Chapter

Endoplasmic Reticulum Involvement in Heart Injury: An Overview

Gaia Favero, Francesca Bonomini, Marzia Gianò and Rita Rezzani

Abstract

The Endoplasmic Reticulum (ER) is a multifunctional organelle present in the cytoplasm of the eukaryotic cells. It is involved in many aspects of cellular physiology and it presents important interaction with other cellular organelles. Different physiological and/or pathological factors may alter ER morphology and homeostasis, resulting in the accumulation of a large number of unfolded/misfolded proteins in the ER lumen and so inducing ER stress. Alterations in ER have been found to be related to different disorders. In particular, ER stress is implicated in the development and progression of various heart injuries, such as myocardial infarction, ischemia/reperfusion, heart failure, diabetic cardiomyopathy, arrhythmias and cardiotoxicity. Furthermore, the efficiency to counteract the ER stress declines significantly during the physiopathological aging process. In this chapter, we present the correlation between the ER and cardiac injury focusing mainly on the aging process and then we report a brief overview of the potential involvement of some bioactive molecules as preventive/therapeutic compounds that can contrast heart disorders through ER modulation.

Keywords: aging, arrhythmias, biomolecules, cardiac hypertrophy, heart, endoplasmic reticulum

1. Introduction

The ER is a complex and multifunctional organelle present in the cytosol of the eukaryotic cells. This organelle is involved in many aspects of cellular physiology such as regulation of calcium, synthesis, transport and folding of protein, synthesis and metabolism of steroids and lipids and, not to be underestimated, it has important interaction with other cellular organelles [1, 2]. The ER is composed of a continuous lipid bilayer that encloses a luminal space [3–6]. It is morphologically characterized by a membrane system with two major shaped domains: the nuclear envelope and the peripheral ER which includes rough leaves and smooth tubules [7]. The nuclear envelope consists of ER membrane wrapped around DNA and various nuclear elements and it is organized in two continuous flat cisternae sheets surrounding the

nucleus, defined outer and inner nuclear membranes [6, 8]; while the peripheral ER presents cisternae and an interconnected nuclear network of tubules [5, 9–11]. The nuclear envelope pores selectively control the transport of molecules inside and outside the nucleus. The inner and outer nuclear membranes are ample flat sheet-like cisternae stacked over each other and separated by the internuclear membrane space. Historically, ER cisternae have been classified as ribosome bound: "rough ER - RER" or ribosome-free: "smooth ER - SER" [10]. The RER presents many ribosomes associated to the membrane surface and extends from the nuclear envelope to the cell periphery, so defining specialized areas for protein synthesis, folding and degradation. Furthermore, the outer membrane of the nuclear envelope may be considered as part of the RER domain because it is physically continuous with the RER membranes [12]. The SER is composed of irregular and convoluted tubules without associated ribosomes. However, it is continuous with the RER and the majority of proteins in this compartment come from the RER domain [13]. SER includes membranes specialized for drug metabolism and steroid synthesis, as well as tubulovesicular elements forming ER exit sites [14]. Differences in membrane curvature ulteriorly differentiate the RER and SER subdomains [11]. The different ER membranes organization in domains or regions observed among different cell types correlates strictly with their functions: cells specialized to the production, storage and secretion of proteins, such as exocrine cells, are rich in RER; whereas, endocrine cells that synthesize steroid hormones and muscle cells are rich in SER [15, 16]. Furthermore, the previously described distribution of RER and SER is clearly observed in hepatocytes, neurons and endocrine cells; however, in some cells there is not a clear distinction between both domains and so tubules with associated ribosomes are mixed with tubules without associated ribosomes.

As previously depicted, the structure of the ER is complex due to the various distinct domains present within one continuous membrane bilayer. These domains are shaped by interactions with the cytoskeleton, by proteins that stabilize membrane shape and by a homotypic fusion machinery that allows the ER membrane to maintain its morphology. The ER also contains domains that control the interaction with other organelles, such as the Golgi apparatus, endosomes, mitochondria, lipid droplets and peroxisomes [9, 10, 17]. The purpose of differently shaped ER domains is still under evaluation to better clarify also the related functions. **Figure 1** schematically reported the main ER specialized domains, the ER compartmentalization with the nuclear membrane and its interaction with cellular organelles.

