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Anti-hypertensive and anti-oxidant activities of walnut almond oil, and corn and candesartan on L-NAME induced hypertensive rats

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Abstract

The present study aims to investigate the effects of almond oil, walnut oil, corn, and candesartan on the blood pressure (BP) and some biochemical parameters in L-NAME-induced hypertensive rats. Hypertension was induced experimentally by administration of L-NAME (40 mg/kg of body weight) dissolved in water by gavage. The animals were randomly divided into six groups: normal control, hypertensive (HT), HT+ Walnut oil (3ml/kg body weight), HT+ Almond oil (3 ml/kg body weight), HT+ Candesartan (3mg/kg body weight) by gavage, and HT+ Corn (%30 of diet), At the end of the experiments blood sample were taken from rats by heart puncture. The results indicated that administration with L-NAME induced hypertension after four weeks in rats by significantly increasing the BP, and significant elevation in the level endothelin1(ET-1), angiotensin I-converting enzyme (ACE), and serum *malondialdehyde* (MDA) were observed. Whereas the levels of nitric oxide (NO) and reduced glutathione (GSH) decreased. Supplementation of walnut oil, corn, and candesartan for three weeks was significantly reduced blood pressures, ACE, ET1, and MDA and a non-significant decrease in ACE concentration by candesartan. While hypertensive rats treated with walnut oil and corn showed significant elevation of NO, GSH. But almond oil supplementation diminished MDA and GSH concentrations. Finally, the results revealed that corn more effectively than walnut oil and near the action of candesartan while almond oil non-significant effect on hypertension.

Introduction

Hypertension is a universal epidemic, the most common serious chronic health problem, and a high-risk factor for myocardial infarction, arteriosclerosis, stroke, and end-stage renal disease [1]. The number of peoples has hypertension increased from 594 million to 1.3 billion only in 40 years from 1975 to 2015 and expected rise about 30% until 2025, the rise was seen largely in low-and middle-income countries. The increase may be due to an increased risk factor in those populations WHO reported in 2019 [2]. Most of the studies reveal that hypertension is caused by endothelial dysfunction [3], endothelial dysfunction can be detected initially when hypertension become develops. Endothelial function is controlled by a balance between vasoconstrictors and vasodilators. It is well-known that NO is released from vascular endothelial cells and causes dilation in the vessel, it's acting an as important role in regulating vascular tone and growth [4]. Administration of L-arginine analogs such as NG-nitro-L-arginine methyl ester hydrochloride (L-NAME) prevents NO production from NO synthase (NOS) and absences of NO enhances vasoconstrictor released in vessels and finally lead to hypertension [5], L-NAME administration to the rats causes vascular endothelium damage and suitable to study about hypertension, cardiovascular and kidney disease [6], this model used in an early stage of hypertension than late vascular alterations and appropriate to test antihypertensive drugs in vascular protection in the context of NO deficiency [7].

Many types of antihypertensive drugs make available, peoples especially in developing countries prefer herbal remedies as alternatives to drugs for control of hypertension and its complications. Furthermore, because their herbal remedies fewer side effects, cost, and better decency direct the researcher attention towards the search for new drugs from natural sources [8], many plants and natural products are pronounced as antihypertensive or hypotensive effects [9], but need more studies to prove the effectiveness and explore the mechanism of action and also reveal the safety profile to use or not [10], there are several species of medicinal plants and their extractions commonly used in the blood pressure regulation, including walnut oil and almond oil [11], they contain a large number of polyphenol compounds, γ-tocopherol, α-linolenic acid (ALA), linoleic acid, L-arginine monounsaturated fatty acids (MUFA), polyunsaturated fatty acid (PUFAs) and anti-oxidant. Whole-grain corn is as healthy as any cereal grain and a good source for fiber and various vitamins, minerals, and antioxidants [12]. Candesartan one of the classes of drugs called angiotensin receptor blockers (ARBs), is using to treat hypertension, strokes, heart attacks, and some other problems via blood to flow more easily in vessels and relaxing blood vessels [13]. This study was aimed to investigate the role of walnut oil, almond oil, and corn in improving blood pressure and endothelial dysfunction in L-NAME-induced hypertensive rats.

