has been burgeoning. Macrophages, an important component of the immune system present in various tissues and organs throughout the body, help eliminate pathogens and cell debris in the body by acting as phagocytic cells. Macrophages exhibit high plasticity and heterogeneity. They can polarize into M1 and M2 phenotypes in response to growth factors and cytokines present in the microenvironment of nasal and olfactory mucosal tissue.[5] M1 phenotype promotes inflammation, producing a large amount of inflammatory cytokines, participates in Th1 response, and regulating early repair and pathogen response processes. On the contrary, M2 phenotype exhibits repair function, characterized by high IL-10 and low IL-12 expression. It stimulates the later repair process, participates in Th2 response, and regulates immune function. Therefore, regulating the balance between the two types of macrophages may become essential for treating CRS.

Owing to the complex pathogenesis of CRS,[6] its clinical treatment has limited efficacy. EPOS 2020 states that CRS is still commonly treated with glucocorticoid-based pharmacotherapy and functional endoscopic sinus surgery (FESS).[4] However, Tokunaga et al[7] showed that nearly 20% of patients with CRSwNP had recurrence of nasal polyps after 12 months of systemic glucocorticoid therapy and/or surgical treatment, and these patients often required secondary or even multiple surgical procedures, which not only affects the quality of life, but also greatly increases the time and economic costs. Other managements for CRS include Traditional Chinese medicines (TCM). TCM has a long history in China, which is an important category of complementary and alternative medicine, its use has increased in place in western countries over the past decade. A review that included some of the herbal medicines used in eastern Asia found symptom improvements in CRS.[8] References to a disorder that may have been CRS, then called bi yuan (excessive turbid nasal discharge), first appeared in the book Huang Di Nei Jing (Yellow Emperor's Classic of Medicine) which dates back to the Han dynasty, and subsequently appear in multiple books until modern times.[9] One review of 30 RCTs illustrated that TCM compared with placebo reported significant reductions in SNOT-20, SNOT-22, VAS-TNS, and MTT.[10]

The Yin-Yang theory is the theoretical basis of TCM, which guides the clinical thinking and diagnostic practice of TCM. We propose that the pro-inflammatory and anti-inflammatory responses in the immune response can be seen as compatible with the Yin-Yang theory in traditional Chinese philosophy, in which Yang represents active, positive, and aggressive factors, whereas Yin represents passive, negative, and inhibitory factors. Therefore, the modulation of macrophage polarization by TCM has a promising future in the treatment of CRS. This article explored the role of macrophage polarization in CRS from the perspective of yin and yang theory and summarized the herbal medicines that can regulate macrophage polarization. in order to provide new ideas for TCM treatment of CRS. We hope it will provide new ideas for the clinical management of CRS in Chinese medicine.

Overview of Macrophages

Origin and Function of Macrophages

Macrophages were first identified and described as phagocytes in marine organisms by Elie Metchnikoff in the 19th century.[11] They are the most widely distributed cells in the body[12] and play crucial roles in maintaining immune homeostasis and facilitating post-traumatic repair. Most, macrophages originate from bone marrow hematopoietic stem cells.[13,14] Monocytes in the bone marrow differentiate into macrophages under the influence of macrophage colony-stimulating factor,[15,16] and subsequently enter different tissues through the circulatory system. However, morphological and functional differences have been observed among tissue-resident macrophages, suggesting that they may not originate solely from circulating monocytes,[17] and can be categorized as monocyte-derived or tissue-resident macrophages.[18] Tissue-resident macrophages originate predominantly from the yolk sac and fetal liver during embryonic development.[19–22] Primitive macrophages are formed by the red marrow lineage progenitor cells of the extraembryonic yolk sac to produce primitive macrophages under the influence of transcription factors. When residing in the fetal liver, red marrow lineage progenitor cells stimulated by

transcription factors produce fetal foetal monocytes.[23] Tissue-resident macrophages have a long lifespan and perform self-renewal in adulthood.[24–26] They serve as the body's first line of defense against infections by responding promptly to external stimuli and regulating the dynamic balance of the body's tissues. Monocyte-derived macrophages complement this function and play a regulatory role in inflammation development.[27]

Macrophage Polarization

When the internal environment of the body is compromised, macrophages play a crucial role in restoring immune homeostasis by removing exogenous substances via phagocytosis and endocytosis. This phenomenon is referred to as macrophage activation. Macrophages show considerable plasticity and heterogeneity. Influenced by various cytokines, macrophages change their appearance and manifest different phenotypes, a phenomenon referred to as macrophage polarization.[28,29] Polarized macrophages primarily exist in two states: Classically activated (M1) macrophages and alternatively-activated (M2) macrophages[30] (Figure 1).

M1-type macrophages primarily polarize through the binding of Th1 cytokines, such as IFN-γ, or are activated by bacterial lipopolysaccharide (LPS) alone. They release pro-inflammatory cytokines such as interleukin (IL)-1α, IL-1β, IL-6, IL-12, IL-23, and COX-2, which actively participate in the elimination of pathogens during infections. Additionally, M1 macrophages contribute to pathogen clearance by over-stimulating the nicotinamide adenine dinucleotide phosphate oxidase system, leading to the production of reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS) levels.[31–33] Consequently, when an external stimulus or inflammation affects an organism, M0 macrophages initially polarize into the M1 phenotype, secrete inflammatory cytokines, stimulate the immune response of Th1 and Th17 cells, and safeguard the host during the early stages of inflammation.[34–36]

M2 macrophages predominantly polarize under the influence of Th2 cell cytokines such as IL-4 and IL-13, leading to the production of anti-inflammatory factors (such as IL-10, CCL17, CCL18, CCL22, CCL24) and pro-fibrotic factors (such as transforming growth factor(TGF)-β, insulin-like growth factor).[37,38] M2-type cells exhibit various phenotypes

