Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 8, Nov. 2024
Manuscript ID ZUMJ-2408-3519 DOI . 10.21608/zumj.2024.312131.3519
REVIEW ARTICLE

Effect of Sodium Nitrite on the Cerebellar Cortex and Neuro-Protective Effects of Quercetin

Maha Amin Abdallah Khattab, Samia Adel Abd El-Baset, Ghada Abdelaziz Elsammak, Aya Ebrahim Abdelfattah Mohammed*
Histology and Cell Biology Department, Faculty of Medicine, Zagazig University,Zagazig, Egypt

Corresponding author*:
Aya Ebrahim Abdelfattah Mohammed

Email:
aya2891994@gmail.com

Submit Date 15-08-2024
Revise Date 13-09-2024
Accept Date 16-09-2024

ABSTRACT

Background: Sodium nitrite is a frequently employed food ingredient; however, extended usage at elevated quantities might result in neurological diseases. Inorganic nitrate is regarded as a source of nitric oxide (NO) and nitrite. Sodium Nitrite is frequently used in several industrial processes including fertilizers and food additives. It can prevent food spoilage and act as antimicrobial agent. Nitrite has a significant impact on controlling intricate physiological and biochemical responses, such as reducing inflammation and preventing blood clotting, which are directly linked to the development and management of cerebrovascular illness. Humans can experience overexposure to nitrite salts through different ways. Excessive amounts of nitrite salts can have harmful effects on human and animal health on different systems including the central nervous system (CNS). Quercetin is a naturally occurring flavonoid with bioactive qualities that has recently garnered significant attention for its protective potential in many diseases. The neuroprotective properties of this substance have been proven by numerous in vitro investigations, as well as in vivo animal experiments and human trials. Multiple researches have documented the potential neuroprotective benefits of quercetin.

Conclusions: A recent discovery has revealed the involvement of nitrite in the development of several CNS disorders including the cerebellum indicating its neurotoxicity. However, administration of Quercetin could attenuate these changes due to its neuroprotective effect against the induced oxidative stress and neuronal injury.

Keywords: Sodium Nitrite; Cerebellar Cortex; Neuro; Quercetin.

INTRODUCTION

Nitrites are widely present in our surroundings. The nitrite ion is composed of a single nitrogen atom bonded to two oxygen atoms. Typically, they are commonly attached to metal cations like Sodium and potassium. Sodium nitrite is an inorganic compound composed of a Sodium ion (Na+) and a nitrite ion (NO2-). Sodium nitrite is a water-soluble compound that exists as a yellowish-white crystalline powder [1, 2].

Studies undertaken since 1980 have indicated that nitrite is a crucial component for human health. Approximately 20% of the body nitrite requirements are met through the consumption of plant-based meals. Leafy plants such as celery, lettuce, spinach, cabbage, and red root are regarded as excellent sources of nitrite. The concentration of nitrite in vegetables is influenced by farming practices, the application of synthetic fertilizers, the quality of water used for irrigation, and the conditions under which the vegetables are stored. Saliva is responsible for the conversion of dietary nitrate into nitrite, which accounts for the remaining 80% of the total daily nitrite [3].

Systemic nitrate and nitrite often circulate throughout the bloodstream, saliva, and tissues following the consumption of a diet rich in nitrates. Approximately 25% of nitrate present in the food can undergo conversion to nitrite within the oral cavity, facilitated by anaerobic bacteria that reside in the deep crypts of the posterior region of the tongue. Within the stomach, the acidic gastric fluid facilitates a non-enzymatic conversion of nitrite to nitric oxide (NO). Nitrites are taken up by the small intestine and enter the bloodstream, where they might act as a source of nitric oxide (NO) under specific circumstances. The majority of the nitrites that are taken in are eventually excreted in urine. Moreover, significant quantities are also expelled through saliva [4].

Nitrites and nitric oxide, which are metabolic byproducts of Sodium Nitrate, play crucial roles in several cellular activities. The ingestion of nitrite in clinical trials has been found to have a multitude of positive effects on health. Physiologically, they modulate blood pressure, facilitate wound healing, regulate immune response, and govern neurological activities. In addition, nitric oxide (NO) controls the flow of blood in the heart muscle and other tissues of the body [5]. On the contrary, Kina-Tanada et al. [6] found that a prolonged lack of dietary nitrate and nitrite is typically associated with metabolic syndrome, endothelial dysfunction, and cardiovascular illnesses. The European Commission Scientific Committee for Food (ECSC) has established an acceptable daily intake (ADI) for nitrite, typically ranging from 0.06-0.07 mg per kilogram of body weight per day [7].

