Review Article

The Role of Oxidative Stress in the Occurrence of Neurological Diseases and Cancer

Zeinab Afrand Khalil Abad[1], Nadia Dehbokri[2], Zahra Heydari[1], Parvin Karimi[3], Seyedeh Helya Siadat[4], Seyed Abbas Pakmehr[5]*, Hamidreza Razzaghi[6]

[1]Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran. [2]Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. [3]Fars Population-Based Cancer Registry, Shiraz University of Medical Sciences, Shiraz, Iran.[4]Faculty of Pharmacy, Medical University of Sofia, Bulgaria. [5]School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [6]Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.

Abstract

The human body needs both types of oxidants (free radicals) and antioxidants for normal metabolism, signal transduction, and order of cellular activities. Free radicals can be useful (necessary) or harmful (toxic) for the body. They have a dual role. The human body has an antioxidant mechanism to fight free radicals. A balance between free radicals and antioxidants is necessary for the physiological functioning of the body. Disturbance of the balance between the production of free radicals and antioxidants is called oxidative stress. This article is a review. Therefore, materials related to the subject were collected and studied using reliable scientific sources. Oxidative stress can change cell membranes and important cell structures such as proteins, lipids, deoxyribonucleotides (DNA), and carbohydrates. Oxidative stress is one of the effective factors in many diseases. In this article, an overview of the damage caused to the body by oxidative stress and its relationship bWe deal with human diseases such as stroke, diabetic nephropathy, Parkinson's, Huntington's, Alzheimer's, autism, cancer, and other phenomena such as aging.

Keywords: *Oxidative stress, Neurology disorder, Cancer, Free radicals*

Introduction

The victory of free radicals over the body's antioxidant defense, or in other words, the disruption of the balance between cell destruction by free radicals and the body's antioxidant defense, is called oxidative stress. Biological attacks on body organisms are usually referred to as oxidative stress. The human body needs both types of oxidants and antioxidants for normal metabolism, signal transduction, and regulation of cellular activities. Therefore, each cell creates conditions for creating a state of homeostasis between oxidant and antioxidant species. Oxidative stress may cause cell death by damaging important cellular components such as proteins, DNA, and membrane lipids. Also, oxidative stress is involved in physiological and pathological processes such as DNA damage, proliferation, cell adhesion, and survival.[1, 2]

Free radicals

Free radicals have unpaired electrons in their outermost layer and are highly reactive, which can start chain reactions by removing an electron from another molecule to complete their outer layer and with nearby molecules and atoms to reach a stable state. react They are only stable for a short time. Free radicals are divided into two general categories active oxygen and nitrogen radicals.[3, 4]

Materials and Methods

The review was conducted based on PubMed, PubMed Central, and Google Scholar online databases. Different forms of the following phrases: "oxidative stress", "Free radicals", "Antioxidants", "Reactive Nitrogen Species" and "Reactive Oxygen Species" were used for research. Finally, 36 articles have been reviewed for this article.

Reactive oxygen species (ROS)

In biological systems, oxygen free radicals are one of the most important radicals produced. Due to the electronic structure of oxygen, whose regeneration is facilitated by the addition of one electron at a time, the production of oxygen radicals leads to cell damage. The step-by-step transfer of electrons to molecular oxygen leads to the production of superoxide anions (O2-), hydrogen peroxide (H2O2), and finally free hydroxyl radicals (OH0). Including internal sources such as mitochondria, flavins, adrenaline, dopamine, peroxisomes,

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: Support_reprints@ccij-online.org

How to cite this article: Afrand Khalil Abad Z, Dehbokri N, Heydari Z, Karimi P, Siadat SH, Pakmehr SA, *et al*. The Role of Oxidative Stress in the Occurrence of Neurological Diseases and Cancer. Clin Cancer Investig J. 2024;13(4):1-6. https://doi.org/10.51847/XQOJjb4ziu

Address for correspondence:
Seyed Abbas Pakmehr, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail:
pakmehrabbas@yahoo.com

Access this article online

Website: www.ccij-online.org

DOI: 10.51847/XQOJjb4ziu

Quick Response Code:

© 2024 Clinical Cancer Investigation Journal

neutrophils, macrophages, eosinophils, oxidase enzymes, peroxidase and cytochrome P450 complex, NADH and external sources such as radiation, light rays, chemical compounds of cigarette smoke and alcohol in creating radicals free oxygen play a role.[5, 6]

Reactive nitrogen species (RNS)

Nitric oxide[7] as a type of reactive nitrogen radical, is formed from the oxidation of L-arginine to L-citrulline by NADPH-dependent nitric oxide synthetase enzyme, which this radical It has high propagation power and also acts as a secondary prophet. Nitric oxide reacts quickly with superoxide radicals after production and produces strong nitrite (ONOO-) and hydroxyl radicals.[8] It should be noted that free radicals, despite being harmful, can play important physiological roles in the body. For example, white blood cells use free radicals in phagocytosis and destroy trapped microbes. Also, nitric oxide produced in the endothelium cells of blood vessels causes dilation of blood vessels and as a result, lowers blood pressure.[9]

Antioxidants

Antioxidants are reducing agents that are found inside and outside the cell and can react with free radical species and the production of free radicals is controlled by them.[10] Antioxidants are the body's defense mechanisms against free radicals. Antioxidants play an important role in removing free radicals and in creating a balance between oxidation and reduction reactions.

Types of antioxidants

Enzyme antioxidants such as superoxide dismutase, catalase, glutathione peroxidase, water and fat-soluble vitamins such as vitamins C and E, minerals such as selenium, manganese, copper and zinc, proteins such as albumin, ceruloplasmin, transferrin, haptoglobin, are flavonoids and phytochemicals,[7, 11] superoxide dismutase is a metalloprotein that is the first enzyme in the antioxidant defense to reduce active oxygen species so that the superoxide radical by this enzyme forms two less dangerous oxidative compounds, hydrogen peroxide and oxygen deleted. Catalase is the most abundant iron-containing antioxidant enzyme that converts hydrogen peroxide into water and molecular oxygen in two steps. Glutathione peroxidase reduces hydrogen peroxide and lipid hydroperoxides to water and alcohol. This enzyme's glutathione is oxidised to glutathione disulfide in this stage, and glutathione reductase reduces it in the last step.[7, 12] Active vitamin C (ascorbic acid) is the most important water-soluble antioxidant in the cytosol and extracellular fluid. This vitamin is a strong detector for hydrogen peroxide, and reactive oxygen species, and hydrogen peroxide formed in water environments acts as a regenerating substance and turns into dehydroascorbic acid. As a supplier of reducing equivalents, ascorbic acid undergoes oxidation. Ascorbic acid plays a supporting role in many cooperative activities, however it is necessary to keep a metal cofactor in a reduced state. This metal cofactor is copper in monooxygenases and iron in dioxygenases.[13] Vitamin E (alpha-tocopherol) with its antioxidant property is the first defense barrier against the peroxidation of unsaturated fatty acids present in cellular and subcellular membrane phospholipids. This vitamin stops the spread of damage through the conversion of peroxyl fatty acid-free radicals into hydroperoxy. caused by free radicals.[14]

When the balance between antioxidants and free radicals is lost, oxidative stress is created, in which case the body's vital biomolecules such as DNA are damaged, and the accumulation of these damages causes changes in message transmission and gene expression, changes and mutations, and ultimately cell death. can be Cells respond to the imbalance of the oxidation and reduction cycle with a set of biological responses such as cell cycle arrest, gene transcription, initiation of transport pathways, and DNA repair, and these changes cause necrosis, senescence, or apoptosis, or the cell may survive and multiply. Find.[15, 16] The attack of free radicals on important cellular components such as lipids, DNA, protein, and carbohydrates causes changes in their structure and function.[17]

Lipids

Free radicals cause peroxidation of membrane lipids and increase membrane permeability by destroying the order of membrane lipid layers, and deactivating membrane receptors and enzymes. As a result of the peroxidation of androgen membrane lipids due to free radicals, the production of toxic products that act as secondary messengers in the cell, these compounds are malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), 2-alkenyl and isoprostanes, which They have toxic effects on cells.[18]

