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Inside

Indian Institute of Toxicology Research
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45th IITR Foundation Day

IITR celebrated its 45th foundation day on Nov. 4, 2010. Dr KC Gupta, director, IITR welcomed the distinguished guests Dr. Vishnu Mohan Katoch, Prof. S S Agrawal, former Directors of CSIR labs, former members of IITR family and members of the scientific community. Dr Gupta briefed about IITR's activities and achievements while presenting Annual Report of the institute, he informed that all the activities of institute are categorized under five broad Research and Development areas viz:

Systems Toxicology & Health Risk Assessment

Food, Drug & Chemical Toxicology

Environmental Toxicology

Nanomaterial Toxicology

Regulatory Toxicology

In the area of Systems Toxicology & Health Risk Assessment certain noteworthy findings that have been published and well received by the scientific community are:

A study that explored association of Single Nucleotide Polymorphism in cytochrome P450 2D6 and N-acetyltransferase-2 found that subjects carrying combination of heterozygous genotypes were found to be at significantly higher risk for Parkinson's disease demonstrating the importance of gene-gene interactions. Similarly, the association of polymorphism in Alcohol Dehydrogenase and its interaction with cytochrome P4502E1 and glutathione-S-transferases M1 suggest the role of interaction amongst the genes in determining the susceptibility to alcoholic liver cirrhosis. In a study, Silymarin pre-treatment was observed to counteract pyrogallol-induced hepatotoxic alteration in the expression of many transcripts associated with oxidative stress, cell cycle, cytoskeletal network, cell-cell adhesion, apoptosis, cell-signaling and intermediary metabolism in pyrogallol-exposed liver. The combinatorial effect of metal mixture (As, Cd and Pb) on rat brain development was investigated. The pups exhibited behavioral disturbances characterized by hyper- locomotion, increased grip strength and learning-memory deficit. Metal mixture was observed to induce synergistic toxicity in astrocytes that may compromise the blood brain barrier, leading to behavioral dysfunction in developing rats. A study showed that rat blood lymphocytes could be used as a surrogate to monitor hepatic expression and regulation of polycyclic aromatic hydrocarbons (PAHs) responsive cytochrome P450. The study to assess the impact of oxidative stress on DNA integrity in human sperms showed that antioxidants superoxide dismutase, catalase and glutathione had a positive association with sperm count and motility. These observations indicate that sperm DNA integrity may serve as a reliable prognostic tool for infertility evaluation.

The area of Food, Drug and Chemical Toxicology is gaining immense importance due to paradigm shifts in rapid urbanization and food security. A wide range of issues were addressed:

Plant products/extracts are being explored for their pharmacological potential: *Fumaria parviflora* extract was found to modulate nimesulide induced pro-and anti-apoptotic proteins in mitochondria and apoptosis in primary rat hepatocyte culture. Similarly, the extract of *Cymbopogon citratus* showed cytoprotective, antioxidative and anti-inflammatory property in murine alveolar macrophages indicating its potential to be used against lung inflammatory diseases. Alpha-lipoic acid, the metabolic antioxidant, showed a dose dependent protective effect on hexavalent chromium induced DNA damage. Alpha-lipoic acid was far better than ascorbate and therefore can be used as a therapeutic agent in occupational workers exposed to hexavalent chromium. In a study it was observed that Polo-like kinase1 gene silencing can enhance the sensitivity of human epithelial carcinoma A431 cells exposed to low doses of Cisplatin by upregulating p73 alpha expression and thus can be used as a possible approach in cancer chemotherapy. A study targeted the effect of food adulterant argemone oil and its major constituent sanguinarine showed the exfoliation of germ cells from sertoli cell, their viability after detachment, cytotoxicity and execution of apoptosis via mitochondrial pathway. These results suggest that alterations in germ cell apoptosis by a disruption in contact mediated communication between the sertoli cells and germ cells, may subsequently lead to testicular impairment. In addition, sanguinarine showed inhibition of cytochrome P450 1A1, 1A2, 2D1, 2E1, 3A1 and Phase II enzymes thereby augmenting its toxicity. In another study, co-administration of *Lathyrus sativus* and Manganese in guinea pigs showed a significant decrease in neuronal nucleotidase and ATP-ase activities along with enhancement of blood brain barrier permeability. These results suggest that Mn may potentiate the neurotoxicity of lathyrus/ P-oxalyl-L-diamino propionic acid by altering the blood-brain barrier permeability. In a study, the presence of novel allergenic proteins of commonly consumed legumes was determined using Pepsin resistance of proteins. A number of non-digestible proteins from the chickpea, black gram, kidney bean and Bengal gram were detected which exhibited IgE binding properties with allergenic patients sera suggesting potential allergenicity.

