*kinases and phosphatases*

MDPI

*Review*

# Exogenous and Endogenous Molecules Potentially Proficient to Modulate Mitophagy in Cardiac Disorders

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**Abstract:** It has been proposed that procedures which upregulate mitochondrial biogenesis and autophagy by replacing damaged mitochondria with healthy ones may prevent the development of several heart diseases. A member of serine and threonine kinases, adenosine monophosphate-activated protein kinase (AMPK), could play essential roles in the autophagy and/or mitophagy. AMPK is widely distributed in various cells, which might play diverse regulatory roles in different tissues and/or organs. In fact, changes in the kinase function of AMPK due to alteration of activity have been linked with diverse pathologies including cardiac disorders. AMPK can regulate mitochondrial biogenesis via peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) signaling and also improve oxidative mitochondrial metabolism through inhibition of mechanistic/mammalian target of rapamycin (mTOR) pathway, which may also modulate the autophagy/mitophagy through autophagy activating kinase 1 (ULK1) and/or transforming growth factor beta (TGF-β) signaling. Therefore, the modulation of AMPK in autophagy/mitophagy pathway might probably be thought as a therapeutic tactic for several cardiac disorders. As kinases are amongst the most controllable proteins, in general, the design of small molecules targeting kinases might be an eye-catching avenue to modulate cardiac function. Some analyses of the molecular biology underlying mitophagy suggest that nutraceuticals and/or drugs including specific AMPK modulator as well as physical exercise and/or dietary restriction that could modulate AMPK may be useful against several heart diseases. These observations may virtually be limited to preclinical studies. Come to think of these, however, it is speculated that some nutraceutical regimens might have positive potential for managing some of cardiac disorders.

**Keywords:** autophagy; mitophagy; AMPK; cardiomyocyte; cardiac arrhythmia; cardiovascular disease; cardiac failure



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## 1. Introduction

Autophagy is a conserved lysosome-dependent pathway, which is also an intracellular self-protective process that can cut down damaged molecules and/or organelles [1]. In conditions of mild stress, autophagy maintains cellular energy homeostasis by recycling damaged organelles. Under severe stress conditions, however, too much increased activation of autophagy may lead to non-selective degradation of related substances and molecules/organelles, thereby exacerbating mitochondrial damage and triggering energy imbalance and/or cellular apoptosis [2]. Therefore, the autophagy may be an adaptive cellular response to oxidative stress, inflammation, aging, hypoxia, starvation, metabolic abnormalities and other external stimuli [3]. Autophagy can exert significant influence on various cardiac pathologies including cardiac arrhythmias, cardiovascular diseases, and/or heart failure [4]. In general, autophagy is also involved in the maintenance of intracellular homeostasis in most types of cells including cardiomyocytes, vascular smooth muscle cells, fibroblasts, macrophages, and endothelial cells [5,6]. Cardiomyocytes are terminally differentiated cells, which might considerably rely on autophagy for the elimination of abnormal

substances [7]. Therefore, the regulation of autophagy is crucial for the safeguarding of heart homeostasis.

Mitophagy is a selective autophagy in mitochondrial damages [8]. The common feature of mitophagy is the form of an autophagic vacuole enclosing damaged mitochondria, which is also well-defined as a mitophagosome [9]. Therefore, mitophagy is a kind of autophagic response that explicitly targets injured and/or cytotoxic mitochondria. Interestingly, imperfections in autophagy or mitophagy have been identified to exacerbate the character to instinctively develop cardiac disorders (Figure 1). For example, the depletion of a key mediator of mitophagy may cause left ventricular dysfunction and pathological cardiac hypertrophy in mice [10]. Mitophagy in the heart can be induced by hypoxia and/or excessive production of reactive oxygen species (ROS) [11]. Aberrant mitophagy may induce the accumulation of damaged mitochondria, decrease in cardiomyocytes, and dysfunction of heart contraction. In addition, the abnormalities in mitochondrial dynamics and mitophagy are directly related to the defective clearance of damaged mitochondria and the activation of inflammatory responses, which eventually contribute to heart failure [12]. Following acute myocardial infarction, for instance, serious impairment of cardiac function may occur, leading to complications such as cardiac arrhythmia and/or severe heart failure. These cardiac disorders with mitochondrial dysfunction being an important factor in their development are the leading reason for death globally. Therefore, protecting the heart and/or improving cardiac function are important therapeutic goals after acute myocardial infarction. Given the abundance of mitochondria in cardiomyocytes, it is expected that dysfunction of mitochondria could impact cellular activity, and may eventually promote the development of those serious heart diseases.

