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Research review paper

Curcumin, the golden spice in treating cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) cause the largest mortality worldwide, and much attention has been focused to unravel the mechanisms and optimize the treatment regimens. Curcumin is an important bioactive component of turmeric that has been widely applied as traditional medicine to prevent and treat various diseases in some countries. Recent studies have demonstrated its potent activities in modulating multiple signaling pathways associated with cellular growth, proliferation, survival, inflammation and oxidative stress. The cardiovascular protective properties of curcumin in CVDs have been fully illustrated in numerous studies. In this review, we first briefly introduce the medicinal history of curcumin. Secondly, we systematically analyze the preclinical studies of curcumin in CVDs such as cardiac hypertrophy, heart failure, drug-induced cardiotoxicity, myocardial infarction, atherosclerosis, abdominal aortic aneurysm, stroke and diabetic cardiovascular complications. The

Abbreviations: AAPH, 2,2′-azobis(2-amidinopropane hydrochloride); ABC, ATP-binding cassette transporter; ABTS, 2,2′-Azinobis-(3-ethylbenzthiazoline-6-sulphonate); ACE, angiotensin-converting enzyme; AGEs, advanced glycation end products; Ang II, angiotensin II; AP-1, activator protein-1; aP2, adipocyte protein 2; ApoE$^{-/-}$, apolipoprotein *E*-deficient; aPTT, activated partial thromboplastin time; AREs, antioxidant response elements; AT1R, Angiotensin II type 1 receptor; AT-LDL, α1-antitrypsin–low-density lipoprotein; BAECs, bovine aortic endothelial cells; CaMKII, calcium/calmodulin-dependent protein kinase II; CBPs, CREB-binding proteins; CD36, cluster of differentiation 36; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CsA, cyclosporin A; CVDs, Cardiovascular diseases; DNMT2, DNA methyltransferase 2; Dox, doxorubicin; DPPH, 1,1-diphenyl-2-picrylhydrazyl; ECM, extracellular matrix; EGR-1, early growth response 1; EPCs, endothelial progenitor cells; ERK, extracellular signal-regulated kinase; GATA4, GATA binding protein 4; GPx, glutathione peroxidase; GSK-3β, glycogen synthase kinase 3 beta; GST, glutathione S-transferase; H/R, hypoxia/reoxygenation; HASMCs, human aortic SMCs; HATs, histone acetyltransferases; HDL, high-density lipoproteins; HMEC, human microvascular endothelial cells; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-co-enzyme A; HO-1, heme oxygenase-1; HUVECs, human umbilical vein endothelial cells; H_2O_2, hydrogen peroxide; I/R, ischemia/reperfusion; ICAM-1, intercellular cell adhesion molecule-1; IKK, IκB kinase; IL-6, interleukin-6; Iso, isoproterenol; IκB, inhibitor of NF-κB; JAK2/STAT3, janus kinase 2/signal transducer and activator of transcription 3; JNK, c-Jun N-terminal kinase; Keap1, Kelch ECH association protein 1; LDH, lactate dehydrogenase; LDLR, low-density lipoprotein receptor; LOX-1, the lectin-like oxidized low-density lipoprotein receptor-1; LPS, lipopolysaccharide; LV, left ventricular; LVFS, left ventricular fractional shortening; LXRα, liver X receptor α; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MMP-9, matrix metalloproteinase-9; mTOR, mammalian target of rapamycine; NADPH, nicotinamide adenine dinucleotide phosphate; NCX, Na^+/Ca^{2+}, exchanger; NFAT, nuclear factor of activated T cells; NFE2L2, nuclear factor (erythroid-derived 2)-like 2; NF-κB, nuclear factor κB; NO, nitric oxide; NQO1, NAD(P)H:quinone acceptor oxidoreductase 1; Nrf2, NF-E2-related factor 2; OS, oxidative stress; oxLDL, oxidized low-density lipoproteins; PARP, poly-ADP-ribose polymerase; PDGF, platelet-derived growth factor; PE, phenylephrine; PI3K/Akt, phosphoinositide 3-kinase/protein kinase b; PKC, protein kinase C; PPARγ, peroxisome proliferator-activated receptor γ; PT, prothrombin time; ROS, reactive oxygen species; SIRT, sirtuin; SMCs, smooth muscle cells; SOD, superoxide dismutase; SP1, specificity protein 1; SR, sarcoplasmic reticulum; SR-A, scavenger receptor class A; SREBP-1, sterol response element-binding protein 1; STZ, strepozotocin; TGF-β1, transforming growth factor β1; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells

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potential molecular targets of curcumin are also summarized. Thirdly, the clinical trials of curcumin in CVDs are overviewed and discussed. Finally, we discuss the therapeutic utility of derivatives of curcumin, and highlight existing problems of curcumin as an effective drug lead in treating CVDs.

1. Introduction

Cardiovascular diseases (CVDs) are global health concerns as they cause the most deaths worldwide, and the morbidity and mortality are still on the rise (World Health Organization, 2016). It has been predicted that, by the year 2030, 40.5% of individuals in the United States will have CVDs, leading to approximately $818 billion for medical costs and $276 billion in indirect costs (due to lost productivity) (Heidenreich et al., 2011). Hence, in addition to the conventional medicine, it is urgent to develop preventive intervention strategies to reduce the costs and cardiovascular complications, and more importantly, to slow down the progression of CVDs (Campbell and Fleenor, 2017). Correspondingly, natural products, which have multi-targeted effects and with less adverse effects than synthetic drugs, have attracted wide attention. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is such a promising drug candidate that has been well investigated for its pleiotropic actions in CVDs. It is a bioactive constituent of the curry spice turmeric, which has been traditionally utilized to treat coughs, jaundice, colds, hepatic disorders, and inflammatory diseases (Ammon and Wahl, 1991). Up to date, curcumin has been demonstrated to be effective in treating chronic inflammatory diseases, cancer, neurodegenerative diseases, arthritic diseases and CVDs (Aggarwal and Harikumar, 2009). Specifically, accumulating studies have shown that curcumin plays a protective role in suppressing the development of cardiac hypertrophy, heart failure, drug-induced cardiotoxicity, myocardial infarction, atherosclerosis, aortic aneurysm, stroke and diabetic cardiovascular complications (Aggarwal and Harikumar, 2009; Campbell and Fleenor, 2017; Farkhondeh and Samarghandian, 2016; Karuppagounder et al., 2017). This article provides a systematic review of the protective effects and molecular targets of curcumin in various types of CVDs as well as the clinical perspective of curcumin and its derivatives.

2. History of curcumin

Curcumin represents the main curcuminoid of the rhizome of turmeric (*Curcuma longa* L., Zingiberaceae family) (Fig. 1), and it is responsible for the intense yellow color of turmeric (Akbik et al., 2014; Kocaadam and Sanlier, 2017). Turmeric contains between 1.5 and 3% of curcumin. Turmeric was used 4, 000 years ago in India, where it is recognized as “Indian saffron” or “Golden Spice” due to its brilliant yellow color. According to Prasad and Aggarwal (Prasad and Aggarwal, 2011), turmeric might reach China before 700 BCE, East Africa before 800 BCE, West Africa before 1200 BCE, and Jamaica in the 18th century. Marco Polo described turmeric as similar as saffron (*Crocus sativus L.*). The rhizome (root of this plant) is the most valuable part for medicinal applications, especially in South Asia, and it is a popular Asian spice, particularly used in Thailand, Pakistan and India (Prasad et al., 2014). Moreover, it is also used in religious ceremonies (Prasad and Aggarwal, 2011). Early by 250 BCE, Susruta's Ayurvedic Compendium had recommended an ointment containing turmeric to work against poisoned food (Prasad and Aggarwal, 2011).

Turmeric powder has been widely applied for ages in indigenous medicine to treating various diseases, including cough, diabetic ulcers, hepatic diseases, biliary disorders, rheumatism, sinusitis and anorexia (Chattopadhyay et al., 2004). According to Ayurvedic practices, turmeric strengthens the overall body energy, expulses gas, improves digestion, regulates menstruation, dissolves gallstones, and alleviates arthritis (Prasad and Aggarwal, 2011).

In the modern era, curcumin has been studied due to its health benefits, namely, antiaging, wound-healing, and anticancer activities (Akbik et al., 2014; Prasad et al., 2014). Curcumin was discovered by Vogel and Pelletier, about two hundred years ago (Vogel and Pelletier, 1815) and it has been obtained as pure compound in 1842 (Vogel, 1842). Past decade witnessed a substantial research interest in curcumin (Fig. 2). Curcumin is light sensible and almost insoluble in water, but can be dissolved in methanol, dimethylsufoxide, acetone and ethanol (Prasad et al., 2014). Chemically, curcumin is a bis-α, β-unsaturated β-diketone with keto-enol tautomerism (Anand et al., 2008). The chemical structure of curcumin was reported in 1910 (Milobedeska et al., 1910) while the synthesis was described in 1913 (Lampe and Milobedeska, 1913). Since then, the pharmacological actions of curcumin have been widely investigated. In 1949, the antibacterial property of curcumin was reported (Schraufstatter and Bernt, 1949), opening the door for other studies focusing on the multiple effects of curcumin (Maheshwari et al., 2006), such as anti-infective, anti-inflammatory (Edwards et al., 2017; Singh and Aggarwal, 1995), antioxidant (Sharma, 1976), anti-coagulant, hypoglycemic/anti-diabetic (Srinivasan, 1972), anti-mutagenic, anti-carcinogenic (Kuttan et al., 1985; Kuttan et al., 1987; Shim et al., 2004), immunomodulatory, and wound healing effects (Akbik et al., 2014; Hussain et al., 2017).

