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Review Article

ROS-Mediated NLRP3 Inflammasome Activation in the Progression of Hypertensive Nephropathy and its Therapeutic Interventions

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ABSTRACT

Among many molecular and cellular level elements which are involved in the development of hypertension, generation of reactive oxygen species not only involved in the pathogenesis of hypertension but also contribute to the cellular processes involved in the complication of hypertension. Reactive Oxygen Species (ROS) influences cellular processes (renal, immune, renin-angiotensin system) in the system that led to the increase in blood pressure. Hypertension leads to many complications like hypertensive retinopathy, stroke and Hypertensive Nephropathy (HN). Reactive oxygen species generation lead to oxidative stress which in turn activate NLRP3 inflammasome. This activated NLRP3 inflammasome is involved in the pathogenesis of Hypertensive Nephropathy (HN). ROS initiated activation of inflammasome and progression of hypertensive nephropathy can be controlled by making various therapeutic interventions which involved controlling of blood pressure, supplementation of nitric oxide, inhibition of ROS and inhibition of renin angiotensin system. This review article collected latest literature by using google scholar, Pubmed, Scopus and explained the pathogenesis of HN and therapeutic intervention by schematic diagrams. This review article also highlighted the significance of herbal medicine to arrest the progression of hypertensive nephropathy by citing literature related to phytomedicine.

Keywords: Hypertensive nephropathy, Inflammation, Oxidative stress, Reactive oxygen species.

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INTRODUCTION

Among many molecular and cellular level elements which are involved in the development of hypertension, generation of Reactive Oxygen Species not only involved in the development of hypertension but also contribute to the cellular processes involved in the complication of hypertension. Reactive oxygen species influences cellular processes (renal, immune, renin-angiotensin system) in the system that lead to the increase in blood pressure.[1] Hypertension leads to many complications like hypertensive retinopathy,[2] stroke[3] and Hypertensive Nephropathy (HN).[4] Current review articles will emphasize on the development of hypertensive nephropathy by involving ROS mediated inflammasome activation and arrest the progression of hypertensive nephropathy.

Data report depicts that in United States 3% of the total adult population have increased level of creatinine in the plasma, while 70% population of these subjects have developed hypertension.[5] It is noteworthy to mention that 75% of the hypertension cases precedes to heart failure.[6] Epidemiological studies have shown that the prevalence of Chronic Kidney Disease (CKD) in the adult population of United States was approximately 11% (19.2 million). Stages wise distribution shows that 3% population had stage 1 of Chronic Kidney Disease (CKD), 3% of the population had stage 2 of Chronic Kidney Disease (CKD), 4% of the population had stage 3 of Chronic Kidney Disease (CKD), 0.2% of the Chronic Kidney Disease (CKD) population had stage 4 of chronic kidney disease and 0.2% had stage 5 of kidney failure. In addition to hypertension and diabetes, age of the patient is a key predictor of CKD.[5] High blood pressure is a dominant promotor and marker of the Glomerular Filtration Rate (GFR) in patients with established Diabetes Mellitus (DM) and Non-Diabetic Kidney Disease (NDKD).[7] Chronic kidney diseases can be divided into the following stages; as shown in Table 1.

Pathogenesis of hypertensive nephropathy

Literature reported mechanism involved in the pathogenesis of hypertensive nephropathy by involving three systems; endocannabinoid system, sympathetic system and renin angiotensin system.[8] Current review articles will emphasize

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on the involvement of ROS-Mediated NLRP3 Inflammasome activation in the progression of hypertensive nephropathy and its therapeutic options. Elevated systemic blood pressure also results in the proportional elevation of pressure to the renal vasculature, which results in increased mechanical stretch to the glomerulus and mesangial cells mediated by cytokines (IL-6, TNF-alpha) and angiotensin II. In addition to the glomerulus, the proximal tubule is the major site for injury and the development of nephropathy.[9] Frequent injury and repair responses can lead to the onset of glomerulosclerosis, which get worse by the onset of proteinuria.[10] Proteinuria is a paramount and independent factor responsible for the progression of nephropathy.[11] Important factors in the pathogenesis of chronic kidney disease include activation of the Renin-Angiotensin System (RAS), elevated Oxidative Stress (OS) and NADPH ox and Endothelin-1 (ET-1).[12]