While nitrate and nitrite are naturally present in the human body and play a role in various physiological processes, an excessive amount of these salts can have harmful effects on human and animal health. Humans can experience overexposure to nitrate and nitrite salts through the consumption of food with high nitrite levels, contaminated water, or breathing of polluted air [8].

The process of development and industrialization has caused environmental disruptions, leading to significant human exposure to undesirable chemicals and harmful compounds. Sodium nitrite is frequently employed in several industrial applications, such as a meat preservative, a food additive, a fertilizer, and in rodenticides. It is utilized in food processing due to its functions as a food coloring agent, a microbial pathogen inhibitor, and an antioxidant [9].

In ancient times, there was a strong desire to prevent the decay of meat and fish by preserving them. During the 19th century, individuals became aware of the varying

degrees of preservative effectiveness among different types of salts. Historical scientists demonstrated that the introduction of nitrate only into the pickling solution leads to the formation of nitrite through the activity of certain microbes. The addition of nitrite to meat is responsible for preserving the red color of the meat for an extended period of time [10].

Bernardo et al. [11] reported that the addition of nitrate and nitrite to meat products was done without scientific understanding of its purpose. In the 1950s and 1960s, the meat industry started using nitrite and nitrate on a regular basis. During the initial half of the 20th century, there was a gradual transition from using nitrates to using nitrites in cured meat products. This change was driven by the desire for faster curing time, higher production capacity, and a deeper understanding of nitrite chemistry [12].

Multiple studies have demonstrated that nitrite has the ability to impede bacterial proliferation and safeguard against food degradation. Nitrate and nitrite have been employed as both preservatives and culinary enhancers in beef, pork, sausage, and salami. Furthermore, they have been employed to impede the oxidation of unsaturated fatty acids (FA) that contribute to food spoilage, as well as to serve as a factor for stabilizing color [13]. The addition of nitrite results in the fixation of a nice red color, which is the most apparent effect [14]. The preservation of the red color of meat is typically achieved by adding nitrite, which undergoes a process of converting into nitric oxide (NO). Nitric oxide then has the capability to bind with the heme pigment (myoglobin) present in the meat, resulting in the preservation of its red color [15].

Govari & Pexara [16] showed that nitrite has significant bacteriostatic and bactericidal effects on several spoilage bacteria and food-borne pathogens commonly found in meat products.

Furthermore, most researches indicated that nitrite has the capacity to impede the growth of Clostridium botulinum spores. Medically, it is employed as an intestine relaxant, vasodilator, and bronchodilator. In addition, Sodium Nitrite is employed in conjunction with Sodium thiosulfate to medically address cyanide toxicity [2, 17].

Furthermore, it is worth noting that apart from consuming processed meat, fruits and vegetables can also have elevated levels of nitrite. In general, the levels of nitrites found in fruits and vegetables are often quite modest. Nevertheless, the quantity of nitrite present in vegetables will vary depending on the specific vegetable and the manner in which it is stored and cooked for consumption. The nitrite concentration in vegetables and fruits can increase when they are spoiled, stored poorly, or pickled or fermented [18].

The unregulated application of nitrogenous fertilizers in agriculture, along with pollution from human and animal waste and inadequate agricultural drainage, has led to a significant rise in nitrite levels in both surface and groundwater. Typically, the levels of nitrate and nitrite salts in groundwater are higher than in surface water sources [19]. Liu et al. [20] stated that the use of chloramine for water disinfection can lead to the production of nitrite in water. The general population is unlikely to be exposed to nitrite through breathing. However, there is a possibility of

inhaling dust from fertilized goods that contain nitrite [19].

Typically, nitrites that are ingested through food or beverages may be eliminated from the human body without causing any harm. Under specific circumstances such as diarrhea and dehydration, the body lacks an adequate amount of fluids. Nitrite has the potential to build up in the body and typically enters the bloodstream in significant amounts. Nitrite present in the bloodstream participates in the process of oxidizing hemoglobin. The iron component of hemoglobin undergoes oxidation from the ferrous state (Fe2+) to the ferric cation (Fe3+), which then causes the conversion of hemoglobin to methemoglobin. The latter is unable to attach to oxygen, which hinders the transportation of oxygen and leads to hypoxia and lactic acidosis. The physical manifestations of Sodium nitrite poisoning can range from bluish discoloration of the skin to respiratory distress, nausea, episodes of vomiting, disorientation, loss of consciousness, and/or seizures. The severity of these symptoms is contingent upon the level of methemoglobin concentration [21].