DNA

Free radicals cause changes in DNA in several ways. These ways include the destruction of DNA building bases, single or double DNA strand breaks, changes in purine and pyrimidine nucleotides or changes in the bond between sugar and base, mutations, deletions or substitutions, and cross-linking with proteins. The formation of 8-OH-G is well known as one of the DNA damages, which is related to oxidative stress and as a biomarker for the detection of cancers. The promoter region of genes contains sequences for binding transcription factors. These areas are rich in GC bases, which can be a factor in the attack of oxidants. The formation of 8-OH-G in the binding regions of transcription factors changes the expression of genes. In addition to 8-OH-G, 8,5-cyclo-2-deoxyadenosine (cyclo-dA), also prevents the transcription of genes with the TATA box in the cell. TATA box binds with transcription initiation proteins and as a result, DNA bends and transcription starts, but due to the presence of cyclo-dA, binding of the TATA box to protein is disrupted.[19] Also, oxidative stress causes instability of microsatellite regions of DNA. Redox-active metal ions and hydroxyl radicals increase the instability of microsatellite regions. Breakage of single DNA strands by free radicals can be tolerated by cells, but double-strand breaks of DNA by ionizing rays have irreparable effects on cell survival. Methylation in CpG islands in DNA is known as one of the

epigenetic mechanisms that can cause gene silencing. Oxidation of 5-methylcytosine to 5-hydroxymethyluracil can be done through deamination/oxidation reactions of thiamine or intermediates of 5-hydroxymethylcytosine.[20, 21]

Proteins

It is well known that ROS compounds can target cellular components. According to the studies conducted in this field, ROS can react with several amino acid units in the in vitro environment. These compounds cause damage to these macromolecules by oxidizing the side branches of amino acids and the main protein framework. Hydroxyl anion is the main factor in the oxidation of proteins, which by oxidation of the disulfide bond of cysteine-containing peptides, causes a bond between the thiol of the protein and the thiol of molecules with a lower molecular weight such as glutathione, and finally the activity of the protein is lost. Cysteine and methionine amino acids in proteins are more sensitive to oxidation. Oxidation of sulfhydryl groups and methionine residues in proteins causes changes in protein structure, protein unfolding, and its destruction. Enzymes that have metal in their active site are more exposed to oxidation, which causes enzyme inactivity. In some cases, specific oxidation may occur in the protein, for example, methionine to methionine sulfoxide, phenylalanine to tyrosine, sulfhydryl groups to disulfide bonds, and carboxyl groups to side chains of proteins. Gamma rays, oxidation of metal catalysts, HOCL, and ozone can cause the formation of carboxyl groups.[22]

Carbohydrates

Carbohydrates are attacked by free radicals such as OH0. A proton is randomly separated from one of the carbon atoms by the free radical OH0 and produces a central carbon radical. This process breaks the carbon chain in molecules such as hyaluronic acid. Also, the production of oxyradicals causes the activity of neutrophils in the inflammatory process in the joint synovial fluid, which can lead to rheumatoid arthritis.[17]

Diseases related to oxidative stress

Many human diseases are caused by oxidative stress or the disease itself causes oxidative stress. In the following, we discuss the relationship between oxidative stress and some human diseases.

Stroke

Cerebrovascular diseases are the most common disabling neurological disorder in the world.[23] In patients with stroke and neurological brain death, the number of free radicals from various sources such as xanthine oxidase, and cyclooxygenase, inflammation of cells and mitochondria increases. Mitochondrial electron transport chain changes during ischemia and reperfusion as well as other sources of free radical production. It has been stated that nitrite oxide created in the endothelium of blood vessels during cerebral ischemia can cause the production of free radicals. Produced superoxide and hydroxyl react with unsaturated lipids of the cell membrane and produce lipid peroxide radicals, lipid hydroperoxide, and products such as malondialdehyde. The concentration of blood cells such as neutrophils, monocytes, and macrophages that occur during reperfusion can also stimulate oxidative stress more.[22, 24]