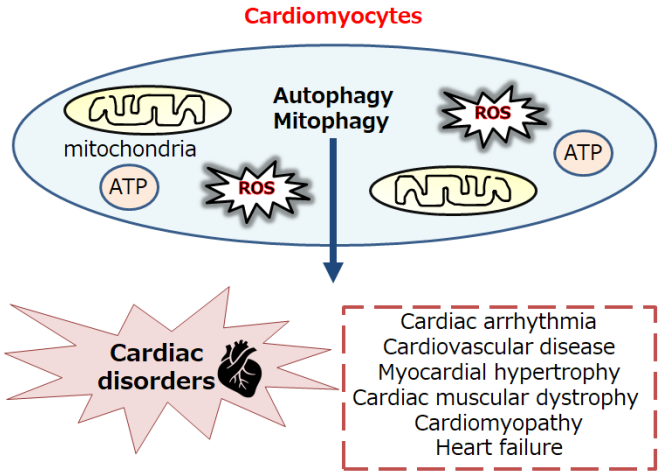


**Figure 1.** Schematic representation of the autophagy and/or mitophagy in cardiomyocytes involved in the cardiac disorders including cardiovascular disease, myocardial hypertrophy, cardiac muscular dystrophy, cardiomyopathy, and acute/chronic heart failure. Note that several important factors and/or severe inflammation with excessive ROS production triggering some critical pathways have been omitted for clarity.

Mitochondria continuously adjust their shape through fission and fusion in response to alterations in adenosine triphosphate (ATP) supply and demand. Interestingly, compared to those in healthy cardiomyocytes, diabetic cardiomyocytes have a reduced mitochondrial size and enlarged spatial density, which may increase the ATP supply of mitochondrial oxidative phosphorylation [13]. In this regard, the role of adenosine monophosphate (AMP)-activated protein kinase (AMPK) in mitochondrial homeostasis has been well-established. The AMPK has been shown to be involved in mitochondrial biogenesis, and promotion of autophagy. For example, resveratrol could function as an antioxidant through the stimulation of AMPK in mitochondria [14]. In addition, the AMPK is considered as an important protein kinase working in the signaling pathway that has been shown to exert prominent cardioprotective effects on the pathophysiological mechanisms of various heart

diseases. In addition, the modification of AMPK activity could be a significant dietary approach for preventing and/or treating several heart diseases [15]. A western-style diet often leads to food overconsumption, which triggers the development of comorbidities such as obesity, hypercholesterolemia, cardiovascular disease, and chronic heart failure. Several studies suggest that intermittent fasting may also protect against the development of those morbidities [16]. Interestingly, it has been shown that fasting may be related to the modulation of autophagy and/or mitophagy [17]. Dietary interventions involving caloric restriction could induce autophagy/mitophagy in the heart [18]. Based on the current evidence, this review may present the potential molecular mechanisms of the beneficial effects by which some diets could play important roles against several heart diseases. Additional nutraceuticals which might have potential modulating effects on mitophagy with heart protective outcomes are also discussed.