Infants under four months of age who consume formula mixed with water from unleaded rural domestic wells are at risk of developing health problems due to exposure to nitrites, according to the Environmental Protection Agency (EPA) (US Agency for Toxic Substances and Diseases 2001) [22]. They have a higher susceptibility to developing methemoglobinemia, which in turn leads to the development of blue baby syndrome. Furthermore, it was mentioned that the pregnant lady and her fetus could exhibit heightened susceptibility to the harmful effects of nitrite. The enhanced oxidative stress was attributable to a high level of consumption. Workers in the explosive and fertilizer industries, together with farmers, are classified as a high-risk population for nitrite exposure. This can happen when dust containing nitrite salts is inhaled or when handling fertilizers [23].

In October 2015, the International Agency for Research on Cancer (IARC) announced that there is a potential risk of developing cancer from consuming red and processed meat. The IARK working group has reported that a prolonged consumption of larger quantities of red meat, particularly processed meat, is associated with elevated mortality rates, as well as an increased risk of colorectal cancer, type II diabetes, and heart disorders in both males and females. Although Sodium nitrite is a subject of much debate, it is extensively utilized in meat products due to its unique ability to suppress the proliferation of clostridium botulinum germs [15].

A previous research has ascribed the harmful impact of nitrites to their capacity to undergo conversion into highly carcinogenic compounds known as nitrosamines and nitrosamides. Several variables influence the development of nitrosamines in processed meat, such as the quantity of nitrite added, the quality of the meat, the level of fat, and the duration and temperature of the processing. Nitrosamines are more abundant in high-quality food sources such as bacon, luncheon meat, hotdogs, sausage, and salami [24].

Nitrosamines and nitrosamides are chemical compounds that may rapidly traverse the cell membrane's two phospholipid layers. They achieve this by inducing oxidative stress and interacting with various target molecules, including lipids, proteins, and DNA. As a

result, these interactions can lead to cell death through either necrosis or apoptosis [25]. An elevated content of sodium nitrite in one's diet is associated with a greater occurrence of several health issues, such as gastrointestinal malignancies, liver damage, and impaired liver function accompanied by an increase in liver enzymes [26]. Furthermore, it has been documented that sodium nitrite can lead to pulmonary and salivary gland toxicity, affecting the lungs of pregnant women [27, 28].

In addition, sodium nitrite is involved in the formation of congenital abnormalities and harm to the nervous system. In addition, a high concentration of sodium nitrite in drinking water or food has a detrimental impact on renal function by increasing the levels of oxidative stress indicators [29, 30]. Zaidi et al. [31] stated that elevated levels of nitrite can cause inflammation, ischemia, and disruption of cerebral energy by disrupting the equilibrium between oxidants and antioxidants, potentially resulting in cellular brain damage.

Sanjari and Hosseini [25] mentioned that the intake of sodium nitrite during pregnancy and lactation leads to elevated levels of uric acid, urea, and creatinine in the bloodstream. This was attributed to the detrimental effects of sodium nitrite on the structure of renal tissue. Nitrite compounds potentially passed from the placenta to the fetuses and neonates of rats, as well as through the milk, resulting in a harm to the structure of their renal tissue. Eissa et al. [4] found that an excessive amount of sodium nitrite might lead to the deterioration of the sperm membrane, as well as a decrease in sperm motility, count, and viability. Additionally, they observed histological changes in the testes as a response to sodium nitrite treatment.

Zedan et al. [17] documented that sodium nitrite treated rats showed multiple changes in the three layers of the cerebellar cortex. Purkinje cells were shrunken with dark stained nuclei and cytoplasm and arranged in many layers. They were surrounded by empty spaces. Some cells were lost leaving empty spaces with multiple vacuolations in the neuropil in the three layers of cerebellar cortex. They attributed this harmful effect as a result of overproduction of reactive oxygen species which are produced by the mitochondrial respiratory chain and could lead to oxidative harm.

Ibegu et al. [32] reported that degeneration of the Purkinje cells of the cerebellar cortex could be due to methemoglobin formation due to nitrite ingestion and increase in concentration of nitrite and extract which could be toxic. Abdel Mohsen et al. [33] explained the abnormal arrangement of Purkinje in prolonged neuronal injury as an adaptive mechanism in a trial to reestablish synaptic contact with other nerve cells to achieve their function.

