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Study of the effect of coenzyme Q10 on high blood pressure resulting from hyperactivity of the adrenal gland in male white rats

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Abstract

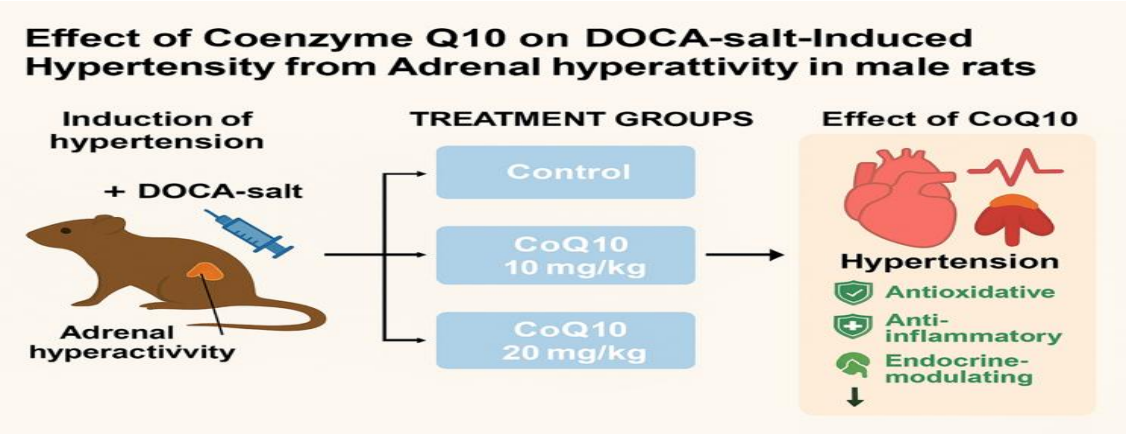
The study aimed to regulate high blood pressure resulting from hyperactivity of the adrenal gland using coenzyme Q10. Hyperactivity of the adrenal gland is one of the secondary causes of high blood pressure as a result of excessive secretion of the hormones cortisol and aldosterone, which are the main causes of sodium and water retention as well as high peripheral vascular resistance.

The study was conducted on 24 white rats whose weight ranged between (200-250) grams, intending to know the effect of Q10 on blood pressure resulting from hyperactivity of the adrenal gland. Which was randomly distributed into four groups. Control group C: The negative control group was given physiological water. The second group, T1: The positive group included animals in which high blood pressure was induced by DOCA-salt, at a concentration of 20 mg/kg of body weight, daily for 14 days. The third group, T2, included animals in which high blood pressure was induced and then dosed with coenzyme Q10 at a concentration of 10 mg/kg of body weight for 30 days. The fourth group, T3, included animals in which high blood pressure was induced. and then dosed with coenzyme Q10 at a concentration of 20 mg/kg) of body weight for 30 days.

After the end of the trial period, the following parameters were studied: hormonal parameters included (corticosterone, Aldosterone, epinephrine), kidney functions. (urea, Creatinine), antioxidants (MDA, CAT, SOD, GSH), and inflammatory factors (TNF, IL6).

The results showed that the rats dosed with ACTH showed a significant increase (P <0.05) in the level of hormonal parameters (corticosterone, Aldosterone, Epinephrine, Norepinephrine) compared to the control group ,kidney function (urea, Creatinine), antioxidants (MDA, CAT, SOD, GSH), and tumor necrosis factors (TNF, IL6), while the results showed that the groups that were dosed with coenzyme Q10 at a concentration of (10 mg/kg) had a slight decrease in the level of blood pressure, while the results showed a significant decrease ($p < 0.05$) in the groups that It was dosed with Q10 supplement at a concentration of (20 mg/kg) of body weight.

Keywords: coenzyme Q10, adrenal gland, blood pressure, corticosterone, Aldosterone, Epinephrine and Norepinephrine



Introduction

High blood pressure is one of the most common causes of cardiovascular disease. It is the main cause of many deaths. Despite continuous dietary and drug regulation of high blood pressure, its control among those with it is still variable (2). This emphasizes the importance of discovering new drug and nutritional interventions to treat high blood pressure disorders by studying the causes of the disease.

