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Epigenetic modification and antioxidant activity of sulforaphane and selenium nanoparticles against brain metabolic dysfunctions leading to Alzheimer's disease in rats

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Abstract

In recent years, the incidental rate of neurodegenerative diseases (NDs), in general, and Alzheimer's disease (AD) in particular, has increased proportionately with the aging population. These diseases are multifactorial and their current treatment strategies are only associated with symptomatic relief rather than curbing their progression. Phytochemicals have been consistently proposed as alternative therapy in modern medicine, but their efficacy in NDs is somewhat limited by the rapid metabolism, insufficient permeability across the BBB, and decreased bioavailability and stability in the brain. Fortunately, current advances in nanotechnology present opportunities to overcome such limitations in delivering active phytochemicals candidates.

The main goal of this study was to examine the effects of Sulforaphane (SFN) and/or Selenium (Se) nanoparticles (NPs) as well as fresh broccoli juice (FBJ), on metabolic, epigenetic, antioxidant, inflammatory and apoptotic markers in rats suffering from an $AlCl_3$-induced neurotoxicity that may eventually lead to Alzheimer's disease (AD). The first phase of this study used high resolution transmission electron microscopy (HR-TEM) images and dynamic light scattering (DLS) charts to characterize the SFN NPs and Se NPs and their results revealed that average size of both particles was in the nano-scale, while analysis of FBJ revealed its high content of various bioactive components. During the animal trial phase, results of Morris water maze test and conditioned avoidance test showed that there was a significant ($P < 0.05$) elevation in learning ability and memory function in all pre/treated rat groups. SFN NPs were the most effective, by virtue of their small size and characteristics, followed by FBJ. Epigenetic and antioxidant effects followed the same direction and were apparent through significantly halting the effects of $AlCl_3$ on histone deacetylase (HDAC) activity as well as the gene expression of DNA methyltransferase-1 (DNMT-1) and heme oxygenase-1 (HO-1); further protecting the downstream endogenous enzymatic and non-enzymatic antioxidant system. Levels of metabolic dysfunction, inflammation and apoptosis markers also reflected the neuroprotective effects of our pre/treatments. These results were confirmed by histological and immunohistochemical examinations. Interestingly, all tested pre/treatments significantly exhibited neuroprotective actions; however, SFN NPs were the most effective.

List of Abbreviations

3×Tg-AD	Triple-transgenic mouse model of AD
A2M	Alpha-2-macroglobulin
Ab	Antibody
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADAD	Autosomal dominant Alzheimer disease
ADMA	Asymmetric Dimethylarginine
AGEs	Advanced Glycation Endproducts
Al	Aluminum
AMPAR	Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AMPK	Adenosine Monophosphate Activated Protein Kinase
ANOVA	Analysis of Variance
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
ARE	Antioxidant Response Element
ATP	Adenosine Triphosphate
Aβ	Amyloid Beta
β-ACT	Beta Actin
BACE	β-secretase (β site-APP cleaving enzyme)
BBB	Blood-Brain Barrier
BDNF	Brain Derived Neurotrophic Factor
BDNs	Broccoli-Derived Nanoparticles
CA	Conditioned Avoidance
CAT	Catalase
CMI	3-((4-chlorophenyl-selanyl)-1-methyl-1-indole
CNS	Central Nervous System
COX	Cyclooxygenase
CSP-3	Caspase-3
d.w.	Distilled Water
DDAH	Dimethylarginine-dimethyl-amino-hydrolase

DLS	Dynamic Light Scattering
DNA	Deoxyribonucleic Acid
DNMTs	DNA Methyltransferases
DPPH^0	2,2'-Diphenyl-1-Picrylhydrazyl
DTNB	5, 5′-dithiobis-(2-nitrobenzoic acid)
EAAT	Excitatory Amino Acid Transporter
ELISA	Enzyme Linked Immunosorbent Assay
ERK	Extracellular signal-Regulated Kinase
ETC	Electron Transport Chain
FBJ	Fresh Broccoli Juice
GAE	Gallic Acid Equivalent
GCLC	Glutamate Cysteine Ligase Catalytic subunit
GDNF	Glial cell line-derived neurotrophic factor
GFAP	Glial Fibrillary Acidic Protein
GIT	Gastrointestinal Tract
Gln	Glutamine
GLs	Glucosinolates
Glu	Glutamate
GLUT	Glucose transporter
GPx	Glutathione Peroxidase
GR	Glutathione Reductase
GSH	Glutathione (Reduced form)
GSK-3β	Glycogen Synthase Kinase-3β
GSSG	Glutathione (Oxidized form)
GST	Glutathione-S-Transferase
HATs	Histone Acetyltransferases
HCys	Homocysteine
HDACs	Histone Deacetylases
HO-1	Heme Oxygenase-1
HPLC	High Performance Liquid Chromatography
HRP	Horseradish Peroxidase
HR-TEM	High Resolution-Transmission Electron Microscope
HUVECs	Human umbilical vein endothelial cells
IL	Interleukin
ITCs	Isothiocyanates

Keap-1	Kelch-like ECH-Associated Protein-1
LDH	lactate dehydrogenase
LPS	lipopolysaccharide
LTP	Long Term Potentiation
MAPT	Microtubule-Associated Protein Tau
MCT	Monocarboxylate Transporter
mGluR	Metabotropic Glutamate Receptor
miRNA	microRNA
MWM	Morris Water Maze
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
ND	Neurodegenerative Disease
NF-κB	Nuclear factor Kappa-light chain- enhancer of B cells (transcription factor)
NFTs	Neurofibrillary Tangles
NMDAR	N-methyl-D-aspartate receptor
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NPs	Nanoparticles
NQO-1	NADPH: quinone oxidoreductase-1
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
OCLT	One Card Learning Task
OD	Optical Density
$ONOO^-$	Peroxynitrite
PBS	Phosphate Buffer Solution
PD	Parkinson's Disease
PSEN	Presenilin
RNA	Ribonucleic Acid
ROS	Reactive oxygen species
RT-PCR	Reverse Transcription- Polymerase Chain Reaction
SAH	S-adenosylhomocysteine
SAHH	S-adenosylhomocysteine hydrolase
SAM	S-Adenosyl Methionine
SCA	Scavenging Activity
Se	Selenium
Se NPs	Selenium Nanoparticles

SFN	Sulforaphane
SFN NPs	Sulforaphane Nanoparticles
SMC	Se-methylselenocysteine
SOD	Superoxide Dismutase
SREBP	Sterol Regulatory Element Binding Protein
STZ	Streptozotocin
TAA	Total Antioxidant Activity
TAC	Total Antioxidant Capacity
TE	Tris-EDTA
TFC	Total flavonoid content
TfR	Transferrin Receptor
TMB	3,3’,5,5’-Tetramethylbenzidine
TNF-α	Tumor Necrosis Factor-Alpha
TPC	Total phenolic content
TrxR-1	thioredoxin reductase-1
WHO	World Health Organization
PRDX-2	Peroxiredoxin-2
Cyt c	Cytochrome c

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