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•Reviews•

Metabolomics and its application in the treatment of coronary heart disease with traditional Chinese medicine

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[ABSTRACT] Traditional Chinese Medicine (TCM) is the treasure of Chinese Nation and gained the gradual acceptance of the international community. However, the methods and theories of TCM understanding of diseases are lack of appropriate modern scientific characterization systems. Moreover, traditional risk factors cannot promote to detection and prevent those patients with coronary artery disease (CAD) who have not developed acute myocardial infarction (MI) in time. To sum up, there is still no objective systematic evaluation system for the therapeutic mechanism of TCM in the prevention and cure of cardiovascular disease. Thus, new ideas and technologies are needed. The development of omics technology, especially metabolomics, can be used to predict the level of metabolites *in vivo* and diagnose the physiological state of the body in time to guide the corresponding intervention. In particular, metabolomics is also a very powerful tool to promote the modernization of TCM and the development of TCM in personalized medicine. This article summarized the application of metabolomics in the early diagnosis, the discovery of biomarkers and the treatment of TCM in CAD.

[KEY WORDS] Traditional Chinese medicine; Metabolomics; Coronary heart disease; Biomarkers; Research progress

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Introduction

Cardiovascular disease, especially coronary artery disease (CAD) seriously harms global human health [1]. In China, the number of patients with CAD is also increasing year by year [2]. The morbidity of CAD has dramatically risen compared with other diseases, which greatly increases people's economic burden [3]. The occurrence of CAD is the result of the interaction between the factors of genetic and environmental, involving a complex abnormal metabolism, which include lipid, amino acid, carbohydrate and bile metabolism. In the early stage of CAD, forming plaques composed of oxidized lipids in the coronary arteries and lead to atherosclerosis [4-6]. Moreover, current detection methods cannot effectively detect high-risk factors in the initial stages of CAD patients [7]. In order to increase the identification of risk factors of CAD, improving the prevention, diagnosis and prognosis of CAD, the new technologies need to be developed urgent [8], which could ultimately affected the early diagnosis and personalized treatment of CAD [9].

Traditional Chinese Medicine (TCM) is a "gem" of China scientific heritage and the accumulation of Chinese Nation's clinical experience for thousands of years. However, the methods and theories of TCM understanding of diseases are lack of appropriate modern scientific characterization systems. Therefore, establishing a bridge between TCM and modern medicine is significantly important and the key of modernization of TCM. The rise and development of systems biology, especially metabolomics, can systematically study the changes of metabolites in the physiological process of the body, gradually playing an important role in identification of metabolic biomarkers and improving the diagnosis as well as

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treatment of diseases [10]. Its method and design resemble those of TCM, which provides opportunities and challenges on modernization of TCM and serves as a bridge between TCM and modern medicine research [11]. In this review, we will review the applications of metabolomics in the early diagnosis, the discovery of biomarkers and the treatment of TCM in CAD, which aims to provide theoretical basis on the prevention and treatment of cardiovascular disease by TCM, and provides new vision and idea for the modernization of TCM.

Application of Metabolomics in the Diagnosis of CAD

The pathological changes of diseases often lead to changes in the body's basal metabolism, which in turn causes corresponding changes in the types or concentrations of molecular metabolites, these changes may occur earlier than clinical symptoms. Using metabolomics techniques to monitor these changes and find biomarkers, are closely related to the disease is a feasible method to realize the early diagnosis of diseases.

Distinguish the differences of TCM syndromes

How to accurately to identify different Chinese medicine syndromes (*Zheng*) in many disease models is one of the most difficult problems as well as the hot topics in medical research at present, which seriously restricts the modernization of TCM [11-12]. The principle of metabolomics is to understand the physiological and pathological states of the organism by comprehensive analyses of the metabolites with low relative molecular weight after external stimuli, which enables study of change in human metabolic relate to disease from the whole perspective [13]. The holistic view of metabolomics is very similar to the theory of TCM and can be used as a method to scientifically express the theory of TCM, such as Chinese medicine syndromes.

