REVIEW ARTICLE

MCBS
Mol Cell Biomed Sci. 2023; 7(2): 58-64
DOI: 10.21705/mcbs.v7i2.288

The Role of Malondialdehyde (MDA) and Ferric Reducing Antioxidant Power (FRAP) in Patients with Hypertension

Roshan Alam[1], Haseeb Ahsan[2], Saba Khan[1]

[1]*Department of Biochemistry, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, India*
[2]*Department of Biochemistry, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India*

Oxidative stress contributes to the pathogenesis of hypertension and studies have shown that hypertension is associated with an increase in oxidative stress. Reactive oxygen species (ROS) lead to hypertension and antioxidants may be beneficial for its prevention. The main cause of oxidative stress in hypertension is endothelial dysfunction due to the malfunctions in the vasodilator systems, specifically the molecular mechanism of ROS and nitric oxide (NO). The level of malondialdehyde (MDA), a biomarker of lipid peroxidation and oxidative stress, is found to be higher in hypertension patients. Total antioxidant capacity (TAC), which has a strong relationship with blood pressure, is determined through the ferric reducing antioxidant power (FRAP). The aim of the review article is to elucidate the role of MDA and FRAP in hypertension.

Keywords: *oxidative stress, hypertension, blood pressure, oxidative damage, malondialdehyde, FRAP*

Introduction

A chronic medical condition, known as hypertension or arterial hypertension, causes high blood pressure in the arteries. The systolic and diastolic blood pressure, which corresponds to the maximum and minimum readings of the two measurements, are used to express blood pressure. The left ventricle is constricted at the systolic pressure, and most relaxed just before the next contraction during the diastolic pressure. Based on the Eighth Joint National Committee (JNC 8) recommendations, hypertension in adults is defined as the blood pressure that is higher than 140/90 mmHg.[1] Meanwhile, based on the Seventh Joint National Committee (JNC 7), blood pressure of 120/80 mmHg is considered normal. In addition, JNC 7 classifies hypertension to prehypertension, primary (essential) hypertension and secondary hypertension (Table 1).[2] Primary hypertension accounts for 90-95% of high blood pressure without an underlying cause.[3] The other 5-10% classified as secondary hypertension, which is hypertension with a known cause, such as aortic or kidney artery constriction, chronic renal disease, or an endocrine disorder due to catecholamines, aldosterone, or cortisol.

Genetic and environmental factors are responsible for hypertension.[4-6] Similarly, other factors such as depression,

Date of submission: June 28, 2022
Last Revised: September 1, 2022
Accepted for publication: September 8, 2022

Corresponding Author:
Saba Khan
Department of Biochemistry
Integral Institute of Medical Sciences and Research
Integral University, Kursi Road, Lucknow, India
e-mail: dr.sabakhan.in@gmail.com; dr.khan.saba@gmail.com

Cell and Biopharmaceutical Institute

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v7i2.288

Table 1. Classification of hypertension based on JNC 7.[2]

Category	SBP (mmHg)	DBP (mmHg)
Normal	<120	<80
Prehypertension	120-139	80-89
Hypertension, stage I	140-159	90-99
Hypertension, stage II	≥ 160	≥100

SBP: Systolic blood pressure; DBP: diastolic blood pressure.

stress, lack of exercise, and obesity can all contribute to high blood pressure. It is less obvious how other variables, such caffeine (coffee) intake and vitamin D deficiency may affect the mean arterial pressure.[7] Insulin resistance and obesity (metabolic syndrome) are also known to cause hypertension.[8] Hypertension is rarely symptomatic and is typically discovered during screening or treatment for other unrelated diseases. Apart from the usual mild symptoms, some people with high blood pressure also experience headaches, especially at the back of the head in the morning[9], which may or may not be directly linked to high blood pressure.[10]