## 2. Relationship between Autophagy/Mitophagy and Diseases, Including Cardiac Disorders

Cardiomyocytes are predominantly occupied by numerous mitochondria, which provide the sufficient and tremendous adenosine triphosphate (ATP) levels required for cardiac function [19]. In addition, the cardiac mitochondria have a critical role in the modulation of calcium storage and/or cell apoptosis [20]. Remarkably, some quota of the $Ca^{2+}$ released from the sarcoplasmic reticulum may be taken up by mitochondria through the interaction between mitochondria and the sarcoplasmic reticulum, which can trigger the production of ATP [21]. Abnormal mitochondrial function would result in inadequate energy supply, thereby increasing the generation of ROS [22]. In general, the ROS accumulation may lead to injury to mitochondrial lipids, proteins, and deoxyribonucleic acids (DNAs) involved in the production of ATP, thereby contributing to severe oxidative damage and/or cell death [23]. Such damage may participate in different diseases, as shown by neurodegenerative and/or cardiovascular diseases or in different terminal organs [24].

As a result, the function of the heart is strongly influenced by the condition of mitochondria, which are often also damaged in various cardiac disorders [25]. Considering the critical role of mitophagy in the removal of damaged mitochondria, accumulating evidence supposes that alterations in mitophagy could contribute to the progression of cardiac disorders [26]. For example, mitophagy may slow down the progression of cardiac arrhythmia by eliminating damaged mitochondria and/or modulating ROS levels [27]. In addition, the dysfunction of mitochondria might affect ATP production and/or cardiac electrical transmission, leading to altered $K^+$ fluxes in the sarcolemma via the ATP-dependent potassium channels [27]. Mitochondrial dysfunction may also act to decrease ATP levels and/or increases ROS levels, which might provoke the heterogeneity of cardiac potential activity [28]. Subsequently, mitochondrial dysfunction might be worsened, associated with reduced ATP production. This detrimental cycle might contribute to electrophysiological modifications and/or cardiac arrhythmia. Therefore, suitable mitophagy is indispensable for the inhibition of cardiac arrhythmia. Alteration of ATP and/or ROS levels may play an imperative role in arrhythmia [29]. The development of arrhythmia and inappropriate energy metabolism with the alteration of mitophagy in cardiomyocytes might be closely connected [30]. Mitophagy may protect cardiac cells from myocardial damage in ischemic heart disease, which is the consequence of insufficient coronary blood flow [31]. However, several myocardial damages in cardiac ischemia could impede mitophagy, which instead induces apoptosis in myocardial cells. Similarly, insufficient mitophagy may further exacerbate heart injury. Decreased levels of mitophagy are frequently detected in patients with severe heart failure that is categorized by mitochondrial dysfunction [32]. The vital role of mitophagy in the progression of heart failure has been also suggested by patients with mild heart failure [33].

It has been shown that activation of a serine–threonine kinase, AMPK, signaling pathway can promote mitophagy, which may also decrease oxidative stress in myocardial cells and improve heart function [34]. Therefore, myocardial remodeling and/or the dysregula-

tion of mitophagy with the alteration of AMPK signaling may be considerable pathological processes in the development of heart failure, characterized by myocardial hypertrophy and/or the apoptosis of myocardial cells [35]. In fact, the maintenance of normal function in myocardial cells may deeply depend on basal levels of autophagy with proper AMPK signaling, and impaired autophagy with inappropriate AMPK signaling might lead to myocardial cell hypertrophy [36]. It has been revealed that insufficient mitophagy during heart failure is associated with the alteration of the PI3K/AKT/mechanistic/mammalian target of rapamycin (mTOR) signaling pathway, as well as impaired AMPK signaling (Figure 2). The upregulation of AMPK along with inhibition of the mTOR pathway may stimulate autophagy, which might lessen myocardial hypertrophy and improve heart failure [37]. AMPK can control other important cellular functions such as energy metabolism, apoptosis, oxidative stress, and inflammation as well as autophagy and mitophagy [38]. Therefore, the activity of AMPK might have a significant role in various heart diseases that could cause cardiac arrhythmias by changing arrhythmogenic circumstances, downregulating ion channels and triggering physiological dysfunction [39]. In addition, activation of AMPK is involved in the reduction in ROS levels [40]. This effect may be related to the improvement in inflammatory responses, which can further reduce the incidence of cardiac arrhythmias [41]. In fact, AMPK$^{-/-}$ mice may exhibit more extensive cardiac inflammation [41]. In addition, the underlying mechanism of several heart diseases may suggest that AMPK can decrease acute oxidative stress-induced cardiac inflammation [42].

