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Therapeutic potential of polyphenols in cardiovascular diseases: Regulation of mTOR signaling pathway

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ABSTRACT

Cardiovascular diseases comprise of non-communicable disorders that involve the heart and/or blood vessels and have become the leading cause of death worldwide with increased prevalence by age. mTOR is a serine/threonine-specific protein kinase which plays a central role in many physiological processes including cardiovascular diseases, and also integrates various proliferative signals, nutrient and energy abundance and stressful situations. mTOR also acts as central regulator during chronic stress, mitochondrial dysfunction and deregulated autophagy which are associated with senescence. Under oxidative stress, mTOR has been reported to exert protective effects regulating apoptosis and autophagy processes and favoring tissue repair. On the other hand, inhibition of mTOR has been suggested to have beneficial effects against atherosclerosis, cardiac hypertrophy and heart failure, and also in extending the lifespan. In this aspect, the use of drugs or natural compounds, which can target mTOR is an interesting approach in order to reduce the number of deaths caused by cardiovascular disease. In the present review, we intend to shed light on the possible effects and molecular mechanism of natural agents like polyphenols via regulating mTOR.

Abbreviations: 4EBP1, 4E-binding protein 1; eIF4E, eukaryotic initiation factor 4E; FoxO3a, the forkhead transcription factor; GSK3β, glycogen synthase kinase-3β; p70S6K, p70 ribosome S6 kinase; PS, phosphatidylserine

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1. Introduction

Cardiovascular diseases (CVDs) are the main cause of death worldwide and according to the World Health Organization (WHO), about 18 million people died in 2015 from CVDs [1]. CVDs comprise a group of non-communicable disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, thrombosis and pulmonary embolism [1]. In order to reduce the number of deaths caused by CVDs, groups of elevated cardiovascular risk such as people with hypertension, diabetes or hyperlipidaemia need to be carefully referenced, monitored and in some cases medicated. Also, CVDs are a heavy burden on the economies of low- and middle-income countries, therefore it is of major importance to find accessible approaches to minimize this impact at health and economic levels. CVDs can be partially prevented by avoiding an unhealthy lifestyle such as tobacco smoking, physical inactivity, excessive consumption of alcohol, obesity and also by implementing a healthy diet, namely the reduction of salt and consumption of fruits and vegetables [1].

In fact, prospective studies show an inverse association between the development of CVDs and the intake of fruit and vegetables [2,3]. This is mainly due to the presence of high content of polyphenols such as stilbenoids and flavonoids. However, the cardioprotective mechanism of action for many of these protective agents has not yet been hypothesized [4,5]. One of the therapeutic approaches for CVDs is the mechanistic target of the protein Mammalian target of rapamycin (mTOR). It belongs to the family of phosphatidylinositol-3-kinase-related kinases (PIKKs) which phosphorylates threonine and serine residues in its substrates. mTOR is involved in many cellular processes, such as cell growth, metabolism, proliferation, survival, transcription, translation, apoptosis, motility and autophagy [6]. The signaling mechanism mediated by mTOR is considered as one of the therapeutic approaches for the treatment of CVDs. The macrolide compound rapamycin is a mTOR inhibitor and its analogs which are so-called rapalogs are considered as the first generation of mTOR inhibitors [7]. Similarly many polyphenols present in fruits and vegetables such as resveratrol, catechin and quercetin have been associated with reduction of mTOR signaling [8]. In this review, we would like to consider the role of polyphenols on mTOR signaling pathway in cardiovascular diseases (Tables 1 and 2).

2. Signaling pathway of mTOR

The mTOR (mammalian target of rapamycin) which belongs to PIKK family (phosphatidylinositol kinase-related kinase) has at its carboxy terminal a Ser/Thr kinase activity domain. mTOR is a nutrient-sensing system and represents the catalytic subunit of two multicomplexes: mTORC1 and mTORC2 (Fig. 1). The regulatory associated protein called as raptor (KIAA1303) associates with mTOR and forms mTOR1 complex, whereas instead of raptor the mTORC2 complex contains the protein RICTOR (rapamycin-insensitive companion of mTOR) [9]. Both complexes contain a common subunit mLST8 (mammalian lethal with sec-13), Deptor and TTI1/TEL2 complex (which increases the stability of mTOR). Apart from mTOR, raptor/rictor, Deptorand mLST8, mTORC1 consists of other raptor binding protein like PRAS40 (proline-rich AKT substrate 40 kDa), and C2 complex consists of Protor-1 (protein observed with rictor-1) and mSIN1 (mammalian stress-activated protein kinase interacting protein 1) (Fig. 1) [10,11].

Since the binding proteins are different for the two complexes, the mechanisms mediated by these complexes are also different. Upstream regulation and downstream outputs of mTORC1 are the better characterized between the two complexes [12]. mTORC1 is activated by diverse growth factors and insulin by PI_3K and AKT kinases signaling but also by some nutrients such as amino acids and is repressed by AMP-activated protein kinase (AMPK), a central sensor of cellular energy status [13]. mTORC1 plays a major role in the regulation of protein synthesis, controlling cell growth and metabolism. In contrast, mTORC2 has been demonstrated to be involved in cell survival, apoptosis and proliferation, although conflicting studies exist on its role in

Table 1
Polyphenols that regulate mTOR function and the proposed mechanisms.

