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Research Progress of Traditional Chinese Medicine Regulating PI3K/AKT/mTOR Signaling Pathway to Improve Myocardial Ischemia-Reperfusion Injury

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Abstract: PI3K/AKT/mTOR signaling pathway is a key pathway of myocardial ischemia-reperfusion injury (MIRI). The mechanism of action is mainly oxidative stress, inflammatory response, calcium overload, ferroptosis, autophagy, and apoptosis. MIRI belongs to the category of chest obstruction in traditional Chinese medicine, and its etiology and pathogenesis are mainly "Yang Wei Yin Xian." Traditional Chinese medicine has the effect of multi-target and multi-component effect, and has played a significant role in the treatment of MIRI in recent years. At present, the monomers of traditional Chinese medicine mainly include saponins, flavonoids, alkaloids, terpenoids, and phenols, and the compounds mainly include Zhigancao Decoction, Zhenyuan Capsule, Jiawei Shenqibai Powder, Qili Qiangxin Capsule, Tongmai Yangxin Pill, Zhilong Huoxue Tongyu Capsule, Guizhi Tongluo Tablets, etc. This paper reviews the research on the improvement of MIRI by regulating PI3K/ AKT/mTOR signaling pathway in recent years, and expounds the mechanism and advantages of traditional Chinese medicine in the treatment of MIRI.

Keywords: Traditional Chinese medicine; PI3K/AKT/mTOR signaling pathway; Myocardial ischemia-reperfusion injury; Review

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1. Introduction

Myocardial ischemia is a primary feature of acute coronary syndrome (ACS). The ACCF/AHA/SCAI guidelines recommend early reperfusion therapy to limit myocardial damage and preserve tissue viability [1]. However, reperfusion therapy can trigger adverse cardiovascular outcomes following myocardial ischemia, cardiac surgery, or circulatory arrest [2]. In recent years, research on myocardial ischemia-reperfusion injury (MIRI) has been continuously proposed to reduce infarct size, with effective targets and signaling pathways becoming key to treatment. Studies have confirmed that the phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) pathway is one of the important signaling pathways involved in MIRI [3],

playing a major role in oxidative stress, autophagy, and apoptosis. Traditional Chinese medicine, with its multi-component, multi-target, and multi-effect approach, has an advantage in treating MIRI. This article reviews recent literature on the regulation of the PI3K/AKT/mTOR pathway by traditional Chinese medicine in the treatment of MIRI.

2. Understanding of myocardial ischemia-reperfusion injury in traditional medicine

In traditional medicine, MIRI is categorized under "chest bi" and "heart palpitations." The "Yellow Emperor's Inner Canon" records that "when pathogens invade the heart, it causes heart pain." Later, the "Jin Kui Yao Lue" proposed the pathogenesis of "Yang deficiency and Yin excess," meaning a lack of chest Yang and condensation of Yin cold. This condition is caused by a deficiency in origin and an excess in manifestation. Subsequent physicians believed that Yang deficiency is the root deficiency, which can manifest as qi deficiency and Yang deficiency, not limited to the heart. Yin excess is the excess manifestation, which can be caused by cold pathogens, phlegm, turbidity, blood stasis, etc [4,5]. The heart is the Yang within Yang, and all Yang qi gathers in the chest. The warming and promoting effects of heart Yang ensure the continuous circulation of blood. If chest Yang is insufficient, turbid Yin can cause heart pain, ultimately leading to blockage of the heart vessels. Clinically, both root deficiency and manifestation excess are often equally important. Chen Bojun's research on the TCM syndrome differentiation of 71 patients after coronary intervention showed that qi deficiency and phlegm-turbidity syndromes were significantly aggravated after surgery, and blood stasis remained the main pathological product and pathogenic factor [6], indicating that both the root and manifestation should be treated. Based on different evolutionary forms of its overall pathogenesis, later physicians proposed different dialectical treatment principles. For example, when Yang deficiency is predominant, the treatment focuses on warming the spleen and kidneys, promoting diuresis, and clearing Yang. Spleen and kidney Yang deficiency can lead to abnormal distribution of body fluids, exacerbating chest bi due to the growth of phlegm-turbidity and retained fluid [7]. When Yin excess is predominant, the treatment focuses on warming Yang and resolving phlegm. Besides the theory of "Yang deficiency and Yin excess," the theory of blood stasis and toxicity is also considered a major etiology and pathogenesis of MIRI. Some studies suggest that mitochondrial dysfunction in cardiomyocytes during MIRI can be interpreted as "qi deficiency and blood stasis." Animal experiments using an ischemia-reperfusion injury rat model have been conducted to explain the pathogenesis of qi deficiency and blood stasis in MIRI [8], focusing on myocardial energy metabolism pathways, myocardial mitochondrial complexes and their subunits, regulation of mitochondrial complex deacetylase-1, the RhoA/Rock1 of the small G protein family, cytoskeleton, myocardial structure, heart function, and cardiac microcirculation dynamics. In addition to the theory of blood stasis and toxicity, some scholars categorize MIRI as belonging to the "Jueyin" category, believing that the disease belongs to Jueyin disease with a lesion location in the pericardium. The symptoms of reperfusion arrhythmia can be attributed to "thirst, qi rushing upward, heat and pain in the heart, hunger but no desire to eat, vomiting of roundworms after eating, and incessant diarrhea after purgation." It is believed that MIRI is caused by the disconnection between Yin and Yang, with Yin predominating and Yang being deficient [9]. This coincides with the theory of "Yang deficiency and Yin excess," and treatment should focus on supporting Yang and promoting blood circulation.

