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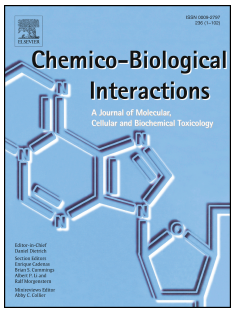


Aliskiren – A promising antioxidant agent beyond hypertension reduction

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**Title: Aliskiren – A promising antioxidant agent beyond hypertension reduction**

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**Abstract**

The renin-angiotensin-aldosterone system (RAAS) is a hormonal system that has a critical role in maintaining the normotensive state and electrolyte balance of the organism. The RAAS also has an important influence in the development of various pathophysiological conditions especially those concerning the renal system, cardiovascular system and hypertension. One of the consequences of the RAAS system is an increase in the generation of the reactive oxygen species (ROS) that causes an increase in oxidative stress, which may play a role in the development or exacerbation of such pathological conditions. Blocking this system at multiple points has been advantageous in the clinical management of these disorders. The key blockers that had gained predominant clinical use for such manifestations were angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors. However, their prolonged use caused a compensatory increase in renin and angiotensin I levels. The blocking of the system at the initial stages by blocking renin was of advantage to overcome such compensation. Such a renin blocker that gained widespread use was aliskiren. It is the first oral renin inhibitor that was approved for use in 2007. Although the opinions are varied about the use and future of renin inhibitors as hypertensive agents, aliskiren has been well documented to have antioxidant effects. Aliskiren functions as an antioxidant by lowering the increase in ROS that are produced by the RAAS system at doses independent of decreasing the blood pressure. In the present review we discuss the antioxidant properties of aliskiren independent of its blood pressure lowering property.

**Key words:** Aliskiren, renin-angiotensin-aldosterone system, oxidative stress, antioxidant.

## 1 Introduction

Aliskiren is an antihypertensive agent that is pharmacologically active in the RAAS [1]. The kidneys secrete the renin as per the changes in blood volume and renal perfusion, which then converts the angiotensinogen to angiotensin I. Angiotensin I is an inactive decapeptide that is hydrolyzed to active octapeptide angiotensin II by removal of the dipeptide His-Leu by ACE [2]. The angiotensin II has vasoconstrictor properties leading to release of catecholamines, increase in aldosterone secretion and reabsorption of sodium. All these events together lead to increase in blood pressure [3]. Prolonged elevation in the blood pressure may damage blood vessels in the brain, heart, and kidneys, resulting in a stroke, heart or kidney failure [4]. In the RAAS, aliskiren acts as a direct renin inhibitor [5]. The inhibition of the renin secretion prevents conversion of angiotensinogen to angiotensin I, which consequently suppresses the formation of angiotensin II. The inhibition of angiotensin II secretion prevents vasoconstriction, thereby relaxing the blood vessels and decreasing hypertension [6]. A decrease in high blood pressure leads to increase in the blood and oxygen supply to the vital organs and thereby prevents any damage to them [7]. However, the RAAS, has a deleterious affect whereby it increases oxidative stress when it is overexpressed. Activated RAAS leads to generation of ROS by activating nitric oxide synthase, the mitochondrial respiratory chain, and the NADPH oxidase enzymatic complex, that leads to increased production of superoxide [8]. Ang II has the ability to stimulate the production of ROS, mainly superoxide anions by activating NADPH oxidase in mesangial cells, inhibition of renin by aliskiren leads to a decrease in the Ang II causing a consequent decrease in oxidative stress (fig.1) [9].

Aliskiren is the first in the class of direct renin inhibitors that was approved for use in the United States in 2007 [10]. This drug was designed to prevent the increase in renin associated with the

long-term use of angiotensin or aldosterone targeting drugs, that are used to prevent hypertension [10]. It is a novel non-peptide, oral renin inhibitor which has an antihypertensive property that is similar to or even better than that of other classes of antihypertensive drugs, that target the RAAS at other points [11]. Aliskiren may be used as monotherapy or in conjunction with other antihypertensive agents with complementary mechanisms to attain a normotensive state [12,13].

