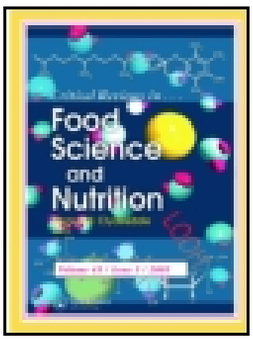

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The More Effective Treatment of Atrial Fibrillation Applying the Natural Compounds; as NADPH Oxidase and Ion Channel Inhibitors

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia that occurs because of several different risk factors, e.g., valvular heart disease, coronary artery disease, age ≥75 years, hypertension and diabetes mellitus. One key risk factor that results in AF, is oxidative stress. Evidence suggests that there is a correlation between oxidative processes and the genesis of AF. Oxidative stress occurs when the generation of reactive oxygen species (ROS) increase due to excessive activity of enzymes including NADPH oxidase (NOX) and xanthine oxidase; or its degradation decrease by dysfunctional antioxidant enzyme systems, such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx). Afterwards, elevated ROS may shift ion channel activity to increase AF susceptibility.

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The outbreak of AF continues to grow. Unfortunately, current treatment strategies may have limited efficacy or adverse effects. On the other hand, the inhibition of ROS formation and alteration of ion channel activity could be important therapeutic targets for prevention or treatments of AF. Additionally, many studies have been shown that several natural compounds have the ability to inhibit NADPH oxidases directly. This review focuses on natural compounds which specially inhibit NOX isoforms and have direct effects on ion channels, suggesting these compounds can be helpful in AF treatment.

Keywords

Atrial fibrillation, Reactive Oxygen Species, Apocynin, Resveratrol, Berberine, Curcumin

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1. Atrial fibrillation

Cardiac arrhythmias refer to disordered rate or rhythm of the heartbeat due to perturbed electrophysiology of myocardium. Among numerous types of clinically remarkable arrhythmias, AF is the most common cardiac dysrhythmia and progressive disease associated with considerable cardiovascular morbidity and mortality; which are mediated predominantly by heart failure, stroke and myocardial infarction (Nattel and Dobrev, 2016). The prevalence of AF is age dependent, such that the incidence rate is 5-fold greater between 90 years or older than among those 67--69 years (Piccini et al., 2012). Limited efficacy and significant adverse effect restrict using present therapeutic approaches. Because of this limitation, substantial efforts inspire to improve conception of the mechanisms underlying AF, with the premise that better understanding of the AF mechanisms will lead to innovative and novel therapeutic approaches (Nattel et al., 2008).

2. Atrial Electrophysiology

During normal sinus rhythm, the activation of different ion channels participates in creating action potentials (APs). APs in atrial cells consist of several phases. APs initiated through voltage-dependent activation of Na^+ channels, responsible for producing depolarizing sodium inward currents (I_{Na}) and APs upstroke. In plateau phase, the activation of L-type Ca^{2+} currents ($I_{Ca,L}$) in cell membrane and ryanodine receptor channel type 2 (RyR2) in sarcoplasmic reticulum (SR) cause to increase intracellular Ca^{2+} transient. Moreover, during the end stage of AP and repolarization phase, the various types of K^+ currents involves, including time-dependent delayed-rectifier K^+ currents such as slow delayed-rectifier K^+ currents [I_{Ks}], rapid delayed-rectifier K^+ currents [I_{Kr}] and ultra-rapid delayed-rectifier K^+ currents [I_{Kur}], and the transient

outward K^+ currents (I_{to}). The basal and acetylcholine-dependent inward-rectifier K^+ currents (I_{K1} and $I_{K,ACh}$) regulate final AP repolarization and determine resting membrane potential. In diastolic phase, the additional Ca^{2+} is collected from the cytoplasm to restore low resting cytosolic Ca^{2+} concentrations through two different processes; the Na^+/Ca^{2+} exchanger (NCX) and the SR Ca^{2+}-ATPase type 2a (SERCA2a) function. Together, these processes allow atrial relaxation (Heijman et al., 2014).

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3. Basic Mechanisms Underlying AF

Detailed molecular mechanisms underlying the development of AF is not entirely clear. However, four principal mechanisms are proposed that participate in AF; structural remodeling, electrical remodeling, autonomic nervous system changes and Ca^{2+} handling abnormalities. Each of these mechanisms can result from cardiac diseases and if these activities progress in the atrium, probably lead to focal ectopic firing and re-entry conditions. Focal ectopic activity and re-entry are the main arrhythmogenic mechanisms of AF initiation and maintenance (Nattel and Harada, 2014).

Focal ectopic firing is required by which initiating AF in a vulnerable substrate. It can also maintain AF when occurring repeatedly at a high frequency. This activity likely occurs as a result of delayed after-depolarizations (DADs) and early after-depolarizations (EADs). DADs are related to Ca^{2+} handling abnormalities particularly Ca^{2+} overload. Moreover, EADs happens when APs becomes abnormally prolonged due to the reduced repolarizing K^+ currents or the increased persistent/late Na^+ currents (Nattel et al., 2008).

Re-entry, a disorder of impulse propagation, occur when an impulse move around an abnormal circuit repetitively when impacts to an anatomic obstacle. The altered expression and/or function

of ion channels and following ion currents in atrium cells such as increased repolarizing K^+ currents, reduced I_{Na} and I_{to} suppression lead to prolong APD and refractory period of the atrial tissues, which then participate in the inhibition of atrial flutter or atrial fibrillation (Nattel and Dobrev, 2016).

4. Oxidative Stress; as an Important Risk Factor in AF

Several risk factors contribute to AF have been identified including hypertension, ischemic attack or stroke, obstructive pulmonary disease, heart failure, metabolic diseases (diabetes mellitus and obesity), hyperthyroidism, vascular disease and sex category (Vlachos et al., 2016). On the other hand, increasing evidence has indicated that oxidative stress likely is an important factor in the pathogenesis of AF. Mechanistic links between adiposity, atrial fibrosis, diabetes, hypertension, age, and AF may involve oxidative stress (Sovari and Dudley, 2010; Ziolo and Mohler, 2015).

Oxidative stress is a condition in which the ROS such as hydrogen peroxide and superoxide elevate in the cells (Figure 2). Enhanced production or decreased degradation of ROS, and also decreased in nitric oxide (NO) bioavailability have been found to be related to AF. In myocardial tissues, increased ROS results in damage to DNA, proteins, and lipids, induces tissue damage and these events cause to cardiac structural and electrical remodeling by which enhance susceptibility to AF. It has been indicated that peroxynitrite ($ONOO^-$) and hydroxyl radical (OH^-) mediate oxidative damage of myofibrils in AF that lead to structural remodeling of atria (Babusikova et al., 2004). In several models of atrial pacing, increased ROS have been detected in cardiac tissues, offering a potential interplay between ROS production and atrial electrical changes which eventually lead to AF (Violi et al., 2014). For example, it has been shown that the

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increased ROS generation genes as well as reduced antioxidant genes expression supports a shift toward pro-oxidation state in AF (Kim et al., 2003) and antioxidant treatment cause to down-regulated NOX by which in turn reduce atrial fibrosis and AF occurrence (Violi et al., 2014).

Increased ROS production may also change multiple cardiac ion channel activities and ionic currents in cardiomyocytes to enhance AF susceptibility (Ziolo and Mohler, 2015). Moreover, ROS have an important arrhythmogenic effect on Na^+ currents that cause to down-regulate cardiac sodium channels (Sovari, 2016). H_2O_2 is promoting an increased late Na^+ current and subsequently, prolong APD and create EAD, result in arrhythmia (Sovari, 2016). Moreover, altered intracellular Ca^{2+} homeostasis has been correlated with the pathogenesis of AF. For instance, H_2O_2 may stimulate I_{Ca} and hydroxyl radicals increase the RyR2 open probability, as well as NCX activity in cardiomyocytes (Sovari, 2016). Oxidative stress also is a major contributor to K^+ current attenuation in cardiomyocytes while the antioxidant enzymes like SOD significantly enhance K^+ currents in myocytes (Shimoni et al., 2005). (Figure 2).

Accumulating evidences have shown that produced ROS in the cardiovascular system are derived from different enzymatic systems/complexes such as NADPH oxidase, xanthine oxidase and myeloperoxidase (MPO) (Youn et al., 2013). Over-expression of these enzymes has been shown in atrial cells in experimental and clinical models of AF (Violi et al., 2014). Among these systems/complexes, NOX has considered as a major initiating source for enhancement of ROS production in cardiovascular diseases.

5. NADPH oxidase in heart

Nicotinamide adenine dinucleotide phosphate oxidase (NAD(P)H oxidase or NOX) was found at first in neutrophils and macrophages, thus it is also known as phagocyte oxidase (phox). NOX is

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a family of the multi-subunit enzymatic complex that plays a major role in the formation of ROS (Youn et al., 2013). It uses NADPH, as an electron donor, to produce free radicals such as superoxide and H_2O_2 in the pathogenesis of cardiovascular diseases like hypertension, atherosclerosis and heart failure (Sirker et al., 2011).

NOX family includes several isoforms, which differ in their expression, structure, and function; such as Nox1-5 and Duox1-2 (dual-function oxidases). NOX structure composes of six subunits; gp91phox and p22phox which are located in the plasma membrane. When these combined with other cytosolic regulatory subunits such as p40phox, p47phox, p67phox, and the small GTPase (Rac), active NOX complex was formed (Lambeth, 2004).

The specific distribution of NOX isoforms has been reported in different tissue. NOX2 express in cardiomyocytes, endothelial cells, and fibroblasts, whilst NOX4 exist in all these cells as well as vascular smooth muscle cells (VSMCs). NOX2 produces superoxide and it has been proposed NOX4 generates H_2O_2 rather than superoxide (Martyn et al., 2006) and as a result, each isoform have cell specific roles. For instance, NOX4-induced H_2O_2 can participate in angiogenesis (Zhang et al., 2010) and pathogenesis of heart failure (Youn et al., 2013; Ago et al., 2010). Additionally, NOX2 function induces fibrosis and cardiac hypertrophy in the heart (Bendall et al., 2002). As it has been mentioned above, the role of NOX has been confirmed in cardiovascular diseases. In the following, it is referred specifically to the effect of NOX enzymes in promoting and maintaining AF.