Renal vascular dysfunction is a commonly a medical complication in patients with hypertension.[13] Renal dysfunction will further cause interstitial tubular fibrosis and renal glomerulus sclerosis.[14] RAS, inflammation, OS, endoplasmic reticulum stress, apoptosis in the kidney and mitochondrial cell dysfunction are among the major contributory factors in hypertensive nephropathy.[15] Besides, other renal inflammation markers (TNF, ILs and ICAM), proteinuria, measurement of Blood Urea Nitrogen (BUN) and glomerular sclerosis are significant pathological markers for kidney.[16] can be attributed to the prevalence of hypertension and its related comorbidities.[7]

Activation of the inflammasome by oxidative stress involves three pathways which are sufficient alone and collectively more powerful to induce hypertensive nephropathy as explained in Figure 1. These pathways involve less production of nitric oxide in the kidney, elevated levels of AGE-RAGE pathway and elevated levels of Ang II. All these three pathways determine the physiology and pathophysiology of the kidney.

It has been reported that treatment with antihypertensive medicine like ACE inhibitors can arrest and reverse proteinuria and renal damage induced by hypertension[17] which is in line with the finding of another study which explain progression of renal disease and impairment of kidney function by controlling blood pressure.[11] It is reported that people with chronic disease of the kidney die from cardiovascular reasons than those without chronic kidney problems.[18] The connection between death and CKD.

Contribution of oxidative stress and inflammasome in the pathogenesis of Hypertensive Nephropathy (HN)

Indeed, the enhancement of (ROS), especially O_2•-, has a major and vital contribution in the onset of hypertension.[19] DOCA/salt hypertension and endothelin-1 (ET-1) sensitive model of hypertension,[20] were proved to be initiated by augmentation of NAD(P)H oxidase activity[21] and reduction in the expression and consequently NOS activity.[22] Most recently, DOCA salt and ang II infusion for 14 days was considered to induce Hypertensive Nephropathy (HN) with glomerulo sclerosis and albuminuria.[23]

Oxidative stress is always elevated either DOCA salt model of hypertension or spontaneously hypertensive model[24] and underlying mechanism may be less bioavailability of NO, fibrosis and inflammation as shown in Figure 2. Oxidative stress not only promotes hypertension in this way but also induce tubular injury in diabetic nephropathy.[25] Noradrenaline and angiotensin II are not only involved in the pathogenesis of hypertension but also involved in the activation of oxidative stress. ROS and conversion of procaspase to active caspase. Active caspases convert the inactive pro-IL-1β and pro-IL-18 to its active form, which subsequently cause inflammation in the kidney and organ damage. This oxidative stress can further initiate the NLRP-3 inflammasome pathway.[26]

Upon activation, NLRP3 inflammasome constitute a macromolecular protein complex that modulate caspase-1 activation along with production and maturation of proinflammatory cytokines (IL-1β and IL-18).[27] Ca^{2+} mobilization is contribute a significant role as the upstream event in NLRP3 activation.[28] Both inflammasome and cholesterol cocrystal also induce IL-1β[29] which ultimately damage podocyte of the kidney.[30] This oxidative stress activates proinflammatory macrophages which release inflammatory cytokines, which cause the loss of nephrin and modulate the expression of Elastic Collagen Membranes (ECM). This turnover in elastin to collagen ratio lead to the renal fibrosis.[31] All these reported events like augmented albuminuria, podocin and nephrin dysfunction led

Table 1: Different stages of nephropathy based on calculated Glomerular Filtration Rate (GFR) measurement.

CKD stages	Stage 1 of CKD	Stage 2 of CKD	Stage 3 of CKD	Stage 4 of CKD	Stage 5 of CKD
Level of kidney damage	Kidney damage present but normal kidney function	Kidney damage with some loss of kidney function	Mild to severe loss of kidney function	Severe loss of kidney function	Kidney failure;
GFR	>90	60-89	30-59	15-29	<15

to glomerulosclerosis and nephropathy which can be attributed to hypertension.

Therapeutic intervention in the progression of hypertensive nephropathy

Management of hypertension is the most important lifesaving intervention in the management of all forms of CKD. ROS initiated activation of inflammasome and progression of hypertensive nephropathy depends on the following therapeutic intervention which can be derived from Figure 2.

- Management of hypertension,
- Supplementation of NO,
- Inhibition of ROS,
- Inhibition of Ang II.

