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ORIGINAL ARTICLE

Protective Effect of Hesperidin Modulates Inflammatory Response, Oxidative Stress Status and Blood Pressure Following Renal Artery Stenosis in Rats

Amany A. Khidr [1], $, Shimaa M. Elshazly[1], Hassan M. El-fayoumy[1, 2], Nabila N. El-maraghy[1, 3]

1)Department of Pharmacology and Toxicology, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt
2)Department of Pharmacology, Toxicology and Biochemistry, Sinai University in Egypt
3)Department of Pharmacology, Toxicology and Biochemistry, Future University in Egypt

Corresponding author
Amany A. Khidr.
E.mail :
Dr.pharmacist.2020@hotmail.com

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ABSTRACT

Background: Hesperidin (HES) is a natural occurring flavonoid extracted from citrus fruits that has been reported to possess many protective effects it has potent antioxidant and anti-inflammatory activities.

The aim of this study is to evaluate the effect of HES in attenuating renovascular hypertension (RVH) by using two kidney one clip (2K1C) renal artery stenosis (RAS) and repairing renal cell injury that occurred due to oxygen free radical.

Methods: Oral Supplementation of HES (50 mg/kg body weight) to renal artery stenosed rats.

Blood pressure was measured, oxidative stress markers and some involved inflammatory mediators tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2) and prostaglandin-E2 (PG-E2).

Results: High blood pressure (BP) was attenuated and HES also down-regulated the expressions of TNF-α, COX-2 and PG-E2 in addition to ameliorate oxidative stress by increasing glutathione reductase (GSH) and decreasing malondialdehyde (MDA)..

Conclusion: These observations show that hesperidin exerts its anti-hypertensive activity up on altering inflammation and oxidation process that results in several cell and organ damage.

Keywords: Blood pressure, Renovascular hypertension, Renal artery stenosis, Inflammation, Hesperidin.

Abbreviations: 2K1C: Two kidney one clip**, ARVD:** Atherosclerotic renovascular disease**, BP**: blood pressure, **CAT:** Catalase, **CKD:** Chronic kidney disease, **COX-2:** Cyclooxygenase-2, **CVD:** Cardiovascular disease**, DBP:** Diastolic blood pressure, **ESRD:** end stage renal disease **GSH**: Reduced Glutathione**, HES:** Hesperidin, **H.R**: Heart rate**, HTN**: Hypertension**, IL-1β:** Interleukin-1 beta, **IL-6:** Interleukin-6, **MAP:** Mean arterial pressure, **MDA**: Malondialdehyde, **NADPH**: Nicotinamide adenine dinucleotide phosphate, **NF-κB**: Nuclear factor kappa-light-chain-enhancer of activated B cells **NIBP**: Non-invasive blood pressure, **NO:** Nitric oxide, **$ONOO^-$:** Peroxynitrite, **OS:** Oxidative stress, **$PG\text{-}E_2$:** Prostaglandin E2, **PGH_2:** Prostaglandin H2, **PGs:** Prostaglandins, **qRT- PCR:** Quantitative reverse transcription polymerase chain reaction, **RAAS**: Renin-angiotensin aldosterone system, **RAS:** Renal artery stenosis, **RIA**: Radioimmunoassay, **ROS:** Reactive oxygen species, **RV:** Renovascular, **RVH:** Renovascular hypertension, **SBP:** Systolic blood pressure, **S.E:** Standard error of mean, **SOD:** Superoxide dismutase, **TNF-α**: Tumor necrosis factor-α.

INTRODUCTION

Hypertension (HTN) is one of the mainly worldwide common diseases. Blood pressure (BP) considered high if systolic blood pressure (SBP) is 140 mm Hg or higher and/or diastolic blood pressure (DBP) is 90 mm Hg or higher **[1]**.

High blood pressure became a leading cause of mortality & disability adjusted life worldwide in 2010 .Millions of people die every year not only from HTN itself but also from its complications **[2]**. Among many of its complications cardiovascular diseases (CVD) and/or chronic kidney disease (CKD) hypertensive nephropathy

(HN) which also is described as hypertensive glomerulosclerosis. Hypertensive nephropathy is considered as one of the leading causes of end-stage renal disease (ESRD) in the developed countries **[3]**.

