Journal of Cytology & Histology
ISSN: 2157-7099

Prakash et al., J Cytol Histol 2017, 8:3
DOI: 10.4172/2157-7099.1000468

Research Article Open Access

The Review of Small Size Silver Nanoparticle Neurotoxicity: A Repeat Study

Pani Jyoti Prakash[1]*, Singh Royana[2], Pani Sankarsan[3] and Shrivastav Rajeev[4]

[1]Deartment of Anatomy, N.Y Tasgaonkar Institute of Medical Science and Research, Karjat, 410201, India
[2]Department of Anatomy, Institute of Medical Sciences Banaras Hindu University Varanasi, 221005, India
[3]Department of Surgery, N.Y Tasgaonkar Institute of Medical Science and Research, Karjat, 410201, India
[4]Department of Cardiothoracic, N.Y Tasgaonkar institute of Medical Science and Research, Karjat, 410201, India

Abstract

Repeated oral gavages silver nanoparticle colloidal solution ingestion procedures for AgNps neural toxicity have been investigated in Swiss albino mouse fetuses' brain at the ultra-structural (TEM) level by transmission electron microscopy and Nikon bright field microscopy. Transmission electron microscopy probe identified neural toxicity in the brain of mice fetuses in the form of mitochondrial autophagy, dysmorphology & dysfunction of cellular organelles vacuolization of neuronal cell, blood brain barrier inflammation, astrocytic swelling, Gliosis and a well visualized differentiation to the reaction products. Multiple reaction product localization was visible in the form of smaller size silver nano particles (1 to 20 nm range) percolation and perimembranous multiple patchy condensations focuses appeared from inside and outside of neuronal cell membrane. Histologically cell and tissue dysmorphology was observed in the form of unipolar brush cell and lugaro cells degeneration with dysmorphology of corticomedullary layers of cerebrum, cerebellum and hippocampus. In twice, lower dose (0.5 and 1 mg/kg b.w./day) and higher dose (10 and 15 mg/kg b.w./day) small size silver nano particles were found adhered both side of cell membrane, mitochondria and endocytotic vesicle. Neural histochemistry of fetal cortex by Golgi staining procedure showed reduction number of dendrite arborisation and unipolar neuron with basket cells degeneration and dysmorphology. But the intensity of such was found almost low or equal to control in lower dose and high in higher dose and concentration. Small size silver nano particles exhibits more neurotoxic effect comparatively to other metal nanoparticles because of easy penetration and disintegrity to BBB.

Keywords: Proinflammatory symptoms; Neurodegenerative disorders; Honey comb deformity; Vacuolation

Introduction

Tiny silver nano particles (AgNps) (1-20 nm range) those metallic nano particles which bears irregular and spiny surfaces in SEM view are specious for vast utility in human usable households, drugs, hardware and software machinery mechanics and tools because of its exceptionally small size [1-3] also subjected for colloidal synthesis for experiment prior to utility. Also small size silver nano particles (AgNps) offers increased attraction in new research field day by day in this recent scientific world till date and attracts the modern scientists to do tedious research for discovery of new hidden facts, but this metal experimental nano particles possess some negligible bad and negative qualities with addition to high percentages good properties. It shows neurotoxicity in repeated oral ingestion by its damageable nature to brain tissue after successful entry through blood brain barrier. In recent past, several studies have reported neurotoxic effects of small size AgNps on various lower group animals like zebra fish, oysters and medaka brain tissues after transmission electron microscopic and immune histochemistry search into in-vitro of treated tissue's and cell's. Some of the insects CNS also affected of small size silver nanoparticle. Small size silver nano particles because of its effluent nature and contrasting characters have received a dynamic interest and emphasis in past. This type of silver nano particles possesses strong tissue healing and antiviral effect. This metal nano particles of extremely small size in this present situation shows vivid application in cell fragmentation and simplification processes, light reflection and refraction error correction mechanics, vehicles internal software processes, cell line sensor, health , cancer diagnostic and other pathological diseases tests fields [4,5]. Due to these vast applications negative impact on atmosphere arises. Human being and other lower group of animals come across and have an exposure to it in different ways; this unnatural way of pierce through respiratory systems and sense organs evokes various devastative effects on human and other lower group of animal's central nervous system and off course the environment in an invisible way in ignorance. These tiny particles after entering into respiratory system, ear, nose and throat migrate to blood vessels and from there it moves to brain and spinal cord through micro channels and cause neurotoxic response by releasing neurotoxins. Its irregular and spiny surfaces cause damage to delicate nervous tissue and gross inflammatory sequels [6,7]. Though colloidal silver nano particles exhibited numerous benefits to human being in lower dose and smaller size, the same also arouses disambiguous effects to CNS and other vital systems at higher dose and bigger size and certain specific parameters. In particular, neurotoxic focuses in various neuronal cell complexions based on chemical links with mosaic spread and cluster presentation of the spiny tiny particles in brain tissues [5]. For the successful study of microscopic living element toxogenic histological and ultra-microscopically collected features, genesis of oxygen sensory genus, find out cause for strenuous periodicals due to imbalance of production of free radicals and detoxification process by neutralization of antioxidants and for the elucidation of apoptotic pathway widely utilization of small size silver nano particles in colloidal form have been reported very helpful till date [7-9]. AgNps induced toxic response to cell lowers the successful activity of cell membrane transportation of nutrition *in vivo* in various