Management of hypertension

As previously reported studies showed that elevated blood pressure has major contribution in the pathogenesis of both the chronic hypertensive retinopathy[32] and the onset of new hypertensive retinopathy.[33] It has been reported that controlling the blood pressure of hypertensive patients have improved hypertensive retinopathy.[34] Similar situation can be applied to hypertensive nephropathy as both diseases are resulting because of complications and consequences of hypertension. It has been reported that aggressive management of blood pressure by multiple antihypertensive medicine in patients with hypertensive nephropathy can arrest the progression to End Stage Renal Disease (ESRD).[35] Sympathetic stimulation may lead to the release of the neurotransmitter noradrenaline which results in an increase in renal vascular resistance, thus affecting renal remodeling.[36] This is an effect of sympathetic stimulation globally while the magnitude of these effects seems to be intense locally in the kidney as catecholamines released by renal sympathetic nerve stimulation is expected to impact the proximal renal tubules, which modulate the sodium reabsorption which consequently will contribute to hypertension.[37] Studies have reported that renal sympathetic nerve denervation restored renal functions and heart rate in rats.[38]

Studies have linked sympathetic nervous system stimulation with inflammasome in cardiovascular system,[39] pressure load hypertrophy[40] and aging. This connection of increased sympathetic tone in the kidney and activation of the inflammasome remained folded. Studies reported that SNS produces an action on cardiac myocytes via β-adrenergic receptors[41] which alters the physiology of cardiac muscle by activating inflammatory cytokines. The inflammatory response generated by β-adrenergic receptors is mediated by multiprotein complexes of inflammasome that accelerate the conversion of procaspase-1 into active caspase-1, which is responsible for the synthesis of Interleukin-18 (IL-18) and IL-1β.[42] Keeping in view the above-mentioned mechanism of SNS-inflammasome activation in the cardiac myocyte, a similar picture can be translated in the kidney where sympathetic nerve

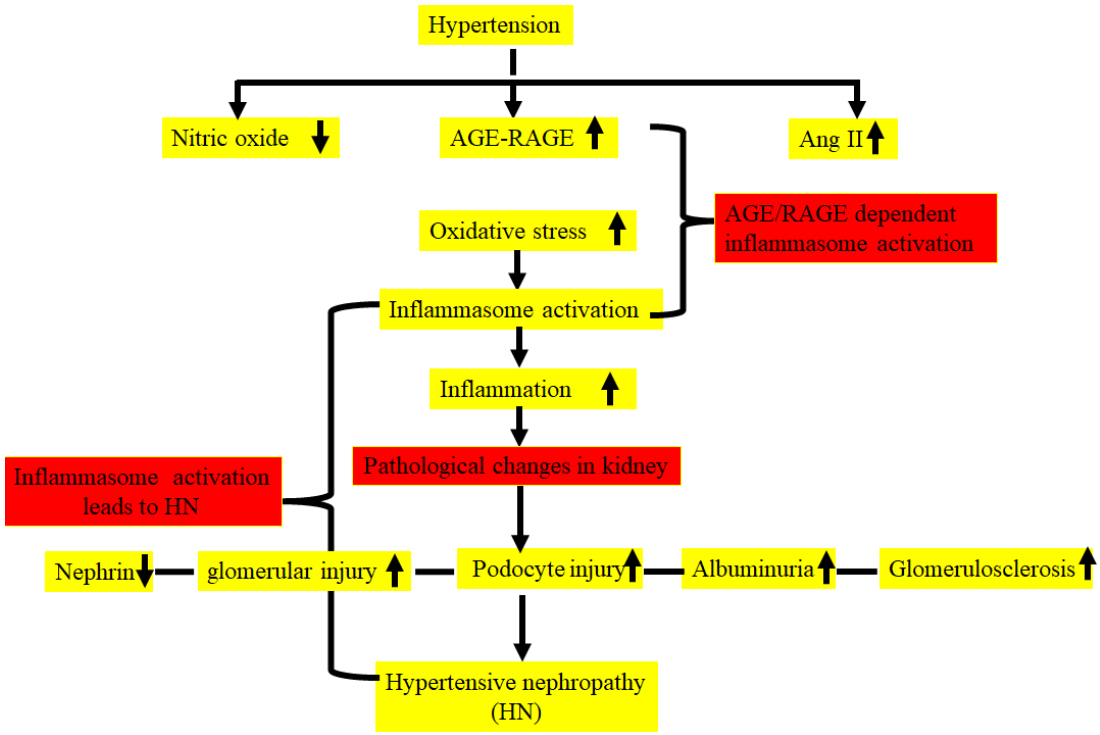

Figure 1: Subsequent events from hypertension to hypertensive nephropathy mediated by ROS induced activation of the inflammasome.

activation will lead to the release of noradrenaline which will activate α1 adrenergic receptors leading to the desensitization of the adrenergic receptors and alter the renal hemodynamics which is in line with several studies.[43] This increased sympathetic tone not only altered renal hemodynamic by direct action but also indirectly leads to the activation of the inflammasome which is involved in the pathogenesis of hypertensive nephropathy[44] and retinopathy.[45]

It can be deduced from the above-mentioned literature that aggressive control of blood pressure by using long-acting antihypertensive agents will not only positively control blood pressure in hypertensive patients but also will prevent the activation of inflammasome which leads to the development of hypertensive nephropathy as shown in Figure 3.