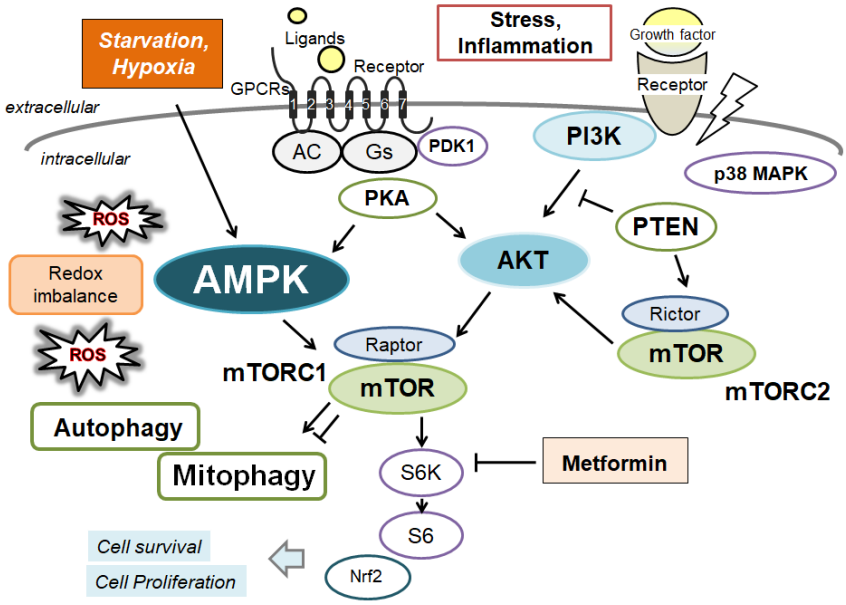


**Figure 2.** An illustrative representation and overview of AMPK, mTOR, and related molecules in the regulatory pathway for autophagy/mitophagy. Several modulator molecules linked to AMPK/PI3K/AKT/mTOR/mTORC1 signaling are also demonstrated. Inflammation, starvation, and/or hypoxia known to act on the autophagy/mitophagy signaling are similarly shown. Arrowhead indicates stimulation whereas hammerhead shows inhibition. Note that several important activities such as cytokine induction and/or intra-cellular inflammatory reactions have been omitted for clarity. Abbreviation: mTOR, mammalian/mechanistic target of rapamycin; PI3K, phosphoinositide-3 kinase; ROS, reactive oxygen species.

## 3. Characterization of AMPK and Connection between AMPK and Autophagy

AMPK is a heterotrimeric complex made up of the three subunits: one catalytic α-subunit and two β- and γ- regulatory subunits. The β subunit has an N-terminus region that can be myristoylated, participating in the regulation of the AMPK recruitment to mitochondria. While the α and β subunits each have two isoforms (α1, α2 and β1, β2), the γ subunit has three isoforms (γ1, γ2, and γ3) [43]. As a result, AMPK is an intricate

heterotrimer that widely exists in eukaryotes. The combination of different isoform subunits may construct different AMPK functions that are differentially expressed in cells, tissues and/or organs. In addition, the structure of AMPK includes a carbohydrate binding segment that permits the binding of AMPK to glycogen, impeding AMPK activity by this means [44]. An increase in AMP triggers the AMPK γ subunit to bind AMP, enhancing the catalytic activity of the complex and increasing the phosphorylation of AMPK [45]. Therefore, AMPK is a kind of sensor of intracellular AMP levels. The carboxy (C)-terminal domain of the β subunit may associate with the α- and γ- subunits, then works as a scaffold protein. The γ subunit enables AMPK to respond to alterations in the AMP/ATP ratio, hence acting as an exact energy sensor [46].