To explore the feasibility of plasma metabolomics in the classification of syndrome diseases combined with animal models. Qiu *et al*. analyzed the heart failure rats caused by ligation of the left coronary artery (LAD) through the plasma metabolomics. The trends of four plasma metabolites are consistent with previous study on patients with the blood stasis syndrome [14]. Similarly, to order to study the correlation between Chinese medical types of CAD [phlegm turbidity syndrome (PTS) and *qi* deficiency syndrome (QDS)] and their metabolites, the serum endogenous metabolites of sixty-five CAD patients are analyzed by metabolomics. Comparison of metabolites showed that contents of serine and 2-hydroxypropionic acid were higher in patients with PTS than QDS, which indicate that metabolomics technology might become a new research method for TCM syndrome typing [15]. In addition, the research shown that there were specific differential metabolites in CAD patients with phlegm and blood stasis, and lipid metabolism disorders occurred more frequently in patients with phlegm. However, the CAD patients with blood stasis were more complicated, and the metabolic disorder mainly includes glucose, fat and protein metabolism and even severe vascular cell membrane injury [16]. Yang *et al* also demonstrated that glucose metabolism and lipid metabolism disorders were the major contributors to the syndrome classification of CAD with blood stasis syndrome by analyzed the metabolite profiles [17].

Metabolomic profiles for the early detection of CAD

Patients with CAD before developing acute MI cannot be diagnosed timely by traditional risk factors. Thus, it is essential to accurately defined patient who is at the risk of acute coronary syndrome by new predictive diagnostic strategy. As one of the research methods of system biology, metabolomics can analyze the diseases from the perspective of metabolism and have an initial advantage in the early diagnosis of CAD.

A research analyzed three groups of serum sample from different patients by UPLC-QTOF-MS/MS, including patients with stable angina, acute MI and control. The results showed significant differences in metabolomic profiles between patients with acute MI and stable angina, which found the ceramides, bile acid, steroids hormone and dehydroepiandrosterone sulfate were closely related to the development of CAD [18]. Identification and treatment of the rupture prone atherosclerotic plaque is a breakthrough in reducing the morbidity and mortality of cardiovascular disease [19-20]. 165 different metabolites in 159 carotid plaques from patients undergoing endarterectomy were measured by targeted metabolomics and that found the different metabolite profiles identified in high-risk and stable plaques were consistent with different transcription levels of metabolic enzymes, suggesting that metabolism of high-risk plaques has changed [21]. The similar research has found that plasma metabolomic characteristics of thrombotic myocardial infarction differ from those of non-thrombotic myocardial infarction and stability CAD [22]. Elucidating the metabolite profiles of MI is essential for its prevention and treatment. Wang *et al*. identified twenty-two different metabolites between the non-infarcted myocardia and infarcted myocardia, which were associated with energy deficit, acidosis, ionic imbalance, oxidative stress and cardiac injury after MI. More importantly, the study found that glutamine, lactate and glutamate have the potential as diagnostic value for MI and have been well validated in the serum [23].

Biomarker of discovery in CAD

There are many risk factors for cardiovascular disease, such as smoking, hypertension, lipid abnormality, and diabetes, However, according to the current evaluation standard for risk factors, approximately half of people developing CAD will be considered low or medium risk [24-27]. The discovery and confirmation of biomarkers is one of the important breakthroughs in terms of improving the diagnosis of risk factors for CAD.