Hypertension has generally been classified into two categories: primary and secondary hypertension. The percentage of patients with secondary hypertension is only about 10%, the causes of which include primary hyperaldosteronism, renal artery stenosis, and monogenic disorders (8). Whereas primary hypertension is associated with unknown causes that will coincide with aging, obesity, and diabetes. Therefore, the process of identifying the mechanisms and causes of the disease is difficult, in addition to the difficulty of finding appropriate interventions for many patients that directly affect high blood pressure. Previous studies of hypertension in animal models have demonstrated multiple factors that contribute to

blood pressure regulation, including environmental, genetic, physiological, and microbial factors (11).

The adrenal gland is one of the most important glandular systems in the body as a result of its active role in regulating the hormonal response to stress as well as the body's chemical balance. The adrenal gland consists of an external structure known as the cortex and an internal structure called the medulla. Both of them play an active role in regulating blood pressure through a group of mechanisms (3), as excessive aldosterone production is caused by the cortex. The adrenal gland is one of the most important secondary causes of high blood pressure through increased sodium and water retention with a low level of potassium, which leads to an increase in blood volume and thus high blood pressure, as it is estimated that about 5-10% of people who suffer from high blood pressure are associated with hyperaldosteronism (5).

Cushing's syndrome, which results from excessive cortisol production by the adrenal gland, affects cardiovascular output by increasing sensitivity to catecholamines, as well as enhancing oxidative inflammation and insulin resistance, and these factors contribute to raising blood pressure (15). A study confirmed that performing a chemical ablation with ethanol of one of the adrenal glands contributed to reducing the level of high blood pressure (17).

Q10 is a fatty compound found in mitochondria. It is an effective antioxidant that protects cells from oxidation as a result of its pivotal role in transferring electrons and producing energy. It is a mobile electron carrier in the respiratory chain within mitochondria, as it is found naturally in the bodies of living organisms, in addition to being a rich nutritional element similar to vitamins (Littarru et al., 2017). Enzyme Q10 is one of the intermediate compounds that plays an active role in transferring electrons from one enzyme compound to another, with its antioxidant properties in inhibiting lipid peroxidation as well as protecting low-density lipoproteins from oxidation. Q10 directly contributes to the prevention of cardiovascular diseases and high blood pressure through its role in enhancing energy while stabilizing mitochondrial membranes (18), as studies have shown that using Q10 as a nutritional supplement for patients with high blood pressure effectively contributed to reducing the level of systolic blood pressure to the level of 17 mm and diastolic to the level

Materials and methods of work

In this experiment, male white rats whose weight ranged from (200-250) grams and whose ages ranged from (3-4) months were used. The rats were placed in special cages and an environment Controlled laboratory conditions of 22±2°C and humidity level of 55±5, with light/dark cycles ranging from (10-14) hours. The animals were provided with water and ration

during the experiment period in a free manner, and the animals were left a week before the experiment to adapt to laboratory conditions.

Induction of high blood pressure

High blood pressure was induced by DOCA-salt at a concentration of 20 mg/kg) of body weight, (18) by subcutaneous injection twice a week over a period of 14 weeks, with the addition of sodium chloride at a rate of 1% and potassium chloride at a rate of 0.2% daily to the water in all treatments except the control group. Blood pressure level was also measured twice a week during the duration of the experiment using a device with a tail-cuff method (Kent Scientific Corporation)

coenzyme Q10

Use Q10 was obtained from a pharmaceutical pharmacy in two doses of 10 mg/kg body weight (16) and 20 mg/kg body weight (7) after completely dissolving the two doses in olive oil at a rate of 1 mm daily for 30 days, except the control group.

Experiment design

This experiment used 24 white male rats ,distributed into four groups randomly; each group included (7) and was then divided as follows:

1- The first group: Control group (C): It included animals that were dosed with the physiological solution of NaCl at a concentration of 0.9% during the duration of the experiment.

2- The second group (T1) included animals in which high blood pressure was induced by (DOCA) at a concentration of (20 mg/kg) of body weight by subcutaneous injection twice a week over a period of 14 weeks.

3- The third group (T2): It included animals that were induced with high blood pressure and were then dosed with coenzyme Q10 at a concentration of (10 mg/kg of body weight) for a period of 30 days using a wine syringe containing a curved needle.

4- The fourth group (T3): It included animals that were induced high blood pressure and then I dosed coenzyme Q10 at a concentration of (10 mg/kg body weight) for 30 days using a wine syringe containing a curved needle.