Continuing suitable levels of mitophagy may be essential in the myocardium. AMPK can respond to heart failure by promoting the creation of autophagosomes and by limiting oxidative stress and/or cardiac apoptosis [47]. Consequently, AMPK might be dynamic in a coordinated intracellular network adjusting cellular homeostasis. [48] (Figure 2). Too much increased cardiac ATP request and/or severe oxidative damages could intensely exacerbate imbalances of ATP production [49]. AMPK can improve energy status by promoting the ATP production pathway and/or by inhibiting the ATP consumption pathway, when the cellular situation would be extremely stirred by external factors [50]. In addition, AMPK can control mitochondrial biogenesis through the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) signaling pathway, which could boost mitochondrial oxidative metabolism in ischemic conditions [51]. AMPK activation leads to significant inhibition of the mTOR signaling pathway, which successfully decreases the apoptosis of cells [52]. Additionally, AMPK can also raise levels of autophagy via autophagy activating kinase 1 (ULK1) and partially by inhibiting transforming growth factor beta (TGF-β) signaling [53]. As a key regulator of cellular metabolism, AMPK may keep energy homeostasis at both cellular and physical levels during metabolic and/or oxidative stresses [54]. As mentioned above, AMPK is generally recognized as an accurate energy sensor due to its critical role in regulating the pathways of energy production and consumption in cells and/or the body [55]. In addition, AMPK could also control various other cellular processes including the inhibition of protein synthesis, cell proliferation, and DNA repair [56]. AMPK might exert several protective effects on the heart by controlling energy homeostasis [57]. Also, AMPK could perform as an imperative endogenous protection character that can punctually respond to damaging stimuli such as cardiac ischemia [58]. Remarkably, AMPK can promote glucose and/or fat oxidation, thereby potentially powerfully improving energy metabolism [59]. Therefore, these distinctive regulatory roles of AMPK in diverse tissues and/or organs may be essential for sustaining normal physiological function [60]. AMPK activation can probably be assumed to play a substantial cardioprotective role against cardiotoxicity, which is faithfully associated with the cardiac remodeling process via mitophagy and/or autophagy.

## 4. Some Molecules Involved in the Regulation of AMPK

Metformin upregulates AMPK to induce autophagy and thus improves severe complications of diabetes, including cardiac remodeling and/or heart failure [61]. Metformin can inhibit complex I of the electron transport chain to increase the cellular level of AMP, increasing the AMP/ATP ratio, which may modulate AMPK, exerting physiological effects [62]. Zinc can also modulate mitophagy to suppress the production of superoxide in mitochondria to alleviate cardiac injury by upregulating PINK1 and Beclin1 [63]. However, zinc overload may increase ROS levels, leading to cell death and impaired mitochondrial function and dynamics [64]. Statins, the most effective lipid/cholesterol-lowering drugs, are commonly used in the treatment of hyperlipidemia. Statins can also activate AMPK, thereby affecting cell autophagy through the AMPK/mTOR signaling pathway [65]. Osmotin, a protein present in tobacco, is structurally and functionally similar to adiponectin, which can also activate AMPK. Interestingly, osmotin can protect mice from Aβ-induced memory impairment and neurodegeneration by reducing cholesterol biosynthesis and