Unstable angina (UA) is a common complication from CAD [28-29]. At present, the diagnosis of UA was mainly judged by some symptoms of angina and electrocardiogram [30]. Nevertheless, it is an important to recognize the limitations of this method, which mainly relate to the back of objectivity regarding symptoms and the nature of the variations in electrocardiogram. The application of metabolomics technique

provides a high practical value for diagnosis of UA. In the study, eighteen biomarkers that may be associated with UA were identified based on serum metabolomics [31], and these biomarkers could promote the early diagnose of UA patients and the development of personalized medicine. Lethal ventricular tachyarrhythmia (LVTA) is the main inducement factor of sudden cardiac death (SCD). To study the metabolic characteristics of the myocardia after undergoing LVTA and discover potential biomarkers for diagnose of LVTA. Aconitine injection or coronary artery ligation was employed to induce two LVTA rat models (cardiac ion channel disease-related and cardiac ischemia-related SCD). Thirty-eight differential metabolites were identified in aconitine-induced LVTA rat, among which thirty-one metabolites were changed, the trends were consistent with coronary artery ligation-related LVTA rats. Moreover, the research found that L-valine, L-leucine and stearic acid have potential in serving as biomarkers for the diagnosis of LVTA-related SCD [32].

Recently, metabolomics has made great progress in CAD biomarker recognition [33-34]. "Functional metabolomics" is an analytical technique that combines biomarker discovery by metabolite profiling with further functional analysis through biological methods. It will fill the gap between the biomarkers and mechanistic relevance to disease pathogenesis. Untargeted metabolomics was employed to analyze the plasma of metabolites from 2324 patients who underwent coronary angiography from 4 independent centers, which identified a total of thirty-six differential metabolites. Targeted quantification was employed to determine the increased level of Neu5Ac in plasma and a key role of Neu5Ac in acute MI was identified [35]. The similar method found that six metabolites had the strongest relationship to CAD by global metabolic perturbation profile analysis, they were palmitic acid, linoleic acid, 4-pyridoxic acid, phosphatidylglycerol, carnitine and lithocholic acid, respectively [36]. The same study also found that five metabolites (*N*-acetyl-D-glucosamine 6-phosphate, methylitaconate, 1-naphthol, 2-naphthol and L-carnitine) in the plasma sample from 40 CAD patients by untargeted metabolomics. Two potential biomarkers (GlcNAc-6-P and L-carnitine) were found be to associate with intestinal microflora [37]. Some other biomarkers discovery in CAD by metabolomics is listed in Table 1. These findings provide further understanding for the pathogenic mechanisms of CAD and may help improving the diagnosis and treatment of patients with CAD.

Table 1 Biomarker discovery in CAD

Methods	Metabolic biomarkers	Refs
LC-MS	Sphingomyelin (28:1), Lysophosphatidylcholine (18:2), Lysophosphatidylcholine (18:1), Monoglyceride (18:2)	[38]
LC-MS	Neu5Ac	[35]
^{1}H-NMR	Lactic acid, Threonine, Creatinine, Glutamic acid, Lysine, Isoleucine, Leucine, Valine	[31]
GC-MS, ^{1}H-NMR	L-Valine, L-leucine, Stearic acid	[32]
LC-MS	1-Naphthol, 2-Naphthol, Methylitaconate, *N*-Acetyl-D-glucosamine 6-phosphate, L-carnitine	[37]
LC-MS	9-*cis*-Retinoic acid, Dehydrophytosphingosine, 1*H*-Indole-3-carboxaldehyde	[39]
LC-MS	Phosphatidylcholine diacyl (36:0), Phosphatidylcholine diacyl (34:2), Phosphatidylinositol diacyl (36:4), Phosphatidic acid (34:1)	[40]
LC-MS	GlcNAc-6-P	[41]
LC-MS	Ceramide C18:0	[42]
GC-MS	Phytanic acid, Hexadecanal dimethyl acetal (16:0), Hexacosanoic acid (26:0)	[43]
LC-MS	Lysophosphatidylcholine, Palmitoylethanolamide, Phytosphingosine, PI (20:4/0:0), Phosphocholine, Phosphatidylcholine, Ethylchenodeoxycholic acid, Creatine, 2-hydroxylauric acid, Tryptophan, Isobutyrylcarnitine, Propionylcarnitine, Acetylcarnitine, Aspartic acid, *N*-phenylacetyl-L-glutamine, Trp Arg Leu, Sphinganine, Eicosatetraenoic acid, Glycocholic acid, Eicosatrienoic acid	[44]

For decades, find new biomarkers for prediction, prevention, diagnosis and prognosis of CAD events have focused on a rather small number of molecules. With the development of technology, the use of mass spectrometry in automated analytical methodologies, revolutionized biomarker research in the past 10 years. However, it is also essential to critically assess the advantages and disadvantages of new technologies. For example, the sensitivity of a method inherently affects the biomarker panel obtainable and reliable interpretation of improved molecular details may also call for more stringent analytical.

