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Review

Research Advances on Pathways of Nickel-Induced Apoptosis

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Abstract: High concentrations of nickel (Ni) are harmful to humans and animals. Ni targets a number of organs and produces multiple toxic effects. Apoptosis is important in Ni-induced toxicity of the kidneys, liver, nerves, and immune system. Apoptotic pathways mediated by reactive oxygen species (ROS), mitochondria, endoplasmic reticulum (ER), Fas, and c-Myc participate in Ni-induced cell apoptosis. However, the exact mechanism of apoptosis caused by Ni is still unclear. Understanding the mechanism of Ni-induced apoptosis may help in designing measures to prevent Ni toxicity.

Keywords: Ni; apoptosis; molecular mechanism; mitochondria; endoplasmic reticulum

1. Chemical Properties and Toxicity of Nickel

1.1. Chemical Properties of Ni

Nickel (Ni) is the 24th most abundant element in the earth's crust [1,2]. It is the fifth heaviest element and is a part of group VIII B of the periodic table. In nature, Ni is found in combination with arsenic, antimony, and sulfur [3]. Elemental Ni is a silver-white solid metal, with high thermal conductivity, electrical conductivity, and melting point. Ni metal is highly stable [4] and is used for electroplating and protective coating. Ordinary Ni has an oxidation state of +2; higher oxidation states (such as Ni^{+3} and Ni^{+4}) occur rarely in certain oxide systems [5]. Ni compounds are classified as soluble and insoluble [5,6]. Strong acid and organic acid Ni salts are soluble, whereas weak inorganic acid Ni salts are insoluble. Due to its chemical properties, gloss, and low price, Ni is used in jewelry, alloys, stainless steel, food processing industries, catalysts, and pigments [7–9]. Ni chloride, nitrate, sulphate, hydroxide, acetate, carbonate, and oxide are the most commercially important Ni compounds [10].

1.2. Biological Properties of Ni

Ni is essential for many microorganisms, plants, and animals [9,11,12]. Some studies have shown that very low levels of Ni are also essential for humans [13]. In rats, Ni deficiency reduces iron content in organs, haemoglobin, and hematocrit [14]. Ni has several biological functions, including activation of calcineurin; action and formation of cGMP [15]; transmission of genetic code (DNA,

RNA) [16]; acting as a cofactor of albumin, proteins, and amino acids; transport of oxygen; stimulation of metabolism through interaction with iron in hemoglobin [17,18]; and formation of urease, carbon monoxide dehydrogenase, and methyl-*S*-coenzyme M reductase [15].

1.3. Ni Toxicity

The widespread use of Ni increases its concentration in biogeochemical cycles and increases human exposure by environmental contamination and occupational exposure [8]. Exposure to Ni commonly occurs by ingestion of contaminated water and food [9,19]. Workers in Ni-producing and processing industries are exposed by inhalation and, to a lesser extent, dermal contact [20]. People may also be exposed through contact with stainless steel, jewelry, and coins. Ni is toxic at high doses to both humans and animals [21]. Exposure to Ni can cause allergy, contact dermatitis, and toxicity of organ systems [22]. Li *et al.* [23] reported that $NiCl_2$ increases the secretion of a pro-inflammatory cytokine, interleukin-1β (IL-1β), in bone marrow-derived macrophages and bone marrow dendritic cells. Ni may cause neurotoxicity, hepatotoxicity, nephrotoxicity, gene toxicity, reproductive toxicity, and increased risk of cancer [20,24–32]. Bones, kidneys, lungs, liver, and heart are the main organs of Ni accumulation [32–34].

Humans, especially Ni metallurgy workers, are exposed to Ni by inhalation and ingestion, with plants being the primary source of Ni for humans [34–36]. Ni may damage multiple organs and cause lung and nasal cancer [19,22,37]. Immediate and delayed hypersensitivity and allergic skin reactions are common adverse effects of Ni. Ni is both an allergen and a potential immunomodulatory and immunotoxic agent [38]. With the exception of metallic Ni, all Ni compounds have been classified as human carcinogens by the International Agency for Research on Cancer, based on studies on Ni workers and laboratory animals [39].