3. Cardiovascular actions of curcumin

3.1. Aortic aneurysm

Aortic aneurysm is a potentially dangerous condition that can cause death in case of dissection or rupture. Key events in the development of aortic aneurysms are chronic inflammation, destructive connective tissue remodeling, and loss of smooth muscle cells in the aortic wall

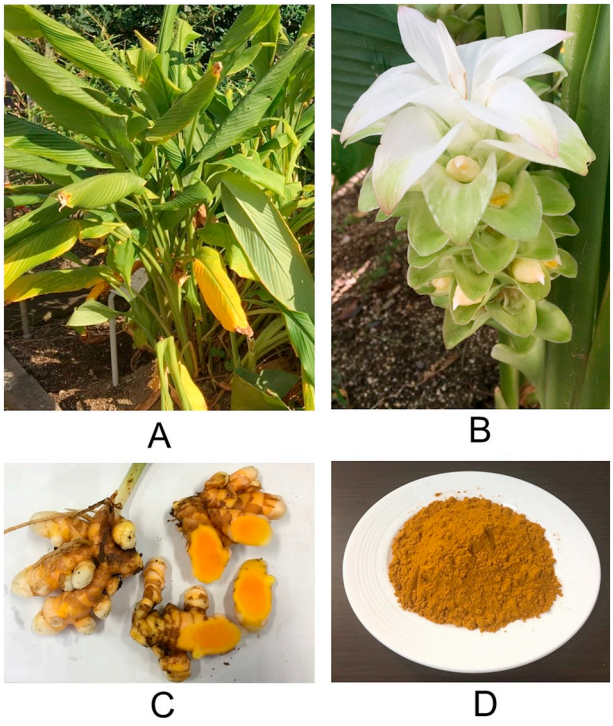

Fig. 1. Pictures of plant (A), flower (B), rhizomes (C) and rhizome powder (D) of turmeric (*Curcuma longa* L.)

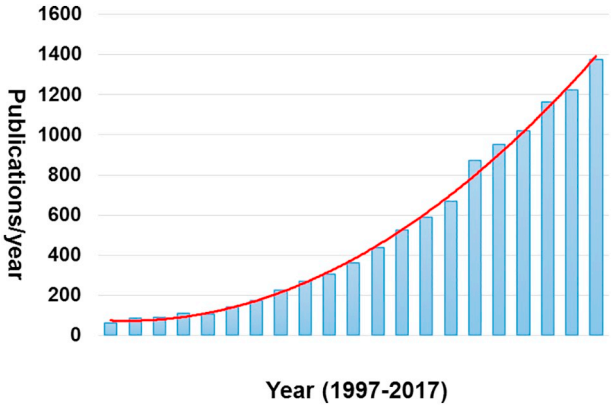

Fig. 2. Trends of curcumin in scientific research.
Pubmed was used as database searching by keyword "curcumin". Last accessed on May 18th, 2018.

(Guo et al., 2006). The protective effects of curcumin were investigated in adult male mice with aortic aneurysm induced by transient elastase perfusion of the abdominal aorta (Parodi et al., 2006). Curcumin treatment (100 mg/kg/day, for 14 days) evidently reduced the increase in aortic diameter, improved the structural integrity of medial elastin and suppressed pro-inflammatory molecules expression by blocking the activation of nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1). Another study reported beneficial effects of curcumin (100 mg/kg/day, for 4 weeks) by significantly ameliorating the $CaCl_2$-induced expansion of the thoracic aortic diameter and preserving elastin fibers in rats (Fan et al., 2012). The mechanism of action seems to be partially mediated by inhibiting the c-Jun N-terminal kinase (JNK) pathway and reducing apoptosis in the walls of aortic aneurysms.

The protective effects of curcumin were also investigated in apoE-deficient ($ApoE^{-/-}$) mice treated with subcutaneous infusion of angiotensin II (Ang II) to induce atherosclerotic plaque formation (Hao et al., 2014). Curcumin pretreatment (100 mg/kg/day, for 4 weeks) reduced the progression of the aortic aneurysm, macrophage infiltration and the production of pro-inflammatory mediators and diminished the activation of extracellular signal-regulated kinase (ERK) signal pathway, but also increased the levels of superoxide dismutase. Li et al., evidenced that curcumin (100 mg/kg/day, for 4 weeks) reduced the thoracic aortic aneurysm size, and in addition, it diminished the neovascularization and the production of vascular endothelial growth factor (VEGF) in the aneurysm in a rat model (Li et al., 2017). Moreover, curcumin reduced immune cell infiltration and decreased the expression of adhesion molecules and proinflammatory mediators in vascular cells. However, until now no clinical trials have been designed to study these beneficial effects of curcumin on aortic aneurysms.

3.2. Atherosclerosis

Atherosclerosis is a chronic and progressive problem of arteries that derives from inflammatory responses, oxidative stress (OS), lipid deregulation, and epigenetic disorders (Hansson, 2005; Stocker and Keaney, 2004; Xu et al., 2018; Xu et al., 2018). This pathology is related to other forms of CVDs, such as coronary artery disease, ischemic stroke, hypertension, and peripheral arterial disease, accounting for the majority of CVDs mortality (Libby, 2001). The occurrence of hyperlipidemia induces the increase and deposition of oxidized low-density lipoproteins (oxLDL) in the sub-endothelial area which in turn favors the development of atherosclerosis (Zingg et al., 2013). In this scenario, it has been evidenced that curcumin possesses hypolipidemic effects, which together with its antioxidant and anti-inflammatory activity, can contribute to reducing the incidence of atherosclerosis (Panahi et al., 2018). The remarkable antioxidant capacity of curcumin reduces lipid peroxidation and the generation of oxLDL, and consequently, reduces the inflammatory response, and the progression of atherosclerosis (Panahi et al., 2018).

A first approach to assess the therapeutic effects of curcumin in atherosclerosis was developed in $ApoE^{-/-}$/$LDLR^{-/-}$ mice (Olszanecki et al., 2005). Curcumin treatment (0.3 mg/d/mouse) for 4 months significantly attenuated the incidence and progression of atherosclerosis, although without effects on triglyceride, cholesterol concentrations or the body weight of the animals. Another study performed in $ApoE^{-/-}$ mice which were fed with curcumin (0.2% *w*/w in diet, 4 months) reported significant changes in gene expression that were associated with leukocyte adhesion and transendothelial migration in aortic tissues (Coban et al., 2012). These effects of curcumin seemed to be mediated by increased expression of inhibitor of NF-κB (IκB) protein and a decrease in NF-κB binding and transcriptional activity after stimulation with tumor necrosis factor-α (TNF-α). Moreover, it was evidenced that curcumin (0.1% *w*/w in diet, 16 weeks) downregulated the activation of toll-like receptor 4 (TLR4), a receptor that recognizes exogenous or endogenous molecular patterns and modulates immune and inflammatory response in $ApoE^{-/-}$ mice (Zhang et al., 2018). The inhibition of TLR4, in turn, reduced the NF-κB activation and the production of pro-inflammatory mediators, which protected against atherogenesis. In an $ApoE^{-/-}$ mouse model of ovalbumin-induced allergic asthma, curcumin (200 mg/kg/day, for 8 weeks) diminished atherosclerotic lesions, ameliorated the increase in Th2 and Th17 cells, increased regulatory T cells and inhibited the expression of pro-inflammatory mediators in M1 macrophages isolated from the spleen (Gao et al., 2019). Zhao et al. also reported beneficial effects in $ApoE^{-/-}$ mice treated with curcumin (20 mg/kg/day) during 4 weeks against atherosclerosis progression (Zhao et al., 2012). In the same study, an *in vitro* procedure with the macrophage cell line J774.A1 was carried out. Curcumin had the capability to reduce cholesterol accumulation in the development of foam cells. In light of the fact that increased lipid uptake (by scavenger receptors) and decreased cholesterol efflux (by cholesterol efflux transporters) contributed to foam cell formation (Tian et al., 2018; Xu et al., 2013). Further studies revealed that curcumin fine-tuned cholesterol homeostasis in macrophages. The anti-atherogenic effects were proposed to be mediated by downregulation of scavenger receptor class A (SR-A) *via* proteasome activation and by upregulating ATP-binding cassette transporter (ABC) A1 *via* liver X receptor α (LXRα) pathway in macrophages (Zhao et al., 2012). Another study with *in vivo* and *in vitro* data evidenced beneficial actions of curcumin in attenuating atherosclerosis and steatohepatosis in $LDLR^{-/-}$ mice and in reducing the uptake of oxLDL in THP-1 macrophages (Hasan et al., 2014). Curcumin intake (500, 1000 and 1500 mg/kg diet) during 16 weeks exerted significant anti-inflammatory effects and also suppressed the adipocyte protein 2 (aP2) and cluster of differentiation 36 (CD36) level in macrophages which are central factors in lipid deposition as well as foam cell formation. In RAW264.7 macrophages induced to develop a M1 subtype, curcumin (6.25 and 12.5 μM) reduced oxLDL-induced pro-inflammatory cytokine production and apoptosis, and upregulated CD36 and ABCA1 by elevating peroxisome proliferator-activated receptor γ (PPARγ) expression (Chen et al., 2015). These results, evidencing an upregulation of CD36, are partially contrary to other studies where an inhibition of scavenger receptors in macrophages (SR-A and CD36) was observed (Hasan et al., 2014), and the authors suggested that curcumin might enhance the capability of M1 macrophages to handle harmful lipids and improve cholesterol homeostasis, thus protected against atherosclerosis development. In a rat model of coronary atherosclerosis heart disease, curcumin (100 mg/kg/day, for 4 weeks) significantly improved the permeability of coronary artery through inhibition of matrix metalloproteinase 9 (MMP-9), CD40L, TNF-α and C-reactive protein (CRP) expression (Li et al., 2015). In a recent work performed in RAW264.7 macrophages, curcumin (10 and 20 μM) prevented inflammatory osteolysis induced by polyethylene particles by enhancing the macrophage cholesterol efflux and maintaining the macrophage M0 phenotype (Liu et al., 2019).