While the current licensed indication for aliskiren is essential hypertension, it has also been associated with cardio, neuro, and reno protective effects; anti-inflammatory and anti-atherosclerotic effects that are independent of its blood pressure lowering activity [14]. Numerous preclinical studies have strongly suggested these protective effects in pathological conditions and induced toxicity models. The mechanism of action for aliskiren to exert these protective effects has been mostly attributed to its ability to ability to improve the antioxidant capacity and decrease the oxidative stress in such conditions by inhibiting the RAAS and preventing the generation of ROS [15,16]. Additive or synergistic effect of aliskiren in decreasing oxidative stress when used in combination with other antioxidants and/or drugs is also known [17, 18, 19]. This feature of aliskiren, independent of its blood pressure lowering property, has been reported to have improved the treatment outcome in various pathological conditions. The present review aims to discuss aliskiren as an antioxidant that can be an essential part of mono or combination therapy to manage various pathological conditions in various vital organs and other systemic disorders. Extensive search was conducted in PubMed and other relevant search engines with the key words, aliskiren, oxidant and antioxidant for the articles published in last ten years (2010-2020), however, the articles that did not cite aliskiren, or did not discuss the antioxidant feature of aliskiren were excluded.

## 2. Aliskiren as antioxidant in vital organopathies and toxicity

There is growing evidence that suggests the role of inappropriate RAAS activation in the pathogenesis of cardiovascular disease, kidney disease and other pathological conditions. One of the possible mechanisms of inflicting damage is the production of ROS by this system [20, 21]. Pharmacological manipulation of RAAS by various inhibitors is a key feature in the management of heart failure, renal disorders and acute myocardial infarction. Aliskiren inhibits the RAAS at its initiation and prevents ROS generation by it alongside inhibiting other unrequired effects [22]. Here we discuss the ROS decreasing property of aliskiren by blocking RAAS in the management of some vital organopathies independent of its blood pressure lowering attribute.

**2.1 Cardiovascular disorders**

In various cardiac disorders, numerous studies suggest that aliskiren decreased the pathological condition/injury mediated by decrease in oxidative stress. ROS are known to play a part in myocyte injury by inducing membrane lipid peroxidation, altering the cell proteins and stimulating the caspase-3 pathway [23]. All these events cause myocyte loss and apoptosis, which may be followed by increased accumulation and deposition of extracellular matrix proteins, especially collagens, in cardiac tissue causing interstitial fibrosis [24]. It is also known that that Ang II, generated from activation of cardiac RAAS, leads to excessive generation of ROS which plays a role in inducing myocardial fibrosis [25]. It is well documented that heart tissue is highly vulnerable to oxidative damage as it has a limited antioxidant defense system, increase in ROS can cause ischemia and reperfusion injury [9]. RAAS is activated during acute myocardial ischemia, causing the Ang-II to aggravate some effects of myocardial ischemia [26]. The RAAS induced oxidative stress, having a certain role to play in detrimental outcomes in cardiac tissue, has been observed to be ameliorated with the treatment with the renin inhibitor aliskiren, which prevents Ang-II generated ROS. Khan et al., (2018) reported a significant decrease in the increase of cardiac

marker enzymes, caspase-3 and the changes in antioxidant enzymes in isoproterenol induced myocardial infarction. Histopathological analysis also confirmed the same in their study [17]. Chen et al.,2017 reported in their study with eNOS knockout eNOS (-/-) and wild-type C57BL/6J mice that aliskiren treatment caused an attenuation of malondialdehyde levels, enhanced superoxide dismutase activity and total antioxidant capacity (T-AOC) in myocardium. Increased SOD and thioredoxin (Trx) proteins expression in wild type mice subjected to 30 minutes of ischemia followed by reperfusion for 24 hours was seen via an eNOS dependent manner [18].

In a model of myocardial ischemia/reperfusion injury, as described by Zhang et al; 2014 an increase in plasma MDA resulting from myocardial I/R was reversed by aliskiren treatment. Aliskiren also reverted the decrease in the expression of the p85a subunit of PI3K, phospho-Akt and phospho-eNOS induced after ischemia [19]. Rashikh et al; 2012 reported that in wistar albino rats with induced cardiomyopathy aliskiren decreased MDA levels and catalase activity and increased the GSH level and activity of SOD in heart tissue [27]. In their study with diabetic cardiomyopathy in C57b16/J mice, Thomas et al., 2013 [16] reported a significant increase in dihydroethidium staining in heart tissue in diabetic mice compared to controls, which was completely prevented by aliskiren treatment [28]. In order to study the changes in the structure of the heart and aorta associated with spontaneous hypertension in rats, Pechanova et al; (2019) reported that a decrease in vasoconstriction of the mesenteric artery, collagen content, and cross-sectional area in the aorta was attained with aliskiren treatment. Increased expression of nNOS and increased NOS activity in the heart was also reported with aliskiren treatment in their study [29]. In his study with heart function, De Mello, (2015) reported that renin increased real time ROS/reactive nitrogen species (ROS/RNS) in ventricular cardiomyocytes causing increase in oxidative stress, this was decreased by aliskiren treatment, which prevented the effect of renin on