References	Polyphenols	Mechanism of regulation
[77,79–83,86–88].	Resveratrol	Inhibition of mTORC1 activation by promoting Deptor/mTOR interaction. Inhibition of phosphorylation of PDK1, Akt, mTOR and p70S6K1. Activation of AMPK-dependent inhibition of mTOR pathway. Reduced expression of the mTOR signaling proteins. Activation of the mTORC2-Rictor survival pathway.
[89,94–96].	Epigallocatechingallate (EGCG)	Inhibition of Akt and downstream targets mTOR and p70S6k phosphorylation. Inhibition of PI_3K/Akt and mTOR activation in an ATP-dependent manner. Attenuation of the activation of NF-κB.
[97–99].	Honokiol	No direct evidence on mTOR inhibition. Activation of mitochondria-localized histone deacetylase SIRT3. Induction of PPAR-gamma activity.
[104–106,108,111,112]	Curcumin	Suppression of Akt and mTOR phosphorylation. Prevention of FOXO1 nuclear localization and activation of FOXO1-induced autophagy. Inhibition p300 histone acetyltransferase-dependent acetylation of the transcriptional factor GATA4. Activation of Nrf2 pathway and inhibition of NF-kB pathway Induction of mTOR/autophagy axis in cardiac hypertrophy and fibrosis
[113,116–119].	Quercetin	Inhibition of mTOR phosphorylation. Inhibition of VEGFR- 2 dependent Akt/mTOR pathway. Activation of AMPK pathway via LKB1. Increased activation of SIRT1.
[122–124],	Oleuropein	Activation of the phosphorylation of AMPK. Activation of PI_3K, Akt, eNOS and STAT-3 signaling pathways. Inhibition of iNOS.
[125]	Baicalein	Inhibition of ERK1/2, NF-κB/p65, calcineurin and Akt/mTOR signaling pathways.
[126]	Fisetin	Inhibition of mTOR phosphorylation and its downstream effector protein p70S6K.
[127]	Cardamonin	Disruption of the association between the mTOR and Raptor protein.
[128]	Hesperidin	Limited excessive autophagy in myocardial infarction by activating the PI_3K/Akt/mTOR pathway.
[129]	Salvianolic acid A	Activation of the Akt/mTOR/4EBP1 pathway.
[130,131]	Ginsenoside Rg1	Reduction of AMPK and GSK-3b phosphorylation. Upregulation of p70S6K

Table 2
Doses of polyphenols that regulate mTOR function in cellular and animal models.

Polyphenol	Dosage
Resveratrol	• 50 μM to serum-starved C2C12 myoblasts [134] • 3 to 100 μM in HT-p21 cells [135] • 10 μM in endothelial cells [136] • 20 mg/kg/day in male four-week-old C57BL/6 mice [83]
Epigallocatechingallate (EGCG)	• 10–100 μM in cardiac myocytes [137] • Inhibition of mTORC1 and mTORC2 kinase activities were observed at the Ki values of 0.37 and 0.23 μM [138]
Honokiol	• 10 μM for 24 hrs in primary cultures of cardiomyocytes [139,140]
Curcumin	• 20 μM in Human Rhabdomyosarcoma Cell Lines (Rh1, Rh30), DU145, MCF-7 and Hela cells [141] • 25 μM in colorectal carcinoma cells (HCT116 CRC) [142] • EA.hy926 endothelial cells treated with curcumin (5-20 μM) [143] • 1, 5, 10, 50 μM in the endothelial cell line HUVECs [144] • 10 μM of curcumin derivate nicotinate-curcumin in THP-1 mocnocyte cell line [145]
Quercetin	• 10-50 μM in HUVECs [146] • 100 mg/kg in male ApoE-knockout (C57BL/6 J background) mice [147,148]
Oleuropein	• 1000 and 2000 mg/kg, intraperitoneally (i.p.) for 14 days using a rat model [122] • 20 mg/kg dissolved in 5% dextrose and administered orally during three or six weeks in a rabbit model [123] • 100 μM, for 24 h, and then treatment with H_2O_2 600 μM for 1 h in human adipose-derived mesenchymal stem cells [124]
Other polyphenols	• The bioflavonoid baicalein at 25 mg/kg in Wild-type (WT) mice [125] • Fisetin (10 μM) in neonatal cardiomyocytes [126] • Cardamonin at 20 mg/kg/day in mice [127] • Hesperidin (200 mg/kg/day) in Adult male Sprague-Dawley rats [128] • Salvianolic acid A at 40 mg/kg in Male adult Sprague-Dawley rats [129]

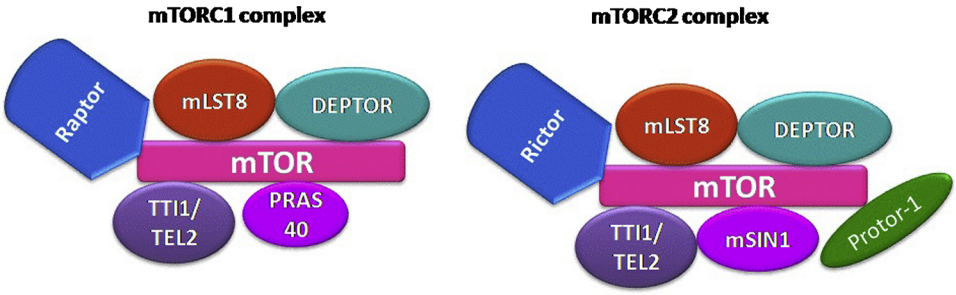

Fig. 1. mTOR: the catalytic subunit of the two multicomplexes mTORC1 and mTORC2 (mTOR: mechanistic target of rapamycin; RAPTOR: regulatory-associated protein of mTOR; mLST8: mammalian lethal with SEC13 protein-8; DEPTOR: DEP domain-containing mTOR-interacting protein; PRAS 40: proline-rich Akt substrate of 40 kDa; TTI1: Tel two interacting protein 1; TEL2: telomere maintenance 2; Protor: protein observed with Rictor-1; mSIN1: mammalian stress-activated protein kinase-interaction protein 1).

