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REVIEW ARTICLE

Nickel and Oxidative Stress: Cell Signaling Mechanisms and Protective Role of Vitamin C

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Abstract: ***Background:*** Nickel activates the signaling pathways through the oxygen sensing mechanism and the signaling cascades that control hypoxia-inducible transcriptional gene expressions through oxidative stress. This review emphasizes on the recent updates of nickel toxicities on oxidant and antioxidant balance, molecular interaction of nickel and its signal transduction through low oxygen microenvironment in the *in-vivo* physiological system.

Discussion: **Nickel and oxidative stress:** Nickel alters intracellular chemical microenvironment by increasing ionized calcium concentration, lipid peroxidation, cyclooxygenase, constitutive nitric oxide synthase, leukotriene B4, prostaglandin E2, interleukins, tumor necrosis factor-α, caspases, complement activation, heat shock protein 70 kDa and hypoxia-inducible factor-1α. The oxidative stress induced by nickel is responsible for the progression of metastasis. It has been observed that nickel exposure induces the generation of reactive oxygen species which leads to the increased expression of p53, NF-kβ, AP-1, and MAPK. Ascorbic acid (vitamin C) prevents lipid peroxidation, oxidation of low-density lipoproteins and advanced oxidation protein products. The mechanism involves that vitamin C is capable of reducing ferric iron to ferrous iron in the duodenum, thus the availability of divalent ferrous ion increases which competes with nickel (a divalent cation itself) and reduces its intestinal absorption and nickel toxicities.

Conclusion: Reports suggested the capability of ascorbic acid as a regulatory factor to influence gene expression, apoptosis and other cellular functions of the living system exposed to heavy metals, including nickel.

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1. INTRODUCTION

Nickel is a naturally occurring element and its concentration mainly depends on the geographical location and anthropogenic input [1]. Nickel, the 28th element in the periodic table, was first purified by Swedish chemist Axel Cronstedt in the year 1751 [2]. Nickel (Ni) is a silvery-white lustrous metal with a slight golden tinge. It belongs to the group of transition metals in the periodic table, which is hard and ductile. Because of its electromagnetic properties and chemico-thermal stabilities, nickel ferrite nanoparticles are widely used in many medical applications like magnetic resonance imaging (MRI), target-based drug delivery and hyperthermia [3].

About 9% Ni produced is used in Ni plating for the corrosion resistance and is widely used in making coins. Nearly about 2 million tonnes of nickel is produced every year around the world [4]. Nickel as a compound finds a lot of applications such as a catalyst for hydrogenation, cathodes for batteries, pigments manufacturing and metal surface treatments. Nickel is an essential trace element for many microbes, plants and animals that have enzymes like glyoxalase I, acireductonedioxygenase etc. which require nickel for their active functioning. The most common form of nickel is Ni^{2+}but compounds with Ni^{0}, Ni^{+} and Ni^{3+} are also well known. However, the rare oxidation states Ni^{2-}, Ni^{-} and Ni^{4-} have also been produced and studied [5].

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It should be noted that the nickel exposure pathway is not only the environmental medium or any route of exposure but also all the elements that link a contaminant source and a receptor population. It is also important to note that the measure of exposure is proportional to variables such as intensity, and frequency and duration of contact with the contaminant is crucial. Ni salts are considered as an important industrial hazard [4].

The nickel toxicity has become a great interest because of its widespread environmental occurrence and the incidence of accidental poisoning in industrial workers where nickel is used as a major raw material [6]. The toxicity of nickel depends on the route of exposure and solubility of nickel compounds. Pulmonary absorption is the major route for nickel toxicity than the gastrointestinal and dermal absorption. Diet is the most significant nickel exposure pathway for some organisms [7]. The absorption of nickel takes place due to soluble Ni^{2+} ions which are either in the form of particulate or as a coordination complex [8]. In detail, Das *et al.* reported the different routes of human exposures, and the pharmacokinetics of nickel in the previous reviews and book chapters [9, 10].

International Agency for Research on Cancer (IARC) informed that there are sufficient reports and research evidence on humans and animals for the carcinogenicity of nickel. According to the US Agency for Toxic Substances and Disease Registry (ATSDR, 2005), approximately 10-20% of the general population is sensitive to nickel [11]. The normal reference values for serum nickel for healthy adults are 0.2μg/L, and in urine, it is 1-3 μg/L [11].

Maintaining a healthy biological system mainly depends on the oxidant and antioxidant balance. At normal physiological conditions, there will be a continuous generation of reactive oxygen species (ROS) and will be counteracted by endogenous antioxidants like superoxide dismutase (SOD), glutathione peroxidase, catalase (CAT) etc. or by exogenous (vitamin C, vitamin E etc.) antioxidant systems [12]. Many *in vivo* and *in vitro* studies demonstrated that environmental heavy metal pollutants like nickel, chromium, vanadium, arsenic, cobalt etc. show their toxicity by stimulating the high production of ROS, decreasing the antioxidants availability, inflammatory pathway and apoptosis pathway [13, 14].

The purpose of the current review is to provide deep insights into nickel mediated oxidative stress mechanisms, altered cell signaling pathways, DNA damage and the protective actions of ascorbic acid on nickel-induced toxicity.

2. NICKEL TOXICITY AND IT'S PUBLIC HEALTH CONSEQUENCES

A major amount of nickel enters our body via food and water intake, but inhalation exposure is most common in occupational workers. It has been reported that acute inhalation exposure of nickel in humans shows symptoms like headache, nausea, respiratory problems, and death [15, 16]. Warner *et al*., in 1979 reported that there is no clinical evidence of developmental and reproductive toxicity in the women working in nickel refinery, but Chashschin *et al.,* reported reproductive and developmental effects of nickel in occupationally exposed populations (0.13-0.2 mg nickel/m^3) [17, 18]. Goyer *et al.,* reported that acute inhalation of nickel carbonyl leads to headache, nausea, vomiting, chest pain, hyperpnea, cyanosis, respiratory failure, and ultimately death if the exposure is severe [19]. In the year 1994, Nicklin and Nielsen categorized asthmatic attack response caused by nickel inhalation as i) a rapid onset attack (antibody-mediated Type I hypersensitivity) with bronchospasm, ii) a late response reaction at 6-12 hours after exposure (antigen-antibody immune complex-mediated inflammatory reaction), and iii) a mixed or combined response [20]. A study reported the increased blood reticulocytes in workers who drank water from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (estimated dose of 7.1–35.7 mg Ni/kg) [11]. Huang *et al.,* conducted a survey of 50 peritoneal dialysis (PD) patients and 50 normal patients for urinary nickel concentration and analyzed the possible association of urinary nickel concentrations with clinical outcomes and inflammatory biomarkers. Based on their study, it was found that nearly 50% of the patients undergoing PD had higher levels of urinary nickel and also these patients had increased serum levels of high sensitivity C-reactive protein [21]. In another research, Jouybari *et al.,* studied the role of toxic elements as biomarkers for breast cancer (BC), which showed a significant difference in the cadmium (Cd) and Ni statuses between healthy and BC patients, clearly indicating a direct and positive association between Cd and Ni concentrations and BC risk [22]. Also, increased urinary total protein levels, β2-macroglobulin, retinal binding protein, and N-acetyl-β-D-glucosaminidase were reported in electroplating workers who consumed nickel contaminated water [23].