Diabetes

Diabetes mellitus is known as one of the most common metabolic disorders. This disease is associated with increased blood sugar, disturbance in the metabolism of carbohydrates, fats, and proteins, and relative or absolute lack of insulin. In the world, 2.5-3% of people suffer from diabetes. Type 2 diabetes accounts for more than 90% of diabetics.[25, 26] Oxidative stress can be related to the process of speeding up the clinical complications of people with type 2 diabetes. During aerobic metabolism, free radicals are produced and in the process of conflict between free radicals and the body's antioxidant system, the level of antioxidants may decrease and as a result of incomplete cleaning of free radicals, lipids, sugars, proteins, and nucleic acids are oxidized, which are Finally, these factors cause extensive pathological consequences in diabetes.[27] Auto-oxidation of sugars is another cause of diabetes that causes oxidative stress. Compounds with alpha-hydroxyaldehyde structure (like glucose) can be converted into enol form and produce oxygen radicals by reducing intermediate elements and then oxygen. Also, as a result of increasing blood glucose by binding sugar to proteins, compounds are formed that play a role in the production of free radicals. Also, as a result of disruption in the amount of NADPH production, the level of reduced glutathione is reduced and then the polyol pathway is activated, which can cause a decrease in antioxidant capacity.

Diabetic nephropathy (kidney damage)

Diabetic kidney damage is a serious complication of diabetes mellitus that has spread in developed countries. Oxidative stress and inflammatory factors play an important role in the development and progression of nephropathy in diabetic patients.[28] The cerebral cortex and hippocampus suffer from oxidative stress and lipid peroxidation caused by hyperglycemia more than other brain regions. Hyperglycemia induces oxidative stress through enzymatic and non-enzymatic mechanisms and by excessive production of oxygen free radicals, and then by increasing the types of free radicals, programmed cell death occurs, which itself causes the death of neurons in the brain. Also, with the increase of inflammatory cytokines in the brain, neurons are damaged,[29, 30] and on the other hand, with the peroxidation of lipids, a variety of nerve mediators such as glutamate, cytochrome C, and the increase of intracellular calcium lead to damage and destruction of neurons. Finally, chronic hyperglycemia causes damage to the kidney, and then, with the increase in blood urea, the function of brain nerve cells is affected and causes cognitive impairment.[31, 32]

Neurodegenerative diseases

Oxidative stress is related to diseases that are associated with the destruction of the nervous system; These diseases include Parkinson's, Huntington's, and Alzheimer's.

Neurodegenerative diseases affect different parts of the brain. Changes in mitochondrial function, damage due to oxidative stress, abnormal presence of proteins and proteasomes, changes in iron metabolism, inflammation, and death of neurons are among the things that happen in these diseases. Failure to remove oxidized proteins by proteasomes leads to abnormal protein accumulation in the cell, which leads to the production of reactive oxygen species. These free radicals can damage mitochondria, increase the amount of calcium ions, inhibit proteasome activity, and eventually destroy and kill neurons.

Parkinson's

Parkinson's disease is one of the most common neurodegenerative diseases after Alzheimer's. Resting tremors, slowness of movement (Bradykinesia), muscle stiffness, and difficulty in starting movement are among the obvious symptoms of this disease and the cause of movement disorders and destruction in the nervous system.[33] Factors such as oxidative stress, DNA damage, reduced glutathione, and increased lipid peroxidation play a role in causing this disease. Oxidative stress not only results in the death of dopaminergic neurons but also diminishes energy and causes oxidative phosphorylation to malfunction.[34, 35] One of the genetic factors effective in causing this disease is the mutation in the PARK2 gene, which encodes the Parkin protein. This protein is one of the components of the ubiquitin E3 ligase complex, which plays a role in the proteasome pathway. Many believe that changes in this gene cause oxidative stress. Also, lack of this protein due to oxidative stress causes damage to mitochondria and ultimately neurodegeneration. By reducing the ubiquitination of the transcription repressor, its level increases, which causes a decrease in the expression of the molecule that regulates mitochondrial function. By creating a defect in the signaling pathway of this important molecule, the mitochondria suffer from dysfunction, and eventually, neurodegeneration occurs.[17, 36] Higher levels of hidden anxiety were associated with increased severity of temporomandibular joint disorders, suggesting psychological stress could exacerbate neurological conditions like Parkinson's disease.[23]