The Pathophysiological Mechanism of CAD Was Elucidated by Metabolomics

CAD is complex metabolic disorders that are affected by the factors of genetic and various environmental, developing a method that evaluates comprehensive metabolic changes will be helpful for the understanding the mechanisms of biological changes in patients with CAD, and to identify indicators for high-risk patients.

Lipid levels in the blood were closely related to cardiovascular disease. Yet the roles of lipid metabolites in atherogenesis remained unrevealed. Among these metabolites, glycerophospholipids have recently been seized as potential biomarkers of cardiovascular disease [45-46]. Phosphatidylcholines (PCs) and lysophosphatidylcholines (lysoPCs) are important members of the glycerophospholipid family [47]. The study found that PC and lysoPC profile had changed in patients with atherosclerotic, and some PCs and lysoPCs were closely

related to heart rate and vascular damage. More importantly, these changes were found to have different behaviors in patients with peripheral arterial disease and CAD by metabolomic analysis [48]. On the other hand, CAD is a major factor in the morbidity and mortality of type 2 diabetes patients (T2DM) [49-50]. A new study found that seven metabolites related to long-term future onset of CAD in Japanese patients with diabetes, and these metabolites were 3-hydroxybutyric acid, glucosamine, thymine, pelargonic acid, creatine, galactosamine, 2-aminoisobutyric acid and hypoxanthine, respectively [51]. Glucosamine play important role in accelerates atherosclerotic change [52]. The level of glucosamine significantly lower in the CAD patients, the data also support the anti-atherosclerotic effect of glucosamine. Creatine and 3-hydroxybutyric acid play important roles in energy metabolism. Interestingly, recent research has found that 3-hydroxybutyric acid can reduce the production of interleukin (IL)-1β and IL-18 by NLRP3 inflammasome in human monocytes [53]. Other studies also reported that creatine also plays an important role in reducing myocardial stunning or cerebral infarction in the mouse model of ischemic [54-55]. However, it is unclear whether creatine can alleviate the onset of CAD. Thymine and 2-aminoisobutyric acid are important metabolites in pyrimidine metabolism. Hypoxanthine is a purine derivative, it has been reported that hypoxanthine increased the area of atherosclerotic plaque and the level of cholesterol in serum with increasing the production of reactive oxygen species (ROS) [56].

Myocardial infarction is caused by long-term myocardial ischemia leading to myocardial necrosis [57, 58]. However, the specific biological mechanisms of myocardial infarction remain unclear. Global profiling based on metabolomics evaluated of changes in metabolic and lipidomic in rat heart tissue after coronary ligation, and the result showed that the S-adenosylmethionine (SAM) concentration and the SAM/*S*-adenosylhomocysteine (SAH) ratio gradually decreased after MI and the levels of SAM-dependent methyltransferases (coenzyme Q3 and Q5) were decreased. In addition, the levels of short and medium chain acylcarnitine gradually decreased, whereas the levels of long chain acylcarnitine increased, the result suggested that these changes were related to down regulated COQ biosynthetic pathway and energy-dependent metabolic pathway [59]. The comprehensive analysis of metabolomics data provides a new direction for understanding the underlying pathophysiological mechanisms of CAD.

Elevated concentration of circulating cystathionine caused by insufficiencies of vitamin B-12, B-6, or folate were associated with the increasing risk of CAD [60-62]. To order to study the effect of elevated plasma cystathionine concentration on metabolism in adult patients with stable angina pectoris (SAP), 80 plasma samples from the Western Norway Coronary Angiography Cohort were analyzed through both targeted and untargeted metabolomics. PLS-DA results showed that an increase in the concentration of cystathionine in plasma can lead to greater catabolism, including higher blood glucose concentration, lower kidney function and lower glutathione SAP associated with branched-chain amino acids, higher glucose and phenylalanine concentrations. The above data suggested that metabolic perturbations caused by elevated plasma cystathionine concentrations in SAP patients can lead to higher risk of CAD [63].