Nitric oxide modulators not only correct the root cause of the progression of hypertension to HN but also antagonizes the other systems which are involved in the pathophysiology of HN. One of the major factors in the progression of HN is the elevated levels of SNS and its neurotransmitter noradrenaline as mentioned above segment.

Supplementation of nitric oxide

One of the mainstays to arrest the progression of hypertension to hypertensive nephropathy is to control blood pressure, while recruitment of nitric oxide modulators like L-arginine in clinical practice will be beneficial not only for the treatment of nephropathy but also to arrest the progression of HN by interactions of NO with other systems.[46]

The Sympathetic Nervous System (SNS) in a dominant manner alters various functions including capabilities of arteries, contraction of vessels and activation and stimulation of adrenergic receptors (and receptors) to manage blood pressure. Noradrenaline is a neurotransmitter of the sympathetic system which elevate the blood pressure.[47] Plasma concentrations of Noradrenaline (NA) are usually taken as a surrogate marker of the Sympathetic Nervous System (SNS) activity.[48] Left Ventricular Hypertrophy (LVH) is reported to have decreased levels of NO and increased levels of NA in the plasma.[49] It is reported that NO plays a double role in functional antagonism of NA and a substantial role in the regulation of catecholamine (noradrenaline) release at sympathetic nerve terminals.[50]

Supplementation of the exogenous nitric oxide precursor or donor is reported to upregulate the NOS/NO/cGMP pathway of the kidney in Left Ventricular Hypertrophy (LVH) rats and reduces the concentration of Ang II in the plasma which in turn enhances the responsiveness of the -adrenergic receptors to noradrenaline, phenylephrine and methoxamine.[43] This enhanced sensitivity of -adrenergic receptors to their adrenergic agonists like noradrenaline, phenylephrine and methoxamine may be multifactorial, but one of the factors is the opposition of nitric oxide to the responses of Ang II on alpha-adrenergic receptors among the rats with LVH. Concentrations of both nitric oxide and Ang II in the body is well balanced in physiological situations in such a manner that inhibiting the one, heightens the concentration of the other one. In the kidney vasculature, data showed that the vasodilator effect of l-arginine were improved