Understanding the mechanisms and implications of renovascular disease remains very important for treating patients with hypertension. HTN secondary to renovascular disease is termed renovascular hypertension (RVH) which results from occlusive lesions of the main renal arteries **[4]**. In this condition this disease is called renal artery stenosis (RAS) in which a fall in renal blood flow and perfusion pressure happens **[5]**. In classical definitions; the conclusion that hypertension is related directly to an arterial lesion, mainly depends upon reversing hypertension after the relief of the obstruction. In practice, the complete "reversal" of hypertension is rarely possible. It is important to know that renovascular diseases often worsen the pre-existing hypertension and also can ultimately threaten the viability of the post-stenotic kidney and impair sodium excretion in subjects with congestive heart failure **[4]**.

The link between HTN and inflammation has now been well demonstrated but though; it is still unclear whether inflammation is a cause or an effect of HTN **[6]**. It has been verified from experimental research that it contributes in the development of HTN by inducing many cellular damages like renal damage ,vascular damage as well as altering the synthesis and degradation rates of vasoconstrictors and vasodilators including nitric oxide (NO) and a lot of inflammatory cytokines, including tumor necrosis factor alpha (TNF-α) which can directly induce oxidative stress (OS) by causing the activation of reactive oxygen species (ROS) producing enzymes, like Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and triggering the interleukin (ILs) release which in turn would lead to the production of Prostaglandin-E_2 (PG-E_2) by cyclooxygenase-2 (COX-2) **[7, 8]**. HTN is also associated with elevated levels of OS markers including, malondialdehyde (MDA) and also decreased levels of catalase (CAT) and/or superoxide dismutase (SOD) in addition to glutathione (GSH) **[9]**.

Hesperidin (HES) is a natural flavonoid extracted from citrus fruits Oranges, grapefruit, lemon, and tangerines contain hesperidin that has anti-inflammatory activities in many disease models. It has been shown in rodent models that it reduces the inflammation and the inflammatory pain by suppressing the cytokine production, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity, and OS **[10]**.

We hypothesize that the anti-inflammatory flavonoid HES could improve RVH and renal damage by its anti-inflammatory and antioxidant effects .As well as our research expands our understanding of OS and inflammatory mediators' role in the progression of RVH pathogenesis.

2. MATERIALS & METHODS

2.1. Animals

Thirty adult male Wistar rats (35-42 days old, 200-250g) were obtained from the Faculty of Veterinary Medicine, Zagazig University, Egypt. The rats were assigned to 3groups randomly and housed 5 rats per cage and kept on a light-dark cycle (12h/12h) at 23±2 ℃ with free access to water and food for seven-day acclimatization period. All animal procedures were approved by the Ethical Committee for Animal Handling at Zagazig University.

2.2. Drugs and Chemicals

Hesperidin was purchased from Sigma–Aldrich (St. Louis, Missouri, USA).

2.3. Rat model of renovascular hypertension (RVH)

Renovascular HTN was induced by the Goldblatt two kidney one clip (2K1C) method as described previously **[11, 12]**.

2.4. Experimental groups

Animals were divided into three groups (10 rats/ group), control (CTR) group (animals received distilled water vehicle), RAS group (animals were subjected to renal stenosis then had free access to water vehicle till the end of the study), HES group (animals were subjected to renal stenosis and were treated with HES (50 mg/kg/day, orally) for four weeks **[13]**.

2.5. Blood pressure measurement

MAP was measured using rat non-invasive blood pressure (NIBP) system (Harvard Apparatus Ltd, Edenbridge, Kent, England). The average of three BP readings was calculated for each animal on weekly interval.