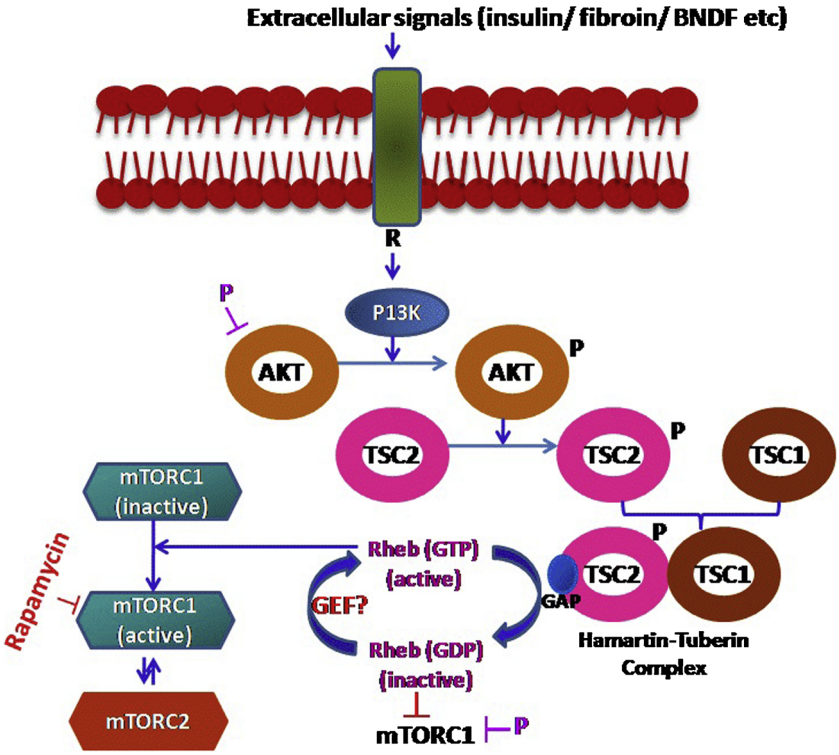

Fig. 2. mTOR regulation by the TSC complex. AKT- Protein kinase B; TSC- Tuberous Sclerosis Complex; Rheb- Ras homolog enriched in brain; BNDF- Brain-derived neurotrophic factor; mTOR- mechanistic target of rapamycin, ⊣ denotes inhibition by Polyphenols (P).

ageing. Though only little information is available on mTORC2, since the disruption or deletion of the ricor protein causes a reduction in the life span, it implies that mTORC2 is also involved in maintaining the cellular functions of the mammals, which needs to be better understood [14]. After the binding of extracellular signals with their respective receptor, the activated PI_3K phosphorylates the AKT (Protein Kinase B) enzyme facilitating the formation of Hamartin-Tuberin Complex (TSC1 and 2 Complex) (Tuberous Sclerosis Complex) and mediating the mTORC1 and mTORC2 signaling mechanism (Fig. 2) [15]. The downstream targets of mTORC1 vary since it controls and balances both catabolism and anabolism depending upon the change in the environmental conditions. The phosphorylation of the downstream target proteins 4EBP (eukaryotic translation Initiation factor 4B (eIF4E) binding protein) and S6K1 (ribosomal protein S6 kinase 1) mediates the mTORC1 mediated protein biosynthesis. Both proteins mediate an opposite effect, because S6K1 which is activated by mTORC1 supports translation whereas 4EBP which is inhibited by mTORC1 inhibits translation. mTORC1 also regulates the cell growth through its downstream target SREBP (sterol responsive element binding protein) which controls the lipogenesis process. Other pathways mediated by mTORC1 include purine and pyrimidine synthesis. mTORC1 also has a role in inhibiting autophagy through its downstream target ULK 1 (Unc-51 Like Autophagy Activating Kinase 1), a serine threonine kinase [16]. On the other hand, mTORC2 mediates its effect mainly through the downstream target proteins AKT, SGK-1 and PKC-α which are termed the AGC-kinase family members [17].

MicroRNAs (miRs) are emerging posttranscriptional modulators of gene expression which can participate in the pathophysiology of CVDs. Accordingly, it has been evidenced a cross talk between miRNAs and the mTOR signaling pathway in CVDs [18]. For example, miR-34 which is upregulated in the heart in response to stress, targets protein phosphatase pH domain leucine-rich repeat protein phosphatase (PHLPP2), a negative regulator of the PI_3K/Akt/mTOR pathway [19]. Also, it has been evidenced the capability of histone NAD + -dependent deacetylase SIRT1 to regulate autophagy in cardiovascular diseases through the Akt/mTOR signaling pathway [20].

