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Inside

CSIR- Indian Institute of Toxicology Research
(Council of Scientific and Industrial Research)
Lucknow, India

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Our motto-
"*Safety to Environment* & *Health and Service* to Nation"

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- Arsenic Detection Kit

CSIR-INDIAN INSTITUTE OF TOXICOLOGY RESEARCH

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EVENTS

National Science Day Celebrated at CSIR – IITR

CSIR – Indian Institute of Toxicology Research celebrated the National Science Day on 28 Feb 2014. The day was observed as an "Open Day" at the institute which threw open its gates to school / college students and citizenry of the city. The celebrations began with a popular science lecture entitled "Chemistry – A Discipline with Diverse Applications" delivered by Prof. TK Chandrashekar, Secretary Science and Engineering Research Board, Dept of Science and Technology, New Delhi. Dr KC Gupta, Director CSIR – IITR, welcomed the gathering and felicitated the guests. Prof. Chandrashekar described the wide applications of Chemistry in our daily lives. He opined that Chemistry plays the role of a "Mother Subject" to the different scientific disciplines. It plays a vital role in living systems, industry, health care, pharmaceuticals, diagnostics and advanced materials to name a few. Some chemicals like nitroglycerine have interesting dual roles as an explosive and as a drug for treatment of angina. The technology of Magnetic Resonance Imaging that draws heavily from Chemistry has received the highest scientific recognition, The Noble Prize in the areas of Physics, Chemistry and Medicine, itself speaks volumes of the importance of Chemistry in our everyday lives, he said. He summed up his talk enumerating the contributions of Dr Mahenderlal Sircar (founder of IACS), Dr Homi J Bhabha, Dr Vikram Sarabhai and Sir CV Raman, the doyen of Indian Science in whose honour the day is celebrated as National Science Day to commemorate his announcement of the Raman Effect.

Dr KC Gupta, Director CSIR – IITR
presenting memento to Prof. Chandrashekar

Prof. SP Gautam, Member, Madhya Pradesh Public service Commission, presided over the function. In his address he emphasized the existence of a scientific temperament in our country from time immemorial. A very convincing parallel was drawn between the Sri Ramacharitra Manas and every day science. He also suggested areas for contribution by CSIR-IITR, in synchronization with the mandate of the institute viz releasing environmental pollution advisories; creation of a GPS enabled Environment Information Service etc.

Dr Mukul Das, Chief Scientist CSIR-IITR proposed the vote of thanks drawing the function to a close. Later in the afternoon, fifty undergraduate science students from Mahila Vidyalaya Degree College visited the institute and were shown a film on the R&D activities of IITR. They were also taken around a few laboratories viz. Food Toxicology, Analytical Chemistry and Nanomaterial Toxicology. The students had a one to one interaction with a few scientists.

KC Gupta, Director CSIR – IITR, felicitating Prof. SP Gautam

Students from Mahila Vidyalaya Degree College interacting with scientist

World Environment Day Celebrated at CSIR-IITR

World Environment Day was celebrated at CSIR-IITR, Lucknow on June 5, 2014. While welcoming the guests, Prof. Ganesh Pandey, Director, Centre of Biomedical Research, Lucknow and Dr SWA Naqvi, Director, CSIR-National Institute of Oceanography, Goa, Dr KC Gupta, Director, IITR said that because of climate change the Carteret islanders of Papua, New Guinea have become the world's first community to be displaced. They are the first official refugees of global warming whose Island would be completely underwater by 2015 and the inhabitants would be moved to safer places. He further said that as India's economy advances, the country needs to produce more energy to provide a better life for its people. In this direction the nation is moving ahead by taking measures to contain its own emissions and to protect its people from climate disruption. Er. AH Khan, Scientist, IITR gave the genesis of the Dr CR Krishna Murti Memorial oration and introduced the Chief guest, Dr Naqvi to the audience. In his oration entitled "Ocean iron fertilization – an update based on the results of LOHAFEX, Dr Naqvi said that Ocean Iron Fertilization (OIF) is one of the potentially important means for sequestering carbon dioxide from the atmosphere, but the efficacy of this technique and its impact on the environment and ecology continue to be debated? In order to address outstanding issues related to OIF, an international experiment LOHAFEX was jointly conducted by India and Germany in the Southern Ocean during Jan.-March, 2009. This study has provided new insights on physical, chemical and biological processes that govern the functioning of plank tonic ecosystems.

Dr Naqvi released the report on "Assessment of ambient air quality of Lucknow city during pre-monsoon 2014". A summary of the report is given below.

The study was carried out during the months of April-May, 2014 to assess the status of air quality by monitoring and assessment of some selected air pollutants namely Respirable Particulate Matter (RSPM or PM_{10}), Sulphur dioxide (SO_2), Oxides of Nitrogen (NOx) and Trace metals-Lead (Pb) and Nickel (Ni) and noise level at 9 representative locations, categorized as residential (four), commercial (four) and industrial (one) areas in Lucknow city. The results revealed the 24 hours concentration of PM_{10} to be in the range of 120.5 to 341.6 µg/m^3 with an average of 214.7 µg/m^3. The average values of PM_{10} irrespective of locations were found to be above the permissible limit (100 µg/m^3 prescribed by MoEF). 24 hours concentration of SO_2 and NOx were found in the range of 10.2 to 28.4 and 19.8 to 72.6 µg/m^3 with an average concentration of 19.7 and 44.7 µg/m^3 respectively and all the values were below the permissible limits (80 µg/m^3). The mean level of trace metals were found Ni = 43.2 and Pb = 154.3 ng/m^3. Noise levels during day and night time were found in the range of 68.4 to 73.2 dB (A) and 53.8 to 68.5 dB (A) which were above the

Release of report on "Assessment of ambient air quality of Lucknow city during pre-monsoon 2014"

Dr SWA Naqvi delivering
Dr CR Krishna Murti Memorial oration

Children participating in painting competition

A child receiving prize from Prof. Ganesh Pandey

respective permissible limits except in industrial area.

The function was presided over by Prof. Ganesh Pandey, Director, Centre of Biomedical Research, Lucknow. He stressed upon the need to implement effective solid waste management techniques since this has emerged to become one of the most important threats to a clean and healthy environment. He also emphasized that a more robust mechanism for technology transfer from the lab to land will ensure all round development for all in addition to safeguarding the environment.

CSIR – IITR conducted a painting competition for school students in two age groups, the prizes for which were distributed on the occasion. The programme concluded with the vote of thanks by Dr Mukul Das, Chief Scientist.

IITR RESEARCH HIGHLIGHTS

Differential expression of cholecystokinin a receptor in gallbladder cancer in the young and elderly suggests two subsets of the same disease?

[Kazmi HR, Chandra A, Baghel K, Singh A, Nigam J, Parmar D, Mahdi AA, Goel SK, Kumar S. . Biomed Res Int. 2014;2014:625695]

Cholecystokinin type A receptor (CCKAR) is known to be overexpressed in variety of human malignancies but information regarding its expression in gallbladder cancer (GBC) is limited. Attempts were now made to investigate expression pattern of CCKAR mRNA and protein in controls and GBC patients and correlate it with various clinicopathological parameters following surgical resection. Gallbladder tissue samples from 64 subjects (GBC: 39; control: 25) were studied. Expression of CCKAR mRNA was evaluated by reverse transcriptase-polymerase chain reaction and confirmed using real-time polymerase chain reaction. Protein expression was studied by enzyme-linked immunosorbent assay. Significantly higher expression of CCKAR mRNA ($P < 0.0001$) and protein ($P < 0.0001$) was observed in GBC tissues. Overexpression was also observed for stage III and in moderately and poorly differentiated tumors. When the clinicopathological parameters were compared, authors found age dependent decrease in CCKAR expression. Relatively higher expression of CCKAR was observed in younger patients (age < 45 years) having more aggressive disease when compared with elderly ones (age ≥45 years). Age related differential expression of CCKAR in GBC may suggest two possible variants of the disease in this endemic belt.

Isolation and functional analysis of a glycolipid producing Rhodococcus sp. strain IITR03 with potential for degradation of 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT)

[Bajaj A, Mayilraj S, Mudiam MK, Patel DK, Manickam N. Bioresour Technol. 2014;167:398-406]

A 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT) degrading bacterium strain IITR03 producing trehalolipid was isolated and characterized from a pesticides contaminated soil. The strain IITR03 was identified as a member of the genus Rhodococcus based on polyphasic

studies. Under aqueous culture conditions, the strain IITR03 degraded 282µM of DDT and could also utilize 10mM concentration each of 4-chlorobenzoic acid, 3-chlorobenzoic acid and benzoic acid as sole carbon and energy source. The catechol 1,2-dioxygenase enzyme activity resulted in conversion of catechol to form cis,cis-muconic acid. Cloning and sequencing of partial nucleotide sequence of catechol 1,2-dioxygenase gene (cat) from strain IITR03 revealed its similarity to catA gene present in Rhodococcus sp. strain Lin-2 (97% identity) and Rhodococcus strain AN22 (96% identity) degrading benzoate and aniline, respectively. The results suggest that the strain IITR03 could be useful for field bioremediation studies of DDT-residues and chlorinated aromatic compounds present in contaminated sites.

Promoter region hypermethylation and MRNA expression of MGMT and p16 genes in tissue and blood samples of human premalignant oral lesions and oral squamous cell carcinoma.

[Bhatia V, Goel MM, Makker A, Tewari S, Yadu A, Shilpi P, Kumar S, Agarwal SP, Goel SK. Biomed Res Int. 2014;2014:248419]

Promoter methylation and relative gene expression of O(6)-methyguanine-DNA-methyltransferase (MGMT) and p16 genes were examined in tissue and blood samples of patients with premalignant oral lesions (PMOLs) and oral squamous cell carcinoma (OSCC). Methylation-specific PCR and reverse transcriptase PCR were performed in 146 tissue and blood samples from controls and patients with PMOLs and OSCC. In PMOL group, significant promoter methylation of MGMT and p16 genes was observed in 59% (P = 0.0010) and 57% (P = 0.0016) of tissue samples, respectively, and 39% (P = 0.0135) and 33% (P = 0.0074) of blood samples, respectively. Promoter methylation of both genes was more frequent in patients with OSCC, that is, 76% (P = 0.0001) and 82% (P = 0.0001) in tissue and 57% (P = 0.0002) and 70% (P = 0.0001) in blood, respectively. Significant down regulation of MGMT and p16 mRNA expression was observed in both tissue and blood samples from patients with PMOLs and OSCC. Hypermethylation-induced transcriptional silencing of MGMT and p16 genes in both precancer and cancer suggests important role of these changes in progression of premalignant state to malignancy. Results support use of blood as potential surrogate to tissue samples for screening or diagnosing PMOLs and early OSCC.

Cerium oxide nanoparticles induced toxicity in human lung cells: role of ROS mediated dna damage and apoptosis.

[Mittal S, Pandey AK. Biomed Res Int. 2014; 2014: 891934].

Cerium oxide nanoparticles (CeO_2 NPs) have promising industrial and biomedical applications. In spite of their applications, the toxicity of these NPs in biological/physiological environment is a major concern. Present study aimed to understand the molecular mechanism underlying the toxicity of CeO_2 NPs on lung adenocarcinoma (A549) cells. After internalization, CeO_2 NPs caused significant cytotoxicity and morphological changes in A549 cells. Further, the cell death was found to be apoptotic as shown by loss in mitochondrial membrane potential and increase in annexin-V positive cells and confirmed by immunoblot analysis of BAX, BCl-2, Cyt C, AIF, caspase-3, and caspase-9. A significant increase in oxidative DNA damage was found which was confirmed by phosphorylation of p53 gene and presence of cleaved poly ADP ribose polymerase (PARP). This damage could be attributed to increased production of reactive oxygen species (ROS) with concomitant decrease in antioxidant "glutathione (GSH)" level. DNA damage and cell death were attenuated by the application of ROS and apoptosis inhibitors N-acetyl-L- cysteine (NAC) and Z-DEVD-fmk, respectively. Present study concludes that ROS mediated DNA damage and cell cycle arrest play a major role in CeO_2 NPs induced apoptotic cell death in A549 cells. Apart from beneficial applications, these NPs also impart potential harmful effects which should be properly evaluated prior to their use.

Hepatic transcriptional analysis in rats treated with *Cassia occidentalis* seed: Involvement of oxidative stress and impairment in xenobiotic metabolism as a putative mechanism of toxicity.

[Panigrahi GK, Yadav A, Yadav A, Ansari KM, Chaturvedi RK, Vashistha VM, Raisuddin S, Das M. Toxicol Lett. 2014;229:273-83].

The present study was undertaken to investigate the effect of *Cassia occidentalis* (CO) seeds on the transcriptional expression patterns of mRNAs in rat liver by microarray analysis. The results indicated that exposure of CO (0.5%) seeds in diet to rats differentially regulated 60 transcripts belonging to various metabolic pathways including, oxidative stress, xenobiotic metabolism, carbohydrate metabolism, cell cycle, apoptosis etc. The expression of AKT1, CAT, SOD1, CYP1A1, CYP2B1, TGF-β, BAX, CREB1, JNK1 and IL-6 were validated by the qRT-PCR. In addition, involvement of oxidative stress was observed due to marked depletion of glutathione, increase in lipid peroxidation and modulation of antioxidant enzymes in hepatic tissue of rats treated with 0.5-2.0% CO in diet. Furthermore, significant decrease in the levels of Phase 1 (EROD, MROD and PROD) and Phase 2 (QR and GST) enzymes following 0.5-2.0% CO exposure indicates the impairment

of xenobiotic metabolism and possible accumulation of toxic ingredients of the seeds in liver. Overall, the study predicts the involvement of multiple pathways and related biomolecules in CO induced hepatotoxicity and the data may be useful in formulating strategies for therapeutic interventions of suspected CO poisoning study cases.

Identification of Drosophila-based endpoints for the assessment and understanding of xenobiotic-mediated male reproductive adversities.

[Misra S, Singh A, Ratnasekhar CH, Sharma V, Mudiam MK, Ravi Ram K. Toxicol Sci. 2014; 141:278-91.]

Men are at risk of becoming completely infertile due to innumerable environmental chemicals and pollutants. These xenobiotics, hence, should be tested for their potential adverse effects on male fertility. However, the testing load, a monumental challenge for employing conventional animal models, compels the pursuit of alternative models. Towards this direction, authors show here that *Drosophila melanogaster*, an invertebrate, with its well characterized/conserved male reproductive processes/proteome, recapitulates male reproductive toxicity phenotypes observed in mammals when exposed to a known reproductive toxicant, dibutyl phthalate (DBP). Analogous to mammals, exposure to DBP reduced fertility, sperm counts, seminal proteins, increased oxidative modification/damage in reproductive tract proteins and altered the activity of a hormone receptor (estrogen related receptor) in Drosophila males. In addition, authors show here that DBP is metabolized to monobutyl phthalate (MBP) in exposed Drosophila males and that MBP is more toxic than DBP, as observed in higher organisms. These findings suggest Drosophila as a potential alternative to traditional animal models for the prescreening of chemicals for their reproductive adversities and also to gain mechanistic insights into chemical-mediated endocrine disruption and male infertility.

Unraveling the mechanism of neuroprotection of curcumin in arsenic induced cholinergic dysfunctions in rats.

[Srivastava P, Yadav RS, Chadravanshi LP, Shukla RK, Dhuriya YK, Chauhan LK, Dwivedi HN, Pant AB, Khanna VK. Toxicol Appl Pharmacol. 2014 ; pii: S0041-008X(14)00229-4.]

Earlier, authors found that arsenic induced cholinergic deficits in rat brain could be protected by curcumin. In continuation to this, the present study is focused to unravel the molecular mechanisms associated with the protective efficacy of curcumin in arsenic induced cholinergic deficits. Exposure to arsenic (20mg/kg body weight, p.o) for 28days in rats resulted to decrease the expression of CHRM2 receptor gene associated with mitochondrial dysfunctions as evident by decrease in the mitochondrial membrane potential, activity of mitochondrial complexes and enhanced apoptosis both in the frontal cortex and hippocampus in comparison to controls. The ultrastructural images of arsenic exposed rats, assessed by transmission electron microscope, exhibited loss of myelin sheath and distorted cristae in the mitochondria both in the frontal cortex and hippocampus as compared to controls. Simultaneous treatment with arsenic (20mg/kg body weight, p.o) and curcumin (100mg/kg body weight, p.o) for 28days in rats was found to protect arsenic induced changes in the mitochondrial membrane potential and activity of mitochondrial complexes both in frontal cortex and hippocampus. Alterations in the expression of pro- and anti-apoptotic proteins and ultrastructural damage in the frontal cortex and hippocampus following arsenic exposure were also protected in rats simultaneously treated with arsenic and curcumin. The data of the present study reveal that curcumin could protect arsenic induced cholinergic deficits by modulating the expression of pro- and anti-apoptotic proteins in the brain. More interestingly, arsenic induced functional and ultrastructural changes in the brain mitochondria were also protected by curcumin.

Deoxynivalenol induced mouse skin cell proliferation and inflammation via MAPK pathway.

