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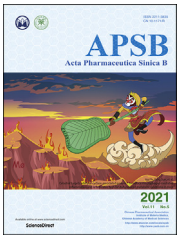

REVIEW

Energy metabolism disorders and potential therapeutic drugs in heart failure

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Abstract Heart failure (HF) is a global public health problem with high morbidity and mortality. A large number of studies have shown that HF is caused by severe energy metabolism disorders, which result in an insufficient heart energy supply. This deficiency causes cardiac pump dysfunction and systemic energy metabolism failure, which determine the development of HF and recovery of heart. Current HF therapy acts by reducing heart rate and cardiac preload and afterload, treating the HF symptomatically or delaying development of the disease. Drugs aimed at cardiac energy metabolism have not yet been developed. In this review, we outline the main characteristics of cardiac energy metabolism in healthy hearts, changes in metabolism during HF, and related pathways and targets of energy metabolism. Finally, we discuss drugs that improve cardiac function *via* energy metabolism to provide new research ideas for the development and application of drugs for treating HF.

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1. Introduction

Heart failure (HF), with high morbidity and mortality, is the final outcome of many end-stage heart diseases[1]. In recent decades, the treatment of HF has seen great innovations in medical treatment and equipment, but its incidence is still increasing, and the quality of life, function, and life expectancy of patients with HF declined to varying degrees of damage[2]. Studies have found that patients with HF will experience severe energy metabolism disorders, including disturbances in substrates absorption and utilization, oxidative phosphorylation, and the adenosine triphosphate (ATP) shuttle, resulting in an inadequate cardiac energy supply. This deficiency causes cardiac pump dysfunction and systemic energy metabolism failure, which determine the development and recovery from HF[3,4]. Therefore, identifying the changes in energy metabolism that occur during HF is of great significance for clarifying the pathophysiology of HF and promoting the development of HF treatment. Existing HF therapies reduce heart load by reducing heart rate, preload, and afterload to treat symptoms and delay disease progression[2]. There are many basic studies on drugs that affect cardiac energy metabolism. Unfortunately, few drugs are available for clinical treatment. In this review, we outline the main characteristics of cardiac energy metabolism in healthy hearts, the transformation of metabolism during HF, pathways and targets related to energy metabolism, and for the first time we discuss potential drugs and natural ingredients that improve heart function through energy metabolism. We hope to provide new research ideas for the development and application of drugs to HF.

2. Normal myocardial energy metabolism

The heart uses various substrates such as glucose, lipids, amino acids, and ketone bodies to provide energy to maintain a normal heart beat. Its preference for substrate change with life cycle physiology, pathology, and external environment[5]. The human fetus gestates in an environment of hypoxia and low fatty acids, relies mainly on glucose and lactate metabolism[6]. After birth, the cardiac hemodynamic load and oxygen tension of the newborn increase, promoting the conversion of energy metabolism. Simultaneously, a rapid increase in the number of mitochondria increases the heart's oxidative capacity[7]. The heart's dependence on glucose decreases, and blood lactic acid level begins to decline. As triacylglycerol content increases, fatty acid oxidation becomes the main source of heart energy[8]. From birth to adulthood, myocardial cells gradually mature, and oxidative capacity increases significantly[6,9]. In the adult heart, fatty acids are the main energy source, accounting for 60%−90%, and the remaining 10%−40% comes from glucose, amino acids, pyruvate, lactic acid, ketone bodies, and other sources[9].

2.1. Fatty acid energy metabolism

Fatty acids are the main energy-supplying substance for the adult heart and provide many necessary coenzyme factors for oxidative phosphorylation by the mitochondria. Fatty acids are transported into cells *via* fatty acid transporters (FAT/CD36) and fatty acid binding proteins (FABP) on the cell membrane and are converted into long-chain fatty acyl-CoA by fatty acyl-CoA synthetase in the cytoplasm; long-chain fatty acyl-CoA is converted to acylcarnitine by carnitine palmitoyl transferase (CPT)-1 on the outer membrane of mitochondria; acylcarnitine is transported to the mitochondrial inner membrane by carnitine transposase, and CPT-2 is used to cut carnitine to reduce the acylcarnitine to long-chain fatty acyl-CoA; and finally, long-chain fatty acyl-CoA undergoes β-oxidation in the mitochondrial matrix[10,11] (Fig. 1). β-Oxidation of fatty acid produces products such as acetyl-CoA, reduced nicotinamide adenine (NADH), and reduced flavin dinucleotide ($FADH_2$). These products are used by the electron transfer chain to generate large amounts of ATP, which provides the heart energy[10].

2.2. Glucose energy metabolism

The glucose used in the heart is derived from exogenous glucose or glycogenolysis, and a lesser amount of glycogen is stored in the heart. Exogenous glucose enters myocardial cells mainly through glucose transporter (GLUT-4), followed by GLUT-1[12]. After entering myocardial cells, glucose is phosphorylated by hexokinase to form glucose-6-phosphate (G-6-P), which is then converted to pyruvate by glycolysis[12]. In the presence of oxygen, pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase in the cell matrix; acetyl-CoA enters the tricarboxylic acid (TCA) cycle, producing ATP to provide energy (Fig. 1). Under hypoxia, pyruvate can produce lactic acid through anaerobic oxidation in the cell matrix, which generates a small amount of ATP for energy[10,11]. In addition, pyruvate can be carboxylated to oxaloacetate or malic acid as an anaplerosis of the citric acid cycle[13].

2.3. Ketone body energy metabolism

Ketone bodies consist of acetoacetic acid (AcAc), β-hydroxybutyric acid (βOHB) and acetone, which are intermediate products of oxidative decomposition of fatty acids in the liver. Ketone body oxidation is the main source of energy metabolism in extrahepatic tissues in many physiological states, such as neonatal period, fasting, and exercise. Ketone bodies are also substrates for the synthesis of fats and sterols in the brain, liver, and breast[14]. Ketone bodies may become one of the high-energy fuels that replace glucose during HF. βOHB is oxidized to AcAc by D-β-hydroxybutyrate dehydrogenase in mitochondria; 3-ketoacyl-CoA transferase 1 (OXCT1) is also known as succinyl-CoA ketoacyl-CoA transferase. OXCT1 catalyzes the exchange of CoA between succinyl-CoA and AcAc to produce AcAc-CoA and succinic acid[15]. This step is the rate-limiting phase of ketone body utilization, because OXCT1 exists in all tissues except the liver[16]. Subsequently, AcAc-CoA is reversibly converted into acetyl CoA under the action of acetoacetyl-CoA thiolase (mThiolase), and enters the TCA cycle to produce ATP in mitochondria. However, this reaction is conducive to the reverse reaction, so continuous consumption of ketone bodies is necessary to promote the conversion of AcAc-CoA to acetyl-CoA[14].

2.4. Molecular mechanism of cardiac substrate metabolism

Cardiac substrate metabolism is mainly determined by the catalytic activity of rate-limiting enzymes and the expression of some enzymes and transporters in the cell[3].

2.4.1. Relationship between substrate metabolism and rate limiting enzymes

The catalytic activity of rate-limiting enzymes is mainly regulated by the allosteric regulation of enzymes and transporters, as well as complex pathways between substrates and products. For example,