3. NICKEL TOXICITY

3.1. Nickel Generates ROS

In authors' laboratory, by experimenting on animals, it has been reported that nickel induces oxidative stress accompanied by the overproduction of reactive oxygen species, lipid peroxides (malondialdehyde) and decreasing concentrations of endogenous antioxidants like SOD, CAT, glutathione (GSH), glutathione peroxidase, glutathione reductase and exogenous antioxidants like l-ascorbic acid and alpha-tocopherol [24-27]. The molecular mechanism of nickel toxicity and carcinogenicity may be due to the overproduction of ROS [28]. Chen *et al.* carried out an experiment to assess the effect of nickel chloride on isolated human lymphocytes and showed that nickel toxicity led to cell membrane oxidative damage by a significant increase in the production of ROS in lymphocytes [29]. Das *et al.,* showed that subchronic exposure of experimental rats to nickel sulphate ($NiSO_4$) led to increased production of ROS, lipid peroxidation and decreased antioxidants [27]. Topal *et al.,* assessed the effect of nickel on nuclear factor kappa-light chain-enhancer of activated B cells (NF-kβ) activity, antioxidative response and histopathological effects on the liver, gill and

kidney tissues of Rainbow trout fish exposed to different concentration of nickel chloride ($NiCl_2$) (1 mg/L and 2 mg/L) for 21 days. They found a significant increase in the lipid peroxidation by promoting peroxidative damage and a resultant increase in antioxidant enzymes SOD and CAT activity [30]. Nickel toxicity may disturb the biochemical and physiological functions of fish by causing changes in NF-kβ activity and oxidative and histopathological damage in the tissues of rainbow trout [30].

3.2. Nickel Influences Cytokines Signaling

Nickel and other heavy metals are absorbed in the intestine, transported by metal transporter protein 1 and then enter into the portal circulation. By the circulatory system, nickel is distributed to all the tissues and organs of the body [31]. It has been reported that the accumulation of heavy metals and increased oxidative stress in hepatocytes stimulate the production kupffer cells and lead to cell necrosis. Many studies have reported that heavy metal poisoning induces an inflammatory pathway via tumor necrosis factor α (TNF)-α signaling pathway [31-33]. It has been shown that Ni^{2+} induces the expression of inflammatory genes such as IL-8 in human primary monocytes [34]. In an experiment conducted to study the expression of interleukin (IL)-8 in human monocytes THP-1 cell, it has been confirmed that $NiCl_2$ induces the expression of IL-8. The use of PX-478 and TAK-242 clearly indicated the expression of IL-8 which is mainly dependent on hypoxia-inducible factor 1 (HIF-1)-α activation [34].

TNF-α is a cell-signaling protein that is involved in systemic inflammation. The primary role of TNF-α is in the regulation of immune cells. Dys-regulation of TNF is associated with many human diseases which include Alzheimer's disease [35], cancer [32], major depression [36] and psoriasis [37]. Ding *et al.,* demonstrated that nickel exposure induces the production of inflammatory cytokine TNF-α and the trans-activation of nuclear factor of activated T cells, NF-kβ and activator protein 1 (AP)-1 in human bronchial epithelial cells (BEAS-2B). Further studies have shown that TNF-α was induced by the exposure of nickel in BEAS-2B cells specifically through extracellular signal-regulated kinases/AP-1 dependent pathway [38].

4. NICKEL AND CELL SIGNALING

4.1. Nickel Induces Expression of COX

Cyclooxygenases (COX) are also called as prostaglandin-endoperoxide synthases (PTGSs). There are two isoforms of cyclooxygenases present in mammals: COX-1 (PTGS1), which is typically expressed in all types of cells at low levels and maintains homeostasis; and COX-2 (PTGS2), is an early expressed gene in response to the wide variety of cell challenges and stress inducers [39]. Both the isoforms catalyze the synthesis of prostaglandins, thromboxanes, and levuloglandins [40]. These COX enzymes are inhibited by aspirin (acetyl salycyclic) and other non-steroidal anti-inflammatory drugs [40]. For decades, COX inhibitors have been in use as anti-inflammatory and anti-pyretic agents and also in the treatment of neurodegenerative disorders and cancer [40]. Ding *et al.,* 2006 reported that nickel exposure up-regulates the expression of COX-2 by the ROS/NF-κB/IKK β/p65-dependent pathway and plays a crucial role in antagonizing nickel-induced cell apoptosis in human bronchial epithelial Beas-2B cells [41]. Many types of medical alloys contain nickel. The elution of Ni ions from these metals causes toxicity and inflation. In a study carried out by Sato *et al.,* it was found that Ni ions eluted from subcutaneous implanted Ni wire increased the expression of COX-2 and mPGES-1 mRNA [42]. The induction of COX-2 and mPEGS-1 mRNA is due to the concentration of Ni ions in the region, but not due to the physiological stimulation of the implemented wire. It has been proved that Ni induced expression of COX-2 is observed not only in mice cells but also in the human cell lines [42]. It has been demonstrated that c-Jun/AP1 downstream pathways of JNK1 play a crucial role in nickel-induced COX-2 expression and carcinogenesis [43].