Material and methods

Experimental animal

Thirty-six male albino rats (*Rattus norvegicus*) of about 250-300) body weight & were used. The experiment was achieved between 4th April 2019 to 4th June 2019. The animals were divided into six groups each group with 6 rats. And they were housed under standard laboratory conditions of 12 hours light: 12 hours dark photoperiod, 22.0 ± 4.0º C, and the animals were given standard rat of pellets and tap water *ad libitum.*

Plant extraction and drug preparation

Almond and walnut oil extraction

A large quantity of the dry repined almond *(Prunus amygdalus)* and walnut *(Juglans regia)* seeds were collected from the Sitek and Hawraman-region of Sulaimania governorates. Seeds were decocted and naked and ground with using Maulinex electrical grinder into a fine powder. Then dried in an air circulating oven and preserved for extraction of the oil in a refrigerator thereafter oil was extracted from this powder by using 30 g of this powder into a thimble with analytical grade petroleum ether (boiling point 60-80^{o} C) for 8 hours as refluxing a solvent using a Soxhlet apparatus (Lab glass-Germany) fitted with 500 ml round-bottomed flask by using a rotary evaporator, the solvent was removed under vacuum and the remains were dried in an oven at 80° C then the oil filtered and preserved in the dark at 4° C until used [14].

Corn preparation

Corn (*Zea mays*) seeds were taken from Altun kopry – Kirkuk governorate. The seeds were dried in an oven at 50° C for 1 hour then the dried seeds were ground with using an electrical grinder into a fine powder then mixed with standard chow about 30% of the total volume.

Candesartan cilexetil preparation

Candesartan (ATACAND - Switzerland) was bought from Hemn Pharmacy and it was administrated 3 ml/kg to rats for 3 weeks [13].

Induction of hypertension

Experimentally, hypertension was induced by oral administration of L-NAME (40 mg/kg/day in the water by gavage for 4 weeks (one week without treatment + 3 weeks with treatment) [15].

Experimental design

The thirty-six rats were divided into six groups, 6 rats in each group; rats in the normal control group were given standard rat chow and tap water *ad libitum* (control). Whereas rats in the L-NAME –treated group were administrated L-NAME (40 mg/kg/day). Animals in the L-NAME-treated group were randomly assigned into

five subgroups, consisting of (1) L-NAME group (model), (2) Animals received Walnut oil, (3 ml/kg), (3) Almond oil (3 ml/kg), (4) Corn (30% of standard chow), and (5) Animals received candesartan (3 mg/kg).

Blood Pressure Recording

Blood pressure (SBP and DBP) were recorded at the starting of the experiment and repeated weekly at the same time. Animals were kept in the cylinders for 5–15 minutes/day for 5 days to recording BP by tail-cuff technique (Kent Scientific, USA), and before recording the blood pressure the rats were heated for 30 minutes at 28° C for better detection of tail artery pulse after recorded for about 15-20 times we concluded the mean of blood pressure. The mean arterial blood pressure (MAP) was calculated [16] using the following formula: MAP=DBP+0.412 (SBP-DBP).

Blood collection

At the end of experiments (4 weeks), all rats fasted during the night and then anesthetized with ketamine hydrochloride (50 mg/ Kg body weight) and xylazine (5 mg/kg), the blood sample was taken by heart puncture put into tubes and the serum were separated by centrifuging at 3000 rpm for 15 minutes.

Estimation of serum biochemical parameters

Serum angiotensin-converting enzyme (ACE), serum nitric oxide (NO), serum endothelin1 (ET1), serum Malondialdehyde (MDA), and serum reduced glutathione (GSH) were measured by enzyme-linked immunosorbent assay (ELISA) kits (Elabsicence, China).

Statistical analysis

Data were analyzed by using the statistical program Graph Pad (Prism 2019), utilizing one way ANOVA with multiple comparisons and TukeyTechnique for descriptive analysis.

Results and Discussion

L-NAME-induced hypertensive rats showed a significant ($p < 0.001$) elevation in the MAP (168.87 ± 12.531) highly significant increase in the level of ET-1 (6.32 ± 0.626) and decrease significantly level of NO (27.22 ± 4.002) when compared to the control rats group (Table 1). Similar results were observed by a previous experimental hypertensive study [15, 17, 18] in which they were revealed that oral administration of 40 mg/kg L-NAME once daily for 7 days induced hypertension in rats model. In which blood pressure and ET-1 increased significantly but decreased significantly NO when compared to the normal control group, L-NAME is recognized as an inhibitor of NOS result in decrease NO and cause alteration balance between vasodilator and vasoconstrictor [18] NO plays a very important role in regulates vascular tone and responsible vasodilation in the endothelium, therefore inhibition generation NO cause vasoconstriction and cause increase blood pressure [19]. Furthermore, Sventek et al. reported L-NAME can be induced expression of ET-1. Moreover, it was recently demonstrated that chronic administration of L-NAME cause induces vascular ET-1 gene expression in large conduit arteries [20]. ET-1 is a powerful peptide vasoconstrictor and responsible to control blood flow that plays an important role in elevate blood pressure in rats model for hypertension.