3. The mechanism of PI3K/AKT/mTOR signaling pathway in MIRI

3.1. Overview of the PI3K/AKT/mTOR signaling pathway

PI3K/AKT/mTOR stands for phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin. PI3K, as the starting point of the signaling pathway, is a dimer complex with phosphatidylinositol kinase activity, which can trigger AKT activation and participate in autophagy regulation [10]. AKT, also known as PKB, is the hub of the signaling pathway. After AKT is activated by P13K, it can promote the further activation of its downstream molecule mTOR through the TSC1/2 complex [11]. AKT is an important protein for maintaining cell homeostasis, while mTOR belongs to PIKK and plays a crucial role in cell growth and proliferation. Its two complexes, mTORC1 and mTORC2, control ribosomes and are pathways for autophagy and growth metabolism, while the latter mainly activate and control proteins [12,13]. PI3K/Akt is the core pathway leading to mTOR. Akt phosphorylates the Ser2448 binding site to activate mTORC1. AKT can directly or indirectly affect mTOR, promoting cell proliferation and migration, which further leads to increased oxidative stress and autophagy [14,15].

3.2. Research progress on PI3K/AKT/mTOR regulation in MIRI

The role of PI3K/AKT/mTOR in MIRI is currently primarily achieved through oxidative stress, inflammatory response, calcium overload, ferroptosis, autophagy, and apoptosis. Oxidative stress (OS) is considered a major factor in MIRI [16]. The restoration of blood flow to ischemic parts increases oxygen, leading to excessive production of reactive oxygen species (ROS), which can damage cellular macromolecules and cause cell death [17]. ROS participates in membrane phospholipid reactions, directly disrupting cell membrane permeability and ion channels, leading to irreversible cell damage. Its production is closely related to the mitochondrial electron transport chain system, NADPH oxidase system, xanthine oxidase (XO) system, and uncoupled nitric oxide synthase [18,19]. Studies have shown that the PI3K/AKT/mTOR signaling pathway is mainly mediated by ROS and is a key pathway in oxidative stress [20]. NADPH, a pyridine dinucleotide cofactor, is a crucial electron reservoir for biosynthetic reduction and defense against oxidative stress, and its level can be influenced by PI3K-AKT signaling [21]. The inflammatory response also plays a significant role in MIRI. Studies have indicated that during MIRI, inflammatory factors such as IL-6, IL-1β, TNF-α, IL-10, and ICAM-1 significantly increase, and reducing these factors' release can significantly alleviate myocardial cell damage [22]. The PI3K/AKT/mTOR signaling pathway regulates downstream cell proliferation and inflammatory target gene expression [23]. Research suggests that this pathway can modulate the expression levels of ALT, AST, IL-1β, IL-6, TNF-α, and ammonia in blood, reducing cell necrosis and inflammatory responses. During myocardial ischemia-reperfusion, ischemia and hypoxia lead to intracellular Ca^{2+} overload, further causing myocardial cell damage [24]. Studies have shown that the PI3K/AKT/mTOR pathway participates in regulating vesicular transport and controlling factors like Ca^{2+} and calpain, affecting MIRI [25]. In 2012, scholars first proposed the role of ferroptosis in cellular metabolism and protein regulation mechanisms [26]. Iron metabolism disorders can cause iron overload, leading to mitochondrial abnormalities and exacerbating ROS production [27]. Ferroptosis can also cause immune dysregulation and mediate inflammatory responses [28]. The aforementioned ROS mediates the PI3K/AKT/mTOR signaling pathway, indirectly proving a connection between ferroptosis, PI3K/AKT/mTOR, and MIRI. PI3K participates in cell membrane formation, and once activated by PI3K, Akt transfers to the cell membrane, phosphorylating mTOR and regulating autophagy. mTORC1 can inhibit autophagy-related proteins like ULK1 and ULK2, thereby suppressing autophagy [29]. Studies have confirmed that PI3K inhibitors can reduce ROS

levels and improve ferroptosis [30]. Ferroptosis is related to autophagy, and MIRI is associated with ferroptosis, indirectly clarifying the relationship between MIRI and autophagy. The PI3K/AKT/mTOR signaling pathway is a signal transduction pathway for autophagy, which can inhibit autophagy to a certain extent, thereby improving MIRI [31]. As a programmed cell death, apoptosis can be directly induced by MIRI or indirectly triggered by oxidative stress and inflammatory responses. Oxidative stress and inflammatory factors caused by reperfusion therapy can activate the PI3K/AKT/mTOR signaling pathway, inducing myocardial cell apoptosis [32]. Current research suggests that MIRI is closely linked to oxidative stress, ferroptosis, calcium overload, apoptosis, and autophagy. The tight interconnection and mutual influence among various mechanisms, coupled with the significant role of the PI3K/AKT/mTOR signaling pathway in these mechanisms, confirm its crucial regulatory function in MIRI. Traditional Chinese medicine can multi-target and multi-actively regulate the PI3K/AKT/mTOR signaling pathway, holding profound clinical significance for improving MIRI.