Different physiological and/or pathological factors may alter ER morphology and homeostasis, resulting in the accumulation of a large number of unfolded or misfolded proteins in the ER lumen and so inducing ER stress (**Figure 2**) [18–20]. Alteration in ER has been found to be related with different disorders [4, 21]; in fact, in various pathologies the morphology/structure of ER was abnormal and various mutation in morphology-regulating proteins have been observed, indicating that morphology and functions of the ER are intrinsically linked. Furthermore, in chronic conditions, a persistent ER stress can induce and exacerbate cellular and tissue senescence accelerating the aging-related process [21, 22]. To counteract ER stress and reduce the synthesis of proteins, cells activate an endogenous adaptive stress response defined Unfolded Protein Reaction (UPR). During this adaptive mechanism, ER showed an increased expression of folding protein and degradation of protein related genes [19, 23]. Therefore, ER stress is an adaptive cell mechanism

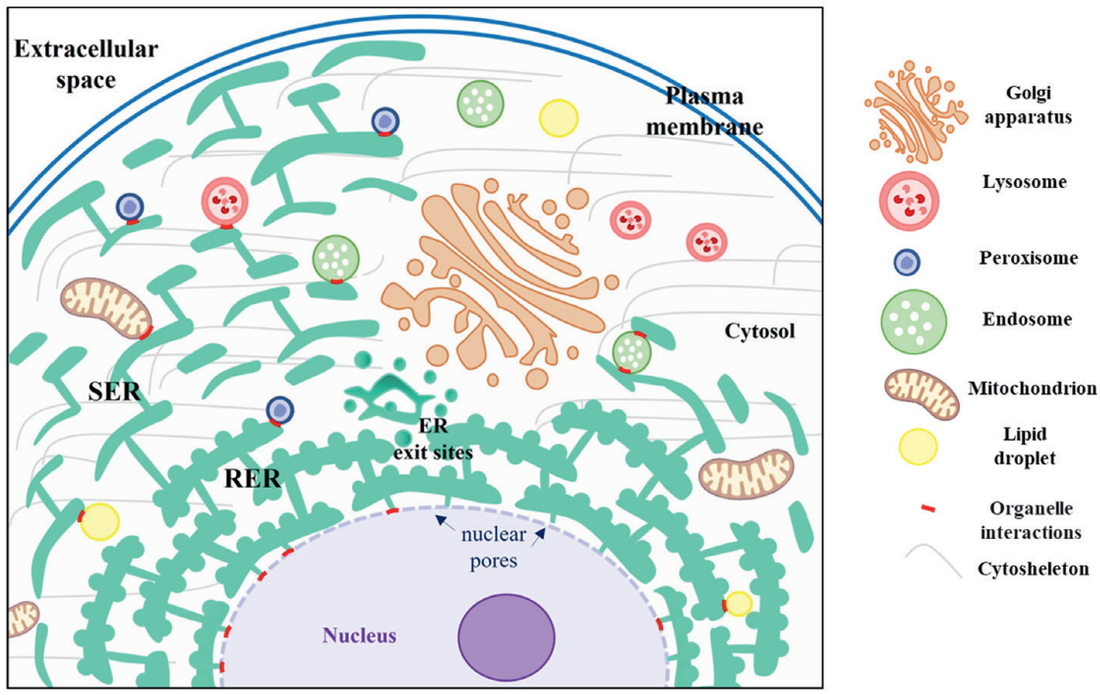

Figure 1.
Schematic representation of the main endoplasmic reticulum specialized domains, the endoplasmic reticulum compartmentalization with the nuclear membrane and its interaction with cellular organelles. RER: Ribosome-free endoplasmic reticulum; SER: Smooth endoplasmic reticulum.