Endothelial dysfunction is present in patients with diverse CVDs, including atherosclerosis (Karimian et al., 2017). Consequently, endothelial cells are potential targets for curcumin in order to improve endothelial function and protect against atherosclerosis. The pretreatment of curcumin (0.1, 0.5 and 1 μM) significantly reduced the adhesion of monocytes to activated human umbilical vein endothelial cells (HUVECs), in a process mediated by inhibition of the expression of genes implicated in adhesion such as vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1 (ICAM-1), and *E*-selectin, which were stimulated by TNF-α (Coban et al., 2012). Using a similar model of TNF-α stimulation of HUVECs, curcumin pre-exposure (0.5–1 μM) reduced endothelial permeability and monocyte adhesion under both static and flow conditions (Monfoulet et al., 2017). Another study showed that curcumin (20 μM) significantly inhibited monocyte adhesion to EA.hy926 endothelial cells by downregulating P-selectin and fractalkine, reducing intracellular reactive oxygen species (ROS) levels and nicotinamide adenine dinucleotide phosphate (NADPH) activation (Pirvulescu et al., 2011). In human microvascular endothelial cells (HMEC-1) stimulated by particulate matter (diameter ≤ 2.5 μm) (Shi et al., 2017), curcumin treatment (50 μM) was capable to reduce apoptosis, OS and inflammation in HMEC-1 by reducing reactive species production, ICAM-1 and VCAM-1 levels, and down-regulating NF-κB.

Another interesting target of curcumin against atherosclerosis is the proliferation and migration of smooth muscle cells (SMCs). Collagen synthesis is critically involved in the development of the disease (Lusis, 2000). The effect of curcumin (1–25 μM) on SMC function was assayed in rat thoracic aorta muscular cells stimulated with platelet-derived growth factor (PDGF) which is secreted when vessels are under injury (Yang et al., 2006). Curcumin significantly reduced the migration, proliferation, and collagen production in a process mediated by blocking PDGF binding and signal transduction. Moreover, curcumin also reduced neointima formation in an experimental rat model of arterial injury induced by carotid artery balloon. In another study, Qin et al. (Qin et al., 2009) analyzed the effects of curcumin on SMC proliferation from rats treated with Chol:MβCD which destroys the structure of caveolae. Curcumin (30 μM) reversed the proliferative effects of Chol:MβCD through recovering caveolin-1 expression, resulting in the inhibition of ERK signaling and cell cycle arrest. In an *in vitro* study, the migration of human aortic SMCs (HASMCs) induced by TNF-α was significantly inhibited by curcumin (10 or 20 μM) (Yu and Lin, 2010), which was mediated by blocking NF-κB translocation and subsequent inhibition of MMP-9 activation and gene expression. Human SMCs from young volunteers treated with curcumin (5 μM) evidenced nucleolar stress (Lewinska et al., 2015). The proposed mechanism of action seemed to be associated with inhibition of rRNA synthesis resulted from sirtuin 7 (SIRT7) down-regulation and rRNA gene hypermethylation by DNA methyltransferase 2 (DNMT2) activation. In addition, curcumin stabilized p53, the protein that can activate p21, causing cell cycle arrest. Also, curcumin (12.5, 25 and 50 μM) has been found to inhibit ox-LDL-induced cholesterol accumulation in rat SMCs by inhibiting nuclear translocation of sterol response element-binding protein 1 (SREBP-1) which is related to cholesterol catabolism, and stimulating the expression of caveolin-1 (Yuan et al., 2008).

In addition to the actions of curcumin in arterial walls and macrophages, some studies investigated the anti-atherogenic effects in other tissues. Alterations in the intestinal barrier is directly associated with the release of gut bacteria-derived products into circulation leading to chronic inflammation and favoring the appearance of metabolic diseases (Pendyala et al., 2012). In this sense, curcumin (100 mg/kg/day, for 16 weeks) ameliorated the western diet-induced increase in plasma lipopolysaccharide (LPS) levels and improved the function of the intestinal barrier preventing glucose intolerance and atherosclerosis in $LDLR^{-/-}$ mice (Ghosh et al., 2014). Another study performed on $LDLR^{-/-}$ mice reported a reduction in atherosclerotic lesions and improved lipid profile after 18 weeks of curcumin intake (0.02% *w*/w in diet) (Shin et al., 2011). The protective effects were mediated in part by hepatic regulation of lipoprotein cholesterol metabolism since hepatic expression of 3-hydroxy-3-methyl-glutaryl-co-enzyme A (HMG-CoA) reductase was inhibited, whereas PPARα and LXRα expression was upregulated by curcumin.

3.3. Cardiac hypertrophy and heart failure

Cardiac hypertrophy is recognized as an adaptive mechanism of the heart when subjects to a variety of pro-hypetrophic stimuli (Haq et al., 2000). Cardiac hypertrophy is characterized by increased size of cardiomyocytes, and more intensive sarcomere. However, sustained hypertrophy results in cardiac decompensation, contractile dysfunction, and consequently heart failure (Barry and Townsend, 2010; Li et al., 2014). Among the various mechanisms, transcription factors have been critically involved in the pathogenesis of both cardiac hypertrophy as well as late-stage heart failure (Barry and Townsend, 2010). Notably, post-transcriptional modifications, such as histone acetylation, play a crucial role in mediating the activation of these transcription factors. The transcriptional co-activator p300, which serves as an intrinsic histone acetyltransferase, is not only essential for physiological development and differentiation but also for the pathological growth of cardiomyocytes. Indeed, p300 deficient mice died for heart differentiation and trabeculation defects (Yao et al., 1998), while those which cardio-specifically-overexpressing p300 developed cardiac hypertrophy and consequently heart failure (Miyamoto et al., 2006). Curcumin is a well-known p300 inhibitor, and has suppressive effects in cardiac hypertrophy as well as heart failure (Ahuja et al., 2011; Chowdhury et al., 2013; Morimoto et al., 2008; Thompson et al., 2015). To further demonstrate the potential mechanisms, several studies have revealed the critical involvement of GATA binding protein 4 (GATA4), a key transcription factor for cardiac development and pathology. Curcumin not only suppressed the localization of GATA4 within the nucleus (Ahuja et al., 2011), but also inhibited the interaction between p300 and GATA4, resulting in a decreased GATA4 acetylation (Morimoto et al., 2008; Thompson et al., 2015), which was responsible for its protective effect against cardiac hypertrophy.

Calcium signaling is important for cardiac contraction and myocytes function, and heart failure is always accompanied by dysregulated calcium level (Barry and Townsend, 2010). Curcumin was able to suppress cardiac hypertrophy and heart failure by affecting calcium-associated molecules. These effects include increasing expression and changing localization of Na^+/Ca^{2+} exchanger (NCX) (Bai et al., 2018), stabilizing the amplitude of oscillation and the Ca^{2+} content of sarcoplasmic reticulum (SR) (Shi et al., 2014), upregulating mRNA and protein expression of SR Ca^{2+}-ATPase (Zhang et al., 2010), as well as deactivating calcium/calmodulin-dependent protein kinase II (CaMK II) and calcineurin-nuclear factor of activated T cells (NFAT) (Ghosh et al., 2010).

Cardiomyocyte apoptosis is a key factor for the transition of cardiac hypertrophy to heart failure. By using AngII-treated cardiomyocytes and mice with right renal artery ligation, Ray et al. found that curcumin (35 mg/kg/day, for 7 days) significantly rescued cardiac dysfunction by downregulating Bax and Cytochrome-c, and decreasing cleaved caspase 3 and poly-ADP-ribose polymerase 1 (PARP1). Curcumin treatment also inhibited the p53 expression and activation in myocardial disease (Ray et al., 2016). Hypoxia not only induces cardiac hypertrophy, but also cardiomyocytes apoptosis (Nehra et al., 2015; Nehra et al., 2015; Ray et al., 2016). Curcumin (50 μM and 500 ng/ml) significantly inhibited hypoxia-induced hypertrophy and apoptosis in cardiomyocytes by rescuing oxidative damage (Nehra et al., 2015), and by inhibiting mitochondrial stress and substrate switching, which subsequently prevented the translocation of p53 to mitochondria (Nehra et al., 2015).

Cardiac fibrosis is a pathological hallmark for the transition to heart failure progressed from cardiac hypertrophy, and is featured by accumulation of extracellular matrix proteins such as collagen type I in the

intermyocardium (Kong et al., 2014). In isoproterenol (Iso)-treated rats, curcumin administration (200 mg/kg/day, for 3 days) reduced the existing collagen matrix degradation and collagen production in the heart (Nirmala et al., 1999). A recent study showed that curcumin (200 mg/kg/day, for 4 weeks) inhibited mammalian target of rapamycine (mTOR)/autophagy signaling pathway and thus reduced cardiac hypertrophy and fibrosis induced by Iso (Liu et al., 2018). Consistently, in rats infused with Ang II, curcumin (150 mg/kg/day, for 2 and 4 weeks) not only decreased the population of macrophages and α-smooth muscle actin positive myofibroblasts with less transforming growth factor β1 (TGF-β1) (Pang et al., 2015), but also inhibited fibroblast migration, proliferation and collagen production (Chung et al., 2014). Further study showed that these effects were mediated by reducing Smad2/3 phosphorylation and inhibiting Akt and ERK1/2 signaling pathways (Chung et al., 2014; Pang et al., 2015). Moreover, increased expression and activity of gelatinase MMP-2 and MMP-9 also contributed to the protective effects of curcumin against chronic heart failure (Tang et al., 2009).