Sample collection

On the 30th day from the end of the experiment, the animals were anesthetized with chloroform, and blood was drawn directly from the heart by stabbing the heart and using a sterile disposable syringe with a capacity of 5 mL; 2 ml of the drawn blood was placed, 3 ml of blood was placed in EDTA-free glass tubes, left for 15-20 minutes at laboratory temperature, and then the samples were placed in the centrifuge. The centrifuge (Heraeus-Christ Gumby) at

a speed of 3000 rpm for 15 minutes for the purpose of separating the serum. The serum was isolated using a micropipette, and the samples were placed in plastic tubes to conduct hormonal and biochemical tests. The serum was stored at a temperature of 20°C until use.

Measuring the level of hormone parameters

The ELISA device was used to measure the hormonal parameters. The hormone (corticosterone), (Adrenocorticotropic), (Aldosterone), (Adrenaline), and (Noradrenaline) was measured according to the instructions of the manufacturer, Enzo Life Sciences.

Measuring the level Immunological standards:

The ELISA device was used to measure hormonal standards. The levels of tumor necrosis factor alpha (TNF-a) and interleukin-6 (IL-6) were estimated according to the instructions of the manufacturer Enzo Life Sciences.

Oxidative indicators

Measuring of the (MDA) level

The level of (MDA) was measured based on the method (8), which relies on the reaction between lipid peroxidation to determine the extent of lipid peroxidation (MDA) and thiobarbituric acid (TBA), and this reaction occurs in an acidic medium which produces a coloured product. The intensity of its absorption is measured at a wavelength of 532 nm using a spectrophotometer.

Measurement of the (CAT) level

The (CAT) level was measured based on the method described by (1), which depends on the difference in absorbance when hydrogen peroxide is transformed into two atoms of water and oxygen, where the absorbance is measured at length The wavelength of 240 nm using a spectrophotometer.

Measuring the MDA level

The level of MDA was measured based on method (2), which relies on the reaction between lipid peroxidation products and thiobarbituric acid (TBA) to determine the extent of lipid peroxidation (MDA) and thiobarbituric acid (TBA), and this reaction occurs in an acidic medium, which produces a coloured product where the intensity is measured. Its absorption is at a wavelength of 532 nm using a spectrophotometer.

Measurement of the (CAT) level

The (CAT) level was measured based on the method described by (1), which depends on the difference in absorbance when hydrogen peroxide is transformed into two atoms of water and

oxygen, where the absorbance is measured at the wavelength of 240 Nanometer using a spectrophotometer.

Measuring the SOD level

SOD level measurement relies on the use of Nitroblue Tetrazolium (NBT), which gives a blue colour when it interacts with free radicals; the concentration of SOD, which inhibits the blue colour when its concentration is high, as it is measured at a wavelength of 560 nm using a spectrophotometer (12).

Measuring of the (GSH) level

which reacts with GSH and is reduced by the (SH group), as it is measured at a wavelength of 412 nm by a spectrophotometer (7).

Measuring the level of kidney functions

The colorimetric method (10) was used, and the kit prepared by the British company Randox was used to measure the level of creatinine in the serum, which depends on the interaction of the creatinine present in the sample with... Picric acid in a basic medium gives a red complex of Creatinine picrate, which has the highest absorbance at 520 nm.

As for measuring the level of urea in the serum, the enzymatic method was used using a ready-made measurement kit from the French company Bio Merieux AS.

Statistical analysis

The results of the experiments were analysed using the SPSS statistical program, as the Least Significant Differences (LSD) was used to express the data, and the test was used. Anova) for multiple comparisons between the studied groups and the control group, and the least significant difference was calculated to test the significance of the results.

Results and Discussion

The results of Table (1) showed that the induction of high blood pressure by DOCA-salt in the (T1) group led to a significant increase in the concentrations of corticosterone (CORT) from 23.9± ng/ml in the control group to 82.7± ng/ml in the (T1) group. The reason for this is attributed to the activation of the (HPA) axis. The stimulating effect of aldosterone increases the secretion of the hormone (ACTH), which in turn rose to a level of 33.7±ng/ml in the group in which blood pressure was induced compared to (C) 11.8±ng/ml (6)