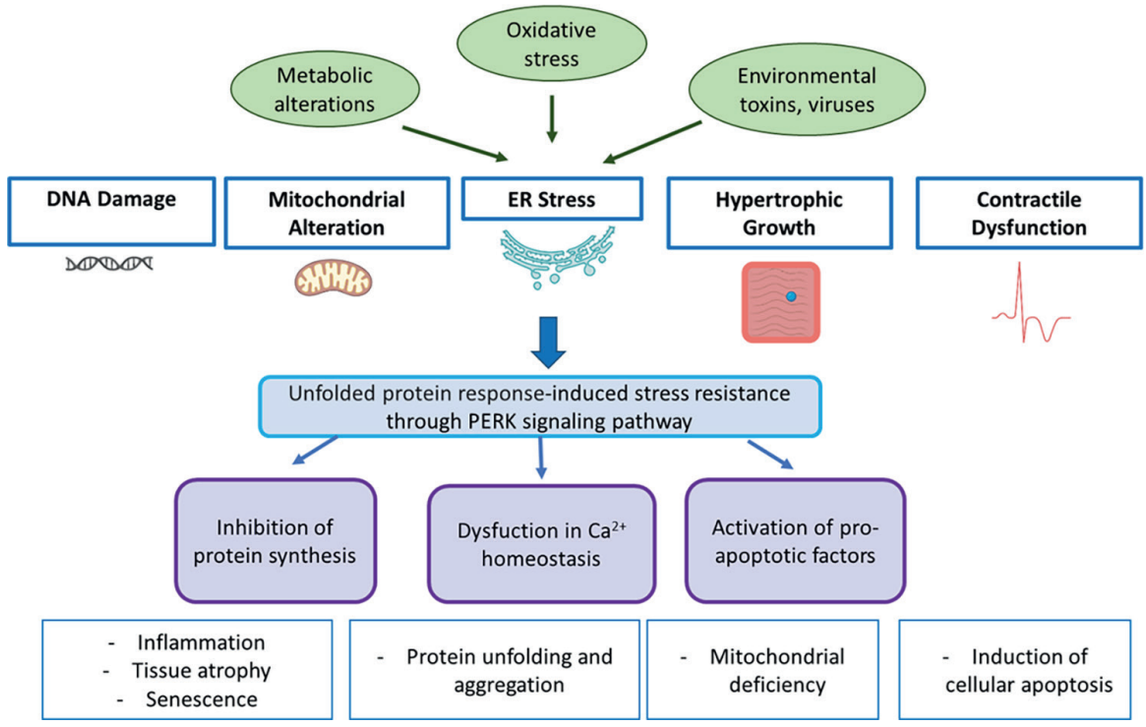

Figure 2.
Cardiomyocyte senescence's markers and regulation of aging process by endoplasmic reticulum stress. Metabolic alterations, oxidative stress, toxins and viruses can induce endoplasmic reticulum stress and activate the unfolded protein reaction via PERK signaling pathway leading to heart injury. ER: Endoplasmic reticulum; PERK: Protein kinase RNA-activated (PKR)-like ER kinase; UPR: Unfolded protein reaction.

activated to restore the ER morphology and functions by triggering UPR; whereas the persistence of the ER stress is deleterious and induces cell apoptosis [24–26]. To date many studies are focused on ER (stress) as a possible target strategy to counteract various diseases progression and drug resistance by hitting UPR components and the complex interplay between UPR, autophagy and apoptosis. The UPR may be activated by different sensors: Inositol Requiring Enzyme1 (IRE1), Activating Transcription Factor6 (ATF6) and Protein Kinase RNA-activated (PKR)-like ER Kinase (PERK), leading to transcriptional and translational reprogramming to counteract unfolded proteins accumulation and upregulating the expression of UPR-related proteins and proteins of the autophagy-related pathway [27]. PERK is involved in a pro-survival pathway, but it can also promote apoptosis through the activation of CHOP, the main mediator of apoptosis induced by the UPR [28, 29]. CHOP induces the expression of ER Oxidoreductase 1 alpha (ERO1α), which promotes cell death through the hyper-oxidation of ER proteins [30]. CHOP also participates in the regulation of autophagy, self-digestive intracellular process through which cells recycle organelles and damaged or unnecessary proteins [31–33]. Prolong ER stress, oxidative stress and inflammation are typical features of many pathologies, including metabolic diseases and different age-related diseases, such as neurodegenerative disorders, various cancers and cardiovascular diseases [22, 34]. Various studies have demonstrated that damage at myocardial tissue level is characterized by accumulation, at ER level, of ubiquitinated proteins and this accumulation at ER level promotes ER stress which, in turn, induces the release of ER-related apoptotic proteins thus contributing, in a vicious cycle, to heart injury [35–37].