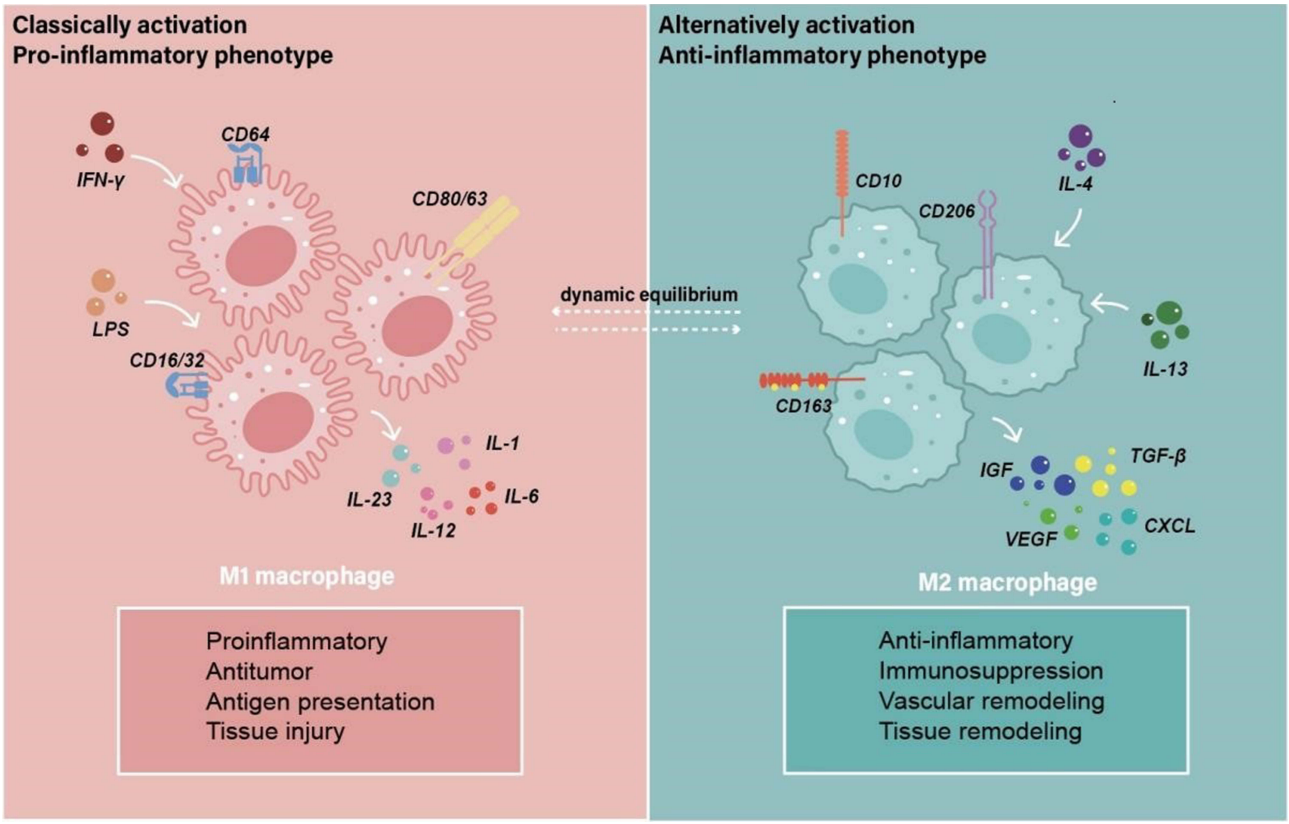

Figure 1 Pattern of Macrophage polarization.

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demonstrating distinct characteristics in response to microenvironmental and signalling stimuli, categorized as M2a, M2b, M2c, and M2d.[28,39–41] M2 macrophages activate TGF-β by modulating the Th2 cell response, and produce matrix metalloproteinases (MMPs) to eliminate necrotic cells and components of destruction generated by the M1 macrophage response, thus mitigating potential tissue injury.[42]

Polarization of Macrophages Intervenes in the Mechanism of CRS

Limited research has been conducted on the role and function of macrophages in the pathogenesis of CRS. Some studies have suggested a notable increase in both M1 and M2 macrophage populations in CRS, particularly among patients with CRSwNP, where M2-type macrophages are markedly increased.[43–45] Notably, an increase in M1-type macrophages was observed in patients with non-eosinophilic CRSwNP, whereas M2-type macrophages were more prevalent in patients with eosinophilic CRSwNP, indicating the potential involvement of M2-type macrophages in the inflammatory response and tissue remodeling processes.[46,47] Despite the increased number of M2-type macrophages in eosinophilic CRSwNP, the quantity and percentage of IL-$10^{+}CD_{68}^{+}$ M2 macrophages decreased. This specific subtype of M2 macrophages exhibits a negative correlation with disease signs and symptoms, polyp size, computed tomography scores, and inflammatory cell counts, suggesting a potential relationship between the inflammatory state of eosinophilic CRSwNP and the IL-10 secretion by M2 macrophages.[48–51]

Tissue remodeling is an important histopathological alteration in CRS.[52–54] Macrophage polarization leads to a state in which the organism or organ is more fibrotic than antifibrotic, resulting in the accumulation of an extracellular matrix (ECM), and ultimately leading to tissue remodelling.[55,56] Once M2 macrophages are polarized, they secrete various cytokines, leading to fibroblast proliferation and disruption in the balance of the extracellular matrix, resulting in the progressive and irreversible destruction of normal tissue structure in organ tissues.[57] Tissue remodeling due to M2 macrophages may be related to the following mechanisms: Upregulating TGF-βexpression may promote tissue remodeling. M2 cells stimulate and upregulate TGF-β expression.[58,59] On the one hand, TGF-β activates both the ERK/MAPK pathway and the TGF-β/Smads signal transduction pathway, promoting collagen sedimentation over degradation, inducing fibroblast proliferation and differentiation and ECM accumulation;[60,61] on the other hand, TGF-β induces the synthesis of arginase-1, which induces a decrease in NOS (nitric oxide synthase) bioavailability, thereby increasing susceptibility to pathogens and exacerbating tissue remodeling.[62] Furthermore, TGF-β stimulates increased expression of VEGF, which leads to the accumulation of cuprocytes, vascular endothelial cells, and an ECM, thereby triggering vascular remodeling and airway inflammation.[63] A regulatory feedback mechanism may exist between M2 macrophages and TGF-β. By activating the ERK/MAPK signalling pathway, TGF-β promotes the polarization of M2 macrophages, which continuously exacerbates the tissue remodeling process.[64] M2 macrophages inhibit MMP-9 hydrolysis and increase tissue vascular permeability by stimulating high expression of TIMP3.[65,66] This increased vascular permeability leads to the accumulation of inflammatory mediators within the tissue, exacerbating tissue remodeling by regulating coagulation mechanisms.[67] M2 macrophages produce FXIII in the tissues, which enhances coagulation and forms stable fibrin polymers that are not degraded by fibrinolysis.[68] M2 macrophages were found to be the major source of FXIII in CRSwNP, exacerbating remodeling by triggering plasma protein retention in nasal polyp tissue and pseudocyst formation.[69]

Mechanisms of the Yin-Yang Theory and Macrophage Polarization in CRS

Yin–Yang Theory and Macrophage Polarization

Researchers have focused on the role of macrophages in diseases and the mechanism of action of traditional Chinese medicine(TCM).[70,71] The foundation of TCM is based on the Yin–Yang principle, which represents interconnected yet opposing pairs of elements in the natural world.[72] This principle is instrumental in explaining physiological and pathological changes in the human body, which can be used to diagnose and treat diseases.[73] Macrophage polarization comprises two mutually antagonistic and unifying states, which we believe are connotatively related to the theory of Yin-Yang in TCM.