Numerous *in vitro*, *in vivo*, and epidemiological studies have documented the carcinogenic quality of Ni [40–45]. The LD50 of oral nickel acetate in rats and mice are 350 and 420 mg/kg, respectively [39]. Dietary $NiCl_2$ at ⩾300 mg/kg can cause reduced growth rate, and at ⩾1100 mg/kg it can cause anemia or death in chickens [12]. Growth inhibition occurs at ⩾700 mg/kg nickel sulfate ($NiSO_4$) and nickel acetate in chicks [46]. Chicks fed a diet containing ⩾250–300 mg/kg Ni can show inhibition of growth and decreased feed intake [47]. Oral $NiCl_2$ decreases body and liver weight in mice [25]. Amudha *et al.* [48] have suggested that intraperitoneal $NiCl_2$ causes significant kidney damage and reduced activities of enzymatic and non-enzymatic antioxidants in rats [48]. Dietary $NiCl_2$ at ⩾300 mg/kg damages the intestines and kidney, and decreases the immune function of the spleen, thymus, and bursa of Fabricius in chickens [49–57].

2. Biological Characteristics of Cell Apoptosis

Apoptosis is required for homeostasis of the cell population and defense during injury [58]. Failure to undergo apoptosis can cause several diseases such as cancer and autoimmune diseases, whereas excessive cell death is responsible for several neurodegenerative diseases [59]. So far, the main focus of research on the mechanism of apoptosis has been on the extrinsic and intrinsic apoptosis pathways (Figure 1) [60–64].

2.1. Bcl-2 Family Protein in Apoptosis

B-cell lymphoma-2 (Bcl-2) family proteins are involved in apoptosis [65], partly through the control and modulation of outer mitochondrial membrane integrity [66,67]. Based on their functions, Bcl-2 family proteins are classified into anti- and pro-apoptotic proteins (Figure 2). A loss of balance between anti- and pro-apoptotic proteins may cause either inhibition or promotion of apoptosis. Bcl-2 family members have single or multiple homology domains, such as Bcl-2 homology (BH1, -2, -3, and -4) that are important in the heterodimeric interaction among Bcl-2 family proteins [68]. Anti-apoptotic Bcl-2 family multi-domain proteins contain BH-(1-4) domains, such as Bcl-2, Bcl-2 homolog of ovary, Bcl-extra long (Bcl-xL), Bcl-w, and A1. Myeloid cell leukemia factor-1 (Mcl-1) is the

only anti-apoptotic Bcl-2 protein with three BH domains: BH-1, -2, and -3 [69]. Based on the number of BH domains, pro-apoptotic Bcl-2 family proteins are classified into two subgroups. Bcl-2 antagonistic killer (Bak), Bcl-2 associated X protein (Bax), Bcl-2 related ovarian killer, and Bcl-extra short have multiple BH domains [68]. There are eight BH3 domain-only members: BH3 interacting domain death agonist (Bid), Bcl-2 interacting mediator of cell death (Bim), hara-kiri, p53-upregulated modulator of apoptosis (Puma), Bcl-2 modifying factor (Bmf), Bcl-2 antagonist of cell death (Bad), Noxa (named for "damage"), and Bcl-2 interacting killer [Bik, also known as natural born killer (Nbk)] [66,70]. In general, BH3 domain-only proteins suppress Bcl-2 anti-apoptotic proteins and induce apoptosis after lethal stress [71]. Bcl-2 maintains Bax and Bak in an inactive state. Furthermore, Bcl-2 titration away from Bax and Bak by BH3-only Bcl-2 family members allows them to oligomerize and form a channel through which cytochrome c (cyt c) can translocate to cytoplasm. Cyt c combines in a very specific stoichiometric fashion with apaf1 to form the apoptosome and activate caspase-9 [68,72].