[Mishra S, Tripathi A, Chaudhari BP, Dwivedi PD, Pandey HP, Das M. Toxicol Appl Pharmacol. 2014;279:186-197]

Several toxicological manifestations of deoxynivalenol (DON), a mycotoxin, are well documented; however, dermal toxicity is not yet explored. The effect of topical application of DON to mice was studied using markers of skin proliferation, inflammation and tumor promotion. Single topical application of DON (84-672nmol/mouse) significantly enhanced dermal hyperplasia and skin edema. DON (336 and 672nmol) caused significant enhancement in [3H]-thymidine uptake in DNA along with increased myeloperoxidase and ornithine decarboxylase activities, suggesting tissue inflammation and cell proliferation. Furthermore, DON (168nmol) caused enhanced expression of RAS, and phosphorylation of PI3K/Akt, ERK, JNK and p38 MAPKs. DON exposure also showed activation of transcription factors, c-fos, c-jun and NF-κB along with phosphorylation of IkBα. Enhanced phosphorylation of NF-κB by DON caused over expression of target proteins, COX-2, cyclin D1 and iNOS in skin. Though a single topical application of DMBA followed by twice weekly application of DON (84 and 168nmol) showed no tumorigenesis after 24weeks, however, histopathological studies suggested hyperplasia of the epidermis and hypertrophy of hair

follicles. Interestingly, intestine was also found to be affected as enlarged Peyer's patches were observed, suggesting inflammatory effects which were supported by elevation of inflammatory cytokines after 24weeks of topical application of DON. These results suggest that DON induced cell proliferation in mouse skin is through the activation of MAPK signaling pathway involving transcription factors NFκB and AP-1, further leading to transcriptional activation of downstream target proteins c-fos, c-jun, cyclin D1, iNOS and COX-2 which might be responsible for its inflammatory potential.

Biocatalytic and antimicrobial activities of gold nanoparticles synthesized by Trichoderma sp.

[Mishra A, Kumari M, Pandey S, Chaudhry V, Gupta KC, . Bioresour Technol. 2014;166:235-42].

The aim of this work was to synthesize gold nanoparticles by *Trichoderma viride* and *Hypocrea lixii*. The biosynthesis of the nanoparticles was very rapid and took 10min at 30°C when cell-free extract of the *T. viride* was used, which was similar by *H. lixii* but at 100°C. Biomolecules present in cell free extracts of both fungi were capable to synthesize and stabilize the formed particles. Synthesis procedure was very quick and environment friendly which did not require subsequent processing. The biosynthesized nanoparticles served as an efficient biocatalyst which reduced 4-nitrophenol to 4-aminophenol in the presence of $NaBH_4$ and had antimicrobial activity against pathogenic bacteria. To the best of our knowledge, this is the first report of such rapid biosynthesis of gold nanoparticles within 10min by Trichoderma having plant growth promoting and plant pathogen control abilities, which served both, as an efficient biocatalyst, and a potent antimicrobial agent.

Mammalian cell-transforming potential of traffic-linked ultrafine particulate matter PM0.056 in urban roadside atmosphere.

[Verma MK, , Sultana S, Kumar S. Mutagenesis. 2014; 29:335-40.]

Authors examined the clastogenic and cell-transforming potential of ultrafine particulate matter fraction PM0.056 of urban ambient aerosol using mammalian cells. PM1.0, PM0.56 and PM0.056 fractions were sampled from roadside atmosphere of an urban area using the cascade impactor MOUDI-NR-110. The potential to induce cytotoxicity, DNA damage and micronuclei formation was examined at the test concentrations of 3, 6, 12.5, 25, 50 and 100 µg/ml using the 3-4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, the plasmid relaxation assay and the C3H10T1/2 (10T1/2) cells. The cell-transforming potential was investigated *in vitro* using 10T1/2 cell transformation assay and the soft agar assay. PM1, PM0.56 and PM0.056 fractions were found to be toxic in dose-dependent manner. These induced cytotoxicity at five test concentrations, the ultrafine particle fraction PM0.056 showed greater cytotoxic potential. PM0.056 induced micronucleus formation in 10T1/2 cells. The effect was statistically significant. The DNA-damaging potential was measured in a plasmid relaxation assay. Both fine and ultrafine particle fraction PM0.56 and PM0.056 displayed greater effect as compared to larger PM1 fraction. DNA damage was found to be dependent on particulate matter intrinsic pro-oxidant chemicals. The ability of the ultrafine particle fraction PM0.056 to induce morphological cell transformation was demonstrated by significant and dose-dependent increases in type III focus formation by morphologically transformed cells in culture flasks and their clonal expansion in soft agar. It is concluded that the traffic-linked ultrafine particle fraction PM0.056 in the atmosphere by the roadside of an urban area is clastogenic and able to induce morphological transformation of mammalian cells.

Differential susceptibility of brain regions to tributyltin chloride toxicity.

[Mitra S, Siddiqui WA, Khandelwal S. Environ Toxicol. 2014; doi: 10.1002/tox.22009.]

Tributyltin (TBT), a well-known endocrine disruptor, is an omnipresent environmental pollutant and is explicitly used in many industrial applications. Previously authors have shown its neurotoxic potential on cerebral cortex of male Wistar rats. As the effect of TBT on other brain regions is not known, authors planned this study to evaluate its effect on four brain regions (cerebellum, hippocampus, hypothalamus, and striatum). Four-week-old male Wistar rats were gavaged with a single dose of TBT-chloride (TBTC) (10, 20, and 30 mg/kg) and sacrificed on days 3 and 7, respectively. Effect of TBTC on blood-brain barrier (BBB) permeability and tin (Sn) accumulation were measured. Oxidative stress indexes such as reactive oxygen species (ROS), reduced and oxidized glutathione (GSH/GSSG) ratio, lipid peroxidation, and protein carbonylation were analyzed as they play an imperative role in various neuropathological conditions. Since metal catalyzed reactions are a major source of oxidant generation, levels of essential metals like iron (Fe), zinc (Zn), and calcium (Ca) were estimated. Authors found that TBTC disrupted BBB and increased Sn accumulation, both of which appear significantly correlated. Altered metal homeostasis and ROS generation accompanied by elevated lipid peroxidation and protein carbonylation indicated oxidative damage which appeared more pronounced in the striatum than in

cerebellum, hippocampus, and hypothalamus. This could be associated to the depleted GSH levels in striatum. These results suggest that striatum is more susceptible to TBTC induced oxidative damage as compared with other brain regions under study.

Heat shock protein-70 (Hsp-70) suppresses paraquat-induced neurodegeneration by inhibiting JNK and caspase-3 activation in Drosophila model of Parkinson's disease.

[Shukla AK, Pragya P, Chaouhan HS, Tiwari AK, Patel DK, Abdin MZ, Chowdhuri DK. PLoS One. 2014;9:e98886.]

Parkinson's disease (PD) is one of the most common neurodegenerative disorders with limited clinical interventions. A number of epidemiological as well as case-control studies have revealed an association between pesticide exposure, especially of paraquat (PQ) and occurrence of PD. Hsp70, a molecular chaperone by function, has been shown as one of the modulators of neurological disorders. However, paucity of information regarding the protective role of Hsp70 on PQ-induced PD like symptoms led us to hypothesize that modulation of hsp70 expression in the dopaminergic neurons would improve the health of these cells. Authors took advantage of Drosophila, which is a well-established model for neurological research and also possesses genetic tools for easy manipulation of gene expression with limited ethical concern. Over-expression of hsp70 was found to reduce PQ-induced oxidative stress along with JNK and caspase-3 mediated dopaminergic neuronal cell death in exposed organism. Further, anti-apoptotic effect of hsp70 was shown to confer better homeostasis in the dopaminergic neurons of PQ-exposed organism as evidenced by their improved locomotor performance and survival. The study has merit in the context of human concern since authors observed protection of dopaminergic neurons in PQ-exposed organism by over-expressing a human homologue of hsp70, HSPA1L, in these cells. The effect was parallel to that observed with Drosophila hsp70. These findings reflect the potential therapeutic applicability of hsp70 against PQ-induced PD like symptoms in an organism.

Cypermethrin induces astrocyte damage: Role of aberrant Ca(2+), ROS, JNK, P38, matrix metalloproteinase 2 and migration related reelin protein.

[Maurya SK, Mishra J, Tripathi VK, Sharma R, . Pestic Biochem Physiol. 2014;111:51-9.]

Cypermethrin is a synthetic type II pyrethroid, derived from a natural pyrethrin of the chrysanthemum plant. Cypermethrin-mediated neurotoxicity is well studied; however, relatively less is known of its effect on astrocyte development and migration. Astrocytes are the major components of blood brain barrier (BBB), and astrocyte damage along with BBB dysfunction impair the tight junction (TJ) proteins resulting in altered cell migration and neurodegeneration. Here, authors studied the mechanism of cypermethin mediated rat astrocyte damage and BBB disruption, and determined any change in expression of proteins associated with cell migration. Through MTT assay authors found that cypermethrin reduced viability of cultured rat astrocytes. Immunolabelling with astrocyte marker, glial fibrillary acidic protein, revealed alteration in astrocyte morphology. The astrocytes demonstrated an enhanced release of intracellular Ca(++) and ROS, and up-regulation in p-JNK and p-P38 levels in a time-dependent manner. Cypermethrin disrupted the BBB (*in vivo*) in developing rats and attenuated the expression of the extracellular matrix molecule (ECM) and claudin-5 in cultured astrocytes. Authors further observed an augmentation in the levels of matrix metalloproteinase 2 (MMP2), known to modulate cellular migration and disrupt the developmental ECM and BBB. Authors observed an increase in the levels of reelin, involved in cell migration, in cultured rat astrocytes. The reelin receptor, α3β1integrin, and a mammalian cytosolic protein Disabled1 (Dab1) were also up-regulated. Overall, study demonstrates that cypermethrin induces astrocyte injury via modulation in Ca(++), ROS, JNK and P38 pathways, which may alter MMP expression and reelin dependent astrocyte migration during brain development.

Differentiating neurons derived from human umbilical cord blood stem cells work as a test system for developmental neurotoxicity.

[Kashyap MP, Kumar V, Singh AK, Tripathi VK, Jahan S, Pandey A, Srivastava RK, Khanna VK, Pant AB. Mol Neurobiol. 2014 ; doi:10.1007/s12035-014-8716-7]

Differentiating neuronal cells derived from human umbilical cord blood stem cells have been used as an *in vitro* tool for the assessment of developmental neurotoxicity of monocrotophos (MCP), an organophosphate pesticide. The differentiating cells were exposed to MCP during the different stages of maturation, viz., days 2, 4, and 8, and changes in the makers of cell proliferation, neuronal differentiation, neuronal injuries, and receptors were studied. Authors found significant upregulation in the different MAPKs, apoptosis, and neurogenesis markers and downregulation in the cell proliferation markers during neuronal differentiation. Authors further identified significant upregulation in the expression of different MAPKs and proteins involved in oxidative stress, apoptosis, and calpain pathways in the mid-differentiating cells exposed to MCP. The

upregulated levels of these proteins seem to be the main cause of alteration during the differentiation process towards apoptosis as a fine-tune of pro-apoptotic and anti-apoptotic proteins are desirable for the process of differentiation without apoptosis. The decreased acetylcholinesterase activity, dopaminergic, and cholinergic receptors and increased acetylcholine levels in the differentiating neuronal cells indicate the vulnerability of these cells towards MCP-induced neurotoxicity. Data confirms that differentiating neuronal cells derived from human umbilical cord stem cells could be used as a powerful tool to assess the developmental neurotoxicity in human beings.

Regioselective synthesis of polycyclic aza-oxa and aza-oxa-thia heteroarenes as Colo-205 and HepG2 carcinoma cells growth inhibitors.

[Maurya HK, Gautam SK, Pratap R, Tandon VK, Kumar A, Kumar B, Saxena S, Tripathi D, Rajwanshi M, Das M, Ram VJ. Eur J Med Chem. 2014;81:367-77.]

An efficient regioselective synthesis of polycyclic diheteroaryl[b,d]pyrans and diheteroaryl [c,e][1,2] diazepines has been reported through ring transformation reactions of 2-oxo-2,5-dihydrothio-chromeno [4,3-b]pyrans (3,4), 2-oxo-5,6-dihydro-2H-benzo[b]pyrano[2,3-d]oxepine/thiepine (8, 9) and 6-oxo-3,6-dihydro-2H-naphtho [1,2-b]pyrano [2,3-d]oxepine (15) by hydrazine, at ambient and reflux temperature. Nine compounds viz 5a,b; 10a,c,d; 12b; 13b; 16 and 1-methylthio-5,6-dihydrobenzo[f]quinoline (0.1-100 µM) were screened for their cytotoxicity in normal (IEC-6), carcinoma (Colo-205) and HepG2 cell lines. None of the compounds showed cytotoxicity in normal IEC-6 cells while 10a,d and 16 resulted in killing of Colo-205 cells with IC50 ranging 20-60 µM while 10c and 13b caused killing of HepG2 cells with IC50 values ranging 60-80 µM concentration. Further, 10a,d and 16 caused apoptosis through a cascade of mitochondrial pathway in Colo-205 cells indicating anticancerous potential against intestinal cancer. Interestingly, compounds 10c and 13b exhibited apoptosis through mitochondrial pathway in HepG2 cells suggesting anticancer activity against hepatic cancer.

Aberrant autophagy and Parkinsonism: Does correction rescue from disease progression?

[Mishra AK, Ur Rasheed MS, Shukla S, Tripathi MK, Dixit A, Singh MP. Mol Neurobiol. 2014; doi:10.1007/s12035-014-8744-3]

Information generated from animal models, genome sequencing, and high-throughput technologies provide valuable sequence of events to understand the Parkinson's disease (PD) pathogenesis. A dynamic equilibrium between biosynthesis and biodegradation of sub-cellular components by ubiquitin proteasome system and autophagy is found to be responsible for sustaining the homeostasis of tyrosine hydroxylase-positive neurons. Autophagy degrades and eliminates α-synuclein, Parkin, ubiquitin, etc., proteins along with damaged cellular components to maintain the homeostasis of the nigrostriatal dopaminergic neurons. Aberrant type II apoptosis is widely implicated in dopaminergic neurodegeneration leading to PD. The current article reviews the elementary role of autophagy in the degradation and elimination of superfluous and aggregated proteins and impaired mitochondria. The article also recapitulates the information, which implicated the role of aberrant autophagy in toxin-induced Parkinsonism. Moreover, the review sheds light on whether or not targeting the defective autophagy could reinstate the normal functioning of dopaminergic neurons, which could ultimately rescue from PD pathogenesis.

Galactomannan-PEI based non-viral vectors for targeted delivery of plasmid to macrophages and hepatocytes.

[Bansal R, Singh AK, Gandhi RP, Pant AB, Kumar P, Gupta KC. Eur J Pharm Biopharm. 2014;87:461-71.]

Intracellular nature and diversified locations of infectious and parasitic diseases such as leishmaniasis, trypanosomiasis, tuberculosis and hepatitis B and C pose a significant global burden and challenge to the scientists working in the area of drug discovery and drug delivery. The macrophages and hepatocytes are considered as potential target sites as they together play an important role in various infectious diseases. The present study scrutinizes the applicability of a natural biopolymer-based chemical vectors, capable of targeting both macrophages and hepatocytes, that can form a complex with plasmid and administer it into cells to produce a desired protein. The investigations were made to develop a novel series of gene carriers by conjugating depolymerized galactomannan (guar gum), a biocompatible polysaccharide with low molecular weight branched PEI (LMWP). A series of conjugates were developed and characterized using physicochemical techniques. All the GP/pDNA complexes showed significantly higher transfection efficiency with GP-3/pDNA, one of the best formulations, showed 2.0-7.7-folds higher transfection efficacy when compared with the standard transfection reagents. Further, GP-3/pDNA displayed significantly higher target specific transfection efficiency under both *in vitro* and *in vivo* conditions. The data demonstrate the potential of GP vectors to deliver nucleic acids simultaneously to macrophages and hepatocytes in gene delivery applications.

Cytogenomics of hexavalent chromium (Cr 6+) exposed cells: a comprehensive review.

[Nigam A, Priya S, Bajpai P, Kumar S1. Indian J Med Res. 2014;139:349-70.]

The altered cellular gene expression profile is being hypothesized as the possible molecular basis navigating the onset or progress of various morbidities. This hypothesis has been evaluated here in respect of Cr 6+ induced toxicity. Several studies using gene microarray show selective and strategic dysregulations of cellular genes and pathways induced by Cr 6+. Relevant literature has been reviewed to unravel these changes in different test systems after exposure to Cr 6+ and also to elucidate association if any, of the altered cytogenomics with Cr 6+ induced toxicity or carcinogenicity. The aim was to verify the hypothesis for critical role of altered cytogenomics in onset of Cr 6+ induced biological/clinical effects by identifying genes modulated commonly by the toxicant irrespective of test system or test concentrations/doses, and by scrutinizing their importance in regulation of the flow of mechanistically linked events crucial for resultant morbidities. Their probability as biomarkers to monitor the toxicant induced biological changes is speculative. The modulated genes have been found to cluster under the pathways that manage onset of oxidative stress, DNA damage, apoptosis, cell-cycle regulation, cytoskeleton, morphological changes, energy metabolism, biosynthesis, oncogenes, bioenergetics, and immune system critical for toxicity. In these studies, the identity of genes has been found to differ remarkably; albeit the trend of pathways' dysregulation has been found to remain similar. Authors conclude that the intensity of dysregulation of genes or pathways involved in mechanistic events forms a sub-threshold or threshold level depending upon the dose and type (including speciation) of the toxicant, duration of exposure, type of target cells, and niche microenvironment of cells, and the intensity of sub-threshold or threshold level of the altered cytogenomics paves way in toxicant exposed cells eventually either to opt for reversal to differentiation and growth, or to result in toxicity like dedifferentiation and apoptosis, respectively.

A mutation in Drosophila methuselah resists paraquat induced Parkinson-like phenotypes.