6. Role of NOX in AF

Many experimental studies on animals or clinic which will be discussed below, have shown that increased NADPH oxidase activity plays an important direct or indirect role in the production of

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ROS in atrial tissues at different stages of AF. Table 1 summarizes studies on oxidative stress in AF patients and experimental models.

6.1. Animal studies

It has been demonstrated that NOX-dependent superoxide levels and Rac1 expression, as a NOX activator, increased in left atrial appendage (LAA). However, the expression of the other NOX isoforms was unchanged (Dudley et al., 2005). Nevertheless, Adam et al. also illustrated increased Rac1 over-expression in age-dependent AF in mice model that was reversed by statin treatment. These animals exhibited evident cardiac hypertrophy and increased atrial collagen contents (Adam et al., 2007). Pitavastatin, as a drug in statins group, not only reduces left atrial enlargement as well as the occurrence of angiotensin II-induced AF but also diminishes fibrosis and cardiac hypertrophy through decreased Rac1 activity in eNOS null mice (Yagi et al., 2010). In the study of pacing-induced AF in goats, the up-regulation of different ROS-produced pathways likely accounts for early development of AF. In addition, NOX2 and p22phox expression were augmented 2 weeks after AF induction and came back to baseline 6 months later (Reilly et al., 2011). Taken together, the studies described above clearly represent Rac1-dependent NOX activation in AF. The usage of transgenic or knockout animal models on different NOX isoform(s) helps to establish whether particular NOX isoform(s) participate in the pathogenesis of AF.

6.2. Clinical studies

Following animal studies, analysis of human LA myocardium displayed significant increased Rac1 GTPase and NOX activity contrast to those in sinus rhythm (control group) in patients with

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AF (Adam et al., 2007). Likewise, the NOX family enzymes are the primitive source of superoxide production in isolated myocytes or RAA from patients with different forms of AF. The superoxide production was inhibited by using inhibitors and substrates of oxidases (Kim et al., 2005). or was significantly enhanced in postoperative AF (Kim et al., 2008). Similarly, short-term treatment of Atorvastatin debilitates NADPH-driven superoxide, demonstrating NOX activation is dependent on Rac1 subunit in RAA (Antoniades et al., 2012) and increased expression of p22phox (Reilly et al., 2011) in postoperative AF patients. Amongst NOX isoforms in clinical studies, NOX2 and NOX4 are an important role in AF patients. It has been shown that there is a significant correlation between NOX2-driven superoxide as well as NOX2 up-regulation with hypertrophy and myolysis in LAA and RAA of AF patients, implicating NOX2-derived oxidative stress has a possible role in atrial remodeling in AF (Chang et al., 2011). In the cardiac tissues from heart transplant patients, it was found not only NOX4 mRNA expression up-regulated but also the production of NOX4-derived H_2O_2 was significantly increased in LAA tissues of AF patients (Zhang et al., 2012). Similarly, the NOX4 serum levels were markedly higher in the patients with different forms of AF compared to the controls (Liu et al., 2015). Taken together, the studies described above clearly demonstrate the correlation between increased NOX2 and NOX4 levels in different types of AF, offering these isoforms involvement in the pathophysiology of AF.

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7. Modulation of oxidative stress in treatment of AF

The more successful therapeutic approach is targeting upstream pathologies, resulting in the emergence of re-entry or focal activity and abnormalities in ionic currents that prevent or reverse atrial remodeling. One of them for the treatment of arrhythmia is oxidative stress (Sovari, 2016).

The modulation of ROS over-production or down-regulating enzymes that produced ROS such as MPO, NOX, or 'uncoupled' NOS, could be investigated as a novel therapeutic procedure to limit or prevent AF occurrence (Violi et al., 2014) (Figure 2). In addition to direct NOX inhibition, some drugs can be able to reduce NOX subunits phosphorylation, block interaction of subunits together and decrease subunits expression. Interestingly, drugs with mentioned ability are generally used in cardiovascular diseases (Rodiño-Janeiro et al., 2013).

Recently, the search for novel and specific NOX inhibitors continues, and naturally, antioxidants represent another suitable approach. Over the years, attention has altered towards natural products as a considerable source of alternative medicines. It is interesting that natural products have a reputation of strong ability with minimum side effects. In the following, natural components which have NADPH oxidase and ion channel inhibition properties will be described.

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8. Apocynin

Apocynin (4-hydroxy-3-methoxyacetophenone; acetovanillone; APO) (Figure 1), also known as a non-specific NOX inhibitor, is a natural compound structurally related to vanillin. It has been isolated from the variety of plant sources such as *Picrorhiza kurroa* and is being studied for its different pharmacological properties (Virdis et al., 2016). The oxidation of APO is essential to trigger its ability to inhibit NOX. APO require to MPO and anion superoxide to form an APO radical for its activity. Afterward, this molecule oxidizes thiols in the NADPH oxidase structure. Indeed, thiols are important groups for the function of p47phox and as a result, APO prevents NADPH oxidase activation (Ximenes et al., 2007; Johnson et al., 2002). MPO expression is normally very low in a physiological situation in the arterial wall. However, it significantly increases in cardiovascular diseases. Thus, APO is perhaps inactive against normal levels of

NOX activity during physiology condition in the endothelial cell, and should only inhibit excessive NOX2-dependent activity related to vascular inflammation and atherogenesis (Anatoliotakis et al., 2013). In the absence of MPO, APO acts as an antioxidant scavenger (Heumüller et al., 2008). On the other hand, vascular p47phox is utilized by NOX2 but not by NOX4, so APO is likely to be relatively selective for NOX2 over NOX4, and for which there is a superiority of *in vivo* data indicating beneficial actions in vascular diseases (Drummond and Sobey, 2014).

In 1990, it was shown that APO was a potent inhibitor of neutrophil superoxiderelease *in vitro* and had anti-inflammatory activity *in vivo* (Aldieri et al., 2008). As it seems, the mechanisms of APO inhibition are not entirely known. One of these which can contribute to NOX inhibition, include the interfering with the critical two cytosolic subunits, p47phox and p67-phox, inhibit NOX assembly through preventing the p47phox/p67phox phosphorylation or translocation in monocytes, leukocytes and endothelial cells membrane, that is a critical step to the NOX function (Virdis et al., 2016; Ximenes et al., 2007) (Figure 2).

8.1. Apocynin and NOX inhibitory function in different diseases

8.1.1. Non-cardiovascular diseases

APO has significant effects in many cells and organs because of the widespread NOX expression. For instance, in Parkinson's model in rats, it was demonstrated that APO was able to hamper NOX activation and ROS production related to alpha-synuclein (Sharma and Nehru, 2016). Moreover, treatment with APO caused to prolong survival and reduce neurodegeneration in mice models and glial cells (Boillée and Cleveland, 2008; Wu et al., 2006). In the hyperglycemic rat model, the high glucose plasma level promoted the development of blood-

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brain barrier permeability, enhanced tissue plasminogen activator-induced hemorrhage and infarct via increasing superoxide production. Thus, hyperglycemia may aggravate stroke and reperfusion injury. This effect was reversed with APO by reduced superoxide production (Won et al., 2011). APO also prohibited hyperglycemia-induced ROS elevation and myocyte dysfunction (Privratsky et al., 2003).

8.1.2. Cardiovascular diseases

APO also could be effective on NOX activity in experimental cardiovascular diseases. For instance, spontaneously hypertensive rats (SHR) are a genetic model of hypertension that imitates essential hypertension in humans. In SHR model, the chronic administration of APO (6 weeks) reduced systemic oxidative stress and cellular ROS, enhanced NO availability through a direct effect on eNOS expression and also diminished blood pressure. APO not only prevented the development of endothelial dysfunction but also it effectively returned over-expression of NOX2 and its subunit; p47phox to primary levels in the aortic endothelial cells (Perassa et al., 2016). Moreover, in deoxycorticosterone acetate-salt-induced hypertensive rats, treatment with APO significantly inhibited the increase in collagen deposition as well as ROS generation and as a result, arterial stiffness was decreased in the thoracic aorta (Chen et al., 2013). APO also decreased superoxide formation in aortic rings and systolic blood pressure accompanied by a slight decrease of p22phox mRNA expression in mineralocorticoid hypertensive rats (Beswick et al., 2001). APO protected the endothelial cell from the initiating occurrences of atherosclerosis by prevention of NADPH oxidase activity and ROS generation *in vitro* and *in vivo* (Meyer and Schmitt, 2000).

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Moreover, APO is able to participate in arachidonic acid metabolism; inhibits the thromboxane synthase and decrease thromboxane-A_2 or elevate prostaglandin-E_2 levels lead to reduce platelet aggregation. This property may be a benefit effect for patients with the cardiovascular disease like AF who are disposed to thrombosis and thromboembolic phenomena (Engels et al., 1992). Moreover, APO treatment prevented NOX activity and decreased ROS levels in endothelial cells (Holland and Johnson, 1999) and aortic tissues (Xiong et al., 2009). Additionally, APO reduced hypertrophy and fibrosis, ameliorated Left ventricular dysfunction and improved cardiac function in heart failure after myocardial infarction. Moreover, APO diminished oxidative stress by inhibiting NADPH oxidase activity and p47phox protein expression (Qin et al., 2007).

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8.2. Apocynin and ion channel activity

Many studies have been demonstrated that APO also had special effects on ion currents by which were able to promote susceptibility to AF. For instance, NOX2 inhibition with APO normalized the total SR Ca^{2+} content in mouse myocytes and improved the SR calcium handling and contractility (Gonzalez et al., 2014) (Figure 2). Additionally, APO diminished Ca^{2+} accumulation due to rapid atrial pacing (RAP) in rabbit atrial tissues. Attenuating Ca^{2+} accumulation and oxidative stress by means of inhibiting NOX activity may be the underlying mechanism of APO that preventing acute atrial electrical remodeling and decreased the inducibility and duration of AF (Zhang et al., 2014). The voltage-gated potassium channel ($K_{v1.5}$) is more abundantly expressed in the human atrium and contribute to the shortening of atrial APD that causing electrical remodeling in AF. Oxidative stress up-regulated $K_{v1.5}$ channel proteins in urate-induced HL-1 cells. Treatment these cells with APO reversed the ROS effect on $K_{v1.5}$ expression (Maharani et al., 2015) (Figure 2).