Treatment of hypertensive rats with walnut oil decreased blood pressure significantly (137.14 ± 13.124) and ET-1 (5.06 ± 0.363) but increased NO (44.171 ± 3.753) when compared with the rats model. This result is in agreement with a previous study [21], walnut oil contains a large amount of omega-3 fatty acids that are essential for human nutrition. Three types of fatty acids mostly found in walnut oil are linoleic, oleic acid, and alpha-linolenic acid. MUFA and PUFA are a presence in walnut and their role in cardiovascular protective was approved. These substances can reduce BP by decrease thromboxane A2 and therefore its vasoconstrictor effect [22]. Demonstrated walnut or walnut oil can significantly decrease BP and total peripheral resistance during stress or rest when consumed with the diet for 5-6 weeks [23]. Zhao et al. revealed that foods and oils containing ALA such as a walnut important role in improve endothelial function and cause reduction of endothelin-1 expression [24]. Ros, 2010 reported the good effect of the walnut extract by regulating redox balance and production of NO. Phenol compounds play an important role in the anti-oxidant and NO production which is a major component of walnut oils [12]. Besides, walnut is good sourcing for L-arginine which is the amino acid precursor of the endogenous vasodilator NO. Thus, a part of the protecting effect of

walnut oil on L-NAME-induced hypertension can describe by its antioxidant properties, endothelial protective, and improvement of endothelium-dependent vasodilation [25].

While Treatment of hypertensive rats with corn decreased blood pressure extremely significantly (125.82 ± 12.387) and ET-1 (4.93 ± 0.727) but increased NO (47.62 ± 5.696) when compared with the control group, this result line with the previous study [26]. Corn possesses antioxidant activity and contains a large amount of phenolic compound that is useful for decrease blood pressure, Shah et al. mentioned that rats induced hypertension were fed corn improve cardiovascular also elevate heart rate [27]. Ohsaki et al. reported hypertensive rats were administrated ferulic acid reduced BP because that ferulic acid limited ACE activity also causes a reduction of plasma ACE. The results of increase NO and decrease ET1 rats received corn may be due to their component that is very rich in component polyphenols that significantly regulate expression of eNOS and ET-1 in the vascular endothelium [28]. The ability of a phenolic compound to elevate the expression of the gene encoding eNOS and reduced expression of the gene encoding the vasoconstrictor ET-1 cause vasodilation and reducing blood pressure [29]. revealed corn extract can increase production NO, moreover showed that NO can inhibits ET-1 production through the suppression of nuclear factor B [30]. There seems to be an opposite relation between NO and ET-1, which may serve to modulate endothelial function in the vasculature.

However treatment of hypertensive rats with almond oil was unable to prevent and treated the hypertensive rats and failed to restored blood pressure (166.76 ± 14.723), ET-1 (6.26 ± 0.532), and NO (31.34 ± 3.682) when compared with the control group, this result agrees with Al Tamimi, 2016 [31]. Even though almond is a good source of alpha-tocopherol which has an important role in improving the health of blood vessels and preventing blood circulation diseases. Al Tamimi et al. reported administration of almond oil to rat model didn't observe any changes in the rat's BP [32], Khoo, 2016 revealed Regardless of recommendation to receive more vitamin E to reduce risk factors of CVD but the effect of vitamin E supplementation on the clinic or ambulatory BP in treated hypertensive patients had not been observed [31], Hussein and Raheem mentioned that administration almond /almond extract may increase serum NO may be due to their component such phenolic compound, flavonoids, folic acid, and vitamin E those elements can modulate vascular function their decrease may due to antioxidant effect of almond oil [33].