4. Research progress on the improvement of MIRI by regulating the PI3K/AKT/mTOR signaling pathway with traditional Chinese medicine

The mechanism of MIRI is intricately linked to oxidative stress, inflammatory response, calcium overload, ferroptosis, autophagy, and apoptosis. Western medicine has achieved precise targeted therapy with moderate efficacy, but its limitation lies in the inability to regulate multiple targets simultaneously. Relevant studies have demonstrated that traditional Chinese medicine, including single herbs and compound prescriptions, possesses rich bioactive components and exhibits significant advantages in treating MIRI by regulating the PI3K/AKT/mTOR signaling pathway through various targets [33].

4.1. Research progress on the improvement of MIRI by regulating PI3K/AKT/mTOR with single herbs in traditional Chinese medicine

Current research has identified several types of single herbs that regulate the PI3K/AKT/mTOR signaling pathway to improve MIRI, mainly including saponins, flavonoids, alkaloids, phenols, and terpenes [34].

4.1.1. Saponins

Saponins are widely found in plants of the Araliaceae family, such as ginseng and *Panax notoginseng*, and have been extensively studied for their roles in treating not only MIRI but also cancer. In exploring the effect and mechanism of ginsenoside Rg5 (G-Rg5) against T-cell acute lymphoblastic leukemia CCRF-CEM cells, it was found that G-Rg5 can significantly reduce the activity of P-PI3K, P-AKT, and P-mTOR protein expression [35]. It may also resist cell proliferation and improve MIRI by inhibiting the PI3K/AKT/mTOR pathway and avoiding apoptosis. Besides ginsenoside, experimental studies have shown that astragaloside IV also improves MIRI-induced cardiomyocyte injury by regulating the PI3K/AKT/mTOR pathway to inhibit cell proliferation, invasion, and metastasis [36]. When investigating the regulation of autophagy and reduction of cellular hypoxia by *Panax notoginseng* saponins (PNS) and the PI3K/Akt/mTOR signaling pathway, it was discovered that PNS can modulate this pathway to inhibit autophagy and alleviate cellular hypoxia. Saponins can indeed improve MIRI through their regulation of autophagy, antioxidation, and other effects via the PI3K/Akt/mTOR signaling pathway.

4.1.2. Flavonoids

Flavonoids exhibit a variety of biological activities. Total flavonoids of *Bidens bipinnata* (TFB) are the main extract from *Bidens bipinnata* and possess anti-inflammatory and antioxidant properties [37]. Dong Fengmei and colleagues confirmed through rat experiments that TFB can lower the systolic blood pressure of hypertensive rats [38], inhibit cardiomyocyte autophagy via the PI3K/Akt/mTOR pathway, reduce oxidative stress and apoptosis, and significantly increase glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) while significantly decreasing endogenous hydrogen peroxide (H_2O_2), malondialdehyde (MDA), and reactive oxygen species (ROS). The effects are also associated with changes in Beclin-1 and LC3B-II/LC3B-I ratios. Studies have indicated that Hibiscus leaf polyphenols (HLP) protect against cellular damage by modulating the PI3K/Akt/mTOR signaling pathway, reducing oxidative stress and autophagy [39]. Another experimental study has demonstrated that total flavonoids from Aromatic Xintahua may alleviate atherosclerosis by regulating the PI3K/Akt/mTOR signaling pathway [40], reducing atherosclerotic plaque area and collagen levels in apolipoprotein E gene knockout mice, inhibiting hepatic lipid deposition and collagen expression, modulating autophagy, and suppressing inflammatory responses. As autophagy, oxidative stress, and apoptosis are major mechanisms of MIRI, flavonoids can regulate the PI3K/Akt/mTOR signaling pathway to ameliorate reperfusion injury.

4.1.3. Alkaloids

Alkaloids are mainly found in plants in nature, such as the Ranunculaceae, Menispermaceae, and Rutaceae families, and exist in the above plant species in forms such as glycosides, amides, and N-oxides. Sun Dafang and others discovered when studying the effect of total alkaloids from *Strychnos nux-vomica* on rheumatoid arthritis (RA) rats in the PI3K/Akt/mTOR signaling pathway that total alkaloids from *Strychnos nux-vomica* can reduce the levels of IL-1β, IL-6, TNF-α, and RANKL in synovial tissue of rats with rheumatoid arthritis, possibly improving inflammatory responses by inhibiting the PI3K/Akt/mTOR pathway [41]. The alkaloid components in *Corydalis* can regulate the PI3K/AKT signaling pathway to reduce the production of CK, LDH, and MDA, exerting antioxidant and anti-inflammatory effects and reducing myocardial cell damage [42].