chemical communication [30]. In heart tissue with ischemia-reperfusion damage, Taskin et al., (2016) reported that rats with induced acute ischemia had a decreased cytosolic total oxidant status while cytosolic and mitochondrial total antioxidant status slightly increased by renin inhibition by aliskiren. Total oxidant status in plasma greatly decreased with inhibition of renin by aliskiren and total antioxidant status in plasma slightly increased by inhibition of renin by aliskiren [31].

In studies with cardiotoxicity also, data suggests that aliskiren has oxidative stress lowering properties. Harbi et al., (2014) reported reversal of tacrolimus associated cardiotoxicity by aliskiren treatment. They reported improvement of cardiac function parameters, decrease in oxidative stress and histopathological and ultra-structural changes with aliskiren treatment. An increase in MDA in cardiac tissue was observed with tacrolimus treatment and decrease in GSH and antioxidant enzymes was reported. These changes were reversed with aliskiren treatment mediated by inhibition of the RAAS generated ROS [32]. Taskin et al., 2016 reported that in Sprague–Dawley rats with adriamycin induced cardiotoxicity, an increased cytosolic oxidative stress index, resulting from increased cytosolic total oxidative stress was observed. Aliskiren treatment decreased the cytosolic total oxidative stress and increase the total antioxidant status, thus decreasing oxidative stress [31].

In Human aortic endothelial cells, Hung et al., 2016 reported that aliskiren did not affect eNOS protein expression but increased eNOS phosphorylation while no significant affect was observed on eNOS mRNA level. IL-6 pretreatment caused a decrease in bradykinin-induced nitric oxide production, which was reverted by pretreatment with aliskiren [33]. Flavahan et al., 2016, while studying endothelial dilator dysfunction in ageing arteries in F344 rats assessed 79-ROS activity using dichlorodihydro-fluorescein diacetate in endothelium lining of young and old arteries. DCDHF fluorescence was seen to be higher in old as compared to young arteries, which was

reduced by renin inhibitors as aliskiren [34]. Savoia et al., (2013) reported that aliskiren leads to increase in nitric oxide production in the vasculature and improves vascular remodelling through different mechanisms with decrease in oxidative stress being one of them [35].

In combinations with other pharmacological agents also, aliskiren has shown additive effect in decreasing oxidative stress in cardiac tissue. Rashidy et al., (2012) reported that treatment with pioglitazone significantly lowered cardiac oxidative injury, lipid peroxidation, and myocardial fibrosis in diabetic nephropathic rats, which was enhanced by treatment with aliskiren. Aliskiren in combination with pioglitazone caused a significant cardioprotection by inhibiting Ang II synthesis. [36]. Higashikuni et al., 2011in their study with myocardial infarction in C57BL/6 mice reported that lipid peroxidation in the peri-infarction area and in the non-infarcted area was ameliorated by aliskiren or valsartan monotherapy compared to phosphate-buffered saline. The combination therapy of aliskiren and valsartan further reduced oxidative stress in the non-infarcted area than monotherapy of aliskiren or valsartan [37]. Santuzzi et al., 2015 also reported that aliskiren along with L-arginine reduced the vasoconstrictor response to phenylephrine and prevented endothelial dysfunction by improving the vascular RAAS and reducing the oxidative stress [38].

All these studies are highly suggestive of protective effect of aliskiren in cardiac tissue acting via decrease in oxidative stress possibly by inhibiting Ang-II induced ROS.