Oral administration of candesartan significantly restored the elevation of blood pressure (108.51 ± 10.234) and ET-1 (3.74 ± 0.511) but increased NO (51.71 ± 3.253) when compared with the control rats, these results are supported by previous finding [34], candesartan is a drug used to control elevated blood pressure by angiotensin II receptor antagonist because Angiotensin II actions as a vasoconstrictor and stimulation aldosterone secretion angiotensin II also cause the release of aldosterone. When aldosterone released cause absorbed sodium along with water and the final result is an elevation in blood pressure, Song et al. results show that Ang II despite stimulation to secretion aldosterone also can up-regulate ETAR expression and enhanced ET-1 binding in the aorta and VSMCs [35]. Observed patients with essential hypertension when treated with candesartan significantly reduction in the level of circulating ET-1 [36]. Moreover, documented NO restored when the AT-1 receptor blockade by candesartan. The mechanism of improved production of NO can be by their action of candesartan which is blockade AT1 receptors and cause an increase in the levels of angiotensin II, then activation of Ang II type 2 (AT2) receptors by increased Ang II. It has been reported that NO is produced via the activation of AT2 receptors and bradykinin B2 receptors [37]. Figures (1, 2, and 3) showed the effect of treatments on BP, NO, and ET1 levels.

Table (1): Effect of walnut oil, almond oil, corn, and candesartan on BP, NO, and ET1 in hypertensive rats.

Parameters / groups	Mean arterial pressure(MAP)mmHg	Serum nitric oxide µmoL/L	Serum endothelin-1 pg/mL
Control	108.91±12.531[a]	63.11 ±5.426[c]	3.54±0.434[b]
Hypertensive	168.87±13.438[b]	27.22± 4.002[b]	6.32±0.626[a]
HT + walnut oil	137.14±13.124[a]	44.17±3. 753[a]	5.06±0.336[c]
HT + almond	166.76±14.723[b]	31.34±3,682 [b]	6.2±0.532[a]
HT + Corn	125.82±12.387[a]	47.62±5.696 [a]	4.9±0.728[c]
HT + Candesartan	108.51±10.234[a]	51.71±+3.253 [a]	3.7±0.511[b]

Value are expressed as mean ± S.E. Different letters indicate significant differences between means * = p<0.05, ** = p<0.01, *** = p<0.00

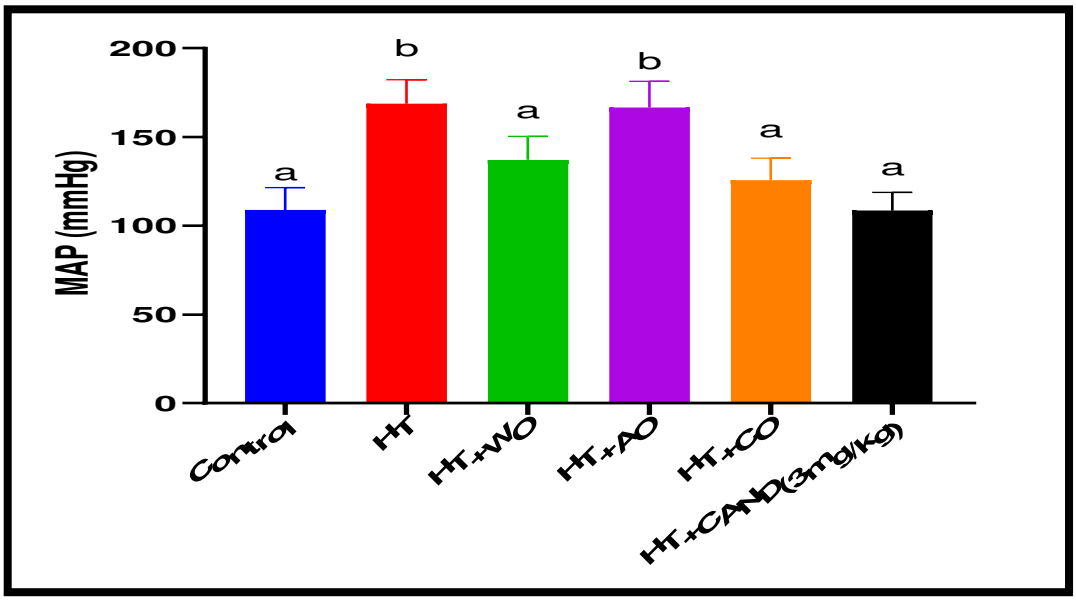

Figure-1: Effect of walnut oil (WO), almond oil (AO), corn (CO), and candesartan (CAND) on MAP in hypertensive (HT) rats.