Secondary hypertension, or hypertension with a known cause, may be indicated with certain specified additional signs and symptoms. Endocrine disorders such as Conn's syndrome, Cushing's syndrome, hypothyroidism, hyperthyroidism, acromegaly, or pheochromocytoma, hyperparathyroidism, and hyperaldosteronism cause secondary hypertension. Other factors that contribute to secondary hypertension are kidney disorders, obesity, sleep apnea, pregnancy, excessive alcohol intake, and a few prescription drugs, herbal treatments, and illicit substances.[11] A low blood pressure in the extremities of the arms and a delayed/missing femoral arterial pulse are the common side effects of aortic coarctation. Pheochromocytoma can result in sudden ("paroxysmal") episodes of hypertension that are accompanied by palpitations, excessive sweating, headache, and a pale complexion.[12] A "hypertensive crisis" is characterized by extremely high blood pressure (systolic 180 mmHg or diastolic readings of 110 mmHg, referred to as malignant or accelerated hypertension), leading to a significant risk of complications. Although people with extremely high blood pressure in this range may not experience any symptoms, they are more likely to experience headaches (22% cases)[13] and dizziness compared to the general population.[14] In addition to these symptoms, "hypertensive crisis" may also cause retinopathy-related vision loss, cardiovascular disease-related shortness of breath, or nephropathy-related sickness.[15] High blood pressure is found in most patients experiencing a "hypertensive crisis", but there may be other factors that cause such emergencies.[16]

Many people with established primary or essential hypertension experience elevated blood pressure with normal cardiac output due to total peripheral resistance, which is an increase in blood flow resistance. Some young individuals with borderline hypertension or prehypertension also have a rapid cardiac output and an increased heart rate, which is known as hyperkinetic borderline hypertension.[17] With advancing age, they develop the usual symptoms of established essential hypertension when their peripheral resistance increases and cardiac output decreases. However, it is contentious whether the same pattern applies to everyone who eventually develops hypertension.[18] The narrowing of arteries and arterioles is responsible for the increased peripheral resistance in established hypertension[19], while a decrease in the number or density of capillaries may be a contributing factor.[20] These findings are based on the JNC 8 report on prevention, detection, evaluation and treatment of high blood pressure (Table 2).[1,21]

Hypertension develops in 8-10% of pregnancies, although most pregnant women with hypertension also have preexisting primary hypertension.[12] The presence of pregnancy-related hypertension is determined by two blood pressure readings taken more than six hours apart and greater than 140/90 mmHg.[22] Preeclampsia, a serious medical condition during the second trimester of pregnancy, and puerperium which is due to high blood pressure, occur in 5% of pregnancies and are responsible for 16% of maternal fatalities worldwide. Moreover, preeclampsia

Table 2. JNC 8 recommendations.[1]

Patient Subgroup	Target SBP (mmHg)	Target DBP (mmHg)
≥60 years	<150	<90
<60 years	<140	<90
>18 with CKD	<140	<90
>18 with DM	<140	<90

SBP: Systolic blood pressure; DBP: diastolic blood pressure; CKD: chronic kidney disease; DM: diabetes mellitus.

also doubles the chances of perinatal death.[12] Preeclampsia typically does not have any symptoms, but it is detected through normal screening. The most common symptoms of preeclampsia include headache, vomiting, epigastric pain, edema, and visual impairment (referred to as "flashing lights"). Furthermore, eclampsia, a hypertensive emergency with multiple complications, such as seizures or convulsions, vision loss, disseminated intravascular coagulation (a blood clotting disorder), pulmonary edema, kidney failure, and brain swelling, may occasionally develop from preeclampsia.[23-27] In this review, we summarize the recent advances in oxidative stress and how it contributes to hypertension in humans.

Oxidative Stress in Hypertension

Oxidative stress is the imbalance between the generation of free radical species and the ability of cellular antioxidants to detoxify them or repair damaged biological molecules.[9] Increased vascular oxidative stress, a significant risk factor for cardiovascular diseases, is linked to hypertension.[28] Therefore, oxidative stress is linked to a decrease in the efficiency of antioxidant defenses or an increase in the generation of free radical species.[29] Oxidative stress leads to proliferation, hypertrophy, and collagen deposition of vascular smooth muscle cells, which thickens and narrows the vascular lumen. Increased oxidative stress can also harm endothelium by impairing endothelium-dependent arterial relaxation and increasing vascular contractile activity, resulting in endothelial dysfunction. Generation of peroxides and free radicals has harmful effects on cellular constituents, such as proteins, lipids, and DNA.[30] Oxidative stress promotes apoptosis and/or necrosis.[31,32] An important harmful feature of oxidative stress is the generation of reactive oxygen species (ROS), including free radicals and peroxides *e.g.* superoxide radical ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$) and hydrogen peroxide (H_2O_2). Some free radical species are converted into more harmful intermediates that cause cellular damage by oxidoreduction reactions in the presence of transition metals or other redox cycling compounds, including quinones.[33] Fenton reaction results in the generation of hydroxide ion (OH^-) and $^{\bullet}OH$ through the reaction between iron (II) or ferrous (Fe^{2+}) ion and H_2O_2.[34] Generation of ROS occurs with the reduction of metal ions, such as ferric (Fe^{3+}) to ferrous (Fe^{2+}) ion by superoxide anion (Fenton reaction), which leads to the breakdown of H_2O_2 to $^{\bullet}OH$ and OH^- (Haber-Weiss reaction).[35,36]