Huntington's disease

This disease is relatively rare and has an obvious autosomal inheritance. Its clinical features include cognitive, motor, and psychological disorders. Recently, the damage induced due to oxidative stress in these patients has been more attention, the increase of three nucleotide CAG repeats in the gene encoding the huntingtin protein (Htt) which causes the change in the spatial shape of the protein and finally accumulates in the cytoplasm and nucleus.[2] This mutant protein binds to the mitochondrial outer membrane and disrupts complexes I and II, thereby disrupting ATP production by producing free radicals. Also, this mutated gene plays a role in the establishment of mitochondria inside the axon and causes disturbances in the placement of mitochondria.[26]

Alzheimer's

This is a progressive neurodegenerative disease that causes the loss of integrity of neurons, the destruction of neurons and synapses, and ultimately memory impairment and reduced cognition. Alzheimer's precursor proteins are processed and cut outside the cell by beta and gamma-secretase enzymes and cause the formation of a structure called beta-amyloid plaques. The tau protein becomes hyperphosphorylated as a result of these plaques. This protein is involved in microtubule organisation and neuronal cell development. By being phosphorylated, this protein is separated from microtubules and accumulates inside the cell. Accumulation of these proteins along with beta amyloid plaques is one of the causes of Alzheimer's disease. Studies have shown that beta-amyloid plaques induce oxidative stress.[20] In this way, the accumulation of beta-amyloid plaques can be caused by the oxidation of carbohydrate side chains of membrane lipids, which leads to the breakdown of the natural structure of the cell membrane and ultimately causes cell destruction and lysis.[31]

Autism

The first three years of life are when developmental disorders like autism first manifest. This illness alters a child's brain, which interferes with social behaviors and communication abilities. Environmental and genetic factors play an important role in the occurrence of this disease. Oxidative stress as a mediator between environmental and genetic factors plays an important role in the occurrence of this disease.[32] Considering that children's brains have less antioxidant capacity compared to adults, they are more exposed to oxidative stress. In general, the brain is more susceptible to oxidative stress as a result of the need for high amounts of lipids, iron, and energy, as well as a lower antioxidant capacity to neutralize free radicals.[1, 23] Among the causes of oxidative stress in autistic patients, are an increase in the amount of 8-hydroxyguanosine at the level of DNA,[24] an increase of 3-nitrotyrosine at the level of proteins, and finally the loss of protein function and their accumulation and breakdown;[25] A decrease in the level of transferrin and ceruloplasmin, as a result of which the abnormal metabolism of iron and copper is involved in the pathology of autism.[26]

Cancer

Due to the interaction and reaction of free radicals with DNA, ROS compounds can activate the initial stages, promotion, and development of carcinogens. These compounds cause mutations in genes and cause cancer with the effect of destruction and damage on DNA components such as bases and deoxyribose sugars.[27, 28] The result of these mutations is the transformation of proto-oncogenes into oncogenes and changes in their expression, which leads to an increase in cell proliferation and finally, the transformation of a normal cell into a malignant proliferating cell. Free radicals play a role in causing cancer by inducing transcription, inducing message transmission pathways, causing replication errors, and genetic instability. Although there are different types of cancers, there is a direct

correlation between the size of a benign tumor and the amount of oxidized DNA products (8-oxoguanine). This process of converting a benign tumor into a malignant one must be understood. High levels of oxidative stress in cancer cells can lead to necrosis or even apoptosis, whilst low levels can stimulate cell division and encourage tumor growth. Free radicals can also result in the peroxidation of cell membranes. The metabolites resulting from the peroxidation of lipids are malondialdehyde, 4-hydroxynoneal, and acrolein, which bind to proteins and change their function, causing enzyme inhibition and changes in the cell receptor structure, and ultimately causing cancer.[29] A recent review of spiral inertial microfluidic devices highlights their potential for bioparticle separation and profiling, including the isolation of circulating tumor cells (CTCs) from blood samples.[33] The authors note that these microfluidic systems can separate particles like CTCs from other blood components based on differences in size and shape. Such technologies may aid cancer diagnosis by allowing the purification of rare CTCs from patient blood samples.[20, 22, 30]