**2.2 Renal disorders**

The local renal and the systemic RAAS have been well documented to have an adverse effect on kidney function. One of the prominent mechanisms seems to be the loss of redox homeostasis and increase in free radicals [20]. The RAAS components, Ang II stimulates ROS production in the kidneys by inducing vascular NADPH oxidase and ET-1 expression and aldosterone exerts a pro-

oxidant action via NADPH oxidase-dependent mechanisms [39]. In the context of an increased RAAS and unbalanced redox mechanisms in renal malfunction, numerous studies have suggested antioxidant effect of aliskiren, where it attenuates the oxidative stress induced. Aliskiren has a strong affinity for renal tissue and prolonged activity, thereby having renoprotective effects since intrarenal RAAS activation has an important role in renal injury [40]. In animals with induced kidney disorders and in CKD patient, treatment with aliskiren significantly lowered the increase in kidney tissue malondialdehyde and prevented the decrease in superoxide dismutase, catalase and reduced glutathione in kidneys [41]. Treatment with aliskiren was found to decrease the glomerular superoxide in *db/db* mice, which was caused by significant suppression of NADPH oxidase activity by aliskiren [42]. Chung et al., (2017) reported that in C57BL/6J mice with renal fibrosis, aliskiren treatment significantly decreased unilateral ureteral obstruction and induced increase of Nox1 and Nox2, but it did not affect the expression of Nox4 in renal tissue, indicating an antioxidant effect of aliskiren [43]. In wistar rats with renovascular hypertension, Mengal et al., (2016) observed a decrease in advanced oxidation protein product, decrease in increased SOD-2 and CAT expression besides increase in the enzyme activity of SOD and catalase with aliskiren treatment [44]. Decrease in urine excretion of 15-F2a- 256 isoprostane was also observed with aliskiren treatment in patients of CKD [45].

One of the complications of diabetes is renal damage resulting due to worsening of renal oxidative stress [46]. This has been reported to decrease with aliskiren treatment alone or in combination with other pharmacological agents. Aldosterone inhibits the production of nitric oxide and its second messenger cyclic guanosine monophosphate that enhances the renal production of 8-isoprostane, which is a marker for endogenous superoxide activity. Although the relation between NO–cGMP pathway, oxidative stress, and the profibrotic actions of aldosterone in diabetic kidney

is not clear. The increase in aldosterone levels in diabetes is associated with worsening of renal oxidative stress and the reduction in levels of aldosterone, induced by aliskiren treatments are known to increase renal levels of NO and cyclic guanosine monophosphate [47]. Zhou et al., 2015 reported an increase in the total urinary output of MDA in diabetic db/db mice compared to non-diabetic db/m mice, which was significantly lowered by aliskiren treatment. They also reported that NAPDH oxidase, was significantly greater in untreated db/db mice, compared to controls, that indicated a renal activation of Nox2 in db/db mice. This was inhibited by aliskiren treatment especially with protein productions of Nox2 and p47phox reduced to levels much lower than normal [48]. Kidokoro et al; 2016observed renoprotective effect of aliskiren in diabetic C57BL/6J mice where its treatment decreased the ROS production and increased the bioavailability of nitric oxide [40]. In NOD/ShiLtJ and NOR/LtJ mice with diabetic nephropathy aliskiren and paricalcitol when given in combination caused significantly lower levels of circulating $H_2O_2$ in comparison to untreated diabetic mice as observed by Riera et al., 2016 [49]. Mahfoz et al; 2016 also reported a significantly elevated kidney GSH and serum SOD and a significantly lowered kidney MDA and kidney NO in diabetic wistar rats with nephropathy when treated with aliskiren [41]. Similar observation was reported by Eren et al; (2014) in Sprague Dawley rats with diabetic nephropathy where decreased MDA production and increased GSH and GPX and SOD Activities in kidney tissue were seen with aliskiren treatment [50].

In diabetic patients with CKD oxidative stress is an important underlying factor for diabetic nephropathy. Diabetic hyperglycemia causes increased production of ROS by stimulating the receptors of advanced glycation end-products, shear stresses and angiotensin II causing increase in NADPH oxidase activity which subsequently increases oxidative stress [51]. Aliskiren was

reported by Abe et al., (2012) to protect against tubulointerstitial injury and reduced oxidative stress in diabetic patients with CKD [52].