[Shukla AK, Pragya P, , Patel DK, Abdin MZ, Kar Chowdhuri D. 2014 Oct;35:2419.e1-2419.e16.]

Parkinson's disease (PD) is a prevalent and devastating neurodegenerative disorder having limited cure options and strong association with the loss of dopaminergic neurons in the substantia nigra region of the mid brain. Etiology of PD includes both genetic and environmental factors. Paraquat (PQ), a widely used herbicide, is known to be associated with pathogenesis of PD. Authors report that a mutation in *Drosophila methuselah* (mth(1)), which is associated with aging, has a role in preventing dopaminergic neuronal cell death in PQ-exposed organism. Exposed mth(1) flies exhibit significant resistance against PQ-induced Parkinson's phenotypes and behavior in terms of oxidative stress, dopaminergic neuronal degeneration, locomotor performance, dopamine content, phosphorylated JNK, pFOXO, Hid, and cleaved caspase-3 levels. Conversely, over-expression of mth in dopaminergic neurons makes the exposed organism more vulnerable to oxidative stress, neuronal cell death, and behavioral deficit. The study suggests that lesser activation of JNK-mediated apoptosis in dopaminergic neurons of exposed mth(1) flies protects the organism from PQ-induced damage, which may be causally linked to a common mechanism for PQ-induced neurodegeneration.

Diethyl maleate inhibits MCA+TPA transformed cell growth via modulation of GSH, MAPK, and cancer pathways.

[Priya S, Nigam A, Bajpai P, Kumar S. Chem Biol Interact. 2014;219C:37-47.]

Murine or human cancer cells have high glutathione levels. Depletion of the elevated GSH inhibits proliferation of cancer cells. Molecular basis for this observation is little understood. In an attempt to find out the underlying mechanism, authors reproduced these effects in transformed C3H10T1/2 and BALB/c 3T3 cells using diethyl maleate and studied cytogenomic changes in the whole mouse genome using spotted 8×60K arrays. Transformed cells revealed an increase in GSH levels. GSH depletion by DEM inhibited the growth of transformed cells. The non-cytotoxic dose of DEM (0.25mM) resulted in GSH depletion, ROS generation, cell cycle arrest, apoptosis, decrease in anchorage independent growth, gene expression changes and activation of all three members of the MAPK family. Increase in intracellular GSH levels by GSHe countered the effect of DEM. These results support the physiological importance of GSH in regulation of gene expression for transformed cell growth restraint. This study is of interest in not only understanding the molecular biology of the transformed cells, but also in identifying new targets for development of gene therapy together with the chemotherapy.

Determination of 17 organophosphate pesticide residues in mango by modified QuEChERS extraction method using GC-NPD/GC-MS and hazard index estimation in Lucknow, India.

[Srivastava AK, Rai S, Srivastava MK, Lohani M, Mudiam MK, Srivastava LP. PLoS One. 2014 May 8;9(5):e96493.]

A total of 162 samples of different varieties of mango: Deshehari, Langra, Safeda in three growing stages (Pre-mature, Unripe and Ripe) were collected from Lucknow, India, and analyzed for the presence of seventeen organophosphate pesticide residues. The QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) method of extraction coupled with gas chromatography was validated for pesticides and qualitatively confirmed by gas chromatography-mass spectrometry. The method was validated with different concentrations of mixture of seventeen organophosphate pesticides (0.05, 0.10, 0.50 mg kg(-1)) in mango. The average recovery varied from 70.20% to 95.25% with less than 10% relative standard deviation. The limit of quantification of different pesticides ranged from 0.007 to 0.033 mg kg(-1). Out of seventeen organophosphate pesticides only malathion and chlorpyriphos were detected. Approximately 20% of the mango samples have shown the presence of these two pesticides. The malathion residues ranged from ND-1.407 mg kg(-1) and chlorpyriphos ND-0.313 mg kg(-1) which is well below the maximum residues limit (PFA-1954). In three varieties of mango at different stages from unpeeled to peeled sample reduction of malathion and chlorpyriphos ranged from 35.48%-100% and 46.66%-100% respectively. The estimated daily intake of malathion ranged from 0.032 to 0.121 µg kg(-1) and chlorpyriphos ranged from zero to 0.022 µg kg(-1) body weight from three different stages of mango. The hazard indices ranged from 0.0015 to 0.0060 for malathion and zero to 0.0022 for chlorpyriphos. It is therefore indicated that seasonal consumption of these three varieties of mango may not pose any health hazards for the population of Lucknow, city, India because the hazard indices for malathion and chlorpyriphos residues were below to one.

Modulation of miR-203 and its regulators as a function of time during the development of 7, 12 dimethylbenz [a] anthracene induced mouse skin tumors in presence or absence of the antitumor agents.

[Tiwari P, Gupta KP. Toxicol Appl Pharmacol. 2014;278:148-58.]

Authors investigated the chemopreventive effects of naturally occurring compounds like butyric acid (BA), nicotinamide (NA) and calcium glucarate (CAG) individually or in combination in 7, 12-dimethylbenz [a] anthracene (DMBA) treated mouse skin at 4 and 16 weeks, the time before and after the tumor development. DMBA application did not show any skin tumors at 4 weeks but well defined tumors appeared at 16 weeks. BA, NA or CAG prevented the tumor development significantly but the protection was highly enhanced when all these compounds were given together. In order to see the molecular changes progressing with tumors, authors showed the downregulation of tumor suppressor miR-203 at 16 weeks and upregulation of histone deacetylases (HDAC), DNA methyltransferase, promoter methylation of miR-203 at 4 or 16 weeks. Regulators of micro RNA biogenesis such as DICER1 and Ago2 were also deregulated by DMBA. Proto-oncogene c-myc and BMI1 were upregulated and tumor suppressor gene p16 was downregulated by DMBA as a function of time. Effects of BA, NA or CAG were more pronounced after 16 weeks as compared to 4 weeks in preventing the tumor development and altered gene expression. Concomitant administration of BA, NA and CAG tried to prevent these alterations more effectively than that of individual compound possibly by regulating miR-203 status through epigenetic or biogenetic modulations before and after the tumor development. Study provides a rationale for chemoprevention by combination of different compounds targeting miR-203.

Characterization of the effect of Cr(VI) on humoral innate immunity using *Drosophila melanogaster.*

[Pragya P, Shukla AK, Murthy RC, Abdin MZ, Kar Chowdhuri D. Environ Toxicol. 2014;doi: 10.1002/ tox. 21999.]

With the advancement of human race, different anthropogenic activities have heaped the environment with chemicals that can cause alteration in the immune system of exposed organism. As a first line of barrier, the evolutionary conserved innate immunity is crucial for the health of an organism. However, there is paucity of information regarding *in vivo* assessment of the effect of environmental chemicals on innate immunity. Therefore, authors examined the effect of a widely used environmental chemical, Cr(VI), on humoral innate immune response using *Drosophila melanogaster*. The adverse effect of Cr(VI) on host humoral response was characterized by decreased gene expression of antimicrobial peptides (AMPs) in the exposed organism. Concurrently, a significantly decreased transcription of humoral pathway receptors (Toll and PGRP) and triglyceride level along with inhibition of antioxidant enzyme activities were observed in exposed organism. This in turn weakened the immune response of exposed organism that was manifested by their reduced resistance against bacterial infection. In addition, overexpression of the components of humoral immunity particularly Diptericin benefits Drosophila from Cr(VI)-induced humoral immune-suppressive effect. To the knowledge of

authors, this is the first report regarding negative impact of an environmental chemical on humoral innate immune response of Drosophila along with subsequent protection by AMPs, which may provide novel insight into host-chemical interactions. Also, data validate the utility and sensitivity of Drosophila as a model that could be used for screening the possible risk of environmental chemicals on innate immunity with minimum ethical concern that can be further extrapolated to higher organisms.

CYP2E1-mediated oxidative stress regulates HO-1 and GST expression in maneb- and paraquat-treated rat polymorphonuclear leukocytes.

[Ahmad I, Shukla S, Singh D, Chauhan AK, , Singh BK, Patel DK, Pandey HP, Singh C. Mol Cell Biochem. 2014;393:209-22.]

Cytochrome P4502E1 (CYP2E1), glutathione-S-transferase A4-4 (GSTA4-4), and inducible nitric oxide synthase (iNOS) are implicated in maneb- and paraquat-induced toxicity leading to various pathological conditions. The study aimed to investigate the role of CYP2E1 in maneb- and paraquat-induced oxidative stress in rat polymorphonuclear leukocytes (PMNs) and its crosstalk with iNOS-mediated nitrosative stress and GSTA4-4-linked protective effect, if any and their consequent links with the nuclear factor erythoid 2-related factor 2 (Nrf2) activation and heme oxygenase-1 (HO-1) expression. Rats were treated with/without maneb and/or paraquat for 1, 2, and 3 weeks along with vehicle controls. Subsets of rats were also treated with diallyl sulfide (DAS) or aminoguanidine (AG) along with the respective controls. Maneb and paraquat augmented the reactive oxygen species (ROS), lipid peroxidation (LPO) and 4-hydroxy nonenal (4-HNE) contents, and superoxide dismutase (SOD) activity in the PMNs. However, maneb and paraquat attenuated the reduced glutathione (GSH) level and the expression/activity of total GST and GST-pi. Maneb and paraquat increased the expression/activity of CYP2E1, GSTA4-4, iNOS, Nrf2 and HO-1, and nitrite content. CYP2E1 inhibitor, DAS noticeably alleviated maneb- and paraquat-induced ROS, LPO, 4-HNE, SOD, Nrf2 and HO-1, GST, GSH, and GST-pi while iNOS, nitrite content and GSTA4-4 levels were unchanged. Conversely, AG, an iNOS inhibitor, attenuated maneb- and paraquat-directed changes in nitrite, LPO, iNOS but it did not alter ROS, GSH, SOD, GST, GST-pi, Nrf2, HO-1, CYP2E1, and GSTA4-4. The results demonstrate that CYP2E1 induces iNOS-independent free radical generation and subsequently modulates the Nrf2-dependent HO-1 and 4-HNE-mediated GST expression in maneb- and paraquat-treated PMNs.

Early cellular responses against tributyltin chloride exposure in primary cultures derived from various brain regions.

[Mitra S, Siddiqui WA, Khandelwal S. Environ Toxicol Pharmacol. 2014;37:1048-59.]

Tributyltin (TBT) is a potent biocide and commonly used in various industrial sectors. Humans are mainly exposed through the food chain. Authors have previously demonstrated tin accumulation in brain following TBT-chloride (TBTC) exposure. In this study, effect of TBTC on dissociated cells from different brain regions was evaluated. Cytotoxicity assay (MTT), mode of cell death (Annexin V/PI assay), oxidative stress parameters (ROS and lipid peroxidation), reducing power of the cell (GSH), mitochondrial membrane potential (MMP) and intracellular Ca(2+) were evaluated to ascertain the effect of TBTC. Expression of glial fibrillary acidic protein (GFAP) was measured to understand the effect on astroglial cells. TBTC as low as 30 nM was found to reduce GSH levels, whereas higher doses of 300 and 3000 nM induced ROS generation and marked loss in cell viability mainly through apoptosis. Striatum showed higher susceptibility than other regions, which may have further implications on various neurological aspects.

Cypermethrin-Induced nigrostriatal dopaminergic neurodegeneration alters the mitochondrial function:A proteomics study.

[Agrawal S, Singh A, Tripathi P, Mishra M, Singh PK, Singh AP. Mol Neurobiol. 2014; doi:10.1007/s12035-014-8696-7]

Cypermethrin induces the slow and progressive degeneration of the nigrostriatal dopaminergic neurons in rats. Postnatal preexposure with low doses of cypermethrin is known to enhance the susceptibility of animals upon adulthood reexposure. The study was undertaken to delineate the role of mitochondria in cypermethrin-induced neurodegeneration. Indexes of dopaminergic neurodegeneration, microglial activation, and mitochondrial dysfunction and its proteome profile were assessed in controls and cypermethrin-treated rats. Cypermethrin increased nigral dopaminergic neurodegeneration and microglial activation while reduced mitochondrial membrane potential and complex I activity. Cypermethrin attenuated striatal dopamine content and differentially regulated the expressions of the nine striatal and ten nigral proteins. Western blot analyses showed that cypermethrin also increased c-Jun N-terminal kinase (JNK), caspase-3, tumor suppressor protein (p53), tumor necrosis factor-α (TNF-α), p38 mitogen-activated protein kinase (p38 MAPK), and heme oxygenase-1 (HO-1) expressions and reduced B cell lymphoma-2 protein (Bcl-2) expression. Syndopa and minocycline rescued from cypermethrin induced

augmentation in microglial activation and reductions in mitochondrial membrane potential and complex I activity, striatal dopamine content, and degeneration of nigral dopaminergic neurons. Syndopa and minocycline, respectively, modulated the expressions of four and six striatal and four and seven nigral proteins. Furthermore, they reinstated the expressions of JNK, caspase-3, Bcl-2, p53, p38 MAPK, TNF-α, and HO-1. The study demonstrates that cypermethrin induces mitochondrial dysfunction and alters mitochondrial proteome leading to oxidative stress and apoptosis, which regulate the nigrostriatal dopaminergic neurodegeneration.

New enlightenment of skin cancer chemopreve-ntion through phytochemicals: *In vitro* and *in vivo* studies and the underlying mechanisms.

[Singh M, Suman S, Shukla Y. Biomed Res Int. 2014;2014:243452. doi: 10.1155/2014/243452.]

Skin cancer is still a major cause of morbidity and mortality worldwide. Skin overexposure to ultraviolet irradiations, chemicals, and several viruses has a capability to cause severe skin-related disorders including immunosuppression and skin cancer. These factors act in sequence at various steps of skin carcinogenesis via initiation, promotion, and/or progression. These days cancer chemoprevention is recognized as the most hopeful and novel approach to prevent, inhibit, or reverse the processes of carcinogenesis by intervention with natural products. Phytochemicals have antioxidant, antimutagenic, anticarcinogenic, and carcinogen detoxification capabilities thereby considered as efficient chemopreventive agents. Considerable efforts have been done to identify the phytochemicals which may possibly act on one or several molecular targets that modulate cellular processes such as inflammation, immunity, cell cycle progression, and apoptosis. Till date several phytochemicals in the light of chemoprevention have been studied by using suitable skin carcinogenic *in vitro* and *in vivo* models and proven as beneficial for prevention of skin cancer. This revision presents a comprehensive knowledge and the main molecular mechanisms of actions of various phytochemicals in the chemoprevention of skin cancer.

Efficacy of crude extract of *Emblica officinalis* (amla) in arsenic-induced oxidative damage and apoptosis in splenocytes of mice

[Singh MK, Yadav SS, Yadav RS, Singh US, Shukla Y, Pant KK, Khattri S. Toxicol Int. 2014;21:8-17.]

Arsenic, an environmental contaminant naturally occurred in groundwater and has been found to be associated with immune-related health problems in humans. In view of increasing risk of arsenic exposure due to occupational and non-occupational settings, the present study has been focused to investigate the protective efficacy of amla against arsenic-induced spleenomegaly in mice. Arsenic exposures (3 mg/kg body weight p.o for 30 days) in mice caused an increase production of ROS (76%), lipid peroxidation (84%) and decrease in the levels of superoxide dismutase (53%) and catalase (54%) in spleen as compared to controls. Arsenic exposure to mice also caused a significant increase in caspases-3 activity (2.8 fold) and decreases cell viability (44%), mitochondrial membrane potential (47%) linked with apoptosis assessed by the cell cycle analysis (subG1-28.72%) and annexin V/PI binding in spleen as compared to controls. Simultaneous treatment of arsenic and amla (500 mg/kg body weight p.o for 30 days) in mice decreased the levels of lipid peroxidation (33%), ROS production (24%), activity of caspase-3 (1.4 fold), apoptosis (subG1 12.72%) and increased cell viability (63%), levels superoxide dismutase (80%), catalase (77%) and mitochondrial membrane potential (66%) as compared to mice treated with arsenic alone. Results of the present study indicate that the effect of arsenic is mainly due to the depletion of glutathione in liver associated with enhanced oxidative stress that has been found to be protected following simultaneous treatment of arsenic and amla.

Analysis of oxytocin in milk samples and intake pattern in different age groups of Indian population.

[Mishra M, Ali S, Das M. Toxicol Mech Methods. 2014;24:342-6.]

Oxytocin (OT) injections have been indiscriminately used to milk cattle in dairy industries. There is no study available regarding surveillance of OT in market milk samples. OT from milk samples was extracted by precipitation with trichloroacetic acid and passed through the solid phase extraction column. OT was eluted and evaporated to dryness under a gentle stream of nitrogen. The residue was either dissolved in milli Q water or buffer for analysis through HPLC or EIA. The intake assessment of OT through milk was assessed through the Food Frequency Recall method employing a Food Frequency Questionnaire. On the basis of milk consumption and the values of OT in milk, the actual intake of OT was calculated. In the present study, a total of 55 milk samples (39 milkman and 16 branded) were analyzed for occurrence of OT by EIA and UV-HPLC from different locations of Lucknow, Uttar Pradesh (India). OT contamination in milkman samples was found to be 21pg/mL to 18.9ng/mL with the mean value of 8.9ng/mL. The average daily intake of OT in terms of µg/day/person was highest (2.3-2.4µg/day/person) in 1-3-year age

group. Since there is no prescribed level of OT in milk and the intake of OT through this commodity is quite high there is need to implement regulatory laws so that non-physiological OT exposure may not occur in children which may have deleterious effects.