A number of cellular antioxidants, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRx), protect the body against ROS. Nitric oxide (NO) and ROS interact three times more quickly than SOD, forming the highly reactive compound known as peroxynitrite, which is produced by the vascular walls. NO dilates the arteries through an increase in the intracellular cyclic guanosine monophosphate (cGMP) content of vascular smooth muscle cells. The inhibition of platelet aggregation or white blood cell adherence to endothelial cells is caused by NO on the arteries that result in the decreased excretion of cell proliferative or migratory stimulatory substances from these blood cells. NO directly prevents the oxidation of low-density lipoprotein (LDL) or the growth of new cells. Therefore, vasoconstriction will occur when NO production declines, leading to the development of atherosclerosis.[37-41]

Malondialdehyde (MDA)

Lipids are one of the primary targets of ROS. ROS causes lipid oxidation or peroxidation (*i.e.*, as degradation products of fats). It has been reported that certain free radicals known as peroxyl radicals, formed by the reaction of molecular oxygen with carbon radicals, remove hydrogen from lipids, producing hydroperoxides (ROOH) that lead to a chain reaction pathway. ROOH reacts with transition metal ions, such as iron or copper to form stable aldehydes that lead to membrane damage.[42] Lipid peroxidation leads to the generation of highly reactive products such as malondialdehyde (MDA), acrolein (2-propenal), 4-hydroxynonenal (HNE), 4-oxononenal (ONE), *etc*.[43] Malondialdehyde (MDA) is one of the most common and important markers of free radical-mediated lipid damage and oxidative stress.[44-46] However, other lipid oxidation product biomarkers, including lipid hydroperoxide (LOOH), N-epsilon-hexanoyl-lysine (HEL), are isoprostanes (IsoPs).

Since ROS have extremely short half-lives and are difficult to detect, they can be measured by using the byproducts of oxidative damage, such as thiobarbituric acid reactive substances (TBARS). MDA is formed through decomposition of some primary and secondary lipid peroxidation products and is estimated in plasma using the colorimetric assay based on the reaction between MDA and thiobarbituric acid (TBA).[46,47] TBARS, which are detected through the TBA assay, is used as an indicator of oxidative stress in various disease models. In diabetic rat models

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v7i2.288

induced by streptozotocin (STZ), the TBARS plasma concentration is elevated.[48-50] TBARS concentration is reduced with several antioxidants, such as aminoguanidine and α-lipoic acid.[49,50] Several studies support the possible role of lipid peroxidation in predicting the progression of metabolic disorders and response to therapy.[51] The role of oxidative damage to cellular components has been recognized in cardiovascular diseases (CVD)[52-54] since the proposal of the oxidative theory of atherogenesis.[52,53] Lipids are potential targets of oxidative damage due to their molecular structure containing long chain hydrocarbons and electron rich benzene rings.[54] Hypertension is associated with increased generation of free radicals, leading to increase in lipid peroxidation products, such as MDA. An increase in generation of $O_2^{\bullet-}$ or a decrease in production of NO may facilitate the development of functional arterial spasms.[55]

Ferric Reducing Antioxidant Power (FRAP)

An antioxidant may reduce oxidative damage through different mechanisms such as blocking/inhibiting reactions that produce free radicals, scavenging/quenching free radicals, converting them into harmless species. Antioxidants must be present in the vicinity of the radical species and/or have higher reactivity and concentration.[56] The endogenous enzymatic antioxidants and exogenous vitamins are usually measured to determine the antioxidant status in blood.[57,58] The foods of plant origin not only provide antioxidant vitamins but also other phytonutrients with antioxidant capacity. Some phytochemicals also provide nutrients and antioxidants for protection against oxidative stress[59-66], which reduce the risk of diabetes and cardiovascular complications.