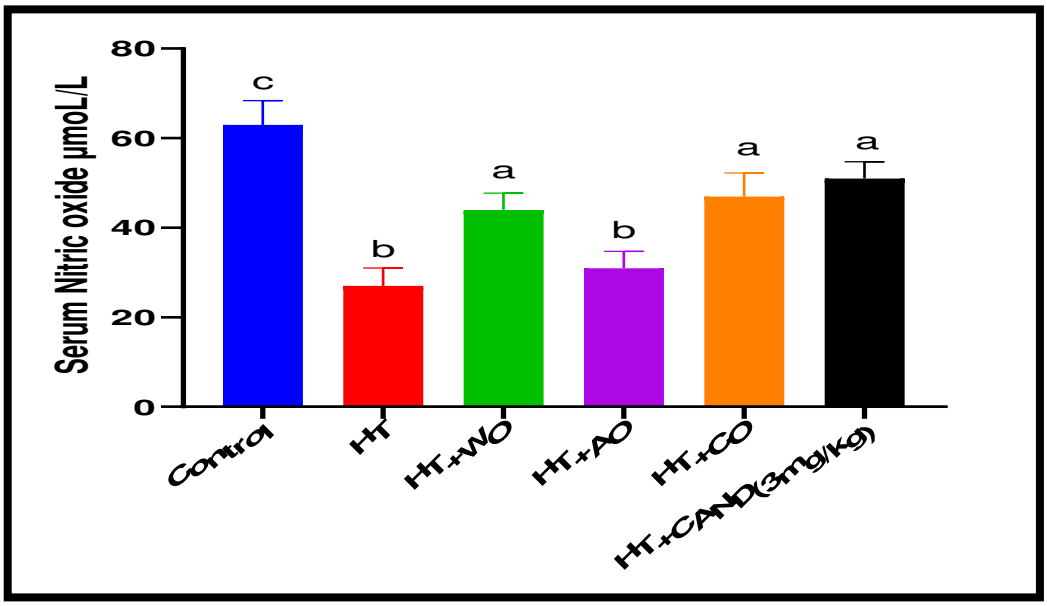

Figure-2: Effect of walnut oil (WO), almond oil (AO), corn (CO), and candesartan (CAND) on Serum nitric oxide (NO) in hypertensive rats.

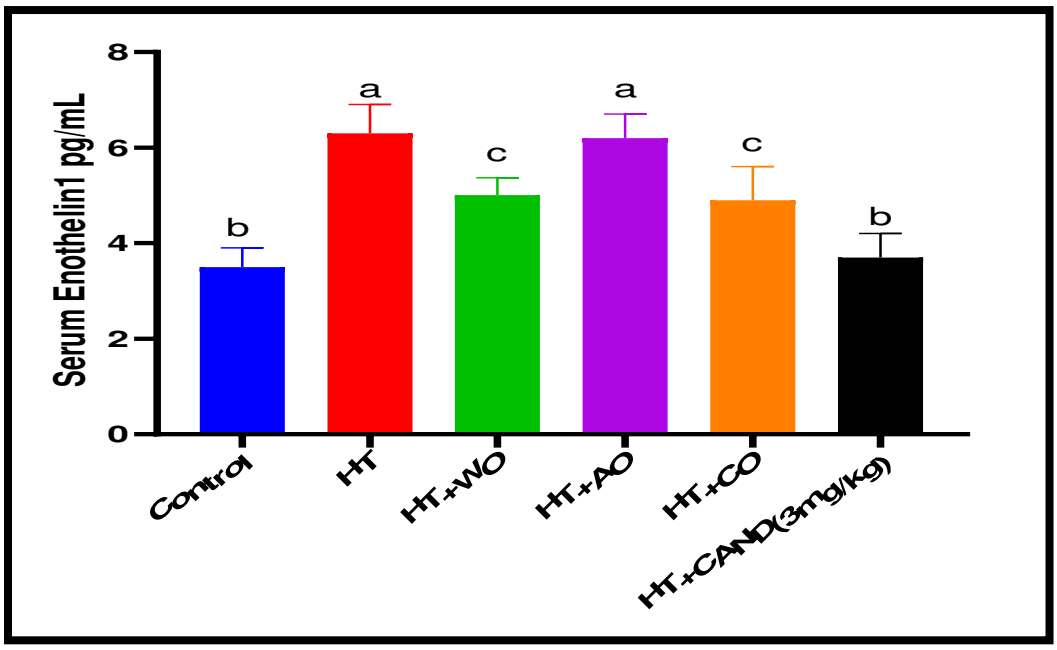

Figure-3: Effect of walnut oil (WO), almond oil (AO), corn (CO), and candesartan (CAND) on Serum endothelin-1(ET-1) in hypertensive rats.