3.4. Drug-induced cardiotoxicity and cardiomyopathy

Doxorubicin (Dox) is one of the most effective chemotherapeutic drugs for various cancers, such as acute leukemia, breast cancer, and Hodgkin's lymphomas, but its clinical use is limited due to its cardiotoxicity, which leads to irreversible cardiac injury (Carvalho et al., 2009). To date, intensive research has been carried out to study the cardiotoxic mechanisms of Dox and related preventive strategies. Curcumin has been found to be effective in inhibiting Dox-induced cardiomyopathy and cardiomyocyte injury. In Dox-treated rats, serum creatine kinase (CK), lactate dehydrogenase (LDH) and cardiac catalase activity were elevated, accompanied by less myocardial glutathione and reduced glutathione peroxidase activity, but these effects were ameliorated by curcumin treatment. Consequently, Dox-induced cardiotoxicity was potentially inhibited by curcumin (Venkatesan, 1998). Similarly, curcumin (200 mg/kg/day, for 4 weeks) was able to prevent cardiac injury in Dox-treated albino rats (Swamy et al., 2012). Furthermore, coadministration of low-dose curcumin (100 mg/kg/day, for 23 days) with nebivolol (Imbaby et al., 2014) was sufficient to reduce the cardiotoxic effect of Dox. By using H9c2 cardiac muscle cells, it was demonstrated that curcumin significantly inhibited Dox-induced myocytes apoptosis by attenuating ROS generation (Hosseinzadeh et al., 2011; Jain and Rani, 2018), which might be mediated by NF-κB suppression (Hosseinzadeh et al., 2011). Recently, Benzer et al. found that curcumin (100 and 200 mg/kg/day, for 7 days) attenuated Dox-induced cardiotoxicity by increasing antioxidant enzyme activities, decreasing inflammation and apoptosis (Benzer et al., 2018). Despite Dox, cardiotoxicity is also a severe adverse effect of other chemotherapeutic agents such as cyclophosphamide, cisplatin, irinotecan and methotrexate; curcumin was found to be effective in ameliorating the related cardiac injury mainly by balancing oxidative stress (Avci et al., 2017; Bahadir et al., 2018; Chakraborty et al., 2017; Ciftci et al., 2018).

Unlike the chemotherapeutic agents, Iso is a non-selective beta-adrenoreceptor agonist clinically applied for bradycardia, heart block and asthma, with severe adverse effects of cardiac damage. Iso induces ischemic injury in the heart as evidenced by elevated heart rate, decreased R amplitude and ST elevation as well as dysfunctional contractility (Nazam Ansari et al., 2007; Nirmala and Puvanakrishnan, 1996b). These effects were mediated by mitochondrial damage, depletion of endogenous antioxidants and lysosomal activity (Izem-Meziane et al., 2012; Nazam Ansari et al., 2007; Nirmala and Puvanakrishnan, 1996a). Curcumin pretreatment was able to increase antioxidant enzymes, such as catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx). The cardiac function was also evidently restored with an important decrease of LDH and CK release (Abuarqoub et al., 2007; Nazam Ansari et al., 2007; Nirmala and Puvanakrishnan, 1996b). Moreover, the mitochondrial function, as indicated by respiration and mitochondrial swelling, was improved by curcumin coadministration (60 mg/kg/day, for 3 days) (Izem-Meziane et al., 2012). Heart injury induced respectively by cyclosporin A (CsA), bisphenol A, alcohol and cold storage could also be inhibited by curcumin (Abuarqoub et al., 2007; Nirmala and Puvanakrishnan, 1996a; Sagiroglu et al., 2014; Valokola et al., 2018; Yan et al., 2017).

3.5. Cardiovascular complications of diabetes

Diabetes is a worldwide progressive disease with a great impact on the quality and expectancy of life due to its complications (Ray et al., 2016). Among them, cardiovascular complications, including diabetic cardiomyopathy, myocardial infarction, and stroke, mainly contribute to the mortality of diabetes (Li et al., 2016). Increasing evidence showed that curcumin was able to reverse the cardiovascular complications or reduce the severity both *in vitro* and *in vivo* (Karuppagounder et al., 2017).

Combined with cilostazol, curcumin (200 mg/kg/day, for 4 weeks) increased the vasodilatory function in diabetic rat aorta (Nurullahoglu-Atalik et al., 2012). Interestingly, curcumin (90 mg/kg/day, for 50 days) supplemented into yoghurt appeared to be effective in increasing paraoxonase and decreasing biomarkers of carbohydrate and lipid disturbances in strepozotocin (STZ)-diabetic rats, suggesting a protective role against diabetic complications (Assis et al., 2017). In addition, several curcumin derivatives have been designed and tested effectively in preventing cardiovascular disorders accompanying diabetes (Karuppagounder et al., 2017).

Diabetic cardiomyopathy is characterized by cardiac structural and functional damage, including myocyte hypertrophy, myocardial fibrosis and consequent heart failure (Trachanas et al., 2014). In STZ-induced diabetic rats, curcumin treatment (200 mg/kg/day, for 16 weeks) significantly reduced advanced glycation end products (AGEs) accumulation, inhibited myocardial dysfunction and cardiac fibrosis, mainly by attenuating OS, apoptosis, and inflammation (Yu et al., 2012). Soetikno et al. showed that curcumin (100 mg/kg/day, for 8 weeks) ameliorated diabetic cardiomyopathy by regulating protein kinase C (PKC), p38 and ERK1/2 pathway with reduced OS and inflammation (Soetikno et al., 2012). Consistently, another study found that, by inhibiting superoxide production and PKC pathway, curcumin supplementation (as nanomicelle, 80 mg/day, for 3 months) reversed diabetes-induced endothelial dysfunction (Rahimi et al., 2016). However, curcumin might have limited effects in restoring antioxidant enzyme levels and aorta reactivity in medium or late stage of STZ-induced diabetes, and the probable reason might be the fact that chronic diabetes resulted in overproduction of free radicals (Majithiya and Balaraman, 2005). Furthermore, Guo et al. showed that, with high-energy diet, STZ evidently induced collagen deposition in the rat hearts, accompanied by increased TGF-β1 production and activated Smad signaling pathway (Guo et al., 2018). Nevertheless, these effects were abolished by curcumin treatment (30 mg/kg/day, for 16 weeks). Interestingly, a recent study showed that curcumin (200 mg/kg/day, for 3 months) ameliorated diabetic cardiomyopathy by regulating the crosstalk between autophagy and apoptosis, as autophagy was activated while apoptosis was suppressed (Yao et al., 2018).

3.6. Myocardial infarction

Myocardial infarction (MI) occurs most frequently in patients with underlying atherosclerotic disease process. The risk factors for MI include hypertension, diabetes mellitus and dyslipidemia. For therapy of acute MI, it is widely acknowledged to apply rapid reperfusion and conventional medicine such as β-blockers, mineralocorticoid receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins (Fraccarollo et al., 2012). Further medication are also required to limit infarct size, and prevent arrhythmia as well as progressive left ventricular (LV) remodeling, which might ultimately contribute to heart

failure (Tantry et al., 2018).

As an alternative and complementary medicine to enalapril, curcumin (50 mg/kg/day, for 6 weeks) caused a synergistic effect in increasing left ventricular fractional shortening (LVFS) and inhibiting perivascular fibrosis in MI rats (Sunagawa et al., 2011). With the application of microarray assay, Hong et al. demonstrated that, beside of improvement in the heart function and the activities of LDH and CK, curcumin treatment (75 mg/kg/day, for 3 days) significantly reduced cardiac infarct size and caused various genes differentially expressed as compared to non-curcumin surgery group (Hong et al., 2010). Those differentially expressed genes were mainly implicated in focal adhesions, extracellular matrix (ECM)-receptor interaction, and cytokine-cytokine receptor interaction, suggesting an anti-inflammatory effect of curcumin in protecting heart function from developing MI (Hong et al., 2010; Lv et al., 2016). Moreover, curcumin could also inhibit cardiomyocyte apoptosis (Geng et al., 2016; Lv et al., 2016), fibroblasts proliferation, and collagen deposition (Lv et al., 2016; Xiao et al., 2016) in the infracted area, which subsequently contributed to smaller infarct size and improved cardiac function. The antiplatelet function of curcumin was also involved in its protective role in MI (Tabeshpour et al., 2018).