***Corresponding author:** Prakash PJ, Assistant Professor of Anatomy, N.Y Tasgaonkar institute of Medical Science and Research, Karjat, 410201, India, Tel: 08433668356; E-mail: jyotiprakashimsbhu@gmail.com

Received July 01, 2017; **Accepted** July 25, 2017; **Published** August 04, 2017

Citation: Prakash PJ, Royana S, Sankarsan P, Rajeev S (2017) The Review of Small Size Silver Nanoparticle Neurotoxicity: A Repeat Study. J Cytol Histol 8: 468. doi: 10.4172/2157-7099.1000468

neural cell micro porous channels by causing cellular porous obstruction through the pathway up to mitochondria internal architecture level and auto regulated shrinkage ultimately leads to malnutriated condition and death [7,10] and accumulation of debris with abnormal secretion of toxins and oxygen sensory genus [11]. Neuronal nutritional status is maintained by membrane junction and balances proper inter cellular organelles and the membrane junction also links the obstructive agent between micro capillary luminal cells of brain and nervous tunica of eye ball and when this pathway is obstructed by accumulation of tiny silver particles arouses neurogenerative disorders with ophthalmic sensory and nervous malnutriated conditions [12]. Tiny silver nano particles disturb stability of haemopoitic system and nervous system also hampers conduit between them it also lowers the luminal cell perfusion rate of nutrition by smooth penetration [13]. Tiny AgNps not only eyes the brain, spinal cords, cranial nerves and ANS but also easily surpasses into the human and lower animals body through external macro porous easily in wide utility regions also produces abnormality in other vital organs [14,15] Surprisingly, Panyala et al. and their principal associate [16] reported that various vital organs can eliminate AgNps and tiny Ag ions after a long period because of its prolong plasma half life. They can also produce smooth interference and access of CNS by coming across the haemopoitic and nervous system separation link [17]. Therefore, there is maximum probability CNS abnormality with small size AgNps exposure. For a matter of fact, Haase et al. [18] reported small size (20 nm) AgNps treated newly regenerated and miscellaneous artificially grown nerve cell from the mouse cortical region of frontal lobe of brain shows a peak within cell Ca^{++} increase followed by a hefty imbalance of production of free radicals and detoxification process by neutralization of antioxidants response. Interestingly in the current year, Xu et al. and their principal associate [19] reported that tiny AgNps induces within cell toxic response and final exit from life of nerve cell which newly evoluted from rat brain cortex through a process which maintain a condition suitable for growth, via modification of cell cytoskeleton components, deviation of system or process from its regular state or path caused by outside influence of Snare and Homer 1 proteins complexes, and disruption of normal function of chondriosome. Dayem et al. and their head collaborator [20] reported that inconsiderable size AgNps may boost neuron cell divergence of a specific human derived cell line by peak rise of within cell singlet oxygen evolution. With respect to a semi permeable membrane separating the blood from the cerebrospinal fluid, and constituting a conduit to the passage of cells, particles, and large molecules, its general response towards neural toxicity, this opinion have proved that inconsiderable size silver nanoparticles inject into the erythropoitic system can initiate impingement of normal function of BBB, inflammation of star shaped glial cell of CNS, along with it also cause neuronal cells and tissue degeneration. Anyway, an interpretation that which way inconsiderable size AgNps can introduce impingement of normal function of BBB and neurotoxicity at the neuron supportive cell level from the outside wall of blood vessels remains unsolved till now. For which, the present study analyses the inter correlation of various small size silver nanoparticles (AgNps) (1-20 nm) and above mentioned dose with the grade of neurotoxicity to identify the rate of association of inflammatory agents in the dilated brain tissue micro channels penetration capacity via the brain blood vessels. There are certain insulting causes for which