The endothelium is a key factor in the development of atherosclerosis and its complications, particularly CAD [64]. The large number of studies suggest that the local microenvironment, which comprehends arterial mechanics, matrix remodeling and lipid deposition, playing an important role in regulating the sensitivity of plaque development and progression and even regulating the endothelial cells function. A study analyzed 23 coronary blood samples from patients using ^{1}H-NMR based on metabolomics. Compared with control group, the contents of leucine, isoleucine, alanine, 2-hydroxybutirate and *N*-acetyl groups increased and the levels of creatine/phosphocreatine, glucose and creatinine decreased in microvascular group. Whereas stenotic disease patients the levels of 3-hydroxybutirate and acetate are higher, the content of 2-hydroxybutirate was lower. These metabolites upregulate NADPH oxidase, leading to oxidative stress, monocyte adhesion and ICAM-1 expression [65]. Creating exerts anti-inflammatory effects by inhibiting the expression of ICAM-1 and E-selectin. Furthermore, creatine can reduce endothelial permeability [66]. the results showed specific that coronary microenvironments were likely associated with distinct development and pathological expression of CAD [67].

Metabolomics Reveal the Therapeutic Effect and Mechanisms of TCM for CAD

CAD is several diseases with high mortality in the worldwide [68]. The currently drugs treating CAD are mainly various synthetic drugs, including calcium antagonists, nitrate preparations and β-blockers. However, long-term use of these synthetic drugs might cause some serious side effects, such as hypotension and bradycardia [69]. Due to TCM specific theory and rich clinical practice in the prevention and treatment of CAD, it is receiving more and more attention from the world. Metabolomics profiling, which focuses on endogenous low molecular weight metabolites, provides a discovery tool for the pharmacological discipline of cardiovascular disease and medications (Table 2) [70].

Danshen Dripping Pill

Danshen Dripping Pill (CDDP) is a Chinese patent medicine, which is mainly used for the treatment of CAD in clinic. In order to understand the mechanism of CDDP in a myocardial ischemia rat model, the urinary metabolomics of rats was analyzed by GC-MS. The results showed that eight of thirty-six metabolites were identified in the urine samples were significantly elevated and recovered to normal level after treatment with CDDP. These metabolites were cysteine, malate, succinate, creatinine, serine, phenylalanine, methionine and tyrosine, respectively [71]. These metabolites are

mainly related to myocardial energy metabolism, especially the TCA cycle. Malate and succinate are important intermediates in the TCA cycle and can enhance the activities of key enzymes (cytochrome oxidase, succinate dehydrogenase) in the mitochondria, which decreases myocardial stunning and increases adenosine triphosphate (ATP) production [72]. Serine, cysteine and methionine all participate in the metabolism of methionine, which is activated by ATP to be further hydrolysis into homocysteine, the homocysteine can produce more cysteine, a precursor of glutathione [73]. Glutathione is an important endogenous antioxidant and scavenger [74]. The result reveals that urinary metabolomics provides a dynamic monitoring method to elucidate the therapeutic effect of CDDP on myocardial ischemia in rat.