ameliorating the pathology of Alzheimer's disease [66]. Ghrelin, a gastric hormone released during fasting, targets the hypothalamus to encourage starvation. The ghrelin can reduce triglyceride production and controls the AMPK and the mTOR signaling pathways to induce autophagy by repairing AMPK phosphorylation and/or preventing mTOR phosphorylation [67]. The ghrelin can activate the AMPK in hypothalamus of the brain, which subsequently stimulates glucose metabolism for energy production, thereby preventing the decline of memory function in rats [68]. Resveratrol can also activate the AMPK by increasing intracellular calcium levels and promotes CaMKKβ-mediated AMPK phosphorylation, which might inhibit the mTOR-induced autophagy to reduce Aβ levels in the brain of Alzheimer's disease. Similarly, resveratrol analogs could also activate the AMPK by promoting CaMKKβ-dependent manner, promoting autophagy to reduce Aβ levels in the brain of Alzheimer's disease [69]. Polygalae radix, a well-known traditional Chinese medicine, can likewise induce autophagy by activating the AMPK/mTOR pathway, thereby reducing Aβ levels of Alzheimer's disease [70]. Instead of exerting a helpful effect, however, the mitophagy activation may also be harmful to disease progression. For example, peroxynitrite treatment may worsen cerebral injury in stroke through the induction of mitophagy [71]. Estrogen could activate the phosphorylation of AMPK and PGC1α via the function of estrogen receptor, which can amend mitochondrial respiration in skeletal muscle cells in vitro [72]. Salsalate is a prodrug of salicylate, which is similar to acetylsalicylic acid, aspirin. Salicylate can stimulate the AMPK through the direct interaction with a serine residue of the AMPK subunit [73]. It has been revealed that cellular effects of *Rosmarinus officinalis* (rosemary) extract are associated with an escalation in levels of AMPK phosphorylation in lung cancer cells [74]. In addition, honokiol treatment could activate AMPK in kidney tubular cells [75]. A small molecule 2,6-disubstituted purine, reversine, can activate the autophagy via upregulation of AMPK in senescent myoblast cells [76]. Leptin is a peptide hormone secreted from fat cells, which can selectively phosphorylate AMPK in skeletal muscle cells [77]. Adiponectin can also activate the AMPK signaling pathway through various mechanisms including by the activation of CaMKKβ [78]. Additionally, adiponectin could bind to α subunit of AMPK to stimulate AMPK heteromerization [79]. Adiponectin can inhibit fatty acid synthesis in obese cells reducing ATP consumption, which may activate the AMPK [80]. Moreover, adiponectin could increase levels of intracellular $NAD^+$, which can indirectly activate AMPK [81]. Furthermore, adiponectin could increase liver glycogenase activity, which also enhances NADH production via glycolysis, indirectly activating AMPK [82]. As a final point, intermittent fasting and ketogenic diets may also activate AMPK and/or inhibit the mTOR pathway, contributing to the suppression of oxidative stress and/or inflammation levels through boosting mitochondrial plasticity [83].

## 5. Possible Treatment Tactics with Certain Small Molecules against Several Heart Diseases

Given the critical role of mitophagy in the pathogenesis of heart disease, mitophagy acts as a promising therapeutic target. The promotion or inhibition of mitophagy could be used to treat the development of heart diseases. In other words, several inhibitors such as metformin could target the AMPK pathway, thereby mediating the modulation of mitophagy for the treatment of heart diseases. Beneficial effects on heart diseases might also be related to the regulation of the cellular antioxidant system as well as mitophagy. Remarkably, modulation of mitophagy may be advantageous both in improving cardiac function and/or in treating several cardiomyopathies. For example, recent studies in animal models of an aging heart have shown that fasting-induced autophagy may improve cardiac function and/or longevity, which may also be related to the autophagic clearance of impaired cellular components [84]. Energy deprivation activates the AMPK as cellular energy sensor, which may successively induce autophagy. Fasting can also release the ghrelin, which can activate AMPK, as mentioned before. Additionally, the administration of metformin could prevent cardiomyopathy by activating AMPK and mitophagy in diabetic mice [85].