malfunction of the BBB along with significant damage executes, also resulted in upraising penetrative sequels in the brain tissue and nerve cells which allows the smooth bypass of inconsiderable micro agents into the brain from capillaries taken as separate entity. Till today, many chronic CNS swelling diseases are involved with affected conduit. Different grade of toxic responses of CNS not dependent upon pathway of injecting small size AgNps, rate of absorption in body system and exposure time but depends upon rate of damage to CNS. The goal of the current study is to compare in triplicate way the different deleterious effects of small size AgNps on CNS by Transmission electron microscopy, routine histochemistry and Golgi staining protocol. Past studies reported inconsiderable size AgNps injected by different route usually translocate and accumulate in CNS which ultimately cause neurotoxicity and other complications [21,22]. Small size silver nano particles executes prolong plasma stay period in long time application within the CNS capillaries in comparison to capillaries of rest organ, so the rate of damages is found more in CNS [23]. Small size AgNps cause nerve cell lyses, such feature demonstrated during the experiment in hippocampus neurons isolated from brain tissue of rat [24,25]. Liu and colleagues propounded that inconsiderable size AgNps promote neurotoxicity and imbalance in production of free radicals ultimately leads to programmed cell death [26]. Yin and colleagues propounded imbalance of production of free radicals and detoxification process by neutralization of antioxidants response is main initiator in neurotoxicity where intensity differs [27]. Hussein et al. propounded AgNps with 15 nm diameter cause upraise in singlet oxygen production [28]. Hence forth we conducted this study through TEM routine histology and Golgi stain approach.

Material and Methods

Small size AgNps (20 nm) in raw powdered form was purchased from Trimurthy scientific Varanasi India. The AgNps colloidal suspensions is prepared by Magnetic stirring and cooling method then diluted 1.5 molar NaCl to required final concentrations. The suspensions were characterized by Dynamic light scattering, zeta potential and image-j estimation. The size of individual AgNps was observed by taking clean photograph and calculated by using TEM (ITRC Lucknow). The size distribution of AgNps suspended in 1.5 molar $NaCl_2$ evaluated by Delsa-TM nano Beckmann Coulter machine UK. Repeated oral gavages at a dose of 0.5, 1 (lower), 10 and 15 (higher) mg/kg/day silver nanoparticle colloidal solution ingestion procedures for AgNps neural toxicity have been investigated in pregnant Swiss albino mouse fetuses' brain at the ultra-structural (TEM) level by transmission electron microscopy and Nikon bright field microscopy. And same thing have been investigated by immunohistochemistry procedure through Golgi staining approach.

Results

Transmission electron microscopy probe identified neural toxicity in the brain of mice fetuses in the form of mitochondrial autophagy, dysmorphology & dysfunction of cellular organelles vacuolization of neuronal cell, blood brain barrier inflammation, astrocytic swelling, Gliosis and a well visualized differentiation to the reaction products. Multiple reaction product localization was visible in the form of smaller size silver nanoparticles (20 to 100 nm range) percolation and perimembranous multiple patchy condensations focuses appeared from inside and outside of neuronal cell membrane and abnormal morphology of neural macrophage. Histologically cell and tissue dysmorphology was observed in the form of unipolar brush cell and lugaro cells degeneration with dysmorphology of corticomedullary layers of cerebrum, cerebellum and hippocampus. In both cases lower dose (0.5 and 1 mg/kg/day) and higher dose (10 and 15 mg/kg/day) reaction products were found accumulated outside and inside of nuclear envelop, rough endoplasmic reticulum (RER) and endocytotic vesicle. Neural histochemistry of fetal cortex by Golgi staining

procedure showed reduction of number of dendrite arborisation and unipolar neuron with basket cells degeneration and dysmorphology. But the intensity of such was found almost low or equal to control in lower dose and high in higher dose and concentration.