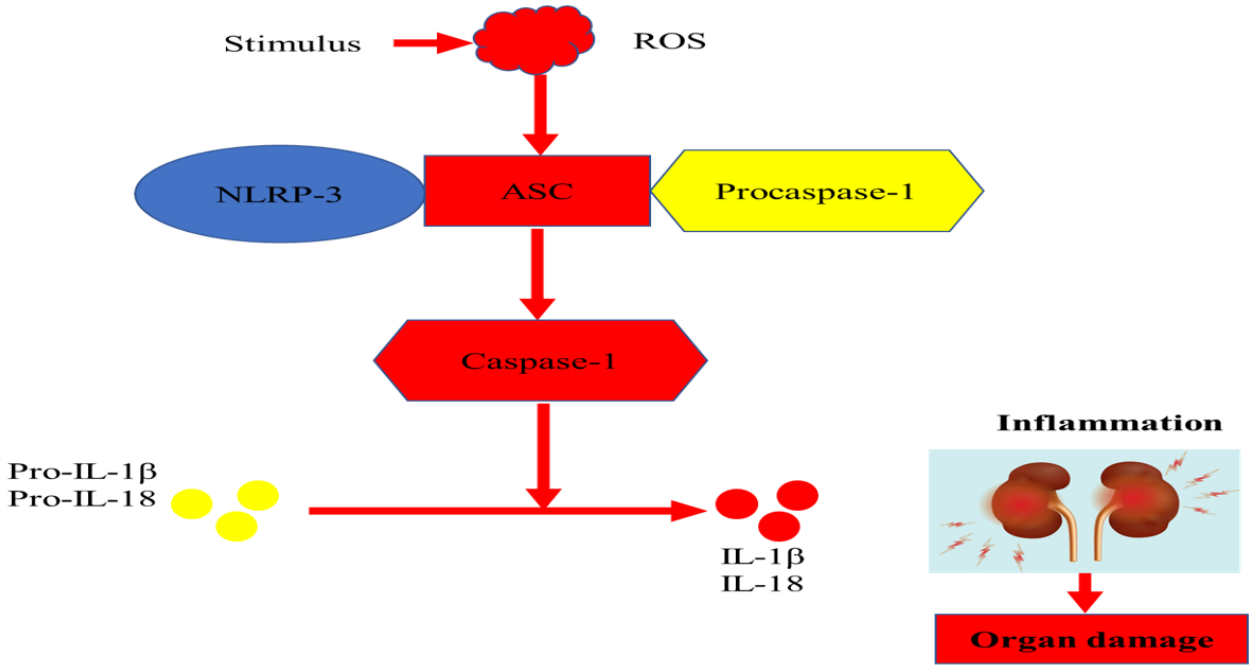

Figure 2: Assemble of 3 domains of inflammasome (NLRP-3, ASC and procaspase-1).

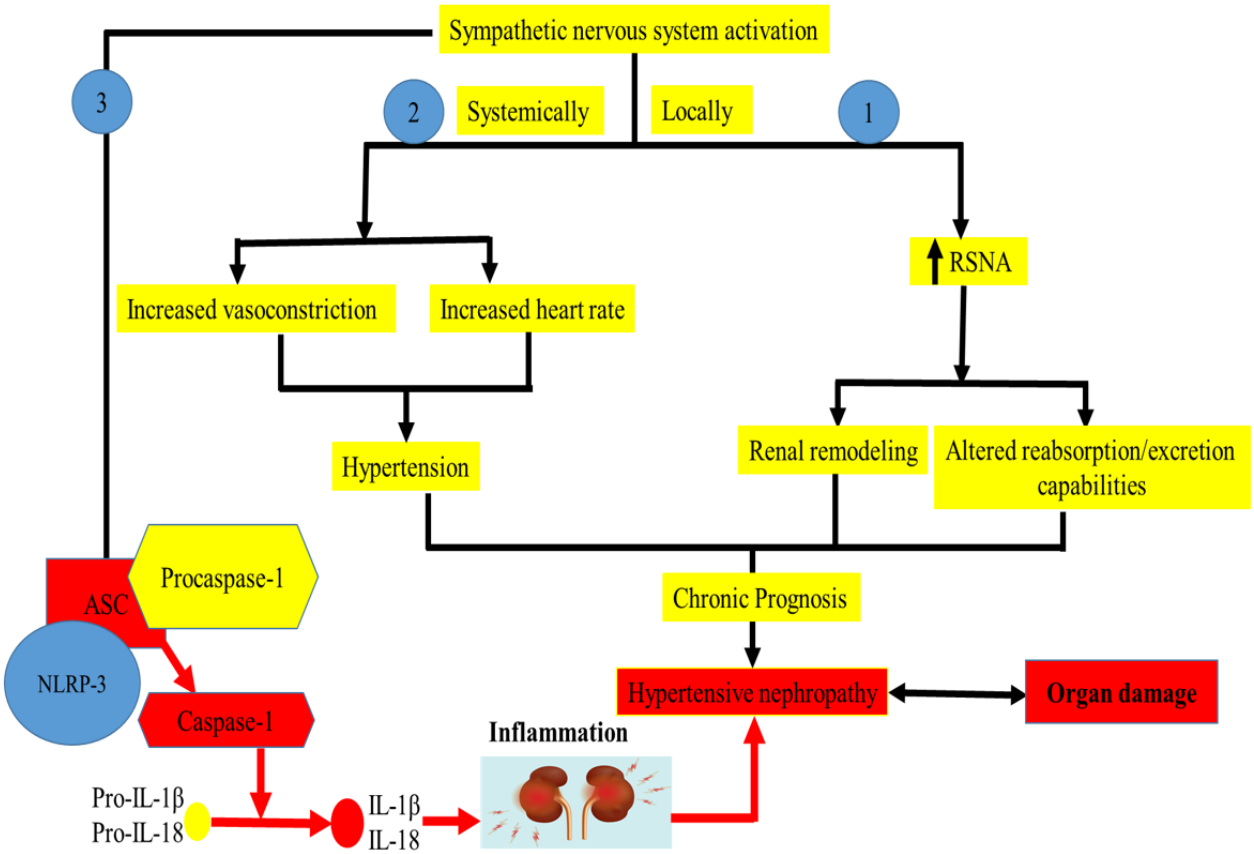

Figure 3: Mechanism of blocking the sympathetic nervous system will attenuate the progression of hypertension to hypertensive nephropathy by three ways.