The results also showed a significant increase in the level of aldosterone in the (T1) group by 540.9±pg/ml compared to the control group, which confirms the increased stimulation of the adrenal cortex to produce mineralocorticoids due to increased sodium and water retention, as

well as the role of DOCA-salt in activating aldosterone receptors as well as increasing oxidative stress (7) Results with the effect of DOCA-salt in stimulating the sodium/water axis and thus activating the sympathetic system with an increase in the effectiveness of mineralocorticoids and glucocorticoids, which in turn is reflected in blood pressure, causing an increase in it, with an increase in the activity of the (HPA) Which contributed to an increase in the level of sympathetic stimulation, which caused a clear increase in blood pressure with endothelial dysfunction, as well as oxidative stress and the resulting disorder in vascular regulation and thus chronic increase in blood pressure (12). As for the Coenzyme Q10 treatment, it showed a significant decrease in the values of all hormonal parameters in the (T2) and (T3) groups compared to Group (T1). This decrease may be attributed to the antioxidant activity of Co Q10, which limits the accumulation of free radicals by reducing the action of oxidative stress on adrenal gland cells and then inhibiting excessive activity of the HPA axis. Which reflects positively on the regulation of hormone secretion. Co Q10 also works to regulate the effectiveness of the sympathetic nervous system, which contributes to gradually reducing the level of (8) adrenaline and norepinephrine while improving both hormonal balance and vascular function (3). As for the effect of Q10 on mineralocorticoids, it is attributed to its active role in regulating the effectiveness of aldosterone by modifying the response to it and thus reducing the level of (ALD) in groups (T2) and (T3) (4), as shown in Table (1)

Table (1) shows the effect of Coenzyme Q10 on hormonal parameters in the serum of male rats in which hypertension was induced by (DOCA).

Group / Parameters	C	T1	T2	T3	LSD
CORT(ng/ml)	23.9±6.8^d	82.7±10.2 ^a	63.5±8.1 ^b	50.8±7.9 ^c	11.2
ACTH(ng/ml)	11.8 ±1.4 ^d	33.7±3.9 ^a	26.0±3.3 ^b	21.1±2.6 ^c	4.2
ALD(pg/ml)	198.6±21.5 ^d	540.9±44.0 ^a	428.4±37.2 ^b	355.6±31.4^c	40.1
A(pg/ml)	61.3±5.9 ^d	356.8±34.5 ^a	283.5±28.8 ^b	242.0±22.6 ^c	27.5
NA(pg/ml)	242.6 ±19.3 ^d	607.4±37.0 ^a	487.9±33.1 ^b	405±27.4 ^c	32.0

Values are expressed as mean ± standard deviation (n=6). Means with different superscript letters within the same row are significantly different ($p < 0.05$). C: Control group; T1: hypertension- induced group; T2: hypertension -induced + Coenzyme Q10 concertation 10ml/kg treatment group; T3: hypertension -induced + Coenzyme Q10 concertation 20ml/kg treatment group

The results of **Table (2)** showed that the induction of high blood pressure by DOCA-salt in the (T1) group led to a significant increase in the concentrations of tumor necrosis factor TNF-α

and interleukin IL-6 compared to the (C) group. The results showed a gradual decrease in the (T2) group, which received a dose of Co Q10 at a concentration of 10 mg/kg, while the decrease was greater in the (T3) group, which received a dose of 20 mg/kg, as this decrease is considered significant compared to (T1). Likewise, the results of IL-6 showed a significant increase in the (T1) group at a concentration of pg/mL ± 38.1 compared to the control group, while the results showed a significant decrease in the (T2) and (T3) groups compared to the (T1) group.

The increase in TNF-α and IL-6 in the group in which high blood pressure was induced compared to the control group indicates the activity of pro-inflammatory factors as a result of the activation of mineralocorticoid receptors (MR) due to hypersecretion of aldosterone and sodium, which works to increase the generation of free radicals as a result of oxidative stress, as well as activating the NF-κB pathway, thus raising the level of cytokine secretion.

Decreased TNF-α and IL-6 in the two groups treated with CoQ10 10 mg/kg and 20 mg/kg f compared to the T1 group. This may explain the role of CoQ10, which reduces the effect of inflammatory factors by inhibiting the NF-κB pathway as well as its role in activating mitochondria and antioxidants and thus reducing the formation of (ROS) (13).

Table (2) shows the effect of Coenzyme Q10 on inflammatory cytokines in the serum of male rats in which hypertension was induced by (DOCA).