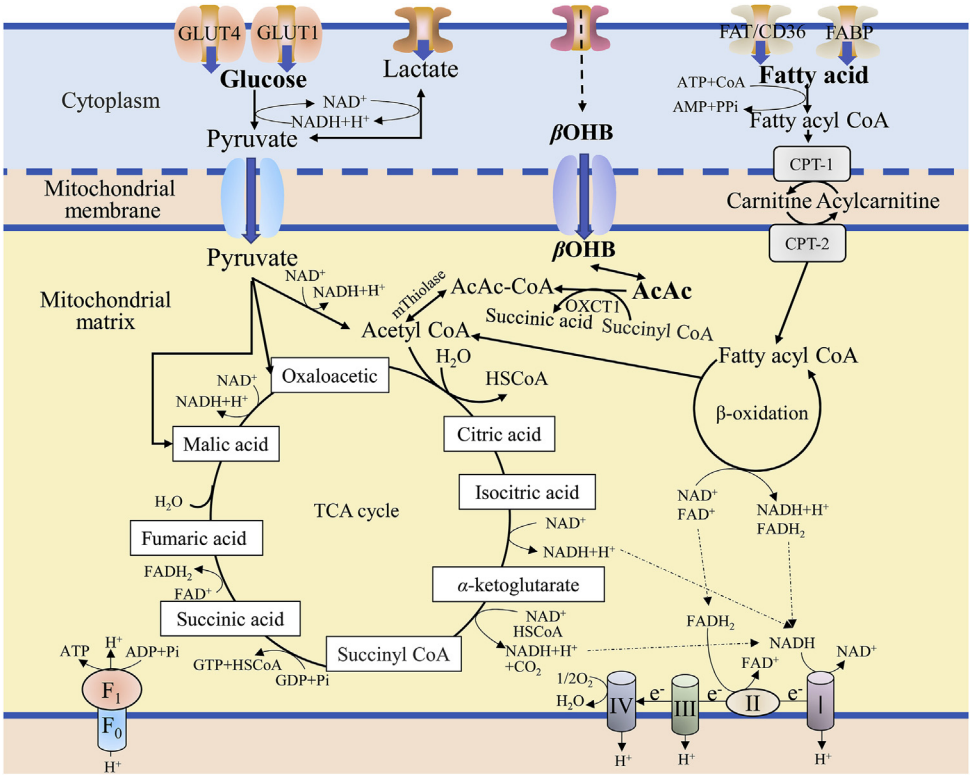

Figure 1 The energy metabolism process of fatty acid, glucose and ketone body. Various metabolic substrates are transported to the cytoplasm to form corresponding intermediate product, such as pyruvate, fatty acyl CoA, etc. These intermediates enter the mitochondrial matrix through a specific transport system and generate NADH, $FADH_2$, GTP through the TCA cycle, fatty acid oxidation and other pathways. Then NADH and $FADH_2$ produce ATP through the electron transfer chain, which provides energy for cardiomyocytes.

malonyl-CoA is one of the key enzymes that regulate the oxidation of cardiac fatty acids. It can inhibit CPT-1 activity by binding to CPT-1. At the same time, malonyl-CoA is regulated by acetyl-CoA carboxylase (ACC) and malonyl-CoA decarboxylase (MCD)[17]. Phosphofructose kinase-1 (PFK-1) is a key regulatory enzyme in the glycolysis pathway, catalyzing the production of fructose 1,6-diphosphate, which in turn can inhibit the activity of PFK-1. In addition, PFK-1 is also regulated by adenosine diphosphate, adenosine monophosphate, phosphate group activation, ATP, fructose 2,6-diphosphate, and citric acid[18]. Pyruvate dehydrogenase (PDH) complex E1 subunit, the glucose oxidation rate-limiting enzyme, can be phosphorylated and inactivated by PDH kinase (PDK), and can be activated by PDH phosphatase dephosphorylation[17]. When fatty acid oxidation increases, PDK expression can increase and inhibit glucose oxidation[17].

2.4.2. Relationship between substrate metabolism and expression of enzymes and transporters

The expression of enzymes and transporters in cells is regulated by transcription and translation processes. For example, the adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling pathway can mediate GLUT4 gene expression and increase glucose uptake[19]. It can also activate peroxidase proliferator-activated receptor alpha (PPARα), increase CD36 translocation, inhibit ACC activity, and increase fatty acid oxidation[20]. PPARs are a transcription factor for lipid metabolism, which can upregulate the related proteins involved in fatty acid uptake and metabolism, and can activate a variety of genes related to oxidative phosphorylation, thereby regulating mitochondrial oxidative phosphorylation metabolism and other functions[21]. Peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1α) can upregulate the expression of several genes in the TCA cycle and mitochondrial fatty acid oxidation pathway, as well as various genes related to oxidative phosphorylation, regulate fatty acid metabolism, glucose metabolism and mitochondrial oxidative phosphorylation metabolic function[22]. In short, various transcription factors and their co-activators interact to form a complex signal network that regulates long-term energy requirements to produce ATP. At the same time, the expression of these enzymes or transporters can also be a target for regulating heart energy metabolism.

3. Changes in energy metabolism during in HF

3.1. Changes in the metabolic substrate

The heart is a highly energy-consuming organ and needs a continuous supply of energy to keep it functioning normally. In normal conditions, fatty acids and glucose can be fully utilized, and they depend on the concentration of metabolic substrates and oxygen. Fig. 2 shows that the amount of ATP produced by the complete oxidation of 1 mol 20-carbon fatty acid (about 134 mol) is much larger than that produced by 1 mol glucose (about

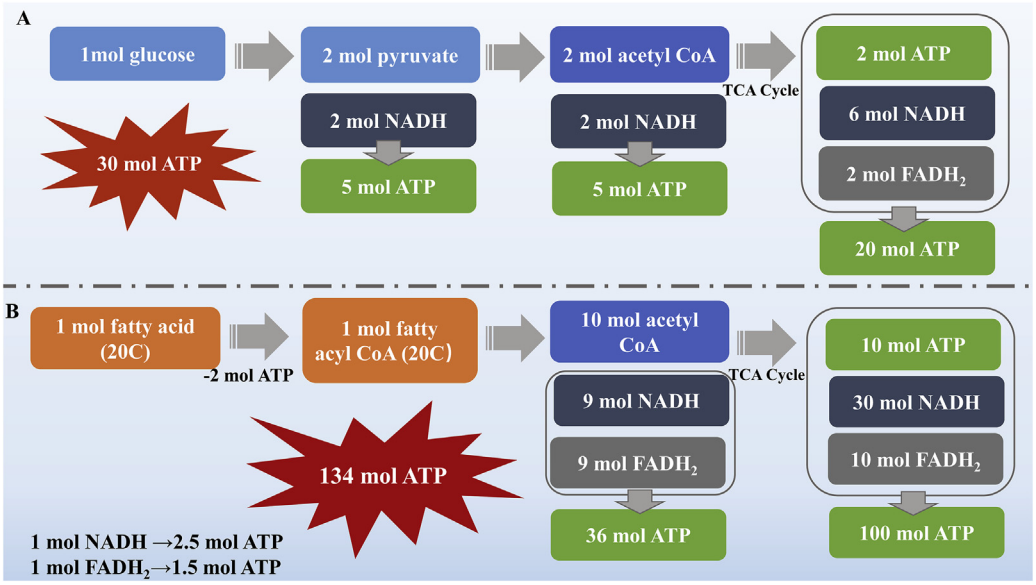

Figure 2 Energy produce of glucose (A) and fatty acid (B) oxidation. In an ideal state, 1 mol glucose is converted into 2 mol pyruvic acid and 2 mol NADH. 1 mol pyruvic acid can produce 1 mol acetyl CoA and 1 mol NADH. 1 mol acetyl CoA can generate 1 mol ATP, 3 mol NADH and 1 mol $FADH_2$ after one TCA cycle. 1 mol NADH and $FADH_2$ can generate corresponding 2.5 mol ATP and 1.5 mol ATP through electron chain transfer respectively. 1 mol glucose is completely oxidized to produce 30 mol ATP. 1 mol fatty acid (20C) consumes 2 ATP can produce 1 mol fatty acyl CoA (20C). After β oxidation, 10 mol of acetyl-CoA can be generated by 1 mol fatty acyl CoA (20C), and then enter the TCA cycle. Therefore, 1 mol of fatty acid can be completely oxidized to generate 134 mol of ATP.

30 mol). Research also shows that when they produce the same amount of ATP, fatty acid oxidation requires more oxygen than glucose oxidation; in the absence of oxygen, the productivity efficiency of fatty acid oxidation is significantly lower than that of glucose oxidation[23]. Studies have shown that the hypoxic environment after HF reverses the heart's energy metabolism toward that of the fetal period, in which glucose metabolism is the main energy source[24]. During HF, glucose intake and glycolysis rates increase significantly to compensate for fatty acid oxidation to provide energy. However, Umbarawan et al.[25] believed that the increase in glucose uptake and glycolysis is used for biosynthesis rather than ATP production, and fatty acid oxidation is still the main source of heart energy. Sung et al.[26] stated that the transformation of metabolic substrate from fatty acid to glucose may be caused by the faster and earlier decrease in fatty acid oxidation rate, rather than the enhancement of glucose oxidation pathway. In addition, because of the failure of fatty acid intake during HF, the utilization of free fatty acids in cardiomyocytes is significantly reduced, and the concentration of free fatty acids in plasma is increased, which may further increase energy metabolism disorders and myocardial damage[27]. Whether the conversion of metabolic substrates from fatty acids to glucose occurs during HF is still controversial, but it is certain that fatty acid oxidation efficiency is significantly reduced in end-stage HF[23].