Deficiency of antioxidant vitamins in the diet is a major factor in the development of hypertension, since antioxidants lower blood pressure and restore endothelial function. Antioxidant vitamins reduce the damage caused by oxidative stress, such as endothelial dysfunction, lipid peroxidation, and tissue damage, but they may not be able to reverse the negative effects of hypertension on other factors *e.g.*, nervous system activity, vascular smooth muscle cell function, or vascular remodeling. The effect of antioxidants on blood pressure varies due to antioxidant types, administration methods, timing and doses.[67] Several studies have shown a strong association between blood pressure and oxidative biomarkers and oxidative stress in the severity of hypertension.[68] These findings suggest a strong association and role of oxidative stress in the pathophysiology of essential hypertension[69-71], which may contribute to the endothelial dysfunction in hypertension.[72,73]

Hypertension markedly reduces the total antioxidant level in patients. Decrease in total antioxidant capacity and increase in lipid peroxidation activate inflammatory immune responses, leading to hypertension and coronary heart diseases.[69] The markers of oxidative damage in plasma and kidney of rats with experimental hypertension induced by chronic inhibition of nitric oxide synthase (NOS) with N omega-nitro-L-arginine methyl ester (L-NAME) have been determined. This inhibition results in the elevation of systolic blood pressure, which is associated with an increase in thiols (-SH) groups concentration in renal cortex, while lipid peroxidation products and ferric reducing antioxidant power (FRAP) in plasma and renal medulla remain unchanged, resulting in the development of renal pathology.[70]

There are several methods to determine the total antioxidant capacity (TAC) in biological samples. FRAP assay uses the reduction of Fe^{3+}-tripyridyltriazine (TPTZ) to produce a blue coloured intermediate Fe^{2+}-TPTZ at low pH.[74,75] This is the only assay that determines the TAC.[76] FRAP assay[77-79] has gained importance due to simplicity, cost-effectiveness, processing time, and reproducibility.[80]

MDA and FRAP in Hypertension

Increased levels of oxidative stress have been associated with various pathological conditions. Higher levels of MDA in the serum are found in hypertensive patients compared to individuals with normal blood pressure.[81] Moreover, pregnant women with hypertension have a decrease in catalase activity compared to normotensive individuals.[82] In preeclampsia, the MDA concentration in cord blood plasma is lower than maternal plasma.[83] Therefore, it is assumed that MDA is a significant biomarker for lipid peroxidation and FRAP is directly correlated with oxidative stress-related parameters and blood pressure. Due to the direct relationship between oxidative stress and hypertension, certain drugs with antioxidant potential may lower blood pressure.[84] In addition, candesartan and valsartan have been shown to decrease oxidative stress in hypertensive patients.[85,86] Hence, antioxidant compounds and vitamins have the potential as anti-hypertensive agents.[87]

Conclusion

The level of MDA is found to be notably higher and FRAP markedly decreases in hypertensive patients. The elevated MDA and decreased FRAP suggest that lipid peroxidation is a causative factor in hypertension. Oxidative stress in hypertension may lead to long term adverse effects, such as atherosclerosis and CVDs.

Authors Contribution

RA and SK were involved in the concepting and design of research. RA, HA, and SK performed the literature survey and collection. HA and SK drafted the manuscript and designed the tables. RA, HA, and SK were involved in analysis of data. HA and SK were involved in critical revision of the manuscript.