when essential treatment of hypertension involved the use of Angiotensin Converting Enzyme (ACE) inhibitors.[51] So, it is proved from scientific evidence that NO plays a central role in the vasodilation of the renal arteries and its heightened levels not only suppresses the production of NA and Ang II locally in the kidney but also offset the responses of already circulating levels of NA and Ang II. This interaction between NO, NA and Ang II in kidney is well explained in reported data[46] and significance of NO in kidney is reported in previous studies.[52]

NO is a protective agent against the devastating effects of NO and Ang II in the kidney but also plays a major role in the suppression of inflammasome, which is a pathological factor in hypertensive nephropathy. Significant amount of data reported that NO suppresses NLRP3 induced inflammasome activation.[53] The role of inflammasome in the kidney is well established in numerous studies.[54] The role of NO in the suppression of NLRP3 induced inflammasome activation can be explained by the reason that pathological situations like endothelial dysfunction and diabetes, which are deficient in NO levels have greater NLRP3 induced inflammasome activities.[54] It can be speculated that the reverse is true if NO levels are enhanced by exogenous administration of NO or endogenously enhancing the NO levels may inhibit the NLRP3 induced inflammasome activation which is justifiable by reported studies.[55] Interaction between NA, Ang II, NLRP3 inflammasome and NO is demonstrated in Figure 4.

Inhibition of ROS

Oxidative stress is among one the factors for the activation of inflammasome and the compound which has antioxidant activity are a viable candidates as anti-inflammatory activity. Despite of unknown factors of inflammasome activation, several oxidative stress-related cellular processes have been considered involved in the inflammasome activation.[56] Upon stimulation, mitochondria alarm the immune system by transmitting stress signals via mitochondrial Reactive Oxygen Species (ROS).[57] Inhibiting the ROS, arrest the inflammasome while induction of oxidative stress by ROS species induces NLRP3-mediated IL-1β secretion.[58] *Quamoclit angulata* Extract (QAE) treatment in type II diabetes mellitus significantly attenuated NLRP3 inflammasome which resulted in kidney damage by involving oxidative stress, apoptosis and fibrosis.[59]

Activation of inflammasomes can be arrested by the administration of antioxidants. Inflammasome inhibition and related cascade reactions could serve as future therapeutic targets for various pathological conditions[60] like nephropathy. This strategy of using antioxidants to suppress the activation of the inflammasome has been employed in many studies in different diseases. Epigallocatechin-3-Gallate (EGCG) has prophylactic effects on lupus nephritis by attenuating kidney NLRP3 inflammasome activation and enhancing systemic Treg cell activity.[61] Short Chain Fatty Acids (SCFAs), suppresses the endothelial Nlrp3 inflammasome by its antioxidant actions.[62]

Oxidative stress is involved in various kidney ailments like AKI, CKD, HN and DN.[63] The role of antioxidants to arrest the progression of nephropathy has been employed in many studies conducted in diabetic retinopathy.[63] Ascorbic acids is a standard antioxidant which was explored to observe its effects in the NLRP3 induced inflammasome activation. Study demonstrated that ascorbic acid attenuated ROS induced inflammation and suppressed the NFκB/Caspase-1/IL-1β pathway.[64] This indicates the protective potential of antioxidants in hypertensive retinopathy by inhibiting ROS induced NLRP3 inflammasome activation. NADPH Oxidase inhibitors and apocyanin (NOX inhibitor) were found to have anti-inflammatory effects and neuroprotective agents in brain injury as results of inflammation.[65] Apocyanin beyond an antioxidant, it is reported to possess anti-inflammatory effects by arresting NLRP3 inflammasome activation and suppressing the NF-κB signaling in acute pancreatitis situations.[66] It was observed that during ischemia reperfusion injury, inflammasome components were upregulated during transcription and post transcription of testicular Ischemia Reperfusion Injury (tIRI). Inhibition of NOX by antioxidants like apocynin prevented ROS accumulation expression of proinflammatory cytokines and NLRP3 inflammasome activation during tIRI[67] Looking at the exploratory results of antioxidants in brain, testes and pancreas, it can be presumed that similar situation may exist in hypertensive retinopathy. Apocyanin treatments in renal fibrotic injury in diabetic nephropathy rats has improved renal function by reducing renal injury, downregulation of NLRP3 in the renal cortex and attenuation of renal fibrosis.[68]