In experimentally induced models of nephrotoxicity also, aliskiren was observed to mitigate the toxicity of the toxicant by reducing the oxidative stress induced. It was reported by Al-Harbi et al., (2015) that aliskiren treatment decreased changes in biochemical markers such as blood urea nitrogen and creatinine and attenuated the effects on oxidative stress parameters such as malondialdehyde, reduced glutathione and catalase in tacrolimus-induced nephrotoxicity in wistar rats [53]. In adriamycin induced nephrotoxicity in Sprague-Dawley rats an increase in mitochondrial and cytosolic TOS was seen, which was decreased with aliskiren treatment [54]. Similar observation was reported by Rashikh et al; (2013) where doxorubicin-induced elevation in kidney tissue MDA and decrease in SOD, CAT and GSH was attenuated by aliskiren treatment in wistar albino rats [55].

Oxidative outcomes in renal ischemia were also improved with aliskiren treatment as reported by Ziypak et al., (2015), they observed a significant up-regulatory effect on iNOS and improved SOD activity and GSH levels in wistar albino rats with renal ischemia/reperfusion injury [56].

All these studies are confirmatory of the antioxidant property of aliskiren in renal disorders and toxicity suggesting its role as a prospective renoprotective agent.

**2.3 Hepatic disorders**

The RAAS is present in almost all the tissues including the hepatic tissue [57]. The dysregulation of both the systemic and local RAAS has been associated with various liver disorders [8]. Excessive Ang II is known to increase the induction of hepatic ROS with pro-oxidant effects in the liver, this has been observed in Ren2 transgenic Ren2 rats with an increased level of endogenous

Ang II [58, 59]. Elevated levels of Ang II may be the starting point of the molecular pathway of numerous liver disorders such as fibrosis, cirrhosis, chronic hepatitis, non-alcoholic fatty liver disease and hepatic steatosis [60]. Ang II-mediated signaling mechanisms lead to increased ROS production and oxidative stress which are a key feature of non-alcoholic fatty liver disease. Activation of NOX proteins and induction of ROS in hepatic stellate cells is caused by angiotensin II which eventually causes liver fibrosis [61]. This results in depletion of mtDNA causing a decrease in mitochondrial content, hence leading to hepatic steatosis [61, 62]. A prevention of this ang -II induced ROS has been attained by aliskiren treatment in numerous studies where aliskiren blocked the RAAS. In hepatic tissue, aliskiren was reported to prevent hepatic steatosis by inhibiting the hepatic uptake of free fatty acids or increased ω-oxidation [63]. In mice with hepatic steatosis Lee et al; 2016 observed that aliskiren lowered angiotensin II associated oxidative stress by phosphorylation of protein kinase B and 5' AMP-activated protein kinase [64]. Kishina et al., 2014observed that in LS-OB/OB MICE with hepatic steatosis, aliskiren remarkably reduced the ratio of 8-OHdG positive cells in liver samples compared with controls [65]. Lee et al., (2013) reported in mice fed with a methionine and choline deficient diet, that aliskiren attenuated steatohepatitis and fibrosis by reduction of angiotensin II, increased hepatic expression of fatty acid transport protein 1 and 4 and stimulated genes associated with fatty acid oxidation. Significant decrease in the level of TBARS, 4-HNE, p47 phox, phospho-p47 phox and increased expression of catalase 1, GPX1 and SOD1 in the C57BL/6 mice with aliskiren treatment in hepatic steatosis was also observed [63].

Karcioglu et al; 2016 reported that aliskiren attenuated the decrease in the SOD activity and glutathione levels and increase in lipid peroxidation levels in the livers of the rats treated with paracetamol [15]. In adriamycin induced hepatotoxicity, it is postulated that Ang-II may be a

contributing factor via mitochondrial oxidative production that leads to decreased mitochondrial membrane potential and ATP levels. The treatment with aliskiren reversed the decrease in mitochondrial membrane potential and increased ATP level [54]. Aliskiren was also observed to significantly increase activities of anti-oxidant enzymes and decrease of TBARS, in liver homogenates of DOCA salt-induced hypertensive rats [66]. El-Kholy et al., 2015 reported a significant decrease in reduced glutathione and significant increase in MDA levels in CCL4 intoxicated rats. Treatment with aliskiren for six week caused significant improvement in oxidative stress markers in their study [67]. Ramalho et al., 2017 in their study to find the effect of aliskiren on non-alcoholic steatohepatitis in metabolic syndrome, reported a decrease in oxidative stress which attenuated liver inflammation, steatosis and fibrosis mediated with aliskiren treatment by blocking Ang-II [68]. All this data strongly suggests that RAAS blockade reduces hepatic inflammation and fibrosis by suppressing the oxidative stress [69, 70].