Macrophage polarization is a dynamic process,[74] in which the M1 and M2 phenotypes represent two extremes, where transitions between these stages can be observed within the same tissue, with macrophages interconversion in specific environments.[75] Notably, M1 and M2 macrophages exhibit a fundamental and interdependent relationship

analogous to the principles of interdependence between yin and yang. In the early stages of inflammation, M1 macrophages primarily play a pro-inflammatory and pathogen-killing role through the release of inflammatory mediators, aligning with the TCM concept of "yang being in charge of activity". In contrast, M2 macrophages focus on anti-inflammation, tissue repair, and remodeling, corresponding to the TCM principle of "yin controlling quiescence".[76] Despite their functional antagonism, M1 and M2 macrophages are functionally unified, with dynamic changes of the yin and yang sides constantly maintaining balance, achieving an ideal state of health. Yang bias creates excessive competition between vital energy and pathogenic factors, damaging positive energy. M1 macrophages excessively promote inflammation and exert antibacterial effects, which are not conducive to tissue repair and may even lead to extensive tissue damage.[77] When yin is in excess and the pathogenic factors are not eliminated, the pathogenic factors transform and cause illness. M2 macrophages overexpress anti-inflammatory factors and suppress immunity, thereby promoting tissue remodeling.[77] However, an imbalance in M1/M2 cell polarization, despite their opposing yet coexisting nature, can results in a negative local inflammatory microenvironment, leading to chronic inflammatory pathological reactions in the body.[78,79]

Treatment of CRS by Adjusting Yin and Yang

Tao Te Ching wrote that "all things carry yin and embrace yang; they achieve harmony by combining these forces".[80] The Yellow Emperor's Canon of Medicine further advises to "carefully observe the location of yin and yang, and adjust them, aiming for balance".[81] The Yin-Yang Theory holds paramount significance in the TCM approach to treating diseases. The human body maintains optimal health only when it achieves a harmonious state of balanced yin and yang. CRS has a complex mechanism, and modern medicine had limited therapeutic effects with high recurrence and multiple side effects.[82,83] TCM stands out for its clear therapeutic effects and advantages for the prevention and treatment of CRS.[84–88]

The CRS is classified under the TCM category of "bi yuan". Through data mining research on "bi yuan", it was found that ancient medical experts approached the differentiation and treatment of nasal congestion from three primary aspects: External pathogenic factors, internal organ heat, and organ deficiency.[89] Bi yuan is considered a condition of deficiency at its origin and excess at its surface. TCM practitioners address bi yuan by lung, spleen, and kidney dysfunction, as well as the obstruction of qi, blood and dampness.[90] Science of Traditional Chinese Medicine Otorhinolaryngology categorizes CRS into five types: Lung meridian wind heat, excessive heat in the cholecyst, damp heat of the spleen and stomach, deficiency and cold of lung qi and splenic dysfunction due to dampness.[91] When M1 macrophages are overly efficient, resulting in an intense pro-inflammatory response, TCM interprets this as an excessive yang transforming into qi, which manifests as a syndrome of excess heat or even yin deficiency. Conversely, when M2 macrophages dominate, leading to an excessive anti-inflammatory response, TCM interprets this as yin shaping, which results in the formation of cold congelation, phlegm dampness, blood stasis and impairment of the body's yang qi.[92] From the perspective of TCM, lung and spleen deficiencies, coupled with dampness accumulation, are considered the primary causes of CRS. The inefficiency of M1 macrophages leads to a state of yang qi deficiency; meanwhile, hyperactive M2 macrophages contribute to the formation of dampness. Qi deficiency and dampness accumulation interacted TCM, which focuses on tonifying the spleen and dispelling dampness, has achieved significant therapeutic effects in CRS treatment[93–96] (Figure 2).

Reducing the Hyperactivity of M2 Macrophages Using TCM

Based on the therapeutic principles of balancing yin and yang, TCM may exert its preventive and therapeutic effects on CRS by reducing the hyperactivity of M2 macrophages in the body (Figure 3). TCM treatment has two methods for reducing the hyperactivity of M2 macrophages: (1) Inhibiting macrophage polarization to the M2 type, and (2) promoting the generation of M1 type macrophages (Table 1).

TCM Inhibits Polarization of Macrophages to M2 Type

Quercetin is a natural flavonoid found in various Chinese medicinal herbs, such as Sophora flowers. It inhibits M2 macrophage polarization and ameliorates kidney damage by downregulating the protein levels of p65 in NF-κB and interferon regulatory factor 5 (IRF5).[97] Peimine, the main component of TCM Fritillaria, can improve pulmonary fibrosis by inhibiting the expression of STAT6, p38MAPK, Akt, and other factors, thus suppressing the M2 polarization of

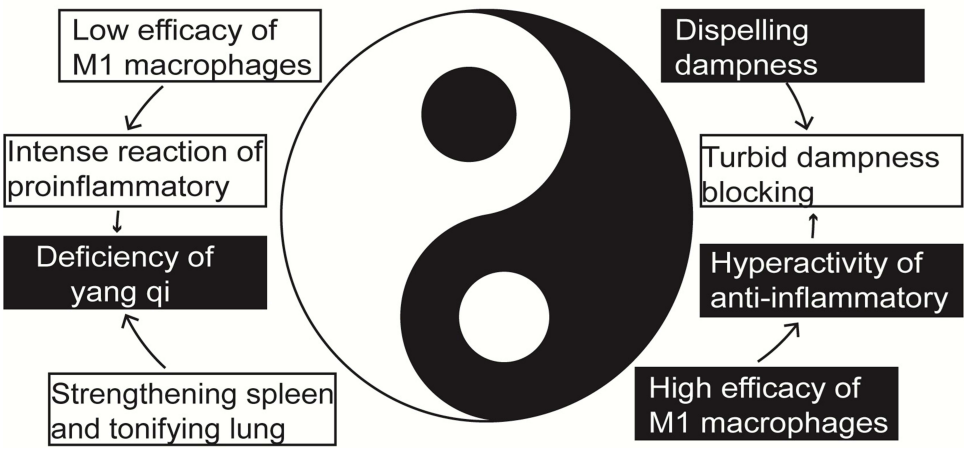

Figure 2 Treatment of CRS by adjusting yin and yang.