4.2. Nickel Influences Oxygen Sensing Cell Signaling

There are multiple explanations for the nickel-induced "oxygen sensor" activation. Earlier research findings showed that intravenous injection of $NiSO_4$ in rats leads to the increased erythrocytosis and development of local tumors [44-46]. Goldberg *et al.,* in 1988 showed enhanced expression of erythropoietin (EPO) mRNA in human hepatoma cells (Hep3B or HepG2) by exposing cells to hypoxic conditions, Ni (II) or Co (II) [47]. Physiologically, up-regulation of EPO mRNA expression is seen when there is diminished oxygen supply to the kidneys. Semenza *et al.,* showed that EPO production and transcription mainly occurs in the control of hypoxia-inducible factor 1 (HIF-1) [48]. Nickel-induced "oxygen sensor" hypothesis infers that less redox-active Ni (II) may impede with high redox-active iron (Fe) (II) metabolism. Fe (II) is an important cofactor for enzymes like dioxygenases and hydroxylases. Hydroxylation of HIF by prolyl hydroxylases (PHD)1-3 is a crucial step for the degradation of HIF which is requires O_2 and ascorbic acid [49]. It has been reported that transition heavy metals like nickel, cobalt etc., induce cellular hypoxia by diminishing heme synthesis which further leads to a decrease in intracellular oxygen tension and inhibits PHD_2 [50]. HIF-1α is considered as the transcriptional regulator which regulates the cellular and developmental response to hypoxia [51]. HIF-1α is a subunit of the heterodimeric transcription factor, Hypoxia-inducible factor 1 that is encoded by the HIF1A gene [48, 49]. The deregulation or overexpression of HIF-1α either by hypoxia or genetic alterations has been associated with cancer and other pathophysiologies of vascularization and angiogenesis, energy metabolism, cell survival and tumor invasion. Under normal oxygen conditions, the HIF 1A gene is expressed in low levels, but in hypoxic conditions, HIF 1A transcription is significantly up-regulated [52, 53]. Some research works have revealed that exposure to nickel causes accumulation of HIF-1α in several cells and trigger HIF-1α to regulate hypoxia-mimic responses which induce overexpression of microRNA-210 (miR-210) which is most sensi-

tive hypoxic mRNA and is ideal for the regulation of hypoxia [53-55]. Viemann *et al.* reported that the contact allergen nickel induced the production of IL-6 by activating HIF-1α in addition to NF-κβ [56].

4.3. Nickel and Calcium Channels

Wani *et al.,* showed that nickel induced aortic hyper contraction by the overproduction of ROS in endothelial cells, increased the release of endothelial hyper contractile prostanoids through COX-2 pathway, and increased the influx of Ca^{2+} through T-type Ca^{2+} channels to smooth muscle cells [57]. They also concluded that acute exposure to nickel increased vascular resistance, which consequently led to the commencement and continuation of hypertension on rats [57].

An opening of calcium channels and Ca^{2+} ions influx into the cells plays an important role in the regulation of blood glucose levels by controlling the secretion of insulin by pancreatic beta cells [58]. It has been shown that although $NiSO_4$ blocks the calcium channel and prevents the release of insulin in the bloodstream which leads to increase in the blood glucose level, but it has been observed that nickel induces low oxygen-sensitive expression of vascular endothelial growth factor (VEGF) protein that mainly depends on intracellular calcium store release, not on extracellular calcium influx. Consistent with these reports, it has been found that intracellular calcium is essential for VEGF induction by nickel compounds irrespective of calcium channel functions [59-61].

5. ANTIOXIDANT VITAMIN C

Vitamin C, also known as ascorbic acid and L-ascorbic acid is a vitamin found in various foods and also available as a dietary supplement. Vitamin C is found to be the most effective antioxidant in humans. Vitamin C functions physiologically as an antioxidant in the aqueous fluid and tissue compartments. As an antioxidant, vitamin l-ascorbic acid has its own significance for years, but now ascorbic acid is also acknowledged to play an important role in hydroxylation reactions of proteins that are involved in many important cell-signaling pathways and in controlling the interactions and functions of many cellular proteins [49]. A co-factor α-ketoglutarate (2OG) dependent non-heme iron-containing dioxygenase enzymes like lysyl, prolyl and asparginyl hydroxylases, and DNA repair enzymes, human ABH2 and ABH3 proteins play an important role in hydroxylation reactions [5, 6]. Iron and 2OG are two important factors required for the dioxygenase enzymes activity and ascorbic acid plays a crucial role in maintaining the iron in Fe (II) active form [62, 63]. It has been shown that vitamin C helps in the generation of other antioxidants within the body, including alpha-tocopherol i.e., Vitamin E [64]. It is specifically required in the activity of various human enzymes involved in the synthesis of collagen, hormones and amino acids [46, 47].

Studies are being conducted to examine the ameliorating effect of vitamin C in preventing or delaying the development of cancers, cardiovascular diseases and other diseases in which oxidative stress plays a crucial role. Frei *et al.,* demonstrated the role of ascorbate in the protection of plasma lipids against peroxidative damage caused by peroxyl radicals [65]. Their experimental results suggested that ascorbate is the most effective antioxidant in human blood plasma which is of major importance in the protection against diseases and degenerative processes caused by oxidative stress [65].

6. NICKEL-INDUCED OXIDATIVE STRESS AND PROTECTIVE ACTION OF VITAMIN C

Many researchers have shown that for anti-oxidant therapy, vitamin C is an ideal compound because it is an endogenous agent and can be given orally and parenterally with similar efficiency [66]. Das *et al.,* conducted a study to find out the effect of ascorbic acid supplementation on nickel-induced lipid peroxidation in the liver of Wistar rats and found that ascorbic acid supplementation showed a remarkable improvement of lipid peroxide, glutathione, SOD, CAT and GSH-Px status in the liver in comparison with rats treated with nickel alone [27]. This shows that ascorbic acid possesses relative protection against nickel hepatotoxicity [27]. In another experiment conducted to study the role of ascorbic acid on nickel-induced hepatic nucleic acid concentration in rats, the effect of oral treatment of ascorbic acid (50 mg/100 g.b.wt.) on $NiSO_4$ induced (2.0 mg/100 g.b.wt.) alteration of nucleic acids. Moreover, the total protein concentration in the liver of rats was also studied. Nucleic acids and total protein concentration significantly decreased in the nickel treated rats when compared to untreated rats. Furthermore, on simultaneous supplementation of ascorbic acid with $NiSO_4$, a remarkable improvement of nucleic acids and total protein concentrations in the liver was observed. These results indicate that nickel influences the expression of genetic information by reducing hepatic DNA, RNA and protein concentration in animals and also the supplementation of ascorbic acid is beneficial against nickel-induced toxicity [67]. Functions of L-ascorbic acid as a protective antioxidant against nickel-induced toxicity aretabulated below (Table **1**).

CONCLUSION

It may be postulated from a series of experiments carried out by the corresponding author of this review and other researchers that nickel causes serious cellular damages by increased ROS production, deprivation of antioxidants availability and by triggering inflammatory pathways (Fig. **1**) [74].