8.3. Apocynin in AF

Some previous studies have been shown the effect of APO on AF. APO decreased atrial electrical remodeling and intracellular ROS generation in myocytes induced by RAP, suggesting that this process depend on membrane NADPH oxidase (Tsai et al., 2010). Furthermore, APO not only markedly reduced AF inducibility but also attenuated atrial structural remodeling in diabetic rabbit's model. Moreover, the increased NOX activity and the expression of gp91phox in left atrial tissue were attenuated by APO treatment (Qiu et al., 2016). In RAP pig's model, APO increased NOX activity contributed to anion superoxide production in both the left atrium (LA) and LAA. The NOX activity was 4.4 times enhanced compared to control group in the LAA of pigs with AF (Dudley et al., 2005). Ultimately, according to above studies, it was proposed that APO might be used in both prevention and management of AF.

9. Resveratrol

Resveratrol (*trans*-3,5,4′-trihydroxystilbene; RSV) (Figure 1) is a non-flavonoid natural polyphenolic compound, belonged to the stilbene group, firstly was found in the roots of the medicinal plant *Polygonum cuspidatum*. It is found in numerous plant-based foods and beverages such as grapes, a variety of berries and peanuts (Alamolhodaei et al., 2017). RSV is considered a phytoalexin because of production by the plant under stress conditions (Tomé-Carneiro et al., 2013). Piceatannol is a combination of the stilbene family and has a chemical structure and beneficial effects similar to RSV that is formed by hydroxylated and metabolized RSV via cytochrome P_{450}1B1 (Tang and Chan, 2014).

The antioxidant properties and anti-inflammatory effects of RSV have been widely illustrated. It can also attenuate oxidative stress by induce major cellular antioxidant enzymes like GPx,

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hemeoxygenase, and SOD in vascular and cardiac cells (Thirunavukkarasu et al., 2007) (Figure 2) or inhibit mitochondrial production of ROS in the vasculature (Ungvari et al., 2009).

The protective effects of RSV against oxidative stress injury are likely to be attributed to modify the expression of endogenous antioxidant systems more than the direct ROS scavenger activity (Bradamante et al., 2004). However, it has been demonstrated that RSV effectively blocked H_2O_2 accumulation (Whitehouse et al., 2016). Furthermore, RSV may be effective on NADPH oxidase activity in vascular tissues. It reduced expression of NOX1, NOX2, NOX4 and up-regulated antioxidative enzymes like SOD and GPx in a model of human endothelial and smooth muscle cells (Spanier et al., 2009). On the other hand, RSV also diminished the activity of the NADPH oxidase enzyme complex probably through inhibiting the regulatory subunits translocation; gp91phox and Rac1 (Chow et al., 2007). In the vascular cells, oxidative stress induced senescence through decrease SIRT1 activation, regulate NOX signaling and increase p47phox expression that RSV treatment prevented the decrease of SIRT1 and the enhancement of p47phox expression (Tang et al., 2012) (Figure 2). Similarly, it had been demonstrated that inhibition of SIRT1 induced endothelial dysfunction through up-regulation of p22phox subunit and NOX4 mRNA expression, lead to an increased vascular superoxide production which reversed by RSV treatment (Zarzuelo et al., 2013).

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9.1. Resveratrol and NOX inhibitory function in different diseases

9.1.1. Non-cardiovascular diseases

The different studies illustrated that RSV prevent or slow the progression of a widespread variety of diseases, like ischemic injuries, type 2 diabetes, obesity, and Alzheimer's diseases (Razavi-Azarkhiavi et al., 2016). RSV treatment can prevent from high glucose-induced fibroblast

proliferation and activation through decreased NOX4 and suppression of ROS overproduction in the mice kidneys, suggesting a potential therapeutic agent versus diabetic renal fibrosis (He et al., 2016).

9.1.2 Cardiovascular diseases

It has been represented that RSV had beneficial effects on cardiovascular diseases. RSV reduced plasma triglyceride and cholesterol accumulation and as a result, protected the heart from ischemia-reperfusion injury (Zern et al., 2003). Additionally, RSV caused to reduce the incidence of coronary artery disease and inhibit low-density lipoprotein (LDL) oxidation by which protects the cardiovascular system against atherosclerosis (Magyar et al., 2012). RSV also inhibited hypertrophic cardiac remodeling process through activation of AMP-activated kinase (AMPK) which seems implicated in the development of AF (Chan et al., 2008). Moreover, RSV decreased the prolonged PR and QTc intervals, increased heart rates and reversed sinus arrhythmia. It also restored a normal left ventricular ejection function, improved cardiac output and stroke volume (Vilar-Pereira et al., 2016).

9.2. Resveratrol and ion channel activity

There are accumulated evidences that RSV is effective on various ion channels. RSV can block calcium channels and decrease calcium influx in CA1 area of rat hippocampal slices (Li et al., 2005) and human platelets (Dobrydneva et al., 2002). Moreover, RSV has a plasma glucose lowering effect by I_{KATP} and I_{KV} inhibition and increased insulin secretion in normal rats (Chen et al., 2007). In the models of ouabain-induced, aconitine-induced, and coronary ligation-induced arrhythmias, RSV inhibited I_{Ca} and selectively increased I_{Ks}, as a result, APD became shorter.

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These findings described the cellular results and the dose-dependently antiarrhythmic effect of RSV on animal models (Zhang et al., 2006). Similarly, RSV prevented DAD and triggered activity induced by ouabain, likely due to the decreased calcium influx in papillary muscles (Zhang et al., 2005).

9.3. Resveratrol in AF

The several studies have indicated that RSV has antiarrhythmic effect through ion channels activity. RSV treatment reduced APD by significantly up-regulation of ion channels like $K_v1.5$ (Chong et al., 2015) that is a considerable therapeutic target channel for AF. In this respect, numerous studies have indicated the inhibitory effects of RSV and derivatives such as compound 1 (C1), on Na^+ channels contributed to their antiarrhythmic actions. Inhibition of late I_{Na} by RSV that results in reduced electrical and contractile dysfunction, has appeared as a potential therapeutic plan for the treatment of ischemia-reperfusion damage and AF (Baczkó and Light, 2015) (Figure 2). The piceatannol antiarrhythmic function caused by elongate APD through delaying I_{Na} inactivation in ischemic-reperfusion in rat (Chen et al., 2009).

Moreover, dose-dependent application of RSV attenuated Ca^{2+} transient duration and suppressed H_2O_2-induced EAD-like arrhythmogenic activity. RSV also markedly diminished H_2O_2-induced diastolic Ca^{2+} accumulation and the late Na^+ current in myocytes (Li et al., 2013) and reduced the inward rectifier K^+ currents (Chen et al., 2007). These data support this concept that RSV has electrophysiological properties and antiarrhythmic effect through L-type Ca^{2+} channels and inward Na^+ currents inhibition, K_{ATP} channel opening, prolonged APD and increased cardiac refractory period in animal models that likely decrease the incidence risk of AF, suggesting RSV could be a suitable natural compound for the treatment of chronic AF.

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10. Berberine

Berberine (BBR) (Fig. 1) is a non-basic quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids. It is a traditional natural compound with a bright yellow color isolated from Chinese herbs such as *Berberis vulgaris* and *Coptis chinensis* with multiple pharmacological activities (Hashemzaei et al., 2017). The genus *Berberis* is known as the most popular edible herbal source of BBR. It is extensively distributed throughout these plants. The bark, roots, rhizomes and stems of genus *Berberis* have different amounts of BBR. However, bark and roots are richer compared to other parts (Ahmed et al., 2015).

Several studies have identified various signaling pathways, relating to BBR therapeutic effects. For instance, BBR inhibit VSMCs proliferation and migration through interfering with Akt and ERK signaling pathways and reduce intracellular ROS (Lee et al., 2006). It suppresses oxidative stress and inflammation by means of multiple mechanisms; such as extinguish superoxide anions and nitric oxide formation and also scavenger activity against the reactive peroxynitrite and hydroxyl radicals (Figure 2). Moreover, BBR increase the activity of SOD in lipopolysaccharide-stimulated murine macrophages and diminish the intracellular superoxide anions (Ahmed et al., 2015). Similarly, BBR effectively prevent NADPH oxidase-mediated intracellular superoxide anions production in the LPS stimulated macrophages by attenuating the expression level of gp91phox subunit (Sarna et al., 2010).

10.1 . Berberine and NOX inhibitory function in different diseases

10.1.1. Non-cardiovascular diseases

BBR with 3000 years long history widely used as a folk medicine. It is able to the treatment of jaundice, dysentery, diarrhea, and is a potent antimicrobial, anti-infective agent against different

fungal, yeast, parasite, protozoa and viral infections (Ahmed et al., 2015). Likewise, clinical investigations highlighted that BBR had significant antihypertensive, antiarrhythmic, antidiabetic, cardioprotective and hypolipidemic effects. Other clinical studies have well established the antioxidant properties of BBR in the various diseases like diabetes, inflammatory conditions and CNS disorders like Alzheimer and cerebral ischemia (Kumar et al., 2015). In inflammatory condition, ROS production is stimulated by over-expression of NOX 2/4 and BBR can suppress this process (Sarna et al., 2010). BBR can also protect CA1 pyramidal neurons against ischemia-induced brain damage through block I_{to} and I_K in a concentration-dependent manner (Wang et al., 2004). Moreover, it has been shown that BBR could be effective on diabetic endothelial dysfunction. For instance, BBR significantly diminished fasting blood glucose, triglyceride levels, NOX4 protein expression and on the contrary, increased protein expression of eNOS, suggesting improved endothelium-dependent vasorelaxation impaired in the thoracic aorta from diabetic rats (Wang et al., 2009).

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10.1.2. Cardiovascular diseases

Furthermore, BBR exhibited the numerous useful cardiovascular pharmacological effects in different conditions such as myocardial ischemia, hypertension, atherosclerosis, and thrombosis, so that has long been considered as a promising antiarrhythmic drug (Imanshahidi and Hosseinzadeh, 2008). In HUVECs cultured, BBR reduced ROS production and decreased expression of NOX4 in cells which treated with free fatty acids (FFA) by AMPK activation as an important inhibitor of NOX enzyme (Zhang et al., 2013). BBR also protected the cardiac cellular membrane from interference by hydroxyl radicals and intracellular calcium overload via stimulating NCX (Lau et al., 2001).