Lindeman et al. [34] documented that Purkinje cells are highly susceptible to injury after exposure to various environmental toxins. Motor coordination is usually impaired due to Purkinje cell loss or degeneration.

Early studies predominantly associated the cerebellum with motor functions; however, more recent studies have shown that the human cerebellum is also associated with non-motor functions including emotion, language and memory. Lesion at the level of the cerebellum leads to motor impairment

called ataxia. Furthermore, it could lead to cognitive syndrome, which is characterized by impairments in working memory, personality change, inappropriate behavior, language deficits and a general lowering of intellectual function [35,36].

Since nitrite causes oxidative stress in the affected organs in rats, treatment with substances with antioxidant activities may reverse and inhibit nitrite toxicity [37]. Natural food sources provide essential antioxidant compounds that have the potential to mitigate the detrimental impacts of toxic toxins in our surroundings. Supplementation with antioxidants may effectively prevent the harmful effects of nitrite poisoning. Hence, it is crucial to seek out secure and economical remedies to mitigate the harmful effects of nitrite toxicity in the impacted organs of both animals and humans. It has been shown that plant flavonoids constitute a significant group of defensive antioxidants. This highlights the relevance of investigating flavonoids like quercetin [26, 38].

Quercetin:

Flavonoids are plant-derived compounds that are classified as secondary metabolites. They are mostly composed of a benzopyrone ring with attached phenolic or polyphenolic groups. These qualities, including antioxidant, anti-inflammatory, anti-allergic, anti-apoptotic, antithrombotic, and vasodilator effects, are found in nearly all fruits and vegetables [39].

Flavonoids are categorized into different groups based on their chemical composition, level of unsaturation, and carbon ring oxidation. Flavonoids are classified into various subgroups, including anthoxanthins (flavonone and flavanol), flavonones, flavanonols, flavans, chalcones, antho-cyanidins, and isoflavonoids [40]. Mirsafaei et al. [41] reported that quercetin is a prototypical flavonoid compound. It is classified as a member of the flavononol group. Quercetin gets its name from the word "quercetum," which refers to an oak grove. Quercetin, also known as 3,5,7,3′,4′-pentahydroxy flavone, is a prevalent flavonoid that is found in abundance throughout nature. It is present in a variety of fruits, including apples, cranberries, cherries, and grapes. Furthermore, it is present in vegetables such as onion, peppers, broccoli, and asparagus. Furthermore, it can be found in various food sources including numerous seeds, buckwheat, almonds, olive oil, and black or green tea. The onion is the primary dietary source of quercetin, which is of utmost significance. The main constituents of it are predominantly quercetin-4’-glucoside and quercetin-3,4’-diglucoside [42].

Quercetin exists in two chemical forms: the unconjugated aglycone, which lacks a carbohydrate component, and the quercetin glycoside, which is formed by attaching a glycosyl group (usually glucose, rhamnose, or rutinose) to one of the OH groups. Quercetin is present in fruits and vegetables as a glycoside, namely as quercetin aglycone linked to glucose or rutinose. Both the glycoside and aglycoside forms are readily absorbed by the body, but the glycoside form exhibits superior bioavailability. It undergoes hydrolysis mostly in the small intestine and also in the large intestine [41].

The amount of flavonoids consumed in the human diet can vary greatly, ranging from 23 mg/day of solely flavonols and flavones to over 500 mg/day of total flavonoids.

Quercetin comprises over 75% of our overall flavonol consumption. Quercetin can be effectively supplemented in the diet at a dosage range of 200-1200 mg per day [43].

The free aglycone remains soluble in the small intestine until it is transported through enterocytes via passive transport. Quercetin undergoes many processes, including methylation, sulfation, and glucuronidation, within the enterocytes before it enters the portal circulation. Quercetin is carried to the liver by albumin in the plasma, where it undergoes transformation into its metabolites, such as isorhamnetin, tamarixetin, and kaempferol. Quercetin and its metabolites have half-lives ranging from 11 to 28 hours, indicating that significant amounts of quercetin remain in the bloodstream after it is consumed [44]. Moreover, the brain retains a significant amount of quercetin metabolites for several hours following the administration of quercetin [45].

Quercetin exhibits diverse biological roles, including neuroprotection, anticancer activity, antidiabetic effects, and anti-inflammatory properties. Quercetin modulates mitochondrial activity by regulating ATP generation through the inhibition of ATPase and hexokinase enzymes. Additionally, research has indicated that quercetin activates the adenosine monophosphate-activated protein kinase (AMPK) complex, which is involved in maintaining cellular energy balance [46].