Although timely reperfusion of the occluded artery is the most effective therapy for acute MI, reperfusion itself may lead to death of cardiomyocytes and further induce myocardium injury (Fraccarollo et al., 2012). Therefore, some studies aim to unravel the mechanisms of ischemia/reperfusion (I/R) injury in the heart and the corresponding strategy to intervene. Up to date, several evidence showed that curcumin was effective in preventing I/R injury. By pretreating rats with curcumin (10, 20 and 30 mg/kg/day, for 8 weeks) for 20 days, Liu et al. found that curcumin activated JAK2/STAT3 pathway and reduced oxidative damage, which in turn inhibited the reperfusion injury as indicated by smaller infarct size (Liu et al., 2017). The role of JAK2/STAT3 pathway in mediating the cardioprotective role of curcumin was confirmed in another study, in which JAK2/STAT3 was found to suppress apoptosis in the myocardium (Kim et al., 2012). Further study showed that, other pro-surviving pathways, such as PI3K/Akt, GSK-3β and mitogen-activated protein kinase (MAPK) pathways, were also implicated (Jeong et al., 2012). In addition, Wang et al. demonstrated that pretreatment of curcumin (150 mg/kg/day, for 5 days) improved I/R injury by downregulating early growth response 1 (EGR-1) and inflammatory factors such as TNF-α, IL-6, P-selectin and ICAM-1 (Wang et al., 2014). In comparison, this group also showed that dietary curcumin (150 mg/kg/day, for 7, 21 and 42 days) during reperfusion was effective in improving cardiac function and inhibiting cardiac remodeling as indicated by reduced malondialdehyde, MMPs activity, smaller collagen-rich scar, and elevated heart weight (Wang et al., 2012). Besides, the cardiac remodeling-related factors such as TGF-β1 and Smad 2/3/7 were regulated by curcumin (Wang et al., 2012). Furthermore, as a critical mediator of the innate immune system, toll-like receptor 2 was activated and transmited inflammation and fibrosis signal in the progress of MI, but this effect could be interfered by curcumin pretreatment (300 mg/kg/day, for 1 week) which restored the cardiac function (Kim et al., 2012). In a cell culture study, cardiomyocytes were treated with hypoxia/reoxygenation (H/R) to mimic the I/R process, but the injury effect was significantly inhibited by curcumin pretreatment, as evidenced by suppression of apoptosis and autophagy (Huang et al., 2015; Kim et al., 2012).

3.7. Stroke

Similar to MI, stroke also results from vascular or microvascular diseases which cause the interruption of cerebral blood supply and consequently brain dysfunction (Kalani et al., 2015). To date, reperfusion is the merely approved treatment for acute ischemic stroke (Li et al., 2017), and consistently thrombolytic/antiplatelet agents and surgery are the only available options (Adams et al., 2007). However, due to the fact that multiple mechanisms are involved in stroke progression, therapeutic effect of current regimens is limited. Agents that possess multiple pharmacological actions have attracted much attention (Li et al., 2016; Ovbiagele, 2008). Inflammation, apoptosis, and oxidative stress are three major mechanisms for the pathogenic proceeding of stroke (Li et al., 2016). Interestingly, curcumin is a well-established agent which is involved in anti-inflammation, anti-apoptosis and antioxidant. Increasing evidence showed that curcumin is effective in ischemic stroke, which accounts for about 80% of all strokes. The protective effects of curcumin were demonstrated both *in vitro* and *in vivo*. Of note, cerebral ischemia was introduced in animals mainly by middle cerebral artery occlusion (Dohare et al., 2008; Li et al., 2016; Wu et al., 2013), leaving some by bilateral common carotid artery occlusion for forebrain ischemia (Altinay et al., 2017) and abdominal aorta occlusion for spinal cord ischemia (Gokce et al., 2016). *In vitro*, cerebral cells were deprived of oxygen and glucose (Dong et al., 2014; Wu et al., 2013). In general, the mechanisms of curcumin in preventing stroke could be attributed into four pathways. Firstly, curcumin activated NF-E2-related factor 2 (Nrf2) and inhibited down-regulation of antioxidant enzymes including SOD, catalase and GPx activity (Li et al., 2016; Wu et al., 2013; Yang et al., 2009). As a result, less ROS was produced (Lan et al., 2018) and OS was attenuated, leading to lipid peroxidation inhibition, increased nitric oxide (NO) production and improvement of endothelial function in arteries (Dohare et al., 2008; Gokce et al., 2016; Kuhad and Chopra, 2007; Lan et al., 2018). Secondly, curcumin inhibited the inflammatory responses in ischemic area, as indicated by reduced activity of NF-κB and decreased level of pro-inflammatory cytokines (Dong et al., 2014; Li et al., 2016). Thirdly, mitochondrial function was restored (Miao et al., 2016) and apoptosis was inhibited (Altinay et al., 2017; Gokce et al., 2016; Kalani et al., 2015; Lan et al., 2018; Miao et al., 2016; Xie et al., 2018), as evidenced by increased Bcl-2 protein level and reduced Bax and caspase 3 protein. Last but not least, several signaling pathways, such as p38 (Dong et al., 2014), ERK1/2 (Lu et al., 2018) and PI3K/Akt (Wu et al., 2013), have been involved in the protective action of curcumin in cerebral ischemia. Taken together, curcumin could prevent stroke and reduce neurobehavioral deficits *via* different mechanisms.

4. Molecular targets of curcumin in cardiovascular diseases

In light of emerging evidence showing the cardiovascular benefits of curcumin, in the next section, we will discuss the molecular targets of curcumin in detail (Fig. 3).

4.1. p300

Histone acetyltransferases (HATs) are enzymes able to acetylate conserved lysine amino acids on histone and non-histone proteins. HATs can be divided, on the basis of sequence homology and functional roles, into several families. The p300/CREB-binding proteins (CBPs) are a family of HATs ubiquitously expressed that act as transcriptional coactivators with several critical roles in cellular function and survival (Chan and La Thangue, 2001). Curcumin is able to induce proteasome-dependent protein degradation of p300. Moreover, curcumin inhibits the acetyltransferase activity of p300 utilizing H3 or p53 as substrate (Marcu et al., 2006). The obtained data with radiolabeled curcumin showed that curcumin established covalent association with p300 in a Michael reaction-dependent manner, which contributed to its HATs-inhibitory activity (Marcu et al., 2006).

Histone acetylation is a regulation point for genes involved in the hypertrophy of myocardium, which have emerged as an adaptive response of the myocardium to various stresses, such as increasing afterload and myocardial infarction (Backs and Olson, 2006). p300-HAT is a coactivator of several transcription factors implicated in cardiac hypertrophy, and thus regulates the expression of genes encoding for proteins involved in myocardial cell hypertrophy (such as atrial

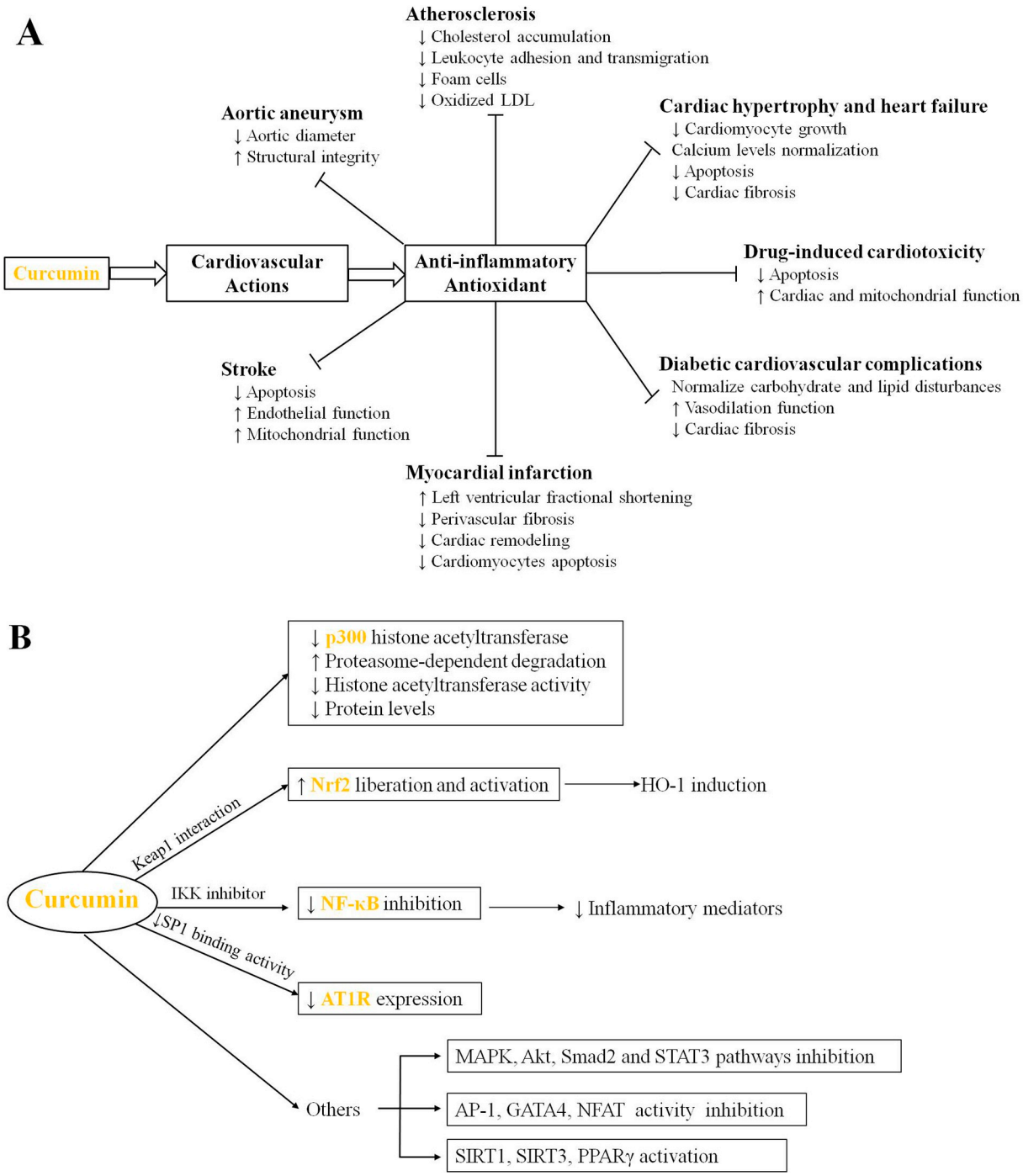

Fig. 3. Cardiovascular actions (A) and molecular targets (B) of curcumin.

natriuretic factor, endotelin-1 and β-myosin heavy chain) (Chan and La Thangue, 2001). As mentioned above, the role of p300 in growth and differentiation of cardiomyocytes during development is also evident in the experiments conducted on p300-deficient mice and transgenic mice with cardiac overexpression of p300 (Miyamoto et al., 2006). Moreover, transcriptional activity of p300 was enhanced in agonist-induced cardiac hypertrophy and this effect disappeared following the inhibition of p300-HAT activity (Gusterson et al., 2003; Yanazume et al., 2003).