Treatment with metformin could also decrease cardiovascular inflammation via increasing AMPK and/or reducing ROS [86]. Some statins have been recognized to have a protective effect on the heart, which could also reduce the severity of myocardial injury [87]. In addition, arachidonic acid could protect against ischemic myocardial damage by endorsing mitochondrial autophagy and/or mitochondrial renewal [88]. The polyamine spermidine can stimulate both mitophagy and mitochondrial biogenesis, and these are associated with improved cardiac function and the prolonged lifespan of individuals. Spermidine treatment can offer a beneficial effect on cardiac mitochondrial alterations associated with aging [89]. Polyamines, such as spermidine and spermine, are aliphatic cations necessary for cell proliferation and/or differentiation, with anti-inflammatory and/or anti-apoptotic effects. They are now evolving as natural autophagy regulators with anti-aging properties. Interestingly, polyamine levels were considerably changed in the skeletal muscles of aged animals [90]. Furthermore, spermine could prevent hypoxia-induced ROS production and a reduction in mitophagy in cardiomyocytes [91]. Berberine has a therapeutic effect on cardiovascular health [92]. Berberine can protect against myocardial injury by inducing mitophagy. Therefore, berberine may serve as a novel therapeutic drug for myocardial injury [93]. In addition, berberine can diminish mitochondrial dysfunction by inducing autophagy, which may contribute to the key cardioprotective mechanisms of berberine [94]. Similarly, treatment of honokiol could improve myocardial injury, which may be significant for the cardioprotective role of honokiol by enhancing autophagy [95]. Carnosic acid, the principal constituent of rosemary, has various biological activities, including anti-inflammatory and antioxidant ones, which could be possible against cardiotoxicity via the modulation of autophagy and/or apoptosis [96]. An elevation in butyrate levels might enhance mitochondrial biogenesis and oxygen consumption and may increase resistance to oxidative/redox stress, hence resulting in an improvement in cardiac function [97]. The protective effect of resveratrol on hypertension-induced cardiac dysfunction has been reported by modulating cellular stress responses and/or mitophagy [98]. In addition, resveratrol could improve cardiomyopathy by promoting autophagy/mitophagy in the heart of a Duchenne muscular dystrophy (DMD) model mouse [99]. Resveratrol can protect mitochondria by modulating mitophagy through the alteration of the AMPK signaling pathway in myocardial cells [100]. Furthermore, resveratrol can inhibit hyperglycemia-induced cardiomyocyte hypertrophy by reducing oxidative stress via stimulating mitophagy to keep mitochondrial homeostasis [101]. Interestingly, resveratrol can dilate retinal arterioles and can protect against retinal neurodegeneration via the AMPK-dependent signaling pathway [102] (Figure 3).

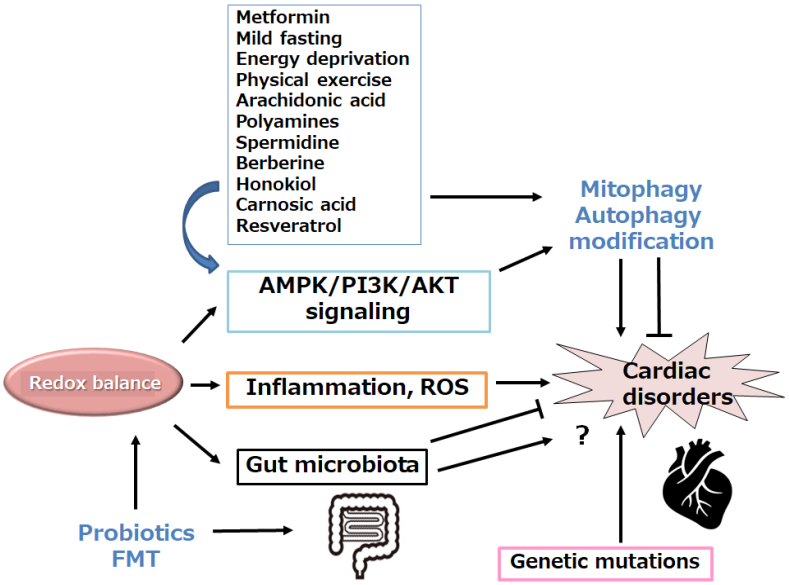


**Figure 3.** Schematic demonstration of the potential inhibitory tactics against the pathogenesis of cardiac disorders. Example compounds including metformin as well as fasting, starvation, and/or exercise,