Table 2 The therapeutic effect and mechanisms of TCM for CAD

TCM	Objects	Experimental Model	Mechanisms	Ref.
Danshen Dripping Pill	SD rats	MI was induced by LAD	Increased the levels of eight metabolites (malate, succinate, creatinine, methionine, cysteine, serine, phenylalanine and tyrosine)	[71]
Extract of *Salvia miltiorrhiza* and *Dalbergia Oborifera*	SD rats	Myocardial ischemia/reperfusion (MI/R) injury was induced by LAD	Ameliorate MI/R injury by intervening energy metabolism, especially TCA cycle and *β*-oxidation of fatty acids (3-hydroxybutyric, palmitoleic acid heptadecanoic acid and arachidonic acid) metabolism	[75]
Xin-Ke-Shu	Wistar rats	MI was induced by subcutaneous injected of isoproterenol	Improved the levels of fifteen metabolites involved in fatty acid *β*-oxidation pathway, sphingolipid metabolism, proteolysis, tryptophan metabolism and purine metabolism	[77]
	Japanese white rabbits	Atherosclerosis in a rabbit model was induced by high cholesterol diet	Regulating the lipid perturbation including fatty acid *β*-oxidation pathway, sphingolipid metabolism, glycerophospholipid metabolism and bile acid biosynthesis	[78]
	SD rats	MI was induced by LAD	Inhibition of Ca^{2+} overload and dysfunction of fatty acid *β*-oxidation-related metabolic pathways	[79]
Wenxin Keli	SD rats	MI/R injury was induced by LAD	Bulk of the key metabolites in energy-substrate metabolism were significantly disturbed by I/R in myocardium	[80]
Xinmaining Tablet	Wistar rats	BBS was induced by ice-cold water for 5 min for eight days	Significantly improved the levels of some metabolites involved in steroid hormone biosynthesis, arachidonic acid metabolism and lipid metabolism	[83]
Baoyuan decoction	SD rats	MI injury was induced by LAD	Regulating the energy homeostasis, oxidative stress, apoptosis, inflammation, cardiac contractile dysfunction and extracellular matrix remodeling	[91]