Hypertensive rats showed a significant elevation in the level of serum ACE (86.06 ± 8.841) and MDA (5.8 ± 0.573) but significantly decreased GSH (8.52 ± 1.643) when compere with the control group (Table 2), the similar result was obtained by a previous experimental hypertensive study [15], L-NAME is recognized as an inhibitor of NOS resulting in decreased NO a vital vasodilator [15, 38]. Acute and chronic inhibition of NO produces endothelial dysfunction [39], moreover showed chronic L-NAME administration can modulation of ACE which is the enzyme responsible for the conversion of Ang I to Ang II, in addition to Ang II induction, the production of ROS and subsequently, oxidative stress is an important pathogenic factor in L-NAME induced hypertension [19], vascular remodeling, fibrosis, inflammation and hypertrophy due to decreased NO, increased Ang II, as well as increased ROS, have all been noted in L-NAME induced hypertension [40].

Orally administration of walnut oil significantly decreased ACE (63.16 ± 9.541) and MDA (4.33 ± 0.503) but elevated GSH (10.84 ± 1.205), this result agrees with a previous study [41], it was reported that the ethanol extract of the walnut fruit can inhibit the effect of angiotensin-converting enzyme CE by 40%. Several studies have reported walnut improved endothelial function and increased flow-mediated dilation in overweight volunteers and the relationship between improved endothelial function and walnuts was confirmed in a systematic review [42], *walnut oil* is a good source of phenolic (flavonoid and non-flavonoid) and due to their content have antioxidant and free radical scavenging properties. It is established the high association between phenol content and radical scavenging activity of walnut oil, additionally, polyphenols, flavonoids, vitamin E, and other antioxidant components present in walnuts can serve as natural antioxidants [43]. Bostani et al. indicated Walnut oil could improve the antioxidant capacity by increasing the activities of antioxidant enzymes and reduction of MDA, also regulating the expression of oxidative stress-related proteins [25]. The lesser presence of end-products such as MDA can be translated into a lesser concentration of peroxyl radicals and hydroperoxyl, both generating factors of lipid oxidation. The reduced concentration of oxidizing agents may be linked to the enhanced GSH content Moreover showed walnut oil can increase the antioxidant capacity of cells, the mechanism improves endothelial function by walnuts maybe through promoting the release of nitric oxide and increased membrane fluidity of endothelial cells [44], a previous study by Pandareesh et al. showed Long-term dietary supplement walnuts 6% or 9% for a long time significantly enhanced antioxidant activity and decreased level of MDA and ROS when compared to the control diet [45].
Treatment of hypertensive rats with corn extremely significantly decreased ACE (59.63 ± 7.293) and MDA (3.71 ± 0.547) while elevated GSH (11.21 ± 0.657) when compared with the control rats, these results agree with previous studies. Fabila-Garca et al. indicted corn extract can inhibit or decrease ACE may be caused by

the presence of soluble components such as peptides in corn [46]. Other studies show corn has antioxidant activity and increases NO production by considering the inhibition of peroxynitrite formation induced by inhibition of tyrosine nitration [47]. The antioxidant activity of maize extracts is maybe due to the presence of phenolic compounds such as flavonoids and ferulic acid [48]. Ohsaki et al. documented ferulic acid decrease blood pressure through the reduction of ACE activity [28]. A previous study showed corn extract can elevation GSH concentration in rats group when treating with corn [49], however, another study showed rats supplement with corn can reduction in the level of MDA [50]. Ramos-Escudero et al. reported corn extract to contain some functional compound can penetrate cell membranes and participate in stimulating release antioxidant enzyme to reduce oxidative damage to cells caused by free radicals and showed a reduction in MDA level can be observed in the group treated with corn may be due to the presence of polyphenols which is responsible to scavenge free radicals and to increase levels of endogenous antioxidant enzymes [51].