Quercetin exhibits properties that reduce high levels of lipids and glucose in the body. Prior research conducted on rats with diabetes demonstrated that the addition of quercetin resulted in a decrease in tumor necrosis factor (TNF - α), blood pressure, body mass index (BMI), hyperinsulinemia, insulin resistance, and dyslipidemia [47].

Quercetin possesses the ability to both eliminate free radicals and decrease the frequency of inflammation. This often happens by suppressing the generation of inflammatory mediators, such as leukotrienes and prostaglandins, while also inhibiting pro-inflammatory enzymes like cyclooxygenase and lipoxygenase [48].

Moreover, quercetin safeguards DNA from oxidative stress-induced harm by inhibiting the creation of reactive oxygen species (ROS). Quercetin plays a role in reducing DNA damage and enhancing the capacity of the DNA repair system. Various investigations have demonstrated that quercetin effectively hinders the growth and advancement of colorectal cancer cell lines [42]. Madiha et al. [49] have shown that quercetin enhances mitochondrial function, reinstates the activity of the electron transport chain, and reduces motor and memory deficits in a rat model with neurodegenerative illness.

Furthermore, Alshammari et al. [50] documented that quercetin has demonstrated the ability to hinder the advancement of diabetic nephropathy and encephalopathy, as well as mitigate spinal cord degeneration and mitochondrial dysfunction in osteoarthritic rats. Quercetin has shown promise in treating metabolic disorders, including obesity, nonalcoholic fatty liver disease, diabetes, and related comorbidities, by positively influencing the gut flora. Hence, quercetin may demonstrate its ability to protect the nervous system not only by reducing oxidative stress but also by influencing the makeup of gut bacteria in instances of diabetic neuropathy [51].

According to Fan et al. [52], quercetin has been found to have neuroprotective properties in spinal cord injury. It can help prevent neuron death, minimize damage to neural tissue, and control inflammatory responses. Furthermore, quercetin effectively decreases the occurrence of necroptosis in oligodendroglia and mitigates the degeneration of myelin and axons following spinal cord injury. Han et al. [53] said that quercetin has the ability to prevent microglial activation, which in turn protects neurons from the harmful effects caused by microglia-induced inflammation.

Since the discovery of quercetin neuroprotective properties, numerous studies have hypothesized that quercetin has a neuroprotective impact in ischemia-reperfusion models. These findings hypothesized that quercetin has the potential to safeguard oligodendrocyte progenitor cells from Hypoxia-Ischemia. Additionally, research has demonstrated that quercetin has the ability to counteract brain inflammation and reduce apoptosis in fetal brain tissue [54]. According to a survey, adding quercetin to the diet was found to reduce the impact of some toxins, such as dimethoate on the cerebellum. Quercetin administration improved viability and morphology of most of the neurons. Purkinje cell layer appeared as a single row of large cells. They had pale central vesicular nuclei and slightly basophilic cytoplasm. Most of the granule cells appeared normal with regular ovoid nuclei. This was explained by the ability of quercetin to counteract oxidative stress-induced cellular damage by activating the Nrf2 - ARE pathway [55]. Abelrahman et al. [56] reported that quercetin could the cellular and molecular effects of some nanoparticles. They proved that quercetin could improve the histological structure of the cerebellar cortex. Most of the cerebellar cortex neurons retained their normal structure. Quercetin could minimize overproduction of reactive oxygen species which could reduce axonal and neuronal damage.

Conflict of interest: none

Financial disclosures: none

REFERENCES

1. **Padovano M, Aromatario M, D'Errico S, Concato M, Manetti F, David MC, et al.** Sodium nitrite intoxication and death: summarizing evidence to facilitate diagnosis. Int J Environ Res Public Health, 2022; 19(21), 13996-4002.
2. **Stephenson L, Wills S, van den Heuvel C, Humphries M & Byard RW.** Increasing use of sodium nitrite in suicides—an emerging trend. Forensic Sci. Med. Pathol., 2022; 18(3), 311-8.
3. **Hord NG**. Dietary nitrates, nitrites, and cardiovascular disease. Curr. Atheroscler. Rep., 2011; 13, 484-92.
4. **Eissa MM, Ahmed MM, Abd Eldaim MA, Orabi SH, Elbaz HT, Mohamed MA, et al.** Methanolic extract of Chlorella vulgaris protects against sodium nitrite-induced reproductive toxicity in male rats. Andrologia, 2020; 52(11), 13811-20.
5. **Ma L, Hu L, Feng X, Wang S.** Nitrate and nitrite in health and disease. Aging dis., 2018; 9(5), 938-46.
6. **Kina-Tanada M, Sakanashi M, Tanimoto A, Kaname T, Matsuzaki T, Noguchi K, et al.** Long-term dietary nitrite and nitrate deficiency causes the metabolic syndrome, endothelial dysfunction and cardiovascular death in mice. Diabetol., 2017; 60, 1138-51.
7. **Mensinga TT, Speijers GJ, Meulenbelt J**. Health implications of exposure to environmental nitrogenous compounds. Toxicol. Rev., 2003; 22, 41-51.