Essential role of PH domain and leucine-rich repeat protein phosphatase 2 in Nrf2 suppression via modulation of Akt/GSK3β/Fyn kinase axis during oxidative hepatocellular toxicity.

[Rizvi F, Shukla S, Kakkar P. Cell Death Dis. 2014;5:e1153.]

Instances of sustained oxidative activity have been shown to involve dysregulation of Nrf2-mediated transcriptional induction; however, mechanisms warranting Nrf2-repression remain unclear. In this study, using primary rat hepatocytes, authors have attempted to identify factors that may negatively influence Nrf2 survival pathway. Though studies indicate a conspicuous association between Akt and Nrf2, a confirmatory link between the two is unaddressed. On inhibiting PI3K/Akt pathway, authors observed compromised activities of antioxidant and detoxification enzymes culminating in oxidative cytotoxicity. This was accompanied by reduced nuclear retention of Nrf2 and its ARE binding affinity, increased Nrf2 ubiquitination and concurrent decline in its downstream targets. Moreover, Akt inhibition enhanced nuclear translocation as well as phosphorylation of Fyn kinase, an enzyme linked to Nrf2 degradation, by relieving GSK3β from phosphorylation-mediated repression. The involvement of Akt and Fyn kinase in influencing Nrf2 signaling was further confirmed in oxidatively stressed hepatocytes by using tert-butyl hydroperoxide (tBHP). tBHP-induced decrease in Nrf2 levels was associated with enhanced Fyn kinase phosphorylation, Fyn kinase nuclear translocation and decreased levels of phosphorylated GSK3β(Ser9) in a time-dependent manner. Interestingly, tBHP induced site-specific deactivation of Akt as only Akt(Ser473) phosphorylation was observed to be affected. Further, protein expression as well as nuclear localization of PHLPP2, a phosphatase specific for Akt(Ser473), was found to be significantly enhanced in tBHP-stressed hepatocytes. Silencing of PHLPP2 not only resulted in considerable restoration of Nrf2 signaling, enhanced Nrf2-ARE binding and reduced Nrf2 ubiquitination but also significantly suppressed tBHP-induced ROS generation and alterations in mitochondrial permeability. Authors infer that cellular PHLPP2 levels may aggravate oxidative toxicity by suppressing Nrf2/ARE transcriptional regulation via Akt(Se473)/GSK3β/Fyn kinase axis. The study indicates that PHLPP2 could serve as a new target for developing strategies to manage pathological conditions exacerbated due to oxidative stress.

Monocrotophos induces the expression and activity of xenobiotic metabolizing enzymes in pre-sensitized cultured human brain cells.

[Tripathi VK, Kumar V, Singh AK, Kashyap MP, Jahan S, Pandey A, Alam S, Khan F, Khanna VK, Yadav S, Lohani M, Pant AB. PLoS One. 2014;9:e91946.]

The expression and metabolic profile of cytochrome P450s (CYPs) is largely missing in human brain due to non-availability of brain tissue. Authors attempted to address the issue by using human brain neuronal (SH-SY5Y) and glial (U373-MG) cells. The expression and activity of CYP1A1, 2B6 and 2E1 were carried out in the cells exposed to CYP inducers viz., 3-methylcholanthrene (3-MC), cyclophosphamide (CPA), ethanol and known neurotoxicant- monocrotophos (MCP), a widely used organophosphorous pesticide. Both the cells show significant induction in the expression and CYP-specific activity against classical inducers and MCP. The induction level of CYPs was comparatively lower in MCP exposed cells than cells exposed to classical inducers. Pre-exposure (12 h) of cells to classical inducers significantly added the MCP induced CYPs expression and activity. The findings were concurrent with protein ligand docking studies, which show a significant modulatory capacity of MCP by strong interaction with CYP regulators-CAR, PXR and AHR. Similarly, the known CYP inducers- 3-MC, CPA and ethanol have also shown significantly high docking scores with all the three studied CYP regulators. The expression of CYPs in neuronal and glial cells has suggested their possible association with the endogenous physiology of the brain. The findings also suggest the xenobiotic metabolizing capabilities of these cells against MCP, if received a pre-sensitization to trigger the xenobiotic metabolizing machinery. MCP induced CYP-specific activity in neuronal cells could help in explaining its effect on neurotransmission, as these CYPs are known to involve in the synthesis/transport of the neurotransmitters. The induction of CYPs in glial cells is also of significance as these cells are thought to be involved in protecting the neurons from environmental insults and safeguard them from toxicity. The data provide better understanding of the metabolizing capability of the human brain cells against xenobiotics.

Disposition and acute toxicity of imidacloprid in female rats after single exposure.

[Kapoor U, Srivastava MK, Trivedi P, Garg V, Srivastava LP. Food Chem Toxicol. 2014;68:190-5.]

Single dose of imidacloprid (IMI-20mg/kg bodyweight) was orally administered in female rats. Its disposition along with two metabolites 6-chloro nicotinic acid (6-CNA)

and 6-hydroxy nicotinic acid (6-HNA) was monitored in organs (brain, liver, kidney, and ovary) and bodily fluids (blood, urine) at 6, 12, 24 and 48h and faeces at 24 and 48h. Maximum concentration (Cmax) of IMI and metabolites in each organ and bodily fluid occurred after 12h. Area under curve (AUC) of IMI ranged from 35 to 358µg/ml/h; 6-CNA: 27.12-1006.42µg/ml/h and 6-HNA: 14.98-302.74µg/ml/h in different organs and bodily fluids. Clearance rate of IMI was maximum in ovary followed by kidney, liver, brain, faeces, blood and urine. Percent inhibition of acetyl-cholinesterase (AChE) was comparable in brain and Red Blood Cells (RBC) at 6-48h which suggests the RBC-AChE as valid biomarker for assessing IMI exposure. It is evident that IMI was absorbed, metabolized, and excreted showing increased level of serum enzymes like Glutamic oxaloacetic transaminase (GOT), Glutamic pyruvic transaminase (GPT) and biochemical constituents like billirubin and Blood Urea Nitrogen (BUN) at 48h. These data suggest that IMI is widely distributed, metabolized and induced toxicology effects at 20mg/kg bodyweight to female rats.

Zinc oxide nanoparticles induce apoptosis by enhancement of autophagy via PI3K/Akt/mTOR inhibition.

[Roy R, Singh SK, Chauhan LK, Das M, Tripathi A, Dwivedi PD. Toxicol Lett. 2014;227:29-40.]

Zinc oxide nanoparticles (ZnO NPs) induced macrophage cell death and its mechanism remains to be solved. Herein, authors report that ZnO NPs induced ROS generation by depleting antioxidant enzymes, increasing lipid peroxidation and protein carbonyl contents in macrophages. The oxidative stress was induced by the inhibition of Nrf2 transcription factor release. ZnO NPs also activated the cleavage of apoptosis markers like caspases 3, 8 and 9. γH2Ax activation and cleavage of poly (ADP-ribose) polymerase (PARP) that are known indicators of genotoxicity were found to be activated by following p53, p21/waf1 signaling. ZnO NPs increased the number of autophagosomes and autophagy marker proteins such as microtubule-associated protein 1 light chain 3-isoform II (MAP-LC3-II) and Beclin 1 after 0.5-24h of treatment. Phosphorylated Akt, PI3K and mTOR were significantly decreased on ZnO NPs exposure. Moreover, the apoptotic and autophagic cell death could be inhibited on blocking of ROS generation by N-acetylcysteine (NAC) which demonstrated the critical role of ROS in both types of cell death. In addition, inhibition of LC3-II by siRNA-dependent knockdown attenuated the cleavage of caspase 3. This study demonstrates autophagy supports apoptosis on ZnO NPs exposure.

Genotoxicity of dichlorvos in strains of *Drosophila melanogaster* defective in DNA repair.

[Mishra M, Sharma A, Shukla AK, Kumar R, Dwivedi UN, Kar Chowdhuri D. Mutat Res Genet Toxicol Environ Mutagen. 2014;766:35-41.]

Dichlorvos (DDVP), an organophosphate pesticide, is reported to be genotoxic at high concentrations. However, the roles of DNA damage repair pathways in DDVP genotoxicity are not well characterized. To test whether pre- and post-replication pathways are involved, authors measured changes in DNA migration (Comet assay) in the midgut cells of *Drosophila melanogaster* Oregon R+ larvae and in some mutants of pre- (mei-9, mus201, and mus207) and post- (mei-41 and mus209)replication DNA repair pathways. Insects were exposed to environmentally relevant concentrations of DDVP (up to 15ng/ml) for 48h. After insect exposure to 0.15ng/ml DDVP, authors observed greater DNA damage in pre-replication repair mutants; effects on Oregon R+ and post-replication repair mutants were insignificant. In contrast, significant DNA damage was observed in the post-replication repair mutants after their exposure to 1.5 and 15ng/ml DDVP. The pre-replication repair mutant mus207 showed maximum sensitivity to DDVP, suggestive of alkylation damage to DNA. Authors also examined mutants (SOD- and urate-null) that are sensitive to oxidative stress and the results indicate that significant oxidative DNA damage occurs in DDVP-exposed mutants. This study suggests involvement of both pre- and post-replication repair pathways against DDVP-induced DNA damage in Drosophila, with oxidative DNA damage leading to genotoxicity.

Association between children death and consumption of *Cassia occidentalis* seeds: Clinical and experimental investigations.

[Panigrahi G, Tiwari S, Ansari KM, Chaturvedi RK, Khanna VK, Chaudhari BP, Vashistha VM, Raisuddin S, Das M. Food Chem Toxicol. 2014 ;67:236-48.]

Recently, children with high mortality rate have been observed in northern parts of India, for which the etiology is still not established, although a case control study has been linked to the consumption of *Cassia occidentalis* (CO) seeds. In the present investigation toxicity of CO seeds (0.5, 1 and 2% w/w) in diet were carried out in wistar rats. After 28 days it was observed that CO seeds caused significant increases in the serum markers viz transaminases, alkaline phosphatase and lactate dehydrogenase along with histopathological lesions in hepatic tissue. CO consumption also showed decrease in grip strength, vacuolization and myopathy of skeletal muscles along with increases in serum creatinine and creatinine phosphokinase suggesting muscular damage

in animals. Neuronal damage in CO treated animals was evident by a marked increase in glial fibrilar acidic protein and decrease in β-tubulin III. The experimental findings of CO consumption showed liver, muscles and brain to be the target organs, which were similar to that of the clinical data of poisoning cases as observed in the present study. Overall, the study suggests that CO seed consumption is the main etiological factor in children population suffering from hepatomyoencephalopathy in India.

Mitochondria: Prospective targets for neuroprotection in parkinson's disease.

[Yadav A, Agrawal S, Tiwari SK, Chaturvedi RK. Curr Pharm Des. 2014;20:5558-73.]

Parkinson's disease is the second most common neurodegenerative disorder characterized by persistent loss of dopaminergic neurons in the SN and clinically associated with cognitive, behavioral and motor deficits. There is an enormous amount of data that provides convincing evidence about the prime involvement of mitochondria in the onset and progression of neurodegeneration. Several studies have also emphasized that accumulation of toxic protein and their aggregates in mitochondria lead to energy deficits, excessive ROS generation, mutations in mitochondrial genome and proteins regulating mitochondrial homeostasis, and impaired mitochondrial dynamics in animal models of PD and patients. Here authors discuss about the bioenergetic agents, which have been tested for reducing the mitochondrial dysfunction and associated disease pathology in cellular and animal models of PD and PD patients with encouraging outcomes. Authors also provide a succinct overview of current therapeutic implications of PGC-1α, SIRT, AMPK, and Nrf2-ARE as salutary targets to overcome the deleterious effects posed by mitochondrial dysfunction in the onset and progression of PD.

O-hexadecyl-dextran entrapped berberine nanoparticles abrogate high glucose stress induced apoptosis in primary rat hepatocytes.

[Kapoor R, Singh S, Tripathi M, Bhatnagar P, Kakkar P, Gupta KC. PLoS One. 2014;9:e89124.]

Nanotized phytochemicals are being explored by researchers for promoting their uptake and effectiveness at lower concentrations. In this study, O-hexadecyl-dextran entrapped berberine chloride nanoparticles (BC-HDD NPs) were prepared, and evaluated for their cytoprotective efficacy in high glucose stressed primary hepatocytes and the results obtained compared with bulk berberine chloride (BBR) treatment. The nanotized formulation treated primary hepatocytes that were exposed to high glucose (40 mM), showed increased viability compared to the bulk BBR treated cells. BC-HDD NPs reduced the ROS generation by 3.5 fold during co-treatment, prevented GSH depletion by 1.6 fold, reduced NO formation by 5 fold and significantly prevented decline in SOD activity in stressed cells. Lipid peroxidation was also prevented by 1.9 fold in the presence of these NPs confirming the antioxidant capacity of the formulation. High glucose stress increased Bax/Bcl2 ratio followed by mitochondrial depolarization and activation of caspase-9/-3 confirming involvement of mitochondrial pathway of apoptosis in the exposed cells. Co- and post-treatment of BC-HDD NPs prevented depolarization of mitochondrial membrane, reduced Bax/Bcl2 ratio and prevented externalization of phosphatidyl-serine confirming their anti-apoptotic capacity in those cells. Sub-G1 phase apparent in high glucose stressed cells was not seen in BC-HDD NPs treated cells. The present study reveals that BC-HDD NPs at 20 fold lower concentration are as effective as BBR in preventing high glucose induced oxidative stress, mitochondrial depolarization and downstream events of apoptotic cell death.

Leucoagglutinating phytohemagglutinin: Purification, characterization, proteolytic digestion and assessment for allergenicity potential in BALB/c mice.

[Kumar S, Sharma A, Das M, Jain SK, Dwivedi PD. Immunopharmacol Immunotoxicol. 2014;36:138-44.]

Red kidney bean (*Phaseolus vulgaris*) is consumed worldwide as a vegetarian protein source. But, at the same time the allergenicity potential of red kidney bean is a matter of concern. This study is aimed towards purification, characterization, thermal stability, proteolytic digestion and allergenicity assessment of one of the clinically relevant allergens of red kidney bean. The purification of red kidney bean allergic protein was carried out with the help of column chromatography, IgE immunoblotting and reverse phase high-pressure liquid chromatography (RP-HPLC). The purified protein was characterized by peptide mass finger printing (PMF) and studied for its thermal stability, and proteolytic resistance using simulated gastric fluid (SGF) assay. The allergenicity potential of the purified protein was studied in BALB/c mice. The purified protein was identified as leucoagglutinating phytohemagglutinin (PHA-L) with molecular weight 29.5? kDa. The PHA-L showed resistance to heat as well as proteolytic enzyme. Higher levels of total IgE, specific IgE, and histamine were observed in PHA-L treated BALB/c mice when compared to control. Overall, PHA-L possesses characteristics of allergens and may play a potential role in the red kidney

bean induced allergy.

Long-term dietary exposure to low concentration of dichloroacetic acid promoted longevity and attenuated cellular and functional declines in aged *Drosophila melanogaster*.

[Pandey A, Vimal D, Chandra S, Saini S, Narayan G, Kar Chowdhuri D. Age (Dordr). 2014;36:9628.]

Dichloroacetic acid (DCA), a water disinfection by-product, has attained emphasis due to its prospect for clinical use against different diseases including cancer along with negative impact on organisms. However, these reports are based on the toxicological as well clinical data using comparatively higher concentrations of DCA without much of environmental relevance. Here, authors evaluate cellular as well as organismal effects of DCA at environmentally and mild clinically relevant concentrations (0.02-20.0 µg/ml) using an established model organism, *Drosophila melanogaster*. Flies were fed on food mixed with test concentrations of DCA for 12-48 h to examine the induction of reactive oxygen species (ROS) generation, oxidative stress (OS), heat shock genes (hsps) and cell death along with organismal responses. Authors also examined locomotor performance, ROS generation, glutathione (GSH) depletion, expression of GSH-synthesizing genes (gclc and gclm), and hsps at different days (0, 10, 20, 30, 40, 50) of the age in flies after prolonged DCA exposure. Authors observed mild OS and induction of antioxidant defence system in 20.0 µg/ml DCA-exposed organism after 24 h. After prolonged exposure to DCA, exposed organism exhibited improved survival, elevated expression of hsp27, gclc, and gclm concomitant with lower ROS generation and GSH depletion and improved locomotor performance. Conversely, hsp27 knockdown flies exhibited reversal of the above end points. The study provides evidence for the attenuation of cellular and functional decline in aged Drosophila after prolonged DCA exposure and the effect of hsp27 modulation which further incites studies towards the therapeutic application of DCA.

Peptide therapeutics in neurodegenerative disorders.

[Tiwari SK, Chaturvedi RK. Curr Med Chem. 2014;21:2610-31.]

Neurodegenerative diseases are characterized by selective and progressive degeneration of neuronal population in the brain, and associated behavioural, motor, psychiatric and cognitive impairments. Aggregation of pathogenic proteins, mitochondrial dysfunction, oxidative stress, transcriptional dysfunction and apoptosis play an important role in the pathogenesis of neurodegenerative disorders such as Parkinson's disease, Huntington's disease, Alzheimer's disease and Amyotrophic lateral sclerosis. Therefore, novel therapies that target each of these mechanisms may be effective in abating the symptoms and slow down the onset and progression of neurodegenerative disorders. This review offers insights into the tremendous utility and versatility of peptides such as neurotrophins, neurotrophic factors (NGF, BDNF and GDNF), neuropeptides, mitochondrial targeted antioxidants/peptides, MitoQ, neurturin, and β-sheet breaker peptides to address the mechanisms and pathogenesis associated with neurodegenerative disorders.