2.6. Sampling

At the end of the experimental study, animals were euthanized under isoflurane inhalation then blood samples were collected from the retro orbital plexus in heparinized tubes and non-heparinized tubes. Non-heparinized blood has been allowed to coagulate and centrifugate at 4000 rpm for 10 min, then the separated serum was used for the estimation of creatinine and urea measurements. Portions of heparinized blood sample were used immediately in oxidative stress measurements where other portions were centrifuged at 4000 rpm for 10 mins for separation of plasma and

erythrocytes. Where plasma samples were aliquoted and preserved at -80 ^{0}C to be used in other biochemical analyses.

Aorta and kidney of each animal were immediately excised after the blood sampling. Part of aorta and kidney were flash frozen and stored at -80 ^{0}C for enzyme-linked immunosorbent assay (ELISA) tests.

2.7. Measurement of kidney function tests

2.7.1. Determination of serum creatinine

Creatinine was measured in serum samples using a colorimetric creatinine assay kit (Bio-diagnostic, Egyptian company of biotechnology, Egypt) according to manufacturer protocol.

2.7.2 Determination of serum urea

Urea was measured in serum samples using a colorimetric urea assay kit (catalogue number: UR 21 10, Bio-diagnostic, Egyptian company of biotechnology, Egypt) according to manufacturer protocol.

2.8. Measurement of nitric oxide levels

Nitric oxide levels were measured in plasma sample by using colorimetric NO assay kit (Bio diagnostic, Egyptian company of biotechnology, Egypt) according to the manufacturer protocol.

2.9. Biochemical analysis of oxidative stress markers

2.9.1. Malondialdehyde analysis

The levels of lipid peroxidation were detected in plasma sample from heparinized blood by measuring the concentration of MDA by using colorimetric assay kit (catalogue number:MD 25 29, Bio-diagnostic kits, Egyptian company of biotechnology, Egypt) as described by the manufacturer.

2.9.2. Reduced glutathione measurement.

GSH was measured in heparinized blood sample by using colorimetric assay kit (catalogue number: GR 25 11 Bio- diagnostic, Egyptian company of biotechnology, Egypt) as described by the manufacturer.

2.10. Measurement of Cyclooxygenase-2 activity

Cyclooxygenase-2 activity was measured in aorta tissue homogenate using a COX-2 ELISA kit according to manufacturer's instructions.

2.11. Measurement of Prostaglandin E-2

Prostaglandin E-2 activity was measured in aorta tissue homogenate using a PGE-2 ELISA kit according to manufacturer's instructions.

2.12. Determination of Tumor necrosis factor-α

The TNF-α levels were evaluated in kidney tissue by using TNF-α ELISA kit according to the manufacturer's instructions.

2.13. Statistical analysis:

All the data were presented as mean ± standard error of mean (S.E). Statistical analysis was performed by using (Graph Pad software, Inc. La Jolla, CA, USA). All group variations were determined by using one-way analysis of variance (ANOVA) followed by the Tukey's multiple comparison test.

3. RESULTS

3.1. Hesperidin effect on blood pressure in renal artery stenosed hypertensive rats.

From the third week RAS caused a significant and a sustained increase in MAP when compared to CTR group. At the same time, animals treated with HES showed a significant decrease in MAP when compared to RAS group; this effect is graphically illustrated in **Figure 1**

3.2 Hesperidin effect on urea and creatinine levels

Renal artery stenosis caused a significant increase in urea and creatinine levels when compared to CTR group while animals treated with HES showed a significant decrease in both levels when compared to RAS group. This is graphically illustrated in **Figure 2 (A-B)**

3.4 Hesperidin effect on plasma nitric oxide levels

Renal artery stenosis caused a significant reduction in plasma NO levels, animals received HES showed a significant increase in NO when compared with RAS group this is graphically illustrated in **Figure 3**.

3.5 Hesperidin effect on oxidative stress

Renovascular HTN was associated with OS which was manifested by suppression of GSH levels and increasing in MDA levels **Figure 4 (A-B)** when compared to CTR group. HES improved both GSH levels, and MDA levels when compared to RAS group.