8. **Shiva S.** Nitrite: a physiological store of nitric oxide and modulator of mitochondrial function. Redox Biol., 2013; 1(1), 40-44.
9. **Bryan NS, Loscalzo J**. Looking forward. Nitrite and Nitrate in Human Health and Disease, 2017; 325-36.
10. **Honikel KO.** The use and control of nitrate and nitrite for the processing of meat products. Meat Sci., 2008; 78(1-2), 68-76.
11. **Bernardo P, Patarata L, Lorenzo JM, Fraqueza MJ**. Nitrate is nitrate: The status quo of using nitrate through vegetable extracts in meat products. Foods, 2021; 10(12), 3019-37.
12. **Shakil MH, Trisha AT, Rahman M, Talukdar S, Kobun R, Huda N, et al.** Nitrites in cured meats, health risk issues, alternatives to nitrites: A review. Foods, 2022; 11(21), 3355-81.
13. **Chamandoost S, Fateh Moradi M, Hosseini MJ.** A review of nitrate and nitrite toxicity in foods. J. Hum. Environ. Stud., 2016; 1(2), 80-6.
14. **Sindelar JJ, Milkowski AL**. Sodium nitrite in processed meat and poultry meats: a review of curing and examining the risk/benefit of its use. AMSA, 2011; 3, 1-14.
15. **Lee SY, Jo C, Yoon Y, Jeong JY, Hur SJ.** Effect on health from consumption of meat and meat products. JAST, 2021; 63(5), 955-77.
16. **Govari M, Pexara A**. Nitrates and Nitrites in meat products. J Hellenic Vet Med Soc, 2015; 66(3), 127-40.
17. **Zedan OI**. Sodium nitrite induced cerebellar cortex toxicity in adult male albino rat and the possible role of metformin (Histological and immunohistochemical study). Egypt. J. Histol., 2023; 46(1), 355-67.
18. **Ansari FA, Ali SN, Arif H, Khan AA**, **Mahmood R**. Acute oral dose of sodium nitrite induces redox imbalance, DNA damage, metabolic and histological changes in rat intestine. PLoS One, 2017; 12(4), e0175196.
19. **Parvizishad M, Dalvand A, Mahvi AH, Goodarzi F.** A review of adverse effects and benefits of nitrate and nitrite in drinking water and food on human health. Health Scope, 2017; 6(3), 14164-73.
20. **Liu X, Liu H, Ding N.** Chloramine disinfection-induced nitrification activities and their potential public health risk indications within deposits of a drinking water supply system. Int. J. Environ. Res. Public Health, 2020; 17(3), 772-82.
21. **Albano GD, La Spina C, Buscemi R, Palmeri M, Malandrino G, Licciardello F, et al**. Systematic review of fatal sodium nitrite ingestion cases: toxicological and forensic implications. Toxics, 2024; 12(2), 124-40.
22. **Kaluai, G. M**. Occurrence Of Select Heavy Metals In Groundwater Sources And Potential Health Risks Among Residents In Informal Settlements Of Kisumu East County, Kenya (Doctoral dissertation, University of Nairobi)., 2022.
23. **Stayner LT, Schullehner J, Semark BD, Jensen AS, Trabjerg BB, Pedersen M, et al**. Exposure to nitrate from drinking water and the risk of childhood cancer in Denmark. Environ. Int., 2021; 155, 106613.
24. **Guéraud F, Buisson C, Promeyrat A, Naud N, Fouché E, Bézirard V, et al.** Effects of sodium nitrite reduction, removal or replacement on cured and cooked meat for microbiological growth, food safety, colon ecosystem, and colorectal carcinogenesis in Fischer 344 rats. J FOOD SCI Journal, 2023; 7(1), 53.
25. **Sanjari R, Hosseini SE**. Effects of Perinatal and Neonatal Sodium Nitrite on Serum Levels of Uric Acid, Urea, Creatinine, and Tissue Structure of Rats' Offspring Kidneys. Intern Med J, 2021; 27(2), 214-29.
26. **Soliman MM, Aldhahrani A, Elshazly SA, Shukry M, Abouzed TK.** Borate ameliorates sodium nitrite-induced oxidative stress through regulation of oxidant/antioxidant status: Involvement of the Nrf2/HO-1 and NF-κB pathways. Biol. Trace Elem. Res., 2021; 200, 197-205.