3. mTOR signaling in cardiovascular disease

Animal studies carried out by deleting mTOR and inducing genetic alteration in mTORC1 have shown that mTORC1 is involved in maintaining the normal cardiac function. The downstream signaling pathways of mTORC2 in heart cells have not been well understood. However, there are reports showing that it interacts with the hippo signaling pathway [14] which is a highly conserved signaling mechanism in all the organisms in regulating the proliferation of the cardiomyocyte and in maintaining the size of the heart [21]. In heart failure patients and in diastolic dysfunction experimental animals, the activation of mTOR and associated S6K1 signaling mechanism have been observed mainly due to the coordinative effect of different factors like inflammatory and immune response and the metabolic signaling [22]. mTOR knockout studies carried out in animals and mTOR/Rheb1 gene deletion studies evidenced that both mTORC1 and mTORC2 are necessary for the survival of the embryo and the development of cardiac cells. These studies have revealed that mTORC1 is necessary for regulating cardiomyocyte homeostasis, proliferation of cardiomyocytes, protecting the cardiomyocytes from apoptosis, cardiac dysfunction and ultimately cardiac failure. Deletion of the rictor gene which will affect the function of mTORC2 also caused abnormality to the cardiac cells [23]. Hence, the reports reveal that the mTOR signaling pathway is highly important for the proliferation of the cardiac cells.

However under conditions like cardiac stress and in aging, partial mTOR inhibition exhibits cardioprotective effect. Since mTORC1 is needed for maintaining the physiological functions of the heart, for providing beneficial effect under cardiac stress conditions, only partial inhibition of mTORC1 will be needed to deal with the mTORC1 malfunction [23]. In this sense, although the inhibition of mTOR suppresses myocardial hypertrophy induced by mechanical stresses in animal models, it was reported that overexpressing mTOR mitigates cardiac dysfunction in response to pressure overload-induced hypertrophy and reduces the inflammatory response [24].

4. Therapeutic benefits of mTOR inhibitors for cardioprotection

Most cardiovascular diseases are caused by atherosclerotic plaque development and rupture, which results from a complex interplay of multiple cell types (endothelial cells, macrophages, smooth muscle cells, macrophages, etc.) and mechanisms (inflammation, oxidative stress, immunity, etc.) [25,26]. mTOR inhibition offers benefit for treatment of many cardiovascular diseases including atherosclerosis. Drugs targeting mTORC1 inhibition limit the atherosclerosis process mainly by correcting the functions of the endothelial layer (which is impaired in the patients) and by inducing autophagy, which reduces the content of macrophages in the plaques and also causes efflux of cholesterol from the plaques. mTORC1 inhibition also reduces the formation of the foam cells which are nothing but fat filled macrophages that takes up LDL and cholesteryl esters [27]. The macrophages which transforms into foam cell are considered as the marker of early stage atherosclerosis, hence reduction of the foam cells can be a treatment option for CVDs. In addition to serving as effective therapeutics for CVD, mTOR inhibitors have been shown to be effective therapies for hypertensive heart disease, such as hypertension, cardiac hypertrophy and heart failure. Hereby, we will discuss the therapeutic potential of mTOR inhibitors in treating several classes of cardiovascular diseases.

4.1. Role of rapamycin and its derivatives (analogs) as mTOR inhibitors for cardioprotection

Rapamycin is a natural macrocyclic lactone with 15 asymmetrical centers and 3 conjugated double bonds isolated from *Streptomyces hygroscopicus* found in Easter Island soilin 1975 [28]. Firstly, studied for its strong antifungal action, rapamycin soon showed remarkable immunosuppressive side effects. This undesirable effect, during the late eighties, inspired the development as a clinically useful drug (sirolimus) and gave rise to extensive structure activity relationship studies (SARs) [29–31]. The first total synthesis was reported in 1993 which was subsequently optimized [32–34]; however, rapamycin chemical synthesis has a purely academic interest due to its complexity [35]. For this reason, most of the first SARs were based on semi-synthetic modification of rapamycin itself in the attempt to optimize the unfavorable pharmacokinetic profile and reducing the immunosuppressive activity [30,31]. Common modifications comprise the substitution of the hydroxyl residue at the 42-position, ring opening reactions or starting from fragments of rapamycin degradation. In addition, rapalogs has also been obtained by enzymatic or genetic manipulations as well as by muta-synthesis approach and precursor-directed biosynthesis [36–39]. A certain number of natural compounds possessing a chemical structure similar to rapamycin have been isolated including the macrolactam FK-506 (tacrolimus, Prograf®), obtained in 1984 from *S.tsukubaensis* [40] and ascomycin (FK-520) isolated from *S. hygroscopicusyakushimaensis* [41]. These two compounds possess a strong immunosuppressive activity [29,42] and have been also subjected to semi-synthetic modifications [31].

Rapamycin and rapalogs bind, at a low nanomolar level to the FK506-binding protein (FKBP12, a protein that binds to immunosuppressants) at the FKBP biding domain, forming a binary complex [43]. The resulting complex, through the effector domain of rapamycin, interferes with the FKBP12-rapamycin binding domain and induces a conformational change in the mTORC1 active site resulting in an allosteric inhibition of mTORC1 enzymatic activity [44]. On the contrary, mTORC2 is not inhibited by rapalogs [45,46]. Nowadays, three rapamycin derivatives obtained from semi-synthetic modification

of the hydroxyl residue at the 42-position have been marketed for human use: temsirolimus (formerly CCI779), everolimus (RAD001), and deforolimus (AP23573).