Aging

There are many theories regarding the theory of the aging process. One of the most prominent theories of aging is the generally accepted free radical theory.[20] This theory is supported and supported due to the increase of free radicals and their damage with age. According to this theory, the body's free radicals harm cellular constituents through oxidative means, altering cell, tissue, and organ function before finally causing death. Also, this hypothesis is supported by the hypothesis of the inverse relationship between metabolism rate and lifespan.[21, 22] Also, this theory is supported by experimental evidence that shows that oxidative damage to DNA, protein, and lipids increases with age. Therefore, free radicals that cause oxidative stress increase with age and provide the basis for the development of other diseases.[23, 29]

In general, respiratory viral infections are linked to the generation of cytokines, inflammation, cell death, and other pathophysiological processes that may be connected to oxidative stress or redox imbalance. As we age, these phenomena become much more prevalent.

Conclusion

Excessive production of free radicals causes oxidative damage to biomolecules such as lipids, proteins, and DNA and leads to the occurrence of diseases such as cancer, diabetes, rheumatoid arthritis, stroke, etc. However, some free radicals have useful properties such that they are used in the immune system to attack and destroy pathogenic agents. Although the body naturally produces antioxidants to fight these free radicals and many studies have shown the reduction of oxidative stress through diet and lifestyle changes, there is a need for more studies in this field.

Acknowledgments

None.

Conflict of interest

None.

Financial support

None.

Ethics statement

None.