27. **Elsherbini AM, Maysarah NM, El-Sherbiny M, Al-Gayyar MM, Elsherbiny NM**. Glycyrrhizic acid ameliorates sodium nitrite-induced lung and salivary gland toxicity: Impact on oxidative stress, inflammation and fibrosis. HET, 2021; 40(4), 707-21.
28. **AlThanoon SA, Taha AM.** Histopathological changes on the pregnant rat's lung induced by sodium nitrite and monosodium glutamate. Iraqi j. vet. sci., 2022; 36(2), 419-24.
29. **Adewale OO, Aremu KH, Adeyemo AT.** Assessment of combined toxic effects of potassium bromateand sodium nitrite in some key renal markers in male Wistar rats. Res. J. Health Sci., 2020; 8(1), 6-17.
30. **Adewale OO, Bakare MI, Adetunji JB.** Mechanism underlying nephroprotective property of curcumin against sodium nitrite-induced nephrotoxicity in male Wistar rat. J. Food Biochem., 2021; 45(3), 13341-51.
31. **Zaidi ZF**. Effects of sodium nitrite-induced hypoxia on cerebellar purkinje cells in adult rats. Pak J Med Sci, 2010; Vol. 26 No. 2, 532-7.
32. **Ibegbu AO, Eze SM, Livinus PP, Adamu SA, Hamman WO, Umana U & Musa SA**.: Effect of ethanolic extract of Ocimum gratissimum on sodium nitrite-induced cerebral cortex toxicity in adult Wistar rats. Afri J of Cell Path, (2015); 4, 54-61.
33. **Abdel Mohsen A F, Ahmed N A W, Altaib Z M, & Zaher S M:** Effect of cisplatin on cerebellar cortex of albino rat and possible protective role of granulocyte Colony stimulating factor versus Citrullus Lanatus juice: a histological study. EJH, (2020):43(3), 702-17.
34. **Lindeman S, Hong S, Kros L, Mejias J F, Romano V, Oostenveld R & De Zeeuw C I**.: Cerebellar Purkinje cells can differentially modulate coherence between sensory and motor cortex depending on region and behavior. PNAS, (2021); 118(2), e2015292118.
35. **Zheng J, Yang Q, Makris N, Huang K, Liang J, Ye C, and Gao Y.:** Three-dimensional digital reconstruction of the cerebellar cortex: lobule thickness, surface area measurements, and layer architecture. The Cerebellum, (2023); 22(2), 249-60.
36. **Schmahmann JD.:** The cerebellum and cognition. Neurosci. Lett, (2019); 688, 62-75.
37. **Soliman MM, Aldhahrani A, Elshazly SA, Shukry M, and Abouzed TK.:** Borate ameliorates sodium nitrite-induced oxidative stress through regulation of oxidant/antioxidant status: Involvement of the Nrf2/HO-1 and NF-κB pathways. Biol. Trace Elem. Res., (2021); 200, 197-205.
38. **AbdElrazek DA, Ibrahim MA, Hassan NH, Hassanen EI, Farroh KY, Abass HI**. Neuroprotective effect of quercetin and nano-quercetin against cyclophosphamide-induced oxidative stress in the rat brain: Role of Nrf2/HO-1/Keap-1 signaling pathway. NeuroToxicology, 2023; 98, 16-28.
39. **Yardim A, Kandemir FM, Ozdemir S, Kucukler S, Comakli S, Gur C, et al.** Quercetin provides protection against the peripheral nerve damage caused by vincristine in rats by suppressing caspase 3, NF-κB, ATF-6 pathways and activating Nrf2, Akt pathways. Neurotoxicology, 2020; 81, 137-46.
40. **Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, et al.** Important flavonoids and their role as a therapeutic agent. Mol., 2020; 25(22), 5243-82.
41. **Mirsafaei L, Reiner Ž, Shafabakhsh R, Asemi Z.** Molecular and biological functions of quercetin as a natural solution for cardiovascular disease prevention and treatment. Plant Foods Hum. Nutr., 2020; 75, 307-15.
42. **Darband SG, Sadighparvar S, Yousefi B, Kaviani M, Ghaderi-Pakdel F, Mihanfar A, et al.** Quercetin attenuated oxidative DNA damage through NRF2 signaling pathway in rats with DMH induced colon carcinogenesis. Life Sci., 2020; 253, 117584-97.