3.6 Hesperidin effect on Cyclooxygenase-2

Renal artery stenosis caused a significant increase in COX-2 levels when compared to CTR group as graphically shown in **Figure 5**, but animals treated with HES showed a significant decrease when compared to RAS group.

3.7 Hesperidin effect on Prostaglandin-E2 expression

Renal artery stenosis caused a significant increase in PG-E2 levels when compared to CTR group while animals treated with HES showed a significant decrease when compared to RAS group and this is graphically illustrated in **Figure 6**.

3.8 Hesperidin effect on Tumor necrosis factor-α

Renal artery stenosis caused a significant increase in TNF-α level when compared to CTR group, while animals treated with HES showed a significant decrease in it when compared to RAS group and this is graphically illustrated in **Figure 7**.

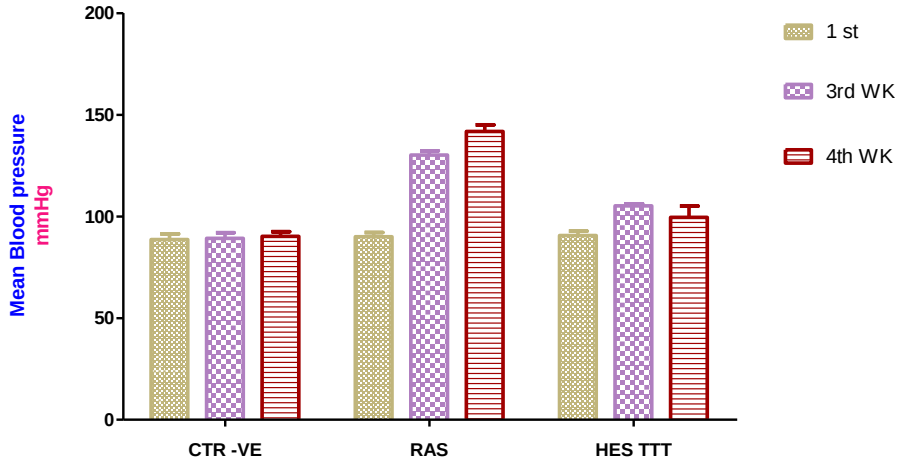


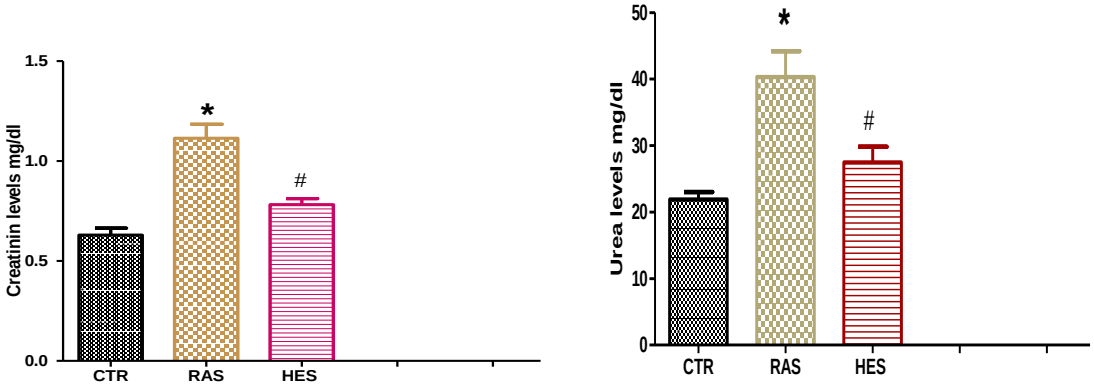
Figure (1), Hesperidin reduced blood pressure in renovascular hypertensive rats.

Hypertension was induced by RAS (2k1c)

Control group normal rats received water vehicle only (CTR group), Animals subjected to RAS received water vehicle only after RAS (RAS group), treated group animals subjected to RAS received water vehicle with dissolved HES orally (50mg/kg/day) for 30 days (HES group).

Mean blood pressure of different groups was measured using rat non-invasive blood pressure measurement.