References

1. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5): 507-20.
2. U.S. Department of Health and Human Services. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Maryland: National Institute of Health; 2004.
3. Gupta R. Trends in hypertension epidemiology in India. J Hum Hypertens. 2004; 18(2): 73-8.
4. Chrissobolis S, Didion SP, Kinzenbaw DA, Schrader LI, Dayal S, Lentz SR, *et al*. Glutathione peroxidase-1 plays a major role in protecting against angiotensin II-induced vascular dysfunction. Hypertension. 2008; 51(4): 872-7.
5. Zhou XJ, Vaziri ND, Wang XQ, Silva FG, Laszik Z. Nitric oxide synthase expression in hypertension induced by inhibition of glutathione synthase. J Pharmacol Exp Ther. 2002; 300(3): 762-7.
6. Vaziri ND. Pathogenesis of lead-induced hypertension: Role of oxidative stress. J Hypertens Suppl. 2002; 20(3): S15-20.
7. Lim CS, Vaziri ND. The effects of iron dextran on the oxidative stress in cardiovascular tissues of rats with chronic renal failure. Kidney Int. 2004; 65(5): 1802-9.
8. Wilcox CS, Pearlman A. Chemistry and antihypertensive effects of tempol and other nitroxides. Pharmacol Rev. 2008; 60(4): 418-69.
9. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res. 2004; 61(3): 461-70.
10. Juránek I, Bezek S. Controversy of free radical hypothesis: reactive oxygen species--cause or consequence of tissue injury? Gen Physiol Biophys. 2005; 24(3): 263-78.
11. Russo C, Olivieri O, Girelli D, Faccini G, Zenari ML, Lombardi S, *et al*. Anti-oxidant status and lipid peroxidation in patients with essential hypertension. J Hypertens. 1998; 16(9): 1267-71.
12. Lassègue B, Griendling KK. Reactive oxygen species in hypertension: An update. Am J Hypertens. 2004; 17(9): 852-60.
13. Touyz RM, Schiffrin EL. Reactive oxygen species in vascular biology: Implications in hypertension. Histochem Cell Biol. 2004; 122(4): 339-52.
14. Granger DN, Kvietys PR. Reperfusion injury and reactive oxygen species: The evolution of a concept. Redox Biol. 2015; 6: 524-51.
15. Tanito M, Nakamura H, Kwon YW, Teratani A, Masutani H, Shioji K, *et al*. Enhanced oxidative stress and impaired thioredoxin expression in spontaneously hypertensive rats. Antioxid Redox Signal. 2004; 6(1): 89-97.
16. Dusting GJ, Akita K, Hickey H, Smith M, Gurevich V. Cyclosporin A and tacrolimus (FK506) suppress expression of inducible nitric oxide synthase in vitro by different mechanisms. Br J Pharmacol. 1999; 128(2): 337-44.
17. Rodrigo R, González J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. Hypertens Res. 2011; 34(4): 431-40.
18. Salo DC, Pacifici RE, Lin SW, Giulivi C, Davies KJ. Superoxide dismutase undergoes proteolysis and fragmentation following oxidative modification and inactivation. J Biol Chem. 1990; 265(20): 11919-27.
19. Sinet PM, Garber P. Inactivation of the human CuZn superoxide dismutase during exposure to O-2 and H2O2. Arch Biochem Biophys. 1981; 212(2): 411-6.
20. Redón J, Oliva MR, Tormos C, Giner V, Chaves J, Iradi A, Sáez GT. Antioxidant activities and oxidative stress byproducts in human hypertension. Hypertension. 2003; 41(5): 1096-101.
21. Gönenç A, Hacışevki A, Tavil Y, Çengel A, Torun M. Oxidative stress in patients with essential hypertension: A comparison of dippers and non-dippers. Eur J Intern Med. 2013; 24(2): 139-44.
22. Grossman E. Does increased oxidative stress cause hypertension? Diabetes Care. 2008; 31 Suppl 2: S185-9.
23. Nishiyama A, Yao L, Nagai Y, Miyata K, Yoshizumi M, Kagami S, *et al*. Possible contributions of reactive oxygen species and mitogen-activated protein kinase to renal injury in aldosterone/salt-induced hypertensive rats. Hypertension. 2004; 43(4): 841-8.
24. Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC, Touyz RM. Oxidative Stress and Hypertension. Circ Res. 2021; 128(7): 993-1020.
25. Puspasari A, Enis RN, Herlambang H. Genetic variant of vascular endothelial growth factor (VEGF)-A rs699947 is associated with preeclampsia. Mol Cell Biomed Sci. 2022; 6(2): 70-6.
26. Akbar MIA, Sari IM, Ernawati E, Aditiawarman A. Plasma level of umbilical cord hemeoxygenase-1 (HO-1) and neonatal outcome in early onset and late onset severe preeclampsia. Mol Cell Biomed Sci. 2019; 3(1): 54-9.
27. Ramadhanti R, Helda H. Association of hypertension and chronic kidney disease in population aged ≥18 years old. Mol Cell Biomed Sci. 2021; 5(3): 137-44.
28. Rodrigo R, Passalacqua W, Araya J, Orellana M, Rivera G. Implications of oxidative stress and homocysteine in the pathophysiology of essential hypertension. J Cardiovasc Pharmacol. 2003; 42(4): 453-61.
29. Neri S, Guidotti S, Bini C, Pelotti S, D'Adamo S, Minguzzi M, Platano D, Santi S, Mariani E, Cattini L, Borzì RM. Oxidative stress-induced DNA damage and repair in primary human osteoarthritis chondrocytes: Focus on IKKα and the DNA mismatch repair system. Free Radic Biol Med. 2021; 166: 212-25.
30. Schafer FQ, Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v7i2.288