References

1. Ziaee M, Khajavi A, Najafzadeh A, Tavakolizadeh M, Karkon Shayan S. Information resources trust and self-care behaviors in prevention of COVID-19 among health workers in Gonabad city, Iran. J Res Health. 2022;12(1):49-56. doi:10.32598/JRH.12.1.1901.2
2. Babaniamansour S, Atarodi A, Babaniamansour P, Firouzabadi MD, Majidi M, Karkon-Shayan S. Clinical findings and prognosis of COVID-19 patients with benign prostatic hyperplasia: A case series. J ISSN. 2021;2766:2276.
3. Aghadavod E, Nasri H. What are the molecular mechanisms of oxidant and antioxidant compounds? Ann Res Antioxid. 2016;1(1).
4. Salmaninejad A, Kangari P, Shakoori A. Oxidative stress: Development and progression of breast cancer. Tehran Univ Med Sci J. 2017;75(1):1-9.
5. Aldini G, Yeum KJ, Niki E, Russell RM, editors. Biomarkers for antioxidant defense and oxidative damage: Principles and practical applications. John Wiley & Sons; 2011.
6. Jourkesh M, Sadri I, Sahranavand A, Ojagil A, Dehyanpoori M. The effects of two different doses of antioxidant vitamin C supplementation on bioenergetics index in male college student. J Am Sci. 2011;6(1):852-8.
7. Najafzadeh H, Razijalali M, Morovvati H, Navvabi L. Evaluation the effect of cimetidine, estradiol and vitamin E on myoglobinuric renal toxicity in rats. Am Eurasian J Toxicol Sci. 2011;3(3):177-83.
8. Rahman T, Hosen I, Towhidul Islam MM, Uddin Shekhar H. Oxidative stress and human health. Adv Biosci Biotechnol. 2012;3(07):997-1019.
9. Karkon-Shayan S, Aliashrafzadeh H, Dianat-Moghadam H, Rastegar-Pouyani N, Majidi M, Zarei M, et al. Resveratrol as an antitumor agent for glioblastoma multiforme: Targeting resistance and promoting apoptotic cell deaths. Acta Histochem. 2023;125(6):152058. doi:10.1016/j.acthis.2023.152058
10. Azani A, Omran SP, Ghasrsaz H, Idani A, Eliaderani MK, Peirovi N, et al. MicroRNAs as biomarkers for early diagnosis, targeting and prognosis of prostate cancer. Pathol Res Pract. 2023;248:154618. doi:10.1016/j.prp.2023.154618
11. Noraldeen SAM, Rasulova I, Lalitha R, Hussin F, Alsaab HO, Alawadi AH, et al. Involving stemness factors to improve CAR T-cell-based cancer immunotherapy. Med Oncol. 2023;40(11):313. doi:10.1007/s12032-023-02191-7
12. Jafarzadeh E, Shoeibi S, Bahramvand Y, Nasrollahi E, Maghsoudi AS, Yazdi F, et al. Turmeric for treatment of irritable bowel syndrome: A systematic review of population-based evidence. Iran J Public Health. 2022;51(6):1223-31. doi:10.18502/ijph.v51i6.9656
13. Ozkul A, Akyol A, Yenisey C, Arpaci E, Kiylioglu N, Tataroglu C. Oxidative stress in acute ischemic stroke. J Clin Neurosci. 2007;14(11):1062-6. doi:10.1016/j.jocn.2006.11.008
14. Azizi Soleiman F, Pahlavani N, Rasad H, Sadeghi O, Gohari MR. The relationship between inflammation, oxidative stress, and metabolic risk factors in type 2 diabetic patients. Iran J Diabetes Obes. 2013;5(4):151-6.
15. Aghadavod E, Khodadadi S, Baradaran A, Nasri P, Bahmani M, Rafieian-Kopaei M. Role of oxidative stress and inflammatory factors in diabetic kidney disease. Iran J Kidney Dis. 2016;10(6):337-43. doi:10.3389/fimmu.2023.1185317
16. Maritim AC, Sanders RA, Watkins JB 3rd. Diabetes, oxidative stress, and antioxidants: A review. J Biochem Mol Toxicol. 2003;17(1):24-38. doi:10.1002/jbt.10058
17. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human