As stated in this review, nickel induces cellular hypoxia which leads to expression and stabilization of HIF-1α followed by the generation of ROS. Overexpression of HIF-1α alters the cell signaling mechanism by changing oxygen sensing gene expressions, which lead to cellular damage. It was further reported that dietary supplements such as vitamin C is beneficial in suppressing the metal or hypoxia-induced oxygen sensing gene expressions [31].

Table 1. Antioxidant vitamin C against nickel-induced oxidative stress.

S. No	Tissue/organ/System Affected	Antioxidant Used	Result	Citation
1	Pulmonary nitrosative stress	l-ascorbic acid	Pulmonary nitrosative stress decreased through NOS3.	Hattiwale *et al*., 2013 [68]
2	Brain tissue	l-ascorbic acid	Lipid peroxide, nitric oxide levels decreased and antioxidant enzymes status restored in serum and brain tissue samples.	Das *et al.,* 2010[69]
3	Regulation of blood glucose	l-ascorbic acid	Blood glucose homeostasis improved.	Tikare *et al.,* 2008 [60]
4	Testicular lipid peroxide and antioxidants	l-ascorbic acid	Testicular lipid peroxides decreased, GSH and antioxidant enzyme activities restored.	Gupta *et al*., 2007 [70]
5	Erythrocyte MDA and antioxidants	l-ascorbic acid	Improved the status of Erythrocyte MDA and all the endogenous erythrocyte antioxidant defence system restored.	Das *et al.,* 2007 [71]
6	Lung antioxidant defence system	l-ascorbic acid	Lung tissue lipid peroxides decreased and antioxidant enzyme concentrations restored.	Gupta *et al.,* 2006 [72]
7	Serum dyslipidemia and pathological changes of Hepatic Tissue	l-ascorbic acid	Dyslipidemia corrected and histopathological alterations corrected.	Das *et al.,* 2006 [73]
8	Hepatic lipid peroxidation	l-ascorbic acid	Hepatic tissue lipid peroxides decreased, GSH and antioxidant enzyme activities improved.	Das *et al.,* 2001 [27]

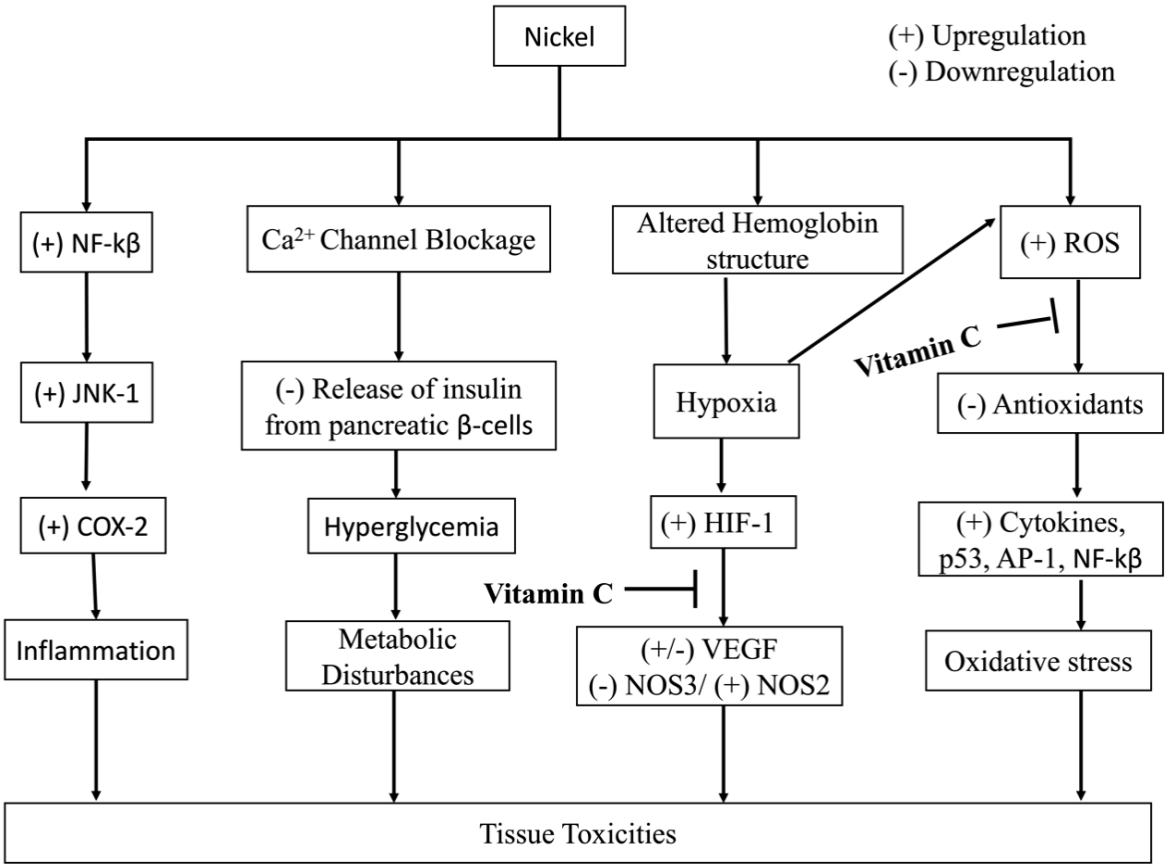

Fig. (1). Nickel Toxicity-Cell Signaling Mechanism and Vitamin C Supplementation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

However, more studies are required for a better understanding of the molecular aspects of nickel toxicities in humans. Precise clinical trials are needed for the physiological, pathological and molecular impact of nickel on the occupationally exposed population to generate more viable therapeutic options in treating nickel toxicity-related diseases.

LIST OF ABBREVIATIONS

AP-1	=	Activator Protein 1
ASTDR	=	Agency for Toxic Substances and Disease Registry
BC	=	Breast Cancer
BEAS	=	Bronchial Epithelial Cells
CAT	=	Catalase
Cd	=	Cadmium
COX	=	Cyclooxygenase
EPO	=	Erythropoietin
Fe	=	Iron
GSH	=	Glutathione
HIF	=	Hypoxia Inducible Factor
IARC	=	International Agency for Research on Cancer
IL	=	Interleukin
MDA	=	Malondialdehyde
miRNA	=	Micro RNA
mPGES	=	Microsomal Prostaglandin E Synthase
MTP	=	Metal Transporter Protein
NF-κβ	=	Nuclear Factor Kappa-Light Chain-Enhancer of Activated B Cells
Ni	=	Nickel
$NiCl_2$	=	Nickel Chloride
$NiSO_4$	=	Nickel Sulphate
NOS	=	Nitric Oxide Synthase
PD	=	Peritoneal Dialysis
PHD	=	Prolyl Hydroxylase
PTGSs	=	Prostaglandin Endoperoxide Synthases
ROS	=	Reactive Oxygen Species
SOD	=	Superoxide Dismutase
TNF	=	Tumor Necrosis Factor:
VEGF	=	Vascular Endothelial Growth Factor

CONSENT FOR PUBLICATION

Not Applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Das, K.K.; Das, S.N.; Dhundasi, S.A. Nickel: Molecular Diversity, Application, Essentiality and Toxicity in Human Health. In: *Biometals: Molecular Structures, Binding Properties and Applications*; Nova Science Publishers Inc, **2010**; pp. 33-58.