Herbal medicine is continuously exploring antioxidants, which can be a suitable therapeutic option in hypertensive nephropathy to inhibit the ROS induced NLRP3 inflammasome activation. Both oxidative stress and inflammatory cytokines result in hypertension induced renal damage[69] and for this reason antioxidants can be a suitable options in hypertensive nephropathy by blocking ROS induced NLRP3 inflammasome activation and arresting the progression of HN. *Salvia miltiorrhiza* and the flower of *Coreopsis tinctoria* Nutt have been utilized to manage high blood pressure and reduced ROS production and showed anti-inflammatory potential by inhibiting ROS and inflammatory cytokines like TNF-α, IL-6 and NF-κB.[70] *Apocynum venetum*, its polyphenols and *Tulbaghia violacea* have been found to have an antioxidant roles by down-regulation of expression of inflammatory cytokines like NF-κB and TGF-β in the kidney of Dahl salt-sensitive rat and protect renal functions.[71] Resveratrol, which is the main component of *Veratrum nigrum* L. and 3-n-butylphthalide, a major component of celery seed, decreased the oxidative stress, cytokines and down-regulation of TGF-β expression in the kidney tissue.[72] The renal protective effect is provided by Galangin which is the main extract of *Alpinia*

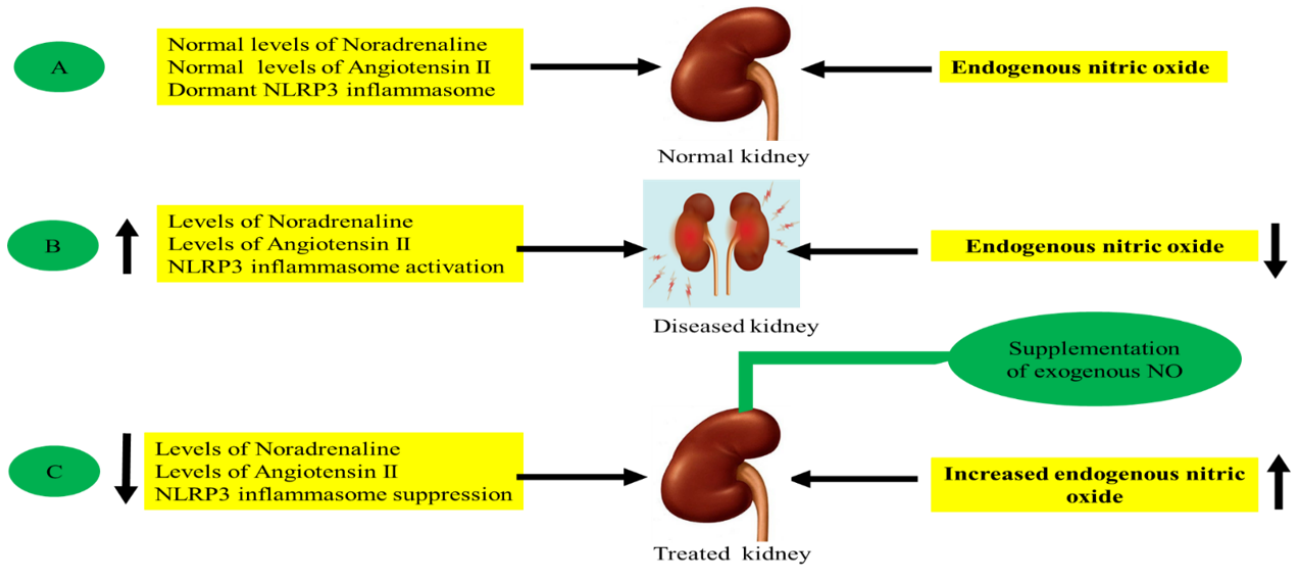

Figure 4: Interaction between noradrenaline, angiotensin II, NLRP3 induced inflammasome and nitric oxide. (A) showing levels of noradrenaline, angiotensin II, NLRP3 induced inflammasome and nitric in normal conditions. (B) showing elevated levels of noradrenaline, angiotensin II, NLRP3 induced inflammasome and reduced levels of nitric oxide. (C) showing exogenous administration of NO results in reduced levels of noradrenaline, angiotensin II, NLRP3 induced inflammasome and increased nitric oxide levels.

officinarum by inhibiting both ROS and inflammatory markers like TNF-α, IL-1β and IL-18.[73]

Exploration of safe antioxidants for commercial market is a target for ethnopharmacology, which will not only increase the antioxidant mechanism of the body but also inhibit the ROS-Mediated NLRP3 Inflammasome Activation in the progression of hypertensive nephropathy.