Groups / Parameters	C	T1	T2	T3	LSD
TNF-α (pg/mL)	6.8±2.1 ^d	28.7±3.9 ^a	22.4 ±2.8 ^b	16.3±2.4 ^c	4.1
IL-6 (pg/mL)	26.4±2.9 ^d	38.1±4.4 ^a	30.7±3.6 ^b	26.4±2.9 ^c	5.0

Values are expressed as mean ± standard deviation (n=6). Means with different superscript letters within the same row are significantly different (p < 0.05). C: Control group; T1: hypertension- induced group; T2: hypertension -induced + Coenzyme Q10 concertation 10ml/kg treatment group; T3: hypertension -induced + Coenzyme Q10 concertation 20ml/kg treatment group.

The results of **Table (3)** showed that inducing blood pressure in the (T1) group by (DOCA) led to a noticeable disturbance in oxidative stress indicators compared to the (T4) group. The results showed a significant increase (P <0.05) in the level of (MDA) by 145.3± ng/ml, while the level of the control group (C)was 102.5± ng/ml. This is attributed to the direct effect of free radicals on the oxidation of unsaturated fatty acids of cellular membranes, which results in MDA as a final product of the lipid peroxidation process (Carocho & Ferreira, 2013). In contrast, there was a significant decrease (P <0.05) in the concentration of (CAT), (SOD), and (GSH) in the (T1) group compared to with the control group, it reached (12.5± pg/ml, 20.9± pg/ml, 232.2± ng/ml), while in group (C), the results were respectively (20.0± pg/ml, 61.2± pg/ml, 341.1± ng/ml), which confirms the decrease in oxidative capacity due to the effect of stress. Oxidative stress associated with high blood pressure (16).

As for the group (T2) and (T3), the results showed a decrease (P <0.05) in the level of (MDA) by (136.6± ng/ml, 123.5± ng/ml), respectively, compared to (T1), while the results showed an increase in the level of (CAT), (SOD), and (GSH) in the (T2) group at a level of (16.2±). pg/ml,36.7± pg/ml,270.14± ng/ml) respectively, while the results recorded a significant improvement in the (T3) group at a level of (16.4± pg/ml, 39.9± pg/ml,288.1± ng/ml) compared to the (T1) group. This improvement may be attributed to the role of Co Q10 as a powerful antioxidant in mitochondria, as it prevents the transfer of incomplete electrons, one of the most important causes of free radicals, with its active role in activating other antioxidants such as vitamin E and GSH, thus lowering the level of MDA while improving the enzymatic activity of antioxidants (CAT) and (SOD) (9).

Table (3) shows the effect of Coenzyme Q10 on oxidative stress indicators in the serum of male rats in which hypertension was induced by (DOCA).

Groups / Parameters	C	T1	T2	T3	LSD
MDA(ng/ml)	102.5±6.1 ^c	145.3±4.2 ^a	136.6±2.4 ^b	123.5±7.6 ^b	8.9
CAT(pg/ml)	20.0±1.9 ^a	12.5±0.7 ^c	16.2±0.5 ^b	16.4±0.6 ^b	1.7
SOD(pg/ml)	61.2±8.1 ^a	20.9±5.2 ^d	36.7±6.32 ^c	39.9±5.8 ^b	7.5
GSH(ng/ml)	341.1±19.0 ^a	232.2±17.5 ^c	270.14±22.9 ^b	288.1±20.0 ^b	25.6

Values are expressed as mean ± standard deviation (n=6). Means with different superscript letters within the same row are significantly different (p < 0.05). C: Control group; T1: hypertension- induced group; T2: hypertension -induced + Coenzyme Q10 concertation 10ml/kg treatment group; T3: hypertension -induced + Coenzyme Q10 concertation 20ml/kg treatment group

The results of **Table (4)** showed a significant increase (P <0.05) in the level of liver enzymes (ALP, ALT, AST) in the group in which high blood pressure was induced compared to the control group, which indicates the occurrence of damage to liver cells as a result of oxidative stress resulting from high blood pressure induced by DOCA, as the levels of (ALP, ALT, AST) levels were recorded respectively in the group (T1) The following values are (152.3± U/L, 47.8± U/L, 66.4± U/L) compared to the control group, where the values of (ALP, ALT, AST) were at the level of (91.5± U/L, 22.2± U/L, 41.5± U/L). (14**).**

While the results recorded a gradual decrease in the level of (ALP, ALT, AST) in the (T2) group, which was treated with CoQ10 at a concentration of 10 mg/kg body weight, the results were respectively (125.8± U/L, 35.3± U/L, 52.9± U/L) compared to the (T1) group. This improvement is attributed to the ability of CoQ10 to restore balance. oxidative stress within liver cells, thus reducing damage to them due to oxidative stress, while the improvement was noticeable in the groups that were treated with CoQ10 at a concentration of 20 mg/kg body weight, as the results showed a significant decrease at the level of (106.2± U/L, 29.32± U/L, 47.5± U/L) compared to (T1), as this indicates that the high dose an amount of 20 mg/kg of CoQ10 was more effective in returning enzyme levels to a level close to normal (13).