Furthermore, autophagy is a crucial process involved also in the development of cardiovascular diseases [38]. A variety of autophagy proteins are localized at the ER level and originate from mitochondrial-associated ER membrane (ER interaction site with mitochondria) [39]. ER is one of the membrane donors required for the formation of autophagosomes, double-membrane vesicles involved in autophagy [40, 41].

Furthermore, ER stress is progressively increased during the physiopathological aging process also at heart level. The modulation of ER stress and an enhancement of the intensity of UPR adaptive stress response could be valid strategies to prevent/treat different diseases.

In the following paragraphs, we present the main ER alterations correlated with cardiac injury focusing mainly on the physiopathological process of aging and then we report a brief overview of the potential involvement of bioactive molecules as preventive/therapeutic compounds that can contrast heart disorders through ER modulation.

2. Endoplasmic reticulum and heart injury

Cardiovascular diseases are to date the leading morbidity and mortality burden in the world [42–44]. The molecular mechanism(s) involved in the pathogenetic processes of cardiac disorders are not fully understood. Age-related changes contribute to reduce heart capacity to adapt to different physiological and pathological factors and, in turn, the ability to restore the "normal" morphology and functions is reduced/impaired [45, 46]. Notably, aging promotes alteration of mitochondrial function, condition strictly linked to increased reactive oxygen species production and oxidative stress (which play a fundamental role in aging-related diseases). In addition, elevated levels of oxidative and nitrosative stress occur in parallel with ER stress [45, 47] and,

therefore, aging-induced ER stress may contribute to mitochondrial dysfunction [36]. In the last decade, various studies have reported that ER stress, mitochondrial injury and oxidative stress are involved in the development and progression of a various heart diseases, such as myocardial infarction, cardiac hypertrophy, ischemia/reperfusion, heart failure, diabetic cardiomyopathies, arrhythmias and cardiotoxicity [48–51]. Furthermore, the cell ability to counteract the ER stress and the efficacy of the UPR signaling adaptive response decline significantly during aging [45]. The UPR is, in fact, fundamental for maintaining heart health because cardiomyocytes lack the ability to replicate or efficiently repair themselves, making them deficient in regenerative capability [52]. If ER stress becomes too severe, the UPR signaling adaptive response leads to cell death through apoptosis or autophagy processes [29, 53]. During ER stress, IRE1 binds to Tumor Necrosis Factor-Receptor-Associated Factor 2 (TRAF2) which in turn activates the Apoptosis Signal-Regulating Kinase 1 (ASK1), a Mitogen-Activated Protein (MAP) Kinase Kinase Kinase (MAP3K). The IRE1-TRAF2-ASK1 complex promotes the activation of p38 and c-Jun N-terminal Kinase (JNK), known apoptosis-regulating MAP kinases (MAPK) [54]. In particular, JNK and p38 may be activated in response to a variety of cell stresses, including oxidative stress, DNA damage and inflammatory cytokines [55]. Under physiological conditions, glucose-regulated protein (GRP)78, a mediator of the UPR, binds to PERK, IRE1 or ATF6 forming a stable and inactive complex which inhibits the transmission of the downstream signals. When the UPR is promoted, GRP78 disassociates from this complex and binds to unfolded or misfolded proteins, activating downstream cascade reactions and promoting cell death [56–58]. It is fundamental to underline that this adaptive process involves a complex correlation between autophagy and apoptosis, fundamental to determine cell fate in response to ER stress. In fact, autophagy promotes cell survival through degradation of misfolded proteins that have been retained in the ER or induces cell death through the autophagy process [52]. Understanding how to suppress IRE1 activity and related downstream pathway to inhibit ER stress-induced apoptosis and autophagy-related cell death is of fundamental importance. Xue et al. [59] observed that Activin A, a member of the transforming growth factor-beta superfamily, has important neuroprotective effects against ER stress-mediated apoptosis and autophagy by inhibiting the activation of the IRE1-TRAF2-ASK1-JNK/p38 complex *in vitro*. This will be an important starting point for better understanding how to modulate ER stress and related injuries.