The protective effects of curcumin in repressing cardiac hypertrophy and heart failure are exerted trough the inhibition of p300-HAT (Morimoto et al., 2008). By treating salt-sensitive hypertensive Dahl rats with 50 mg/kg/d of curcumin for 7 weeks, they observed a remarkable restoration of the systolic function, accompanied by a downregulation of GATA4. Consistently, in the rats with MI surgery, curcumin increased the systolic function and repressed the hypertrophy of the non-infarcted myocardium. Curcumin also prevented the p300/GATA4 complex formation followed by phenylephrine (PE) treatment and inhibited agonist- and p300-stimulated hypertrophic responses in rat cardiomyocytes (Morimoto et al., 2008).

4.2. *Nrf2*

Curcumin within its pleiotropic spectrum of activity has been discovered as a strong inducer of Nrf2 and related downstream protecting enzymes (Balogun et al., 2003). Nrf2, also known as Nuclear factor

(erythroid-derived 2)-like 2 (NFE2L2), is a transcription factor that represents one of the most important endogenous defence systems against electrophilic and oxidative stress, and is critically involved in the maintenance of cellular redox homeostasis (Battino et al., 2017). Physiologically, Nrf2 is restored in the cytoplasm in a non-active form due to the formation of a complex with Kelch ECH association protein 1 (Keap1). Indeed, low level of free Nrf2 is detected in the cytoplasm since it is ubiquitinated by E3 ubiquitin ligase complex. Stressful injuries promote the release of Nrf2 from its complex with Keap1 into the nucleus. At this level, Nrf2 interacts with antioxidant response elements (AREs) of target genes and promotes gene transcription. Nrf2 is able to induce the transcription of hundreds of genes encoding for direct antioxidant (*e.g.* SOD, GPx, glutathione reductase) and phase II enzymes [*e.g.* heme oxygenase-1 (HO-1), glutathione S-transferase (GST), and NAD(P)H:quinone acceptor oxidoreductase 1(NQO1)] (Battino et al., 2017). Curcumin due to its electrophilic moiety can undergo Michael reaction with thiol residues of Keap1 (mainly Cys 151) that in turn liberates and activates Nrf2 (Ye et al., 2007). HO-1 induction in response to Nrf2 activation is responsible of strong cytoprotective and anti-inflammatory effects against oxidative/nitrosative stress especially in cardiovascular and related diseases (Amata et al., 2017; Pittala et al., 2018; Shehzad et al., 2011). Indeed, HO-1 induction seems to mediate most of the effects induced by curcumin (Balogun et al., 2003) and, through this pathway, curcumin can ameliorate CVDs and related complications (Kanitkar et al., 2008). In SMCs, curcumin *via* Nrf2 and PI3K/Akt activation, was able to increase the expression of the aldose reductase, suggesting an important cellular role in response to oxidative stress (Kang et al., 2007). Curcumin was also able to inhibit SMC proliferation through Nrf2-dependent HO-1 overexpression, indicating an important role in counteracting abnormal SMCs growth in atherosclerosis lesions and angioplasty following restenosis (Pae et al., 2007). In addition, curcumin supplementation was reported to counteract the pathogenesis of obesity-induced CVDs by exerting protective effects against arterial damages induced by high-fat diet, which was mediated by Nrf2 induction and NF-κB inhibition (Li et al., 2015). The mechanism was also implicated in the cardioprotective action of curcumin in I/R-induced heart injury (Li et al., 2015).

4.3. NF-κB

The multimodal effects of curcumin and its therapeutic properties are exerted through the modulation of several cellular and molecular targets. NF-κB is among the main transcription factors potently regulated, mostly indirectly, by curcumin (Singh and Aggarwal, 1995). Different stimuli, such as cytokines and ROS, are able to induce NF-κB expression. NF-κB upregulation is often observed in conditions such as inflammation diseases and cancers (Hoesel and Schmid, 2013). NF-κB is a transcription factor belonging to a family of dimers able to bind the κB site on the DNA. It regulates genes involved in cell proliferation and survival. Under physiological conditions, NF-κB is localized in the cytoplasm as an inactive pair of dimers complexed with IκB. Upon inflammatory/carcinogenic insults, NF-κB is activated by specific phosphorylation at Ser^{276}, Ser^{529}, and Ser^{536} residues, and dissociation from IκB phosphorylated by its kinase IKK. As a result, the dimers translocate into the nucleus and trigger the expression of genes in inflammatory pathways (Takada et al., 2004). Curcumin was found to be a specific IKK inhibitor and therefore is able to potently block up-stream NF-κB and IκB activation (Duarte et al., 2010; Reddy and Aggarwal, 1994). Endothelial cell dysfunction plays a pivotal role in the onset of vascular damages. Curcumin improved endothelial functions and lowered TNF-α-induced monocyte adhesion to endothelial cells by inhibiting NF-κB, the most important transcription factor triggered by TNF-α (Kim et al., 2007; Kumar et al., 1998; Lee et al., 2010; Monfoulet et al., 2017). $ApoE^{-/-}$ mice supplemented with curcumin showed a 26% reduction in atherosclerotic lesions along with a different pattern of gene expression implicated in adhesion phenomenon and transendothelial migration (Coban et al., 2012). Moreover, by inhibiting NF-κB pathway, curcumin treatment diminished PM2.5-induced OS, which was associated with reduced oxLDL and inflammation in human microvascular endothelial cells (Shi et al., 2017). It was also reported that curcumin triggered re-endothelialization upon vascular injuries in endothelial progenitor cells (EPCs), which might be mediated by the inhibition of the Id1/PI3K/Akt/NF-κB/survivin signaling pathway (Li et al., 2012). In cultured HUVECs, curcumin reduced the amount of ROS, finely tuned lipoprotein composition, and reduced OS by stimulating antioxidant processes by inhibiting NF-κB pathway and stimulating NO production (Lee et al., 2010). In addition, curcumin reduced the release of ICAM-1, MCP-1, and IL-8, most probably *via* reducing phosphorylation of p38, NF-κB, and STAT3 (Kim et al., 2007).

4.4. AT1R

Angiotensin II type 1 receptor (AT1R) represents a promising therapeutic target for CVDs prevention. Multiple AT1R antagonists are clinically used in treating CVDs. Curcumin has been shown to exert beneficial effects on CVDs by influencing the biological functionality and expression of AT1R. One of the first data reported on curcumin effect on AT1R has been reported by Kang et al. (Kang et al., 2010) who showed that curcumin pretreatment (5–10 μM) reduced the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and AT1R expression, and inhibited LOX-1-mediated increase of hypertrophic markers in adult mouse cardiomyocytes. Yao et al. (Yao et al., 2016) reported the down-regulation of AT1R expression in A10 cells by curcumin. Specifically, curcumin decreased the binding of the specificity protein 1 (SP1) with the AT1R gene promoter in a concentration (10^{-5}–10^{-9} M, 24 h)- and time (10^{-6} M, 2–30 h)-dependent manner. The same authors observed, in an Ang II-induced hypertensive model using eight-week-old C57Bl/6J mice, the decrease in AT1R expression after treatment with curcumin (300 mg/kg/d), resulting in an inhibition of AT1R-mediated vasoconstriction and subsequently onset of hypertension. The regulation of the ATIR expression by curcumin has also been reported by Pang et al. (Pang et al., 2015) in Male Sprague Dawley rats treated with 150 mg/kg/day of curcumin for 2 and 4 weeks after Ang II infusion (500 ng/kg/min). In comparison with the animals treated with only Ang II infusion, curcumin reduced AT1R but up-regulated AT2R expression, resulting in less locally expressed AT1R and enhanced AT2R into the intra-cardiac vessels as well as at myocardium level.