4.1.4. Terpenes

Triterpenes are terpene compounds that exist in plants in free form or as glycosides and esters. *Ilex pubescens* triterpenoid saponins are derived from *Ilex pubescens*. Studies have shown that *Ilex pubescens* triterpenoid saponins can regulate the PI3K/Akt part of the PI3K/Akt/mTOR signaling pathway to improve myocardial ischemia [43], indicating in a sense that *Ilex pubescens* triterpenoid saponins can reduce the degree of MIRI. Total triterpenes from *Chaenomeles speciosa* are important active ingredients of *Chaenomeles speciosa*. Studies on the mechanism of action between total triterpenes from *Chaenomeles speciosa* and gastric cancer cell mitochondria have found that total triterpenes from *Chaenomeles speciosa* can inhibit mitochondrial activity and cell proliferation in cancer HGC-27 cells, which may be related to the PI3K/Akt/mTOR/p70S6K signaling pathway [44]. This suggests that total triterpenes from *Chaenomeles speciosa* can regulate the PI3K/Akt/mTOR signaling pathway to exert good antioxidant stress activity and, to some extent, improve the oxidative stress response of MIRI to protect myocardial cells.

4.1.5. Phenols

Phenols are widely found in various traditional Chinese medicines. For example, magnolol is one of the effective active ingredients of *Magnolia officinalis*, and it has antioxidant, anti-inflammatory, and autophagy-regulating effects in cardiovascular diseases [45]. Current research has found that magnolol can improve lipopolysaccharide-induced myocardial injury in mice by inhibiting the TLR4/PI3K/Akt/mTOR signaling pathway and upregulating autophagy to reduce autophagy [46]. *Salvia miltiorrhiza* is widely used in various cardiovascular diseases, such as acute myocardial infarction and angina pectoris. Salvianolic acid B is the main effective component of *Salvia miltiorrhiza*. Studies have shown that salvianolic acid B can enhance the proliferation of senescent macrophages and reduce apoptosis and inflammatory responses by regulating the PI3K/AKT/mTOR signaling pathway [47]. It can also reverse the senescence of mesenchymal stem cells, promote cell proliferation to avoid excessive apoptosis, and promote autophagy to resist myocardial fibrosis [48,49]. Eugenol can improve mitochondrial dysfunction by reducing cellular ROS and superoxide anion levels through the PI3K/AKT pathway, thereby reducing oxidative stress and improving MIRI [50].

4.2. Research progress on the improvement of MIRI by regulating PI3K/AKT/mTOR with traditional Chinese medicine compounds

4.2.1. Zhigancao Decoction

Derived from the "Treatise on Febrile Diseases," Zhigancao Decoction treats "palpitations and irregular pulses." It has significant clinical effects on arrhythmias, viral myocarditis, dilated cardiomyopathy, and coronary heart disease [51]. Zheng *et al*. explored the mechanism of Zhigancao Decoction (consisting of 12g licorice, 9g ginger, 9g cassia twig, 6g ginseng, 50g rehmannia root, 6g donkey-hide gelatin, 10g ophiopogon root, 10g hemp seed, and 10 dates) on rats with MIRI-induced arrhythmias [52]. The results showed that Zhigancao Decoction significantly reduced myocardial enzymes CK, LDH, AST, and CtnI, inhibited autophagy, upregulated the expression of PI3K, Akt, and mTOR, and effectively regulated the PI3K/AKT/mTOR signaling pathway to resist reperfusion arrhythmias.

4.2.2. Zhenyuan Capsule

Zhenyuan Capsule is a traditional Chinese medicine preparation with ginseng fruit saponins as the main component, including Rb1, Rb2, Rc, Rd, Re, Rg1, Rg2, etc., among which ginsenoside Re accounts for up to 85%. Ginseng greatly replenishes qi, and saponin compounds have significant antioxidant effects. Based on this, the traditional Chinese medicine preparation Zhenyuan Capsule was developed. Studies exploring the mechanism of Zhenyuan Capsule in treating MIRI rat models have found that it can resist oxidative stress, inhibit myocardial cell damage, and inhibit cell apoptosis and autophagy by activating the PI3K/Akt/mTOR signaling pathway [53].

4.2.3. Modified Shenqi Posan

Modified Shenqi Posan consists of American ginseng, pseudo-ginseng, amber, turmeric, and St. John's wort. It originates from Professor Yue Meizhong, a famous traditional Chinese medicine practitioner, and is modified from "Ginseng and Pseudo-Ginseng Amber Powder." In this formula, ginseng is the monarch ingredient, greatly replenishing qi; pseudo-ginseng and amber are the minister ingredients, working together to promote blood circulation and remove blood stasis, and calm the nerves; turmeric and St. John's wort are added as assistants

to enhance the effects of soothing the liver and regulating qi, promoting blood circulation and relieving depression. Studies have shown that Modified Shenqi Posan inhibits autophagy by suppressing the PI3K/Akt/mTOR signaling pathway, reduces inflammatory responses to protect against MIRI, and also has antidepressant effects [54].

4.2.4. Qili Qiangxin Capsule

Qili Qiangxin Capsule, whose main ingredients include Astragalus, Ginseng, Radix Aconiti Lateralis Preparata, Salviae Miltiorrhizae Radix et Rhizoma, Semen Lepidii Apetalae, Alismatis Rhizoma, Polygonatum Odoratum, Cassia Twig, Carthami Flos, Citrus Reticulata Pericarpium, and Cortex Periplocae, can nourish qi and invigorate blood circulation, warm yang, and facilitate diuresis. Studies on the mechanism of Qili Qiangxin Capsule's effect on MIRI rats have confirmed that it can regulate the PI3K/AKT/FOXO3 signaling pathway to modulate autophagy, reduce cardiomyocyte apoptosis, maintain mitochondrial membrane potential stability, and improve cardiomyocyte energy supply [55].