Peptide based immunotherapy: A pivotal tool for allergy treatment.

[Gupta K, Kumar S, Das M, Dwivedi PD. Int Immunopharmacol. 2014;19:391-8.]

Immunotherapies with T-cell epitope peptides have shown a promising impact over allergic diseases as a potential therapeutic tool in *in vitro* and *in vivo* conditions. It is recognized as an effective treatment with long lasting clinical effects and subsequent reduction of the allergic inflammatory reactions. In this review, authors have summarized the role of peptide based immunotherapy and emphasis has been given to the recent advancement in pollen, cat, hymenoptera venom, and food allergy.

Neuroprotective potentials of neurotrophin rich olfactory ensheathing cell's conditioned media against 6OHDA-induced oxidative damage.

[Shukla A, Mohapatra TM, Parmar D, Seth K. Free Radic Res. 2014;48:560-71.]

On the basis of recent reports, authors propose that impaired neurotrophin signaling (PI3k/Akt), low antioxidant levels, and generation of reactive oxygen species (ROS) conjointly participate in the progressive events responsible for the dopaminergic cell loss in Parkinson's disease (PD). In the present study authors tried to target these deficits collectively through multiple neurotrophic factors (NTFs) support in the form of Olfactory Ensheathing Cell's Conditioned Media (OEC CM) using human SH-SY5Y neuroblastoma cell line exposed to 6 hydroxydopamine (6OHDA). 6OHDA exposure induced, oxidative stress-mediated apoptotic cell death viz. enhanced ROS generation, diffused cytosolic cytochrome c (cyt c), impaired Bcl-2: Bax levels along with decrease in GSH content. These changes were accompanied by loss in Akt phosphorylation and TH levels in SH-SY5Y cells. OEC CM significantly checked apoptotic cell death by preserving pAkt levels which coincided with enhanced GSH and suppressed oxidative

injury. Functional integrity of OEC CM supported cells was evident by maintained tyrosine hydroxylase (TH) expression. Intercepting Akt signaling by specific inhibitor LY294002 blocked the protective effect. Taken together findings provide important evidence that the key to protective effect of multiple NTF support via OEC CM is enhanced Akt survival signaling which promotes antioxidant defence leading to suppression of oxidative damage.

Reversibility of changes in brain cholinergic receptors and acetylcholinesterase activity in rats following early life arsenic exposure.

[Chandravanshi LP, Yadav RS, Shukla RK, Singh A, Sultana S, Pant AB, Parmar D, Khanna VK. Int J Dev Neurosci. 2014;34:60-75.]

In view of the increasing incidences of arsenic induced health effects and the vulnerability of the developing brain to its toxic effects, studies have been carried out to investigate the mechanism of arsenic induced cholinergic alterations and understand if such changes are persistent or transient on withdrawal of arsenic exposure. Male rats were exposed to arsenic (2 mg/kg or 4 mg/kg body weight, p.o) from post-lactational day (PD)22 to PD59, and the effect on selected behavioral and neurochemical end points associated with cholinergic functions was assessed on PD60 and PD90. Decrease in the binding of muscarinic-cholinergic receptors in frontal cortex (26%, 43%) and hippocampus (21%, 34%) associated with reduced CHRM2 mRNA levels, acetylcholinesterase activity and expression of ChAT and PKC β-1 was observed in arsenic exposed rats on PD60 as compared to controls. Spatial learning and memory and muscle strength were affected following arsenic exposure in rats on PD60 and associated with arsenic induced cholinergic alterations. Enhanced oxidative stress associated with increased expression of pro-apoptotic proteins and decreased expression of anti-apoptotic proteins was distinct in both frontal cortex and hippocampus following arsenic exposure in rats on PD60. The cholinergic alterations and other neurochemical modifications were found to be linked with increased arsenic levels in frontal cortex (1.39, 3.90-fold) and hippocampus (3.23, 5.48-fold) on PD60. Although a trend of recovery was observed both in behavioral and neurochemical endpoints on withdrawal of arsenic exposure on PD90, the results indicate that continuous arsenic exposure may have detrimental effects.

Over-expression of superoxide dismutase ameliorates Cr(VI) induced adverse effects via modulating cellular immune system of *Drosophila melanogaster.*

[Pragya P, Shukla AK, Murthy RC, Abdin MZ, Kar Chowdhuri D. PLoS One. 2014 4;9:e88181.]

The evolutionarily conserved innate immune system plays critical role for maintaining the health of an organism. However, a number of environmental chemicals including metals are known to exert adverse effects on immune system. The present study assessed the *in vivo* effect of a major environmental chemical, Cr(VI), on cellular immune response using *Drosophila melanogaster* and subsequently the protective role of superoxide dismutase (SOD) based on the comparable performance of the tested anti-oxidant enzymes. The immuno-modulatory potential of Cr(VI) was demonstrated by observing a significant reduction in the total hemocyte count along with impaired phagocytic activity in exposed organism. Concurrently, a significant increase in the percentage of Annexin V-FITC positive cells, activation of DEVDase activity, generation of free radical species along with inhibition of anti-oxidant enzyme activities was observed in the hemocytes of exposed organism. In addition, authors have shown that ONOO(-) is primarily responsible for Cr(VI) induced adverse effects on Drosophila hemocytes along with O2(-). While generation of O2(-)/ONOO(-) in Cr(VI) exposed Drosophila hemocytes was found to be responsible for the suppression of Drosophila cellular immune response, Cr(VI) induced alteration was significantly reduced by the over-expression of sod in Drosophila hemocytes. Overall, results suggest that manipulation of one of the anti-oxidant genes, sod, benefits the organism from Cr(VI) induced alteration in cellular immunity. Further, this study demonstrates the applicability of *D. melanogaster* to examine the possible effects of environmental chemicals on innate immunity which can be extrapolated to higher organisms due to evolutionary conservation of innate immune system between Drosophila and mammals.

CDK5-induced p-ppary(ser 112) downregulates gfap via ppres in developing rat brain: Effect of metal mixture and troglitazone in astrocytes.

[Rai A, Tripathi S, Kushwaha R, Singh P, Srivastava P, Sanyal S, Bandyopadhyay S. Cell Death Dis. 2014;5:e1033.]

The peroxisome proliferator-activated receptor gamma (PPARγ), a group of ligand-activated transcriptional factors, is expressed in glial fibrillary acidic protein (GFAP)-immunoreactive astrocytes. Here, authors investigated the role of PPARγ in regulating GFAP using a mixture of As, Cd and Pb (metal mixture, MM) that induces apoptosis and aberrant morphology in rat brain astrocytes. Authors observed a phospho PPARγ (serine 112 (S112)) (p-PPARγ (S112))-mediated downregulation

of GFAP in the MM-exposed astrocytes. Validated this using pure PPARγ agonist, troglitazone (TZ). As reported with MM, TZ induced astrocyte damage owing to reduced GFAP. *In silico* analysis in the non-coding region of GFAP gene revealed two PPARγ response elements (PPREs); inverted repeat 10 and direct repeat 1 sequences. Gel shift and chromatin immune precipitation assays demonstrated enhancement in binding of p-PPARγ (S112) to the sequences, and luciferase reporter assay revealed strong repression of GFAP via PPREs, in response to both MM and TZ. This indicated that suppression in GFAP indeed occurs through direct regulation of these elements by p-PPARγ (S112). Signaling studies proved that MM, as well as TZ, activated the cyclin-dependent kinase 5 (CDK5) and enhanced its interaction with PPARγ resulting into increased p-PPARγ (S112). The p-CDK5 levels were dependent on proximal activation of extracellular signal-regulated protein kinase 1/2 and downstream Jun N-terminal kinase. Taken together, these results are the first to delineate downregulation of GFAP through genomic and non-genomic signaling of PPARγ. It also brings forth a resemblance of TZ with MM in terms of astrocyte disarray in developing brain.

Phaseolin: A 47.5kda protein of red kidney bean (*Phaseolus vulgaris* l.) plays a pivotal role in hypersensitivity induction.

[Kumar S, Verma AK, Sharma A, Roy R, Kumar D, Bh G, Tripathi A, Chaudhari BP, Das M, Jain SK, Dwivedi PD. Int Immunopharmacol. 2014;19:178-90.]

Red kidney bean (*Phaseolus vulgaris* L.), a protein rich legume, is consumed globally due to its delicacy. This study was aimed to purify, characterize and assess allergenicity of one of its clinically relevant allergens, later identified as phaseolin. This study was carried out using clinical, *in vivo* and ex vivo approaches. Phaseolin, an abundant protein of red kidney bean, was purified by column chromatography and reverse-phase-HPLC techniques and characterized by peptide mass fingerprinting. The IgE immunoblotting using red kidney bean allergic patients sera showed phaseolin as a major IgE binding protein of red kidney bean. Phaseolin treated mice demonstrated enhanced levels of specific IgE and IgG1, mouse mast cell protease-1, mRNA expressions of IL-4, IL-5, IL-13 and GATA-3 in the lungs, spleen and intestine along with anaphylactic symptoms indicative of allergic responses. Further, flow cytometry analysis and immune-histochemical studies indicated increased levels of IL-4, IL-5, IL-13 and GATA-3, respectively as compared to controls. The level of Foxp3 was found suppressed in the intestine of phaseolin treated mice when compared to the control. Further, phaseolin treated mice showed positive results in type 1 skin test. Bone marrow derived mast cells (BMMCs) and rat basophilic leukemia (RBL-2H3) cells showed enhanced release of allergic mediators like β-hexosaminidase, histamine, cysteinyl leukotrienes and prostaglandin D2. Taken together, phaseolin was found to possess characteristics of a potential allergen that may lead to hypersensitivity responses in the susceptible individuals and this may be one of the major proteins responsible for allergenicity of red kidney bean.

Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/β-catenin pathway.

[Tiwari SK, Agarwal S, Seth B, Yadav A, Nair S, Bhatnagar P, Karmakar M, Kumari M, Chauhan LK, Patel DK, Srivastava V, Singh D, Gupta SK, Tripathi A, Chaturvedi RK, Gupta KC. ACS Nano. 2014;8:76-103.]

Neurogenesis, a process of generation of new neurons, is reported to be reduced in several neurodegenerative disorders including Alzheimer's disease (AD). Induction of neurogenesis by targeting endogenous neural stem cells (NSC) could be a promising therapeutic approach to such diseases by influencing the brain self-regenerative capacity. Curcumin, a neuroprotective agent, has poor brain bioavailability. Herein, authors report that curcumin-encapsulated PLGA nanoparticles (Cur-PLGA-NPs) potently induce NSC proliferation and neuronal differentiation *in vitro* and in the hippocampus and subventricular zone of adult rats, as compared to uncoated bulk curcumin. Cur-PLGA-NPs induce neurogenesis by internalization into the hippocampal NSC. Cur-PLGA-NPs significantly increase expression of genes involved in cell proliferation (reelin, nestin, and Pax6) and neuronal differentiation (neurogenin, neuroD1, neuregulin, neuroligin, and Stat3). Curcumin nanoparticles increase neuronal differentiation by activating the Wnt/β-catenin pathway, involved in regulation of neurogenesis. These nanoparticles caused enhanced nuclear translocation of β-catenin, decreased GSK-3β levels, and increased promoter activity of the TCF/LEF and cyclin-D1. Pharmacological and siRNA-mediated genetic inhibition of the Wnt pathway blocked neurogenesis-stimulating effects of curcumin. These nanoparticles reverse learning and memory impairments in an amyloid beta induced rat model of AD-like phenotypes, by inducing neurogenesis. *In silico* molecular docking studies suggest that curcumin interacts with Wif-1, Dkk, and GSK-3β. These results suggest that curcumin nanoparticles induce adult neurogenesis through activation of the canonical Wnt/β-catenin pathway and may offer a therapeutic approach to

treating neurodegenerative diseases such as AD, by enhancing a brain self-repair mechanism.

In silico prediction of toxicity of non-congeneric industrial chemicals using ensemble learning based modeling approaches.

[Singh KP, Gupta S. Toxicol Appl Pharmacol. 2014;275:198-212.]

Ensemble learning approach based decision tree boost (DTB) and decision tree forest (DTF) models are introduced in order to establish quantitative structure-toxicity relationship (QSTR) for the prediction of toxicity of 1450 diverse chemicals. Eight non-quantum mechanical molecular descriptors were derived. Structural diversity of the chemicals was evaluated using Tanimoto similarity index. Stochastic gradient boosting and bagging algorithms supplemented DTB and DTF models were constructed for classification and function optimization problems using the toxicity end-point in *T. pyriformis*. Special attention was drawn to prediction ability and robustness of the models, investigated both in external and 10-fold cross validation processes. In complete data, optimal DTB and DTF models rendered accuracies of 98.90%, 98.83% in two-category and 98.14%, 98.14% in four-category toxicity classifications. Both the models further yielded classification accuracies of 100% in external toxicity data of *T. pyriformis*. The constructed regression models (DTB and DTF) using five descriptors yielded correlation coefficients (R(2)) of 0.945, 0.944 between the measured and predicted toxicities with mean squared errors (MSEs) of 0.059, and 0.064 in complete *T. pyriformis* data. The *T. pyriformis* regression models (DTB and DTF) applied to the external toxicity data sets yielded R(2) and MSE values of 0.637, 0.655; 0.534, 0.507 (marine bacteria) and 0.741, 0.691; 0.155, 0.173 (algae). The results suggest for wide applicability of the inter-species models in predicting toxicity of new chemicals for regulatory purposes. These approaches provide useful strategy and robust tools in the screening of ecotoxicological risk or environmental hazard potential of chemicals.

Mechanism of uptake of ZnO nanoparticles and inflammatory responses in macrophages require PI3K mediated MAPKs signaling.

[Roy R, Parashar V, Chauhan LK, Shanker R, Das M, Tripathi A, Dwivedi PD. Toxicol In Vitro. 2014;28:457-67.]

The inflammatory responses after exposure to zinc oxide nanoparticles (ZNPs) are known, however, the molecular mechanisms and direct consequences of particle uptake are still unclear. Dose and time-dependent increase in the uptake of ZNPs by macrophages has been observed by flow cytometry. Macrophages treated with ZNPs showed a significantly enhanced phagocytic activity. Inhibition of different internalization receptors caused a reduction in uptake of ZNPs in macrophages. The strongest inhibition in internalization was observed by blocking clathrin, caveolae and scavenger receptor mediated endocytic pathways. However, FcR and complement receptor-mediated phagocytic pathways also contributed significantly to control. Further, exposure of primary macrophages to ZNPs (2.5 µg/ml) caused (i) significant enhancement of Ras, PI3K, (ii) enhanced phosphorylation and subsequent activation of its downstream signaling pathways via ERK1/2, p38 and JNK MAPKs (iii) overexpression of c-Jun, c-Fos and NF-κB. Results demonstrate that ZNPs induce the generation of reactive nitrogen species and overexpression of Cox-2, iNOS, pro-inflammatory cytokines (IL-6, IFN-γ, TNF-α, IL-17 and regulatory cytokine IL-10) and MAPKs which were found to be inhibited after blocking internalization of ZNPs through caveolae receptor pathway. These results indicate that ZNPs are internalized through caveolae pathway and the inflammatory responses involve PI3K mediated MAPKs signaling cascade.

Involvement of epigenetics and microRNA-29b in the urethane induced inception and establishment of mouse lung tumors.

[Pandey M, Sultana S, Gupta KP. Exp Mol Pathol. 2014;96:61-70.]

Epigenetic changes are correlated with tumor development showing aberrations in DNA methylation and histone modifications. To find the early changes, authors evaluated the epigenetic events from early to late stage of the urethane induced lung tumor development in mouse model and tried to correlate the molecular events with the progression of tumor. Authors addressed the hypothesis by examining the tumor development, status of DNMTs, HDACs and MBDs, DNA methylation and expression of microRNA-29b during 1 to 36 weeks after urethane exposure that included the period before and after the tumor appearance. Tumors did not appear after 1 or 4 weeks but well defined tumors appeared after 12 weeks and larger tumors appeared at 36 weeks which was prevented by IP6. DNMT1, DNMT3a and DNMT3b were upregulated after urethane exposure at the time of no tumor till the tumor developed and showed its upregulated functional activity. DNMTs are shown to be the targets of microRNA-29b and authors showed that microRNA-29b was downregulated in the line of DNMT upregulation. HDAC, the histone modifier, also showed progressive upregulation. Periodic increase in methyl binding proteins, MBD2, supported the expression of

gene silencing pathways in terms of the downregulation of tumor suppressor genes, p16 and MLH1. All these molecular alterations were protected in the presence of IP6. Results showed that the key steps of epigenetics, DNMTs, mir29b, and HDAC1, are altered both before and after the development of tumors.

Selective blocking of primary amines in branched polyethylenimine with biocompatible ligand alleviates cytotoxicity and augments gene delivery efficacy in mammalian cells.

[Tripathi SK, Gupta N, Mahato M, Gupta KC, Kumar P. Colloids Surf B Biointerfaces. 2014 ;115:79-85.]