**2.4 Brain disorders**

Extensive data is still lacking that indicates antioxidant property of aliskiren in brain disorders, however, numerous studies suggest neuroprotective effect of aliskiren mediated by decrease in ROS. It has been observed in experimental mice that continuous activation of the brain RAAS disrupts cognitive function by stimulation of the ang-II type 1 receptor, lowering of the cerebral surface blood flow and an elevation of oxidative stress [71]. Inhibition of the brain RAAS by aliskiren has been observed to improve the outcomes in various brain disorders. The brain renin is involved in chronic cerebral hypoperfusion-induced vascular dementia and other related brain injuries [72]. Renin inhibition by aliskiren improved such conditions by lowering NADPH oxidase-mediated brain oxidative stress. Since, decrease of brain nitrotyrosine is assigned to be a result of inhibition of brain NADPH oxidase activity, nitric oxide production and nNOS expression

by aliskiren [73]. Alzheimer's disease is presented by accumulation of amyloid β-peptide in senile plaques, which results in neuronal degeneration, with increased oxidative stress being one of the mechanisms [74, 75]. In their study of induced amyloid β toxicity, Chen et al., 2012 reported aliskiren to have neuroprotective action by downregulation of renin expression induced by amyloid β, which may have importance in management of Alzheimer's disease [76]. Aliskiren has been reported to block cognitive impairment resulting from hypo-perfusion through reduction of oxidative stress in mice [77]. In studies with ischemic stroke aliskiren had neuroprotective effects via various mechanisms such as upregulation of p-PI3K, p-AKT, Bcl-2 expression, attenuation of Bax expression and possible decrease in oxidative stress [78]. The inhibition of central RAAS has been reported to be beneficial in decreasing the incidence of stroke besides alleviating neuronal injuries following stroke [79, 80].

Panahpour et al., also reported neuroprotective effects of aliskiren in cerebral ischemia by decreasing the oxidative stress. They induced cerebral ischemia in mice by middle cerebral artery occlusion, that resulted in a significant increase in MDA levels and decreased the activities of antioxidant enzyme in the ischemic hemispheres. Treatment with Aliskiren significantly improved oxidative stress outcomes by reducing the MDA concentration and elevating superoxide dismutase and glutathione peroxidase activities [81]. Oxidative stress and lipid peroxidation seem to have a pivotal role in the development of postischemic damage. The outcomes in postischemic damage have been observed to be improved by aliskiren mediated by increase in eNOS and RAAS inhibition [82-84].

All these studies suggest that renin inhibition might be a hopeful therapeutic strategy for various brain disorders.

### 2.5 Pulmonary disorders

Very few studies have been carried out to study the antioxidant effect of aliskiren in pulmonary disorders. In pulmonary disorders like pulmonary fibrosis aliskiren is reported to decrease the progress of the disease by decreasing the overexpressed MMP-9, transforming the growth factor β1 and anti-oxidant activity [85]. In sepsis and sepsis-related acute lung injuries RAAS is known to play a significant role as a producer of oxidants. Akpinar et al., 2014 reported that aliskiren, significantly improved the lung damage of rats after sepsis by the inhibition of ROS formation, which is one of the critical mechanisms of organ injury in model of cecal ligation and puncture - induced sepsis [86]. Aliskiren was reported to protect the lungs from carrageenan-induced pleurisy damage by regulating antioxidant-oxidant balance via RAAS inhibition [Bayir]. Aliskiren shows antifibrotic properties in various experimental models, where it interferes with the levels of fibrogenic cytokines and oxidative stress [88].

## 3. Antioxidant properties of aliskiren in systemic disorders.

In systemic disorders, chiefly hypertension and metabolic syndrome, aliskiren is known to have ROS decreasing properties at doses independent of its blood pressure lowering feature. Overexpression of RAAS has been observed to be a key feature of hypertension and metabolic syndrome and RAAS generated increase in oxidative stress seems to be the underlying mechanism. RAAS inhibition leads to decrease in the outcomes or comorbidities associated with these systemic disorders. Here we discuss the antioxidant properties of aliskiren, in hypertension and metabolic syndrome.