As the substrate of cardiac metabolism, ketone bodies have received widespread attention in recent years. Compared with fatty acids and glucose, ketone bodies are more easily converted to acetyl-CoA and more easily enter the TCA cycle[28]. They could reduce oxygen consumption and increase energy output to ensure heart efficiency, especially under hypoxia and high energy requirements[29]. A clinical study showed a significant increase of ketone body intake in HF patients with left ventricular hypertrophy due to reduced ejection fraction, and increase of fatty acid intake in HF patients with left ventricular hypertrophy due to aortic stenosis[30]. It is worth noting that energy metabolism is more complex in HF patients with diabetes. Insulin resistance significantly reduces glucose oxidation, increases dependence on fatty acid oxidation, activates β-oxidation, and increases ketone body production[31]. At the same time, the presence of ketone bodies will competitively inhibit the uptake and oxidation of fatty acids, thereby improving the utilization of ketone bodies[29,32]. A study showed that ketone bodies uptake in HF patients with diabetes was higher than that of non-diabetic patients with HF[33]. A recent study showed that an increase of the ketone body oxidation rate increased overall energy production without affecting glucose or fatty acid metabolism, but it did not increase the efficiency of the heart[34]. It is necessary to study whether ketone bodies can be used as the source of energy metabolism substrates and whether their utilization is adaptive in HF.

It is unclear whether the conversion of substrate metabolism after HF is a favorable compensatory response or maladaptive pathological changes, as well as should promote the use of fatty acids or glucose in the heart. Therefore, it is not advisable to simply regulate the metabolism of a certain substrate. In the study of energy metabolism of HF, we should pay attention to the balance between the metabolism of various substrates and increase the total energy supply, which is also the direction and difficulty of the development of HF drugs.

3.2. *Mitochondrial changes*

Ninety percent of the energy in the normal adult heart is provided by oxidative phosphorylation of the mitochondria, which plays an important role in providing energy for cell life activities. In recent years, many studies have confirmed that cardiovascular diseases, such as arrhythmia, cardiomyopathy and HF, are related to

changes in mitochondrial function and structure[35,36]. For example, the number of mitochondria in the cardiomyocytes of patients with congestive HF is 78% lower than that of normal cardiomyocytes[37]. Changes in mitochondrial quantity, morphology, and function have also been observed in patients with hypertrophic cardiomyopathy[38]. What's more, mitochondrial dysfunction could cause a large amount of reactive oxygen species (ROS) to be produced[39]. Excessive accumulation of ROS will attack and damage mitochondrial DNA and mitochondrial proteins, cause mitochondrial dysfunction, and trigger cardiomyocyte apoptosis induced by mitochondria, forming a vicious cycle[40]. Studies have shown that the mutation rate of mitochondrial genes is significantly increased in HF myocardial cells, causing mitochondrial distortion, affecting the activity of mitochondrial oxidative respiratory chain related enzyme complexes and mitochondrial protein synthesis[41]. These changes lead to mitochondrial dysfunction, affect mitochondrial energy metabolism, deplete the energy in myocardial cells, and promote HF. In addition, the oxidative damage caused by the large amounts of ROS impairs the calcium ion transport mechanism, allowing a large amount of calcium ions to enter the cardiac muscle cells[42]. Excessive calcium ions damage the inner membrane and structure of the mitochondria[43].

4. Related pathways and targets of energy metabolism

4.1. *Sirtuin protein family*

Sirtuin (SIRT) is a highly conserved deacetylase present in life forms ranging from bacteria to humans. There are seven recognized members of the human sirtuin family, SIRT1−SIRT7. They can affect many metabolic functions, such as the TCA cycle, the urea cycle, amino acid metabolism, and fatty acid oxidation. Furthermore, they are involved in stress response, gene expression, DNA damage repair, body aging, and autophagy[44]. Research reported that sirtuin proteins play an important role in delaying the progression of cardiovascular disease[45]. For example, all of SIRT1, SIRT2, SIRT6, and SIRT7 reduce myocardial hypertrophy and maintain cardiac function[46−49]. In addition, SIRT1 regulates cardiac electrophysiology by acetylating sodium channels[50]. SIRT3, SIRT5, and SIRT6 regulate cardiac remodeling and reduce myocardial ischemia reperfusion injury[51−53]. SIRT7 increases the resistance of cardiomyocytes, prevents apoptosis and prevents the occurrence of cardiomyopathy[54]. The effect of SIRT4 on the heart is unclear. A study reported that SIRT4 can increase ROS levels in the heart, promote myocardial hypertrophic growth, and produce fibrosis and cardiac dysfunction[55]. Table 1[56−69] summarizes their biological functions related to energy metabolism.

4.2. *AMPK signaling pathway*

AMPK is an energy sensor in the body. When energy supply is insufficient, AMPK can regulate the balance between energy supply and consumption by regulating mitochondrial synthesis, glucose metabolism, fatty acid absorption and oxidation, and activating the mammalian target of rapamycin (mTOR) pathway (Fig. 3)[70−72]. Research shows that AMPK could increase energy supply, reduce stress response and delay HF progression[73].

AMPK has important regulatory effects on mitochondrial gene expression and mitochondrial occurrence. On the one hand, it directly regulates the function of PGC-1α, activates mitochondrial DNA replication and transcription, and promotes mitochondrial synthesis[73]. On the other hand, AMPK also indirectly regulates PGC-1α. When the AMP/ATP ratio is increased, AMPK is activated to promote lipid oxidation in the mitochondria and promote the expression of nicotinamide phosphate ribose transferase. These signals increase the level of nicotinamide adenine dinucleotide (NAD^+) in the cell, which in turn activates SIRT1 and eventually catalyzes the deacetylation of PGC-1α to activate it, thereby promoting mitochondrial synthesis[73].

AMPK also regulates glucose metabolism and fatty acid metabolism. AMPK activation promotes intracellular transport of GLUT4 from the vesicles to the sarcolemma, increase glucose uptake by the cells, inhibits the GLUT4 endocytic cycle, and increases GLU4 content[19,74]. At the same time, its activation promotes the phosphorylation of phosphofructokinase-2 (PFK-2), upregulates glycolysis, inhibits glycogen synthesis, and reduces energy consumption[75,76]. In addition, AMPK upregulates the fatty acid transporter CD36, promoting fatty acids into cells[20,77]. AMPK phosphorylation inhibits ACC, activates MCD, and increases the conversion of malondialdehyde-CoA to acetyl-CoA, reducing CPT-1 inhibition and promoting fatty acid oxidation[78].

4.3. *mTOR signaling pathway*

mTOR is a serine/threonine protein kinase with a molecular weight of 289 kDa. It belongs to the phosphoinositide 3-kinase (PI3K) protein family[79]. It plays a role in regulating cell functions mainly through two different protein complexes, mTORC1 and mTORC2. mTORC1 plays a key regulatory role in protein synthesis, cell proliferation and differentiation, ribosome and mitochondrial origin, autophagy and metabolism[80,81]. mTORC2 is related to cell survival and cytoskeleton formation[82,83]. mTOR senses the nutrition, oxygen, energy and other states of cells, and then regulates cell survival and metabolism to respond to environmental changes (Fig. 3). Nutrients such as amino acids are transported into cells by binding to corresponding receptors, which directly activates mTORC[84]. When energy is consumed, AMPK is activated and phosphorylates tuberous sclerosis 2 (TSC2) to inhibit mTORC1 activation. Hypoxia also promotes TSC1/2 activation and inhibits mTOR1 signaling[85]. Furthermore, AMPK also directly phosphorylates to inhibit mTORC1 activation, regulating lipid metabolism, protein synthesis, cell autophagy and other functions[80].