couple. Free Radic Biol Med. 2001; 30(11): 1191-212.
31. Lennon SV, Martin SJ, Cotter TG. Dose-dependent induction of apoptosis in human tumour cell lines by widely diverging stimuli. Cell Prolif. 1991; 24(2): 203-14.
32. Jusup I, Batubara L, Ngestiningsih D, Fulyani F, Paveta DA, Ate Bancin PTL. Association between malondialdehyde, GSH/GSSG ratio and bone mineral density in postmenopausal women. Mol Cell Biomed Sci. 2021; 5(1): 13-7.
33. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Curr Med Chem. 2005; 12(10): 1161-208.
34. Fischbacher A, von Sonntag C, Schmidt TC. Hydroxyl radical yields in the Fenton process under various pH, ligand concentrations and hydrogen peroxide/Fe(II) ratios. Chemosphere. 2017; 182: 738-44.
35. Kehrer JP. The Haber-Weiss reaction and mechanisms of toxicity. Toxicology. 2000; 149(1): 43-50.
36. Dziubla T, Butterfield DA. Oxidative Stress and Biomaterials. 1st ed. Amsterdam: Academic Press; 2016.
37. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, *et al*. Pathophysiology of atherosclerosis. Int J Mol Sci. 2022; 23(6): 3346. doi: 10.3390/ijms23063346.
38. Sun HJ, Wu ZY, Nie XW, Bian JS. Role of endothelial dysfunction in cardiovascular diseases: The link between inflammation and hydrogen sulfide. Front Pharmacol. 2020; 10: 1568. doi: 10.3389/fphar.2019.01568.
39. Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, *et al*. The vascular endothelium and human diseases. Int J Biol Sci. 2013; 9(10): 1057-69.
40. Hamilos M, Petousis S, Parthenakis F. Interaction between platelets and endothelium: From pathophysiology to new therapeutic options. Cardiovasc Diagn Ther. 2018; 8(5): 568-80.
41. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: Molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018; 17(1): 121. doi: 10.1186/s12933-018-0763-3.
42. Halliwell B. Biochemistry of oxidative stress. Biochem Soc Trans. 2007; 35(Pt 5): 1147-50.
43. Guo L, Chen Z, Amarnath V, Davies SS. Identification of novel bioactive aldehyde-modified phosphatidylethanolamines formed by lipid peroxidation. Free Radic Biol Med. 2012; 53(6): 1226-38.
44. Shodehinde SA, Oboh G. Antioxidant properties of aqueous extracts of unripe Musa paradisiaca on sodium nitroprusside induced lipid peroxidation in rat pancreas in vitro. Asian Pac J Trop Biomed. 2013; 3(6): 449-57.
45. Serudji J, Irawati N, Mose JC, Ali H, Yusrawati Y. Elevated serum reactive oxygen species level predicts early abortion. Mol Cell Biomed Sci. 2021; 5(1): 37-40.
46. Pryor WA. The antioxidant nutrients and disease prevention--what do we know and what do we need to find out? Am J Clin Nutr. 1991; 53(1 Suppl): 391S-3S.
47. Janero DR. Malondialdehyde and thiobarbituric acid-reactivity as diagnostic indices of lipid peroxidation and peroxidative tissue injury. Free Radic Biol Med. 1990; 9(6): 515-40.
48. Ozansoy G, Akin B, Aktan F, Karasu C. Short-term gemfibrozil treatment reverses lipid profile and peroxidation but does not alter blood glucose and tissue antioxidant enzymes in chronically diabetic rats. Mol Cell Biochem. 2001; 216(1-2): 59-63.
49. Kedziora-Kornatowska KZ, Luciak M, Blaszczyk J, Pawlak W. Effect of aminoguanidine on erythrocyte lipid peroxidation and activities of antioxidant enzymes in experimental diabetes. Clin Chem Lab Med. 1998; 36(10): 771-5.