[2] Royal Society of Chemistry. *Elements and Periodic Table History.,* http://www.rsc.org/periodic-table/element/28/nickel

[3] Ahamed, M.; Akhtar, M.J.; Siddiqui, M.A.; Ahmad, J.; Musarrat, J.; Al-Khedhairy, A.A.; AlSalhi, M.S.; Alrokayan, S.A. Oxidative stress mediated apoptosis induced by nickel ferrite nanoparticles in cultured A549 cells. *Toxicology,* **2011**, *283*(2-3), 101-108. [http://dx.doi.org/10.1016/j.tox.2011.02.010] [PMID: 21382431]

[4] Suparman, E.; Smf, B.; Kedokteran, F.; Sam, U.; Manado, R.; Manado, R.D.K. Peran GnRH Agonis *Biomedik (JBM.),* **2016**, *8*(1), 1-7.

[5] Greenwood, A. Earnshaw Butterworth –Heinemann. In: *Chemistry of the Elements,* 2nd ed; N.N. Oxford, **1997**.

[6] Coogan, T.P.; Latta, D.M.; Snow, E.T.; Costa, M. Toxicity and carcinogenicity of nickel compounds. *Crit. Rev. Toxicol.,* **1989**, *19*(4), 341-384. [http://dx.doi.org/10.3109/10408448909029327] [PMID: 2663022]

[7] Croteau, M.N.; Luoma, S.N. Predicting dietborne metal toxicity from metal influxes. *Environ. Sci. Technol.,* **2009**, *43*(13), 4915-4921. [http://dx.doi.org/10.1021/es9007454] [PMID: 19673285]

[8] Costa, M.; Mollenhauer, H.H. Carcinogenic activity of particulate nickel compounds is proportional to their cellular uptake. *Science,* **1980**, *209*(4455), 515-517. [http://dx.doi.org/10.1126/science.7394519] [PMID: 7394519]

[9] Das, K.K.; Das, S.N.; Dhundasi, S.A. *Nickel: Molecular Diversity, Application, Essentiality and Toxicity in Human Health.* ; Biometals: Molecular Structures, Binding Properties and Applications, **2010**, pp. 33-58.

[10] Das, K.K.; Das, S.N.; Dhundasi, S.A. Nickel, its adverse health effects & oxidative stress. *Indian J. Med. Res.,* **2008**, *128*(4), 412-425. [PMID: 19106437]

[11] ATSDR, U.S. Department of Health and Human Services. *Toxicological Profile for Nickel,* **2005**.

[12] He, L.; He, T.; Farrar, S.; Ji, L.; Liu, T.; Ma, X. Antioxidants Maintain Cellular Redox Homeostasis by Elimination of Reactive Oxygen Species. *Cell. Physiol. Biochem.,* **2017**, *44*(2), 532-553. [http://dx.doi.org/10.1159/000485089] [PMID: 29145191]

[13] Jargar, J.G.; Yendigeri, S.M.; Hattiwale, S.H.; Dhundasi, S.A.; Das, K.K. α-Tocopherol ameliorates nickel induced testicular oxidative and nitrosative stress in albino rats. *J. Basic Clin. Physiol. Pharmacol.,* **2012**, *23*(2), 77-82. [http://dx.doi.org/10.1515/jbcpp-2012-0013] [PMID: 23092795]

[14] Deng, J.; Guo, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Wang, X.; Zhao, L. Oxidative stress and inflammatory responses involved in dietary nickel chloride ($NiCl_2$)-induced pulmonary toxicity in broiler chickens. *Toxicol. Res. (Camb.),* **2016**, *5*(5), 1421-1433. [http://dx.doi.org/10.1039/C6TX00197A] [PMID: 30090446]

[15] Rendall, R.E.G.; Phillips, J.I.; Renton, K.A. Death following exposure to fine particulate nickel from a metal arc process. *Ann. Occup. Hyg.,* **1994**, *38*(6), 921-930.

[PMID: 7825932]

[16] Das, K.K.; Buchner, V. Effect of nickel exposure on peripheral tissues: role of oxidative stress in toxicity and possible protection by ascorbic acid. *Rev. Environ. Health,* **2007**, *22*(2), 157-173. [http://dx.doi.org/10.1515/REVEH.2007.22.2.157] [PMID: 17894205]

[17] Warner, J.S. Nickel carbonyl: prenatal exposure. *Science,* **1979**, *203*(4386), 1194-1195. [http://dx.doi.org/10.1126/science.424746] [PMID: 424746]

[18] Chashschin, V.P.; Artunina, G.P.; Norseth, T. Congenital defects, abortion and other health effects in nickel refinery workers. *Sci. Total Environ.,* **1994**, *148*(2-3), 287-291. [http://dx.doi.org/10.1016/0048-9697(94)90405-7] [PMID: 8029704]

[19] Goyer, R. Toxic effects of metals In: *Casarett and Doull's Toxicology,* 4th; Amdur, M.O.; Doull, J.D.; Klaassen, C.D., Eds.; Pergamon Press: New York, **1991**; pp. 623-680.

[20] Nicklin, S.; Nielsen, G.D. Nickel and the immune system: current concepts In: *Nickel and Human Health – Current perspectives*; John Wiley and Sons, Inc.: New York, **1992**; 25, pp. 239-259.