Administration of almond oil to hypertensive rats the level serum ACE (84.33 ± 11.252) was not restored significantly in comparison to the control group while MDA (4.37 ± 0.328) and GSH (10.33 ± 0.876) were restored significantly. Al-Attar documented the same result [52]. Almond oil can be inhibiting or reducing the progress of various oxidative stress-related diseases through antioxidant and antiradical activity [33], the reduction in the level of serum MDA in those groups treating with almond oil potentially by anti-oxidant properties of almonds oil [53]. Moayedi et al. mentioned almond oil supplementation can improve antioxidant defenses and reduce biomarkers of oxidative also reduce serum concentrations of malondialdehyde MDA and cholesterol [54]. Moreover, Jia et al. reported that almond oil significantly inhibited the formation of MDA due to the high content of antioxidants [55]. Moreover, the ability of vitamin-E to scavenge lipid peroxyl radicals by blocking lipid peroxidation of polyunsaturated fatty acids in membranes, it keeps against lipid peroxidation through its chain-breaking antioxidant activity [56]. Furthermore, Etim et al. demonstrate chronic supplement vitamin E improves the GSH/GSSG ratio in patients with essential hypertension [57].

In the present study, serum ACE (87.62 ± 10.832) in hypertensive treated rat with candesartan did not improve while can improve MDA (3.27 ± 0.317) and GSH (12.34 ± 1.424) when compared with control, similar results were obtained by a previous studies [58] candesartan blockade binding Ang II with their receptor and causes elevation of the plasma angiotensin II (Ang II) level and ACE because of a lack of negative feedback on renin activity or competition of Ang II with the AT1 receptor [59]. Takeda et al. reported candesartan increased ACE also elevated Angiotensin-converting enzyme 2 (ACE2), it is a homolog of the ACE enzyme expressed primarily in the vascular endothelium, produce Ang 1–7 by delete single amino acid from the carboxy-terminus of Ang II [60]. Previous studies suggested that the ACE2–Ang 1–7 axis has an important role in hypertensive disease [61], Ang (1-7) is a vasodilator agent that plays important roles in cardiovascular organs such as the heart, blood vessels, and kidneys having functions frequently opposed to those attributed to the major effector component of the RAS Ang II [60].

Chan et al. mentioned candesartan anti-oxidative effect significantly decreased lipid peroxidation level (MDA) and increased GSH level in the liver tissues compared with induced animals. The antioxidant and anti-inflammatory effect of candesartan was attributed to the blockade of angiotensin receptor and inhibition of Ang-II which is responsible for the generation of ROS via activation of (NADPH-oxidase) enzyme which is a major source of ROS and oxidative stress in different tissues that mediates tissue damage [62].

Table (2): Effect of walnut oil, almond oil, corn, and candesartan on ACE, MDA, and GSH in the hypertensive rat.

Parameter / Group	Serum angiotensin-converting enzyme (ACE) ng/g	Serum Malondialdehyde (MDA) µmol/L	Serum Glutathione (GSH) µg/mg
control	53.13±7.825[a]	2.63 ±0.361[a]	14.74±1.425[a]
Hypertensive	86.06 ±8.841[b]	5.8± 0.573[b]	8.52±1.643[b]
HT + walnut oil	61.66± 9.541[a]	4.33± 0.503[c]	10.84±1.205[c]
HT + almond	84.33±11.252[b]	4.37± 0.328 [c]	10.33±0.876[bc]
HT + Corn	57.63± 7.293[a]	3.71±0.547 [cd]	11.21±0.657[c]
HT+Cand	87.62±10.832[b]	3.27±0.317 [ad]	12.34±1.424[c]

Value are expressed as mean ± S.E. Different letters indicate significant differences between means * = p<0.05, ** = p<0.01, *** =p<0.001

Conclusion

The present study provides evidence that the walnut oil and corn exhibited considerable antihypertensive potential. Walnut oil, corn, and candesartan significantly normalized the elevated systolic and diastolic BP as well as the pulse rate after three weeks of treatment, while almond oil non-significant effect on blood pressure in hypertensive rats. Walnut oil and corn were efficient to improve endothelial dysfunction and reversed the effect of L-NAME-induced hypertension as well. Moreover, the present study suggested a multimechanistic action mediating the walnut oil and corn antihypertensive effect including antioxidant, ET-1, and ACE inhibitory action in addition to the up-regulation of eNOS expression. These findings point out the augmented beneficial effects of walnut oil and corn as a complementary treatment in the management of hypertension and its complications.

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