Recently, polyethylenimines (PEIs) have emerged as efficient vectors for nucleic acids delivery. However, inherent cytotoxicity has limited their *in vivo* applications. To address this concern as well as to incorporate hydrophobic domains for improving interactions with the lipid bilayers in the cell membranes, authors have tethered varying amounts of amphiphilic pyridoxyl moieties onto bPEI to generate a small series of pyridoxyl-PEI (PyP) polymers. Spectroscopic characterization confirms the formation of PyP polymers, which subsequently form stable complexes with pDNA in nanometric range with positive surface charge. The projected modification not only accounts for a decrease in the density of 1° amines but also allows formation of relatively loose complexes with pDNA (cf. bPEI). Alleviation of the cytotoxicity, efficient interaction with cell membranes and easy disassembly of the pDNA complexes have led to the remarkable enhancement in the transfection efficiency of PyP/pDNA complexes in mammalian cells with one of the formulations, PyP-3/pDNA complex, showing transfection in 68% cells compared to 16% cells by Lipofectamine/pDNA complex. Further, the efficacy of PyP-3 vector has been established by delivering GFP-specific siRNA resulting in 88% suppression of the target gene expression. These results demonstrate the efficacy of the projected carriers that can be used in future gene therapy applications.

Comparative toxicity of carbaryl, carbofuran, cypermethrin and fenvalerate in *Metaphire posthuma* and *Eisenia fetida* -a possible mechanism.

[Saxena PN, Gupta SK, Murthy RC. Ecotoxicol Environ Saf. 2014;100:218-25.]

To establish the use of *Metaphire posthuma* as a sensitive test model for ecotoxicological studies, acute toxicity testing of carbaryl, carbofuran, cypermethrin and fenvalerate on *Eisenia fetida* and *Metaphire posthuma* were carried out. Two different types of bioassays, contact filter paper toxicity and soil toxicity bioassays were used to determine LC50 values for these insecticides. Among the tested chemicals, carbofuran was the most toxic to both the earthworm species. In paper contact method, 72 h-LC50 values of carbofuran in *M. posthuma* and *E. fetida* were found to be 0.08 µg/cm(2) and 1.55 µg/cm(2) respectively while in soil test, 14-d LC50 values were 0.49 mg/kg and 21.15 mg/kg respectively. On comparing the toxicity data of these chemicals for both the earthworm species, *M. posthuma* was found to be more sensitive than *E. fetida*. Based on the acute toxicity data, the order of toxicity of insecticides in both the test procedures was carbofuran> cypermethrin> carbaryl> fenvalerate for *M. posthuma* whereas for *E. fetida* it was carbofuran> carbaryl> fenvalerate> cypermethrin. Morphological changes also appeared in the organisms exposed to these chemicals which were more pronounced in *M. posthuma* at lower concentrations than *E. fetida* in both the test procedures. The results of the present study advocates the use of *M. posthuma* for ecotoxicity studies, being a more sensitive and reliable model than *E. fetida*. Based on the data on partial atomic charges, structural features and spectroscopic studies on carbaryl and carbofuran, a possible mechanism of toxicity of carbamate insecticides in earthworm was proposed.

Molecularly imprinted polymer coupled with dispersive liquid-liquid microextraction and injector port silylation: A novel approach for the determination of 3-phenoxybenzoic acid in complex biological samples using gas chromatography-tandem mass spectrometry.

[Mudiam MK, Chauhan A, Jain R, Dhuriya YK, Saxena PN, Khanna VK. J Chromatogr B Analyt Technol Biomed Life Sci. 2014;945-946:23-30.]

A novel analytical approach based on molecularly imprinted solid phase extraction (MISPE) coupled with dispersive liquid-liquid microextraction (DLLME), and injector port silylation (IPS) has been developed for the selective preconcentration, derivatization and analysis of 3-phenoxybenzoic acid (3-PBA) using gas chromatography-tandem mass spectrometry (GC-MS/MS) in complex biological samples such as rat blood and liver. Factors affecting the synthesis of MIP were evaluated and the best monomer and cross-linker were selected based on binding affinity studies. Various parameters of MISPE, DLLME and IPS were optimized for the selective preconcentration and derivatization of 3-PBA. The developed method offers a good linearity over the calibration range of 0.02-2.5ngmg(-1) and 7.5-2000ngmL(-1) for liver and blood respectively. Under optimized conditions, the recovery of 3-PBA in liver and blood samples were found to be in the range of 83-91%. The detection limit was found to be 0.0045ngmg(-1) and

1.82ngmL(-1) in liver and blood respectively. SRM transition of 271→227 and 271→197 has been selected as quantifier and qualifier transition for 3-PBA derivative. Intra and inter-day precision for five replicates in a day and for five, successive days was found to be less than 8%. The method developed was successfully applied to real samples, i.e. rat blood and tissue for quantitative evaluation of 3-PBA. The analytical approach developed is rapid, economic, simple, eco-friendly and possess immense utility for the analysis of analytes with polar functional groups in complex biological samples by GC-MS/MS.

Interactive threats of nanoparticles to the biological system.

[Roy R, Kumar S, Tripathi A, Das M, Dwivedi PD. Immunol Lett. 2014;158:79-87.]

The use of nanoscale materials is growing exponentially, but concerns rise about the human hazards cannot be ignored. Nanotechnology has penetrated deep into our lives in diversified areas as engineering, information technology and diagnostics. Nonetheless owing to their peculiar properties these new materials also present new health risks upon interacting with biological systems. This is a typical case of technology preceding toxicity and therefore, various toxicological aspects for an array of nanomaterials are just beginning to be assessed. Several deleterious effects are being noticed, particularly *in vitro* situations as well as in mammalian system. Nanoparticles toxicity is compellingly related to oxidative stress, alteration of calcium homeostasis, gene expression, pro-inflammatory responses and cellular signalling events. It is therefore critical to understand the nature and origin of the toxicity imposed by nanomaterials. Keeping all these points in mind, the present review provides updated information on the various aspects such as sources of production, effect of different physical properties, interaction with biological system and mechanisms of engineered nanoparticles induced toxicities.

Comparative toxicity of low dose tributyltin chloride on serum, liver, lung and kidney following subchronic exposure.

[Mitra S, Gera R, Singh V, Khandelwal S. Food Chem Toxicol. 2014;64:335-43]

Tributyltin (TBT) pollution is rampant worldwide and is a growing threat due to its bio-accumulative property. Isolated studies of TBT toxicity on different organs are available but consolidated information is greatly lacking. Authors planned this study to delineate the effect of subchronic (1 month) exposure to low dose TBT-chloride (TBTC) (1 and 5 mg/kg) in male Wistar rats. Total tin concentration was found to be significantly increased in liver, kidney and blood, and marginally in lungs. Organo-somatic indices were seen to be altered with little effect on serum biochemical markers (liver and kidney function, and general parameters). Reactive oxygen species but not lipid peroxidation content was observed to be significantly elevated both in the tissues and serum. TBTC was found to act as a hyperlipidemic agent and it also affected heme biosynthetic pathway. Hematological analysis showed that TBTC exposure resulted in minor alterations in RBC parameters. Histological studies demonstrated marked tissue damage in all the 3 organs. Calcium inhibitors (BAPTA-AM, EGTA) and antioxidants (NAC, C-PC) significantly restored TBTC induced loss in cell viability, under *(ex-vivo)* conditions. Antioxidants were evidently more efficient in comparison to the calcium inhibitors, implying major role of oxidative stress pathways in TBTC toxicity.

Cellular and molecular mechanism of ofloxacin induced apoptotic cell death under ambient UV-A and sunlight exposure.

[Dwivedi A, Mujtaba SF, Yadav N, Kushwaha HN, Amar SK, Singh SK, Pant MC, Ray RS. Free Radic Res. 2014;48:333-46.]

Ofloxacin (OFLX) is a racemic mixture of levofloxacin which revealed phototoxicity in patients exposed with sunlight after medication. Here, authors have been addressed the possible cellular and molecular mechanisms of OFLX induced apoptosis under ambient UV-A and sunlight exposure using HaCaT cell line as a model. The results showed that Photodegradation and three photo-products formation of OFLX by LC-MS/MS under ambient intensities of UV-A (1.5 and 2.2 mW/cm(2)) and sunlight. OFLX produced (1)O2, O2(.-), and OH radicals via type-II- and type-I-dependent reaction mechanism, which corroborated by its specific quenchers. 2'-dGua degradation in photochemical and % tail DNA formation in cell line using comet test advocated the genotoxic potential of OFLX. Photocytotoxic assays (MTT and NRU) revealed the considerable decline in cell viability by OFLX. OFLX triggered apoptosis, proved by cell cycle, Annexin V/PI double staining along with acridine orange (AO)/ethidium bromide (EB), and Hoechst staining as well as caspase-3 activity by colorimetric assay. OFLX induced lysosomal disruption and mitochondrial membrane destabilization confirmed through fluorescence staining with AO/JC-1. OFLX significantly upregulated the expression of p21 and bax genes. In conclusion, the study revealed that photosensitized OFLX induced apoptosis via ROS-mediated DNA damage, destabilization of lysosomal and mitochondrial membrane, and upregulation of p21, bax,

and caspase-3 genes.

Influence of temperature and pH on the degradation of deoxynivalenol (DON) in aqueous medium: Comparative cytotoxicity of DON and degraded product.

[Mishra S, Dixit S, Dwivedi PD, Pandey HP, Das M. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2014;31:121-31.]

Deoxynivalenol (DON), a toxic fungal metabolite, is stable under different processing conditions; however, its stability in aqueous medium at different temperatures and low pH (1-2) (present in the gastrointestinal tract) has not been investigated. In the present study, DON standard was used to study the influence of temperature and pH on DON stability in aqueous medium, the characterisation of the degraded product, and the comparative toxicity profile of the degraded and the parent compound. The results suggest that standard DON was unstable at 125-250°C showing 16-100% degradation whereas DON at pH 1-3 had 30-66% degradation, with a concomitant increase in the formation of a degraded product. Further ESI-MS characterisation of the dominant precursor ion of the HPLC eluate of the DON-degraded product was found to be m/z 279, resembling the known metabolite DOM-1. The degraded product of DON was reconfirmed as DOM-1 by comparison with standard DOM-1 and both gave a similar λmax at 208 nm. Comparative studies of both standard DOM-1 and the degraded product of DON showed no cytotoxicity up to 6400 ng ml(-1) while significant cytotoxicity was observed for DON (400 ng ml(-1)). The results suggest that a highly acidic environment (pH 1-2) could be responsible for the de-epoxydation of DON leading to the formation of DOM-1.

Zinc oxide nanoparticles provide an adjuvant effect to ovalbumin via a Th2 response in Balb/c mice.

[Roy R, Kumar S, Verma AK, Sharma A, Chaudhari BP, Tripathi A, Das M, Dwivedi PD. Int Innunol. 2014;26:159-72.]

Zinc oxide nanoparticles (ZNPs) have been used in dietary supplements and may cause an immunomodulatory effect. The present study investigated the effect of ZNPs on antigen-specific immune responses in mice sensitized with the T-cell-dependent antigen ovalbumin (OVA). BALB/c mice were intraperitoneally administered ZNPs (0.25, 0.5, 1 and 3mg) once, in combination with OVA, and the serum antibodies, splenocyte reactivity and activation of antigen-presenting cells were examined. The serum levels of OVA-specific IgG1 and IgE were found significantly enhanced by treatment with ZNPs over control. An increased level of IL-2, IL-4, IL-6, IL-17 and decreased level of IL-10 and TNF-α in splenocytes administered with ZNPs were observed in comparison with control. The ZNPs and OVA-stimulated T lymphocytes showed enhanced proliferation compared with control. Macrophages and B cells showed high expression of MHC class II, whereas higher expression of CD11b in macrophages of the ZNPs and ZNPs/OVA treated groups was observed. The lungs and spleen had increased eosinophils and mast cell numbers. Also, myeloperoxidase activity in lungs was found to be increased by 2.5-fold in the case of ZNPs and 3.75-fold increase in ZNPs/OVA, whereas in intestine, there was significant increase in both the groups. Increased expression of the genes for GATA-3, SOCS-3, TLR-4, IL-13 and IL-5 in the intestine was observed. Collectively, these data indicate that systemic exposure to a single administration of ZNPs could enhance subsequent antigen-specific immune reactions, including the serum production of antigen-specific antibodies, and the functionality of T cells.

Gene expression profiling of candidate genes in peripheral blood mononuclear cells for predicting toxicity of diesel exhaust particles.

[Srivastava A, Sharma A, Yadav S, Flora SJ, Dwivedi UN, Parmar D. Free Radic Biol Med. 2014;67:188-94.]

To validate gene expression profiling of peripheral blood mononuclear cells (PBMCs) as a surrogate for monitoring tissue expression, this study using RT-PCR-based TaqMan low-density array (TLDA) was initiated to investigate similarities in the mRNA expression of target genes altered by exposure to diesel exhaust particles (DEPs) in freshly prepared PBMCs and in lungs. Adult Wistar rats were treated transtracheally with a single dose of 7.5 or 15 or 30mg/kg DEPs and sacrificed 24h later. Blood and lungs were immediately taken out and processed for RT-PCR. DEP treatment induced similar patterns of increase in the expression of polycyclic aromatic hydrocarbon-responsive cytochrome P450s, the phase II enzymes, and their associated transcription factors in both lungs and PBMCs, at all doses. Similar to that seen in lungs, a dose-dependent increase was observed in the expression of genes involved in inflammation, such as cytokines, chemokines, and adhesion molecules, in PBMCs. The expression of various genes involved in DNA repair and apoptosis was also increased in a dose-dependent manner in PBMCs and lungs. The present TLDA data indicating similarities in the responsiveness of candidate genes involved in the toxicity of DEPs between PBMCs and lungs after exposure to DEPs demonstrate that expression profiles of genes in PBMCs could be used as a surrogate for monitoring the acute toxicity of fine and ultrafine particulate matter present in vehicular emissions.

Endosulfan induced cell death in Sertoli-germ cells of

male Wistar rat follows intrinsic mode of cell death.

[Rastogi D, Narayan R, Saxena DK, Chowdhuri DK. Chemosphere. 2014 Jan;94:104-15.]

Health of germ cells may affect production of quality gametes either due to endogenous or exogenous factors. Pesticides are among the exogenous factors that can enter the organisms through various routes of exposure and also can affect the reproductive system of an organism. Endosulfan is an organochlorine cyclodiene pesticide used widely for controlling agricultural pests. It has been shown to induce reproductive dysfunctions such as sperm abnormalities, reduced intracellular spermatid count in exposed organisms. Germ cells being the progenitor cells for male gametes and Sertoli cells as their nourishing cells, authors examined whether endosulfan induces cell death in Sertoli-germ cells of male rats. Sertoli-germ cells, isolated from 28 d old male Wistar rats, were exposed to endosulfan (2.0, 20.0 and 40.0 µg mL(-1)) for 24-72 h. Cytotoxicity, endosulfan concentration, reactive oxygen species (ROS) generation, oxidative stress parameters were measured in these cells in the absence or presence of endosulfan for the above mentioned exposure periods and subsequently, cell death endpoints were measured. Authors detected endosulfan in the exposed cells and demonstrated increased cell death in exposed Sertoli-germ cells as evidenced by a significant increase in annexin-V staining, depolarization of mitochondrial membrane, caspase-9 and -3 activities and BAD and PARP cleavage activities and DNA ladder formation along with non-significant increase in autophagic cell death. The study suggests that endosulfan can cause cell death in exposed Sertoli-germ cells due to higher oxidative damage with the activation of intrinsic cell death pathway which may eventually affect the production of quality gametes.

SOCS3 dictates the transition of divergent time-phased events in granulocyte TNF-α signaling.

[Chhabra JK, Chattopadhyay B, Paul BN. Cell Mol Immunol. 2014;11:105-6.]

Tumor-necrosis factor-α (TNF-α)-driven nuclear factor-κB (NF-κB) activation and apoptosis are opposing pathways; the growing recognition of these conflicting roles of TNF-α is perplexing. Here, authors show that inflammation and apoptosis are time-phased events following TNF-α signaling and that emergence of suppressor of cytokine signaling 3 (SOCS3) expression limits the ongoing NF-κB activation and promotes apoptosis; further, authors suggest an altered view of how inflammatory diseases are initiated and sustained. *In vitro*, TNF-α (50 ng/ml) induced granulocyte SOCS3 protein, inhibited nuclear accumulation of the p65NF-κB subunit and enhanced apoptosis, as shown by DNA laddering, annexin V positivity, and overexpression of caspase-3 and Bax in the late phase, whereas the early phase was marked by NF-κB activation. Conversely, SOCS3 knockdown by small interfering RNA (siRNA) inhibited granulocyte apoptosis and enhanced nuclear accumulation of p65 and 5' lipooxygenase expression in the late phase of TNF-α signaling. As apoptosis is associated with SOCS3 abundance, authors suggest that these divergent TNF-α-driven events are time-phased, interconnected, opposing control mechanisms and one of the central features through which the immune system resolves pulmonary inflammation. Dysregulation may initiate mucosal inflammation, thus changing the landscape of asthma therapy.

Does restraining nitric oxide biosynthesis rescue from toxins-induced parkinsonism and sporadic Parkinson's disease?

[Gupta SP, Yadav S, Singhal NK, Tiwari MN, Mishra SK, Singh MP. Mol Neurobiol. 2014;49:262-75.]

Nitric oxide (NO) is an important inorganic molecule of the biological system owing to diverse physiological implications. NO is synthesised from a semi-essential amino acid L-arginine. NO biosynthesis is catalysed by a family of enzymes referred to as nitric oxide synthases (NOSs). NO is accused in many acute and chronic illnesses, which include central nervous system disorders, inflammatory diseases, reproductive impairments, cancer and cardiovascular anomalies. Owing to very unstable nature, NO gets converted into nitrite, peroxynitrite and other reactive nitrogen species that could lead to nitrosative stress in the nigrostriatal system. Nitrosative stress is widely implicated in Parkinson's disease (PD), and its beneficial and harmful effects are demonstrated in *in vitro*, rodent and primate models of toxins-induced parkinsonism and in the blood, cerebrospinal fluid and nigrostriatal tissues of sporadic PD patients. The current article updates the roles of NO and NOSs in sporadic PD and toxins-induced parkinsonism in rodents along with the scrutiny of how inhibitors of NOSs could open a new line of approach to moderately rescue from PD pathogenesis based on the existing literature. The article also provides a perspective concerning the lack of ample admiration to such an approach and how to minimise the underlying lacunae.