10.2. Berberine and ion channel activity

It had been shown that oral administration of BBR attenuated ischemia-induced arrhythmias. Actually, BBR remarkably reduced the prolonged QTc interval and also restored the diminished I_{to} and I_{Ca} currents (Wang et al., 2012) or inhibited K_{ATP} channel activation in cardiac myocytes (Wang et al., 1996). Additionally, BBR blocked I_{Kr} at concentrations of 0.3-30 μM and in higher dose inhibited I_{to} (Sánchez-Chapula, 1996) (Figure 2). Raisanberine (RS), a derivative of BBR, presumably suppressed the calcium influx through L-type Ca^{2+} channels and inhibited NOX activity in the pulmonary arteriole and cardiac cells (Li et al., 2008).

8-Oxoberberine (JKL1073A), a synthetic derivative of berberine, has also an antiarrhythmic activity similar to BBR. It was able to change ouabain-induced arrhythmia in atria isolated from guinea-pig and ischemia-reperfusion-induced arrhythmia in isolated from rat. Furthermore, JKL1073A demonstrated positive inotropic and negative chronotropic actions on rat atrial preparations. It increased atrial contractility and prolonged APD through strong I_{to} blocking activity in a voltage-dependent manner and weak I_{KI} blocking (Chi et al., 1996). JKL1073A also diminished the maximal rate of AP upstroke via the suppressed effects on I_{Na} in rat and human cardiac myocytes contribute partially to its antiarrhythmic activity (Chi et al., 1997). Taken together, it is hypothesized that BBR as a specific K^+ channel blocker, may be a novel therapeutic medication and will play a more important role for the AF treatment.

10.3. Berberine in AF

Previous studies have revealed that BBR possessed positive inotropic, antiarrhythmic and vasodilator properties and may significantly prolonged APD (Rodriguez-Menchaca et al., 2006). The BBR antiarrhythmic effects that occurred via the APD prolongation, due to prevent a great

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many of ion currents. BBR suppressed acetylcholine-induced AF through prolonged APD in atrial rabbit myocytes and increased atrial effective refractory period. Importantly, BBR also lengthened the RR interval and ERP. As a result, BBR treatment leads to the termination of the acetylcholine-induced AF (Zhou et al., 2015). The study on arrhythmic patients showed that treatment of patients with BBR for 1--4 weeks significantly caused to decrease premature beats (Yao et al., 2015).

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11. Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] (Figure 1) is the main natural polyphenolic yellow pigment found in the Indian turmeric root (*Curcuma longa* and others *Curcuma* spp.) (Razavi-Azarkhiavi et al., 2016). Turmeric is a perennial plant belonging to the Zingiberaceae family that contains a wide variety of phytochemical compounds, is widely used as a spice in food or additive composition in cosmetics, and also herbal medicine for a long time. Curcumin is an important bioactive ingredient, derived from the rhizome of turmeric plants (Sarkar et al., 2016).

Curcumin is a sparingly water soluble molecule with a lipophilic structure composed of two aromatic rings which connected by two unsaturated carbonyl groups. In the middle of the molecule, two hydroxyl groups involve in hydrogen bond formation and subsequently, the molecule stabilizes. This part of curcumin structure is an important functional site relating to the free radical scavenger properties and other biological activities (Sarkar et al., 2016) (Figure 2). Because of lipophilic property, it is assumed that this compound accumulates in biological membranes and disturbs proteins especially subunits of NOX which are located in the plasma membrane (Ingolfsson et al., 2007). Curcumin rapidly enter the cells and interact with their

membrane, lead to inhibit the superoxide production via preventing the assembly of NOX subunits when added before NOX activation (Derochette et al., 2013).

Moreover, the cells pretreatment with curcumin markedly reduced angiotensin II-mediated ROS generation, the different NOX subunits (p22phox and p40phox) and NF-κB expression in cardiomyocytes (Kang et al., 2010) (Figure 2). Furthermore, curcumin treatment leads to decrease intracellular ROS production through inhibition of LPS-induced p47phox over-expression in a dose-dependent manner in VSMCs (Meng et al., 2013) or prevent phosphorylation of NOX subunits via reducing PKC expression (Soetikno et al., 2011).

11.1. Curcumin and NOX inhibitory function in different diseases

11.1.1. Non-cardiovascular diseases

In traditional East Asian medicine, curcumin has been used to treat a diversity of diseases. More studies had confirmed that curcumin has a direct antioxidant property by scavenging free radicals (Sarkar et al., 2016) and may function indirectly as an antioxidant through augmenting the activity of enzymes such as SOD, glutathione S-transferase (GST), catalase and GSH (Kapakos et al., 2012).

In diabetes-induced vascular inflammation, curcumin reduced leukocyte-endothelium interaction, decreased ROS overproduction, and inhibited ICAM-1 and NOX2 especially p47phox expression (Wongeakin et al., 2014) (Figure 2). Curcumin treatment had a protective effect against cisplatin-induced fibrosis through reduce NADPH oxidase subunits levels; p47phox and gp91phox and prevent tubular superoxide production (Trujillo et al., 2016). In streptozotocin-induced diabetic neuropathy rat's model, has been reported that treatment with

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curcumin or apocynin significantly reversed up-regulation of gp91phox and p47phox and inhibited the spinal NADPH oxidases activity (Zhao et al., 2014).

11.1.2. Cardiovascular diseases

More evidences showed the protective effects of curcumin upon cardiovascular pathologies, such as atherosclerosis, cardiac hypertrophy, hypertension, vascular dysfunction and heart failure (Kapakos et al., 2012). In cardioprotective effects related to oxidative stress, curcumin decreased p47phox subunit and superoxide generation, diminished oxidative stress and improved vascular dysfunction in hypertensive rats (Boonla et al., 2014). Moreover, it attenuated the expansion of hypertension in L-NAME-induced hypertensive rats by the increase in endothelial eNOS and GSH levels, and diminishes of oxidative stress (Kapakos et al., 2012). Curcumin intake might decrease the risk of coronary heart disease. The different concentrations of curcumin attenuated MI-induced oxidative stress and caused to enhance the antioxidant enzymes activities (SOD, CAT, and GPx) (Liu et al., 2017). Additionally, treatment with curcumin considerably suppressed the enhanced activity of Rac1, as well as the increased expression of gp91phox and p47phox in cardiomyocytes in diabetic cardiomyopathy model (Yu et al., 2016) (Figure 2). The dietary curcumin supplementation improved age-related large elastic artery stiffening and also vascular endothelial dysfunction. In animals, was observed greater superoxide production and NADPH oxidase p67 subunit expression versus lower SOD levels which were reversed with curcumin (Fleenor et al., 2013).

11.2. Curcumin and ion channel activity

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Several studies focused on inhibitory effects of curcumin which resulted in block ion channels in cardiovascular cells. Curcumin decreased the K_v currents in a dose-dependent manner in rabbit coronary arterial smooth muscle cells (Son et al., 2013). Moreover, it has been shown that curcumin inhibited hERG K^+ currents in HEK293 cells. Inhibition of these channels leads to prolong cardiac repolarization and hence, hERG K^+ channels can be considered as the therapeutic targets for antiarrhythmic agents (Hu et al., 2012). Although precise studies in association with AF are not available, curcumin may be used as a therapeutic and protective agent to relieve AF through reduced superoxide generation, decrease in NADPH oxidase activity and also inhibit ion currents which contribute to the pathophysiology of AF and thus, deserve further investigation in the clinical practice.

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13. Conclusion

In atrial fibrillation, complicated conditions are created that lead to difficult cure. The use of modern medications in some patients cause to drug resistance and also side effects. Therefore, novel treatments can replace to current medications. It is clear that natural compounds are able to open new horizons in the prevention or treatment of cardiovascular diseases such as AF. Natural compounds like apocynin, resveratrol, berberine, and curcumin can play an important role in upstream therapy through reduction of ROS formation; as an important risk factor for AF.

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15. Conflict of interest

The authors declared no conflict of interest.

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16. References

Adam, O., Frost, G., Custodis, F., Sussman, M. A., Schäfers, H.-J., Böhm, M. and Laufs, U. (2007). Role of Rac1 GTPase activation in atrial fibrillation. *Journal of the American College of Cardiology.* **50**: 359--367.

Ago, T., Kuroda, J., Pain, J., Fu, C., Li, H. and Sadoshima, J. (2010). Upregulation of Nox4 by hypertrophic stimuli promotes apoptosis and mitochondrial dysfunction in cardiac myocytes. *Circulation research.* **106**: 1253--1264.

Ahmed, T., Abdollahi, M., Daglia, M., Nabavi, S. F. and Nabavi, S. M. (2015). Berberine and neurodegeneration: A review of literature. *Pharmacological Reports.* **67**: 970--979.

Alamolhodaei, N. S., Tsatsakis, A. M., Ramezani, M., Hayes, A. W. and Karimi, G. (2017). Resveratrol as MDR reversion molecule in breast cancer: An overview. *Food and Chemical Toxicology.* **103**: 223--232.

Aldieri, E., Riganti, C., Polimeni, M., Gazzano, E., Lussiana, C., Campia, I. and Ghigo, D. (2008). Classical inhibitors of NOX NAD (P) H oxidases are not specific. *Current drug metabolism.* **9**: 686--696.

Anatoliotakis, N., Deftereos, S., Bouras, G., Giannopoulos, G., Tsounis, D., Angelidis, C., Kaoukis, A. and Stefanadis, C. (2013). Myeloperoxidase: expressing inflammation and oxidative stress in cardiovascular disease. *Current topics in medicinal chemistry.* **13**: 115--138.

Antoniades, C., Demosthenous, M., Reilly, S., Margaritis, M., Zhang, M.-H., Antonopoulos, A., Marinou, K., Nahar, K., Jayaram, R. and Tousoulis, D. (2012). Myocardial redox state

predicts in-hospital clinical outcome after cardiac surgery: Effects of short-term pre-operative statin treatment. *Journal of the American College of Cardiology*. **59**: 60--70.

Babusikova, E., Kaplan, P., Lehotsky, J., Jesenak, M. and Dobrota, D. (2004). Oxidative modification of rat cardiac mitochondrial membranes and myofibrils by hydroxyl radicals. *General physiology and biophysics.* **23**: 327--336.