Therefore, investigate the ER stress also in aging-related heart injury is actually an important research focus which needs more studies.

For the first time, Sreedhar et al. [60] identified the involvement of ER stress-induced apoptosis in the hearts of SAMP8 mice, known aging mouse model [61, 62], demonstrating that ER is an important factor in cardiac aging. In particular, SAMP8 mice showed an increased p38 expression at heart level, suggesting a relation between MAPK signaling cascade and ER stress. At heart level, the SAMP8 mice presented elevated expression of the pro-apoptotic transcription factor CHOP and caspases, highlighting that p38 induces ER stress-related apoptosis. Currently, a weak/moderate ER stress is considered beneficial for heart function by restoring ER morphology and homeostasis and protecting cardiomyocytes through an adaptive mechanism. On the contrary, a prolonged and severe ER stress promotes cardiomyocyte death [63–65]. Notably, mitochondrial damage and ER stress have been well recognized as important cardiac ischemia/reperfusion injury upstream factors controlling the cardiomyocyte death [20, 66]. Aging decreases the efficacy of the endogenous adaptive response and increases ER-mediated myocardial apoptotic signaling after ischemic/reperfusion injuries [24, 67].

Cardiomyopathy is the most common cause of morbidity and mortality in diabetic patients [68]. Diabetic conditions promote ER stress response by oxidative mechanisms which contribute to eliminate unhealthy cells and lead to diabetic cardiomyopathy development. Such conditions have been shown to promote cardiac hypertrophy, collagen deposition, stiffness and so important cardiac dysfunction. ER stress activation indeed has been observed in both hypertrophic and failing hearts [20, 68, 69]. Accumulating studies have demonstrated that the ER stress response is also involved in the cardiac hypertrophy progression which is typically characterized by increased size of cardiomyocyte, interstitial fibrosis, apoptosis and contractile dysfunction [43, 70]. STING, an ER-resident protein regulating innate immunity, is highly expressed in hearts of patients with dilated cardiomyopathy or hypertrophic cardiomyopathy [71]. In addition, Zhang et al. [71] reported that STING knockout attenuated cardiac hypertrophy induced by aortic banding showing a significant alteration of cardiomyocyte size, ER stress and hypertrophic markers expression. Moreover, STING deletion significantly reduced inflammation and fibrosis at heart level. The authors so concluded that the modulation of STING expression was, at least in part, regulated by ER stress, underling its important contribution in the cardiac hypertrophy progression. Furthermore, Yao et al. reported a fundamental physiological role of AGGF1: it may regulate ER stress signaling and blocking ER stress-induced apoptosis in cardiac hypertrophy [51]. The authors described that ER stress induces the downregulation of AGGF1 level in a mouse model and human patients with heart failure. In detail, AGGF1 regulates ER stress signaling through CHOP pathway and so inhibits ER stress-induced apoptosis. Liu et al. [72] observed that the expression of SOCS3, a mechanical stress inducible gene, is involved in hypertrophic hearts after 2 weeks of transverse aortic constriction, well-established animal model of pressure overload-induced cardiac hypertrophy [72, 73]. Pressure overload promotes ER stress-induced apoptosis of cardiomyocytes, leading to cardiac hypertrophy and heart failure [74]. In detail, the authors observed that SOCS3-GRP78-ER stress signaling promotes the transition from cardiac hypertrophy to heart failure during pressure overload *in vivo*. In fact, prolonged pressure overload significantly decreases SOCS3 expression that, acting as a negative regulator of cardiac hypertrophy, interacts with GRP78 and induces GRP78 ubiquitination and proteasomal degradation so modulating ER stress. Moreover, cardiac-specific SOCS3 knockout mice presented significant cardiac hypertrophy, chamber dilatation and abnormal myofilament calcium sensitivity after pressure overload. Notably, the treatment of mice with 4-phenylbutyric acid, a short chain fatty acid that is clinically used to treat urea cycle disorders, for 4 weeks attenuates ER stress and related downstream pathways targeting GRP78 and so determining inhibition of cardiac hypertrophy and dysfunction.