An area of research that is being revisited due to release of new chemical entities from unorganised sector, GMOs, and now engineered nanomaterials is Environmental Toxicology. This area encompasses the development and application of alternate animal models, microorganisms and remedial approaches. Heat shock protein, Hsp70 expression in accessory glands of male flies and ovaries

of females was enhanced with tissue damage in *Drosophila melanogaster* exposed to leachates from tannery solid waste. The study suggests that tannery waste leachates cause adverse effects on the expression of genes encoding seminal proteins and that Hsp70 may be used as a marker of cellular damage. In another study, the effects of co- exposure of benzene, toluene and xylene to transgenic *Drosophila melanogaster* (heat shock proteins) showed antagonistic effect of xylene and toluene on benzene toxicity. These studies support the contention that Drosophila can serve as an alternative animal model for first tier screening of adverse effects of chemical mixtures.

In the domain of remediation the studies addressed issues using molecular modeling of catabolic enzymes and metabolic diversity of microbial communities to detoxify pollutants: Molecular phylogenetic approach was used to understand bacterial communities associated with sites contaminated with chlorinated pesticides like Hexa-chloro-cyclohexane, DDT and Endosulfan. The development and application of plant or plant material based approaches for removal of Hexavalent chromium, Pb, Zn and Mn from drinking water and zinc mine tailings indicated remediation potential of such approaches. A bacterial co-culture decolourized post methanated distillery effluent with formation of a number of metabolic products in waste water that exhibited reduced toxicity in plant model. A number of studies explored microbiological quality of the surface and potable water. Linear and nonlinear models were developed for the performance evaluation of an up-flow anaerobic sludge blanket (UASB) reactor based wastewater treatment plant. Artificial neural networks modeling methods developed and applied to predict simultaneously the Dissolved Oxygen and Biochemical Oxygen Demand levels using eleven input variables measured in the Gomti river water at eight different sites over a period of ten years.

The understanding that Technology is always ahead of Toxicology also holds true for Nanotechnology with availability of more than 1000 products in the world market. This has led to emergence of Nanomaterial Toxicology to assess safety/ toxicity of engineered nanomaterials and devices. Certain interesting observations made in the studies by IITR scientists include:

Tumor-specific gene delivery is the primary challenge in non-viral mediated gene therapy. In a study, branched polyethylenimine (bPEI) was modified by forming nanoconstructs with a natural polysaccharide, chondroitin sulfate (CS), to impart site-specific property. The CS-PEI (CP) nanoconstructs possess significantly lower toxicity and enhanced transfection efficiency compared to PEI and commercial transfection reagents. These findings demonstrate that CP nanoconstructs could be exploited as carriers for nanomedicine for efficient management of solid tumor. In another study, nanostructured hydroxyapatite—titania bio-implant scaffolds with different morphologies were synthesised that were corrosion resistant and biocompatible as compared to bare titanium foil. In a mechanistic study, silica nanoparticles were found to exert toxicity in human lung epithelial cells through the reactive oxygen species and lipid peroxidation rather than the depletion of glutathione. In a study, cytotoxic and genotoxic evaluation of glycolipid-conjugated silver and gold nanoparticles was conducted. Gold nanoparticles were found to be more cyto-compatible compared to the same concentration of silver nanoparticles. It was also demonstrated that silver nanoparticles cause more DNA damage compared to gold nanoparticles.

Societal Activities

An epidemiological study was conducted to evaluate health risks of employees working in pesticide retail shops in urban areas of Lucknow and Barabanki based on socio-economic status, family history, personal habits and work practices. The study revealed significant decrease of Motor Nerve Conduction Velocity and low Peak Expiratory Flow Rate among shopkeepers. Neurological, ocular, cardiovascular and musculo-skeletal symptoms were also found to be higher among shopkeepers. These findings provide a prima facie evidence of clinical manifestations because of multiple exposures to pesticides and poor safety culture at work place.

Monitoring of pesticide residues in market basket samples of vegetables from Lucknow City was carried out. The study assessed 48 pesticide residues including organochlorines, organophosphates, synthetic pyrethroids, and herbicides in 20 types of vegetables (including leafy, root, modified stem, and fruity vegetables like bitter gourd, jack fruit, French-bean, onion, colocassia, pointed gourd, capsicum, spinach, potato, fenugreek seeds, carrot, radish, cucumber, beetroot, brinjal, cauliflower, cabbage, tomato, okra, and bottle gourd). Twenty-three pesticides were detected of the 48 pesticides analyzed in the samples with the range of 0.005-12.35 mg kg-1. In some vegetables like radish, cucumber, cauliflower, cabbage, and okra, the detected pesticides (I-HCH, Permethrin-II, Dichlorvos, and Chlorofenvinfos) were above maximum residues limit.