Baczkó, I. and Light, P. E. (2015). Resveratrol and derivatives for the treatment of atrial fibrillation. *Annals of the New York Academy of Sciences.* **1348**: 68--74.

Bendall, J. K., Cave, A. C., Heymes, C., Gall, N. and Shah, A. M. (2002). Pivotal role of a gp91phox-containing NADPH oxidase in angiotensin II-induced cardiac hypertrophy in mice. *Circulation*. **105**: 293--296.

Beswick, R. A., Dorrance, A. M., Leite, R. and Webb, R. C. (2001). NADH/NADPH oxidase and enhanced superoxide production in the mineralocorticoid hypertensive rat. *Hypertension.* **38**: 1107--1111.

Boillée, S. and Cleveland, D. W. (2008). Revisiting oxidative damage in ALS: microglia, Nox, and mutant SOD1. *The Journal of clinical investigation.* **118**: 474--478.

Boonla, O., Kukongviriyapan, U., Pakdeechote, P., Kukongviriyapan, V., Pannangpetch, P., Prachaney, P. and Greenwald, S. E. (2014). Curcumin improves endothelial dysfunction and vascular remodeling in 2K-1C hypertensive rats by raising nitric oxide availability and reducing oxidative stress. *Nitric Oxide.* **42**: 44--53.

Bradamante, S., Barenghi, L. and Villa, A. (2004). Cardiovascular protective effects of resveratrol. *Cardiovascular Therapeutics.* **22**: 169--188.

Downloaded by [University of Cambridge] at 22:17 19 September 2017

ACCEPTED MANUSCRIPT

Chan, A. Y., Dolinsky, V. W., Soltys, C.-L. M., Viollet, B., Baksh, S., Light, P. E. and Dyck, J. R. (2008). Resveratrol inhibits cardiac hypertrophy via AMP-activated protein kinase and Akt. *Journal of Biological Chemistry.* **283**: 24194--24201.

Chang, J.-P., Chen, M.-C., Liu, W.-H., Yang, C.-H., Chen, C.-J., Chen, Y.-L., Pan, K.-L., Tsai, T.-H. and Chang, H.-W. (2011). Atrial myocardial nox2 containing NADPH oxidase activity contribution to oxidative stress in mitral regurgitation: potential mechanism for atrial remodeling. *Cardiovascular Pathology.* **20**: 99--106.

Chen, Q.-Z., Han, W.-Q., Chen, J., Zhu, D.-L. and Gao, P.-J. (2013). Anti-stiffness effect of apocynin in deoxycorticosterone acetate-salt hypertensive rats via inhibition of oxidative stress. *Hypertension Research.* **36**: 306--312.

Chen, W. P., Hung, L. M., Hsueh, C. H., Lai, L. P. and Su, M. J. (2009). Piceatannol, a derivative of resveratrol, moderately slows INa inactivation and exerts antiarrhythmic action in ischaemia-reperfused rat hearts. *British journal of pharmacology.* **157**: 381--391.

Chen, W.-P., Chi, T.-C., Chuang, L.-M. and Su, M.-J. (2007). Resveratrol enhances insulin secretion by blocking K ATP and K V channels of beta cells. *European journal of pharmacology.* **568**: 269--277.

Chen, W.-P., Su, M.-J. and Hung, L.-M. (2007). In vitro electrophysiological mechanisms for antiarrhythmic efficacy of resveratrol, a red wine antioxidant. *European journal of pharmacology.* **554**: 196--204.

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 ACCEPTED MANUSCRIPT

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Chi, J. F., Chu, S. H., Lee, C. S., Chou, N. K. and Su, M. J. (1996). Mechanical and electrophysiological effects of 8-oxoberberine (JKL1073A) on atrial tissue. *British journal of pharmacology.* **118**: 503--512.

Chi, J.-F., Chu, S.-H., Lee, C.-S. and Su, M.-J. (1997). Effects of 8-oxoberberine on sodium current in rat ventricular and human atrial myocytes. *The Canadian journal of cardiology.* **13**: 1103--1110.

Chong, E., Chang, S.-L., Hsiao, Y.-W., Singhal, R., Liu, S.-H., Leha, T., Lin, W.-Y., Hsu, C.-P., Chen, Y.-C. and Chen, Y.-J. (2015). Resveratrol, a red wine antioxidant, reduces atrial fibrillation susceptibility in the failing heart by PI3K/AKT/eNOS signaling pathway activation. *Heart Rhythm.* **12**: 1046--1056.

Chow, S.-E., Hshu, Y.-C., Wang, J.-S. and Chen, J.-K. (2007). Resveratrol attenuates oxLDL-stimulated NADPH oxidase activity and protects endothelial cells from oxidative functional damages. *Journal of Applied Physiology.* **102**: 1520--1527.

Derochette, S., Franck, T., Mouithys-Mickalad, A., Ceusters, J., Deby-Dupont, G., Lejeune, J.-P., Neven, P. and Serteyn, D. (2013). Curcumin and resveratrol act by different ways on NADPH oxidase activity and reactive oxygen species produced by equine neutrophils. *Chemico-biological interactions.* **206**: 186--193.

Dobrydneva, Y., Williams, R. L., Morris, G. Z. and Blackmore, P. F. (2002). Dietary phytoestrogens and their synthetic structural analogues as calcium channel blockers in human platelets. *Journal of cardiovascular pharmacology.* **40**: 399--410.

Drummond, G. R. and Sobey, C. G. (2014). Endothelial NADPH oxidases: which NOX to target in vascular disease? *Trends in Endocrinology & Metabolism.* **25**: 452--463.

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 ACCEPTED MANUSCRIPT

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Dudley, S. C., Hoch, N. E., McCann, L. A., Honeycutt, C., Diamandopoulos, L., Fukai, T., Harrison, D. G., Dikalov, S. I. and Langberg, J. (2005). Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage. *Circulation.* **112**: 1266--1273.

Engels, F., Renirie, B. F., A't Hart, B., Labadie, R. P. and Nijkamp, F. P. (1992). Effects of apocynin, a drug isolated from the roots of Picrorhiza kurroa, on arachidonic acid metabolism. *FEBS letters.* **305**: 254--256.

Fleenor, B. S., Sindler, A. L., Marvi, N. K., Howell, K. L., Zigler, M. L., Yoshizawa, M. and Seals, D. R. (2013). Curcumin ameliorates arterial dysfunction and oxidative stress with aging. *Experimental gerontology.* **48**: 269--276.

Gonzalez, D. R., Treuer, A. V., Lamirault, G., Mayo, V., Cao, Y., Dulce, R. A. and Hare, J. M. (2014). NADPH oxidase-2 inhibition restores contractility and intracellular calcium handling and reduces arrhythmogenicity in dystrophic cardiomyopathy. *American Journal of Physiology-Heart and Circulatory Physiology.* **307**: H710-H721.

Hashemzaei, M., Heravi, R. E., Rezaee, R., Roohbakhsh, A. and Karimi, G. (2017). Regulation of autophagy by some natural products as a potential therapeutic strategy for cardiovascular disorders. *European journal of pharmacology.* **802**: 44--51.

He, T., Xiong, J., Nie, L., Yu, Y., Guan, X., Xu, X., Xiao, T., Yang, K., Liu, L. and Zhang, D. (2016). Resveratrol inhibits renal interstitial fibrosis in diabetic nephropathy by regulating AMPK/NOX4/ROS pathway. *Journal of Molecular Medicine.* **94**: 1359--1371.

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ACCEPTED MANUSCRIPT

Heijman, J., Voigt, N., Nattel, S. and Dobrev, D. (2014). Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. *Circulation research.* **114**: 1483--1499.

Heumüller, S., Wind, S., Barbosa-Sicard, E., Schmidt, H. H., Busse, R., Schröder, K. and Brandes, R. P. (2008). Apocynin is not an inhibitor of vascular NADPH oxidases but an antioxidant. *Hypertension.* **51**: 211--217.

Holland, J. A. and Johnson, D. K. (1999). Prevention of atherosclerosis using NADPH oxidase inhibitors. *Google Patents.*

Hu, C.-W., Sheng, Y., Zhang, Q., Liu, H.-B., Xie, X., Ma, W.-C., Huo, R. and Dong, D.-L. (2012). Curcumin inhibits hERG potassium channels in vitro. *Toxicology letters.* **208**: 192--196.

Imanshahidi, M. and Hosseinzadeh, H. (2008). Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. *Phytotherapy research.* **22**: 999--1012.

Ingolfsson, H. I., Koeppe, R. E. and Andersen, O. S. (2007). Curcumin is a modulator of bilayer material properties. *Biochemistry.* **46**: 10384--10391.

Johnson, D. K., Schillinger, K. J., Kwait, D. M., Hughes, C. V., McNamara, E. J., Ishmael, F., O'Donnell, R. W., Chang, M.-M., Hogg, M. G. and Dordick, J. S. (2002). Inhibition of NADPH oxidase activation in endothelial cells by ortho-methoxy-substituted catechols. *Endothelium.* **9**: 191--203.

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Kang, B.-Y., Khan, J. A., Ryu, S., Shekhar, R., Seung, K.-B. and Mehta, J. L. (2010). Curcumin reduces angiotensin II-mediated cardiomyocyte growth via LOX-1 inhibition. *Journal of cardiovascular pharmacology*. **55**: 176--183.

Kapakos, G., Youreva, V. and Srivastava, A. K. (2012). Cardiovascular protection by curcumin: molecular aspects. *Indian Journal of Biochemistry & Biophysics*. **49**: 306--15.

Kim, Y. H., Lee, J. H., Shim, W. J., Ro, Y. M., Park, G. H., Becker, K. G., Cho-Chung, Y. S. and Kim, M.-k. (2003). Gene expression profiling of oxidative stress on atrial fibrillation in humans. *Experimental & molecular medicine*. **35**: 336.

Kim, Y. M., Guzik, T. J., Zhang, Y. H., Zhang, M. H., Kattach, H., Ratnatunga, C., Pillai, R., Channon, K. M. and Casadei, B. (2005). A myocardial Nox2 containing NAD (P) H oxidase contributes to oxidative stress in human atrial fibrillation. *Circulation research*. **97**: 629--636.