50. van Dam PS, van Asbeck BS, Van Oirschot JF, Biessels GJ, Hamers FP, Marx JJ. Glutathione and alpha-lipoate in diabetic rats: Nerve function, blood flow and oxidative state. Eur J Clin Invest. 2001; 31(5): 417-24.
51. Ho E, Karimi Galougahi K, Liu CC, Bhindi R, Figtree GA. Biological markers of oxidative stress: Applications to cardiovascular research and practice. Redox Biol. 2013; 1(1): 483-91.
52. Steinberg D. Low density lipoprotein oxidation and its pathobiological significance. J Biol Chem. 1997; 272(34): 20963-6.
53. Chisolm GM, Steinberg D. The oxidative modification hypothesis of atherogenesis: An overview. Free Radic Biol Med. 2000; 28(12): 1815-26.
54. Porter NA, Caldwell SE, Mills KA. Mechanisms of free radical oxidation of unsaturated lipids. Lipids. 1995; 30(4): 277-90.
55. de la Sierra A, Larrousse M. Endothelial dysfunction is associated with increased levels of biomarkers in essential hypertension. J Hum Hypertens. 2010; 24(6): 373-9.
56. Zhao Z. Iron and oxidizing species in oxidative stress and Alzheimer's disease. Aging Med. 2019; 2(2): 82-7.
57. Kaneto H, Kajimoto Y, Miyagawa J, Matsuoka T, Fujitani Y, Umayahara Y, *et al*. Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. Diabetes. 1999; 48(12): 2398-406.
58. Dandu AM, Inamdar NM. Evaluation of beneficial effects of antioxidant properties of aqueous leaf extract of Andrographis paniculata in STZ-induced diabetes. Pak J Pharm Sci. 2009; 22(1): 49-52.
59. Subash-Babu P, Alshatwi AA, Ignacimuthu S. Beneficial antioxidative and antiperoxidative effect of cinnamaldehyde protect streptozotocin-induced pancreatic β-cells damage in Wistar rats. Biomol Ther. 2014; 22(1): 47-54.
60. Domekouo UL, Longo F, Tarkang PA, Tchinda AT, Tsabang N, Donfagsiteli NT, *et al*. Evaluation of the antidiabetic and antioxidant properties of Morinda lucida stem bark extract in streptozotocin intoxicated rats. Pak J Pharm Sci. 2016; 29(3): 903-11.
61. Hajleh MNA, Khleifat KM, Alqaraleh M, Al-Hraishat E, Al-Limoun MO, Qaralleh H, *et al*. Antioxidant and antihyperglycemic effects of Ephedra foeminea aqueous extract in streptozotocin-induced diabetic rats. Nutrients. 2022; 14(11): 2338. doi: 10.3390/nu14112338.
62. Nasri H, Shirzad H, Baradaran A, Rafieian-Kopaei M. Antioxidant plants and diabetes mellitus. J Res Med Sci. 2015; 20(5): 491-502.
63. Przeor M. Some common medicinal plants with antidiabetic activity, known and available in Europe (a mini-eview). Pharmaceuticals. 2022; 15(1): 65. doi: 10.3390/ph15010065.
64. Salehi B, Ata A, V Anil Kumar N, Sharopov F, Ramírez-Alarcón K, Ruiz-Ortega A, *et al*. Antidiabetic potential of medicinal plants and their active components. Biomolecules. 2019; 9(10): 551. doi: 10.3390/biom9100551.
65. Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP, *et al*. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. Molecules. 2015; 20(12): 21138-56.
66. Forni C, Facchiano F, Bartoli M, Pieretti S, Facchiano A, D'Arcangelo D, *et al*. Beneficial role of phytochemicals on oxidative stress and age-related diseases. Biomed Res Int. 2019; 2019: 8748253. doi: 10.1155/2019/8748253.
67. Carr A, Frei B. The role of natural antioxidants in preserving the biological activity of endothelium-derived nitric oxide. Free Radic