In another surveillance study, Curcumin, the principal curcuminoid of turmeric responsible for its yellow color and measure of quality was monitored in loose versus branded turmeric powders. The study shows that curcumin content in branded samples ranged from 2 to 4% while non-branded samples had 0.3 to 2.7%. Almost 17% of loose powders showed presence of extraneous color-metanil yellow, in the range of 1 - 8.6 mg per g. Thus there is a need to prescribe realistic curcumin limits for

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turmeric powder.

While highlighting the publications of institute Dr Gupta said that institute published 145 papers in peer-reviewed journals with 46 papers having impact factor of 3.0 and above including 7 papers with impact factor of > 5. Dr Gupta concluded his lecture by the slogan Jai Bharat, Jai Vigyan.

Dr Vishwa Mohan Katoch, Secretary Government of India, Department of Health Research, Ministry of Health and Family Welfare and Director General, Indian Council of Medical Research, New Delhi delivered 14th Professor Sibte Hasan Zaidi Oration entitled "Relevance of Toxicology Research in the context of Advances in Health Sciences" Prof. SH Zaidi Oration is being held every year to honour Prof. SH Zaidi, the founder Director of IITR. While delivering his lecture Dr Katoch said that toxicological investigations have always been very important for many applications which include testing of the therapeutic compounds/products and also for knowing the effect of various toxic materials to which we are commonly exposed. With the changing times, profile changes. During the last one decade, Nanomedicine has emerged as a potential area for developing diagnostics for imaging as well as therapeutics for difficult diseases like cancer. As the character of the Nanomaterials totally changes and becomes unpredictable, it is important that their toxicology is investigated with utmost care and depth. Similarly because of many chemical industries and also the exposure to many chemicals sometimes as major disasters, this knowledge assumes great importance. It is important to update the technology for the same. Similarly the need to reduce the animal experimentation and shift to non animal living cell system for toxicology testing has become a necessity. It is thus important that their standardization and usefulness is investigated appropriately so that results are meaningful and reliable. He concluded that many opportunities are ahead of us in developing this scene further.

Prof. SS Agrawal in his presidential address at the outset appreciated the concluding remark (Jai Bharat, Jai Vigyan) of Dr KC Gupta's presentation. He said that Dr Gupta's slogan is very timely and appropriate because development and upliftment of nation lies in scientific achievement and scientific developments are nothing but value addition. He further said that celebration of Annual day is an exercise to assess and recognize the institute's achievements, it is an stock checking and goal setting process. He raised the question that by changing the institutes name from ITRC to IITR is there any change in mandate of institute? Are there any extra responsibilities on the shoulder of institute?

He said when we think of environment, there is a need to change the total mind set. With reference to environment health and disease, there are three types of environment:-

1. Home environment
2. Occupational environment
3. Leisure environment

Health and disease is a multi-factorial phenomenon, there are many factors, and one of them is genetic determinant. Environment plays a role of modifier in the process of disease development. He raised his concern about the genetically modified food products, since all these biological interventions are going to modify the immune response; there is a challenge for the scientists to find out the stem cell responsible for allergenicity. He further said that the study of environment is required in totality, not as individual aspects. Prof. SS Agrawal also honoured the following staff members, selected as best workers by IITR S&T staff: Mr. Kallimuddin, Mr. Kamta Prasad, Mr. Mukund Sahai

Dr Mukul Das proposed the vote of thanks

Inaugurations of Annual Day function by lighting the lamp

Release of IITR annual report in CD

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Dr Katoch delivering the Zaidi oration

Dr KC Gupta presenting memento to Dr Katoch

A view of audience

Lighter moments during the foundation day function

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Alternate Animal Models in Biological Research: Present and Future Perspectives in Toxicology

An International Symposium on "Alternate Animal Models in Biological Research: Present and Future Perspective in Toxicology" was organized by Indian Institute of Toxicology Research, Lucknow, India during Oct 29-31, 2010, as a part of international collaborative programme between Indian Institute of Toxicology Research, India and University of Nottingham, UK under aegis of a UK-IERI major research award project. The rationale behind this symposium was to critically discuss the future prospects of toxicological research on alternate animal models and provide insights in relation to toxicology to offer better environmental health for the entire biota. The symposium provided a platform for the experts around the globe to share their views and ideas about the challenges in biological/toxicological research involving alternate animal models.