disease. Int J Biochem Cell Biol. 2007;39(1):44-84. doi:10.1016/j.biocel.2006.07.001
18. Doraghi F, Pegah Aledavoud S, Fakhrioliaei A, Larijani B, Mahdavi M. Ring-Opening Cross-Coupling/Cyclization reaction of cyclopropanols with organic compounds. ChemistrySelect. 2023;8(32):e202301438.
19. Fakhrioliaei A, Abedinifar F, Salehi Darjani P, Mohammadi-Khanaposhtani M, Larijani B, Ahangar N, et al. Hybridization of the effective pharmacophores for treatment of epilepsy: Design, synthesis, in vivo anticonvulsant activity, and in silico studies of phenoxyphenyl-1,3,4-oxadiazole-thio-N-phenylacetamid hybrids. BMC Chem. 2023;17(1):80. doi:10.1186/s13065-023-01000-6
20. Mostafavi M, Ghanavi J. U.S. Patent Application No. 12/870,792. 2011. doi:10.13140/RG.2.2.33091.62246
21. Safapoor S, Halimi M, Ghomi MK, Noori M, Dastyafteh N, Javanshir S, et al. Synthesis, ADMT prediction, and *in vitro* and *in silico* α-glucosidase inhibition evaluations of new quinoline-quinazolinone-thioacetamides. RSC Adv. 2023;13(28):19243-56. doi:10.1039/d3ra01790g
22. Ghanavi J, Mostafavi M, Ghanavi Z. U.S. Patent No. 9,487,399. Washington, DC: U.S. Patent and Trademark Office. 2016.
23. Anbari F, Yazdani Kachooei Z, Salemi M, Anbari F. Anxiety and temporomandibular joint disorders among law students in Iran. J Dentomaxillofac Radiol Pathol Surg. 2020;9(4):33-9. doi:10.52547/3dj.9.4.33
24. Melnyk S, Fuchs GJ, Schulz E, Lopez M, Kahler SG, Fussell JJ, et al. Metabolic imbalance associated with methylation dysregulation and oxidative damage in children with autism. J Autism Dev Disord. 2012;42(3):367-77. doi:10.1007/s10803-011-1260-7
25. Shayan SK, Aliashrafzadeh H, Rezayitalab F, Sobhani M, Zarei M. Comparison of the outcome of altplas administration after acute ischemic stroke in patients over 80 years and under 80 years admitted. J Pharm Negat Results. 2022;13(S3):684-8. doi:10.47750/pnr.2022.13.S03.105
26. Hajialilo M, Haghjo AG, Darbandi H, Shayan SK, Shayan FK. Association of systemic lupus erythematosus activity with serum levelsof sTWEAK and CD160: A cross-sectional study. J Res in Clin Med. 2018;6(3):121-8. doi:10.15171/jarcm.2018.019
27. Shayan SK, Nasrollahi E, Bahramvand Y, Zarei M, Atarodi A, Farsi Y, et al. Percutaneous coronary intervention associated with a higher risk of hypoxemia and COVID-19 severity. Curr Med Chem. 2024;31(10):1265-77. doi:10.2174/0929867330666230222104345
28. Mirsani A, Shayan SK, Sadeghian A, Baradaran R. Ureteral injury following posterior lumbar interbody fusion after five years: A rare case. Nephrourol Mon. 2022;14(2). doi:10.5812/numonthly.120605
29. Asna Ashari M, Berijani A, Anbari F, Yazdani Z, Zandian A. Comparison of the effectiveness of combined diode laser and GLUMA bonding therapy with combined diode laser and 5% sodium fluoride varnish in patients with dentin hypersensitivity. J Lasers Med Sci. 2021;12:e62. doi:10.34172/jlms.2021.62
30. Saghafian M, Seyedzadeh H, Moradmand A. Numerical simulation of electroosmotic flow in a rectangular microchannel with use of magnetic and electric fields. Sci Iran. 2023. doi:10.24200/SCI.2023.58474.5742
31. Zhang L, Pakmehr SA, Shahhosseini R, Hariri M, Fakhrioliaei A, Karkon Shayan F, et al. Oncolytic viruses improve cancer immunotherapy by reprogramming solid tumor microenvironment. Med Oncol. 2023;41(1):8. doi:10.1007/s12032-023-02233-0
32. Mollazadeh M, Azizian H, Fakhrioliaei A, Iraji A, Avizheh L, Valizadeh Y, et al. Different barbiturate derivatives linked to aryl hydrazone moieties as urease inhibitors; design, synthesis, urease inhibitory evaluations, and molecular dynamic simulations. Med Chem Res. 2023;32(5):930-43. doi:10.1007/s00044-023-03050-w
33. Bagi M, Amjad F, Ghoreishian SM, Sohrabi Shahsavari S, Huh YS, Moraveji MK, et al. Advances in technical assessment of spiral inertial microfluidic devices toward bioparticle separation and profiling: A critical review. Biochip J. 2024:1-23. doi:10.1007/s13206-023-00131-1
34. Gorgzadeh A, Hheidari A, Ghanbarikondori P, Arastonejad M, Goki TG, Aria M, et al. Investigating the properties and cytotoxicity of cisplatin-loaded nano-polybutylcyanoacrylate on breast cancer cells. Asian Pac J Cancer Biol. 2023;8(4):345-50.
35. Basmenj ER, Arastonejad M, Mamizadeh M, Alem M, KhalatbariLimaki M, Ghiabi S, et al. Engineering and design of promising T-cell-based multi-epitope vaccine candidates against leishmaniasis. Sci Rep. 2023;13(1):19421. doi:10.1038/s41598-023-46408-1
36. Pourali G, Kazemi D, Chadeganipour AS, Arastonejad M, Kashani SN, Pourali R, et al. Microbiome as a biomarker and therapeutic target in pancreatic cancer. BMC Microbiol. 2024;24(1):16. doi:10.1186/s12866-023-03166-4