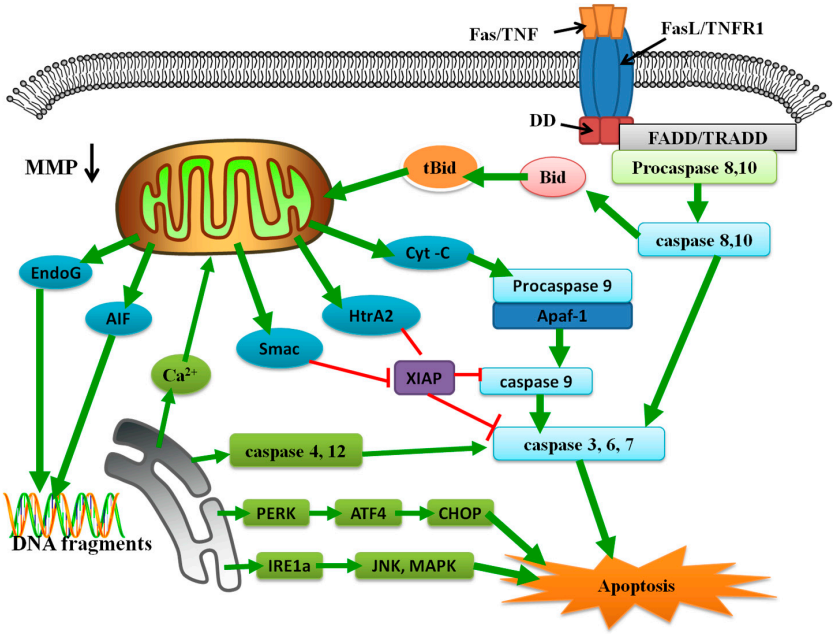

Figure 1. Summary of the extrinsic and intrinsic pathway in apoptosis. Extrinsic apoptosis: The combination of a ligand (FasL/TNFR1) and a death receptor (Fas/TNF) starts the extrinsic apoptosis pathway. This binding can attract the combination of FADD, TRADD and procaspase 8. Activated caspase 8 then activates downstream effector caspases or truncates the Bid. tBid can disrupt the mitochondria, and then induces mitochondria-mediated apoptosis. Intrinsic apoptosis: Mitochondria-mediated apoptosis pathway: The MMP disruption results in the release of cyt c, Smac, HtrA2, AIF and Endo G from mitochondrial intermembrane space to cytoplasm. Cytoplasmic cyt c promotes the aggregation of procaspase 9 and apaf1, and then activates caspase-9. Activated caspase-9 cleaves and activates caspase-3, 6, 7, which then induces apoptosis. Concurrently, Smac and HtrA2 inhibit XIAP expression for also contributing to the apoptosis. AIF and Endo G activate the caspase-independent mitochondria-mediated pathway. ER-mediate apoptosis pathway: Under prolonged ER stress, protein kinase RNA (PKR)-like ER kinase (PERK) pathway can induce apoptosis. Activated transcription factor 4 (ATF4) is an important transcription factor that accumulates via an un-conventional mechanism following PERK activation. ATF4 accumulation up-regulates the pro-apoptotic transcriptional factor, e.g., C/EBP homologous protein (CHOP), which induces apoptosis. The IRE1α pathway is also the important mechanism of ER stress. IRE1α mediates apoptosis through activation of c-Jun amino terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) pathways. After the ER damage, acute translocation of Ca^{2+} from ER to mitochondria promotes Ca^{2+}-mediated mitochondrial cell death. In addition, caspases-4 and -12 are also involved in ER stress-induced apoptosis.

Figure 2. Bcl-2 Proteins. The Bcl-2 proteins can be subdivided into pro-survival and pro-apoptotic members, and have single or mutiple conserved functional Bcl-2 homology domains.

Some studies have shown that p53 can regulate Bcl-2 proteins, but the specific mechanism is not clear [73]. The phosphoinositide-3-kinase/serine-threonine kinase (PI3K/Akt) pathway inhibits apoptosis via the modulation of Bcl-2 proteins [74–76]. This pathway increases anti-apoptotic proteins (Bcl-2 and Bcl-xL) and decreases pro-apoptotic proteins (Bad and Bax) [77–80].

2.2. Caspases in Apoptosis

Caspases are cysteine proteases that are extremely important for intracellular apoptotic pathways [81–83]. After various intracellular and extracellular stimuli have occurred, caspases can be activated to execute apoptosis [84]. Pro-caspases are omnipresent in the cell, so apoptosis can occur rapidly without the need of transcription and translation. The removal of sick, damaged, and senescent cells provides a distinct survival advantage [85]. Caspases are divided into initiators and executioners, based on their physiological functions (Figure 3) [72,86–89].