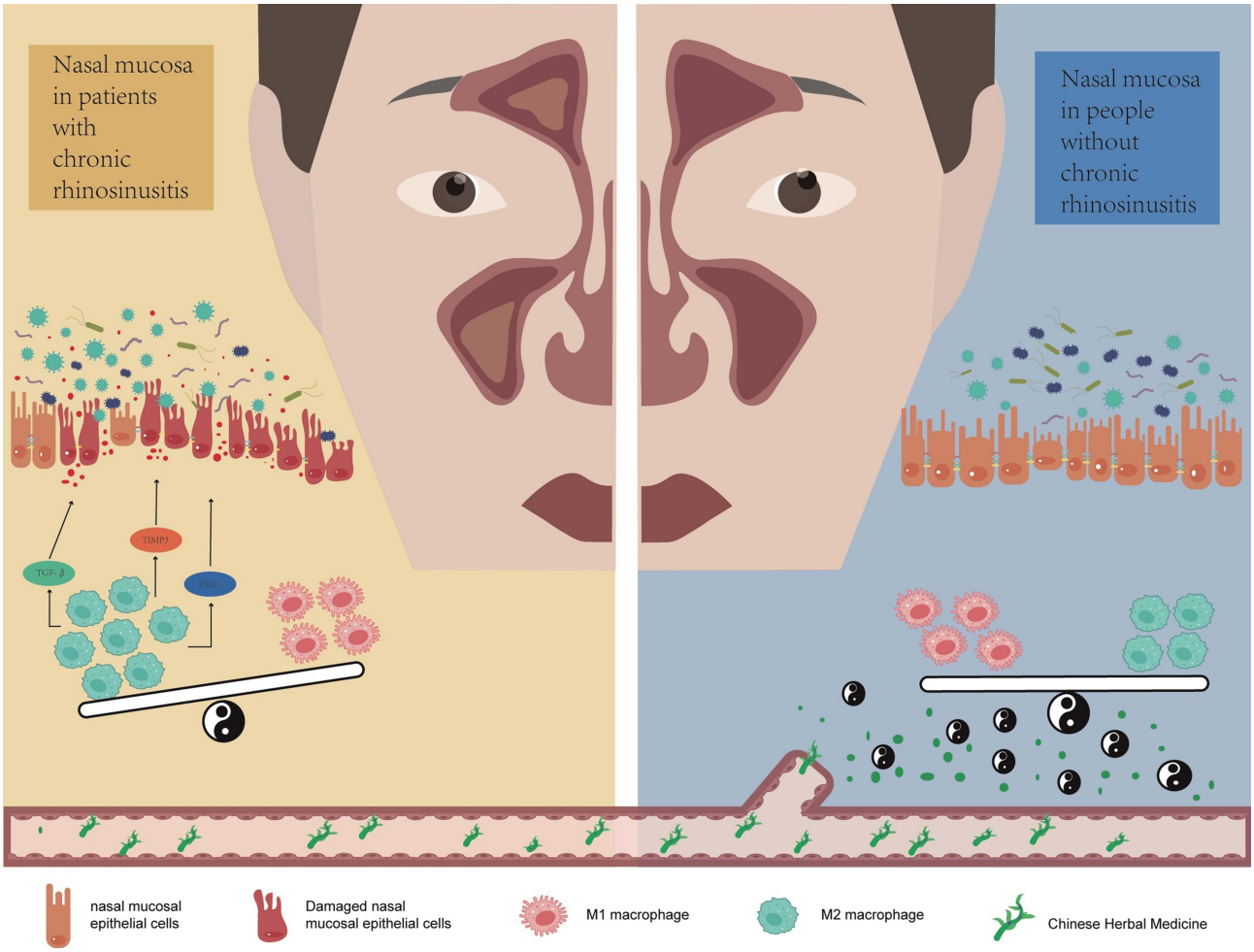

Figure 3 Reducing the hyperactivity of M2 macrophages using TCM based on the Yin-Yang Theory.

Table 1 TCM That Reduces the Hyperactivity of M2 Macrophages

No.	TCMs and its active ingredients	In vivo/vitro	Cells/animals	Mechanism	Directions	Disease	Ref
1	Quercetin	Both	RAW264.7/ICR/JCL	NF-κB	M2↓	Kiney injury	[97]
2	Peimine	Both	MH-S/Sprague–Dawley	P38/Akt/STAT6	M2↓	Pulmonary fibrosis	[98]
3	Emodin	Both	Peritoneal macrophage of mice/EO771	IRF4/STAT6 C/EBPβ	M2↓	Breast cancer	[99]
4	Astragaloside IV	Both	THP-1/C57BL	AMPK	M2↓	Lung cancer	[100]
5	Resveratrol	Both	THP-1/C3H/He	STAT3	M2↓	Lymphangiogenesis	[101]
6	Isoliquiritigenin	Both	RAW264.7/Balb/c	PGE2/ IL-6	M2↓	Colorectal cancer	[102]
7	Protostemonine	Both	BMDM/C57BL/6	STAT6/KLF4/IRF4	M2↓	Asthma	[103]]
8	Osthole	In vitro	RAW 264.7	p-STAT6 p-ERK1/2-C/EBP b	M2↓	Pancreatic cancer	[104]
9	Gujin Xiao Liu Tang	In vitro	RAW 264.7	AKT/FOXO3a/bim	M2↓	Non-small cell lung cancer	[105]
10	Jianpi Yangzheng Xiaozheng recipe	In vivo	615	PI3K/Akt	M2↓	Gastric cancer	[106]
11	Mai Men Dong Decoction	Both	THP-1/C57BL/6	PI3K/Akt/FOXO3a	M2↓	Pulmonary fibrosis	[107]
12	Baicalein	Both	THP-1/C57BL/6J Balb/c	PI3Kγ/ NF-κB	M1↑	Breast cancer and Melanoma	[108]
13	Anemoside A3	In vitro	THP-1	TLR4/NF-κB/MAPK	M1↑	Breast cancer	[109]
14	WCCP-N-b	In vitro	RAW264.7	STAT6/MAPKs /NF-κB	M1↑M2↓	Melanoma	[110]
15	Poria cocos polysaccharide	In vitro	RAW 264.7	NF-κB	M1↑	Bladder cancer	[111]
16	Ginsenoside Rh2	Both	RAW264.7/C57BL/6	/	M1↑M2↓	Non-small cell lung cancer	[112]
17	Ganoderma lucidum polysaccharide	In vitro	RAW264. 7	Notch	Bi-Directional regulation	/	[113]
18	Water extract of ginseng and astragalus	Both	THP-1/C57BL/6	/	M1↑M2↓	Non-small cell lung cancer	[114]

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macrophages.[98] Emodin inhibits the signalling of IRF4, STAT6, and C/EBPβ, while increasing the inhibitory histone H3 lysine 27 tri-methylation (H3K27m3) on M2-associated gene promoters, thereby suppressing tumor-associated macrophage infiltration and M2 polarization.[99] AS-IV inhibits IL-13 and IL-4-induced M2-like macrophage polarization via the AMPK pathway, which reduces lung cancer growth, invasion, migration, and angiogenesis.[100] Resveratrol, extracted from the TCM Polygonum, can prevent tumor growth and metastasis by inhibiting tumor-associated macrophage M2-like polarization, which may be related to STAT3 signalling.[101,115] Isoliquiritigenin(ISG) is a dietary flavonoid derived from licorice.[116] Studies have shown that ISG blocks M2 polarization during colitis-associated tumorigenesis by down-regulating the expression of PGE2 and IL-6 expression.[102] Protostemonine (PSN) is an active substance extracted from the TCM Baibu, which has anti-inflammatory properties and exerts therapeutic effects in acute lung injury and acute liver failure.[117] Song et al[103] found that PSN improved the inflammatory manifestations of asthma by inhibiting the phosphorylation of STAT6 and suppressing M2 polarization. Wang et al[104] found that osthole suppressed M2 polarization and attenuated the development of pancreatic cancer in mice by inhibiting the phosphorylation of STAT6.

Lin Weibo[105] found that Gujin Xiao Liu Tang promoted the apoptosis of M2-Tumor-associated macrophage(TAMs) through the expression of AKT/FOXO3a/bim and pro-apoptotic proteins, inhibiting the cell migration ability of A549 cells in the co-culture system. Min et al[106] discovered that the a Jianpi Yangzheng Xiaozheng recipe inhibited the number of M2-type TAMs in gastric cancer, thereby suppressing the occurrence of epithelial-mesenchymal transition. The mechanism underlying this effect may be related to the PI3K/AKT signaling pathway. Mai Men Dong Decoction (MMDD), a TCM formula, can mediate fibroblast activation through the PI3K/Akt/FOXO3a signaling pathway by regulating M2 macrophage polarization, and inhibiting pulmonary fibrosis.[107]