4.2.5. Guizhi Tongluo Tablet

Guizhi Tongluo Tablet, whose main ingredients include *Cassia* twig, *Ilex pubescens* root, and *Sargassum*, can warm the meridians and promote blood circulation, and treat heart diseases caused by Yang deficiency and Yin excess. Previous studies have confirmed that Guizhi Tongluo Tablet can significantly reduce the expression of inflammatory factors such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in atherosclerotic mice [56,57]. Studies have also shown that Guizhi Tongluo Tablet can improve heart function, inhibit inflammatory response, reduce cardiomyocyte apoptosis, suppress IL-1β, IL-6, and TNF-α levels, and improve MIRI by reducing cardiac inflammatory response through the regulation of the PI3K/Akt signaling pathway [58].

4.2.6. Tongmai Yangxin Pill

Tongmai Yangxin Pill is a modified combination of Glycyrrhizae Radix et Rhizoma Decoction and Shengmai Powder prescribed by Professor Ruan Shiyi. It consists of Rehmanniae Radix et Rhizoma, Caulis Spatholobi, Ophiopogonis Radix, Glycyrrhizae Radix et Rhizoma, Schisandrae Chinensis Fructus, Polygoni Multiflori Radix Praeparata, Codonopsis Radix, Carapax et Plastrum Testudinis, Colla Corii Asini, Jujubae Fructus, and Cassia Twig. With Rehmanniae Radix et Rhizoma and Glycyrrhizae Radix et Rhizoma as the monarch drugs, it has the effect of nourishing qi and Yin, clearing meridians, and relieving pain [59]. Previous studies have confirmed the significant efficacy of Tongmai Yangxin Pill in MIRI. It participates in various metabolic, oxidative stress, and inflammatory responses, and improves the gene expression levels of ERα, PI3K, AKT, and the protein expression levels of ERα, p-PI3K, p-AKT to regulate MIRI-induced heart damage. Its mechanism may be related to the ERα/PI3K/AKT pathway [60,61].

4.2.7. Zhilong Huoxue Tongyu Capsule

Zhilong Huoxue Tongyu Capsule consists of *Astragalus*, *Hirudo*, *Lumbricus*, *Sargentodoxa cuneata*, and *Cassia* twig. It contains a large amount of effective compounds such as saponins and flavonoids. Previous studies have shown that Zhilong Huoxue Tongyu Capsule can inhibit inflammatory response, protect vascular endothelium, promote cardiomyocyte proliferation, and have other protective effects on cardiomyocytes in MIRI [62]. On this

basis, existing research shows that Zhilong Huoxue Tongyu Capsule can regulate the PI3K/AKT/Nrf2 signaling pathway to promote HO-1/GPX4 expression, thereby improving the ferroptosis induced by myocardial ischemia-reperfusion and improving MIRI [63].

5. Summary and outlook

The PI3K/Akt/mTOR pathway, as one of the key pathways in MIRI, is a current research hotspot. Existing research on traditional Chinese medicine monomers is more reflected in experimental studies. Currently, compound prescriptions and monomer prescriptions can mutually verify and complement each other, confirming the effectiveness of traditional Chinese medicine in regulating the PI3K/Akt/mTOR signaling pathway to improve MIRI. The current research on traditional Chinese medicine monomers mainly focuses on saponins, flavonoids, alkaloids, terpenes, and phenols. The mechanism of regulating PI3K/Akt/mTOR is primarily manifested in oxidative stress and inflammatory responses, while research on autophagy, apoptosis, and ferroptosis mechanisms targeting MIRI is relatively limited. The number of studies on traditional Chinese medicine compounds acting on the complete PI3K/Akt/mTOR signaling pathway is limited. In summary, the research on the mechanism of multi-component and multi-target regulation of the PI3K/Akt/mTOR signaling pathway by traditional Chinese medicine is still incomplete.

In the future, potential targets should continue to be explored, and the interaction between drugs and the body should be explored through network pharmacology and other means, focusing on system biology and biological network balance. This approach can reveal multi-pathway regulation of signaling pathways, improve treatment effectiveness and the success rate of clinical trials for new drugs, and provide a research foundation for the development of new preparations for the treatment of MIRI. Especially in the treatment of multi-target and complex diseases, combining the holistic concepts of traditional Chinese medicine and formula compatibility can offer new ideas for the complex system of traditional Chinese medicine.

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References

[1] Levine GN, Bates ER, Blankenship JC, et al., 2011, American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions.2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol, 58(24): e44–122.

[2] Frank A, Bonney M, Bonney S, et al., 2012, Myocardial Ischemia Reperfusion Injury: From Basic Science to Clinical Bedside. Semin Cardiothorac Vasc Anesth, 16(3): 123–132.

[3] Huang J, Chen L, Wu J, et al., 2022, Targeting the PI3K/AKT/mTOR Signaling Pathway in the Treatment of Human Diseases: Current Status, Trends, and Solutions. J Med Chem, 65(24): 16033–16061.

[4] Tian Y, 2012, Initial Exploration of the Meaning of "Yang Micro and Yin String" in the Differential Treatment of Chest Bi Syndrome. Liaoning Journal of Traditional Chinese Medicine, 39(3): 451–452.