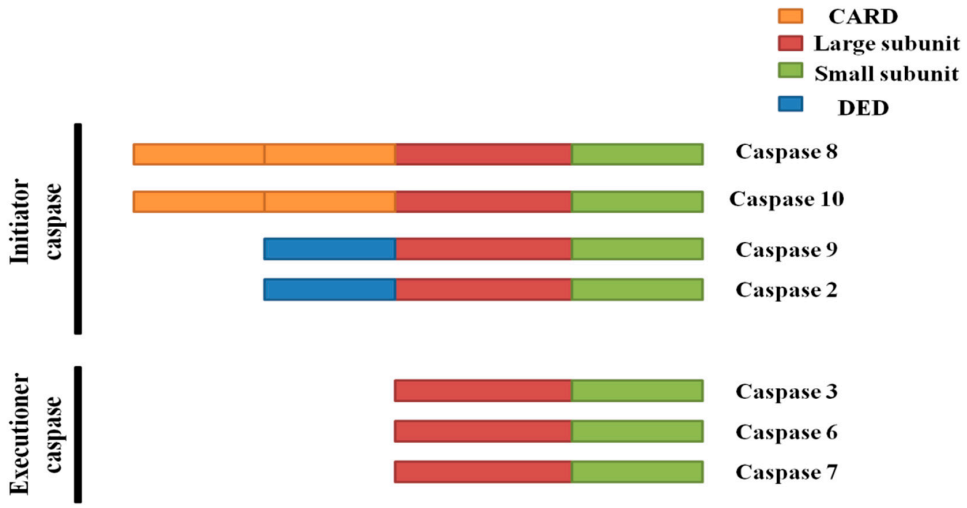

Figure 3. Caspase classification.

Caspases-2, -8, -9 and -10 are initiators, as they are closely coupled to pro-apoptotic signals [90]. The initiator caspases exist in normal cells as inactive pro-caspase monomers and are activated by dimerization rather than cleavage. [91–93]. Dimerization promotes autocatalytic cleavage of caspase monomers into a large and a small subunit that results in dimer stabilization [94].

Caspases-3, -6, and -7 are executioners and exist as inactive pro-caspase dimers [95]. The initiator caspases activate executioner caspases by cleavage [94,96], which causes a conformational change that brings the two active sites of the executioner caspase dimer together and creates a functional mature protease [97]. Caspases-3 and -7 have identical cleavage sites. On being activated, an accelerated feedback loop of caspase activation occurs, ultimately causing cell death [97].

Murine caspase-12 and human caspase-4 belong to the interleukin-1-converting enzyme subfamily. Murine caspase-12 and human caspase-4 have 48% homology at the amino acid level and have structures similar to initiator caspases [98,99]. Caspase-12 and -4 are involved in endoplasmic reticulum (ER) stress-induced apoptosis [98–100].

2.3. Extrinsic Pathway in Apoptosis

The extrinsic apoptosis pathway is activated by the binding of extracellular death ligands to cell-surface death receptors [101]. The tumor necrosis factor (TNF) receptor gene super family is a member of the death receptors, which have a death domain (DD) that is important for apoptotic signal transduction [102,103]. FasL/FasR, TNF-α/TNFR1, Apo3L/DR3, Apo2L/DR4, and Apo2L/DR5 are the notable ligands and their corresponding death receptors [104–106].

FasL/FasR and TNF-α/TNFR1 are the characteristic models in the extrinsic apoptotic pathway. The extrinsic pathway is initiated by the binding of an extracellular death ligand to its cell surface transmembrane death receptor, causing oligomerization of the receptor [107]. This binding recruits the intracellular domain of the receptor (e.g., Fas associated death domain (FADD), TNF receptor associated death domain (TRADD)) and initiator caspases (e.g., procaspase-8 or -10) [108]. These complexes are regarded as death-inducing signaling complexes (DISC) [102,109–111]. The formation of these complexes promotes the oligomerization of procaspase-8 and -10 and auto-activation through self-cleavage [112].

Activated caspase-8 cleaves and activates downstream effector caspases such as caspase-1, -3, -6, and -7 [113]. As an important executioner of apoptosis, caspase-3 can activate many proteins, including the nuclear enzyme poly ADP-ribose polymerase (PARP) through proteolytic cleavage [114]. These downstream cleavage events are the morphological characteristics of apoptosis.

2.4. Intrinsic Pathway in Apoptosis

The intrinsic signaling pathways are known as mitochondria- and ER-initiated apoptosis [115,116].