TCM Inhibits Promotes the Generation of M1 Phenotype Macrophages

Baicalein (baicalin), extracted from *Scutellaria baicalensis*, can promote macrophage polarization toward M1 and slow tumor growth through the NF-κB signalling pathway.[108] Yin et al[109] found that anemoside A3, the active ingredient of *Pulsatilla chinensis*, increased the polarization of M1 macrophages and inhibited tumor growth and angiogenesis in a dose-dependent manner. A novel polysaccharide, WCCP-N-b, isolated from *Cantharellus cibarius*, can inhibit the polarization of M2-like macrophages by suppressing STAT6 activation and convert M2-like macrophages to the M1 type through the activation of MAPK and degradation of IκB-α.[110] Poria cocos polysaccharide (PPS), the primary components of *Polyporus umbellatus*, can inhibit the polarization of M2 macrophages through the NF-κB signaling pathway, while promoting the generation of M1-TAMs and the release of M1-related cytokines.[111,118] Ginsenoside Rh2 effectively converts macrophages from the M2 phenotype to the M1 phenotype, and simultaneously reduces the expression levels of VEGF, MMP2, and MMP9 in a lung cancer cell-macrophage co-culture system, suggesting that it inhibits the migration of lung cancer cells.[112] The *Ganoderma lucidum* polysaccharide (PSG-1) dynamically regulates the macrophage M1/M2 polarization phenotype via the Notch signaling pathway, thereby altering the inflammatory state of the body.[113] Water extracts of ginseng and astragalus promote M1 polarization of macrophages and inhibit M2 polarization, thereby suppressing the proliferation of lung cancer cells and synergistically enhancing the anticancer effect of cisplatin.[114]

Conclusion

Overall, M2 polarization macrophage drives the development of CRS by altering the inflammatory environment and tissue remodeling. However, the specific mechanisms governing the occurrence and development of CRS, as well as the mechanisms of TCM, remain unclear and require further research. Guided by the Yin-Yang Theory of TCM, there are broad prospects for achieving the prevention and treatment of CRS by balancing macrophage polarization by adjusting the body's yin, yang, qi, and blood. Exploring the role of macrophages in CRS based on the Yin-Yang doctrine can deepen our understanding of the pathogenesis of CRS and enrich the connotation of the Yin-Yang doctrine in TCM. This study serves not only as an exploration of the mechanism of TCM from a modern perspective, but also serves as a positive means for treating CRS with the help of TCM. Such an approach is of considerable importance for improving patients' quality of life and reducing the societal burden associated with CRS.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflict of interest.

References

1. Liu Z, Chen J, Cheng L, et al. Chinese society of allergy and Chinese society of otorhinolaryngology-head and neck surgery guideline for chronic rhinosinusitis. *Allergy Asthma Immunol Res*. 2020;12(2):176–237. doi:10.4168/aair.2020.12.2.176
2. Subspecialty Group of Rhinology EBoCJoOH, Neck S, Subspecialty Group of Rhinology SoOH, Neck Surgery CMA. [Chinese guidelines for diagnosis and treatment of chronic rhinosinusitis (2018)]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2019;54(2):81–100. doi:10.3760/cma.j.issn.1673-0860.2019.02.001 Hawaiian
3. Kucuksezer UC, Ozdemir C, Akdis M, Akdis CA. Chronic rhinosinusitis: pathogenesis, therapy options, and more. *Expert Opin Pharmacother*. 2018;19(16):1805–1815. doi:10.1080/14656566.2018.1527904
4. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(Suppl S29):1–464. doi:10.4193/Rhin20.401
5. Banks CA, Schlosser RJ, Wang EW, et al. Macrophage infiltrate is elevated in crswnp sinonasal tissue regardless of atopic status. *Otolaryngol Head Neck Surg*. 2014;151(2):215–220. doi:10.1177/0194599814528672
6. Stevens WW, Lee RJ, Schleimer RP, Cohen NA. Chronic rhinosinusitis pathogenesis. *J Allergy Clin Immunol*. 2015;136(6):1442–1453. doi:10.1016/j.jaci.2015.10.009
7. Tokunaga T, Sakashita M, Haruna T, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC study. *Allergy*. 2015;70(8):995–1003. doi:10.1111/all.12644
8. Anushiravani M, Bakhshaee M, Taghipour A, et al. A systematic review of randomized controlled trials with herbal medicine on chronic rhinosinusitis. *Phytother Res*. 2018;32(3):395–401. doi:10.1002/ptr.5968
9. May BH, Lin W. Ch 3. classical Chinese medicine literature. In: Xue CC, Lu C, Zhang AL, Guo X, Wen Z, editors. *Evidence-Based Clinical Chinese Medicine Volume 25: Rhinosinusitis. 25*. Singapore: World Scientific Publishing Co; 2022.
10. Cui J, Lin W, May BH, et al. Chinese herbal therapy in the management of rhinosinusitis-A systematic review and meta-analysis. *PLoS One*. 2022;17(12):e0278492. doi:10.1371/journal.pone.0278492
11. Gentek R, Molawi K, Sieweke MH. Tissue macrophage identity and self-renewal. *Immunol Rev*. 2014;262(1):56–73. doi:10.1111/imr.12224
12. Kunwei S. *Clinical Observation of Wenfei Huatan Tongluo Soup in the Treatment of Acute Onset of COPD*. Guangzhou University of Chinese Medicine; 2020.
13. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol*. 2014;5:491. doi:10.3389/fimmu.2014.00491
14. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):762–774. doi:10.1001/jama.2016.0288
15. Guilliams M, Mildner A, Yona S. Developmental and functional heterogeneity of monocytes. *Immunity*. 2018;49(4):595–613. doi:10.1016/j.immuni.2018.10.005
16. Mantovani A, Sica A, Locati M. Macrophage polarization comes of age. *Immunity*. 2005;23(4):344–346. doi:10.1016/j.immuni.2005.10.001
17. Epelman S, Lavine KJ, Randolph GJ. Origin and functions of tissue macrophages. *Immunity*. 2014;41(1):21–35. doi:10.1016/j.immuni.2014.06.013
18. Yang D, Yang L, Cai J, et al. A sweet spot for macrophages: focusing on polarization. *Pharmacol Res*. 2021;167:105576. doi:10.1016/j.phrs.2021.105576
19. Hoeffel G, Ginhoux F. Fetal monocytes and the origins of tissue-resident macrophages. *Cell Immunol*. 2018;330:5–15. doi:10.1016/j.cellimm.2018.01.001
20. Zhao Y, Zou W, Du J, Zhao Y. The origins and homeostasis of monocytes and tissue-resident macrophages in physiological situation. *J Cell Physiol*. 2018;233(10):6425–6439. doi:10.1002/jcp.26461

21. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. *Nat Rev Immunol*. 2019;19(6):369–382. doi:10.1038/s41577-019-0127-6
22. Franken L, Schiwon M, Kurts C. Macrophages: sentinels and regulators of the immune system. *Cell Microbiol*. 2016;18(4):475–487. doi:10.1111/cmi.12580
23. Gomez Perdiguero E, Klapproth K, Schulz C, et al. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature*. 2015;518(7540):547–551. doi:10.1038/nature13989
24. Zheng X, Gan H, Li L, Hu X, Fang Y, Chu L. [Astragaloside IV inhibits inflammation after cerebral ischemia in rats through promoting microglia/macrophage M2 polarization]. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2020;49(6):679–686. doi:10.3785/j.issn.1008-9292.2020.12.02 Danish
25. Kono Y, Colley T, To M, et al. Cigarette smoke-induced impairment of autophagy in macrophages increases galectin-8 and inflammation. *Sci Rep*. 2021;11(1):335. doi:10.1038/s41598-020-79848-0
26. Hashimoto D, Chow A, Noizat C, et al. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. *Immunity*. 2013;38(4):792–804. doi:10.1016/j.immuni.2013.04.004
27. Sieweke MH, Allen JE. Beyond stem cells: self-renewal of differentiated macrophages. *Science*. 2013;342(6161):1242974. doi:10.1126/science.1242974
28. Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol*. 2018;233(9):6425–6440. doi:10.1002/jcp.26429
29. Murray PJ. Macrophage Polarization. *Annu Rev Physiol*. 2017;79:541–566. doi:10.1146/annurev-physiol-022516-034339
30. Orecchioni M, Ghosheh Y, Pramod AB, Ley K. Macrophage polarization: different gene signatures in M1(LPS+) vs. classically and M2(LPS-) vs. alternatively activated macrophages. *Front Immunol*. 2019;10:1084. doi:10.3389/fimmu.2019.01084
31. Golledge J, Tsao PS, Dalman RL, Norman PE. Circulating markers of abdominal aortic aneurysm presence and progression. *Circulation*. 2008;118(23):2382–2392. doi:10.1161/CIRCULATIONAHA.108.802074
32. Kong X, Gao J. Macrophage polarization: a key event in the secondary phase of acute spinal cord injury. *J Cell Mol Med*. 2017;21(5):941–954. doi:10.1111/jcmm.13034
33. Recalcati S, Gammella E, Cairo G. Ironing out macrophage immunometabolism. *Pharmaceuticals*. 2019;12(2):94. doi:10.3390/ph12020094
34. Ivashkiv LB. IFNgamma: signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy. *Nat Rev Immunol*. 2018;18(9):545–558. doi:10.1038/s41577-018-0029-z
35. Marrocco A, Ortiz LA. Role of metabolic reprogramming in pro-inflammatory cytokine secretion from LPS or silica-activated macrophages. *Front Immunol*. 2022;13:936167. doi:10.3389/fimmu.2022.936167
36. Ahmad F, Rani A, Alam A, et al. Macrophage: a cell with many faces and functions in tuberculosis. *Front Immunol*. 2022;13:747799. doi:10.3389/fimmu.2022.747799
37. Wang Y, Han CC, Cui D, Li Y, Ma Y, Wei W. Is macrophage polarization important in rheumatoid arthritis? *Int Immunopharmacol*. 2017;50:345–352. doi:10.1016/j.intimp.2017.07.019
38. Rui JYH. Research progress on relationship between macrophage M1/ M2 polarization and immune inflammatory diseases. *Chin J Immunol*. 2021;37(22):2791–2797.
39. Wang LX, Zhang SX, Wu HJ, Rong XL, Guo J. M2b macrophage polarization and its roles in diseases. *J Leukoc Biol*. 2019;106(2):345–358. doi:10.1002/JLB.3RU1018-378RR
40. Zhang YH, He M, Wang Y, Liao AH. Modulators of the balance between M1 and M2 macrophages during pregnancy. *Front Immunol*. 2017;8:120. doi:10.3389/fimmu.2017.00120
41. Roszer T. Understanding the mysterious M2 macrophage through activation markers and effector mechanisms. *Mediators Inflamm*. 2015;2015:816460. doi:10.1155/2015/816460
42. Ma S, Zhang J, Liu H, Li S, Wang Q. The role of tissue-resident macrophages in the development and treatment of inflammatory bowel disease. *Front Cell Dev Biol*. 2022;10:896591. doi:10.3389/fcell.2022.896591
43. Xie Y, Li M, Chen K, et al. Necroptosis underlies neutrophilic inflammation associated with the Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). *J Inflamm Res*. 2021;14:3969–3983. doi:10.2147/JIR.S322875
44. Bayar Muluk N, Arikan OK, Atasoy P, Kilic R, Tuna Yalcinozan E. The role of CD68 (+) histiocytic macrophages in nasal polyp development. *J Neurol Surg B Skull Base*. 2021;82(6):700–708. doi:10.1055/s-0040-1715593
45. Krysko O, Holtappels G, Zhang N, et al. Alternatively activated macrophages and impaired phagocytosis of S. aureus in chronic rhinosinusitis. *Allergy*. 2011;66(3):396–403. doi:10.1111/j.1398-9995.2010.02498.x
46. Peterson S, Poposki JA, Nagarkar DR, et al. Increased expression of CC chemokine ligand 18 in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2012;129(1):119–27e1–9. doi:10.1016/j.jaci.2011.08.021
47. Minutti CM, Knipper JA, Allen JE, Zaiss DM. Tissue-specific contribution of macrophages to wound healing. *Semin Cell Dev Biol*. 2017;61:3–11. doi:10.1016/j.semcdb.2016.08.006
48. Wang ZC, Yao Y, Wang N, et al. Deficiency in interleukin-10 production by M2 macrophages in eosinophilic chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. 2018;8(11):1323–1333. doi:10.1002/alr.22218
49. Xiong G, Xie X, Wang Q, et al. Immune cell infiltration and related core genes expression characteristics in eosinophilic and non-eosinophilic chronic rhinosinusitis with nasal polyps. *Exp Ther Med*. 2020;20(6):180. doi:10.3892/etm.2020.9310
50. Yao Y, Wang ZC, Liu JX, et al. Increased expression of TIPE2 in alternatively activated macrophages is associated with eosinophilic inflammation and disease severity in chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. 2017;7(10):963–972. doi:10.1002/alr.21984
51. Lan F, Zhong H, Zhang N, et al. IFN-lambda1 enhances Staphylococcus aureus clearance in healthy nasal mucosa but not in nasal polyps. *J Allergy Clin Immunol*. 2019;143(4):1416–1425e4. doi:10.1016/j.jaci.2018.09.041
52. Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy*. 2006;61(11):1280–1289. doi:10.1111/j.1398-9995.2006.01225.x
53. Takabayashi T, Kato A, Peters AT, et al. Excessive fibrin deposition in nasal polyps caused by fibrinolytic impairment through reduction of tissue plasminogen activator expression. *Am J Respir Crit Care Med*. 2013;187(1):49–57. doi:10.1164/rccm.201207-1292OC