43. **Rahdar A, Hasanein P, Bilal M, Beyzaei H, Kyzas GZ.** Quercetin-loaded F127 nanomicelles: Antioxidant activity and protection against renal injury induced by gentamicin in rats. Life Sci., 2021; 276, 119420-31.
44. **Zaplatic E, Bule M, Shah SZA, Uddin MS, Niaz K.** Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimer's disease. Life Sci., 2019; 224, 109-19.
45. **Zargar S, Wani TA.** Protective role of quercetin in carbon tetrachloride induced toxicity in rat brain: biochemical, spectrophotometric assays and computational approach. Mol., 2021; 26(24), 7526-38.
46. **Bule M, Abdurahman A, Nikfar S, Abdollahi M, Amini M**. Antidiabetic effect of quercetin: A systematic review and meta-analysis of animal studies. Food Chem Toxicol, 2019; 125, 494-502.
47. **Jaishree V, Narsimha S.** Swertiamarin and quercetin combination ameliorates hyperglycemia, hyperlipidemia and oxidative stress in streptozotocin-induced type 2 diabetes mellitus in wistar rats. Biomed Pharmacother, 2020; 130, 110561-9.
48. **Tu H, Ma D, Luo Y, Tang S, Li Y, Chen G, et al.** Quercetin alleviates chronic renal failure by targeting the PI3k/Akt pathway. Bioeng., 2021; 12(1), 6538-58.
49. **Madiha S, Batool Z, Tabassum S, Liaquat L, Sadir S, Shahzad S, et al.** Quercetin exhibits potent antioxidant activity, restores motor and non-motor deficits induced by rotenone toxicity. Public Library of Science One, 2021; 16(11), e0258928-e54.
50. **Alshammari GM, Al-Qahtani WH, AlFaris NA, Albekairi NA, Alqahtani S, Eid R, et al**. Quercetin alleviates cadmium chloride-induced renal damage in rats by suppressing endoplasmic reticulum stress through SIRT1-dependent deacetylation of Xbp-1s and eIF2α. Biomed Pharmacother, 2021; 141, 111862-78.
51. **Xie J, Song W, Liang X, Zhang Q, Shi Y, Liu W, et al**. Protective effect of quercetin on streptozotocin-induced diabetic peripheral neuropathy rats through modulating gut microbiota and reactive oxygen species level. Biomed Pharmacother, 2020; 127, 110147-61.
52. **Fan H, Tang HB, Shan LQ, Liu SC, Huang DG, Chen X, et al**. Quercetin prevents necroptosis of oligodendrocytes by inhibiting macrophages/ microglia polarization to M1 phenotype after spinal cord injury in rats. J. Neuroinflammation, 2019; 16(1), 1-15.
53. **Han X, Xu T, Fang Q, Zhang H, Yue L, Hu G, et al.** Quercetin hinders microglial activation to alleviate neurotoxicity via the interplay between NLRP3 inflammasome and mitophagy. Redox Biol., 2021; 44, 102010-28.
54. **El-Sayyad H.** Therapeutic potential of quercetin in rat offspring cerebellum and testis of father subjected to Cisplatin treatment. Anal Quant Cytol Histol, 2020; 1(1), 36-41.
55. **Abdelghany EM, Amira EA, Hassan H**. Beneficial effect of quercetin against dimethoate induced cerebellar cortex injury in adult male albino rat: histological and immunohistochemical study. Med J Cairo Univ, 2019; 87(December), 5121-34.
56. **Abdelrahman SA, El-Shal AS, Abdelrahman AA, Saleh EZH, Mahmoud AA.** Neuroprotective effects of quercetin on the cerebellum of zinc oxide nanoparticles (ZnoNps)-exposed rats. Tissue Barriers, 2023; 11(3), 2115273-89.

Citation:

Rashad, M., El-Din Boghdady, F., Azab, S., Neemat-Allah, M., Sami, M., Mohammed El Hindawy, E. Vitamin D Status in Infants, Toddlers and Preschool Children with Pneumonia. *Zagazig University Medical Journal*, 2024; (4457-4469): -. doi: 10.21608/zumj.2024.318458.3563