Insulin affects mTOR in two ways. One is to influence mTORC1 and mTORC2 through PI3K-AKT signaling, and the other is to activate mTORC2 directly through PI3K phosphorylation, regulating cell activity[82]. Modulation of the mTOR pathway may be a potential therapeutic intervention for cardiovascular disease. A study showed that deletion of the mTORC1 gene under normal physiological conditions can lead to strong induction of atrial and brain natriuretic peptides and β-myosin heavy chains, and changes in multiple genes involved in regulating energy metabolism[86]. Under stress overload, mTORC1 gene-deficient mice developed dilated cardiomyopathy and accelerated HF, which may be related to apoptosis, autophagy, and increased mitochondrial dysfunction[87,88]. There are fewer reports about cardiovascular effects of mTORC2 than of mTORC1, but it is essential for normal heart development and the maintenance of heart structure and function after birth. Deletion of mTORC2 results in significant activation of mammalian sterile 20-like kinase 1, leading to cardiac dysfunction and dilation, affecting cardiac growth and adaption to stress overload[89,90].

Table 1 Biological functions of sirtuin proteins related to energy metabolism.

Protein	Location	Enzyme activity	Biological functions related to energy metabolism
SIRT1	Nucleus	Deacetylase	◆ SIRT1 controls gluconeogenesis and glycolysis in the liver by activating PGC-1, but does not regulate the effect of PGC-1 on mitochondrial genes[56]. ◆ SIRT1 inhibits PPAR-γ activity, which in turn promotes fat mobilization in white adipose tissue when calorie intake is reduced[57]. ◆ SIRT1 inhibits the expression of uncoupling protein 2 gene and regulates insulin secretion of islet B cells[58].
SIRT2	Cytoplasm Nucleus	Deacetylase	◆ SIRT2 promotes deacetylated hepatocyte nuclear factor (FOXO1) to bind to PPARγ, thereby inhibiting PPARγ activity and promoting adipocyte differentiation[59]. ◆ SIRT2 deacetylates phosphoenolpyruvate carboxykinase, FOXO1, and PGC-1α. Then it regulates gluconeogenesis through a variety of pathways[60].
SIRT3	Mitochondria	Deacetylase	◆ SIRT3 regulates the metabolic transition between mitochondrial respiration and glycolysis in endothelial cells[61]. ◆ SIRT3 activation attenuates the damage caused by ROS through superoxide dismutase 2 and hypoxia-inducible factor-1α (HIF-1α) regulated pathways[53]. ◆ An increase in SIRT3 activity restores complex I activity and ATP levels in the mitochondrial electron transport chain[62].
SIRT4	Mitochondria	ADP-ribosyltransferase	◆ SIRT4 regulates insulin secretion by inhibiting glutamate dehydrogenase activity in the mitochondrial matrix[63]. ◆ SIRT4 inhibits malonyl-CoA decarboxylase activity in mitochondria *via* deacetylation, thereby increasing malonyl CoA and regulating fatty acid oxidation[64]. ◆ SIRT4 inhibits pyruvate dehydrogenase activity, which affects glycolysis and TCA cycle[65].
SIRT5	Mitochondria	Deacetylase	◆ SIRT5 regulates glycolysis, β-oxidation of fatty acids, TCA cycle and electron transport chain[52]. ◆ Denucleated SIRT5 regulates the activity of 3-hydroxy-3-methylglutaryl-COA synthetase 2 to regulate ketone body formation[66].
SIRT6	Nucleus	Deacetylase/ ADP-ribosyltransferase	◆ SIRT6 affects glucose metabolism by inhibiting the expression of HIF-1α and other glycolytic genes[67]. ◆ SIRT6 acetylates PGC-1α by modifying the activity of acetyltransferase general control non-depressible 5, and indirectly controls hepatic glycogenogenesis[68]. ◆ SIRT6 negatively regulates triacylglycerol synthesis, thereby participating in lipid metabolism[69].
SIRT7	Nucleolus	Deacetylase	◆ SIRT7 deacetylates the lysine on the (GABP) subunit β1 and promotes the formation and transcriptional activation of α and GA-binding protein β heterotetramers, thereby regulating the expression of nuclear-encoded mitochondrial genes and maintaining mitochondrial steady state[47].

4.4. *Insulin signal*

The heart is an organ of insulin dependence and high energy consumption, which is rich in insulin receptors. Insulin can bind to insulin receptor in cardiomyocytes and mediate its signal transduction. Insulin combines with insulin receptor (such as insulin-like-1 receptor, IGF-1R) in cardiac myocytes, which makes insulin receptor self-phosphorylate, thus increasing the activity of insulin substrate (IRS) protein, and activating intracellular signal pathways including PI3K-AKT, mitogen-activated protein kinases (MAPK), mTOR, etc., so as to regulate the uptake of glucose, fatty acid oxidation and mitochondrial metabolism in the heart[91,92]. When the insulin receptor is missing, the insulin signaling is interrupted, which will cause the heart to become smaller and mitochondrial dysfunction after birth[93]. IRS protein activation is an important initial step of insulin and IGF receptor signaling, and also necessary for the next level of signaling. Studies have shown that the absence of IRS-1 and IRS-2 genes can lead to unconstrained autophagy, cardiac energy deficiency, mitochondrial dysfunction, myocardial structural damage and loss of contractile function, leading to myocardial cell loss, and premature death[94,95]. In fact, glucose metabolism and fatty acid metabolism in the heart are strictly controlled by insulin signal. Impaired insulin signal or insulin resistance play a decisive role in the occurrence and development of HF[96]. Therefore, the correction of insulin resistance and the elimination of insulin signal-mediated interference factors in patients with HF are of positive significance to prevent heart disease and improve the prognosis of patients with HF.

4.5. *Purine signal*

Purine signaling is mediated by purine receptors, which are expressed in most of the heart and blood vessels. It is divided

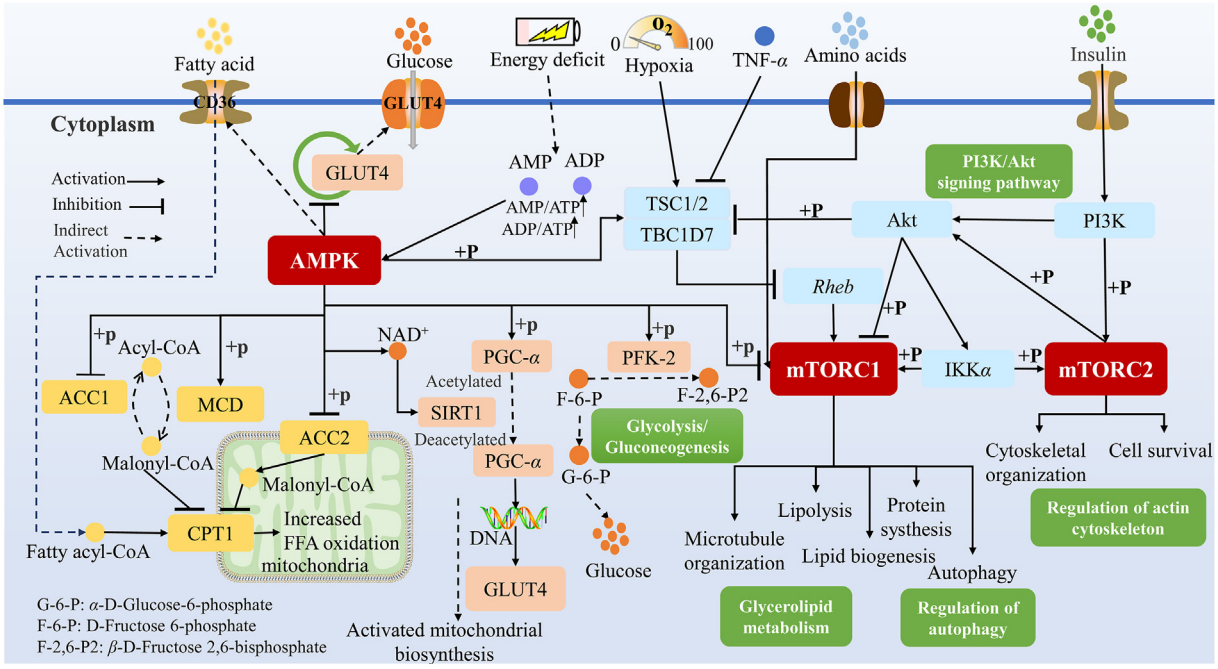

Figure 3 AMPK and mTOR signaling pathway. When energy is insufficient, AMPK can be activated to increase the intake of fatty acids and glucose, inhibit glycogen synthesis, promote fatty acid oxidation and increase energy production. At the same time, it can promote the synthesis of mitochondria by regulating PGC-α. AMPK activation, hypoxia conditions and insulin can also inhibit mTORC1 activation, so as to regulate fatty acid metabolism, protein synthesis, autophagy, etc. Insulin can also directly activate mTORC2, regulate cell survival and cytoskeleton formation.