2.4.1. Mitochondria in the Intrinsic Pathway

The apoptotic stimuli cause changes in the Bcl-2 proteins. Bcl-2 titration away from Bax and Bak by BH3-only Bcl-2 family members allows them to oligomerize. This step opens the mitochondrial permeability transition pore (MPT) and disrupts the mitochondrial membrane potential (MMP), which translocates some pro-apoptotic proteins from the intermembrane space to the cytosol [117]. These pro-apoptotic proteins include cyt c, second mitochondrial activator of caspases/direct inhibitors of apoptosis binding protein with low pI (Smac/Diablo), the serine protease high-temperature-requirement protein A2/Omi (HtrA2/Omi), apoptosis inducing factor (AIF), and endonuclease G (Endo G) [61,118–121].

Apoptosis induced by cyt c, Smac/Diablo, and HtrA2/Omi requires the participation of caspases. Cyt c binds and activates apoptotic peptidase activating factor 1 (Apaf-1) and procaspase-9 to form an apoptosome [61]. The clustering of procaspase-9 in this apoptosome leads to caspase-9 activation. Caspase-9 activates downstream caspases, including caspase-3, -6, and -7,

causing apoptosis. Inhibitors of apoptosis proteins (IAP) suppress apoptosis by directly inhibiting caspases [122,123]. Smac/DIABLO and HtrA2/Omi can promote apoptosis by inhibiting IAP proteins activity [124].

AIF and Endo G activate the caspase-independent mitochondrial pathway. After disruption of the mitochondrial membrane potential, AIF and Endo G translocate to the nucleus and cause DNA fragmentation and apoptosis [125–127].

2.4.2. ER in the Intrinsic Pathway

Recent studies have shown that the ER also plays an important role in the intrinsic pathway [128,129]. The main function of ER is synthesis, folding, and translocation of proteins [130]. ER stress is activated by the disruption of ER function, which leads to the accumulation of misfolded and unfolded proteins in the ER lumen. ER stress induces an adaptive signal, Unfolded Protein Response (UPR), which restores ER homeostasis and protects the cell [116]. In the absence of this response, apoptosis occurs [116].

Under ER stress, protein kinase RNA (PKR)-like ER kinase (PERK) activates and phosphorylates eukaryotic translation initiation factor 2α (eIF2α), causing a translational arrest. However, under prolonged ER stress, it can promote apoptosis. Activated transcription factor 4 (ATF4) is an important transcription factor that accumulates via an unconventional mechanism following activation of the protein PERK [131]. Prolonged accumulation of ATF4 leads to apoptosis by a variety of mechanisms. ATF4 can upregulate the pro-apoptotic transcriptional factors, e.g., CHOP (C/EBP homologous protein, also called the growth arrest and DNA-damage-inducible 153, GADD153) [132]. CHOP promotes apoptosis through activation of downstream factors such as GADD34, a caspase-activating cell-surface death receptor of the tumor necrosis factor death receptor 5 (DR5), and endoplasmic reticulum oxidoreductase 1α (ERO1α) [133]. GADD34 inhibits the phosphorylation of eIF2α [131]. This inhibition causes the accumulation of unfolded proteins in the ER lumen and translation of pro-apoptotic proteins. CHOP suppresses Bcl-2 transcription [134] and increases Bim expression [135], thereby promoting apoptosis. ERO1α activates the inositol triphosphate receptor (IP3R), which stimulates the translocation of excessive Ca^{2+} to the mitochondria and triggers the mitochondria-mediated apoptotic pathway [136]. ATF4 also regulates Noxa (a BH3-only protein) [137,138]. Noxa activates the effector proteins Bax and/or Bak [139] and induces mitochondria-mediated apoptosis.

The inositol-requiring enzyme/endonuclease 1α (IRE1α) pathway also plays an important part in ER stress. The IRE1α pathway has a pro-survival function, but it may cause apoptosis under prolonged ER stress [140]. IRE1α stimulates the activation of TNF receptor-associated factor 2 (TRAF2), which activates the apoptosis signal-regulating kinase 1/c-Jun amino terminal kinase (ASK1/JNK) cascade [141,142]. In addition, ER stress induces apoptosis through p38 mitogen-activated protein kinase (MAPK), which is activated by ASK1. p38 MAPK phosphorylates and activates CHOP and induces apoptosis [143]. Additionally, both p38 MAPK and JNK promote apoptosis through an increase in Bax [144].

The ER is the reservoir of Ca^{2+} in cells [145]. Ca^{2+} translocation from the ER to mitochondria triggers mitochondria-mediated apoptosis [146,147]. Excessive Ca^{2+} can disrupt the balance between Bcl-2 proteins and induce the translocation of cyt c [148].