Discussion

Small size silver nanoparticles have been significantly utilized in cosmetics, medicine, electronics, and food additives as trademark commercial products. The appropriate dose for this commercial purpose is either low or medium which proves to be beneficiary for world population but higher dose acts as poisonous hood for same. However, the bad effects of this small size metal on mice fetuses' brain has been studied and reported well but not on human brain. Our study indicates inconsiderable size AgNps cause high grade neurotoxicity. Various research studies have reported that small size AgNps can enter the CNS through blood brain barrier by disrupting the barrier integrity and induce brain oedema and neurotoxicity. After 10 days of repeated gastrointestinal oral gavages exposure of small size colloidal silver 0.5, 1 (lower) mg/kg/b.w. or 10, 15 mg/kg/b.w. In pregnant Swiss Albino mice, Astrocyte swelling was the most significant change observed in delivered fetuses brain after scheduled TEM and Golgi staining approach when compared with double distilled water vehicle control but at lower dose the sign and symptoms observed negotiable whereas at higher dose the same are observed in significant Intensity. TEM exploration is done for intra cellular features whereas Golgi staining exploration is done for gross morphological and histological cell and tissue features at the end correlation has been made. Furthermore, small size AgNps chemically reacted with CNS and their blood supply resulted in over production of oxygen sensory genus and singlet oxygen with inflammatory agents, which upraises blood brain barrier permeability and disrupts barrier integrity. The biological effects of small size AgNps on the blood brain barrier and brain is disruption of integrity and more dilatation of micro porous which cause easy passage of this small size nano metal. Cause of injury to the vital microscopic structures inside brain is irregular, spiny and sharp surfaces of these small nano metals. The above cause provokes neural cell toxic response in a small size AgNps colloidal solution treated blood brain barrier model of fetuses' brain. In this study, we analyzed triple variety neurotoxicity and its grade by small size AgNps ingestion on observing the ultra-structure and micro structural changes using TEM, routine histology and Golgi stain protocol in treated Swiss Albino mice fetuses' brain. In the present study we observed mitochondrial autophagy, dysmorphology, dysfunction of cellular organelles vacuolization of neuronal cell (honey comb deformity), blood brain barrier inflammation, astrocytic swelling, Gliosis and a well visualized differentiation to the reaction products. Multiple reaction product localization , percolation and perimembranous multiple patchy condensations focuses from inside and outside of neuronal cell membrane , In both cases lower dose (0.5 and 1 mg/kg/day) and higher dose (10 and 15 mg/kg/day) reaction products were found accumulated outside and inside of nuclear envelop, rough endoplasmic reticulum (RER) and endocytotic vesicle in TEM approach. Cell and tissue dysmorphology was observed in the form of unipolar brush cell and lugaro cells degeneration with dysmorphology of corticomedullary layers of cerebrum, cerebellum and hippocampus in routine histology approach. We also observed reduction of number of dendrite arborisation and unipolar neuron with basket cells degeneration and dysmorphology in Golgi staining approach in the same dose. In the current study, we developed a TEM, routine histology and Golgi stain triple model treated with small size colloidal nano silver at higher dose and lower dose. The model fetuses' brain represented more or less same deviated and damaged ultra-structural, histological and morphological features. Previous researches reported supportive Glial cells of CNS directly or indirectly take role in maturation and development of blood brain barrier and these Glial cells such as Astrocytes and other type plays vital role in intactness of endothelium conduit membrane of blood vessels whereas Astrocytes shows higher percentage compare to other type of Glial cells. Furthermore as per previous study reporting, astrocytes decrease the pericellular infiltration of brain nerve inner luminal cells isolated from rat brain tissue. The existing study indicates predominant features of Astrocyte swelling, Gliosis and abnormal accumulation outside and inside of nuclear envelop, rough endoplasmic reticulum (RER) and endocytotic vesicle the in TEM exploration, degeneration and dysmorphology of neurons and atrophic features of grey matter observed through routine histology exploration, Golgi staining demonstrated reduction of number of dendrite arborisation and unipolar neuron with basket cells degeneration and dysmorphology in the triplet presentation of brain tissue. The acquired features from triplet presentation of brain tissue also show similarity to blood brain barrier disruption *in vivo*. As per previous research commentaries the separation membrane between hematopoietic and nervous system shows good example for neurotoxicity and blood toxicity transfer between the two. The current experiment indicates same small size AgNps treated tissue features by three protocols was utilized to evaluate the hazardous and toxic effects of small size AgNps in fetuses' brain *in vivo* after repeated oral gavages ingestion of small size AgNps colloidal suspension to pregnant mice. Past researches indicate swelling and lower activity of neuroglial cells cause BBB damage and nervous ailment. Secondary research is absolutely necessary to find out does tiny AgNps cause depletion activity of neuroglial cells and nerve cell damage or not. Our study report demonstrates significant Chondriosome vacuolation with autophagy and endoplasmic reticulum damage, also tiny silver nano particles accumulation, inside neurons in ultra-structure exploration, this feature so mote indicates that tiny AgNps easily penetrate supportive neuroglial cells and luminal cells and evokes neurotoxicity. Liu ZW, Allaker RP and their principal scientist propounded that inconsiderable size AgNps executes edematous effects after smooth penetration to brain and spinal cord also induces nerve cell toxic response [29]. Our research also shows similarity with past research, our research reports oxygen sensory genus and singlet oxygen generation, proinflammatory effects with programmed cell death are main features of small size AgNps induced toxicity. Xu et al. and their leading head researcher of team demonstrated tiny size AgNps eliminate adequate and in scattered form small silver atom or molecule with a net electric charge where all these surpasses the central nervous system conduit membrane and after crossing it in due course of time severely damages neural cells and supportive neuroglial cells [30,31] also Sharma et al. scientists and their team leader exclamated that most of the time tiny size silver nano particles plays a different and specific chemistry with the invisible circulatory channels of front brain part also adequately secretes oxygen sensory genus and singlet oxygen along with it shows deep swelling effects while surpassing inside it, it also simultaneously increases the rate of penetration in conduit membrane which differentiates between brain and blood [32]. At the same time some of the past study also suggested neuroglial cells significantly supplies nutrition to the blood brain barrier and brain. These nutritive agents boosts singlet oxygen and free radicals in the brain as they have peak metabolic percentage and high percentage, which stimulates neuroglial cells better active to small size AgNps induced reactive oxygen species and with this their counteract and defense capability is depleted and subjected to swelling and injury.