***In vitro* cytogenetic assessment of trichloroacetic acid in human peripheral blood lymphocytes.**

[Varshney M, Chandra A, Chauhan LK, Goel SK. Environ Sci Pollut Res Int. 2014;21:843-50.]

Trichloroacetic acid (TCA), a common water disinfection byproduct and a persistent metabolite of trichloroethylene

(TCE), has been examined for its genotoxic potential in human lymphocytes. Chromosomal aberration (CA) and cytokinesis-block micronucleus (CBMN) assay were employed to assess the toxicity of TCA. Lymphocytes obtained from three healthy donors were exposed to 25, 50, and 100 µg/ml concentration of TCA separately. TCA exposure resulted in chromosomal anomalies and the formation of micronuclei in lymphocytes. Chromosome analysis revealed the dose-dependent and significant induction of CA. Chromatid break/chromosome break, fragments, and chromatid exchanges were commonly observed. Exposure of higher concentration (50 and 100 µg/ml) significantly inhibited mitotic index. Data obtained with CBMN assay indicated that the induction of micronucleus (MN) formation was greater than that of CA. At 25 µg/ml, TCA induced significant frequencies of MN as compared to control cells. Significant induction of MN at the lowest concentration indicates TCA may also interact with mitotic spindles. Lower percentage of CA and MN at 100 µg/ml as compared to 50 µg/ml indicates occurrence of severe cytotoxicity on exposure of 100 µg/ml TCA in lymphocytes. Collectively, results of both cytogenetic assays indicate that exposure of TCA can induce significant genotoxic and cytotoxic effects.

Cytotoxicity and apoptosis induction by nanoscale talc particles from two different geographical regions in human lung epithelial cells.

[Akhtar MJ, Ahamed M, Khan MA, Alrokayan SA, Ahmad I, Kumar S. Environ Toxicol. 2014;29:394-406.]

Authors have characterized the physicochemical properties of nanotalc particles from two different geographical regions and examined their toxicity mechanisms in human lung epithelial (A549) cells. Indigenous nanotalc (IN) of Indian origin and commercial nanotalc (CN) of American origin were used in this study. Physicochemical properties of nanotalc particles were characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM), energy dispersive X-ray spectroscopy (EDS), Brunauer-Emmet-Teller (BET), and dynamic light scattering (DLS). Results showed that both IN and CN particles significantly induce cytotoxicity and alteration in cell cycle phases. Both IN and CN particles were found to induce oxidative stress indicated by induction of reactive oxygen species (ROS), lipid peroxidation, and depletion of antioxidant levels. DNA fragmentation and caspase-3 enzyme activation due to IN and CN particles exposure were also observed. Authors further showed that after iron chelation, IN and CN particles produce significantly less cytotoxicity, oxidative stress, and genotoxicity to A549 cells as compared with nonchelated particles. In conclusion, this study demonstrated that redox active iron plays significant role in the toxicity of IN and CN particles, which may be mediated through ROS generation and oxidative stress.

RESEARCH DIGEST

High-fibre diet may protect against allergic asthma

[New Scientist News: Nature Medicine 20, 159–166 (2014) doi:10.1038/nm.3444]

Eating a high-fibre diet could trigger changes in the immune system that protect against allergic asthma. Research in mice has shown for the first time that levels of dietary fibre, found in fruit and vegetables, can influence the balance of microbes in the gut in ways that make the airways more or less prone to the inflammation seen in allergic airway diseases. Asthma is caused by inflammation of the bronchi, the small tubes that carry air in and out of the lungs. The inflammation can be triggered by exercise, cold air or smoke, for example, or it can be caused by allergies to things such as house dust mites or pollen. The 1980s and 1990s saw large increases in the incidence of allergy-triggered asthma in many developed countries. Many researchers have linked this to marked changes in diet, including a decrease in the amount of fibre eaten. To investigate this link, Benjamin Marsland at the University Hospital of Lausanne in Switzerland and colleagues looked at how the immune and inflammatory responses of mice varied with the fibre in their diet.

They found that when the mice were exposed to an extract of house dust mites, those whose feed contained less than 0.3 per cent fibre had double the number of a specific type of immune cell associated with asthmatic inflammation in their airways, compared with those on a standard diet containing 4 per cent fibre. Mice given additional fibre supplements on top of a standard diet showed a reduction in these immune cells – but only if the supplement was easily fermentable in the gut. This suggested that the protective effect can be traced back to the bacteria in the animals' guts. To check on this, the researchers sequenced the DNA in the mice's faeces, which allowed them to deduce the gut microbe populations. This sequencing revealed that the mice given the fermentable fibre supplements had increased levels of bacteria that convert fibre into metabolites called short-chain fatty acids (SCFAs). They also had elevated levels of SCFAs in their blood. When Marsland added the two SCFAs whose levels increased the most to the drinking water of a new set of mice, sure enough, their allergic lung inflammation in response to house dust mite extract was reduced, suggesting that it is the action of these metabolites that is triggering the effect.

Further tests showed that the immune cells generated in the bone marrow of mice given one of these SCFAs were less able to trigger inflammatory responses in the airways. "We have shown that changing dietary fibre intake affects the development of immune-cell precursors in the bone marrow, which then go on to have effects in the lung," says Marsland. "We know that bacteria in the gut have an effect on allergic airway disease in the lung, however nobody has really explained why," says Christian Taube at Leiden University Medical Center in the Netherlands. "This work provides a mechanism for this link. It may also help to partially explain the asthma epidemic we have seen in the Western world." "Obviously more work would be needed," says Marsland, "but I don't think it's such a huge step to consider using purified SCFA in supplements for respiratory inflammatory diseases," says Marsland. "From a simple dietary intervention perspective, when we think about what the components of a balanced and healthy diet are, having higher amounts of fermentable fibre could be important."

Going vegetarian halves CO_2 emissions from your food

[New Scientist News :Climatic Change, July 2014, Volume 125, Issue 2, pp 179-192,]

If you stop eating meat, your food-related carbon footprint could plummet to less than half of what it was. That is a much bigger drop than many previous estimates, and it comes from a study of people's real diets. As much as a quarter of our greenhouse gas emissions come from food production. But it's not clear how much would really be saved if people swapped their beef steaks for tofu burgers. On some estimates, going vegetarian could cut out 25 per cent of your diet-related emissions. But it all depends on what you eat instead of the meat. With some substitutions,emissions could even rise. So Peter Scarborough and his colleagues at the University of Oxford took data on the real diets of more than 50,000 people in the UK, and calculated their diet-related carbon footprints. "This is the first paper to confirm and quantify the difference," says Scarborough. They found that the benefits could be huge. If those eating more than 100 grams of meat a day – a fairly small rump steak – went vegan, their food-related carbon footprint would shrink by 60 per cent, saving the equivalent of 1.5 tonnes of carbon dioxide a year. Perhaps more realistically, if someone eating more than 100 grams of meat a day simply cut down to less than 50 grams a day, their food-related emissions would fall by a third. That would save almost a tonne of CO_2 each year, about as much as an economy return flight between London and New York. Pescatarians, who eat fish but not other meat, are almost as carbon-friendly as vegetarians, creating only about 2.5 per cent more food-related emissions. But vegans can

feel the most superior, pumping out 25 per cent less emissions than vegetarians, who still eat eggs and dairy. "In general there is a clear and strong trend with reduced greenhouse gas emissions in diets that contain less meat," says Scarborough.

There are other ways of reducing emissions, such as driving and flying less, but changing food habits will be easier for many, says Scarborough. "I think it is easier to change your diet than to change your travel behaviour, but others may not agree." "This research presents a strong case for the greenhouse gas benefits of a low-meat diet," says Christopher Jones of the University of California, Berkeley. In 2011, Jones compared all the ways US households can cut their emissions. Although food was not the biggest source of emissions, it was where people could make the biggest and most cost-effective savings, by wasting less food and eating less meat. Jones calculated that saving each tonne of CO_2 emissions would also save the household $600 to $700 (Environmental Science & Technology, DOI: 10.1021/es102221h). "Americans waste about a third of the food they buy, and eat about 30 per cent more calories than recommended, on average," says Jones. "Reducing food purchases and physical consumption would have even greater greenhouse gas benefits than reducing meat consumption in the American case."

Time to kick cigarette butts – they're toxic trash

[New Scientist News 30 June 2014]

Poisons leach from the 4 trillion cigarette filters that we chuck each year, harming health and environment alike. They should be banned. For the past two decades, the environmental group Ocean Conservancy has organised the annual International Coastal Cleanup. Hundreds of thousands of volunteers scour beaches all over the world, picking up trash. By far the most common item they pick up is cigarette butts. Last year they removed more than 2 million of them. Cigarette butts are also the most common item collected during urban litter surveys.By one estimate, around two-thirds of the 6 trillion cigarettes smoked worldwide every year end up being dropped, flicked or dumped into the environment – around 750,000 tonnes in total. The effects of cigarettes on smokers' health is well known. I think it is time we paid more attention to the effects of cigarette waste on public health and the environment. Cigarette Butt Pollution Project has studied cigarette waste from a number of perspectives, including toxicity, accidental consumption by children and animals, and potential for human health effects. The results suggest that we urgently need to reduce this burden of toxic waste. Used cigarette butts are not just pieces of non-biodegradable plastic. They also contain the

carcinogens, nicotine and toxins found in all tobacco products. We have found that one cigarette butt soaked in a litre of water for 96 hours leaches out enough toxins to kill half of the fresh or salt water fish exposed to them. We know that children and animals consume these pieces of toxic trash, that there are costs to the communities that must deal with them, and that there is biological plausibility to the idea that so many cigarette butts tossed into the environment each year may leach out chemicals that could impact human health. We have also found that the tobacco industry has thoroughly distanced itself from any sense of responsibility. Many other industries have signed up to Extended Producer Responsibility (EPR), a principle which assigns responsibility for the environmental management of consumer waste to manufacturers of the original product. EPR has been applied to electrical appliances, batteries, paint, mattresses, car tyres, electronic gadgets, beverage containers and other consumer products, and has dramatically reduced the environmental blight and health risks associated with these products. However, it has been assiduously avoided by the makers of the most deadly of all consumer products, cigarettes. The tobacco industry is aware of the problem of cigarette butt waste but has largely left responsibility for clean-up to communities and individual smokers. Its own efforts are more about image than action, such as supporting reputable environmental groups' clean-up campaigns and distributing hand-held ashtrays, as if these might somehow encourage smokers to refrain from butt-flicking. These approaches have not worked. Some in the tobacco industry have proposed replacing plastic filters with biodegradable ones. This is not the answer.

Biodegradable filters would still leach out toxins while falsely reassuring smokers that they were protecting the environment. They would be more likely to dump their butts without feeling as guilty as they do now. We have proposed a number of options to address the problem. One in particular holds promise: get rid of filters altogether. According to the US Surgeon General and the US National Cancer Institute, filters do not have any health benefits for smokers; in fact, cancer risks have actually increased over the 50 years they have been used. Filters were originally designed to keep loose tobacco out of smokers' mouths, not to protect their health. So they are really a marketing tool. They seem to reassure smokers that they are doing something to limit the health consequences of smoking and thus may discourage them from quitting. They also make smoking more palatable and make it easier for children to start. The ventilation provided by the filter may reduce the tar and nicotine yields of cigarettes as measured by a machine, but smokers compensate by changing their puffing behaviour and inhaling more deeply. For these reasons, filters may be considered a health hazard. If their purpose is simply to market cigarettes and make it easier to get addicted, they should be banned. This would simultaneously slash the environmental burden of cigarette butt waste and decrease the addiction potential of tobacco. Both the environment and public health would benefit.

Wireless devices: A health threat during pregnancy?

[http://www.newscientist.com/article/dn25694-wireless-devices-a-health-threat-during-pregnancy. html#. U_2 BcsWSzfs]

A new campaign in the US says cellphones and wireless equipment risk the health of developing babies. A former member of the UK Advisory Group on Non-Ionising Radiation examines the claims. A group of doctors, scientists and non-profit organisations have launched an unofficial campaign encouraging pregnant women to limit their exposure to radiation from phones, Wi-Fi routers, computers and wireless telecommunications equipment in general "to protect themselves and their unborn children".How seriously should we take this warning, and is the campaigners' advice on steps to limit exposure sensible? Public concern about mobile telephony has centred largely on the question of cancer risk, but this new initiative – called the BabySafe Project – focuses on potential exposure of the fetus in the womb and suggests this could result in neurological and behavioural problems. There are good reasons to cast a critical eye over its claims. The non-ionising radio frequency radiation through which devices such as mobile phones communicate is of low energy, and as yet no plausible biophysical mechanism has been established by which

exposures below internationally recommended limits could cause adverse effects in humans. Furthermore, this radiation generally penetrates tissues poorly, giving up its energy as heat in the first few centimetres. Thus, the fetal brain should be well shielded. Nevertheless, if adverse effects were possible, the developing brain might be particularly vulnerable, as it is to toxic substances in the environment, such as lead. Partly for this reason, the Stewart Committee – set up in the UK to examine the potential health implications of cellphone use – in 2000 recommended that, as a precaution, children should avoid unnecessary use of such phones. Since then, a few studies have looked for effects on cognitive function and behaviour, either experimentally in lab animals or through epidemiological observation of human populations. Most were included in an authoritative review by the Advisory Group on Non-Ionising Radiation (which provides independent advice to the UK government) published in 2012. The review concluded that evidence for such effects in animals was "not strong", but noted that relatively few experimental models had been investigated.

The US campaign cites a more recent study which found evidence of symptoms similar to those of attention-deficit hyperactivity disorder in the offspring of mice exposed to cellphone radiation. But that paper clearly states "the exposures used… are not identical to those experienced by the human fetus" and that "the extrapolation of this animal model to humans is limited". Furthermore, the exposure system used – a phone suspended in the animals' cage – did not meet currently recommended standards to allow an accurate assessment of exposure. Four epidemiological studies, three considered by the UK advisory group in 2012 and a have suggested small effects on neurological development from prenatal maternal use of mobile phones, but the three the review considered had important methodological limitations, and the advisory group considered that stronger prospective

studies – those in which exposures are assessed before any negative effects are observed and not estimated post-hoc, from memory - were needed before conclusions could be drawn. Research in this area has been fraught with suggestive positive findings that could not be replicated in later, more rigorous studies. Even though suspicions of a hazard are not strong, more information is needed about possible effects on cognitive development, and it has been identified as a research priority by the World Health Organization.

Lack of vitamin D more than doubles risk of dementia

[New Scientist News: http:// www. neurology. org/ content /early/2014/08/06/WNL.0000000000000755.full.html]

Lack of vitamin D may put elderly people at increased risk of dementia or Alzheimer's disease, a study of 1658 American adults has concluded. The study is the largest ever to investigate possible links between vitamin D deficiency and dementia, and confirms the findings of earlier, smaller studies. "We expected to find an association between low vitamin D levels and the risk of dementia and Alzheimer's disease, but the results were surprising as we actually found that the association was twice as strong as we expected," says David Llewellyn of the University of Exeter Medical School in the UK, and head of the study team. Llewellyn and his colleagues followed the participants, whose average age at the outset was 74, for six years to observe how many developed heart disease, dementia or strokes during that time. The amount of vitamin D in their blood was measured once, at the start of the study. In all, 171 people developed a type of dementia, which in 102 cases was Alzheimer's disease. Participants whose blood contained the lowest levels of vitamin D had a disproportionately higher risk of developing both dementia and Alzheimer's. After the six years, participants severely deficient in vitamin D – defined as having less than 10 micrograms of the vitamin per litre of their blood – were 122 per cent more likely to have Alzheimer's and 125 per cent more likely to have other forms of dementia than those whose blood contained sufficient amounts. This was defined as having a blood concentration level of more than 20 micrograms per litre, as recommended by the US Institute of Medicine. Those moderately deficient in the vitamin, with corresponding blood levels between 10 and 20 micrograms per litre, were 59 per cent more likely to develop dementia and 69 per cent more likely to develop Alzheimer's.

Llewellyn warns that the study does not prove that vitamin D protects against the diseases, or that a lack of it causes them. Further trials are needed, he says, to see if raising a person's blood concentrations of vitamin D above 20 micrograms per litre of blood reduces their risk of disease. In the summer, exposure to around 15 minutes of sunlight a day typically generates enough vitamin D. Otherwise, people can consume extra amounts in oily fish and supplements. The UK National Health Service recommends that elderly people over 65 take supplements containing 10 micrograms of vitamin D daily."Vitamin D is essential for keeping our bodies healthy, and although these results don't suggest people should start dosing up on supplements, it's important for people to ensure they are getting enough vitamin D," says Simon Ridley, head of research at the charity, Alzheimer's Research UK. Ridley says that other ways to lower the risk of dementia include eating healthily, exercising regularly and keeping blood pressure and weight down.Inflammatory conditions such as diabetes, obesity and atherosclerosis can also contribute, and a recent pilot trial of etanercept, a drug that combats inflammation, showed promising signs of halting progression in Alzheimer's disease although again, much larger trials are needed to validate the initial findings.