Although rapamycin has widely been used as an immunosuppressant in patients having renal transplant rejection as well as a therapeutic drug for renal carcinoma, this compound has broad applications in cardiovascular medicine [47]. Rapamycin and rapalogs have been reported to limit and stabilize atherosclerotic plaques in several experimental animal models of atherosclerosis [48–50]. Mechanistically, mTORC1 inhibition by rapamycin and rapalogs inhibits atherosclerosis by preventing endothelial dysfunction, inhibiting the proliferation and migration of smooth muscle cell proliferation, decreasing macrophage accumulation via inhibiting monocyte adhesion and enhancing autophagy [51]. mTORC1 inhibition also promotes cholesterol efflux from macrophages [52] decreasing the extent of foam cell formation and lipid deposition in the plaques [53]. In clinic, transplantation recipients have increased the risk of developing CVD. Treatment with rapalogs decreased the incidence of cardiac allograft vasculopathy [47]. However, administration of rapamycin and rapalogs has several side effects, such as dyslipidemia, hyperglycemia and insulin resistance [47] which can be ameliorated by combination therapy with lipid-lowering statins, PCSK9 inhibitors, and AMPK activators such as metformin [51]. Moreover, rapamycin has been used as drug-eluting stents in coronary angioplasty [47]. Nevertheless, caution needs to be taken when being used in drug eluting stents, since there is a report showing that negatively affect stent endothelization, thereby increasing potential risks of thromboembolism after placement of stents [54].

In view of the emerging evidences showing the involvement of autophagy in cardiac remodeling, rapamycin and its analogs could be effective therapeutic agents for hypertensive heart diseases. mTOR signaling pathway and associated smooth muscle cell proliferation were highly activated in pulmonary artery hypertension (PAH) [55]. A recent study has shown that rapamycin-loaded nanoparticles attenuated PAH via mTOR inhibitory effects [56]. In agreement with this evidence, rapamycin also inhibits the development of PAH induced by TSC1 knockout in smooth muscle cells by attenuating activation of mTORC1 and mTORC2 [57]. A recent metabolomics study performed in pulmonary smooth muscle cells indicates that rapamycin reverses metabolic abnormalities in lipogenesis, glutathione, glycosylation, and NAD metabolism in PAH [58]. In addition to PAH, rapamycin has been shown to attenuate cardiac dysfunction and remodeling in animal models of cardiac hypertrophy and heart failure (induced by transverse aortic constriction) by inhibiting mTOR [59–63].These studies suggest that targeting mTOR by rapamycin and rapalogs may represent a novel therapeutic strategy in treating hypertrophic disease and associated heart failure.

4.2. Metformin as a cardioprotective agent through mTOR inhibition

Metformin is one of the most commonly used oral anti-diabetic drugs in the family of biguanide. Interestingly, metformin administration has also been related to a reduced risk of cardiovascular diseases, the common complications of diabetes [64]. Diverse evidences reported that metformin indirectly inhibits mTORC1 through AMPK-dependent and –independent mechanisms [65]. Metformin has been shown to attenuate the development of atherosclerosis in several animal models. Giacchi et al. [66] observed that metformin treated hypercholesterolemic rabbits showed reduced atherosclerotic lesions in the carotid artery. Marquie [67] observed similar phenomenon of decreased radiolabelled acetate incorporation into lipids. Recent evidences suggest that metformin could ameliorate and stabilize atherosclerotic plaques through several new mechanisms, such as inhibiting oxidized and glycated LDL induced endoplasmic reticulum stress [68], inhibition of angiotensin II type 1 receptor [69], upregulation of SOD1 [69], repressing monocyte/macrophage differentiation [70], inhibition of dynamin-related protein 1 (DRP1)-mediated mitochondrial fission [71], as well as upregulating anti-aging molecule SIRT1 [72]. A recent study has shown that AMPK activation by metoformin and other drugs elicits a common transcriptional program in the ApoE-/- mouse liver, underlying the therapeutic potential of metformin in treating cardiovascular disease [73]. Metformin also prevents MCP1-induced migration of pro-inflammatory $Ly6C^{hi}$ monocytes from the bone marrow into the plaques [74]. In addition, metformin attenuates atherosclerosis by promoting ABCA1, ABCG1 mediated reverse cholesterol transport, as well as macrophage polarization to anti-inflammatory M2 subtype [75]. Fu et al. [76] has shown that chronic treatment with metformin (200 mg kg/d, 6 weeks) diminishes cardiac hypertrophy induced by transverse aortic constriction (TAC). The protective mechanism is linked to AMPKa2-dependent inhibition of the activation of Akt/mTOR pathway [76], thus indicating the therapeutic potential of metformin in preventing pathological cardiac hypertrophy.