### 3.1 Hypertension

RAAS has an important role in controlling hemodynamic stability by regulating blood pressure, and any alteration in any component of RAAS contributes to development of hypertension [17]. One of the crucial mechanisms by which an activated RAAS can lead to hypertension is generation of ROS. ROS may be generated in various vascular cell types, such as endothelial cells and vascular smooth muscle cells, by activation of xanthine oxidase, nitric oxide synthase and NADPH oxidase enzymatic complex, that leads to increased production of superoxide [8]. This leads to lesser bioavailability of NO and leads to impaired endothelial function causing hypertension [89]. Inhibition of the RAAS with aliskiren and the resulting decrease in the oxidative stress is known to have improved outcomes in numerous studies. In spontaneously hypertensive rats, increased expression of endothelial nitric oxide synthase, decreased levels of malondialdehyde and increased total antioxidant capacity and superoxide dismutase activity in thoracic aorta was observed with aliskiren treatment by Gu et al;2016 [90]. Tiradentes et al., (2015) in their study with hypertensive wistar rats reported an increased expression of the gp91phox -containing NADPH oxidase protein in aliskiren treatment groups compared with the sham group [91]. In hypertensive Wistar–Kyoto rats fed on high-fructose diets, increased lipid peroxide levels were reported in the aorta compared with control rats, while aliskiren treatment lowered such high lipid peroxide levels [92]. Tain et al., (2011) reported that treatment with aliskiren mitigated increase in ADMA, restored l-Arg-to-ADMA ratios, enhanced neuronal NOS-α, inhibited decrease in nNOS-β levels in the kidney-which ultimately restored NO bioavailability in hypertensive rats [93]. Aliskiren treatment increased the bioactivity of eNOS in hypertensive rats which might have modulated the intra- or extrahepatic resistance [94]. In a model of renovascular hypertension aliskiren alone in combination with arginine significantly increased the nNOS expression [38]. Ciocoiu et al; (2016) reported that in blood pressure the use of aliskiren combined with polyphenolic extract of *S. nigra*

ensured an increased protection and improved the results as compared to mono-therapy and improved the total antioxidant capacity [95]. Aliskiren treatment increased ferric reducing ability of plasma and decreased malondialdehyde and lipoperoxides in hypertensive patients as reported by Virdis et al., (2012) [96].

### 3.2 Metabolic syndrome

Metabolic syndrome is becoming a worldwide challenge with a rapid increase all over the world and is presented by obesity, hypertension, insulin resistance and dyslipidemia [97]. A cluster of risk factors are being associated with it having numerous underlying mechanisms. One of the mechanisms strongly being associated with metabolic syndrome is increased oxidative stress. An increase in the oxidative stress has been strongly associated with an increase in adiposity and impaired insulin sensitivity in humans, indicting ROS to be contributing factors in the generation of obesity-related insulin resistance [98]. Increase in insulin resistance is also known to be an outcome of an activated RAAS, by ROS generation [99]. The adipose tissue is crucial in the development of insulin resistance as an extended exposure of adipose cells to increased oxidative assault leads to a decreased insulin-stimulated glucose transport, lipogenesis, and activity of glycogen synthase that is coherent to impaired insulin action [8]. Excessive mitochondrial generation of ROS by activated RAAS is also known to be a contributing factor for development of insulin resistance and diabetes [100]. The decrease in the RAAS generated ROS is reported to have beneficial effects on insulin sensitivity. Inhibition of RAAS by aliskiren leads to improved oxidative stress outcomes in models of metabolic syndrome. In fructose-fed rats it has been reported that enhanced NADPH oxidase- mediated oxidative stress and increased lipid peroxidation could be a possible mechanism in the development of these metabolic disturbances

and aliskiren is reported to prevent insulin resistance and improve oxidative stress associated with it [101, 102]. In fructose-fed hypertensive rats, Chou et al., (2013) reported that aliskiren prevented and ameliorated insulin resistance, aortic endothelial dysfunction and oxidative vascular remodeling In their study, rats fed with high-fructose diet had significantly reduced serum and visceral adipose adiponectin levels; increased serum and visceral adipose leptin, increased the visceral fat pad weight and adipocyte size; elevated Ang II and NOX isoforms expressions; and caused oxidative stress by reducing adipose SOD activity. These deleterious changes were ameliorated by aliskiren treatment [92]. In e C57BL/6J mice with insulin resistance O2 production and NAD(P)H oxidase activities were significantly higher in the skeletal muscle of myocardial infarction and this increase was inhibited by aliskiren. Also, activities of the NAD(P)H oxidase subunits, NOX2, p22phox, and p47phox mRNA levels were all higher in the myocardial infarction than the Sham group which were significantly inhibited by aliskiren [103]. Aliskiren treatments improved dyslipidemia, hyperglycemia, reduced adipose lipid peroxide and increased adipose SOD activity and visceral adipose NOX isoforms expressions [104]. Matavelli et al, (2013) reported that, aliskiren increased renal interstitial fluid and nitric oxide in diabetic rats, indicating a decrease in oxidative stress [47]. Hassanin and Malek, (2014) also reported a decrease in the increase in serum lipid peroxidation and increased activity of serum super oxide dismutase enzyme in diabetic rats treated with aliskiren [105].