4.5. Others

In addition to the above-mentioned molecular targets, other signaling pathways and transcription factors were also implicated in the protective effects of curcumin. For example, MAPK pathways are important not only to cell physiology, but also to the pathology of cardiovascular system. All three major MAPK cascades, JNK, p38 and ERK1/2 pathways, were found to be activated in various cell types, such as cardiomyocytes, cardiac fibroblasts, endothelial cells, macrophages and smooth muscle cells, upon stimulation with disease-causing stimuli. Nevertheless, the activation was inhibited by curcumin pretreatment (Chung et al., 2014; Dong et al., 2014; Liu et al., 2016; Liu et al., 2014; Qin et al., 2009). In cardiomyocytes, curcumin could activate SIRT3 (Wang et al., 2018) but inhibit the activation of AP-1 (Skayian and Kreydiyyeh, 2006), GATA4 (Morimoto et al., 2008) and NFAT (Hernandez et al., 2016), three transcription factors involved in cardiomyocyte hypertrophy and apoptosis. Consistently, AP-1 was deactivated by curcumin in endothelial cells (Pendurthi et al., 1997) and SMCs (Qin et al., 2009), in which the STAT3 pathway was also inhibited (Kim et al., 2007; Lin et al., 2016). In endothelial cells and cardiac fibroblasts, Akt pathway was blocked by curcumin and thus the cell apoptosis and proliferation were inhibited (Chung et al., 2014; Rafiee et al., 2010). Specifically, curcumin inhibited cardiac fibroblast differentiation and activation partially by suppressing Smad2 signaling

pathways (Chung et al., 2014; Liu et al., 2016). Moreover, it was demonstrated that SIRT1 and PPARγ were activated by curcumin in cardiac fibroblasts (Meng et al., 2014; Xiao et al., 2016) and macrophages (Bai et al., 2016; Lin et al., 2015), respectively. From these evidences, curcumin is a natural product with multi-targets property and has multiple therapeutic applications in CVDs.

5. Clinical trials of curcumin in cardiovascular diseases

In addition to the cardiovascular benefits observed in experimental animals and cultured cells, curcumin also confers protective effects in patients with CVDs. Information of clinical trials involving curcumin is summarized in Table 1.

For example, a 12-week randomized placebo controlled trial on 118 subjects showed that curcumin supplementation reduced the risk of developing acute cardiovascular events in patients affected by type 2 diabetes complicated by dyslipidaemia (Panahi et al., 2017). Another study was performed in 10 male participants to examine the role of curcumin in exercise-induced OS. It was found that curcumin had the ability to attenuate the exercise-induced OS (Takahashi et al., 2014). Another randomized placebo-controlled study on 45 postmenopausal women revealed that the reduction in the left ventricular afterload was at a greater extent with the combination of endurance exercise along with curcumin intake. The systolic blood pressure also decreased in those patients who received endurance exercise and curcumin together. Moreover, no significant changes of the hemodynamic parameters with respect to the baseline were observed (Sugawara et al., 2012).

A significant attenuation in the concentration of serum triglyceride was reported after curcuminoids supplementation for 7 days (Pungcharoenkul and Thongnopnua, 2011). Similar effect was also reported from another clinical trial which was conducted in obese individuals after 4-week supplementation of curcuminoids at 1 g daily dose (Mohammadi et al., 2013). A randomized controlled trial on 87 subjects with non-alcoholic fatty liver diseases revealed a significant decrease in total cholesterol, non-high-density lipoproteins (HDL) cholesterol, uric acid, and triglycerides followed by 1 g curcumin supplementation for 8 weeks (Panahi et al., 2016). Study with lower dose of curcumin (80 mg/day) was conducted on 38 healthy volunteers to examine the effect of curcumin on the well-being of study subjects. It was found that curcumin significantly lowered the plasma triglyceride levels and some other important parameters, like plasma beta amyloid protein, salivary amylase *etc.*, but CRP level was unchanged (DiSilvestro et al., 2012). A study involving 30 subjects was conducted and it was found that for curcumin treated arm, no adverse effect was reported (Ramirez-Bosca et al., 2000). Moreover, curcumin deceased the LDL and Apo B levels and enhanced the Apo A1 and HDL levels. The lower Apo B-Apo A ratio was thus helpful in the prevention of atherosclerosis (Ramirez-Bosca et al., 2000). A study was carried out on 121 patients to evaluate the effect of curcuminoids at higher dose (4 g/day) in prevention of myocardial infarction after coronary artery bypass grafting. The results clearly demonstrated that the in-hospital myocardial infarction was decreased from 30% to 13% in placebo and curcuminoids treated group, respectively. In addition, in the curcumin-treated group, CRP, N-terminal pro-B-type natriuretic peptide and malondialdehyde levels were also lowered (Wongcharoen et al., 2012). In another clinical trial, curcumin pretreatment (45 mg/day, for 14 days) led to positive effects in children undergone corrective surgery for tetralogy of Fallot. Several parameters such as glutathione levels, monoaldehyde, caspase-3 expression, NF-κB translocation, and activity of JNK were evaluated. The study revealed that there was substantial decrease of activated JNK protein from the pre-ischemia to the phase of reperfusion. Curcumin also suppressed the expression of caspase-3 in ischemia phase, and ameliorated myocardial performance, body temperature and oxygen saturation at 6-h stage. The authors recommended the plausible use of curcumin as a standard procedure before tetralogy of Fallot correction (Sukardi et al., 2016).

In addition, the effect of 6-month curcumin consumption was investigated in patients with type 2 diabetes (Chuengsamarn et al., 2014). The intervention significantly reduced pulse wave velocity and serum levels of leptin and increased serum levels of adiponectin. It was also reported to have an improvement in serum metabolic profile with a reduction in homeostasis model assessment-insulin resistance, triglycerides and uric acid levels together with a reduction in visceral total body fat (Chuengsamarn et al., 2014). In another study, patients with chronic obstructive pulmonary disease (COPD) were supplemented with highly bioavailable curcumin (Theracurmin®, nanocurcumin) for 24 weeks (Funamoto et al., 2016). The treatment reduced the level of atherosclerotic α1-antitrypsin-LDL (AT-LDL) complex (which is a form of modified LDL that appears in human serum and atherosclerotic lesions), leading to the prevention of atherosclerosis. Finally, a clinical trial (https://clinicaltrials.gov, NCT02998918) is being developed to determine the effects of acute and short-term (1-week) curcumin and polyphenol supplementation in humans on inflammation and on cholesterol efflux properties of HDL particles (Sarzynski, 2018). In most of the trials, curcumin was used as a capsule formulation and in one case it was used as tablet. It was also found that curcumin was sometimes utilized as nano or phytosome formulations and with piperine to enhance the bioavailability (Table 1). We additionally searched for the registered clinical trials in www.clinicaltrials.gov.in and it was found that total 147 clinical studies are registered, and 58 of them were completed while 49 are ongoing (Table 2), indicating the broad interest of studying the clinical utility of curcumin in treating various kinds of human diseases.

6. New development of curcumin derivatives

Along with extensive studies on the biological activities of curcumin, there are also a large number of studies reporting the synthesis of curcumin and its derivatives. Most of these studies are focused on improving synthetic routes of curcumin and its derivatives, enhancing bioavailability and pharmacological activities (Amalraj et al., 2017; Anand et al., 2008; Basile et al., 2009). Low solubility and poor bioavailability of curcumin have always been a matter of concern among researchers. In this regard, there have been many attempts to design derivatives or drug delivery systems with improved bioavailability, which are well covered in previous review articles (Anand et al., 2007; Basnet and Skalko-Basnet, 2011; Liu et al., 2016; Szymusiak et al., 2016). As the bioavailability of curcumin is not among the objectives of this paper, only the curcumin derivatives designed for cardiovascular applications are discussed in this section.

Both natural (Fig. 4) and synthetic derivatives of curcumin have been evaluated for their beneficial effects in the prevention or treatment of cardiovascular disorders. Kim et al. (Kim et al., 2012) evaluated the anticoagulant activities of curcumin and its derivative bisdemethoxycurcumin by evaluating the prothrombin time and partial thromboplastin time (PT and aPTT, respectively), and the production of activated factor X and thrombin. Treatment with both curcumin and bisdemethoxycurcumin prolonged aPTT and PT, reduced the generation of thrombin and activated factor X, suggesting potent anticoagulant activity. Curcumin showed higher anticoagulant activity as compared to bisdemethoxycurcumin. Li et al. (Li et al., 2015) synthesized the allylated and prenylated mono-carbonyl derivatives and evaluated their protective activities against myocardial ischemia reperfusion injury. Among 32 derivatives screened, a compound (1E,4E)-1-(3-Allyl-4-methoxyphenyl)-5-(2-chlorophenyl) penta-1,4-dien-3-one, named as 14p, attenuated hydrogen peroxide (H_2O_2)-induced OS, inhibited ROS-induced cell death and apoptosis by elevating Nrf2 activity in H9c2 cells. In *in-vivo* model using male C57BL/6 mice, 14p limited the

Table 1
Clinical trials of curcumin in treating cardiovascular and metabolic diseases.