Data were analyzed using one way ANOVA followed by Tukey's multiple comparison test and are represented as mean ± SE (*, $P < 0.05$ compared to CTR group. #, $P < 0.05$ compared to RVH group. N≥6).



(A) (B)

Figure 2 (A-B) Hesperidin reduced both urea and creatinine in renovascular hypertensive rats.

(A) Serum urea levels were measured.

(B) Serum Creatinine levels were measured.

Control group (CTR group), Animals with RAS (RAS group), treated group animals (HES group)

Data were analyzed using one way ANOVA followed by Tukey's multiple comparison test and are represented as mean ± SE (*, $P < 0.05$ compared to CTR group. #, $P < 0.05$ compared to RVH group. N≥6).

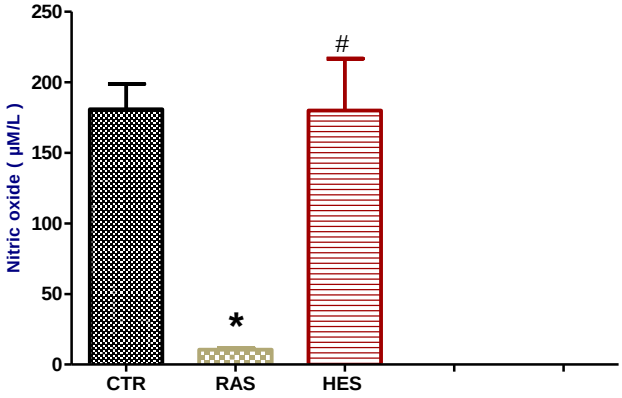
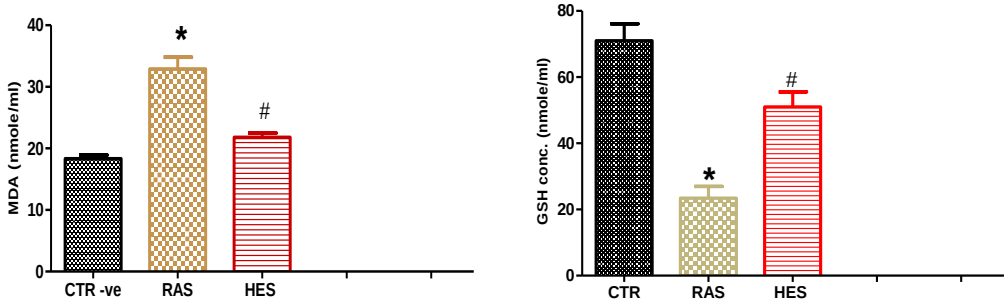


Figure (3). Hesperidin increased nitric oxide in renovascular hypertensive rats.
Control group (CTR group), Animals with RAS (RAS group), treated group animals (HES group)
Plasma NO measurement.
Data were analyzed using one way ANOVA followed by Tukey's multiple comparison test and are represented as mean ± SE (*, P < 0.05 compared to CTR group. #, P < 0.05 compared to RVH group. N≥6).



(A) **(B)**

Figure 4 (A-B), Hesperidin increased glutathione in renovascular hypertensive rats.
(A) Glutathione measurement.
(B) Malondialdehyde measurement.
Control group (CTR group), Animals with RAS (RAS group), treated group animals (HES group)
Data were analyzed using one way ANOVA followed by Tukey's multiple comparison test and are represented as mean ± SE (*, P < 0.05 compared to CTR group. #, P < 0.05 compared to RVH group. N≥6).