4.3. mTOR inhibitory potential of natural polyphenols

4.3.1. Resveratrol

Resveratrol is a wine-derived natural polyphenol that has strong antioxidant, anti- inflammatory and anti-aging activities. It has protective effects against several cardiovascular diseases. Recent studies have shown that resveratrol has the capability to inhibit mTORC1 activation by promoting Deptor/mTOR interaction [77]. In 2007, Kueck et al. reported that resveratrol inhibits glucose metabolism via inhibiting Akt and mTOR in epithelial ovarian cancer cells [78]. Later studies confirmed that resveratrol inhibits mTOR [79] (albeit less effective than rapamycin) in the vasculature, including smooth muscle cells and endothelial cells, contributing to its inhibitory effects against oxLDL induced proliferation of smooth muscle cells and aging-associated endothelial dysfunction [80] as well as oxidative stress induced endothelial injury [81]. oxLDL induced proliferation of smooth muscle cells is considered as one of the major contributing factors for atherosclerosis, which develops the fibro-atheroma plaques, mainly by activating the PI_3K/Akt signaling. This in turn mediates the phosphorylation of mTOR at Ser2448 and Thr2446 by the Akt enzyme. Treatment of rabbit femoral smooth muscle cells with resveratrol showed that the polyphenol was able to inhibit the oxLDL induced phosphorylation of the proteins PDK1, Akt, mTOR and p70S6K1 [82]. In addition, resveratrol was reported to significantly reduce the palmitic acid (PA)-induced generation of reactive oxygen species (ROS) and ameliorate endothelial dysfunction though inducing autophagy mediated by the AMPK-mTOR pathway in human aortic endothelial cells [83].These beneficial effects exerted through mTOR inhibition could potentially contribute to its therapeutic effects in ameliorating atherosclerosis in several animal models of atherosclerosis [84,85]. Due to prominent SIRT1 and AMPK activation capacity, the cardiovascular protective effects of resveratrol could also involve both targets. A landmark study by Dolinsky et al. [86] has shown that resveratrol reduces cardiac hypertrophy in spontaneously hypertensive rats by activating LKB1/AMPK-dependent inhibition of mTOR/p70S6 kinase system, suggesting that resveratrol can be exploited as an effective therapeutic agent for patients with cardiac hypertrophy. Resveratrol also offers a protective effect against cardiomyopathy, which is one of the major complications of heart failure in diabetic patients. In the H9c2 cardiac myoblast cell line exposed to high glucose combined with palmitate, resveratrol was able to promote autophagy through inhibition of the mTOR pathway. It was mainly mediated through decrease in Ser2448 phosphorylation of mTOR and reduced expression of the mTOR signaling proteins namely p70S6K1(p70 ribosomal protein S6 kinase 1) and 4EBP1 (4E-binding protein 1) [87]. Moreover, another mechanism by which resveratrol exerts cardioprotection against I/R injury involve autophagy induction by the mTORC2 pathway [88]. In this study, the administration of resveratrol to H9c2 cardiac myoblast cells and I/R rat model attenuated the activation of mTORC1, but also significantly induced the expression of Rictor activating the mTORC2-Rictor survival pathway.

4.3.2. Epigallocatechingallate (EGCG)

EGCG is a bioactive polyphenol isolated from tea which improves vascular health and diseases. Li et al. [89] first described EGCG as pharmacological inhibitor of mTOR that limits cardiac hypertrophy. In the cardiac myocytes treated with angiotensin-II, EGCG was able to inhibit Akt and its downstream targets mTOR and p70S6k phosphorylation. The beneficial effect of EGCG for the treatment of cardiac hypertrophy is mainly mediated through its activity to block transactivation of EGFR (epidermal growth factor receptor) [89]. EGCG has been shown to exert broad atheroprotective effects in several animal models via its anti-oxidant, anti-inflammatory and lipid-modulating effects [90]. As such, EGCG suppresses vascular inflammation [91], foam cell formation [92] and the apoptosis of smooth muscle cells [93]. Previous studies have shown that EGCG has prominent protective effects in ameliorating cardiac hypertrophy. Van Aller biochemically characterized the inhibitory effects of EGCG on PI_3K and mTOR. The authors conclude that EGCG inhibits PI_3K/Akt and mTOR activation in an ATP-dependent manner with submicromolar K(i) values [94]. Mechanistic studies indicate that EGCG (50 mg/kg) inhibited the expression of pro-fibrotic marker genes (CTGF, FN) by attenuating the activation of nuclear factor kappa B (NF-κB), suggesting the potential of EGCG in treating subjects suffering from pressure overload-induced hypertrophy [95]. In agreement with this finding, Sheng et al. [96] showed that EGCG (25, 50 and 100 mg/kg) attenuated cardiac hypertrophy in rats undergoing transverse abdominal aortic constriction. Taken together, these evidences indicate that EGCG is a promising cardiovascular protective drug that can treat cardiac hypertrophy and probably heart failure in human patients.

4.3.3. Honokiol

In 2015, Pillai et al. showed that honokiol inhibits both agonists- and pressure overload-induced cardiac hypertrophy in mice by activating mitochondria-localized histone deacetylase SIRT3. The delaying of cardiac toxicity by honokiol which is mediated through mitochondrial protection is speculated to the effect of honokiol on the target proteins like EGFR and mTOR [97]. Two recent independent studies have also shown that honokiol reduces doxorubicin-induced cardiotoxicity and cardiomyopathy in mice [98,99]. The mechanism is linked to reducing mitochondrial DNA damage, mitochondria dysfunction, and enhancing PPAR-gamma activity [98,99]. Although direct evidence showing the involvement of honokiol mediated mTOR inhibition in preventing cardiac hypertrophy is lacking, in light of the fact that mitochondria dysfunction including autophagy in present in cardiac hypertrophy, it can be anticipated that the mTOR inhibitory effects of honokiol can be partially responsible for the cardioprotective effects of honokiol.

4.3.4. Curcumin

Numerous studies have shown that curcumin, the bioactive compound from turmeric, prevents atherosclerosis in several animal models via multiple mechanisms, including anti-aging [100], anti-oxidant [101], anti-inflammatory effects [101]. In 2006, Beevers et al., described curcumin as a pharmacological inhibitor of mTOR signaling pathway in cancer cells [102]. The mTOR inhibitory effects of curcumin have been subsequently confirmed [103]. Most importantly, curcumin also inhibits mTOR activation in the vasculature. For example, curcumin was reported to protect endothelial cell against oxidative stress induced damage and apoptosis via promoting autophagy by mTOR inhibition [104,105]. A recent study has shown that nicotinate-curcumin hybrid impedes macrophage-derived foam cell formation through enhancing autophagy, which might be dependent on its mTOR inhibitory effects [106]. Similarly, another curcumin derivative hydroxyl acetylated curcumin, has similar effects in retarding foam cell formation [107].