Inhibition of Angiotensin II

Therapeutic agents which block RAS are considered as renal protective agent among patients with diabetic and non-diabetic Chronic Kidney Diseases (CKD).[74] Round clock control of blood pressure by using sympatholytic agents is considered a promising strategy to protect kidney. Vaccarin isolated from the medicinal plant *Vaccaria segetalis* seed plays a protective role for the kidney in hypertensive by attenuation of fibrosis, reducing the concentrations of inflammatory molecules, oxidative stress marker, Ang II levels and AT1 receptor expression levels.[75] It appears from the published data that round-the clock control of BP and inhibition of the RAS are major objectives in CKD. Nephropathy can be diagnosed by knowing the markers of kidney function like expression levels of podocin and nephrin in the kidney, albuminuria and proteinuria. Ang II is involved in vascular damage by the activation of inflammasome[76] and endothelial dysfunction in hypertensive mice.[77] Study reported that the important role of the NLRP3 inflammasome in mediating Ang II-induced podocyte injury and mitochondrial dysfunction, suggesting that the NLRP3 inflammasome might be an effective therapeutic target against podocytopathy.[78] Role of inflammasome in the kidney is reported in a substantial number of studies where interesting data is reported *in vitro* data at cellular and molecular levels.

It is obvious from the above-mentioned literature that any therapeutic agents which blocks either the production of Ang II or blocker receptors of Ang II will be a therapeutic moiety to arrest the NLRP3 inflammasome activation. This argument can be strengthened by published data reporting that candesartan has anti-inflammatory effects and can be repositioned to ameliorate NLRP3-associated complications.[79] Angiotensin II receptor blockers can be a double edge sword which will not only protect the kidney by inhibiting the NLRP3 inflammasome activation but also inhibit the oxidative stress induced by Ang II. Oxidative stress is a major pathological factor for the inflammasome activation and development of hypertensive nephropathy. Studies demonstrated that candesartan suppresses inflammatory cytokine production a dominant manner by inhibiting oxidative stress, rather than blocking AT1 receptor activity.[80] Similar concept was used in brain injury where Telmisartan attenuated the cerebral edema by inhibition of NLRP3 inflammasome in mice[81] while pre-stroke administration of fimasartan could potentially attenuate brain injury by targeting the inflammasome.[82] Gaseous transmitter Hydrogen Sulphide (H^2S), which is having ACE inhibitor-like activities, is reported to play a pivotal role in the P2X7R/NLRP3 inflammasome-associated neuroinflammatory response in the pathogenesis of secondary brain injury.[83]

It can be concluded that either inhibition of the production of Ang II or the blocker of Ang II receptors will be a therapeutic moiety to inhibit the NLRP3 inflammasome activation and development of hypertensive nephropathy.

CONCLUSION

Hypertensive nephropathy results from uncontrolled hypertension which may be the reason of increased reactive oxidative stress, decrease supplementation of nitric oxide, or increased vasoconstrictors like sympathetic nervous system and renin angiotensin system. Increased oxidative NA and Ang II lead to the generation of ROS, which further activates the NLRP3 inflammasome activation in the kidney and results in hypertensive nephropathy. Therapeutic interventions include management of hypertension by controlling blood pressure, inhibition of ROS, supplementation of NO to offset the effects of SNS and inhibition of renin angiotensin system.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ROS: Reactive oxygen species; **NLRP3:** Nucleotide-binding domain, Leucine-Rich-containing family, Pyrin domain-containing-3; **HN:** Hypertensive Nephropathy; **CKD:** Chronic Kidney Disease; **GFR:** Glomerular Filtration Rate; **NDKD:** Non-Diabetic Kidney Disease; **IL-6 :** Interleukin 6; **TNF-α:** Tumor Necrosis Factor-alpha; **RAS:** Renin Angiotensin System; **ET-1:** Endothelin-1; **NADPH ox:** Nicotinamide Adenine Dinucleotide Phosphate oxidase; **ICAM:** Intracellular Adehsion Molecule; **BUN:** Blood Urea Nitrogen; **AGE-RAGE:** Advanced Glycation Endproduct and Receptors of Advanced glycation Endproduct; **ACE:** Angiotensin Converting Enzyme; **DOCA:** Deoxycorticosterone acetate; **NO:** Nitric Oxide; **ECM:** Elastic Collagen Membranes; **ESRD:** End Stage Renal Disease; **SNS:** Sympathetic Nervous System; **NA:** Noradrenaline; **LVH:** Left Ventricular Hypertrophy; **cGMP:** Cyclic Guanosine Monophosphate; **ASC:** Associated Speck-like Protein; **H2S:** Hydrogen Sulphide.

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