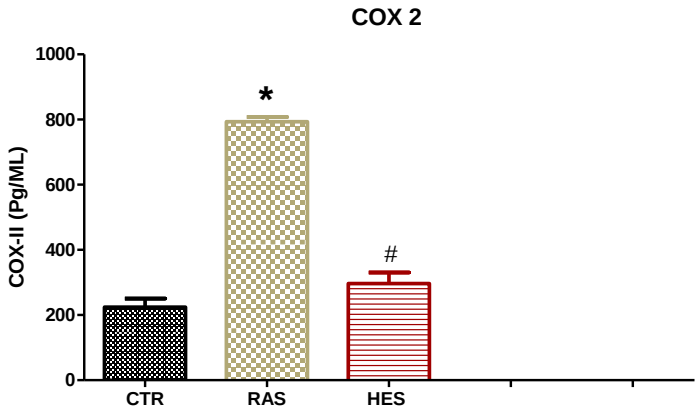


Figure (5), Hesperidin decreased COX-2 in renovascular hypertensive rats.
Control group (CTR group), Animals with RAS (RAS group), treated group animals (HES group)
Data were analyzed using one way ANOVA followed by Tukey's multiple comparison test and are represented as mean ± SE (*, P < 0.05 compared to CTR group. #, P < 0.05 compared to RVH group. N≥6).

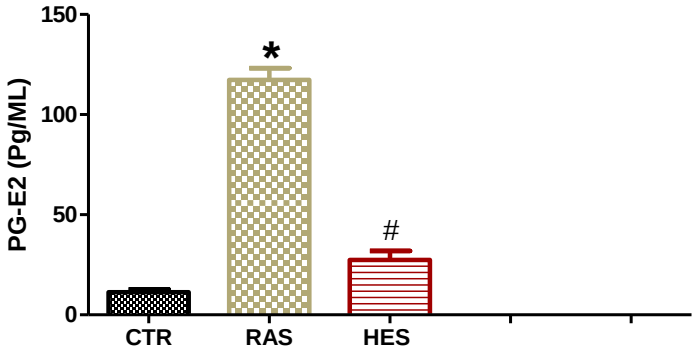


Figure (6), Hesperidin decreased PG-E2 in renovascular hypertensive rats.
Control group (CTR group), Animals with RAS (RAS group), treated group animals (HES group)
Data were analyzed using one way ANOVA followed by Tukey's multiple comparison test and are represented as mean ± SE (*, P < 0.05 compared to CTR group. #, P < 0.05 compared to RVH group. N≥6).

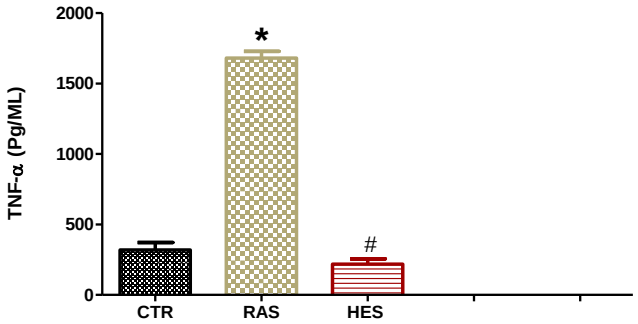


Figure (7), Hesperidin decreased TNF-α in renovascular hypertensive rats.
Control group (CTR group), Animals with RAS (RAS group), treated group animals (HES group)
Data were analyzed using one way ANOVA followed by Tukey's multiple comparison test and are represented as mean ± SE (*, P < 0.05 compared to CTR group. #, P < 0.05 compared to RVH group. N≥6).

DISCUSSION

Hypertension (HTN) is a very important global health challenge resulting in many major risk factors such as CVD and/or CKD **[14]**. It is very important to determine whether autoimmunity, inflammation and/or OS lead to HTN or vice versa **[15]**. The present study provides for the first-time new insights into the anti-inflammatory effects of HES on RAS and sheds some light on the role of oxidative stress in RVH modulation by HES.

Renal artery stenosis caused a significant increase in urea and creatinine levels along with a significant elevation of BP and OS biomarkers while it caused a significant reduction in NO plasma levels. It also caused upregulation of TNF-α, PG-E2 and COX-2 expression.

On the contrary, the oral administration of HES reduced BP in renal artery stenosed rats by attenuating many parameters which contributed to the progression of the case that includes the NO production increase and restoring the antioxidant status of hypertensive rats. Furthermore, HES administration also attenuated kidney function that was reflected by the reduction of urea and creatinine high levels besides it down-regulated inflammatory mediators PG-E2, COX-2 and TNF-α expression.