In addition, some studies have suggested that caspase-12 is a specific marker of ER stress-induced apoptosis [128]. Mouse caspase-12 cleaves and activates caapase-9 and -3 and induces apoptosis [98,149]. However, human caspase-12 has no parallel function due to a frameshift disruption of its gene, resulting in a premature stop codon. In addition, human caspase-12 also contains amino acid substitutions in the caspase activity area [150]. Instead, human caspase-4 is specifically cleaved under ER stress, suggesting that it may be a functional ortholog of mouse caspase-12 in ER stress-induced apoptosis [99,151]. So far, little is known about how caspase-4 is activated in ER stress-triggered apoptosis.

3. Apoptosis Induced by Ni

Studies have demonstrated that Ni can increase apoptosis. Su *et al.* and Liu *et al.* [152,153] reported that $NiSO_4$ induces DNA damage, apoptosis and oxidative damage in the liver and testes of mouse. Also, $NiSO_4$ induces JNK-mediated oxidative damage and apoptosis in the liver of *Carassius auratus* [154]. $NiCl_2$ has been proved to induce apoptosis in the liver of Kunming mice [153]. Our previous studies indicated that $NiCl_2 \geqslant 300$ mg/kg (dietary) can increase apoptosis percentages thymus, spleen, and cecal tonsil of broiler chickens [49,155,156].

In vitro research of Ni-induced apoptosis, Ni compounds can promote apoptosis in B cells [157], human T hybridoma cells [158], human hepatoma cells [159], keratinocytes [160], human airway epithelial (HEp-2) and human breast cancer (MCF-7) cells [161], human liver cells (HepG2) [162], and normal rat kidney cells [27], as well as human neutrophils and lymphocytes [163,164]. Shiao *et al.* [165] have reported that DNA fragmentation is detected in Chinese hamster ovary (CHO) cells treated with ⩾160 μM Ni(II) and its intensity increases with increasing Ni(II) concentration.

4. Pathways or Mechanisms of Ni-Induced Cell Apoptosis

4.1. ROS-Mediated Apoptosis

Reactive oxygen species (ROS) acts as a crucial factor in the early stages of apoptosis. Mitochondria are both the source and target of ROS. When excess ROS is generated, it induces MMP depolarization and cyt c release, which triggers caspase activation [166–169]. The ROS generation can also induce DNA damage, which then promotes apoptosis [170].

Ni can induce oxidative stress *in vitro* and *in vivo* [171,172]. Ma *et al.* [173] demonstrated that Ni NWs induce apoptosis through ROS generation, and that ROS induces apoptosis through mitochondrial damage or activation of cell cycle checkpoints in HeLa cells. Nickel subsulfide (Ni_3S_2) induces ROS-mediated apoptosis in human bronchial epithelial cells (BEAS-2B) [174]. Ahamed [175] suggests that nickel nanoparticle (NiNPs) induces oxidative damage, which decreases glutathione (GSH), and induces ROS and lipid peroxidation (LPO) in human lung epithelial A549 cells.

Excess generation of ROS will result in oxidative stress that mediates apoptosis. The reduction of antioxidant defense is the main reason for ROS generation. Superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GSH-Px) and glutathione-*S*-transferase (GST) and GSH are the important antioxidant molecules. Some studies have reported that $NiCl_2$ can decrease the antioxidative system in the *Tigriopus japonicas*, goldfish and broiler [48,50,53,155,156,176–178]. $NiSO_4$ can decrease the GSH levels and activities of SOD and GSH-Px [154]. An amount of 13 uM Ni decreases CAT and GST activities in *M. galloprovincialis* (Lam) [179]. After exposure to NiNPs, ROS-induced apoptosis is observed in human skin epidermal cells [180]. However, Tyagi *et al.* [11] reported that renal SOD activity and GSH content are significantly increased after a high dose of $NiCl_2$ has been used in rat.

Yet, Ni (II) at concentrations of 10–50 μM does not increase the intracellular ROS generation, but can activate the Nrf2 (NF-E2-related factor 2) signaling that is an antioxidant pathway [181]. The GSH depletion is due to the Ni-GSH complexes or Ni-mediated ROS formation [182].