[21] Huang, Y.C.; Ning, H.C.; Chen, S.S.; Lin, C.N.; Wang, I.K.; Weng, S.M.; Weng, C.H.; Hsu, C.W.; Huang, W.H.; Lu, J.J.; Wu, T.L.; Yen, T.H. Survey of urinary nickel in peritoneal dialysis patients. *Oncotarget,* **2017**, *8*(36), 60469-60478. [http://dx.doi.org/10.18632/oncotarget.19730] [PMID: 28947985]

[22] Jouybari, L.; Saei Ghare Naz, M.; Sanagoo, A.; Kiani, F.; Sayehmiri, F.; Sayehmiri, K.; Hasanpour Dehkordi, A. Toxic elements as biomarkers for breast cancer: a meta-analysis study. *Cancer Manag. Res.,* **2018**, *10*, 69-79. [http://dx.doi.org/10.2147/CMAR.S151324] [PMID: 29391828]

[23] Valko, M.; Morris, H.; Cronin, M.T.D. Metals, toxicity and oxidative stress. *Curr. Med. Chem.,* **2005**, *12*(10), 1161-1208. [http://dx.doi.org/10.2174/0929867053764635] [PMID: 15892631]

[24] Das, K.K.; Reddy, R.C.; Bagoji, I.B.; Das, S.; Bagali, S.; Mullur, L.; Khodnapur, J.P.; Biradar, M.S. Primary concept of nickel toxicity - an overview. *J. Basic Clin. Physiol. Pharmacol.,* **2018**, *30*(2), 141-152. [http://dx.doi.org/10.1515/jbcpp-2017-0171] [PMID: 30179849]

[25] Buege, J.A.; Aust, S.D. Microsomal lipid peroxidation. *Methods Enzymol.,* **1978**, *52*, 302-310. [http://dx.doi.org/10.1016/S0076-6879(78)52032-6] [PMID: 672633]

[26] Basha, M.P.; Sujitha, N.S. Chronic fluoride toxicity and myocardial damage: antioxidant offered protection in second generation rats. *Toxicol. Int.,* **2011**, *18*(2), 99-104. [http://dx.doi.org/10.4103/0971-6580.84260] [PMID: 21976813]

[27] Das, K.K.; Das, S.N.; DasGupta, S. The influence of ascorbic acid on nickel-induced hepatic lipid peroxidation in rats. *J. Basic Clin. Physiol. Pharmacol.,* **2001**, *12*(3), 187-195. [http://dx.doi.org/10.1515/JBCPP.2001.12.3.187] [PMID: 11762690]

[28] Salnikow, K.; Gao, M.; Voitkun, V.; Huang, X.; Costa, M. Altered oxidative stress responses in nickel-resistant mammalian cells. *Cancer Res.,* **1994**, *54*(24), 6407-6412. [PMID: 7987835]

[29] Chen, C.Y.; Wang, Y.F.; Lin, Y.H.; Yen, S.F. Nickel-induced oxidative stress and effect of antioxidants in human lymphocytes. *Arch. Toxicol.,* **2003**, *77*(3), 123-130. [http://dx.doi.org/10.1007/s00204-002-0427-6] [PMID: 12632251]

[30] Topal, A.; Atamanalp, M.; Oruç, E.; Erol, H.S. Physiological and biochemical effects of nickel on rainbow trout (Oncorhynchus mykiss) tissues: Assessment of nuclear factor kappa B activation, oxidative stress and histopathological changes. *Chemosphere,* **2017**, *166*, 445-452. [http://dx.doi.org/10.1016/j.chemosphere.2016.09.106] [PMID: 27705832]

[31] Das, K. K.; Honnutagi, R.; Mullur, L.; Reddy, R.C.; Das, S.; Majid, Dhundasi.S; Biradar, M.S. Heavy Metals and Low-Oxygen Microenvironment—Its Impact on Liver Metabolism and Dietary Supplementation *Dietary Interventions in Liver Disease,* **2019**, 315-332.

[32] Locksley, R.M.; Killeen, N.; Lenardo, M.J. The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell,* **2001**, *104*(4), 487-501. [http://dx.doi.org/10.1016/S0092-8674(01)00237-9] [PMID: 11239407]

[33] Chuang, H.C.; Hsueh, T.W.; Chang, C.C.; Hwang, J.S.; Chuang, K.J.; Yan, Y.H.; Cheng, T.J. Nickel-regulated heart rate variability: the roles of oxidative stress and inflammation. *Toxicol. Appl. Pharmacol.,* **2013**, *266*(2), 298-306. [http://dx.doi.org/10.1016/j.taap.2012.11.006] [PMID: 23164665]

[34] Gölz, L.; Buerfent, B.C.; Hofmann, A.; Rühl, H.; Fricker, N.; Stamminger, W.; Oldenburg, J.; Deschner, J.; Hoerauf, A.; Nöthen, M.M.; Schumacher, J.; Hübner, M.P.; Jäger, A. Genome-wide transcriptome induced by nickel in human monocytes. *Acta Biomater.,* **2016**, *43*, 369-382. [http://dx.doi.org/10.1016/j.actbio.2016.07.047] [PMID: 27477848]

[35] Swardfager, W.; Lanctôt, K.; Rothenburg, L.; Wong, A.; Cappell, J.; Herrmann, N. A meta-analysis of cytokines in Alzheimer's disease. *Biol. Psychiatry,* **2010**, *68*(10), 930-941. [http://dx.doi.org/10.1016/j.biopsych.2010.06.012] [PMID: 20692646]

[36] Dowlati, Y.; Herrmann, N.; Swardfager, W.; Liu, H.; Sham, L.; Reim, E.K.; Lanctôt, K.L. A meta-analysis of cytokines in major depression. *Biol. Psychiatry,* **2010**, *67*(5), 446-457. [http://dx.doi.org/10.1016/j.biopsych.2009.09.033] [PMID: 20015486]

[37] Victor, F.C.; Gottlieb, A.B. TNF-alpha and apoptosis: implications for the pathogenesis and treatment of psoriasis. *J. Drugs Dermatol.,* **2002**, *1*(3), 264-275. [PMID: 12851985]

[38] Ding, J.; Huang, Y.; Ning, B.; Gong, W.; Li, J.; Wang, H.; Chen, C.Y.; Huang, C. TNF-alpha induction by nickel compounds is specific through ERKs/AP-1-dependent pathway in human bronchial epithelial cells. *Curr. Cancer Drug Targets,* **2009**, *9*(1), 81-90. [http://dx.doi.org/10.2174/156800909787313995] [PMID: 19200052]

[39] Jaén, R.I.; Prieto, P.; Casado, M.; Martín-Sanz, P.; Boscá, L. Post-translational modifications of prostaglandin-endoperoxide synthase 2 in colorectal cancer: An update. *World J. Gastroenterol.,* **2018**, *24*(48), 5454-5461. [http://dx.doi.org/10.3748/wjg.v24.i48.5454] [PMID: 30622375]