[5] Hu N, Wang B, 2016, Discussion on the Treatment of Chest Bi and Heartache from the Perspective of "Yang Micro and Yin String." Zhejiang Journal of Traditional Chinese Medicine, 51(5): 374.

[6] Chen B, Pan Z, Su X, et al., 2007, Study on the Changes of TCM Syndrome Types Before and After Interventional Therapy for Coronary Heart Disease. Chinese Journal of Integrated Traditional and Western Medicine, (08): 689–691.

[7] Wang X, Zhang S, Shu H, et al., 2016, Examples of Professor Chen Xinyu's Theory Application of "Yang Micro and Yin String Means Chest Bi and Pain." Chinese Journal of Emergency in Traditional Chinese Medicine, 25(5): 819–820 + 838.

[8] Han J, 2019, Scientific Connotation of Heart Qi Deficiency and Blood Stasis and the Mechanism of Qi Shen Yi Qi Dropping Pills in Tonifying Qi and Activating Blood. World Science and Technology—Modernization of Traditional Chinese Medicine, 21(02): 139–147.

[9] Chen C, Dong B, 2019, Analysis of the Etiology and Pathogenesis of Myocardial Ischemia-Reperfusion Injury from the Perspective of Jueyin Disease in Traditional Chinese Medicine. Journal of Integrated Traditional Chinese and Western Medicine in Cardiovascular and Cerebrovascular Diseases, (5): 783–785.

[10] Sarris EG, Saif MW, Syrigos KN, 2012, The Biological Role of PI3K Pathway in Lung Cancer. Pharmaceuticals (Basel), 5(11): 1236–1264.

[11] Xue JF, Shi ZM, Zou J, et al., 2017, Inhibition of PI3K / AKT / mTOR Signaling Pathway Promotes Autophagy of Articular Chondrocytes and Attenuates Inflammatory Response in Rats with Osteoarthritis. Biomed Pharmacother, 89: 1252–1261.

[12] Wullschleger S, Loewith R, Hall MN, 2006, TOR Signaling in Growth and Metabolism. Cell, 124(3): 471–484.

[13] Pattingre S, Espert L, Biard-Piechaczyk M, et al., 2008, Regulation of Macroautophagy by mTOR and Beclin 1 Complexes. Biochimie, 90(2): 313–323.

[14] Ghomlaghi M, Yang G, Shin SY, et al., 2021, Dynamic Modelling of the PI3K/mTOR Signalling Network Uncovers Biphasic Dependence of mTORC1 Activity on the mTORC2 Subunit SIN1. PLoS Comput Biol, 17(9): e1008513.

[15] Li M, Wang H, 2018, Research Progress on the Anti-atherosclerotic Effect of Emodin in Processed Polygonum Multiflorum. Journal of Practical Traditional Chinese Medicine, 34(8): 1012–1014.

[16] Goncharov RG, Sharapov MG, 2023, Ischemia-reperfusion Injury: Molecular Mechanisms of Pathogenesis and Methods of Their Correction. Mol Biol, 57(6): 1143.

[17] Heusch G, Andreadou I, Bell R, et al., 2023, Health Position Paper and Redox Perspectives on Reactive Oxygen Species as Signals and Targets of Cardioprotection. Redox Biol, 67: 102894.

[18] Lee MCI, Velayutham M, Komatsu T, et al., 2014, Measurement and Characterization of Superoxide Generation from Xanthine Dehydrogenase: A Redox-regulated Pathway of Radical Generation in Ischemic Tissues. Biochemistry, 53(41): 6615.

[19] Ma MW, Wang J, Zhang Q, et al., 2017, NADPH Oxidase in Brain Injury and Neurodegenerative Disorders. MolNeurodegener, 12(1): 7.

[20] Kurian GA, Rajagopal R, Vedantham S, et al., 2016, The Role of Oxidative Stress in Myocardial Ischemia and Reperfusion Injury and Remodeling: Revisited. Oxid Med Cell Longev, 2016: 1656450.

[21] Hoxhaj G, Manning BD, 2020, The PI3K-AKT Network at the Interface of Oncogenic Signalling and Cancer

Metabolism. Nat Rev Cancer, 20(2): 74–88.

[22] Xu X, Liang T, Lin X, et al., 2015, Effect of the Total Extract of Averrhoacarambola (Oxalidaceae) Root on the Expression Levels of TLR4 and NF-κB in Streptozotocin-Induced Diabetic Mice. Cell Physiol Biochem, 36(6): 2307–2316.

[23] Stark AK, Sriskantharajah S, Hessel EM, et al., 2015, PI3K Inhibitors in Inflammation, Autoimmunity and Cancer. Curr Opin Pharmacol, 23: 82–91.

[24] Ye J, Wang R, Wang M, et al., 2021, Hydroxysafflor Yellow A Ameliorates Myocardial Ischemia/Reperfusion Injury by Suppressing Calcium Overload and Apoptosis. Oxid Med Cell Longev, 2021: 6643615.

[25] Murphy E, Steenbergen C, 2008, Mechanisms Underlying Acute Protection from Cardiac Ischemia-reperfusion Injury. Physiol Rev, 88(2): 581–609.