4.2. The Extrinsic Pathway of Ni-Induced Apoptosis

At present, there are few studies on the extrinsic pathway of Ni-induced apoptosis. The results of Zhao *et al.* [183] suggest that metallic nickel particles can increase Fas, FADD, DR 3, and caspase-8 expression, but not DR6 and TNF-R2. Also, this study detects the formation of DISC. These data indicate that the extrinsic apoptotic pathway is involved in the apoptotic process caused by metallic nickel particles in JB6 cells. Bonin *et al.* [184] reported that higher expression levels of caspase-8 mRNA are detected in the Ni-exposed workers.

4.3. The Intrinsic Pathway of Ni-Induced Apoptosis

The mitochondria play a dominant role in the intrinsic apoptotic pathway [115,185]. Wang *et al.* [186] suggested that Nickel acetate induces MMP loss and apoptosis. Ni NWs-induced MMP disruption and apoptosis, and nickel ferrite nanoparticle-induced MMP loss are also found in HeLa cells [173] and in HepG2 and MCF-7 cells [187]. After the MMP loss, there are several apoptotic factor releases from the mitochondria. There is evidence that cyt c and caspases-9, -3 and -6 protein expression is increased after nickel acetate has been added in human proximal tubule cells [186]. Nickel nanoparticles and nickel fine particles can increase cyt c and AIF translocation from mitochondria to the cytoplasm [184]. AIF can induce apoptosis through caspase-independent pathway. However, cyt c can activate the caspase-dependent pathway. It has been demonstrated that fine nickel particles and nickel nanoparticles increase the protein expression and activation of caspase-3, -6, and -9 [183]. Additionally, $NiSO_4$ increases caspase-3 activity in *Carassius auratus* liver [154]. Patel *et al.* [188] suggested that $NiCl_2$ increases caspae-3, caspase-7 protein expression in human lung epithelial cells. Caspase-3 activity is obviously up-regulated with the increase in time and Ni NPs dose [175]. It has been also demonstrated that NiO nanoparticles (NiONPs) increases the numbers of apoptotic cells and the activaty of caspase-3 [189]. p53-defective human leukemic cells (U937) exposed to bis (*S*-citronellalthiosemicarbazonato) nickel(II) ([Ni(tcitr)2]) cause MMP disruption and caspase-3 activation [190]. Also, nickel nanoparticles (NiNPs) increases caspase-3 activity and apoptosis in A431 cells [180]. After exposure to nickel ferrite nanoparticles, the activation and gene expression of caspase-3 and caspase-9 are increased in HepG2 and MFC-7 cancer cells [187]. Dietary $NiCl_2$ can increase caspase-3 expression in the thymus, spleen, and cecal tonsil in broiler chickens [49,155,156]. Abovementioned results show that the intrinsic signal pathway takes part in the apoptotic process induced by Ni and Ni compounds.

The Bcl-2 family of proteins is important in the modulation of the outer mitochondrial membrane integrity. In studies of Ni-induced apoptosis, Ni can alter the expression of Bcl-2 family proteins. Liu *et al.* [153] reported that $NiCl_2$ can decrease the Bcl-2 protein expression and increase the Bax protein expression through suppression of PI3K/Akt pathway in the liver of Kunming mice. Ahamed *et al.* [187] suggest that nickel ferrite nanoparticles increase Bax mRNA expression through the p53 pathway, and decrease Bcl-2 mRNA expression. $NiSO_4$ increases Bax protein expression and decreases Bcl-2 protein expression in *Carassius auratus* liver [154]. Reduction of Bcl-2 and Bcl-xL protein expression and enhancement of Bad, Bcl-Xs, Bax protein expression are observed after human proximal tubule cells and human bronchial epithelial cells have been cultured with nickel acetate and NiONPs [186,189]. Human BEAS-2B cells exposed to Ni_3S_2 show down-regulation of several antiapoptotic proteins (Bcl-2 and Bcl-xL) [174]. Dietary $NiCl_2$ can increase Bax expression and Bax/Bcl-2 ratio and decrease Bcl-2 expression in the thymus, spleen, and cecal tonsil of broiler chickens [49,155,156]. However, the results of Zhao *et al.* [183] show that nickel nanoparticles and nickel fine particles can increase Bcl-2 expression and decrease Bax expression.

Up to now, there is only one report that nickel acetate can induce ER stress and increase CHOP protein expression in NRK52E cells and Hepa-1c1c7 cells [191].