into four P1G protein coupled receptor subtypes (A_1, A_{2A}, A_{2B} and A_3), seven $P2X_{(1-7)}$ ion channel subtypes and eight P2Y protein coupled receptor subtypes ($P2Y_{1/2/4/6/11/12/13/14}$). Among them, A_1, A_{2A}, A_{2B}, A_3, $P2Y_4$, $P2Y_6$, $P2Y_{12}$, $P2Y_{11}$, $P2X_3$, $P2X_4$, and $P2X_7$ have all been studied in the treatment of heart disease, but the therapeutic potential of other receptors has not been confirmed except of A_1 receptor[97]. As early as the end of the 20th century, adenosine (A_1 receptor agonist) has been shown to protect the heart of patients with chronic HF through A_1 and A_3 receptors[98]. In recent years, some adenosine A_1 agonists have been proved to be effective drugs in the treatment of HF, with the potential to enhance cardiac metabolism, calcium homeostasis, cardiac structure and function, and prognosis of patients[99]. Purine signal protection of the heart may be related to energy metabolism. For example, adenosine can improve the transmission efficiency of mitochondrial electron chain, and has the potential to improve the efficiency of ATP synthesis and reduce the generation of excessive reactive oxygen species[100]. Animal studies have shown that some A_1 receptor agonists can increase the expression of GLUT1 and GLUT4 glucose transporters to near normal levels[101]. In addition, the treatment of some A_1R agonists is also related to the normalization of protein levels that mediate fatty acid oxidation and reduced plasma levels of free fatty acids[102].

4.6. *PPARs*

PPARs are a nuclear receptor superfamily of transcription factors (including three subtypes of PPARα, PPARβ/δ, and PPARγ) and play an important central role in the fatty acid and glucose metabolism of the heart[21,103]. PPARα affects left ventricular function and fatty acid oxidation efficiency in HF mice. The left ventricular function and fatty acid oxidation rate of HF model mice with transverse aortic constriction decrease with a decrease in PPARα expression; when PPARα is activated, fatty acid metabolism rate significantly increases and left ventricular function is retained[104]. Deletion of PPARβ/δ inhibits fatty acid oxidation in the heart, and a healthy heart will develop lipotoxic cardiomyopathy hypertrophy and HF[105]. Overexpression of PPARβ/δ does not affect fatty acid oxidation, but increases oxidative phosphorylation of glucose, GLUT4 expression, and insulin sensitivity[106]. PPARγ agonists reduce the concentration of triglycerides in the plasma by increasing the accumulation of lipids in adipose tissue, thereby reducing the absorption and oxidation of fatty acids by the heart, increasing oxidative phosphorylation of glucose and lactate, and increasing cardiac contractility[107]. These research results indicate that PPARα, PPARβ/δ, and PPARγ may be potential targets for treating HF and improving myocardial function and energy metabolism.

4.7. *PGC-1α*

PGC-1α is a 91 kDa transcription factor that regulates lipid metabolism and long-chain fatty acid oxidation by upregulating the expression of several genes in the TCA cycle and the mitochondrial fatty acid oxidation pathway[22,108]. In addition, PGC-1α activates a variety of genes related to oxidative phosphorylation, such as PPARα and nuclear respiration factors, and regulates the mitochondrial oxidative phosphorylation metabolism function, thereby regulating systemic energy balance[22]. PGC-1α may be an important therapeutic target for the reducing morbidity and mortality of HF. PGC-1α deletion results in impaired mitochondrial respiratory

function and reduced expression of genes involved in multiple mitochondrial metabolic pathways[109]. Mitochondrial enzyme activity and ATP levels are decreased in the heart of PGC-1α knockout mice[110].

4.8. *Creatine kinase*

Creatine kinase (CK) is a mobile energy store in the cytoplasm. It can catalyze the reversible reaction of creatine phosphate (PCr)+ ADP+H^+ → creatine+ATP[111]. A study showed that the rate of ATP resynthesis by CK in normal myocardium is faster than that of ATP produced by oxidative phosphorylation[112]. At high energy requirements, CK can generate creatine phosphate through oxidative phosphorylation, which produces a large amount of ATP[112]. CK may be an important target for the treatment of myocardial ischemia. Its moderate overexpression does not adversely affect cell metabolism, mitochondria or cardiac function, but it changes the opening of mitochondrial permeability transition pores, reduces ischemia−reperfusion injury, and promotes cardiac function recovery[113]. Animal study has found that when heart function is normal, CK overexpression increases ATP content without affecting systolic function, and it improves cardiac systolic function in HF[114]. In the early stages of HF, CK overexpression does not improve left ventricular remodeling and function, but it maintains cardiac energy changes, which is of great significance for increasing the survival rate of HF during the acute compensation[115].

4.9. *SET and MYND domain-containing protein 1 (SMYD1)*

SMYD1 is a muscle-specific histone methyltransferase whose role in bone and myocardial development is well known. The absence of SMYD1 will cause the hypertrophic growth of mouse heart, and then develop into HF[116]. In the recent study, SMYD1 has been found to regulate the energy metabolism of the heart[117]. In SMYD1 deficient mice, the mitochondrial protein involved in oxidative phosphorylation was down regulated and the respiratory capacity of mitochondria was also reduced[117]. This study demonstrated the role of SMYD1 as the main regulator of heart energy.

5. Potential drugs for reducing HF by regulating energy metabolism

5.1. *Hormones*

Hormones are essential substances, playing important roles in regulating metabolism, growth, development, reproduction and other processes. In recent years, some hormonal drugs, including thyroxine, relaxin and estrogen, have been used to treat cardiovascular and cerebrovascular diseases. Thyroxine is an indispensable growth hormone in the body and is related to growth, apoptosis and energy metabolism. A recent study has shown that thyroxine reduces myocardial cell apoptosis, reduces energy loss, and prevents heart damage caused by doxorubicin *via* the LKB1/AMPK/mTOR pathway[118]. It is expected to become a new drug for clinical prevention of heart damage caused by doxorubicin chemotherapy. Relaxin is a polypeptide hormone that has a relaxing effect on the birth canal before delivery in mammals. It is produced mainly during pregnancy and is present at very low levels in normal humans[119]. A large number of clinical studies and translational studies on relaxin have shown that it may be effective in treating cardiovascular diseases, especially HF[120,121]. A clinical study has shown that relaxin-2, administered in the same amounts as produced during pregnancy, can prolong survival in patients with acute HF[122]. The molecular mechanism of relaxin for HF is currently unknown, and it may be related to the synthesis of endogenous long-chain polyunsaturated fatty acids, energy metabolism in modification of amino acid, and cardiovascular structural regulation[123]. Estrogen is the primary female sex hormone. It promotes the maturation of female accessory sexual organs and the appearance of secondary sexual characteristics, and it maintains normal sexual desire and reproductive function. Research has shown that estrogen protects the right ventricular function of pulmonary hypertension model mice by preserving mitochondrial content and oxidative capacity[124].

5.2. *Synthetic drugs*

5.2.1. *Metformin*

Metformin is the first choice in the treatment of type 2 diabetes. Clinical observation shows that metformin increases the myocardial efficiency, reduces oxygen consumption and improves cardiac function in patients with non-diabetes HF[125]. Studies show that metformin restores left ventricular diastolic function and weakens immune and inflammatory response to a certain extent[126]. It also increases the contractile function of mice with postinfarction HF and reduces apoptosis of myocardial cells[127]. The mechanism of metformin improving cardiac function may be related to regulating glucose absorption, mitochondrial function, and oxidative stress. Metformin increases glucose uptake by stimulating the PI3K−PKB/AKT pathway and AMPK activation, and this positive effect has been observed in both insulin-resistant cardiomyocytes and normal insulin-sensitive cardiomyocytes[128]. Metformin also improves the heart function in mice by regulating the level of PGC-1α acetylation that is reduced by SIRT3, reducing the damaged mitochondrial membrane potential and increasing mitochondrial respiratory function[127]. Furthermore, it reduces the cardiotoxicity caused by doxorubicin by inhibiting oxidative stress and reducing HSCoA consumption in the mitochondria, increasing cardiac glutathione, HSCoA, ATP levels, and mRNA expression levels of catalase and NAD(P)H quinone dehydrogenase 1[129].