54. Sun Q, Liu L, Mandal J, et al. PDGF-BB induces PRMT1 expression through ERK1/2 dependent STAT1 activation and regulates remodeling in primary human lung fibroblasts. *Cell Signal*. 2022;89:110114. doi:10.1016/j.cellsig.2021.110114
55. Adhyatmika A, Putri KS, Beljaars L, Melgert BN. The elusive antifibrotic macrophage. *Front Med*. 2015;2:81. doi:10.3389/fmed.2015.00081
56. Guo X, Li T, Xu Y, et al. Increased levels of Gab1 and Gab2 adaptor proteins skew interleukin-4 (IL-4) signaling toward M2 macrophage-driven pulmonary fibrosis in mice. *J Biol Chem*. 2017;292(34):14003–14015. doi:10.1074/jbc.M117.802066
57. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity*. 2010;32(5):593–604. doi:10.1016/j.immuni.2010.05.007
58. Wang X, Zhao C, Ji W, Xu Y, Guo H. Relationship of TLR2, TLR4 and tissue remodeling in chronic rhinosinusitis. *Int J Clin Exp Pathol*. 2015;8(2):1199–1212.
59. Little SC, Early SB, Woodard CR, et al. Dual action of TGF-beta1 on nasal-polyp derived fibroblasts. *Laryngoscope*. 2008;118(2):320–324. doi:10.1097/MLG.0b013e318159cc0b
60. Honda E, Park AM, Yoshida K, Tabuchi M, Munakata H. Myofibroblasts: biochemical and proteomic approaches to fibrosis. *Tohoku J Exp Med*. 2013;230(2):67–73. doi:10.1620/tjem.230.67
61. Gratchev A. TGF-beta signalling in tumour associated macrophages. *Immunobiology*. 2017;222(1):75–81. doi:10.1016/j.imbio.2015.11.016
62. Kitowska K, Zakrzewicz D, Konigshoff M, et al. Functional role and species-specific contribution of arginases in pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol*. 2008;294(1):L34–45. doi:10.1152/ajplung.00007.2007
63. Shimizu S, Gabazza EC, Ogawa T, et al. Role of thrombin in chronic rhinosinusitis-associated tissue remodeling. *Am J Rhinol Allergy*. 2011;25(1):7–11. doi:10.2500/ajra.2011.25.3535
64. Su N, Li Y, Wang J, et al. Role of MAPK signal pathways in differentiation process of M2 macrophages induced by high-ambient glucose and TGF-beta1. *J Recept Signal Transduction Res*. 2015;35(5):396–401. doi:10.3109/10799893.2014.960933
65. Meng J, Zhou P, Liu Y, et al. The development of nasal polyp disease involves early nasal mucosal inflammation and remodelling. *PLoS One*. 2013;8(12):e82373. doi:10.1371/journal.pone.0082373
66. Zou F, Zhang J, Xiang G, Jiao H, Gao H. Association of Matrix Metalloproteinase 9 (MMP-9) polymorphisms with asthma risk: a meta-analysis. *Can Respir J*. 2019;2019:9260495. doi:10.1155/2019/9260495
67. Wang LF, Chien CY, Chiang FY, Chai CY, Tai CF. Corelationship between matrix metalloproteinase 2 and 9 expression and severity of chronic rhinosinusitis with nasal polyposis. *Am J Rhinol Allergy*. 2012;26(1):e1–4. doi:10.2500/ajra.2012.26.3724
68. Barath B, Bogati R, Miklos T, et al. Effect of alpha2-plasmin inhibitor heterogeneity on the risk of venous thromboembolism. *Thromb Res*. 2021;203:110–116. doi:10.1016/j.thromres.2021.05.003
69. Takabayashi T, Kato A, Peters AT, et al. Increased expression of factor XIII-A in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2013;132(3):584–592e4. doi:10.1016/j.jaci.2013.02.003
70. Gao Z, Wang Y. Exploring the relationship between macrophage autophagy and atherosclerosis based on the theory of spleen deficiency generating phlegm. *J Traditional Chin Med*. 2017;58(22):1902–1905.
71. Xiahou ZK, Hong XI, Jun HA. Shakuyakukanzoto relieves ulcerative colitis in mice by regulating the expression of NDUFS1 and inhibiting the polarization of macrophages to M1. *Prog Biochem Biophys*. 2023;1–18.
72. Can Yan LW. *Basic Theory of Traditional Chinese Medicine*. Beijing: China Press of Traditional Chinese Medicine; 2019.
73. Yuhan Ao JS, Zhang M. Discussion of the pathogenesis and treatment of HF complicated with insomnia in TCM based on the theory of "Yin-Yang-Fire-Water". *J Liaoning Univ Trad Chin Med*. 2023;1–14.
74. Ma RY, Black A, Qian BZ. Macrophage diversity in cancer revisited in the era of single-cell omics. *Trends Immunol*. 2022;43(7):546–563. doi:10.1016/j.it.2022.04.008
75. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell*. 2010;141(1):39–51. doi:10.1016/j.cell.2010.03.014
76. Lulu Zhu HW, Dongyong L. Role of macrophages polarization in liver fibrosis based on the Yin and Yang theory of traditional Chinese medicine. *J Traditional Chin Med*. 2019;60(12):1025–1029.
77. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol*. 2011;11(11):723–737. doi:10.1038/nri3073
78. de Las Casas-Engel M, Corbi AL. Serotonin modulation of macrophage polarization: inflammation and beyond. *Adv Exp Med Biol*. 2014;824:89–115. doi:10.1007/978-3-319-07320-0_9
79. Li Pang LY, Xinguo G. Relationship between inflammatory tumor microenvironment and balance of yin and yang in traditional Chinese medicine. *J Traditional Chin Med*. 2018;59(21):1832–1835.
80. Laozi LA. *The Scripture of Ethics*. Shanghai: ShangHai Jiao Tong University Press; 2021.
81. Yin Su PW. *Selected Readings From Huangdi Neijing*. Shanghai: Shanghai Scientific and Technical Publishers; 2018.
82. Walker A, Philpott C, Hopkins C. What is the most appropriate treatment for chronic rhinosinusitis? *Postgrad Med J*. 2019;95(1127):493–496. doi:10.1136/postgradmedj-2019-136519
83. Chen S, Zhou A, Emmanuel B, Thomas K, Guiang H. Systematic literature review of the epidemiology and clinical burden of chronic rhinosinusitis with nasal polyposis. *Curr Med Res Opin*. 2020;36(11):1897–1911. doi:10.1080/03007995.2020.1815682
84. Liu J, Zhou L, Yao X, Wu Y. Research progress in TCM for the improvement of nasal mucosa remodeling after endoscopy in chronic sinusitis. *Chin J Inf TCM*. 2023;1–6.
85. Si X, Han X, Zhao S. clinical efficacy of huangqin beimutang in treatment of chronic rhinosinusitis in children. *Chin J Exp Trad Med Formulae*. 2023;29(10):160–165.
86. Xinming Xu JC, Jingbo L. Clinical study on the treatment of chronic sinusitis with deficiency–cold of Lung Qi by Wenyang Zhiti decoction. *J Nanjing Univ Tradit Chin Med*. 2022;38(02):109–114.
87. Qi TF, Ma ZZ, Huang JW, Zhu ZH. Clinical study on Yangyin Qingfei decoction combined with eucalyptol limonene pinene enteric soft capsules on chronic rhinosinusitis with Yin deficiency and internal heat syndrome. *Chin J Inf TCM*. 2021;28(12):93–97.
88. Zhang LM, Li JB, Cai JT, Chen WM. Short-term effect of modified kaijie huatantang on chronic rhinosinusitis with nasal polyp due to Qi Stagnation Phlegm syndrome. *Chin J Exp Trad Med Formulae*. 2021;27(03):123–128.