The chief scientist Sengillo et al. propounded that neuroglial cell reduction and deactivation results in simultaneous conduit membrane destruction and forbids central nervous system ailments [33]. Also researcher Sarkar S and their scientific team propounded tiny size silver nano particles depletes specific protein marker in brain cells, these marker cells are present adhered to inside of chondrioplasm also responsible for over production of singlet oxygen and initiates programmed cell death. This experiment is done in Danio Rario. Ultimately the existing research demonstrates, small size AgNps also induced proinflammation and apoptosis sequels in neuroglial cells. This statement clarifies the explanation of small size AgNps neurotoxicity. Further research is essential to know which way the neurotoxic episodes are induced by small size AgNps in neuroglial cells of various types which ultimately influences neuron functions [33,34].

Conclusion

We established a triple model using TEM, routine histology (H and E) and immunohistochemistry (Golgi staining protocol) after Day 18 in brain of small size AgNps treated Swiss Albino mice fetuses. After 0.5, 1, 10 and 15 mg/kg/b.w. and 20 nm size AgNps colloidal exposure for 10 days, the blood brain barrier accesses ability and penetration rate upraised highly by disruption of integrity and Gliosis features shoot up when analyzed with non treated. Severe mitochondrial autophagy and damage, Endoplasmic Reticulum damage and chondriosome vacuolization were located in neuroglial cells. With correlation to the above statement, as per several past studies reporting small size AgNps significantly decreases the amount of two types of newly discovered genes, which saves neurons from oxidation tension, proinflammation, and apoptosis. AgNps induced neurotoxicity in CNS by reducing production of free radicals in neuroglial cell types. Also as per some past study reporting, small size AgNps also induced singlet oxygen regeneration, proinflammatory effects, programmed cell death in various neuroglial cells. Small size AgNps significantly suppressed cell's consumption capacity also suppresses fermentation and simplification process in various neuroglial cells and influence astrocytes dysfunction in brain and spinal cord for which upraise neurotoxicity sequels.

Conflicts of Interest

Author declares no conflict of interest.

Acknowledgement

The authors gratefully acknowledge UGC, India for their technical support in financing the project. ITRC, IITR TEM division Lucknow is highly appraised for characterization of small size silver nano particles colloidal and Dr. Sanjay Singh (Professor IIT, Pharmaceutical Division) for his feedback and help for DLS estimation.

References

1. Nel A, Xia T, Madler L (2006) Toxic potential of materials at the nanolevel. Science 311: 622-627.
2. Moore MN (2006) Do nanoparticles present ecotoxicological risks for the health of the aquatic environment? Environ Int 32: 967-976.
3. Frattini A, Pellegri N, Nicastro D (2005) Effect of amine groups in the synthesis of Ag nanoparticles using aminosilanes. Mater. Chem. Phys 94: 148-152.
4. Capek I (2004) Preparation of metal nanoparticles in water-in-oil (w/o) microemulsions. Adv Colloid Interface Sci 110: 49-74.
5. Xia T., Kovochich M., Liong M (2008) Cationic polystyrene nanosphere toxicity depends on cell-specific endocytic and mitochondrial injury pathways. ACS Nano 2: 85-96.
6. Asharani P, Sethu S, Lim HK (2012) Differential regulation of intracellular factors mediating cell cycle, DNA repair and inflammation following exposure to silver nanoparticles in human cells. Genome Integr 3: 2.
7. Han JW, Gurunathan S, Jeong JK (2014) Oxidative stress mediated cytotoxicity of biologically synthesized silver nanoparticles in human lung epithelial adenocarcinoma cell line. Nanoscale Res Lett 9: 459.