Drug could protect against radiation exposure

http://news.sciencemag.org/health/2014/05/drug-could-protect-against-radiation-exposure

Drugs could one day help save the lives of those who have been exposed to high levels of radiation, such as in the case of a nuclear accident. It may not work against Godzilla, but a new drug could protect people from deadly doses of radiation. The compound, already in clinical trials to treat a blood disorder, may also make radiation therapy for cancer safer. “What's really exciting about this work is that not only have they found this countermeasure to mitigate radiation-induced [damage], but the fact that it works in a time window of 24 hours after exposure,” says radiation oncologist David Kirsch of Duke University Medical Center in Durham, North Carolina. Radiation first

strikes the bone marrow, wiping out the production of

blood cells important for fighting infections, clotting, and carrying oxygen throughout the body. At high levels, radiation fries the gastrointestinal tract, damaging outer layers of the intestines and colon, and causing fluid loss, diarrhoea, vomiting, and local infections, which can become more systemic and lead to death. The condition is known as radiation-induced gastrointestinal syndrome (RIGS), and there are currently no approved drugs to treat it. Researchers had suspected that two proteins known as hypoxia-inducible factors 1 and 2 (HIF-1 and HIF-2) play a role in maintaining the integrity of the intestines during various times of stress. To test whether they were linked to RIGS, radiation oncologist Amato Giaccia of the Stanford University School of Medicine in California engineered mice to lack a family of proteins called PHDs that normally destabilize HIF-1 and HIF-2. Without the PHDs, mice have higher-than-usual levels of the HIF proteins. Whereas normal mice all died within 10 days of exposure to a high dose of radiation aimed at the abdomen, 70% of mice lacking PHDs were still alive after 30 days. “We were very surprised by the magnitude of the response,” Giaccia says. Next, his team tried to replicate the results with a drug. They turned to dimethyloxalylglycine (DMOG), a compound known to block the PHD proteins and already in clinical trials to treat chronic anemia. Like mice lacking the PHDs, animals that received a dose of DMOG-even 24 hours after radiation exposure-survived longer than usual. Two-thirds of them were still alive 60 days after the exposure, the team reports today in Science Translational Medicine. DMOG didn't alter the initial damage done to the gastrointestinal tract by radiation, but it helped the gut recover. Boosted levels of one HIF protein in particular, HIF-2α, the researchers showed, were key to the recovery. “What we're accomplishing with DMOG is that we're modifying the physiology of the normal tissue to give it time to repair and regenerate,” Giaccia explains. The new findings, Kirsch says, point toward an intervention that could be given in the 24 hours following a radiation emergency-such as the meltdown of nuclear reactors in Fukushima, Japan, in 2011-to save lives. Giaccia would also like to find out if the findings can benefit cancer patients. A drug like DMOG, he says, might ease the toxicity that accompanies radiation therapy. Patients taking it might also tolerate higher doses of radiation, applied more broadly throughout the body, killing more cancer cells than current methods. But Kirsch warns that it's too soon to say whether DMOG, or other PHD-blocking drugs, can be used in cancer patients. “There's some literature suggesting that targeting the HIF pathway could actually protect tumors from radiation,” he says, which would be counterproductive. “More studies need to be done to show that these compounds don't affect tumor response.”

विज्ञान परिक्रमा

(साभार जी न्यूज़ विज्ञान समाचार)

अब एक कण से होगा अवसाद का इलाज

वे लोग जो अवसाद के शिकार हैं, अब उनकी पहचान मनुष्य के अंदर मौजूद सूक्ष्म कण (मॉलेक्यूल) से की जा सकती है। एक नए अध्ययन में इसका खुलासा किया गया है। शोध के मुताबित मनुष्य के अंदर पाया जाने वाला एमआइआर-1202 उन लोगों में पाया जाता है जो अवसाद के शिकार होते हैं। कनाडा के मांन्ट्रियल में स्थित एमसी गिल यूनिवर्सिटी के प्रोफेसर और डगलस इंस्टीट्यूट के साइकेट्रिस्ट गुस्तवो तुरेकी का कहना है कि हमने स्वस्थ व्यक्ति और अवसादग्रस्त व्यक्ति में ब्रेन टिश्यूज का अध्ययन किया और उसकी तुलना की और पाया कि इस कण का अहम योगदान है। टीम ने कई सारे प्रयोग किए और पाया कि जो व्यक्ति अवसाद में नहीं है। उनमें माइक्रो आरएनए का लेवल कुछ और होता है। तुरेकी ने यह भी पाया कि यद्यपि एंटीडेस्प्रेंट्स साफ तौर पर प्रभावित करता है लेकिन इसके भी कई प्रकार होते हैं जो व्यक्ति के इलाज पर निर्भर करते हैं। यह अध्ययन अवसाद को कम करने के लिए इलाज में काफी प्रभावी साबित होगा। यह अध्ययन नेचर मेडिसिन नाम की पत्रिका में प्रकाशित हुआ था।

ग्लोबल वार्मिंग से बचा सकती है चींटी

चींटी हमें ग्लोबल वार्मिंग से बचा सकती है। शोधार्थियों के मुताबित, चींटियों ने 6.5 करोड़ साल पहले अपनी उत्पत्ति के बाद से बड़ी मात्र में हवा से कार्बन डाईऑक्साइड को सोखा है। एक चींटी का जीवन एक साल से अधिक का नहीं होता लेकिन जैसे-जैसे उसकी संख्या बढ़ती है, वैसे-वैसे वह वातावरण को ठंडा करने में मदद करती है। टेंप शहर में स्थित अरिजोना स्टेट विश्वविद्यालय के एक भूगर्भशास्त्री रोनाल्ड डॉर्न ने कहा, चींटियां पर्यावरण को बदल रही हैं। डॉर्न ने पाया कि चींटियों की कुछ प्रजाति खनिज में हवा को सोख कर कैल्शियम कार्बोनेट या लाइमस्टोन बनाने में मदद करती हैं। लाइमस्टोन बनाने की प्रक्रिया में चींटी हवा से कार्बन डाईऑक्साइड की कुछ मात्रा घटा देती है। अध्ययन दल ने यह भी पाया कि चींटियां बेसाल्ट पत्थर के टूटने में भी मदद करती है। उनके मुताबित, बेसाल्ट पत्थर को यदि खुले में छोड़ दिया जाए तो जितने समय में यह टूट-फूट कर मिट्टी में मिल जाएगा, चींटियां यह काम 50 से 300 गुणा अधिक तेजी से कर सकती हैं। डॉर्न ने कहा, चींटियां खनिज से कैल्शियम और मैग्निशियम निकाल सकती हैं और उसका उपयोग लाइमस्टोन बनाने में करती हैं। इस प्रक्रिया में वे कार्बन डाईऑक्साइड गैस की कुछ मात्रा पत्थरों में कैद कर लेती हैं। यह अध्ययन शोध पत्रिका जियोलॉजी में प्रकाशित हुआ है।

ज्यादा देर तक टीवी देखने से अकाल मौत का खतरा

एक नए शोध में कहा गया है कि एक दिन में लगातार तीन घंटे या उससे ज्यादा समय तक टेलिविजन देखने वाले लोगों में अकाल मृत्यु का जोखिम अपेक्षोकृत कम टेलिविजन देखने वालो की तुलना में दोगुना होने की आशंका रहती है। समाचार एजेंसी सिन्हुआ के मुताबित, अमेरिकन हार्ट एसोसिएशन के शोधकर्ताओं ने तीन किस्म के सुस्त व्यवहार और सभी वजहों-टेलिविजन देखने के समय, कम्प्यूटर पर काम करने के समय और वाहन चलाने के समय से होने वाली मौत के खतरे के बीच का संबंध पता लगाने के लिए स्पैनिश यूनिवर्सिटी के 13,284 युवा एवं सेहतमंद स्नातकोत्तरों का

मूल्यांकन किया। शोध में पाया गया कि एक दिन में तीन घंटे या उससे ज्यादा देर टेजीविजन देखने वाले प्रतिभागियों की मौत का खतरा कम टेलिविजन देखने वालों की अपेक्षा दोगुना अधिक था। शोधकर्ताओं को कम्प्यूटर प्रयोग या वाहन चलाने में बिताए गए समय और सभी कारणों से होने वाली अकाल मृत्यु के उच्च खतरे के बीच कोई महत्वपूर्ण संबंध नहीं मिला।

तनाव से घट सकती है स्मरण क्षमता

बिना वजह के तनाव से दूर रहिए, वरना समय से पहले ही आपकी स्मरण शक्ति कमजोर हो सकती है। शोधकर्ताओं के अनुसार, तनाव पैदा करने वाले हार्मोन का स्तर अधिक होता है, वृद्धावस्था में उनके मस्तिष्क में रचनात्मक परिवर्तन और स्मरण शक्ति में अल्पकालिक कमी दिखाई पड़ता है। चूहों पर किए गए इस शोध में शोधकर्ताओं ने अल्पकालिक स्मृति के लिए जिम्मेदार मस्तिष्क के प्रीफंटल कॉर्टिक्स के कोशिकाओं की जांच की। गौरतलब है कि चूहों में तनाव के लिए जिम्मेदार हार्मोन 'कोर्टिकोस्टेरॉन' मानवों में पाए जाने वाले हार्मोन 'कोर्टिसोल' के समान ही होता है। शोधकर्ताओं के अनुसार जिन चूहों में कॉर्टिकोस्टेरॉन का स्तर अधिक था, उनके प्रीफंटल कॉर्टेक्स की कोशिकाओं के बीच का संयोजन, अपेक्षाकृत कम कॉटिकोस्टेरॉन वाले चूहों से बेहद कम था। स्टेनफोर्ड विश्वविद्यालय के प्राध्यापक रॉबर्ट सैपोस्की ने कहा, मस्तिष्क के प्रीफंटल क्षेत्र में यह हार्मोन उम्र बढ़ाने वाले एक पेसमेकर की तरह काम कर सकता है। सैपोस्की हालांकि इस शोध से जुड़े नहीं हैं। रैडली कहते हैं, अध्ययन से पता चलता है कि मस्तिष्क में इस हार्मोन का प्रभाव जैसा पहले समझा जाता था उससे कहीं ज्यादा पड़ता हैं।

दुनिया का सबसे ज्यादा प्रदूषित शहर है दिल्ली

विश्व स्वास्थ्य संगठन के मुताबित देश की राजधानी दिल्ली दुनियां का सबसे ज्यादा प्रदूषित शहर है। 91 देशों के 1600 शहरों में कराए गए सर्वे में यह बात सामने आई है। 'ऐम्बिएंट एयर पॉल्यूशन' नामक इस रिपोर्ट के 2014 के संस्करण में 91 देशों के करीब 1600 शहरों में वायु प्रदूषण के ताजा हालात का ब्योरा दिया गया है। देश की राजधानी दिल्ली की हवाओं में $PM_{2.5}$ (पार्टिकुलेट मैटर) यानि सांस के साथ अंदर जाने वाले पार्टिकल, 2.5 माइक्रोन्स से छोटे पार्टिकल का कॉन्सनट्रेशन सबसे ज्यादा है। दिल्ली में यह 153 माइक्रोग्राम प्रति घन मीटर है। एशिया के दूसरे सघन आबादी वाले शहरों में भी दिल्ली के मुकाबले वायु प्रदूषण कम है। पाकिस्तान के करांची में यह 117 मइक्रोग्राम प्रति घन मीटर है, जबकि चीन के बीजिंग में 56 और शंघाई में 36 है। विश्व स्वास्थ्य संगठन के मानक के अनुसार $PM_{2.5}$ का कॉन्सनट्रेशन प्रति घन मीटर 10 माइक्रोग्राम से ज्यादा नहीं होना चाहिए। WHO की इस रिपोर्ट के बाद यह साफ है कि अगर जल्दी ही दिल्ली में प्रदूषण को कम करने के लिए ठोस पहल नहीं किए गये तो आने वाले दिनों में यहां बीमारियों में इजाफा हो सकता है।

सेक्स हार्मोन एस्ट्रोजन बनाता है महिलाओं को अवसादग्रस्त

महिलाओं के अवसाद और फिक्र या चिंता संबंधित बीमारियों से ग्रसित होने की संभावना अधिक है क्योंकि सेक्स हार्मोन एस्ट्रोजन पुरूषों की तुलना में महिलाओं के सिर में रक्त का अधिक प्रवाह करता है। एक महत्वपूर्ण शोध में ऐसा संकेत दिया गया है कि संभवतः यौवन के दौरान लिंग अंतर उत्पन्न हो सकता है। पेन्सिलवेनिया युनिवर्सिटी के प्रोफेसर थेओडोर सैटर्थवेट ने बताया कि ये नतीजे संभवतः किशोरा वस्था शुरू होने के साथ होने वाले तंत्रिका संबंधी महत्वपूर्ण विकार और मूड विकार, व्यग्रता या उत्कंठा विकार और एक

तरह की पागलपन सरीखी लिंग विषमताओं के प्रभाव हो सकते है। सैटर्थवेट ने समझाया कि आमतौर पर महिलाओं में चिंता या फिक्र की व्यापकता या फैलाव का स्तर अधिक होता है और पुरूषों में मानसिक विकारों का फैलाव ज्यादा होता है। शोधकर्ताओं ने शोध के लिए आठ से लेकर 22 वर्ष के बीच की 922 युवतियों के मस्तिष्क रक्त प्रवाह के विकास का विश्लेषण करने के लिए चुंबकीय प्रतिध्वनि इमेजिंग (एमआरआई) स्कैन का प्रयोग किया। शोध में पाया गया कि लड़की के मस्तिष्क के जिन हिस्सों में रक्त प्रवाह सबसे अधिक देखा गया, वे हिस्से वे हैं जो मनोभावों से निबटते हैं और सामाजिक स्थितियों पर नियंत्रण करते हैं। यह शोध 'प्रोसीडिंग ऑफ द नेशनल एकेडमी ऑफ साइंसेज' पत्रिका में प्रकाशित हुआ है।

GLP Compliance Certificate Awarded to CSIR-IITR

CSIR-Indian Institute of Toxicology Research (CSIR-IITR), Lucknow received the GLP Compliance Certification from the National GLP Compliance Monitoring Authority (NGCMA), Government of India. The certificate is issued with respect to toxicity and mutagenicity studies. GLP is an internationally accepted quality system concerned with the organizational process and the conditions under which pre-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. The national and international regulatory authorities/ agencies require the safety data of all new products including industrial chemicals, pharmaceuticals, veterinary drugs, pesticides, cosmetic products, food products and feed additives, etc., prior to their launch into the market. GLP is a system, which has been evolved by Organisation for Economic Co-operation and Development (OECD) and is used for achieving such safety goals.

It is also noteworthy that CSIR-IITR is the first CSIR Laboratory which has received this international accreditation. The GLP certification is a testament to high quality research by way of thorough SOP-driven Good Laboratory Practices, competent well-trained personnel and systematic documentation at CSIR-IITR. CSIR-IITR is committed to realize its mission towards serving the global needs in the area of toxicology and bio-safety. The certificate states that specified studies in the areas of toxicity and mutagenicity conducted at CSIR-IITR comply with OECD principles for GLP. This is a leap forward in the field of quality compliance and best practices in the public sector. The GLP Laboratories at CSIR-IITR are designed as per OECD guidelines, which make the integrity and quality of the Laboratory data adequate for regulatory submissions across the globe. India has a full adherence member status of OECD's Working Group on GLP, so the toxicity/ bio-safety data generated for chemicals/ formulations from GLP certified facility of CSIR-IITR will be accepted as such by the regulatory authorities in all the thirty four OECD member countries and all other associated non-member countries. CSIR-IITR is serving the international community for about fifty years in a unique way with the charter "Safety to Environment & Health and Service to Nation." The uniqueness of CSIR-

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राष्ट्रीय उत्तम प्रयोगशाला पद्धति (जी एल पी) अनुपालन निगरानी प्राधिकरण (एन जी सी एम ए)

जी एल पी अनुपालन प्रमाण-पत्र

निरीक्षण और तत्पश्चात अनुवर्ती कार्रवाईयों के आधार पर

विषैलापन जांच : जी एल पी जांच सुविधा

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एम. जी. मार्ग, लखनऊ–226001

को उत्तम प्रयोगशाला पद्धति (जी एल पी) के आर्थिक सहयोग एवं विकास संगठन (ओ ई सी डी) सिद्धांतो के अनुसार निम्नलिखित जांच/अध्ययन करने में सक्षम होने के लिए प्रमाणित किया जाता है:

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सुविज्ञता के विशिष्ट क्षेत्रों, रसायनों के प्रकार और जांच प्रणालियों को निम्नलिखित अनुलग्नक में सूचीबद्ध किया गया है।

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यह प्रमाण पत्र इस शर्त के अध्यधीन है कि जांच सुविधा राष्ट्रीय जी एल पी अनुपालन निगरानी प्राधिकरण के प्रलेख संख्या जी एल पी – 101 के निबंधन एवं शर्तों और जी एल पी के ओ ई सी डी सिद्धांतों का अनुपालन करती है।

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(डी आर प्रसादा राव)
प्रमुख, राष्ट्रीय जी एल पी
अनुपालन निगरानी प्राधिकरण

IITR has been further strengthened by the GLP certification and it is now the only institute in the CSIR family having the credentials to generate data for regulatory acceptance worldwide. We, as a team of GLP certified toxicologists are trying to put our utmost efforts to improve the public health by identifying toxicants, understand the mechanisms of their toxicity and minimize the potential impacts of their exposures on human health.

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Any feedback on this publication is welcome
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