5.2.2. *Sodium-glucose transporter 2 inhibitor*

Sodium-glucose transporter 2 (SGLT2) inhibitors are recently developed class of antidiabetic drugs, such as dapagliflozin, empagliflozin, canagliflozin, and ipragliflozin. Interestingly, SGLT2 inhibitors have been found to be potential cardiovascular protecting drugs and can be used to treat HF when clinically evaluated for cardiovascular safety[130]. Clinical studies have found that dapagliflozin reduces the risk of diabetic cardiomyopathy and improves left ventricular function in patients with type 2 diabetes and HF[131]. In addition, dapagliflozin can also reduce symptoms, improve physical function and quality of life for HF patients, and reduce the mortality rate from cardiovascular disease and the progression of HF[132]. It has also been observed that empagliflozin and canagliflozin improve the condition of patients with HF[133,134]. The mechanism of SGLT2 in the treatment of HF is not clear.

According to existing research, it may be related to the following pathways:

- Increasing ketone bodies. SGLT2 inhibitors reduce the blood glucose levels, thus reducing insulin levels and increasing glucagon. Glucagon promotes the degradation of adipose tissue and releases free fatty acids, which is conducive to the increase in ketone bodies[29]. Kim and Lee[135] found that SGLT-2 inhibitors can increase β-hydroxybutyrate levels throughout the body and by upregulating ketogenic-related enzymes and transporters in the liver, kidney, and intestine. The latest literature reported that englitazine can also reduce the activation of NLRP3 inflammatory body through ketone body and insulin, thus playing a role in heart protection[136].
- Regulating of mitochondrial function. Ipragliflozin reduces mitochondrial dysfunction caused by a high-fat diet by restoring optic atrophy factor 1 (OPA1) and mitofusion 2 to normal levels in the body[137]. Empagliflozin restores the mitochondrial morphology and quantity in the hearts of diabetic rats by upregulating superoxide dismutase 2 and catalase, and protects against the mitochondrial morphological changes of diabetic-induced myocardial infarction in rats by inhibiting ROS and promoting autophagy[138]. In another study, empagliflozin inhibited mitochondrial division in an AMPK-dependent manner, thereby inhibiting oxidative stress and maintaining the barrier function of cardiac microvascular endothelial cells[139].
- Changing intracellular sodium homeostasis and promoting sodium-mediated cardiac protection. Dapagliflozin, empagliflozin and canagliflozin, can directly inhibit the cardiac Na^+/H^+ exchanger flux by binding to the Na^+ binding site of Na^+/H^+ exchanger-1, reducing the Na^+ concentration in the heart muscle, and slow heart rate for cardiac protection[140].

5.2.3. *Pioglitazone*

Pioglitazone is an insulin sensitized thiazolidinedione and a PPARγ agonist. Study has shown that it reduces cardiovascular events and diabetes in patients with insulin resistance after a recent apoplexia or transient ischemic attack[141]. A study found that pioglitazone can reverse severe pulmonary hypertension and vascular remodeling and prevent right ventricular HF, which is related to the regulation of cardiac hypertrophy, fibrosis, myocardial contractility, fatty acid transport/oxidation and transforming growth factor signal transduction through miRNA/mRNA network[142].

5.2.4. *Simvastatin*

Pressure overload induced by angiotensin II is one cause of the HF pathogenesis[143]. Simvastatin is an angiotensin II receptor inhibitor and is commonly used to treat hyperlipidemia and hypertension. Clinical observation found that taking simvastatin for 20 days significantly reduces the levels of proinflammatory markers interleukin-6 and C-reactive protein in patients with chronic HF[144]. It also induces lipid droplet accumulation, provides energy for maintaining mitochondrial function, promotes mitochondrial autophagy and phagocytosis, and inhibits mitochondrial damage and cardiomyocyte apoptosis[145]. In addition, simvastatin also reduces oxidative stress, endothelial thrombosis and atrial fibrillation in rats with ischemic HF by reducing atrial induced nitric oxide synthase, sodium calcium exchanger and *Rac1* expression activities[146].

5.2.5. *Fenofibrate*

Fenofibrate is a fibrate lipid-lowering drug. It is a highly selective and efficient PPARα ligand, that reduces levels of low-density lipoprotein, total cholesterol, and triglycerides and increases high-density lipoprotein[147]. Labinskyy et al.[148] found that fenofibrate prevents the transformation of cardiac metabolic substrates in HF model dogs and moderately improves cardiac function. A study showed that fenofibrate promotes fatty acid oxidation in the mitochondria of isoproterenol-induced HF rats, increases myocardial energy metabolism and oxidative stress, and protects heart function[149]. In addition, fenofibrate also reducing aldosterone-induced myocardial hypertrophy, but it may not be related to fatty acid oxidation[150].

5.2.6. *Trimetazidine*

Trimetazidine is commonly used to treat angina pectoris and is one of the most widely studied drugs in metabolic therapy. Clinical studies have found that it improves cardiac function classification, exercise tolerance, quality of life, left ventricular ejection fraction, and heart volume in patients with HF[151]. It may inhibit fatty acid oxidation by inhibiting long-chain mitochondrial 3-ketoacyl CoA thiolase, promote glucose metabolism, and maintain the PCr/ATP ratio in cells[152].

5.2.7. *Carvedilol*

Carvedilol is an α1 and β receptor blocker and has a vasodilating effect. It is often used to treat patients with mild or moderate hypertension, or with renal insufficiency and diabetes. A clinic study showed that long-term use of carvedilol can increase survival in patients with non-ischemic HF and higher dosages (7.5 mg/day) of carvedilol increase survival for HF patients with low heart rate and low ejection fraction[153]. But carvedilol is not effective for patients with ejection fraction retention[153]. Carvedilol reduces myocardial fatty acid utilization in patients with congestive HF but has no effect on glucose utilization[154]. It can also increase ejection fraction, reduce New York Heart Association heart grade, increase PCr/ATP ratio and metabolic equivalent, and maintain myocardial high-energy phosphate levels[155]. In addition, it can increase the mitochondrial energy charge and reduce the lag of phosphorylation in myocardial ischemia model rats, and improve mitochondrial function during myocardial ischemia[156].

These synthetic drugs to treat HF have been found to improve energy metabolism and protect the heart muscle in the treatment of other diseases, rather than specifically developed to improve energy metabolism of HF. This suggests that we can find new or best therapeutic targets for HF through the mechanism of these drugs *in vivo* and it provides a possibility to develop drugs to treat HF from clinical drugs. Meanwhile, it is necessary to further study the specificity and safety of these synthetic drugs and their derivatives for treating HF caused by different factors, providing more references for their clinical application.

Table 2 Related mechanisms of polyphenols in HF treatment.

Compound	Source	HF model	Dosage	Result
Resveratrol	Wine	Pressure-overload	450 mg/kg/day, 2 weeks	Resveratrol increase exercise capacity of HF mice, increase skeletal muscle insulin sensitivity, and increase systemic glucose utilization and basal metabolic rate[158].
		Tesaglitazar induction	100 mg/kg/day, 6weeks	Resveratrol reduces cardiac dysfunction and corrects myocardial mitochondrial respiration by mediating SIRT1 activation in tesaglitazar-induced C57BL/6 mice and diabetic mice, but it has no effect on myocardium in SIRT1 deficient mice[159].
		Myocardial infarction	200 mg/kg/day, 2 weeks	Resveratrol significantly increase ejection fraction and physical activity of myocardial infarction rats, restore myocardial fatty acid oxidation levels, significantly increases myocardial energy metabolism, and reduces left ventricular and atrial remodeling caused by myocardial infarction[160].
		Ischemia−reperfusion (I/R) injury	50 mg/kg/day, 2 weeks	Inhibit stromal interaction molecule1 -induced intracellular Ca^{2+} accumulation, reduce the mortality of myocardial I/R injured mice, reduce the area of myocardial infarction, and improve cardiac function[161].
Epigallocatechin gallate (EGCG)	Green tea	Knockout manganese superoxide dismutase	20 mg/kg/day, 8weeks	EGCG reduces oxidative stress and free fatty acid levels. At the same time, it also delays the progression of HF by preventing the increased expression of nitric oxide synthase 2, nitrotyrosine, fatty acid synthase, Toll-like receptor 4 and SIRT1[162].
		Pressure-overload	50 mg/kg/day, 12 weeks	EGCG prevents left ventricular dilatation, increase ejection fraction and left ventricular short axis shortening rate, maintain cardiac function and upregulation of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) *via* the modification of histone acetylation to prevent HF caused by stress overload[163].
		Pressure-overload	10 mg/kg/day, 4 weeks	EGCG reverses changes in left ventricular diastolic diameter and systolic diameter of HF mice, increase ejection fraction; inhibits myocardial fibrosis; reduces oxidative stress, inflammation, and myocardial cell apoptosis; and reduces collagen I and III expression levels, thereby inhibiting myocardial fibrosis and reducing ventricular collagen remodeling, delaying the occurrence and progression of HF. It may work by inhibiting the transforming TGF-β1/SMAD3 signaling pathway[164].
		Pressure-overload	25,50 or 100 mg/kg/day, 4 weeks	EGCG can reduce the desensitization of β1 receptor by inhibiting G protein-coupled receptor kinase 2 (GRK2) transfer membrane. It can also regulate left ventricular end-diastolic pressure, mean blood pressure, heart weight and posterior wall thickness, left ventricular systolic pressure, left ventricular maximum pressure rise rate ($+dP/dt_{max}$), and left ventricular maximum pressure drop rate ($-dP/dt_{max}$) and other constants to improve cardiomyocyte morphology[165].