8. Sanchez-Perez Y, Chirino YI, Osornio-Vargas AR (2009) DNA damage response of A549 cells treated with particulate matter (PM10) of urban air pollutants. Cancer Lett 278: 192-200.
9. Ye SF, Zhong LM, Wu YH (2009) Multi-walled carbon nanotubes exposure induces oxidative stress and depolarizes mitochondrial membrane potential in cultured A549 cells. Chem J Chin Univ 30: 497-501.
10. Gurunathan S, Jeong JK, Han JW (2015) Multidimensional effects of biologically synthesized silver nanoparticles in Helicobacter pylori, Helicobacter felis, and human lung (L132) and lung carcinoma A549 cells. Nanoscale Res Lett 10: 1-17.
11. Carlson C, Hussain SM, Schrand AM (2008) Unique cellular interaction of silver nanoparticles: Size-dependent generation of reactive oxygen species. J Phys Chem B 112: 13608-13619.
12. Antonetti DA, Barber AJ, Khin S (1998) Vascular permeability in experimental diabetes is associated with reduced endothelial occludin content: Vascular endothelial growth factor decreases occludin in retinal endothelial cells. Diabetes 47: 1953-1959.
13. Trickler WJ, Lantz SM, Murdock RC (2010) Silver Nanoparticle Induced Blood-Brain Barrier Inflammation and Increased Permeability in Primary Rat Brain Microvessel Endothelial Cells. Toxicol Sci 118: 160-170.
14. Austin CA, Umbreit TH, Brown KM (2012) Distribution of silver nanoparticles in pregnant mice and developing embryos. Nanotoxicology 6: 912-922.
15. Tang JL, Xiong L, Wang S (2009) Distribution, Translocation and Accumulation of Silver Nanoparticles in Rats. J Nanosci Nanotechnol 9: 4924-4932.
16. Panyala NR, Pena-Mendez EM, Havel J (2008) Silver or silver nanoparticles: A hazardous threat to the environment and human health? J Appl Biomed 6: 117-129.
17. Tang JL, Xiong L, Zhou GF (2010) Silver Nanoparticles Crossing Through and Distribution in the Blood-Brain Barrier In Vitro. J Nanosci Nanotechnol 10: 6313-6317.
18. Haase A, Rott S, Mantion A (2012) Effects of silver nanoparticles on primary mixed neural cell cultures: Uptake, oxidative stress and acute calcium responses. Toxicol Sci 126: 457-468.
19. Xu FL, Piett C, Farkas S (2013) Silver nanoparticles (AgNps) cause degeneration of cytoskeleton and disrupt synaptic machinery of cultured cortical neurons. Mol Brain 6: 1.
20. Dayem AA, Kim B, Gurunathan S (2014) Biologically synthesized silver nanoparticles induce neuronal differentiation of SH-SY5Y cells via modulation of reactive oxygen species, phosphatases, and kinase signaling pathways. Biotechnol J 9: 934-943.
21. Klaper R, Crago J, Barr J (2009) Toxicity biomarker expression in daphnids exposed to manufactured nanoparticles: changes in toxicity with functionalization. Environ Pollut 157: 1152-1156.
22. Comfort KK, Maurer EI, Braydich-Stolle LK (2011) Interference of Silver, gold, and iron oxide nanoparticles on epidermal growth factor signal transduction in epithelial cells. ACS Nano 5: 10000-10008.
23. Hsin YH, Chen CF, Huang S (2008) The apoptotic effect of nanosilver is mediated by a ROS and JNK-dependent mechanism involving the mitochondrial pathway in NIH3T3 cells. Toxicol Lett 179: 130-139.
24. Trickler WJ, Lantz SM, Murdock RC (2012) Silver nanoparticle induced blood-brain barrier inflammation and increased permeability in primary rat brain microvessel endothelial cells. Toxicol Sci 2010 kfq244.
25. Cha K, Hong HW, Choi YG (2008) Comparison of acute responses of mice livers to short-term exposure to nano-sized or microsized silver particles. Biotechnol Lett 30: 1893-1896.
26. Liu Z, Ren G, Zhang T (2009) Action potential changes associated with the inhibitory effects on voltage-gated sodium current of hippocampal CA1 neurons by silver nanoparticles. Toxicology 264: 179-184.
27. Yin N, Liu Q, Liu J (2013) Silver nanoparticle exposure attenuatesthe viability of rat cerebellum granule cells through apoptosis coupled to oxidative stress. Small 9: 1831-1841.