Kim, Y. M., Kattach, H., Ratnatunga, C., Pillai, R., Channon, K. M. and Casadei, B. (2008). Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. *Journal of the American College of Cardiology*. **51**: 68--74.

Kumar, A., Chopra, K., Mukherjee, M., Pottabathini, R. and Dhull, D. K. (2015). Current knowledge and pharmacological profile of berberine: an update. *European journal of pharmacology*. **761**: 288--297.

Lambeth, J. D. (2004). NOX enzymes and the biology of reactive oxygen. *Nature Reviews Immunology*. **4**: 181--189.

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Lau, C. W., Yao, X. Q., Chen, Z. Y., Ko, W. H. and Huang, Y. (2001). Cardiovascular actions of berberine. *Cardiovascular Drug Reviews.* **19**: 234--244.

Lee, S., Lim, H.-J., Park, H.-Y., Lee, K.-S., Park, J.-H. and Jang, Y. (2006). Berberine inhibits rat vascular smooth muscle cell proliferation and migration in vitro and improves neointima formation after balloon injury in vivo: berberine improves neointima formation in a rat model. *Atherosclerosis.* **186**: 29--37.

Li, M., Wang, Q., Chen, Y., Wang, Z., Liu, Z. and Guo, S. (2005). Resveratrol inhibits neuronal discharges in rat hippocampal CA1 area. *Acta Physiologica Sinica.* **57**: 355.

Li, N., Yang, L., Dai, D. Z., Wang, Q. J. and Dai, Y. (2008). Chiral separation of racemate CPU86017, an anti-arrhythmic agent, produces stereoisomers possessing favourable ion channel blockade and less α-adrenoceptor antagonism. *Clinical and Experimental Pharmacology and Physiology.* **35**: 643--650.

Li, W., Wang, Y.-p., Gao, L., Zhang, P.-p., Zhou, Q., Xu, Q.-f., Zhou, Z.-w., Guo, K., Chen, R.-h. and Yang, H.-t. (2013). Resveratrol protects rabbit ventricular myocytes against oxidative stress-induced arrhythmogenic activity and Ca2+ overload. *Acta Pharmacologica Sinica.* **34**: 1164--1173.

Liu, H., Wang, C., Qiao, Z. and Xu, Y. (2017). Protective effect of curcumin against myocardium injury in ischemia reperfusion rats. *Pharmaceutical biology.* **55**: 1144--1148.

Liu, T., Shao, Q., Korantzopoulos, P., Liu, E., Xu, G. and Li, G. (2015). Serum levels of nicotinamide‐adenine dinucleotide phosphate oxidase 4 are associated with non‐valvular atrial fibrillation. *Biomedical reports.* **3**: 864--868.

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ACCEPTED MANUSCRIPT

Magyar, K., Halmosi, R., Palfi, A., Feher, G., Czopf, L., Fulop, A., Battyany, I., Sumegi, B., Toth, K. and Szabados, E. (2012). Cardioprotection by resveratrol: A human clinical trial in patients with stable coronary artery disease. *Clinical hemorheology and microcirculation.* **50**: 179--187.

Maharani, N., Ting, Y. K., Cheng, J., Hasegawa, A., Kurata, Y., Li, P., Nakayama, Y., Ninomiya, H., Ikeda, N. and Morikawa, K. (2015). Molecular mechanisms underlying urate-induced enhancement of Kv1. 5 channel expression in HL-1 atrial myocytes. *Circulation Journal.* **79**: 2659--2668.

Martyn, K. D., Frederick, L. M., von Loehneysen, K., Dinauer, M. C. and Knaus, U. G. (2006). Functional analysis of Nox4 reveals unique characteristics compared to other NADPH oxidases. *Cellular signalling.* **18**: 69--82.

Meng, Z., Yan, C., Deng, Q., Gao, D.-f. and Niu, X.-l. (2013). Curcumin inhibits LPS-induced inflammation in rat vascular smooth muscle cells in vitro via ROS-relative TLR4-MAPK/NF-κB pathways. *Acta Pharmacologica Sinica.* **34**: 901--911.

Meyer, J. W. and Schmitt, M. E. (2000). A central role for the endothelial NADPH oxidase in atherosclerosis. *FEBS letters.* **472**: 1--4.

Nattel, S., Burstein, B. and Dobrev, D. (2008). Atrial remodeling and atrial fibrillation. *Circulation: Arrhythmia and Electrophysiology.* **1**: 62--73.

Nattel, S. and Dobrev, D. (2016). Electrophysiological and molecular mechanisms of paroxysmal atrial fibrillation. *Nature Reviews Cardiology.* **13**: 575–590.

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 ACCEPTED MANUSCRIPT

Nattel, S. and Harada, M. (2014). Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *Journal of the American College of Cardiology.* **63**: 2335--2345.

Perassa, L. A., Graton, M. E., Potje, S. R., Troiano, J. A., Lima, M. S., Vale, G. T., Pereira, A. A., Nakamune, A. C. M., Sumida, D. H. and Tirapelli, C. R. (2016). Apocynin reduces blood pressure and restores the proper function of vascular endothelium in SHR. *Vascular Pharmacology.* **87**: 38--48.

Piccini, J. P., Hammill, B. G., Sinner, M. F., Jensen, P. N., Hernandez, A. F., Heckbert, S. R., Benjamin, E. J. and Curtis, L. H. (2012). Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circulation: Cardiovascular Quality and Outcomes.* **5**: 85--93.

Privratsky, J. R., Wold, L. E., Sowers, J. R., Quinn, M. T. and Ren, J. (2003). AT1 blockade prevents glucose-induced cardiac dysfunction in ventricular myocytes. *Hypertension.* **42**: 206--212.

Qin, F., Simeone, M. and Patel, R. (2007). Inhibition of NADPH oxidase reduces myocardial oxidative stress and apoptosis and improves cardiac function in heart failure after myocardial infarction. *Free radical biology and medicine.* **43**: 271--281.

Qiu, J., Zhao, J., Li, J., Liang, X., Yang, Y., Zhang, Z., Zhang, X., Fu, H., Korantzopoulos, P. and Liu, T. (2016). NADPH oxidase inhibitor apocynin prevents atrial remodeling in alloxan-induced diabetic rabbits. *International Journal of Cardiology.* **221**: 812--819.

Downloaded by [University of Cambridge] at 22:17 19 September 2017

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Razavi-Azarkhiavi, K., Iranshahy, M., Sahebkar, A., Shirani, K. and Karimi, G. (2016). The Protective Role of Phenolic Compounds Against Doxorubicin-induced Cardiotoxicity: A Comprehensive Review. *Nutrition and Cancer*. **68**: 892--917.

Reilly, S. N., Jayaram, R., Nahar, K., Antoniades, C., Verheule, S., Channon, K. M., Alp, N. J., Schotten, U. and Casadei, B. (2011). Atrial Sources of Reactive Oxygen Species Vary With the Duration and Substrate of Atrial Fibrillation Clinical Perspective. *Circulation.* **124**: 1107--1117.

Rodiño-Janeiro, B. K., Paradela-Dobarro, B., Castiñeiras-Landeira, M. I., Raposeiras-Roubín, S., González-Juanatey, J. R. and Álvarez, E. (2013). Current status of NADPH oxidase research in cardiovascular pharmacology. *Vascular Health and Risk Management.* **9**: 401--428.

Rodriguez-Menchaca, A., Ferrer-Villada, T., Lara, J., Fernandez, D., Navarro-Polanco, R. A. and Sanchez-Chapula, J. A. (2006). Block of HERG channels by berberine: mechanisms of voltage-and state-dependence probed with site-directed mutant channels. *Journal of cardiovascular pharmacology*. **47**: 21--29.

Sánchez-Chapula, J. (1996). Increase in action potential duration and inhibition of the delayed rectifier outward current IK by berberine in cat ventricular myocytes. *British journal of pharmacology*. **117**: 1427--1434.

Sarkar, A., De, R. and Mukhopadhyay, A. K. (2016). Curcumin as a potential therapeutic candidate for Helicobacter pylori associated diseases. *World journal of gastroenterology*. **22**: 2736.

Downloaded by [University of Cambridge] at 22:17 19 September 2017

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Sarna, L. K., Wu, N., Hwang, S.-Y., Siow, Y. L. and O, K. (2010). Berberine inhibits NADPH oxidase mediated superoxide anion production in macrophages. *Canadian journal of physiology and pharmacology*. **88**: 369--378.

Sharma, N. and Nehru, B. (2016). Apocyanin, a Microglial NADPH Oxidase Inhibitor Prevents Dopaminergic Neuronal Degeneration in Lipopolysaccharide-Induced Parkinson's Disease Model. *Molecular neurobiology*. **53**: 3326--3337.

Shimoni, Y., Hunt, D., Chuang, M., Chen, K., Kargacin, G. and Severson, D. (2005). Modulation of potassium currents by angiotensin and oxidative stress in cardiac cells from the diabetic rat. *The Journal of Physiology*. **567**: 177--190.

Sirker, A., Zhang, M. and Shah, A. M. (2011). NADPH oxidases in cardiovascular disease: insights from in vivo models and clinical studies. *Basic research in cardiology*. **106**: 735--747.

Soetikno, V., Watanabe, K., Sari, F. R., Harima, M., Thandavarayan, R. A., Veeraveedu, P. T., Arozal, W., Sukumaran, V., Lakshmanan, A. P. and Arumugam, S. (2011). Curcumin attenuates diabetic nephropathy by inhibiting PKC-α and PKC-β1 activity in streptozotocin-induced type I diabetic rats. *Molecular nutrition & food research*. **55**: 1655--1665.

Son, Y. K., Choi, I.-W. and Park, W. S. (2013). The inhibitory effect of curcumin on voltage-dependent K+ channels in rabbit coronary arterial smooth muscle cells. *Biochemical and biophysical research communications*. **430**: 307--312.

Sovari, A. and Dudley, S. (2010). Atrial fibrillation and oxidative stress. *Studies on cardiovascular disorders*. **1**: 373--389.

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Sovari, A. A. (2016). Cellular and molecular mechanisms of arrhythmia by oxidative stress. *Cardiology research and practice.* **2016**: 9656078.