(*continued on next page*)

Table 2 (*continued*)

Compound	Source	HF model	Dosage	Result
Puerarin	Puerariae Radix	Pressure-overload	60 mg/kg/day, 4 weeks	Puerarin reduces the activity of lactate dehydrogenase and succinate dehydrogenase, increase the expression level of GLUT4, and reduces the expression level of CD36. It also reduces the levels of inflammatory factors in myocardial tissue and regulate PPARα and its downstream target genes[166].
		Myocardial infarction with diabetes	100 mg/kg/day, 4 weeks	Puerarin increases AKT phosphorylation, decreases PPARα expression, increases GLUT4 expression and translocation, and reduces CD36 expression and translocation, thereby regulating cardiac energy metabolism, increasing heart function and improving survival rate in mice with HF[167].
Tanshinone IIA	*Salvia miltiorrhiza* Bunge	Pressure-overload	1.5 mg/kg/day, 4 weeks	Tanshinone IIA mediates the expression of related molecules by upregulating AMPK and downregulating mTOR to increase autophagy and inhibit apoptosis[168].
		Pressure-overload	20 mg/kg/day, 8 weeks	Tanshinone IIA reduce inflammatory response and cardiomyocyte apoptosis in HF rats by regulating serum B-type brain natriuretic peptide, interleukin 6 and C-reactive protein levels and myocardial B-cell lymphoma-2 associated X protein levels[169].
7,8-Dihydroxyflavone	/	Doxorubicin-induction	5 mg/kg/day, 2 weeks	7,8-Dihydroxyflavone increase cell viability *in vitro* and reduce doxorubicin-induced cell death. At the same time, it improves the heart function of HF mice, reduces heart injury, and restores AMPK and signal transducing activator of transcription 3 (STAT3) expression by increasing mitochondrial respiration, membrane potential and OPA1 protein expression *in vivo*[170].
Isoquercetin	/	Lipopolysaccharide induction	50 mg/kg/day, 5 days	Isoquercetin significantly reduces the inflammatory response and reduces the energy deficiency caused by lipopolysaccharide. It acts by increasing the expression of PGC1β and PPARα, activating AMPKα, and increasing fatty acid oxidation, thereby increasing cardiac and cellular ATP levels[171].
Naringenin	/	I/R injury	50 mg/kg/day, 1 week	Naringenin reduces infarct size and myocardial cell index and reduces ischemia−reperfusion injury by inhibiting mitochondrial oxidative stress and increasing mitochondrial biogenesis through AMPK−SIRT3 signing[172].

Note: "/" means that its resource is rich.

5.3. *Natural products*

5.3.1. *Polyphenols*

Polyphenols are a large group of phytochemicals that are present in variety of foods, such as fruits, vegetables, beans, cereals, cocoa or chocolate, and beverages including red wine, coffee, and tea. According to their structural characteristics, they can be roughly divided into flavonoids, phenolic acids, lignans and stilbene. Polyphenols, such as resveratrol, quercetin, curcumin and epigallocatechin gallate, have obvious protective effects against atherosclerosis, hypertension, myocardial infarction, cardiomyopathy caused by anthracyclines, angiogenesis, and HF[157]. Table 2[158−172] summarizes the polyphenols to treat HF *via* energy metabolism mechanisms. A large number of polyphenols have

been proven to be effective by reducing cardiovascular disease through energy metabolism, but only resveratrol has entered a systematic and standardized clinical trial[173]. In addition, some polyphenol-rich extracts deserve attention. For example, long-term use of green tea extract can improve the cellular mechanical properties and intracellular calcium dynamics of normal cardiomyocytes, increase energy utilization, and eliminate the inhibitory effect of phospholamban on sarcoplasmic reticulum Ca^{2+}-dependent ATPase 2a[174]. *Amalaki rasayana* is a traditional herbal from India. It is rich in polyphenols and can reverse the remodeling changes of left ventricular myocardial hypertrophy and age-related cardiac dysfunction by improving myocardial energy metabolism, muscle contraction function, and exercise endurance[175].

5.3.2. *Saponins*

At present, ginsenosides are the main saponins used to HF. Ginseng total saponins increase cardiac energy metabolism by activating specific proteins in the TCA cycle[176]. Ginsenoside Rb1 restores heart and mitochondrial function, increases glucose uptake and prevents cardiac remodeling through TGF-β1/SMAD ERK and AKT signaling pathways[177]. Ginsenoside Rb3 protects the heart by regulating PPARα receptors to regulate fatty acid oxidation, protect the integrity of the mitochondrial membrane, and exert antiapoptotic effects[178]. Arjunolic acid, a naturally occurring chiral triterpenoid saponin, significantly inhibits the phosphorylation of $P47^{phox}$ and ERK in neutrophils from myocardial infarction, and reduces oxidative phosphorylation activity, reactive oxygen levels and oxidative stress in cardiomyocytes to reduce mitochondrial dysfunction and increase glycolysis rate[179]. Furthermore, it upregulates PPARα, reduces the phosphorylation level of TAK1, decreases p38 MAPK and NF-κB P65 activation, reduces excessive collagen synthesis and cardiac hypertrophy, and protects the heart[180]. Astragaloside IV is an extract from Astragali Radix. It increases the expression of PPARα, medium-chain acyl-CoA dehydrogenase (MCAD) and muscle carnitine palmitoyl transferase-1 (MCP1) and increases utilization of free fatty acids in chronic HF rats to improve cardiac function and inhibit ventricular remodeling[181]. It also stimulates fatty acid beta oxidation and improves mitochondrial function in HF animals, and is a potential drug to inhibit the progress of HF[182].

5.3.3. *Polysaccharides*

Many polysaccharides, extracted from plants, have therapeutic effects on cardiovascular diseases, which are related to their anti-inflammatory and antioxidant effects[183–185]. There are limited reports on whether polysaccharides regulate cardiac energy metabolism. Only *Ophiopogon* polysaccharides, *Lycium barbarum* polysaccharides and *Astragalus* polysaccharides have been reported. *Ophiopogon* polysaccharides significantly reduce the levels of aminotransferase, lactate dehydrogenase, CK and CK-MB, increase ATPase activity, and exert protective effects on ischemia-induced myocardial injury[186]. The extract of *Lycium barbarum* promotes muscle differentiation and energy metabolism by upregulating mitochondrial biological gene regulatory factors[187]. *Lycium barbarum* polysaccharides exert a cardioprotective effect by reducing inflammatory cytokines and lipid peroxidation in HF mice[188]. *Astragalus* polysaccharides regulate the energy biosynthesis mediated by TNF-α/PGC-1 signaling pathway, decrease the mRNA and protein expression of ANP, increase the ratios of ATP/ADP and ATP/AMP, and reduce the free fatty acids content and cardiomyocyte hypertrophy[189].