89. Fan X. *Ancient Literature of Traditional Chinese medicine Treatment of Nasosinusitis Based on Data Mining*. Jiangxi University of Chinese Medicine; 2021.
90. Li Y. Syndrome differentiation of chronic sinusitis. *J Otolaryngol Ophthalmol Shandong Univ*. 2018;32(03):27–30.
91. liu P. *Traditional Chinese Medicine Otolaryngology*. Beijing: China Press of Traditional Chinese Medicine; 2021.
92. Yajing Diao SX. Role of macrophage polarization in atherosclerosis based on the yin and yang theory of tradition Chinese medicine. *World Chinese Medicine*. 2023;18(06):823–827.
93. Zhang W. *Clinical Observation on Modified Shenling BaizhuPoweder in Treating Chronic Rhinosinusitis with Deficiency of Spleen Qi After Nasal Endoscopy*. Fujian University of Chinese Medicine; 2020.
94. Wang M. *Clinical Observation of Jianpi Qingrelishi Decoction in the Treatment of Sinusitis in Children with Damp Heat Syndrome*. Shandong University of Chinese Medicine; 2019.
95. Huang G. Clinical analysis of the treatment of chronic rhinosinusitis with nasal polyps using warm-yang and dampness-dispelling therapy. *Guangming J Chin Med*. 2019;34(10):1477–1479.
96. Ma L. The treatment of chronic sinusitis with the method of strengthening the spleen and promoting dampness: a report of 110 cases. *Guangming J Chin Med*. 2013;28(07):1362–1363.
97. Lu H, Wu L, Liu L, et al. Quercetin ameliorates kidney injury and fibrosis by modulating M1/M2 macrophage polarization. *Biochem Pharmacol*. 2018;154:203–212. doi:10.1016/j.bcp.2018.05.007
98. Cai ZH, Tian YG, Li JZ, et al. Peimine ameliorates pulmonary fibrosis via the inhibition of M2-type macrophage polarization through the suppression of P38/Akt/STAT6 signals. *Biosci Rep*. 2022;42(10). doi:10.1042/BSR20220986
99. Iwanowycz S, Wang J, Hodge J, Wang Y, Yu F, Fan D. Emodin inhibits breast cancer growth by blocking the tumor-promoting feedforward loop between cancer cells and macrophages. *Mol Cancer Ther*. 2016;15(8):1931–1942. doi:10.1158/1535-7163.MCT-15-0987
100. Xu F, Cui WQ, Wei Y, et al. Astragaloside IV inhibits lung cancer progression and metastasis by modulating macrophage polarization through AMPK signaling. *J Exp Clin Cancer Res*. 2018;37(1):207. doi:10.1186/s13046-018-0878-0
101. Sun L, Chen B, Jiang R, Li J, Wang B. Resveratrol inhibits lung cancer growth by suppressing M2-like polarization of tumor associated macrophages. *Cell Immunol*. 2017;311:86–93. doi:10.1016/j.cellimm.2016.11.002
102. Zhao H, Zhang X, Chen X, et al. Isoliquiritigenin, a flavonoid from licorice, blocks M2 macrophage polarization in colitis-associated tumorigenesis through downregulating PGE2 and IL-6. *Toxicol Appl Pharmacol*. 2014;279(3):311–321. doi:10.1016/j.taap.2014.07.001
103. Song Y, Wu Y, Li X, et al. Protostemonine attenuates alternatively activated macrophage and DRA-induced asthmatic inflammation. *Biochem Pharmacol*. 2018;155:198–206. doi:10.1016/j.bcp.2018.07.003
104. Wang B, Zheng X, Liu J, et al. Osthole inhibits pancreatic cancer progression by directly exerting negative effects on cancer cells and attenuating tumor-infiltrating M2 macrophages. *J Pharmacol Sci*. 2018;137(3):290–298. doi:10.1016/j.jphs.2018.07.007
105. Lin W. *Gujin Xiao Liu Tang Induces Apoptosis of M2 Polarized Tumor Associated Macrophages and Its clinical Application in Stage IV NSCLC Patients*. Guangzhou University of Chinese Medicine; 2021.
106. Chen M. *Study on Jianpi Yangzheng Xiaozheng Recipe Inhibiting Gastric Cancer EMT Through TAM*. Nanjing University of Chinese Medicine; 2016.
107. Shuangshuang H, Mengmeng S, Lan Z, Fang Z, Yu L. Maimendong decoction regulates M2 macrophage polarization to suppress pulmonary fibrosis via PI3K/Akt/FOXO3a signalling pathway-mediated fibroblast activation. *J Ethnopharmacol*. 2024;319(Pt 3):117308. doi:10.1016/j.jep.2023.117308
108. He S, Wang S, Liu S, Li Z, Liu X, Wu J. Baicalein potentiated M1 macrophage polarization in cancer through targeting PI3Kgamma/NF-kappaB signaling. *Front Pharmacol*. 2021;12:743837. doi:10.3389/fphar.2021.743837
109. Yin L, Fan Z, Liu P, et al. Anemoside A3 activates TLR4-dependent M1-phenotype macrophage polarization to represses breast tumor growth and angiogenesis. *Toxicol Appl Pharmacol*. 2021;432:115755. doi:10.1016/j.taap.2021.115755
110. Meng Y, Qu Y, Wu W, et al. Galactan isolated from Cantharellus cibarius modulates antitumor immune response by converting tumor-associated macrophages toward M1-like phenotype. *Carbohydr Polym*. 2019;226:115295. doi:10.1016/j.carbpol.2019.115295
111. Liu CP, Zhang X, Tan QL, et al. NF-kappaB pathways are involved in M1 polarization of RAW 264.7 macrophage by polyporus polysaccharide in the tumor microenvironment. *PLoS One*. 2017;12(11):e0188317. doi:10.1371/journal.pone.0188317
112. Li H, Huang N, Zhu W, et al. Modulation the crosstalk between tumor-associated macrophages and non-small cell lung cancer to inhibit tumor migration and invasion by ginsenoside Rh2. *BMC Cancer*. 2018;18(1):579. doi:10.1186/s12885-018-4299-4
113. Li T, Zhang YS, Wan M, Wu W, Yao YF, Li WJ. Ganoderma atrum polysaccharide modulates the M1/M2 polarization of macrophages linked to the notch signaling pathway. *Food Funct*. 2022;13(7):4216–4228. doi:10.1039/d1fo04309a
114. Chen Y, Bi L, Luo H, et al. Water extract of ginseng and astragalus regulates macrophage polarization and synergistically enhances DDP's anticancer effect. *J Ethnopharmacol*. 2019;232:11–20. doi:10.1016/j.jep.2018.12.003
115. Kimura Y, Sumiyoshi M. Resveratrol prevents tumor growth and metastasis by inhibiting lymphangiogenesis and M2 macrophage activation and differentiation in tumor-associated macrophages. *Nutr Cancer*. 2016;68(4):667–678. doi:10.1080/01635581.2016.1158295
116. Zhao TT, Xu YQ, Hu HM, Gong HB, Zhu HL. Isoliquiritigenin (ISL) and its formulations: potential antitumor agents. *Curr Med Chem*. 2019;26(37):6786–6796. doi:10.2174/0929867325666181112091700
117. Liu Y, Shen Y, Teng L, et al. The traditional uses, phytochemistry, and pharmacology of stemona species: a review. *J Ethnopharmacol*. 2021;265:113112. doi:10.1016/j.jep.2020.113112
118. Tan QL, Zhou CY, Liu CP. Investigation on the effects of polyporus polysaccharides on morphological changes and immune function in human macrophages. *China J Tradition Chinese Med Pharm*. 2018;33(05):1891–1896.