[40] Fitzpatrick, F.A. Cyclooxygenase enzymes: regulation and function. *Curr. Pharm. Des.,* **2004**, *10*(6), 577-588. [http://dx.doi.org/10.2174/1381612043453144] [PMID: 14965321]

[41] Ding, J.; Zhang, X.; Li, J.; Song, L.; Ouyang, W.; Zhang, D.; Xue, C.; Costa, M.; Meléndez, J.A.; Huang, C. Nickel compounds render anti-apoptotic effect to human bronchial epithelial Beas-2B cells by induction of cyclooxygenase-2 through an IKKbeta/p65-dependent and IKKalpha- and p50-independent pathway. *J. Biol. Chem.,* **2006**, *281*(51), 39022-39032. [http://dx.doi.org/10.1074/jbc.M604798200] [PMID: 16982623]

[42] Sato, T.; Kishimoto, Y.; Asakawa, S.; Mizuno, N.; Hiratsuka, M.; Hirasawa, N. Involvement of COX-2 in nickel elution from a wire implanted subcutaneously in mice. *Toxicology,* **2016**, *363-364*, 37-45. [http://dx.doi.org/10.1016/j.tox.2016.07.013] [PMID: 27452194]

[43] Zhang, D.; Li, J.; Wu, K.; Ouyang, W.; Ding, J.; Liu, Z.G.; Costa, M.; Huang, C. JNK1, but not JNK2, is required for COX-2 induction by nickel compounds. *Carcinogenesis,* **2007**, *28*(4), 883-891. [http://dx.doi.org/10.1093/carcin/bgl186] [PMID: 17065197]

[44] Solymoss, B.; Jasmin, G. Studies of the mechanism of polycythemia induced in rats by Ni3S2. *Exp. Hematol.,* **1978**, *6*(1), 43-47. [PMID: 624333]

[45] Morse, E.E.; Lee, T.Y.; Reiss, R.F.; Sunderman, F.W., Jr Dose-response and time-response study of erythrocytosis in rats after intrarenal injection of nickel subsulfide. *Ann. Clin. Lab. Sci.,* **1977**, *7*(1), 17-24. [PMID: 836000]

[46] Sunderman, F.W., Jr Carcinogenicity of nickel compounds in animals. *IARC Sci. Publ.,* **1984**, (53), 127-142. [PMID: 6532978]

[47] Goldberg, M.A.; Dunning, S.P.; Bunn, H.F. Regulation of the erythropoietin gene: evidence that the oxygen sensor is a heme protein. *Science,* **1988**, *242*(4884), 1412-1415. [http://dx.doi.org/10.1126/science.2849206] [PMID: 2849206]

[48] Semenza, G.L.; Rue, E.A.; Iyer, N.V.; Pang, M.G.; Kearns, W.G. Assignment of the hypoxia-inducible factor 1α gene to a region of conserved synteny on mouse chromosome 12 and human chromosome 14q. *Genomics,* **1996**, *34*(3), 437-439. [http://dx.doi.org/10.1006/geno.1996.0311] [PMID: 8786149]

[49] Salnikow, K.; Kasprzak, K.S. Ascorbate depletion: a critical step in nickel carcinogenesis? *Environ. Health Perspect.,* **2005**, *113*(5), 577-584. [http://dx.doi.org/10.1289/ehp.7605] [PMID: 15866766]

[50] Michiels, C. Physiological and pathological responses to hypoxia. *Am. J. Pathol.,* **2004**, *164*(6), 1875-1882. [http://dx.doi.org/10.1016/S0002-9440(10)63747-9] [PMID: 15161623]

[51] Iyer, N.V.; Kotch, L.E.; Agani, F.; Leung, S.W.; Laughner, E.; Wenger, R.H.; Gassmann, M.; Gearhart, J.D.; Lawler, A.M.; Yu, A.Y.; Semenza, G.L. Cellular and developmental control of O2 homeostasis by hypoxia-inducible factor 1 α. *Genes Dev.,* **1998**, *12*(2), 149-162. [http://dx.doi.org/10.1101/gad.12.2.149] [PMID: 9436976]

[52] Hogenesch, J.B.; Chan, W.K.; Jackiw, V.H.; Brown, R.C.; Gu, Y.Z.; Pray-Grant, M.; Perdew, G.H.; Bradfield, C.A. Characterization of a subset of the basic-helix-loop-helix-PAS superfamily that interacts with components of the dioxin signaling pathway. *J. Biol. Chem.,* **1997**, *272*(13), 8581-8593. [http://dx.doi.org/10.1074/jbc.272.13.8581] [PMID: 9079689]

[53] Ladoux, A.; Frelin, C. Cardiac expressions of HIF-1 α and HLF/EPAS, two basic loop helix/PAS domain transcription factors involved in adaptative responses to hypoxic stresses. *Biochem. Biophys. Res. Commun.,* **1997**, *240*(3), 552-556. [http://dx.doi.org/10.1006/bbrc.1997.7708] [PMID: 9398602]

[54] Song, X.; Fiati Kenston, S.S.; Kong, L.; Zhao, J. Molecular mechanisms of nickel induced neurotoxicity and chemoprevention. *Toxicology,* **2017**, *392*, 47-54. [http://dx.doi.org/10.1016/j.tox.2017.10.006] [PMID: 29032222]

[55] He, M.; Lu, Y.; Xu, S.; Mao, L.; Zhang, L.; Duan, W.; Liu, C.; Pi, H.; Zhang, Y.; Zhong, M.; Yu, Z.; Zhou, Z. MiRNA-210 modulates a nickel-induced cellular energy metabolism shift by repressing the iron-sulfur cluster assembly proteins ISCU1/2 in Neuro-2a cells. *Cell Death Dis.,* **2014**, *5*(2)e1090 [http://dx.doi.org/10.1038/cddis.2014.60] [PMID: 24577088]

[56] Viemann, D.; Schmidt, M.; Tenbrock, K.; Schmid, S.; Müller, V.; Klimmek, K.; Ludwig, S.; Roth, J.; Goebeler, M. The contact allergen nickel triggers a unique inflammatory and proangiogenic gene expression pattern via activation of NF-kappaB and hypoxia-inducible factor-1alpha. *J. Immunol.,* **2007**, *178*(5), 3198-3207. [http://dx.doi.org/10.4049/jimmunol.178.5.3198] [PMID: 17312168]

[57] Wani, S.A.; Khan, L.A.; Basir, S.F. Role of calcium channels and endothelial factors in nickel induced aortic hypercontraction in Wistar rats. *J. Smooth Muscle Res.,* **2018**, *54*(0), 71-82. [http://dx.doi.org/10.1540/jsmr.54.71] [PMID: 30210089]

[58] Fu, Z.; Gilbert, E.R.; Liu, D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. *Curr. Diabetes Rev.,* **2013**, *9*(1), 25-53. [http://dx.doi.org/10.2174/157339913804143225] [PMID: 22974359]

[59] Das, K.K.; Das, S.N.; Ambekar, J.G. *Hypoxia and Oxidative Stress : Cell Signaling Mechanisms and Protective Role of Vitamin C and Cilnidipine. Lipid Peroxidation: Inhibition*; Effects and Mechanisms, **2017**, pp. 249-262.