STING, AGGF1 and SOCS3 may represent new targets not only for cardiovascular diseases, but also for other diseases associated with ER stress.

During aging, the proteostasis network becomes unable to maintain proteostasis and key UPR molecules, such as PERK, are damaged leading to misfolded proteins accumulation within the ER [75–78]. Age-related injury due to protein misfolding, aggregating proteins and dysfunctional UPR sensors has been shown to lead to diabetes mellitus, neurodegeneration, cancer, heart diseases and arrhythmias [75, 77]. Due to the strict morphological and functional link between ER protein and calcium homeostasis, mounting evidences report that prolonged ER stress is correlated with heart arrhythmic risk via perturbed redox status within the ER as well as downregulation of cardiac ion channel proteins. Furthermore, UPR is involved directly and indirectly in proarrhythmic cardiac remodeling through UPR-induced oxidative stress, altered

glycosylation and modulation of ion channels involved in excitation-contraction (including ER calcium handling proteins) [72], so ulteriorly correlating ER stress to heart arrhythmias. Importantly, inhibition of PERK may prevent downregulation of these channels, attenuate aberrant electrical remodeling, reduce ventricular arrhythmia inducibility and improve survival after myocardial infarct *in vivo*. Therefore, it is fundamental that cardiomyocytes carefully balance the UPR to safely counteract ER stress and maintain proteostasis [78]. Recently, Nakamura et al. [70] reported that ER stress, activating nuclear factor-kappa B (NF-kB) pathway, promotes ventricular arrhythmia in failing hearts via the cardiac dopamine receptor D1 (D1R) upregulation. D1R is upregulated in cardiomyocytes of failing hearts (in mice and humans) leading to heart failure-associated ventricular arrhythmia. ER stress-induced NF-κB signaling pathway could potentially serve as a target to improve the prognosis of heart failure patients [79]. Moreover, Hamilton et al. [80] recently observed a novel association interacting complex Ryanodine Receptor (RyR2)-Endoplasmic Reticulum protein44 (ERp44) which may be stabilized by Ero1α in cardiac hypertrophy. Cardiac hypertrophy-mediated upregulation of Ero1α results in the removal of ERp44 from the complex, inducing RyR2 dysfunction. This dysfunction increases the risk of calcium-dependent ventricular arrhythmias. The authors, notably, concluded that Ero1α may be a promising target to reduce arrhythmogenesis and to improve cardiac function during hypertrophy and heart failure, without disturbing the finely balanced intra-ER redox environment.

Autophagy is also impaired in arrhythmogenic cardiomyopathy. Pitsch et al. [81] observed, in an animal model of arrhythmogenic cardiomyopathy, signs of increased autophagy prior to structural disease onset in the "normal"-appearing mutant myocardium. In particular, the authors reported, at heart level, numerous autophagy-related vacuoles and the upregulation of autophagy during onset and progression of the arrhythmogenic cardiomyopathy. Furthermore, ventricles presented elevated expression of the pro-apoptotic ER stress marker CHOP both at disease onset and during chronic disease progression. In addition, reduced Ryr2 mRNA expression together with severe enlarged ER cisternae underlined ER dysfunction.

Furthermore, it has been documented that ER stress is involved also in cardiotoxicity and heart injury that potentially may evolve into heart failure. Interestingly, Ni et al. [82] observed upregulation of ER chaperones in patients with end-stage heart failure. In detail, the authors investigated the expression of various ER stress factors in hearts of 4 patients subjected to heart transplantation who suffered from dilated cardiomyopathy with end-stage heart failure and 9 patients undergoing mitral valve replacement, as well as 4 healthy subjects. This study, interestingly, reported a significant upregulation of the phosphorylated level of PERK together with c-Jun phosphorylation in failing hearts compared with healthy hearts. These results indicated that prolonged ER stress and associated apoptosis are general occurrence in human failing hearts. Similar results were subsequently found in isoproterenol-stimulated cardiomyocytes and in a rat model of heart failure after abdominal aortic constriction and isoproterenol subcutaneous injection. Furthermore, the authors observed also that long-term oral treatment with β-adrenergic receptor blockers inhibits ER stress, correlated to cardiac hypertrophy and heart failure.