All these studies suggest that aliskiren prevents metabolic syndrome by improving oxidative stress and adiposity.

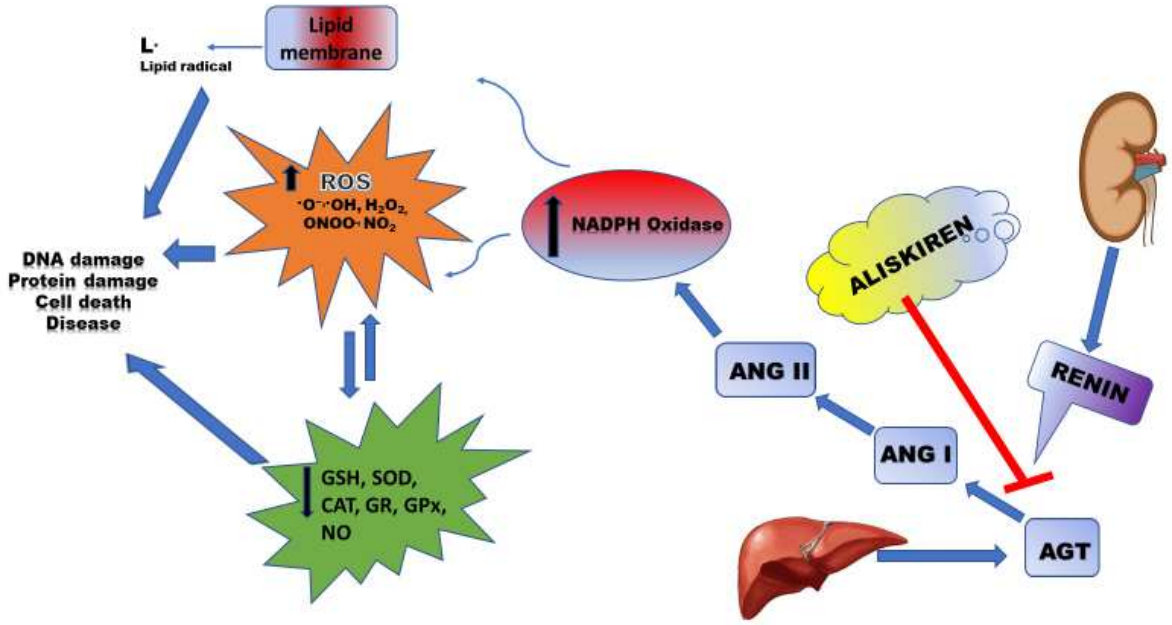


**Fig1: Aliskiren blocks renin and prevents the RAAS induced oxidative stress cascade.**

## 4. Conclusion

An overactivated systemic and local RAAS is central in the development of many pathological conditions, where it leads to an increase in oxidative stress. Aliskiren has an antioxidant property by inhibition of the RAAS, which is strongly suggested by various preclinical studies. This antioxidant property of aliskiren is independent of its blood pressure lowering dose. The treatment with aliskiren can be of value in improving the outcomes of numerous such disorders where RAAS has role in the pathogenesis. It may be used as a good alternative to natural antioxidants to improve and enhance the main therapeutic outcomes in disease and disorders. Its use as an add on therapy in patients already on medication can be encouraged to attain maximum benefit.

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Highlights

- RAAS may contribute to disease development through generation of oxidative stress.
- Blocking RAAS can prevent such RAAS generated ROS.
- Aliskiren is an antihypertensive agent, that blocks RAAS.
- RAAS blockage by aliskiren prevents ROS generation, so reducing severity of disease.
- Aliskiren may be used as antioxidant, independent of its antihypertensive action.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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| None |