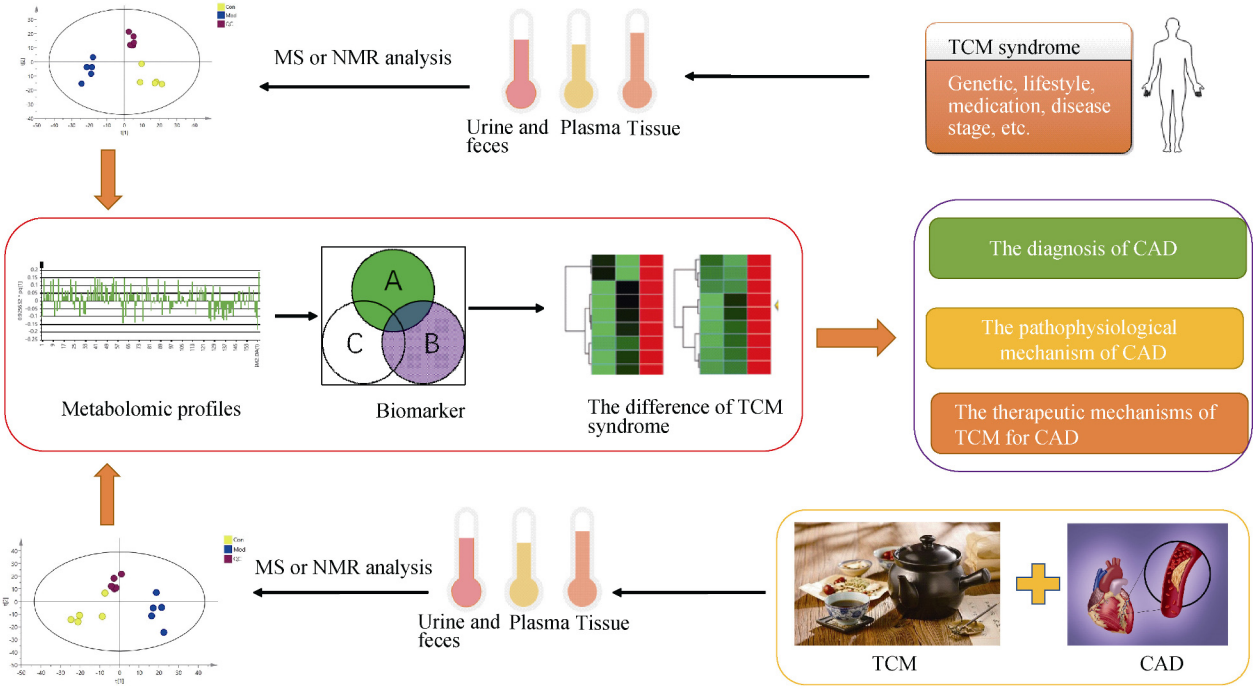

Fig. 1 The future potential of TCM for the treatment of CAD by metabolomic

Extract of Salvia miltiorrhiza

Extract of *Salvia miltiorrhiza* and *Dalbergia odorifera* (SM-DOO) has been used for the prevention and treatment of cardiovascular disease for a long time. However, unfortunately, the mechanism by which they exert therapeutic effect remains unknown. Systematic analysis of endogenous metabolites profiling by metabolomics revealed that potential biomarkers associated with the therapeutic effect of SM-DOO were mainly related to energy metabolism, especially *β*-oxidation of fatty acids (3-hydroxybutyric, heptadecanoic acid, palmitoleic acid and arachidonic acid) and TCA cycle (citric acid). Besides, the protein expression of p-AMPK and p-ACC in SM-DOO group were significantly elevated, the results indicated that SM-DOO improved myocardial energy metabolism through activation of the AMPK signaling pathway [75]. In addition, the results also showed that SM-DOO exerted synergistic therapeutic efficacies to exhibit a greater effect on rats with MI/R injury, compared with the other pretreatment groups. This effect may be achieved partly through anti-apoptotic, antioxidant and anti-inflammatory activities [76].

Xin-Ke-Shu

Xin-Ke-Shu (XKS) is a patent drug used for CAD in China. A metabolomics approach was developed by UPLC-QTOF-MS to evaluate the protective effect of XKS against isoproterenol (ISO)-induced myocardial infarction. A total of seventeen biomarkers were recognized in rats by pretreatment of XKS, which mainly involved in lipid pathways, amino acid metabolism and purine metabolism [77]. Moreover, XKS was able to regulate the levels of twenty potential biomarkers involving to fatty acid β-oxidation pathway, glycerophospholipid metabolism, and sphingolipid metabolism and bile acid biosynthesis in atherosclerosis rabbits [78]. To evaluate whether altered metabolome was coincident with clinical features, the molecular mechanism of the XKS anti-myocardial infarction needs to be validated. In the study, tissue targeted metabolomics was developed to analyze whether metabolic changes associated with XKS treatment in the heart tissue of rats. The results showed XKS therapeutic effect on metabolic perturbations in LAD induced myocardial infarction was mainly by inhibiting the Ca^{2+} overload and fatty acid *β*-oxidation dysfunction. Not only that, XKS could reversed the over-expression of the four key proteins, carnitine palmitoyl transferase-1 (CPT1B), phospholipase A2IIA (PLA2IIA), long-chain acyl-CoA synthetase 1 (ACSL1) and calcium/calmodulin -dependent kinase II (CaMKII), inhibition of Ca^{2+} overload and dysfunction of fatty acid *β*-oxidation related metabolic pathways likely underlie the therapeutic effects of XKS against myocardial infarction [79].

WenXin Keli

WenXin Keli (WXKL) is a Chinese patent medicine recorded in Pharmacopeia of the People's Republic of China. In this study, metabolomics was employed to analyze the metabolic profile in plasma after myocardial ischemia reperfusion injury (MIRI) in rat, and the result revealed that energy- substrate metabolism was significantly affected after myocardial ischemia reperfusion and the level of the key metabolites could be further modulated by verapamil and/or WXKL. Furthermore, glucose oxidation and branched-chain amino acids (BCAAs) degradation were significantly improved by the treatment of WXKL to content the heart's energy demands. Compared with MIRI group, the WXKL treated group could significantly increase the level of glucose in plasma while the level of plasma lipids no significant changed. The phenomenon indicated that WXKL could promoted the decomposition of hepatic glycogen to supplement blood glucose. Moreover, plasma BCAAs (valine, isoleucine and leucine) significant decreased in WXKL group indicated that the WXKL may also modulate the degradations of BCAAs for providing more Acyl-CoA derivatives to generate ATP [80].