Spanier, G., Xu, H., Xia, N., Tobias, S., Deng, S., Wojnowski, L., Forstermann, U. and Li, H. (2009). Resveratrol reduces endothelial oxidative stress by modulating the gene expression of superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPx1) and NADPH oxidase subunit (Nox4). *J Physiol Pharmacol.* **60**: 111--116.

Tang, Y., Xu, J., Qu, W., Peng, X., Xin, P., Yang, X., Ying, C., Sun, X. and Hao, L. (2012). Resveratrol reduces vascular cell senescence through attenuation of oxidative stress by SIRT1/NADPH oxidase-dependent mechanisms. *The Journal of nutritional biochemistry.* **23**: 1410--1416.

Tang, Y. L. and Chan, S. W. (2014). A review of the pharmacological effects of piceatannol on cardiovascular diseases. *Phytotherapy research.* **28**: 1581--1588.

Thirunavukkarasu, M., Penumathsa, S. V., Koneru, S., Juhasz, B., Zhan, L., Otani, H., Bagchi, D., Das, D. K. and Maulik, N. (2007). Resveratrol alleviates cardiac dysfunction in streptozotocin-induced diabetes: Role of nitric oxide, thioredoxin, and heme oxygenase. *Free Radical Biology and Medicine.* **43**: 720--729.

Tomé-Carneiro, J., Gonzálvez, M., Larrosa, M., Yáñez-Gascón, M. J., García-Almagro, F. J., Ruiz-Ros, J. A., Tomás-Barberán, F. A., García-Conesa, M. T. and Espín, J. C. (2013). Resveratrol in primary and secondary prevention of cardiovascular disease: a dietary and clinical perspective. *Annals of the New York Academy of Sciences.* **1290**: 37--51.

Trujillo, J., Molina-Jijón, E., Medina-Campos, O. N., Rodríguez-Muñoz, R., Reyes, J. L., Loredo, M. L., Barrera-Oviedo, D., Pinzón, E., Rodríguez-Rangel, D. S. and Pedraza-

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Chaverri, J. (2016). Curcumin prevents cisplatin-induced decrease in the tight and adherens junctions: relation to oxidative stress. *Food & function.* **7**: 279--293.

Tsai, C.-T., Tseng, C.-D., Hwang, J.-J., Wu, C.-K., Yu, C.-C., Wang, Y.-C., Chen, W.-P., Lai, L.-P., Chiang, F.-T. and Lin, J.-L. (2010). Tachycardia of atrial myocytes induces collagen expression in atrial fibroblasts through transforming growth factor β1. *Cardiovascular research.* **89**: 805--815.

Ungvari, Z., Labinskyy, N., Mukhopadhyay, P., Pinto, J. T., Bagi, Z., Ballabh, P., Zhang, C., Pacher, P. and Csiszar, A. (2009). Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. *American Journal of Physiology-Heart and Circulatory Physiology.* **297**: H1876-H1881.

Vilar-Pereira, G., Carneiro, V. C., Mata-Santos, H., Vicentino, A. R., Ramos, I. P., Giarola, N. L., Feijó, D. F., Meyer-Fernandes, J. R., Paula-Neto, H. A. and Medei, E. (2016). Resveratrol Reverses Functional Chagas Heart Disease in Mice. *PLoS Pathog.* **12**: e1005947.

Violi, F., Pastori, D., Pignatelli, P. and Loffredo, L. (2014). Antioxidants for prevention of atrial fibrillation: a potentially useful future therapeutic approach? A review of the literature and meta-analysis. *Europace.* **16**: 1107--1116.

Virdis, A., Gesi, M. and Taddei, S. (2016). Impact of apocynin on vascular disease in hypertension. *Vascular Pharmacology.* **87**: 1--5.

Vlachos, K., Letsas, K. P., Korantzopoulos, P., Liu, T., Georgopoulos, S., Bakalakos, A., Karamichalakis, N., Xydonas, S., Efremidis, M. and Sideris, A. (2016). Prediction of

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atrial fibrillation development and progression: Current perspectives. *World journal of cardiology*. **8**: 267.

Wang, C., Li, J., Lv, X., Zhang, M., Song, Y., Chen, L. and Liu, Y. (2009). Ameliorative effect of berberine on endothelial dysfunction in diabetic rats induced by high-fat diet and streptozotocin. *European journal of pharmacology*. **620**: 131--137.

Wang, F., Zhao, G., Cheng, L., Zhou, H.-Y., Fu, L.-Y. and Yao, W.-X. (2004). Effects of berberine on potassium currents in acutely isolated CA1 pyramidal neurons of rat hippocampus. *Brain research*. **999**: 91--97.

Wang, L.-H., Li, X.-L., Li, Q., Fu, Y., Yu, H.-J., Sun, Y.-Q., Zhang, L. and Shan, H.-L. (2012). Berberine alleviates ischemic arrhythmias via recovering depressed I to and I Ca currents in diabetic rats. *Phytomedicine*. **19**: 206--210.

Wang, Y.-X., Zheng, Y.-M. and Zhou, X.-B. (1996). Inhibitory effects of berberine on ATP-sensitive K+ channels in cardiac myocytes. *European journal of pharmacology*. **316**: 307--315.

Whitehouse, S., Chen, P.-L., Greenshields, A. L., Nightingale, M., Hoskin, D. W. and Bedard, K. (2016). Resveratrol, piperine and apigenin differ in their NADPH-oxidase inhibitory and reactive oxygen species-scavenging properties. *Phytomedicine*. **23**: 1494--1503.

Won, S. J., Tang, X. N., Suh, S. W., Yenari, M. A. and Swanson, R. A. (2011). Hyperglycemia promotes tissue plasminogen activator-induced hemorrhage by Increasing superoxide production. *Annals of neurology*. **70**: 583--590.

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Wongeakin, N., Bhattarakosol, P. and Patumraj, S. (2014). Molecular mechanisms of curcumin on diabetes-induced endothelial dysfunctions: Txnip, ICAM-1, and NOX2 expressions. *BioMed research international.* **2014**: 161346.

Wu, D.-C., Ré, D. B., Nagai, M., Ischiropoulos, H. and Przedborski, S. (2006). The inflammatory NADPH oxidase enzyme modulates motor neuron degeneration in amyotrophic lateral sclerosis mice. *Proceedings of the National Academy of Sciences.* **103**: 12132--12137.

Ximenes, V. F., Kanegae, M. P., Rissato, S. R. and Galhiane, M. S. (2007). The oxidation of apocynin catalyzed by myeloperoxidase: proposal for NADPH oxidase inhibition. *Archives of Biochemistry and Biophysics.* **457**: 134--141.

Xiong, W., Mactaggart, J., Knispel, R., Worth, J., Zhu, Z., Li, Y., Sun, Y., Baxter, B. T. and Johanning, J. (2009). Inhibition of reactive oxygen species attenuates aneurysm formation in a murine model. *Atherosclerosis.* **202**: 128--134.

Yagi, S., Akaike, M., Aihara, K.-i., Ishikawa, K., Iwase, T., Ikeda, Y., Soeki, T., Yoshida, S., Sumitomo-Ueda, Y. and Matsumoto, T. (2010). Endothelial Nitric Oxide Synthase–Independent Protective Action of Statin Against Angiotensin II–Induced Atrial Remodeling via Reduced Oxidant Injury. *Hypertension.* **55**: 918--923.

Yao, J., Kong, W. and Jiang, J. (2015). Learning from berberine: Treating chronic diseases through multiple targets. *Science China Life Sciences.* **58**: 854--859.

Youn, J.-Y., Zhang, J., Zhang, Y., Chen, H., Liu, D., Ping, P., Weiss, J. N. and Cai, H. (2013). Oxidative stress in atrial fibrillation: an emerging role of NADPH oxidase. *Journal of molecular and cellular cardiology.* **62**: 72--79.

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Yu, W., Zha, W., Ke, Z., Min, Q., Li, C., Sun, H. and Liu, C. (2016). Curcumin protects neonatal rat cardiomyocytes against high glucose-induced apoptosis via PI3K/Akt signalling pathway. *Journal of diabetes research.* **2016**: 4158591.

Zarzuelo, M. J., López-Sepúlveda, R., Sánchez, M., Romero, M., Gómez-Guzmán, M., Ungvary, Z., Pérez-Vizcaíno, F., Jiménez, R. and Duarte, J. (2013). SIRT1 inhibits NADPH oxidase activation and protects endothelial function in the rat aorta: implications for vascular aging. *Biochemical pharmacology.* **85**: 1288--1296.

Zern, T. L., West, K. L. and Fernandez, M. L. (2003). Grape polyphenols decrease plasma triglycerides and cholesterol accumulation in the aorta of ovariectomized guinea pigs. *The Journal of nutrition.* **133**: 2268--2272.

Zhang, D.-X., Ren, K., Guan, Y., Wang, Y.-T. and Shan, Z.-L. (2014). Protective effects of apocynin on atrial electrical remodeling and oxidative stress in a rabbit rapid atrial pacing model. *Chin J Physiol.* **57**: 76--82.

Zhang, J., Youn, J. Y., Kim, A., Ramire, R., Gao, L., Ngo, D., Scovotti, J., Mahajan, A. and Cai, H. L. (2012). NOX4-dependent hydrogen peroxide overproduction in human atrial fibrillation and HL-1 atrial cells: relationship to hypertension. *Frontiers in physiology.* **3**: 140.

Zhang, L.-P., Ma, H.-J., Zhao, J. and Wang, Q.-S. (2005). Effects of resveratrol on delayed afterdepolarization and triggered activity induced by ouabain in guinea pig papillary muscles. *Acta physiologica Sinica.* **57**: 361--366.

Zhang, M., Brewer, A. C., Schröder, K., Santos, C. X., Grieve, D. J., Wang, M., Anilkumar, N., Yu, B., Dong, X. and Walker, S. J. (2010). NADPH oxidase-4 mediates protection

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against chronic load-induced stress in mouse hearts by enhancing angiogenesis. *Proceedings of the National Academy of Sciences.* **107**: 18121--18126.

Zhang, M., Wang, C.-M., Li, J., Meng, Z.-J., Wei, S.-N., Li, J., Bucala, R., Li, Y.-L. and Chen, L. (2013). Berberine protects against palmitate-induced endothelial dysfunction: involvements of upregulation of AMPK and eNOS and downregulation of NOX4. *Mediators of inflammation.* **2013**: 260464.