3. Possible endoplasmic reticulum modulation against heart injury

To date, the protective and therapeutic strategies against cardiovascular diseases are not fully efficient and effective especially in elderly people, so amplify the actual

knowledge on ER stress involvement in heart injury will be helpful in finding novel drug targets. In the last decade, at this aim, different potential therapeutic biomolecules have been investigated; however, there are still many unresolved questions that need to be debated and investigated in deep.

Different studies have indicated that sirtuin 1, NAD^+-dependent deacetylases implicated in many aspects of aging process [83], is involved in the regulation of ER stress in cardiomyocytes [84–86]. Hsu et al. [45] hypothesized that sirtuin 1 is able to protect aging heart. In detail, the authors observed a significative contractile dysfunction associated with improved ER stress and oxidative stress in aged sirtuin $1^{-/-}$ mouse hearts. The study demonstrated also, *in vitro*, that a sirtuin 1 activator reduced ER stress and myocardial apoptosis induced by oxidative stress; whereas a sirtuin 1 inhibitor reversed the sirtuin 1 protective effect at cardiomyocytes level. Therefore, the development of "drugs" targeting sirtuin 1 could have interesting preventive/therapeutic potentials against cardiac contractile injury aging-related.

Recently, Monceaux et al. [63] evaluated the ability of ten phenolic phytonutrients (resveratrol, berberine, butein, catechin, ferulic acid, isoliquiritigenin, malvidin, piceatannol, pterostilbene and tyrosol) to modulate ER stress. Interestingly, all these bioactive compounds are able to protect the heart from severe ER stress. Investigating in deep the mechanisms of action of the phytonutrients, the authors reported that ferulic acid, pterostilbene and tyrosol protect cardiomyocytes from severe ER stress by selectively downregulating the PERK pathway of the UPR signaling through sirtuin 1-mediated deacetylation of the translation initiation factor eIF2α (factor which modulates the transcription of UPR target genes, such as ATF4). Interestingly, this study reported that ferulic acid, pterostilbene and tyrosol, by downregulating the PERK/eIF2α/ATF4 pathway, reduce the level of the pro-apoptotic transcription factor CHOP and so limit ER stress-related apoptosis at heart level (**Figure 3**).

Furthermore, Liu et al. [72] evaluated the protective role in reducing the activation of the UPR under ER stress conditions of Wenxin Granules (mix of five drugs: Codonopsis, Rhizoma Polygoni, Panax notoginseng, Amber and Gansong), known traditional Chinese medicine with important effects in the inhibition of myocardial remodeling, modulation of cardiac conduction systems and heart arrhythmias [87, 88]. The authors performed an in vivo study with a rat model of myocardial infarction obtained through the ligation of the anterior descending branch of the left coronary artery and Wenxin Granules were administered intragastrically once per day for two consecutive weeks. In detail, the human daily dose of Wenxin Granules was converted into an equivalent dose for rats (approximately 6 times the human dose for the low-dose group and approximately 12 times the human dose for the high-dose group). Compared with the sham operated group, the myocardial infarction model group showed larger hearts and a significant increase of the left ventricular inner diameter; whereas Wenxin Granules improved significantly the morphological myocardial alteration observed in the infarction model group. Furthermore, the myocardial infarction model group presented elevated expression levels of the ER stress proteins GRP78, PERK, ATF6 and XBP1 and, notably, the expression levels of the ER stress pathway proteins were reduced after Wenxin Granules administration. Furthermore, the expression levels of the apoptotic CHOP and Bax in the myocardial infarction model group significantly increased compared with the sham group, whereas the Bcl-2/Bax ratio significantly decreased. Notably, Wenxin Granules were able to improve ventricular remodeling, prevented the excessive ER stress-mediated UPR activation and inhibited myocardial cell apoptosis [72].