Trial scheme	Sample size (treatment/control)	Diagnosis	Duration	Intervention		Formulation type	Outcome measures	Reference
R, DB, PC	45 (11/11/11/12)	Effect on central arterial hemodynamics	8 weeks	Curcumin (Exercise + Curcumin)	Placebo Exercise + Placebo	Curcumin pill (25 mg curcumin dispersed with colloidalnanoparticles)	BP, HR, APWV, and POC	(Sugawara et al., 2012)
R, P, DB, PC	121 (61/60)	Acute myocardial infarction	8 days[#]	Curcumin	Placebo	Curcuminoid capsule (caplet form)	CRP, malondialdehyde, and N-terminal pro-B-type natriuretic peptide	(Wongcharoen et al., 2012)
R, DB, PC, CO	32 (16/16)	Dyslipidemia	30 days	Curcumin	Placebo	Capsule	TC, LDL-C, HDL-C, and HsCRP	(Mohammadi et al., 2013)
SC, DB, PC	45 (22/23)	Tetralogy of fallot	30 days	Curcumin	Placebo	Oral curcumin (formulation not given)	Malondialdehyde and glutathione, NF-κB, JNK, caspase-3	(Sukardi et al., 2016)
NA	30 (12)	Atherosclerosis	30 days	Curcumin		Tablet	LDL, HDL, Apo B, Apo A	(Ramirez-Bosca et al., 2000)
DB, PC	240 (107/106)	Assessment of atherogenic risk reduction in diabetes patients	9 months	Curcumin	Placebo	Capsule	PWV, increased adiponectin or decreased leptin	(Chuengsamarn et al., 2014)
R, DB, PG	39 (22/17)	Assessment of serum atherosclerotic low-density lipoprotein levels mild COPD patients	24 weeks	Curcumin	Placebo	Capsule	CRP, LDL-C, HDL-C *etc.*	(Funamoto et al., 2016)
R, PC	10 (10/10 same healthy volunteers at different time)	Effect on exercise induced oxidative stress	2 h before exercise	Curcumin	Placebo	Capsule	SOD, CAT, GPX, GR, reactive oxygen metabolites	(Takahashi et al., 2014)
R	24 (8/8/8)	Effect on antioxidant capacity and cholesterol levels	7 days	Curcumin (two groups)	Vitamin E	Capsule	Plasma ORAC, TC and TG	(Pungcharoenkul and Thongnopnua, 2011)
R, PC	102 (50/52)	Serum levels in NFALD patients	8 weeks	Curcumin	Placebo	Capsule (phytosomal formulation)	TC, LDL-C, TG, non-HDL-C, UA	(Panahi et al., 2016)
R, PC	118 (50/50)	Lipid profile in diabetes patients	12 weeks	Curcumin	Placebo	Capsule	TC, LDL-C, HDL-C, TG, Lp(a), and non-HDL-C	(Panahi et al., 2017)
NA	38 (19/19)	Effect on healthy people	4 weeks	Curcumin	Placebo	Capsule	TC, TG, LDL, HDL and ALT	(DiSilvestro et al., 2012)

Abbreviations: Apo, apolipoprotein; ALT, alanine aminotransferase; APWV, aortic pulse wave velocity; BP, blood pressure; CAT, catalase; CO, cross over; DB, houble-blind; GPX, glutathione peroxidase; GR, glutathione reductase; HDL-C, high-density lipoprotein cholesterol; HsCRP, high sensitive C-reactive protein; HR, heart rate; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; NF-κB, nuclear factor kappa B; ORAC, plasma oxygen absorbance capacity; PG, parallel-group; PC, placebo-controlled; POC, peak oxygen consumption; PWV, pulse wave velocity; R, randomized; SC, single cantered; SOD, superoxide dismutase; TC, total cholesterol; TG, triglyceride; UA, uric acid.

[#] 3 days before the scheduled surgery (coronary artery bypass grafting) until 5 days after surgery.

Table 2
Status of clinical trials registered with curcumin in www.clinicaltrials.gov.in accessed on Jan 3rd, 2019.

Trial status	Number of studies
Total number of trials registered with the name "curcumin"	147
Clinical trials completed	58
Clinical trials withdrawn	07
Clinical trials terminated	06
Clinical trials suspended	01
Clinical trials with unknown status	26
Ongoing clinical trials	49

ischemia/reperfusion injury and reduced the myocardial apoptosis. These curcumin derivatives were also evaluated for their protective effects against macrophage inflammation in RAW 264.7 cells (Liu et al., 2014). Park et al. (Park et al., 2015) synthesized various alkylsulfonyl and substituted benzenesulfonyl derivatives of curcumin and evaluated their vasodilatory effects. Different compounds showed varying vasodilatory effects on depolarization or ET-1 induced basilar artery contraction. The authors suggested that these curcumin derivatives (termed as curcumin mimics), serve as blockers of L-type calcium channel and endothelin A/B2 receptors in SMCs and might be potent leads for the discovery of anti-hypertensive drugs. Ahn et al. (Ahn et al., 2009) evaluated the vasodilatory effects of different amide type and sulfonyl amide type mimics of curcumin on basilar artery of rabbits. Some compounds showed more potent and rapid vasodilatory effects as compared to curcumin at same concentration. Aromatic enones using substituted chalcone backbone were also synthesized and evaluated for their anti-proliferative activity on endothelial cells, and some showed comparable or higher potency in inhibiting endothelial cell growth (Robinson et al., 2005). Similarly, Shim et al. (Shim et al., 2002) synthesized hydrazino and hydrazinobenzoyl derivatives of curcumin and evaluated their inhibitory activity on endothelial cell proliferation. Among synthesized compounds, hydrazinocurcumin showed higher inhibitory activity than that of curcumin and other natural curcumin derivatives. Moreover, while a monocarbonyl derivative of curcumin showed inhibitory activity on migration and tube formation of HUVECs (Sun et al., 2014), ferrocenyl derivatives of curcuminoids inhibited tubulin polymerization on endothelial cells (Arezki et al., 2011). Furthermore, another study demonstrated the preventive effect of a curcumin analogue (2E,6E)-2,6-bis(2-(trifluoromethyl)benzylidene) cyclohexanone, named as C66, on diabetic cardiomyopathy through inhibition of JNK pathway (Wang et al., 2014).

Apart from their cardiovascular actions, many of the synthetic curcumin derivatives are studied for their antioxidant, anti-tumor and anti-inflammatory activities as reported in a recent review by Amalraj et al. (Amalraj et al., 2017). In an interesting study, Li and Liu (Li and Liu, 2011) synthesized an organometollic derivative of curcumin, *i.e.* ferrocenylidene curcumin, and evaluated its *in-vitro* antioxidant activities. Ferrocenylidene curcumin showed DNA protective activity against Cu^{2+}/GSH induced oxidation, 2,2′-azobis(2-amidinopropane hydrochloride) (AAPH)-induced oxidation and also showed antiradical activities against 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-Azinobis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS). Computational and in-silico docking studies have also been performed to analyze different biological activities of curcumin derivatives (Alisi et al., 2018; Banuppriya et al., 2016; Hobani et al., 2017; Sohilait et al., 2017).

7. Conclusions and perspectives

Curcumin is a multimodal nutraceutical and pharmaceutical agent which has different therapeutic applications, such as cancer, neurological disorders, chronic inflammatory diseases, and CVDs (Chen et al., 2018; Chowdhury et al., 2013; Doello et al., 2018; Kalani et al., 2015). As exemplified in this review, curcumin plays a critical role in protecting humans and animals from cardiovascular dysfunction which is always the primary step for CVDs including atherosclerosis, aortic aneurysm, MI and stroke (Campbell and Fleenor, 2017; Li et al., 2017). Furthermore, its antioxidant, anti-inflammatory and anti-apoptotic properties have been reported to be effective in improving cardiac hypertrophy, heart failure, diabetic cardiovascular complications and cardiotoxicity (Bai et al., 2018; Chung et al., 2014; Karuppagounder et al., 2017; Venkatesan, 1998). The potential mechanisms have been studied in depth both *in vitro* and *in vivo* investigation, and some of these effects have also been validated by clinical trials (Campbell and Fleenor, 2017; Chuengsamarn et al., 2014). Due to its safety (Anand et al., 2008) and efficacy use in human clinical trials, it has been considered "generally regarded as safe" by the US Food and Drug Administration (CFR, 2017). However, curcumin was limited in clinical use due to its low bioavailability, which might be caused by poor absorption and rapid metabolism (Aggarwal and Harikumar, 2009). To overcome this obstacle, on the one hand, various formulations of curcumin have been investigated (Campbell and Fleenor, 2017; Nehra et al., 2015; Rahimi et al., 2016; Ray et al., 2016), and proper drug combinations were also suggested (Assis et al., 2017; Chakraborty et al., 2017; Tantry et al., 2018). On the other hand, by structural modification of curcumin, researchers have found numbers of synthetic derivatives with better bioavailability, some of which exert comparable/better pharmacokinetic/pharmacodynamics profile as compared to curcumin; however, toxicological data are up to date lacking (Lin et al., 2014; Wang et al., 2015; Zheng et al., 2016). As a food component, curcumin is well-tolerated and its safety was demonstrated up to 12 g/day (Lao et al., 2006). Therefore, curcumin will become a routine food supplement such as vitamins and fish oil, to prevent or treat CVDs. Nonetheless, further studies and clinical trials, with larger sample size and optimized dosage, are required to validate the current findings in preventing and treating CVDs.

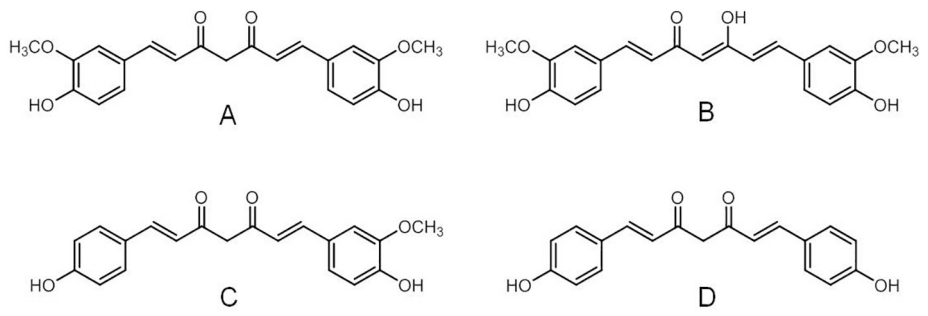

Fig. 4. Structures of bis-keto and enol-form of curcumin (A and B, respectively) and its derivatives demethoxycurcumin (C) and bisdemethoxycurcumin (D).

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