Zhang, Y., Liu, Y., Wang, T., Li, B., Li, H., Wang, Z. and Yang, B. (2006). Resveratrol, a natural ingredient of grape skin: antiarrhythmic efficacy and ionic mechanisms. *Biochemical and biophysical research communications.* **340**: 1192--1199.

Zhao, W.-C., Zhang, B., Liao, M.-J., Zhang, W.-X., He, W.-Y., Wang, H.-B. and Yang, C.-X. (2014). Curcumin ameliorated diabetic neuropathy partially by inhibition of NADPH oxidase mediating oxidative stress in the spinal cord. *Neuroscience letters.* **560**: 81--85.

Zhou, Z.-W., Zheng, H.-C., Zhao, L.-F., Li, W., Hou, J.-W., Yu, Y., Miao, P.-Z. and Zhu, J.-M. (2015). Effect of berberine on acetylcholine-induced atrial fibrillation in rabbit. *American journal of translational research.* **7**: 1450.

Ziolo, M. T. and Mohler, P. J. (2015). Defining the role of oxidative stress in atrial fibrillation and diabetes. *Journal of cardiovascular electrophysiology.* **26**: 223.

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Table 1. Summary of studies on oxidative stress in AF.

Types of experiments	Experimental model	Analyzed tissues	Description of the effects in AF	Inhibitors	Ref
Animal studies	Pig RAP	LA, LAA	↑ Superoxide ↑ Rac1 ↑ NAD(P)H oxidase activity ↑ Xanthine oxidase activity	Apocynin	Dudley et al. (2005)
	Old mice	LA, LV	↑ Rac1 ↑ NADPH oxidase activity	Rosuvastatin	Adam et al. (2007)
	eNOS null mice	LA	↑ Superoxide ↓ eNOS expression ↑ p22phox, p67phox ↑ Rac1	Pitavastatin	Yagi et al. (2010)
	Goat RAP	LA	↑ Rac1 ↑ NAD(P)H oxidase activity ↑ p22phox, NOX2	Apocynin	Reilly et al. (2011)
Clinical studies	permanent AF patients (n = 15)	LAA	↑ Rac1 ↑ NADPH oxidase activity		Adam et al. (2007)
	postoperative AF patients (n = 32)	RA	↑ Superoxide ↑ NADPH oxidase activity ↑ Rac1 ↑ p22phox, NOX2	Atorvastatin Apocynin	Reilly et al. (2011)
	AF Patients (n = 15)	RAA	↑ Superoxide ↑ NADPH oxidase activity ↑ p22phox, p47phox, p67phox	Apocynin	Kim et al. (2005)
	AF Patients (n = 8)	LAA, RAA	↑ Superoxide ↑ NOX2		Chang et al. (2011)
	AF Patients (n = 18)	LAA	↑ H2O2 ↑ NOX4		Zhang et al. (2012)

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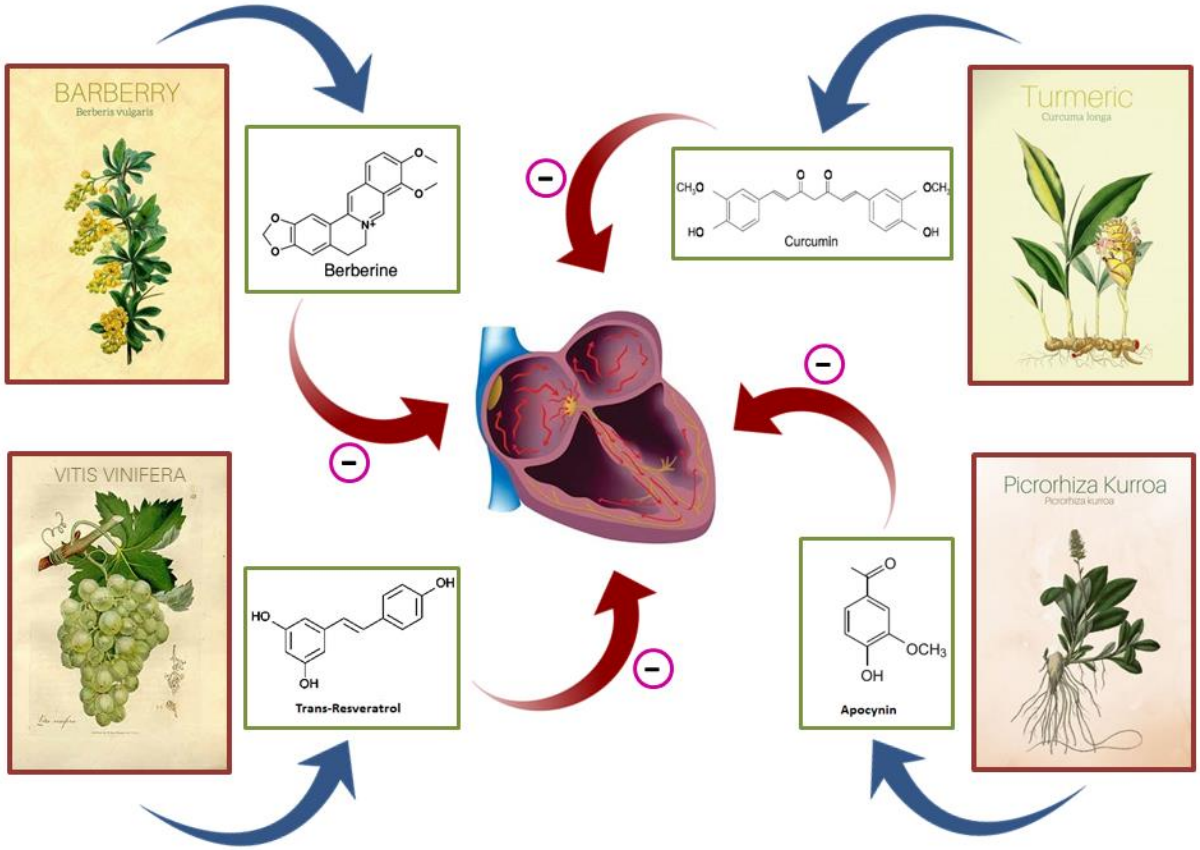

Figure 1 Chemical structure of apocynin, resveratrol, berberine, and curcumin. These compounds can be effective on atrial fibrillation.

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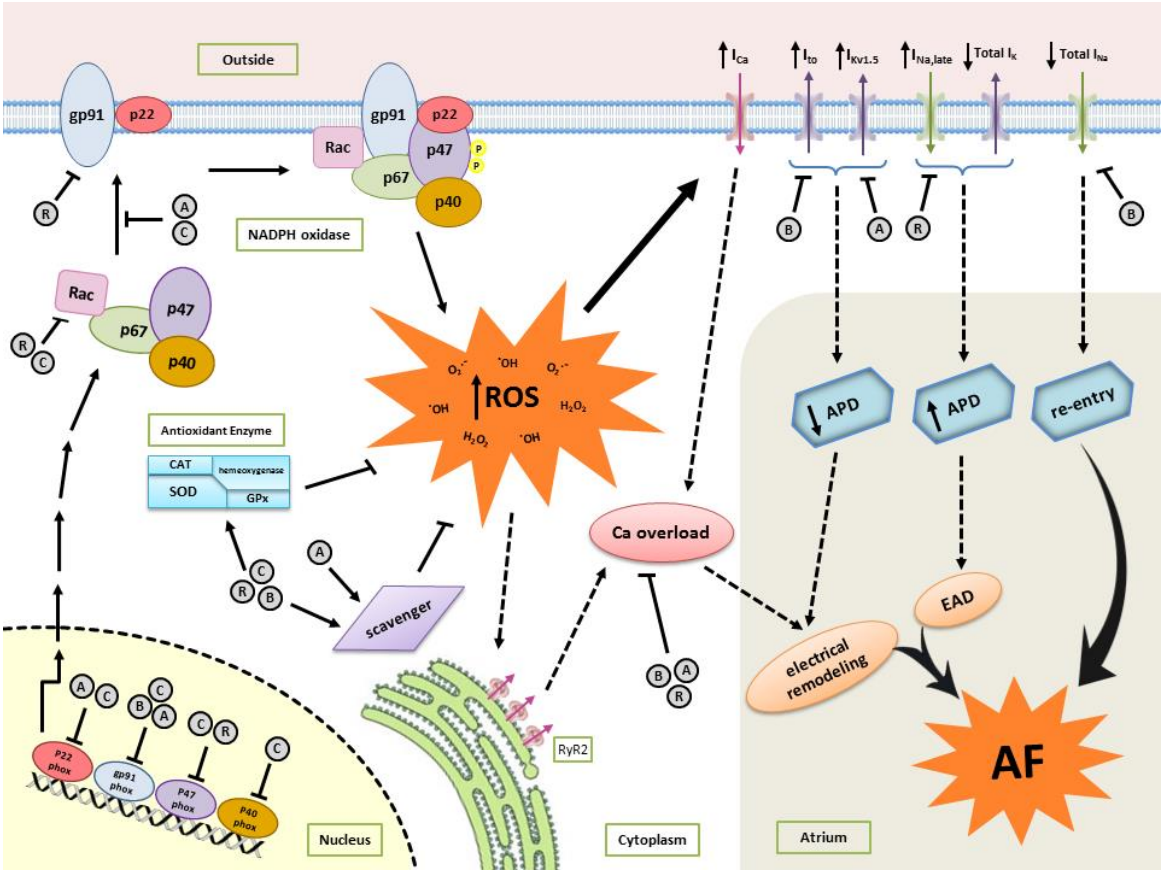

Figure 2 The role of oxidative stress in promoting and perpetuating AF. Increased ROS in atrial cells can cause to outbreak of AF through the effect on ion channels in cytoplasmic membrane and ryanodine receptor channel type 2 (RyR2) in endoplasmic reticulum. The natural compounds such as apocynin (A), resveratrol (R), berberine (B), and curcumin (C) can diminish ROS via different processes; the reduced NADPH oxidase gene expression, the decreased assembly and activation of NADPH oxidase, the straight scavenger activity and also the induced activity of internal antioxidant enzymes. However, these compounds have direct effects on ion channels that lead to change the arrhythmogenic mechanisms of AF.