Xueshuan Xinmaining Tablet

Blood stasis syndrome (BSS) is the most condition in patients with CAD [81], mainly characterized was a slowing or pooling of blood [82]. Xueshuan Xinmaining Tablet (XXT) formula is widely used in China for the treatment of cerebrovascular and cardiovascular diseases. The recent study showed XXT could significantly change some metabolites like 3*α*, 21-dihydroxy-5*β*-pregnane-11, 20-dione, cortexolone and 19S-hete and leukotriene A4, these metabolites mainly involved in lipid metabolism, arachidonic acid metabolism and steroid hormone biosynthesis [83].

Sheng Mai San

Sheng Mai San (SMS) is composed of *Ginseng Radix* at Rhizoma, *Ophiopogonis Radix* and *Schisandrae Chinensis Fructus*. It is widely used for the treatment of CAD in clinic. The research showed ophiopogonin D, schizandrin, ginsenoside Rg1 and Rb1 were the main active components of SMS responsible for cardioprotection [84-87]. It remains unknown what is the difference between the effect of individual bioactive component and multi-components combination affecting acute MI. ^{1}H NMR spectroscopy was employed to analyze the metabolic profiles of serum samples. Single administration of ginsenosides and schizandrin affected the metabolism of glucose, *β*-hydroxybutyrate (*β*-HB) and choline. Treated with combined medication leaded to more metabolic changes including glycerol and *O*-acetyl glycoprotein. Eight biomarkers (glucose, lactate, choline, glycerol, glycerophosphocholine, phosphorylcholine, *β*-hydroxybutyrate and *O*-acetyl glycoprotein) significantly modulated under the combined treatment indicated that improved myocardial energy metabolism and anti-inflammation activities was the major synergistic effect [88].

Baoyuan decoction

MI is a disorder characterized the lack of blood supply due to coronary artery obstruction, results in insufficient nutrition and oxygen supply in cardiomyocytes, and further causes changes in myocardial cell metabolism, structure and function of cardiomyocytes. These changes can seriously affect the function of cardiomyocytes, leading to myocardial

infarction, fibrosis and heart failure. At present, how to improve the prevention and treatment of MI is still a great challenge [89-90]. Therefore, search for effective drugs, effectively ameliorating the MI, has great clinical significance and health value for patient's health and economic burden. *Baoyuan* decoction (BYD) is a TCM formula with cardioprotective activity, however, its pharmacological characteristics and mechanisms are obscured. A multi-omics strategy (metabolomics, transcriptomics and pharmacodynamics) was used to investigate the effect and molecular mechanisms of BYD, the results showed that the cardioprotective of BYD were mainly involved in the regulation of energy homeostasis, inflammation, oxidative stress, apoptosis and cardiac contractile dysfunction [91].

Conclusion

Cardiovascular disease, especially CAD, is the leading cause of mortality and morbidity worldwide. Despite many initiatives have been established for CAD prevention and risk management, and new therapies are applied to treat existing CAD, patients continue to die from cardiac events. Clearly, we need to identify new therapeutic targets and strategies. Metabolomics provides a novel solution to this problem, and it provides the detailed profiling of metabolic status, which can do a favor to gain an insight in the molecular mechanisms underlying CAD. The quantification of large numbers of circulating metabolites across multiple pathways may also identifies metabolic changes prior to the onset of overt disease, and hereby potentially leads to earlier and more accurate identification of individual at high cardiovascular risk [45, 92]. It also capable of elucidating the mechanism of TCM treatment of CAD. With the continuous development of metabolomics, the modernization of traditional Chinese medicine will continue, and breakthrough will be made in the diagnosis, prevention and treatment of CAD. The discovery and application of biomarkers for different types and stages of CAD will become a reality, and greatly improve the current treatment status of CAD.

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