4.4. Others

It has been shown that c-Myc amplifies the mitochondrial pathway and promotes and/or amplifies the death receptor pathway [192]. c-Myc can increase FasL expression, provoke combination of tBid and mitochondria, affect DISC components, inhibit Bcl-X expression and disrupt nuclear factor-κB (NF-κB) activation [193]. Besides, c-Myc activation provokes cyt c release [194]. c-Myc can selectively suppress Bcl-2 family proteins [193,195].

$NiSO_4$ increases c-Myc protein and mRNA expression in non-tumorigenic Beas-2B and human keratinocyte HaCaT cells. It has been proved that the c-Myc is important in Ni-induced apoptosis through knockout and restoration technology. ERK/MEK (extracellular regulated protein kinases/mitogen-activated protein kinase) inhibitors (U0126 and PD98059) attenuate c-Myc

expression. These results indicate that the ERK-dependent c-Myc pathway takes part in Ni-induced Beas-2B cell apoptosis [196].

5. Conclusions and Future Perspectives

A number of studies have explored the molecular mechanism of Ni and Ni compounds-induced apoptosis. However, the precise mechanisms of Ni-induced apoptosis are inconclusive up to now. As shown in Figure 4, previous studies demonstrated that ROS-, mitochondria-, ER-, Fas- and c-Myc-mediated apoptotis are all involved in Ni-induced cell apoptosis. Most of these studies focus on the ROS- and mitochondria-mediated apoptosis. Only one study presents the ER-, Fas- and c-Myc-mediated apoptosis pathway. Therefore, more research should be conducted to explore whether ER-, Fas- and c-Myc-mediate apoptotic pathways are involved in Ni-induced apoptosis.

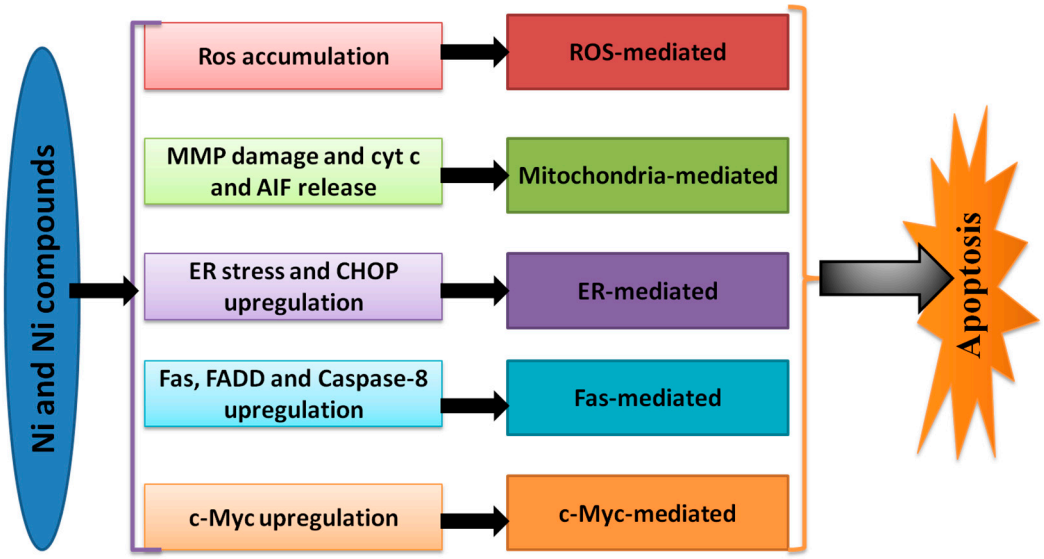

Figure 4. Pathways of Ni-induced apoptosis. The ROS-, mitochondria-, ER-, Fas- and c-Myc-mediated apoptotic pathway are all involved in Ni-induced cell apoptosis.

In addition to the conventional apoptotic proteins, another molecule has been found to regulate apoptosis. MicroRNAs (miRNAs) negatively regulate gene expression. Recent studies have reported that miRNAs participate in development, differentiation, and cell apoptosis [197–199].

Disorders of apoptosis may be important in the Ni or/and Ni compound toxicology, which includes neurotoxicity, hepatotoxicity, renaltoxicity, toxicity of the autoimmune system, and carcinogenicity. Revealing the mechanisms of Ni-induced apoptosis may contribute to the prevention of Ni toxicity.

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Conflicts of Interest: The authors declare no conflict of interest.

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