[60] Tikare, S.N.; Das Gupta, A.; Dhundasi, S.A.; Das, K.K. Effect of antioxidants L-ascorbic acid and alpha-tocopherol supplementation in nickel exposed hyperglycemic rats. *J. Basic Clin. Physiol. Pharmacol.,* **2008**, *19*(2), 89-101. [http://dx.doi.org/10.1515/JBCPP.2008.19.2.89] [PMID: 19024927]

[61] Metzen, E.; Fandrey, J.; Jelkmann, W. Evidence against a major role for Ca^{2+} in hypoxia-induced gene expression in human hepatoma cells (Hep3B). *J. Physiol.,* **1999**, *517*(Pt 3), 651-657. [http://dx.doi.org/10.1111/j.1469-7793.1999.0651s.x] [PMID: 10358107]

[62] Szarka, A.; Lőrincz, T. The role of ascorbate in protein folding. *Protoplasma,* **2014**, *251*(3), 489-497. [http://dx.doi.org/10.1007/s00709-013-0560-5] [PMID: 24150425]

[63] Myllylä, R.; Majamaa, K.; Günzler, V.; Hanauske-Abel, H.M.; Kivirikko, K.I. Ascorbate is consumed stoichiometrically in the uncoupled reactions catalyzed by prolyl 4-hydroxylase and lysyl hydroxylase. *J. Biol. Chem.,* **1984**, *259*(9), 5403-5405. [PMID: 6325436]

[64] Jacob, R.A.; Sotoudeh, G.; Vitamin, C. Vitamin C function and status in chronic disease. *Nutr. Clin. Care,* **2002**, *5*(2), 66-74. [http://dx.doi.org/10.1046/j.1523-5408.2002.00005.x] [PMID: 12134712]

[65] Frei, B.; England, L.; Ames, B.N. Ascorbate is an outstanding antioxidant in human blood plasma. *Proc. Natl. Acad. Sci. USA,* **1989**, *86*(16), 6377-6381. [http://dx.doi.org/10.1073/pnas.86.16.6377] [PMID: 2762330]

[66] Lehr, H.A.; Frei, B.; Olofsson, A.M.; Carew, T.E.; Arfors, K.E. Protection from oxidized LDL-induced leukocyte adhesion to microvascular and macrovascular endothelium *in vivo* by vitamin C but not by vitamin E. *Circulation,* **1995**, *91*(5), 1525-1532. [http://dx.doi.org/10.1161/01.CIR.91.5.1525] [PMID: 7867194]

[67] Das, K.K.; Das, S.N. Studies on the role of ascorbic acid on nickel induced hepatic nucleic acid concentrations in rats. *J. Basic Clin. Physiol. Pharmacol.,* **2004**, *15*(3-4), 185-195. [http://dx.doi.org/10.1515/JBCPP.2004.15.3-4.185] [PMID: 15803957]

[68] Hattiwale, S.H.; Saha, S.; Yendigeri, S.M.; Jargar, J.G.; Dhundasi, S.A.; Das, K.K. Protective effect of L-ascorbic acid on nickel induced pulmonary nitrosative stress in male albino rats. *Biometals,* **2013**, *26*(2), 329-336. [http://dx.doi.org/10.1007/s10534-013-9617-3] [PMID: 23463385]

[69] Das, K.K.; Saha, S. L-ascorbic acid and α tocopherol supplementation and antioxidant status in nickel- or lead-exposed rat brain tissue. *J. Basic Clin. Physiol. Pharmacol.,* **2010**, *21*(4), 325-346. [http://dx.doi.org/10.1515/JBCPP.2010.21.4.325] [PMID: 21305849]

[70] Gupta, A.D.; Dhundasi, S.A.; Ambekar, J.G.; Das, K.K. Effect of l-ascorbic acid on antioxidant defense system in testes of albino rats exposed to nickel sulfate. *J. Basic Clin. Physiol. Pharmacol.,* **2007**, *18*(4), 255-266. [http://dx.doi.org/10.1515/JBCPP.2007.18.4.255] [PMID: 18380167]

[71] Das, K.K.; Gupta, A.D.; Dhundasi, S.A.; Patil, A.M.; Das, S.N.; Ambekar, J.G. Protective role of L-ascorbic acid on antioxidant defense system in erythrocytes of albino rats exposed to nickel sulfate. *Biometals,* **2007**, *20*(2), 177-184. [http://dx.doi.org/10.1007/s10534-006-9025-z] [PMID: 16900397]

[72] Gupta, A.D.; Patil, A.M.; Ambekar, J.G.; Das, S.N.; Dhundasi, S.A.; Das, K.K. L-ascorbic acid protects the antioxidant defense system in nickel-exposed albino rat lung tissue. *J. Basic Clin. Physiol. Pharmacol.,* **2006**, *17*(2), 87-100. [http://dx.doi.org/10.1515/JBCPP.2006.17.2.87] [PMID: 16910314]

[73] Das, K.K.; Gupta, A.D.; Dhundasi, S.A.; Patil, A.M.; Das, S.N.; Ambekar, J.G. Effect of L-ascorbic acid on nickel-induced alterations in serum lipid profiles and liver histopathology in rats. *J. Basic Clin. Physiol. Pharmacol.,* **2006**, *17*(1), 29-44. [http://dx.doi.org/10.1515/JBCPP.2006.17.1.29] [PMID: 16639878]

[74] Pandareesh, M.D.; Kandikattu, H.K.; Razack, S.; Amruta, N.; Choudhari, R.; Vikram, A.; Doddapattar, P. Nutrition and Nutraceuticals in Neuroinflammatory and Brain Metabolic Stress: Implications for Neurodegenerative Disorders. *CNS Neurol. Disord. Drug Targets,* **2018**, *17*(9), 680-688. [http://dx.doi.org/10.2174/1871527317666180625104753] [PMID: 29938622]