[26] Dixon SJ, Lemberg KM, Lamprecht MR, et al., 2012, Ferroptosis: An Iron-dependent Form of Nonapoptotic Cell Death. Cell, 149(5): 1060–1072.

[27] Wang L, Wang Z, Yu L, et al., 2022, Research Progress on Iron Metabolism and Iron Homeostasis Imbalance. Journal of Public Health and Preventive Medicine, 33(3): 118–122.

[28] Tang D, Chen X, Kang R, et al., 2021, Ferroptosis: Molecular Mechanisms and Health Implications. Cell Research, 31(2): 107–125.

[29] Zou C, Chen C, Wang F, et al., 2021, Research Progress on Autophagy Modulators based on the PI3K/Akt/mTOR Signaling Pathway. Chinese Journal of Medicinal Chemistry, 31(10): 825–833.

[30] Jia M, Qiu H, Lin L, et al., 2022, Inhibition of the PI3K/AKT/mTOR Signaling Pathway Activates Autophagy and Suppresses Peritoneal Fibrosis in the Process of Peritoneal Dialysis. Frontiers in Physiology, 13: 778479.

[31] Zheng W, Zhan Z, Wu Z, et al., 2023, Alprostadil Regulates the PI3K/AKT/mTOR Pathway to Inhibit Autophagy Induced by Myocardial Ischemia-reperfusion Injury. Chinese Journal of Gerontology, 43(13): 3280–3285.

[32] Yao M, Zhang J, Li Z, et al., 2021, Liraglutide Protects Nucleus Pulposus Cells Against High-Glucose Induced Apoptosis by Activating PI3K/Akt/mTOR/Caspase-3 and PI3K/Akt/GSK3beta/Caspase-3 Signaling Pathways. Front Med (Lausanne), 8: 630962.

[33] Li J, Guo Z, Xu J, et al., 2022, Research Progress on the Dose-effect Relationship of Traditional Chinese Medicine Intervention in Myocardial Ischemia-reperfusion Injury. Chinese Archives of Traditional Chinese Medicine, 40(10): 8–11.

[34] Li X, Yu H, Wang S, et al., 2025, Research Progress on the Treatment of Myocardial Ischemia-reperfusion Injury by Regulating the PI3K/AKT/mTOR Signaling Pathway with Monomeric Components of Traditional Chinese Medicine. Journal of Liaoning University of Traditional Chinese Medicine, 27(04): 203–208.

[35] Gui C, Xu L, Ma N, 2025, Ginsenoside Rg5 Inhibits the Growth of Acute Leukemia Cells by Regulating the PI3K Signaling Pathway. Journal of Qiqihar University of Medicine, 46(04): 317–320.

[36] Yin S, Gao Y, Dai H, et al., 2025, Study on the Inhibitory Effect of Astragaloside II on the Proliferation, Invasion, and Metastasis of Triple-negative Breast Cancer Cells. Journal of Taizhou Vocational and Technical College, 25(01): 63–66 + 96.

[37] Xu J, Pan K, Liu F, 2017, Research Progress on the Pharmacodynamics of Total Flavonoids from Bidens Bipinnata. Journal of Traditional Chinese Medicine, 32(4): 610–612.

[38] Dong F, Han L, 2023, Effects of Total Flavonoids from Bidens Bipinnata on Myocardial Fibrosis in Hypertensive Rats by Regulating the PI3K/Akt/mTOR Autophagy Pathway. Guangdong Medical Journal, 44(06): 720–728.

[39] Chen J, Lee M, Wang C, et al., 2017, Autophagic Effects of Hibiscus Sabdariffa Leaf Polyphenolsand Epicatechin

Gallate (ECG) Against Oxidized LDL-induced Injury of Humanendothelial Cells. European Journal of Nutrition, 56(5): 1963–1981.

[40] Ma X, 2023, Study on the Mechanism of Action of Total Flavonoids from Aromatic Ziziphora Improving AS by Regulating the PI3K/Akt/mTOR Pathway, dissertation, Shihezi University.

[41] Sun D, Niu Z, Zhang S, et al., 2023, Exploring the Effect and Mechanism of Total Alkaloids from Strychnos Nux-vomica on Rats with Rheumatoid Arthritis based on the PI3K/Akt/mTOR Pathway. Modern Chinese Medicine, 25(12): 2521–2527.

[42] Li J, Wu J, Huang J, et al., 2022, Uncovering the Effect and Mechanism of Rhizoma Corydalis on Myocardial Infarction Through an Integrated Network Pharmacology Approach and Experimental Verification. Front Pharmacol, 13: 927488.

[43] Wu J, Chen S, Wu P, et al., 2022, Cathepsin B/HSP70 Complex Induced by Ilexsaponin I Suppresses NLRP3 Inflammasome Activation in Myocardial Ischemia/reperfusion Injury. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 105: 154358.

[44] Feng M, Xu H, He H, et al., 2019, Total Triterpenes from Chaenomeles Speciosa induce Apoptosis in Gastric Cancer Cells by Regulating miR-10a and the PI3K/Akt/mTOR/p70S6K Signaling Pathway. Chinese Medicinal Materials, 42(12): 2929–2935.

[45] Zhang M, Shen Y, 2022, Research Progress on the Cardiovascular Pharmacological Effects of Magnolol. Anti-Infection Pharmacy, 19(10): 1395–1400.