known to act on mitophagy signaling, are also shown. Note that some of important activities such as autophagy initiation, inflammatory reaction, and reactive oxygen species (ROS) production have been misplaced for clarity. In particular, some kinds of probiotics and/or fecal microbiota transplantation (FMT) might assist the alteration of gut microbiota for the modification of autophagy/mitophagy, which might be advantageous for the treatment of several cardiac disorders. "?" means for author speculation.

## 6. Future Perspectives

Abnormal cardiac function due to damage to mitochondria may remain the main pathogenesis in several heart diseases. Therefore, mitochondrial autophagy/mitophagy might be a hot subject among the molecular mechanisms of organelle-specific autophagy. The induction of mitophagy can strongly alleviate damaged mitochondria and keep suitable mitochondria for normal cellular homeostasis. The mechanisms for the mitophagy are complicated and firmly regulated by multiple interlinked factors. These factors may function during important biological processes, including cell growth, cell differentiation, cell senescence, and cell death. Aberrant regulation of mitophagy may affect normal cellular function and also influence several heart diseases, thereby providing mitophagy a promising therapeutic target for those heart diseases.

Interestingly, it has been shown that AMPK is required for cofilin activation. Pyridoxal phosphatase (PDXP) is known to directly dephosphorylate the cofilin, which may be involved in mitochondrial fission and/or mitophagy [103]. The cofilin signaling pathway induces the activation of TGFβ and/or the PDGF pathway for the vascularization in pluripotent stem cell-derived cardiac organoids [104]. Some researchers have revealed that stem cells can repair damaged myocardium and/or improve heart function [105]. Therefore, AMPK and PDXP might be a key regulator for the regeneration of vascularization and/or cardiomyocytes.

Continual progress has been made in identifying the constituents of natural plant products that are cardioprotective by modulating the AMPK signaling pathway. However, preclinical research and clinical trials would be mandatory to confirm the safety and/or efficacy of the plant metabolites for the treatment and/or prevention of several heart diseases. Whether the induction or inhibition of autophagy/mitophagy are helpful for the pathogenesis of heart disease remains to be more precisely understood. It is possible that mitophagy may be contributed to by the distinctive characteristics of altered molecules. Future studies are also indispensable for the explanation of various effects of various molecules involved in the induction of mitophagy in several heart diseases. Further comprehension into the molecular mechanisms of mitophagy/autophagy in the heart could facilitate in our understanding of how to prevent cardiac disorders.

## 7. Conclusions

Damaged mitochondria may play an important role in maintaining the normal function of cardiovascular cells. An in-depth knowledge of the role of AMPK and autophagy/mitophagy in heart diseases may be valuable for developing new clinical treatment. This review may provide possible insight to support future research into understanding this AMPK signaling axis in cardiac disorders.

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## Abbreviations

| | |
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| AMP | adenosine monophosphate |
| ATP | adenosine triphosphate |
| AMPK | adenosine monophosphate-activated protein kinase |
| DNAs | deoxyribonucleic acids |
| FMT | fecal microbiota transplantation |
| mTOR | mechanistic/mammalian target of rapamycin |
| PDXP | pyridoxal phosphatase |
| PGC1α | peroxisome proliferator-activated receptor gamma coactivator 1-alpha |
| QOL | quality of life |
| ROS | reactive oxygen species |
| TGF-β | transforming growth factor beta |
| ULK1 | autophagy activating kinase 1 |

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