Several studies presented the anti-inflammatory effect of HES including cardioprotective activity in ischemic heart disease in diabetic rats **[16]** and the protective effect on HTN and cerebral thrombosis in stroke-prone in spontaneously hypertensive rats **[17]**.

In the earlier phase of renal damage serum creatinine level as a parameter is more important than the urea level **[18]**.HES ameliorating effects of urea and creatinine levels can be credited to its antioxidant activity as ROS has been reported to be involved in the impairment of glomerular filtration rate and eventually HTN **[19]**. The results of our study confirmed that RVH is associated with an increase in serum urea and creatinine levels which concurs with a previous reported study **[20]**.

Oxidative stress occurs when there is an imbalance between producing ROS and the ability of the cell to normalize that by antioxidants. Hypertensive patients Compared to normotensive volunteers were reported to have higher levels of oxidized/reduced glutathione ratios and MDA

along with lower glutathione peroxidase activities **[9]**.

In the current study OS was indicated by a reduction in the levels of non-enzymatic antioxidant GSH and the elevation of MDA levels in renovascular hypertensive rats. HES treatment decreased MDA levels and increased GSH levels. These results are consistent with the notion that the attenuation of HTN is associated with the reduction in OS biomarkers as mentioned in several studies that reported the protective effects of HES and its derivatives in inflammation, pain and OS in different models **[21]**. Where there are also some suggestions that the flavonoids posses its antioxidant activity by having hydrogen-donating and free-radical scavenging properties **[22]**.

Nitric oxide is an endothelium-derived vasodilator that plays a vital role in maintaining vascular tone and BP **[23]**. Consistently, the current study demonstrates that RVH caused by RAS is associated with a reduction in NO levels however, HES reduced BP and restored the blunted NO level in RVH rats. In accordance to our findings, a previous study revealed that HES prevented NO deficiency-induced cardiovascular remodeling in rats **[21]**.

The experimental model of RVH proposed by Goldblatt et al. (1934) resembles human RVH. In this model which is known by 2K1C model, the unilateral RAS reduces renal perfusion and triggers the release of many proinflammatory cytokines that results in the elevation of TNF-α level **[24]**. Moreover, a study of Carvalho-Galvão A et al. reported that the inhibition of TNF-α reduced HTN due to attenuating OS in the rostral ventrolateral medulla in RVH rats **[25]**. In agreement with that hypothesis, our results demonstrate that the inhibition of TNF-α by HES, promotes a reduction in BP compared to non-treated hypertensive rats, suggesting the essential role of TNF-α in the progression of RVH.

A previous study has demonstrated that HES inhibited COX-2 gene and protein expression and suggested that HES regulated COX-2 expression via the inhibition of NF-κB activity **[26]**. Cyclooxygenase is an enzyme that is responsible for the initial rate-limiting step of the metabolism of arachidonic acid to prostaglandins (PGs). Yielding prostaglandin-H2 (PGH_2) which is subsequently metabolized by several enzymes into the primary bioactive prostaglandins, including PG-E2 that is involved in the regulation of water and sodium reabsorption and increases potassium secretion mostly by stimulating the secretion of renin **[27]**. Therefore, in the current study the increase in COX-2/PG-E2 cascade contributed to the elevation of BP caused by RAS that agrees with another previous study **[28]**.

After all, the present study manifested that the antihypertensive activity of HES was significantly demonstrated in modulating blood pressure levels in renal artery stenosed rats. The administration of HES showed significantly the corrective effect of HES on RVH, inflammation and oxidative stress consistently.

In conclusion, the findings of this study proposed a possible mechanism for the antihypertensive activity of HES in RVH model in rats. This effect was affirmed by increasing the NO levels. Also, reduced inflammatory mediators such as TNF-α and COX-2 and PGE-2 in turn diminish the OS. Hence, inflammation and oxidative stress present a potential target to inhibit damages associated with RVH.

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All the authors have participated in this research in the concept and design, analysis and interpretation of data, drafting and revising the manuscript and they have approved the manuscript as submitted.

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