5.3.4. *Alkaloids*

Salsolinol is an alkaloid from the *Aconitum* plants. It reduces doxorubicin-induced chronic HF, reduces serum myocardial injury marker levels, decreases tissue damage to the heart, and increases the relative mRNA expression levels of key enzymes downstream of the TCA cycle to increase cardiac energy metabolism[190]. Higenamine, a typical β2-adrenergic selective receptor activator, is also an alkaloid in *Aconitum* plants that significantly increases myocardial contractility[191]. Combined with 6-gingerol, it upregulates PPARα/PGC-1α/SIRT3 pathway, increases cell viability, ameliorates doxorubicin-induced mitochondrial dysfunction, improves mitochondrial oxygen consumption and extracellular acidification rates, promotes mitochondrial energy metabolism and prevents HF[192]. Ligustrazine, also known as tetramethylpyrazine, is an alkaloid isolated from *Ligusticum chuanxiong*. It promotes the transfer of BCL-2 to mitochondria and improves mitochondrial function of by upregulating the expression of *14-3-3*γ, thereby preventing myocardial damage caused by lipopolysaccharide[193]. It also alleviates H9c2 apoptosis induced by hypoxia by downregulating miR-499a, upregulating SIRT1, and activating the PI3K/AKT pathway[194].

5.3.5. *Traditional Chinese medicine patent prescription*

Different natural products have different mechanisms for increasing cardiac energy metabolism. In traditional Chinese medicine, natural products of different mechanisms or even several herbs are combined according to certain rules so as to maximize their efficacy and reduce toxicity and side effects. This therapy is used as in clinical complementary and alternative therapies. Shengmai injection consists of *Panax ginseng* C.A. Mey., *Ophiopogon japonicus* (Thunb.) Ker Gawl., and *Schisandra chinensis* (Turcz.) Baill. extracts. It inhibits myocardial cell hypertrophy and apoptosis by activating the AMPK energy-dependent signaling pathway[195]. Shenfu granules are composed of *Panax ginseng* C.A. Mey. and *Radix aconiti lateralis preparata*. Clinical studies have found that oral Shenfu granules significantly improve the quality of life of patients with chronic HF[196]. Shenfu injection reduces the area of myocardial infarction and protects the myocardium by stimulating antioxidant and changing phospholipid levels, distribution, and levels of taurine, glutathione and phospholipid[197]. In addition, clinical observations have found that Qili Qiangxin capsule, consisting of 11 herbal extracts, improves the quality of life of patients with HF and reduces the incidence of cardiovascular disease and rehospitalization[198]. It has not been demonstrated whether the effect of Qili Qiangxin capsule is related to increasing energy metabolism. However, some of its components, such as astragaloside[181], ginsenoside[176], salsolinol[192], and higenamine[190], have been reported to be related to improving energy metabolism. At present, the combined use and safety of some natural ingredients and herbs are still being studied, but they provide possibilities for replacement and complementary therapy of HF and the development of HF drugs.

In recent years, natural products have received widespread attention for their unique safety and therapeutic effects. Natural products, such as polyphenols, saponins, polysaccharides, and alkaloids, have found components that can alleviate HF by regulating energy metabolism. It provides an idea for

Table 3 Summary of known pathways, targets and metabolic pathways of drugs.

Drug	Known pathway or target	Known metabolic pathway
Metformin	PI3k-PKB/AKT, AMPK, PGC-1α	Glucose metabolism, mitochondrial function, oxidative stress
Pioglitazone	PPARγ	Fatty acid oxidation, mitochondrial function
SGLT2 inhibitors	AMPK, Na^+/H^+ exchanger-1, NLRP3 inflammatory corpuscle	Ketone metabolism, mitochondrial function, intracellular sodium homeostasis, insulin signaling, oxidative stress
Simvastatin	iNOSitol, INCX, Rac1	Mitochondrial function, oxidative stress
Fenofibrate	PPARα	Fatty acid metabolism
Trimetazidine	Long-chain mitochondrial 3-ketoacyl CoA thiolase	Glucose metabolism, fatty acid metabolism
Carvedilol	α1, β receptor	Fatty acid metabolism, mitochondrial function
Resveratrol	SIRT1, CYP1B2, stromal interaction molecule1	Glucose metabolism, fatty acid metabolism, mitochondrial function, insulin signal, Ca^{2+} concentration
EGCG	TGF-β1/SMAD3, Toll-like receptor 4, SIRT1, SERCA2a, GRK2 transfer membrane, nitric oxide synthase 2, nitrotyrosine, fatty acid synthase,	Fatty acid metabolism, oxidative stress, cell function
Puerarin	GLU4, CD36, PPARα	Glucose metabolism, fatty acid metabolism
Tanshinone IIA	AMPK, mTOR	Apoptosis
7,8-Dihydroxyflavone	AMPK, STAT3	Mitochondrial function
Isoquercetin	PGC1β, PPARα, AMPKα	Fatty acid metabolism
Naringenin	AMPK-SIRT3	Mitochondrial function
Ginsenoside Rb1	TGF-β1/SMAD ERK, AKT	Glucose metabolism
Ginsenoside Rb3	PPARα	Fatty acid metabolism, mitochondrial function
Arjunolic acid	$P47^{phox}$, ERK, PPARα, TAK1, p38 MAPK, NF-κB P65	Glucose metabolism, mitochondrial function, oxidative stress
Astragaloside IV	PPARα, MCAD, MCP1	Fatty acid metabolism, mitochondrial function
Ophiopogon polysaccharide	AST, LDH, CK, CK-MB, ATPase	Mitochondrial function
Lycium barbarum polysaccharide	Mitochondrial biological gene regulatory factors	Fatty acid metabolism, mitochondrial function
Astragalus polysaccharide	TNF-α/PGC-1	Fatty acid metabolism
Higenamine	PPARα/PGC-1α/SIRT3	Mitochondrial function
Tetramethylpyrazine	*14-3-3*γ, miR-499a, SIRT1, PI3K/AKT	Mitochondrial function
Thyroxine	LKB1/AMPK/mTOR	Fatty acid metabolism
Salsolinol	−	Mitochondrial function
Relaxin	−	Fatty acid synthesis, amino acid metabolism
Estrogen	−	Mitochondrial function

−Unclear.

complementary and alternative therapy to treat HF. However, the content of natural products is low, and the technical requirements for its separation, extraction and purification are high. In addition, clinical researches of natural products are relatively insufficiency, and their mechanism and safety in the combine use are still in the exploration and research stage. These may be the reasons that limit their development into HF drugs.

5.4. Integration analysis of drug, target and metabolic pathway

We have sorted out and summarized the hormones, synthetic drugs and natural products mentioned above (Table 3). It is found that most of the drugs or components can act on multiple pathways or targets, and regulate multiple substrate metabolism. This suggests that we can consider the combination of different drugs, especially some drugs with large dosage and narrow safety window, which can reduce dosage, drug resistance and side effects. At present, some components, such as relaxin, estrogen, salsolinol and Chinese patent medicine, have been found to regulate cardiac energy metabolism, but their molecular is unclear. These components should be further study and provide reliable data for its development and application. In addition, we should also focus on utilizing the *in vivo* mechanisms of these drugs to find new or optimal therapeutic targets for HF. Then, we should apply the theoretical results of the study to clinical practice and develop more effective drugs and reasonable treatment strategies for treating HF.

6. Conclusions and prospects

Much evidence shows that optimizing myocardial energy metabolism, especially regulating substrate metabolism, preserves or improves myocardial mechanical function, delays the progression of HF, and improves cardiac function classification, exercise tolerance, quality of life, left ventricular ejection scores and even survival rates. However, it is a research direction, as well as an urgent problem for HF drugs how to select appropriate substrate for adequate metabolism, promote the activity of myocardial metabolizer and increase the overall energy supply according to

different pathological conditions. In addition, the development of most drugs to treat HF *via* energy metabolism is still in the basic research stage, and the changes in efficacy and application of these drugs also lack clinical data support. Researchers should further explore the association between the pathogenesis of HF and changes in myocardial energy metabolism, elucidate reveal the signaling pathways and key regulatory factors that affect HF energy metabolism, and develop effective new methods, including natural medicines, for preventing the occurrence and development of HF.

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Author contributions

Li Han, Ming Yang, Dingkun Zhang and Yanan He designed the study; Lumeng Cheng, Runchun Xu, Nan Li, and Fang Wang supplied materials and analytic tools; Yanan He, Chen Zhang, Dingkun Zhang and Wei Huang wrote the paper.

Conflicts of interest

There are no conflicts to declare.

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