28. Curtin JF, Donovan M, Cotter TG (2002) Regulation and measurement of oxidative stress in apoptosis. J Immunol Methods 265: 49-72.

29. Hussein SM, Javorina AK, Schrand AM (2006) The interaction of manganese nanoparticles with PC-12 cells induces dopamine depletion. Toxicol Sci 92: 456-463.

30. Yang Z, Liu ZW, Allaker RP (2010) A review of nanoparticle functionality and toxicity on the central nervous system. J R Soc Interface 7: S411-S422.

31. Xu L, Shao A, Zhao Y (2014) Neurotoxicity of silver nanoparticles in rat brain after intragastric exposure. J Nanosci Nanotechnol 14: 1-9.

32. Sharma HS, Ali SF, Tian ZR (2009) Chronic treatment with nanoparticles exacerbate hyperthermia induced blood-brain barrier breakdown, cognitive dysfunction and brain pathology in the rat. Neuroprotective effects of nanowired-antioxidant compound H-290/51. J Nanosci Nanotechnol 9: 5073-5090.

33. Sengillo JD, Winkler EA, Walker CT (2013) Deficiency in mural vascular cells coincides with blood-brain barrier disruption in Alzheimer's disease. Brain Pathol 23: 303-310.

34. Sarkar S, Mukherjee S, Chattopadhyay A (2014) Low dose of arsenic trioxide triggers oxidative stress in zebrafsh brain: expression of antioxidant genes. Ecotoxicol Environ Saf 107C: 1-8.