A landmark study by Morimoto et al. has elegantly shown that curcumin reduces the incidence of hypertensive heart disease in two rat models (i.e., salt-sensitive Dahl rats and myocardial infarcted rats), by inhibiting p300 histone acetyltransferase-dependent acetylation of pro-hypertrophic transcriptional factor GATA4 [108]. Later on, the anti-hypertrophic effects of curcumin were confirmed by other studies using a rat model of myocardial infarction by coronary artery ligation [109]. In light of the usefulness of transcriptomic analysis in cardiovascular medicine [110], the authors performed the analysis of curcumin treated rats undergoing myocardial infarction, and discovered that several important pathways, such as cytokine-cytokine receptor interaction could be involved in curcumin-mediated cardioprotection [109]. Curcumin also inhibits diet-induced cardiac fibrosis and hypertrophy by activating anti-oxidant Nrf2 pathway and inhibiting pro-inflammatory NF-κB pathway [111]. Though curcumin has been reported to exhibit protective effect in many studies including myocardial ischemia/reperfusion (I/R) injury models through inhibition of mTOR and activation of autophagy, it is interesting to note that, in isoprenaline induced cardiac hypertrophy and fibrosis experimental animal model, curcumin was able to offer a protective effect by activating mTOR and inhibiting autophagy [112].

4.3.5. Quercetin

Quercetin is an abundant flavonoid found in fruits and vegetables. In 2010, quercetin was reported to act as mTOR inhibitor by blocking mTOR phosphorylation in basal as well as radiation treated HaCaT cells [113]. By inhibiting mTOR, quercetin halts cancer progression via enhancing autophagy, cell cycle arrest and apoptosis of cancer cells [114]. The mTOR inhibiting activity could partially contribute the anti-atherosclerotic effects of quercetin as it was observed in cultured cells and animal models of atherosclerosis [115]. A recent study has shown that quercetin inhibits angiogenesis via inhibiting VEGFR- 2 dependent Akt/mTOR pathway [116]. The accumulation of lipids, especially oxidized LDL, in the liver and macrophages contribute to nonalcoholic fatty liver disease and atherosclerosis. A recent study has showed that quercetin attenuates lipid accumulation in the liver by inhibiting mTOR and CD36, as well as scavenger receptor A mediated lipid uptake [117]. Due to the fact that quercetin activates AMPK pathway via LKB1 in vascular smooth muscle cells, and contributes to inhibition of PE-induced contraction of rat aorta, it is plausible that quercetin inhibits mTOR via AMPK dependent pathway [118]. Quercetin also boosts SIRT1 activation in oxLDL stimulated endothelial cells, which could also contribute to its mTOR inhibiting effects [119]. Currently, direct evidence is lacking as to whether mTOR inhibition is involved in quercetin induced atheroprotection.

4.3.6. Oleuropein

Oleuropein, phenolic bitter compound belonging to the secoiridoids group is mainly found in unprocessed olive leaves and green olive skin [120]. Oleuropein has been reported to activate the phosphorylation of AMPK, antagonizing mTORC1 at the functional level. For example, Menendez et al. [121] evidenced that extra virgin olive oil (EVOO) phenolic extracts enriched in the secoiridoids activated AMPK and suppressed key genes involved in the Warburg effect and the regenerative capacity of cancer stem cells. Regarding its potential cardioprotective action, the role of oleuropein in chronic doxorubicin-induced cardiomyopathy in a rat model [122]. The treatment with oleuropein significantly protected against the histopathological, structural, functional and cardiac alterations induced by chronic DXR exposure in a process mediated by activation of AMPK and suppression of iNOS. The same group of researchers also investigated the effects of the effects of oleuropein and ischemic preconditioning in rabbits subjected to myocardial ischemia followed by reperfusion [123]. The results evidenced that oleuropein protected normal and hypercholesterolemic rabbits after an ischemic/reperfusion procedure similarly to preconditioning and reduced oxidative stress. The mechanism of action was associated to the activation of diverse intracellular signaling pathways including AMPK but also PI_3K, Akt, eNOS and STAT-3. The

protective activity of oleuropein against oxidative stress and autophagic cell death in mesenchymal stem cells, which can protect against ischemic diseases, were investigated [124]. Oleuropein reduced H_2O_2-induced mesenchymal stem cells autophagy and apoptosis through the inhibition of the AMPK/mTOR signaling pathway.