Table (4) shows the effect of Coenzyme Q10 on kidney function in the serum of male rats in which hypertension was induced by (DOCA).

Groups / Parameters	C	T1	T2	T3	LSD
Creatinine(mg/dl)	0.32±0.05 ^d	0.51±0.02 ^a	0.46±0.02 ^b	0.37±0.01 ^c	0.06
Urea(mg/dl)	22.0±3.2 ^d	37.1±2.0 ^a	31.1±2.4 ^b	28.5±1,9 ^c	4.1

Values are expressed as mean ± standard deviation (n=6). Means with different superscript letters within the same row are significantly different ($p < 0.05$). C: Control group; T1: hypertension- induced group; T2: hypertension -induced + Coenzyme Q10 concertation 10ml/kg treatment group; T3: hypertension -induced + Coenzyme Q10 concertation 20ml/kg treatment group.

Conclusion:

The results showed that the use of Coenzyme Q10 at a dose of (10 mg/kg) and (20 mg/kg) contributed effectively to improving the disturbance in adrenal gland functions resulting from the induction of blood pressure by (DOCA) at a concentration of (20 mg/kg) of body weight. The results confirmed the significant decrease in the level of (corticosterone, Aldosterone, Epinephrine, Norepinephrine), liver enzymes included (AST, ALT, ALP), kidney functions (urea, Creatinine), antioxidants (MDA, CAT, SOD, GSH), and tumor necrosis factors (TNF, IL6), which were closer to Normal values in groups that were dosed with Coenzyme Q10 at a concentration of (20 mg/kg) of body weight, which indicates that the effect of Coenzyme Q10 as a result depends on the amount of dose due to its effective role as a fat-soluble antioxidant that helps activate mitochondria and improve cell functions.

Refrences

1. Al Ghorani, H.., Götzinger, F.., Böhm, M., andMahfoud, F. (2022). Arterial hypertension – clinical trials update 2021. *Nutrition, Metabolism and Cardiovascular Diseases*, *32*(1), 21-31. https://doi.org/https://doi.org/10.1016/j.numecd.2021.09.007
2. Amin, B.., Elahi, A.., Cappiello, G.., Ištuk, N.., Dunne, E.., Krewer, F.., Quinn, A. M.., Lowery, A.., Prakash, P.., Dennedy, M. C., andO'Halloran, M. (2024). Dielectric characterisation of human adrenal glands and adrenal tumours for the development of microwave ablation technologies for hypertension treatment. *Scientific Reports*, *14*(1), 19451. https://doi.org/10.1038/s41598-024-70476-6
3. Amponsah-Offeh, M.., Diaba-Nuhoho, P.., Speier, S., andMorawietz, H. (2023). Oxidative stress, antioxidants and hypertension. *Antioxidants*, *12*(2). https://doi.org/10.3390/antiox12020281
4. Araujo-Castro, M. (2020). Treatment of primary hyperaldosteronism. *Medicina Clínica (English Edition)*, *155*(7), 302-308. https://doi.org/https://doi.org/10.1016/j.medcle.2020.04.022
5. Basting, T., andLazartigues, E. (2017). Doca-salt hypertension: An update. *Current Hypertension Reports*, *19*(4), 32. https://doi.org/10.1007/s11906-017-0731-4
6. Bauerova, K.., Kucharska, J.., Mihalova, D.., Navarova, J.., Gvozdjakova, A., andSumbalova, Z. (2005). Effect of coenzyme q(10) supplementation in the rat model of adjuvant arthritis. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*, *149*(2), 501-503. https://doi.org/10.5507/bp.2005.090
7. Ferreira, N. S.., Tostes, R. C.., Paradis, P., andSchiffrin, E. L. (2021). Aldosterone, inflammation, immune system, and hypertension. *American Journal of Hypertension*, *34*(1), 15-27. https://doi.org/10.1093/ajh/hpaa137
8. Guo, H.., Xu, D.., Kuroki, M.., Lu, Z.., Xu, X.., Geurts, A.., Osborn, J. W., andChen, Y. (2020). Kidney failure, arterial hypertension and left ventricular hypertrophy in rats with loss of function mutation of sod3. *Free Radical Biology and Medicine*, *152*, 787-796. https://doi.org/https://doi.org/10.1016/j.freeradbiomed.2020.01.023
9. Hayakawa, Y.., Komaki, H.., Minatoguchi, S.., Yamada, Y.., Kanamori, H.., Nishigaki, K., andMinatoguchi, S. (2020). High-salt intake accelerates functional and histological renal damage associated with renal tissue overexpression of (pro)renin receptors and at1 receptors in spontaneously hypertensive rats. *Clinical and Experimental Nephrology*, *24*(7), 582-589. https://doi.org/10.1007/s10157-020-01888-7