[46] Du B, Lu M, Sui H, et al., 2025, Magnolol Regulates the TLR4/PI3K/Akt/mTOR Signaling Pathway and Autophagy to Improve Lipopolysaccharide-induced Myocardial Injury. Chinese Journal of Hospital Pharmacy, 45(09): 1000–1005 + 1014.

[47] Huang J, Mao J, Gu Y, et al., 2024, Study on the Effect of Salvianolic Acid B on the Biological Function of Senescent Macrophages through the PI3K/AKT/mTOR Signaling Pathway. New Chinese Medicine, 56(12): 197–203.

[48] Wang F, 2024, Salvianolic Acid B Reverses High Glucose-induced Senescence of Human Adipose-derived Mesenchymal Stem Cells by Inhibiting the PI3K/AKT/mTOR Signaling Pathway, dissertation, Chuanbei Medical College.

[49] Du J, Shi K, Zhao Y, et al., 2019, Salvianolic Acid B Promotes Autophagy and Reduces Myocardial Fibrosis in Rats by Inhibiting the PI3K/AKT/mTOR Pathway. Progress in Modern Biomedicine, 19(20): 3812–3817.

[50] Zhang ZD, Yang YJ, Liu XW, et al., 2021, The Protective Effect of Aspirin Eugenol Ester on Oxidative Stress to PC12Cells Stimulated with H2O2 through Regulating PI3K/Akt Signal Pathway. Oxid Med Cell Longev, 2021: 5527475.

[51] Qiao D, Zhou Y, 2017, Clinical Application of Zhi Gan Cao Tang in Cardiovascular Diseases. Journal of Emergency in Traditional Chinese Medicine, 26(10): 1775–1776.

[52] Zheng X, Ma C, Chen Y, et al., 2020, Exploring the Mechanism of Zhi Gan Cao Tang's Effect on Ventricular Tachycardia and Ventricular Fibrillation Caused by MIRI in Rats Based on the PI3K/Akt/mTOR Signaling Pathway. Chinese Journal of Experimental Traditional Medical Formulae, 26(17): 1–8.

[53] Sun M, 2020, Zhenyuan Capsule Protects Rat Myocardial Ischemia-Reperfusion Injury by Regulating Autophagy via the PI3K/Akt/mTOR Signaling Pathway, dissertation, Jilin University.

[54] Xu J, Liu J, Chen L, et al., 2024, Modified Shenqi Posan Protects Ischemic Myocardium in Rats with Acute Myocardial Infarction Combined with Psychological Stress by Regulating the PI3K/Akt/mTOR Signaling Pathway. Chinese Journal of Integrated Traditional and Western Medicine, 44(12): 1462–1470.

[55] Wu N, 2024, Study on the Effect and Mechanism of Qili Qiangxin Capsule in Reducing Myocardial Ischemia-

Reperfusion Injury via the PI3K/AKT/FOXO3 Signaling Pathway, dissertation, Guangzhou University of Chinese Medicine.

[56] Pan X, Xu H, Ding Z, et al., 2024, Guizhitongluo Tablet Inhibits Atherosclerosis and Foam Cell Formation through Regulating Piezo1/NLRP3 Mediated Macrophage Pyroptosis. Phytomedicine, 132: 155827.

[57] He X, Li S, Li Z, et al., 2025, Study on the Efficacy and Mechanism of Guizhi Tongluo Tablets in Alleviating Atherosclerosis by Inhibiting CD72hi Macrophages. China Journal of Chinese Materia Medica, 50(5): 1298.

[58] Zhang J, Yao M, Pang S, et al., 2025, Study on the Effect and Mechanism of Guizhi Tongluo Tablets in Activating the PI3K/Akt Pathway to Reduce Cardiac Inflammation and Improve Myocardial Ischemia-reperfusion Injury in Mice. China Journal of Chinese Materia Medica, 1–9.

[59] Pang J, Yang J, Chen S, et al., 2021, Clinical Study on the Treatment of Stable Angina Pectoris with Deficiency of Both Qi and Yin Using Tongmai Yangxin Pills. Liaoning Journal of Traditional Chinese Medicine, 48(10): 115–119.

[60] Cai XM, Du J, Li L, et al., 2018, Clinical Metabolomics Analysis of Therapeutic Mechanism of Tongmai Yangxin Pill on Stable Angina. Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences, 1100–1101, 106–112.

[61] Yu L, 2024, Study on the Mechanism of Tongmai Yangxin Pills in Intervening Myocardial Ischemia/reperfusion Injury in Rats by Activating the ERα/PI3K/AKT Signaling Pathway, dissertation, Tianjin University of Traditional Chinese Medicine.

[62] Tang R, Zhang J, Ren W, et al., 2022, Research Progress on the Prevention and Treatment of Cardiovascular Diseases with Zhilong Huoxue Tongyu Capsule. Pharmacology and Clinics of Chinese Materia Medica, 38(03): 237–240.

[63] Zhao X, 2024, Zhilong Huoxue Tongyu Capsule Inhibits Ferroptosis of Cardiomyocytes and Reduces Ischemia-reperfusion Injury through the PI3K/AKT/Nrf2 Axis, dissertation, Southwest Medical University.