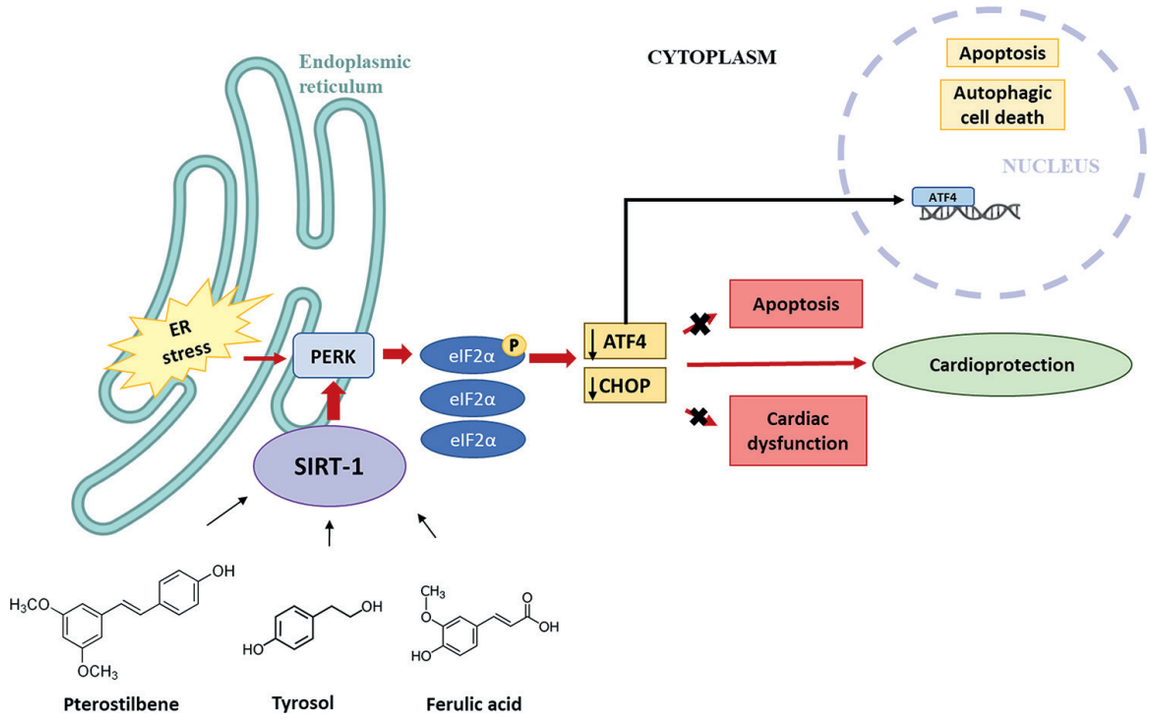

Figure 3.
Polyphenol cardioprotection's mechanism against endoplasmic reticulum stress. Pterostilbene, tyrosol and ferulic acid protect cardiomyocytes downregulating the PERK signaling pathway mediated by sirtuin 1. This pathway decreases the expression of ATF4 and CHOP inhibiting apoptosis and cardiac dysfunction. Modified from Monceaux et al. [63]. ATF4: Activating transcription factor4; ER: Endoplasmic reticulum; PERK: Protein kinase RNA-activated (PKR)-like ER kinase.

Recently, Tu et al. [89] analyzed for the first time the effects of fish oil against atrial fibrillation vulnerability by reducing ER stress in a canine model. The atrial fibrillation model animals were obtained using long-term rapid atrial pacing; the animals were fed with a chow supplemented with fish oil (0.6 dietary ω-3 fatty acids/kg/day) and initiated the treatment 1 week before surgery and continued for 4 weeks post-surgery. The fish oil treatment not only reduced myocardial ER stress, but decreased also pro-inflammatory factors, calcium handling-related proteins and reversed the elevated level of CHOP and caspase12 in the atrial fibrillation group, so significantly reduced atrial fibrillation inducibility and duration.

4. Conclusion

The actual knowledge on the role of ER stress in heart injury are mainly from *in vivo* animal studies, so the understanding of the ER and UPR involvement in human diseases is still limited. Due to that, ER stress plays a central role in heart injury development, ER stress inhibitors could be important for preventive/therapeutic interventions. The development of novel therapeutic/protective approaches modulating the ER stress pathway may reduce the drain of health care costs and resources resulting from the worldwide spread against cardiovascular diseases.

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