10. Hosseini Roknabadi, S. M.., Abolhassani, A.., Davoodi, E.., Moghaddam Rad, F. Z., andJafarnejad, S. (2025). The protective effects of coenzyme q10 on blood pressure: A narrative review of anti-inflammatory and antioxidant mechanisms. *Inflammopharmacology*, *33*(9), 5191-5202. https://doi.org/10.1007/s10787-025-01897-6
11. Jama, H. A.., Muralitharan, R. R.., Xu, C.., O'Donnell, J. A.., Bertagnolli, M.., Broughton, B. R. S.., Head, G. A., andMarques, F. Z. (2022). Rodent models of hypertension. *British Journal of Pharmacology*, *179*(5), 918-937. https://doi.org/https://doi.org/10.1111/bph.15650
12. Littarru, G. P.., Bruge, F., andTiano, L. (2017). Biochemistry of coenzyme q10. In G. Balercia, L. Gandini, A. Lenzi, & F. Lombardo (Eds.), *Antioxidants in andrology* (pp. 23-34). Springer International Publishing. https://doi.org/10.1007/978-3-319-41749-3_2
13. McRae, M. P. (2023). Coenzyme q10 supplementation in reducing inflammation: An umbrella review. Journal of Chiropractic Medicine, 22(2), 131-137. https://doi.org/https://doi.org/10.1016/j.jcm.2022.07.001
14. Nickel, N. P.., Galura, G. M.., Zuckerman, M. J.., Hakim, M. N.., Alkhateeb, H.., Mukherjee, D.., Austin, E. D., andHeresi, G. A. (2021). Liver abnormalities in pulmonary arterial hypertension. Pulmonary Circulation, 11(4), 20458940211054304. https://doi.org/10.1177/20458940211054304 .
15. Petrák, O.., Krátká, Z.., Holaj, R.., Zítek, M.., Nguyen Nikrýnová, T.., Klímová, J.., Kološová, B.., Waldauf, P.., Michalský, D.., Novák, K.., Markvartová, A.., Zlatohlávek, L.., Grus, T.., Dušková, J.., Widimský, J., andZelinka, T. (2024). Cardiovascular complications in pheochromocytoma and paraganglioma: Does phenotype matter? *Hypertension*, *81*(3), 595-603. https://doi.org/10.1161/HYPERTENSIONAHA.123.21902 .
16. Samimi, F.., Baazm, M.., Eftekhar, E., andJalali Mashayekh, F. (2019). Effect of coenzyme q10 supplementation on liver total oxidant/antioxidant status in streptozotocin-induced diabetic rats. *HBI_Journals*, *22*(4), 28. https://doi.org/10.32598/JAMS.22.4.30 .
17. Szabo Yamashita, T.., Shariq, O. A.., Foster, T. R.., Lyden, M. L.., Dy, B. M.., Young, W. F.., Bancos, I., andMcKenzie, T. J. (2023). Unilateral adrenalectomy for primary aldosteronism due to bilateral adrenal disease can result in resolution of hypokalemia and amelioration of hypertension. *World Journal of Surgery*, *47*(2), 314-318. https://doi.org/10.1007/s00268-022-06780-x .
18. Wu, H.., Lam, T. Y. C.., Shum, T.-F.., Tsai, T.-Y., andChiou, J. (2022). Hypotensive effect of captopril on deoxycorticosterone acetate-salt-induced hypertensive rat is associated with gut microbiota alteration. *Hypertension Research*, *45*(2), 270-282. https://doi.org/10.1038/s41440-021-00796-x .