4.3.7. Other polyphenols

The bioflavonoid baicalein which was originally found in the Chinese herb, *Scutellaria baicalensis*, when injected to the mice prevented cardiac hypertrophy and fibrosis induced by angiotensin II. The study shows that the preventive effect of baicalein against angiotensin II induced hypertensive heart diseases is associated with its effect in inhibiting the signaling mechanisms mediated through proteins ERK1/2, NF-κB/p65, calcineurin and AKT/mTOR [125]. Even the polyphenol fisetin which is present in many natural plants including strawberries has a protective effect against cardiac hypertrophy. In the *in vitro* model cells, fisetin reduced cardiac hypertrophy by inhibiting the phosphorylation level of mTOR and its downstream effector protein P70 S6 kinase (p70S6K) [126]. In the myocardial infarction induced mice, the chalconoidcardamonin reduced the cardiac hypertrophy and cardiac dysfunction by inhibiting mTOR through disrupting the association between the mTOR and Raptor protein [127]. People who are suffering from CVDs experience I/R injury. Potential treatments for myocardial infarction (MI) are also exhibited by polyphenols, which reduces the infarct size mainly by activating mTOR, since autophagy plays a major role for maintaining the homeostasis of the myocardium. Though autophagy exhibits a protective effect during MI, excessive autophagy contributes to facilitated death of the myocytes, which need to be prevented. mTOR is one of the signaling pathways which regulate autophagy and it is observed through experimental studies that inhibition of mTOR induces autophagy in the cells. Hence when there is excess autophagy which happens in MI, one of the best therapeutic approaches will be to take drugs which inhibits autophagy through activation of signaling mechanisms like mTOR. It was observed that the flavanon glycoside hesperidin most commonly present in citrus fruits limited the excessive autophagy and enhanced the recovery of the heart by activating the PI_3K/Akt/mTOR pathway [128]. Salvianolic acid A, a polyphenol mainly found in *Salvia miltiorrhiza* roots, was found to exert protective effects against renal I/R injury in a rat model of renal injury and in in vitro model using proximal renal tubular cells (HK-2) [129]. The treatment with salvianolic acid A ameliorated renal I/R injury and increased tubular cell survival partially through activation the Akt/mTOR/4EBP1 pathway. The protective effects of ginsenoside Rg1 were investigated in NRK-52E rat renal tubular cells exposed to aldosterone which is characterized to increase autophagy and ROS [130]. The treatment with ginsenoside Rg1 ameliorated the autophagy and production of ROS induced by aldosterone, by reducing AMPK phosphorylation and, consequently, maintaining mTOR activity. The same researchers also evidenced similar results after Rg1 administration to rat podocytes pre-treated with angiotensin II associated to a down-regulation of the activity of AMPK and GSK-3b and an upregulation of p70S6K [131].

5. Conclusion and future prospects

The role of mTOR in cardiovascular diseases, although promising, remains controversial. In fact, if from one side it plays an essential role in prenatal and postnatal phase in the protection of vascular integrity, mechanical stress, cardiac structure, compensation of ventricular hypertrophy and preservation of cardiomyocytes from death [132], on the other side, as described above, inhibition of mTOR functions can be beneficial in inhibiting atherosclerosis, cardiac hypertrophy and heart failure. These dual and opposite behaviors may depend on several variable factors not easy to investigate, such as the “threshold” of mTOR inhibition or activation, the effects of its positive or negative modulators in pre-clinical versus pathological conditions, the influence of mTOR up- downstream effectors on its activity and the level of expression of its adapter protein regulators. Other confounding factors are represented by the subcellular localization of mTOR complexes and the different mode of regulation of mTORC1 versus mTORC2, which implies that the efficacy of an inhibitor on one complex may exert opposite effects on the other. In fact, as mentioned above, the protective effects of mTORC2 against mechanical stress in heart can be reversed to harmful response in the presence of dual mTOR inhibitors. Therefore, new and high selective modulators able to differentially affect mTOR complexes are welcomed. In addition, this class of novel compounds must show efficacy in both pre-clinical models and clinical trials should be designed to assess the cardiac effects (development, physiology, and stress) of mTOR modulation.

To this aim, the use of natural agents, which show the capacity to interfere with mTOR functions can be highly desirable. However, as emerged from the above paragraphs, the efficacy of polyphenols as mTOR inhibitors in cardiovascular diseases suffers of the same critical issues evidenced for their application in the prevention and therapy of other degenerative diseases, such as cancer [133]. Shortly, it is very difficult to identify the polyphenol “first hits”, after they have entered the cells; therefore, it is hard to discriminate if the downstream effects measured in terms of cardioprotection represent the direct cause of their biological activity or epiphenomena due to pleiotropic mode of action of these compounds. In fact, without the identification of a specific and direct cellular target, it is very difficult to evaluate their clinical relevance. An additional key issue regards “who does the job”, the parental molecule (e.g., quercetin, curcumin, resveratrol aglycones, etc.) or one of its metabolites? In fact, it is well known and demonstrated that polyphenols undergo rapid and extensive metabolic transformation in the upper intestinal tract followed by liver, kidney and peripheral tissues metabolism, as well as in the colon-rectum by colonic microbiota. Consequently, their circulating concentrations, as aglycones, are extremely low and even not compatible with oral administration at very high (pharmacological) doses. Finally, the almost total absence of studies demonstrating the clinical efficacy of polyphenols in this field raises serious doubts on the possibility that this class of mTOR inhibitors may find, in a short time, applicative outcomes in the therapy of different forms of cardiovascular diseases.

To escape from this conundrum, a possible approach may consist in a careful selection of the experimental models to be employed in these studies. It appears premature to reach conclusions on the efficacy of polyphenols as cardioprotective agents via mTOR modulation simply working on vascular cells or similar cellular models. However, this preclinical approach is essential in view of the identification of the cellular and specific substrate(s), if any, triggered by the putative active compound. As soon as this goal is obtained, adequate animal models, among the several available and mentioned above, can help to verify if the effects of the mTOR inhibitor under investigation, to ameliorate the cardiovascular functions are confirmed *in vivo*. In this case, a further complication regards the need to identify and quantitate the active metabolites if the systemic concentration of the lead compound is too low or undetectable. Our prediction is that in the coming years, we will see a significant progress in this field considering not only the enormous scientific interest, but also the economic pressure exerted by nutraceutical and pharmaceutical companies.

Declaration of competing Interest

Authors declare no conflict of interest.

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