Biol Med. 2000; 28(12): 1806-14.
68. Soydinç S, Çelik A, Demiryürek S, Davutoğlu V, Tarakçıoğlu M, Aksoy M. The relationship between oxidative stress, nitric oxide and coronary artery disease. Eur J Gen Med 2007; 4(2): 62-6.
69. Kizhakekuttu TJ, Widlansky ME. Natural antioxidants and hypertension: promise and challenges. Cardiovasc Ther. 2010; 28(4): e20-32.
70. Rodrigo R, Prat H, Passalacqua W, Araya J, Guichard C, Bächler JP. Relationship between oxidative stress and essential hypertension. Hypertens Res. 2007; 30(12): 1159-67.
71. Rodrigo R, Libuy M, Feliú F, Hasson D. Oxidative stress-related biomarkers in essential hypertension and ischemia-reperfusion myocardial damage. Dis Markers. 2013; 35(6): 773-90.
72. Kurlak LO, Green A, Loughna P, Broughton Pipkin F. Oxidative stress markers in hypertensive states of pregnancy: Preterm and term disease. Front Physiol. 2014; 5: 310. doi: 10.3389/fphys.2014.00310.
73. Bahadoran Z, Carlström M, Ghasemi A, Mirmiran P, Azizi F, Hadaegh F. Total antioxidant capacity of the diet modulates the association between habitual nitrate intake and cardiovascular events: A longitudinal follow-up in Tehran Lipid and Glucose Study. Nutr Metab. 2018; 15: 19. doi: 10.1186/s12986-018-0254-2.
74. Wojdylo A, Oszmianski J, Czemerys R. Antioxidant activity and phenolic compounds in 32 selected herbs. Food Chem. 2007; 105(3): 940-9.
75. Benzie IF, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": The FRAP assay. Anal Biochem. 1996; 239(1): 70-6.
76. Payne AC, Mazzer A, Clarkson GJ, Taylor G. Antioxidant assays - consistent findings from FRAP and ORAC reveal a negative impact of organic cultivation on antioxidant potential in spinach but not watercress or rocket leaves. Food Sci Nutr. 2013; 1(6): 439-44.
77. Hisalkar P, Patne A, Karnik A, Fawade MM, Mumbare SS, *et al*. Ferric reducing ability of plasma with lipid peroxidation in type 2 diabetes. Int J Pharm Biol Sci. 2012; 42: 8–70.
78. Prior RL, Wu X, Schaich K. Standardized methods for the determination of antioxidant capacity and phenolics in foods and dietary supplements. J Agric Food Chem. 2005; 53(10): 4290-302.
79. Ndhlala AR, Moyo M, Van Staden J. Natural antioxidants: Fascinating or mythical biomolecules? Molecules. 2010; 15(10): 6905-30.
80. Hsieh C, Rajashekaraiah V. Ferric reducing ability of plasma: a potential oxidative stress marker in stored plasma. Acta Haematol Pol. 2021; 52(1): 61-67.
81. Armas-Padilla MC, Armas-Hernández MJ, Sosa-Canache B, Cammarata R, Pacheco B, Guerrero J, *et al*. Nitric oxide and malondialdehyde in human hypertension. Am J Ther. 2007; 14(2): 172-6.
82. Krishna Mohan S, Venkataramana G. Status of lipid peroxidation, glutathione, ascorbic acid, vitamin E and antioxidant enzymes in patients with pregnancy--induced hypertension. Indian J Physiol Pharmacol. 2007; 51(3): 284-8.
83. EI-Bana SM, El-Din AE, Isamil ZA. Fetal and maternal oxidative stress in normal and abnormal pregancies. Ain Shans Med J. 2001; 52: 421- 31.
84. Wassmann S, Laufs U, Müller K, Konkol C, Ahlbory K, Bäumer AT, *et al*. Cellular antioxidant effects of atorvastatin in vitro and in vivo. Arterioscler Thromb Vasc Biol. 2002; 22(2): 300-5.
85. Miyajima K, Minatoguchi S, Ito Y, Hukunishi M, Matsuno Y, Kakami M, *et al*. Reduction of QTc dispersion by the angiotensin II receptor blocker valsartan may be related to its anti-oxidative stress effect in patients with essential hypertension. Hypertens Res. 2007; 30(4): 307-13.
86. Dohi Y, Ohashi M, Sugiyama M, Takase H, Sato K, Ueda R. Candesartan reduces oxidative stress and inflammation in patients with essential hypertension. Hypertens Res. 2003; 26(9): 691-7.
87. Rodrigo R, Guichard C, Charles R. Clinical pharmacology and therapeutic use of antioxidant vitamins. Fundam Clin Pharmacol. 2007; 21(2): 111-27.