In the inaugural function Prof. Subash Chandra Lakhotia, Professor of Zoology and DST Ramanna Fellow, Banaras Hindu University, Varanasi was the Chief Guest and Prof. David De Pomerai, School of Biology, Nottingham University, UK was the Guest of Honour. The function was presided over by Dr. RC Srimal, Former Director, IITR. Dr. KC Gupta, Director-IITR and Chairman of the symposium highlighted the need to look for alternatives in biological research. Dr. D Kar Chowdhuri, Convener of the symposium, gave the

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genesis of the symposium. Prof. Lakhotia in his Keynote Address emphasized the importance of fly based screens to resolve the complex networks underlying neurodegenerative diseases that have posed a major challenge for therapeutics. During the symposium, there were plenary, invited, platform presentations, accompanied with poster/oral presentations by students. In addition, there was an interactive session between scientists and students, from varied academic background.

After inauguration, during the first scientific session on **Stress Biology and Genotoxicity,** the speakers highlighted how information generated through multifaceted approach involving two invertebrate models, *Caenorhabditis elegans* and *Drosophila melanogaster* can provide a simplified and sketchy overview of a toxicant's acute effects. Subsequent lectures in this session highlighted the use of aquatic species for evaluation monitoring of aquatic environment. The last session of the day, **Development and Differentiation,** witnessed the use of alternate animal models towards understanding the role of a particular set of genes in development and role of proteins in mRNA metabolism and cell signaling as well as differentiation.

The first session of day two, on October 30, 2010 was dedicated to **Comparative and functional genomics**. The presentations highlighted the use of alternate animal models like Drosophila and Zebra fish and a disease causing organism, *Mycobacterium tuberculosis,* for exploring the way how DNA sequence and chromatin architecture combine to facilitate special temporal control of gene expression and to understand patterns of genomic changes, genomic architecture underlying complex behaviors and to develop maps for better biological interpretations. The next session was focused on **Models and applications**. This session highlighted (i) Potential of Drosophila as a model for elucidating mechanism of neurodegenerative disease, spinocerebellar ataxia 2 (ii) Comparative and functional genomic studies for assessing transgenerational potential of environmental effects of adult exposure in fly model (iii) Hydra as a functional model for studying evolution of cell signaling, and (iv) Understanding biological basis of complex behaviours using an emerging model prairie vole (*Microtus ochrogaster*) using genomic approaches. **Computational and Mathematical modeling** session highlighted the importance of inter-disciplinary interactions/collaborations in understanding complex biological networks. The talks focused on how eukaryotic stress response networks, gene regulator networks and toxicity can be understood using mathematics and computational methods.

The third and the last day, October 31, 2010, of AAMBR started with session on **Ecology and Environmental safety,** wherein, presentations highlighted the use of various alternate models (fish, *C. elegans* and Drosophila) for getting insights into ecotoxicological and disease aspects. The next session, **Physiology and aging,** witnessed presentations on how hormones, metabolism and dietary restrictions influence the life span and the utility of Drosophila in understanding mechanisms underlying cell cycle progression under metabolic stress. The session also witnessed efficacy of blood lymphocyte Cytochrome P450 as markers for monitoring toxicity. The last session of the symposium was scheduled as platform presentations by research students. The session provided an excellent opportunity for the students to highlight their research findings and also to have excellent inputs from the peers. Mr. Manish Mishra, DBT-SRF from IITR, won the best presentation award for his talk on "Hexavalent chromium causes double strand breaks in *Drosophila melanogaster*: Evidences from *in vivo* studies"

Apart from these sessions, the symposium also witnessed youthful poster sessions which included the presentations by research scholars focusing on studying gene network, reproductive performance, myogenesis, neuromodulation, oxidative stress and cellular toxicity using various alternate model systems, such as Drosophila, *C. elegans*, *Musca domestica*, bacteria, fish etc**.** Ms. Akanksha (BHU, India), Ms. Divya Singh (BHU, India), Mr. Anurag Sharma (IITR, India), and Mr. P. Jitendra (CLRI, India) won first, second, third and fourth best poster presentation awards, respectively. In parallel to the poster session, an interactive session between school, college and university students with the eminent scientists and teachers was held wherein importance of basic sciences in solving fundamental questions in biology was discussed. In a panel discussion recommendations were made for future

Inaugural ceremony of the conference

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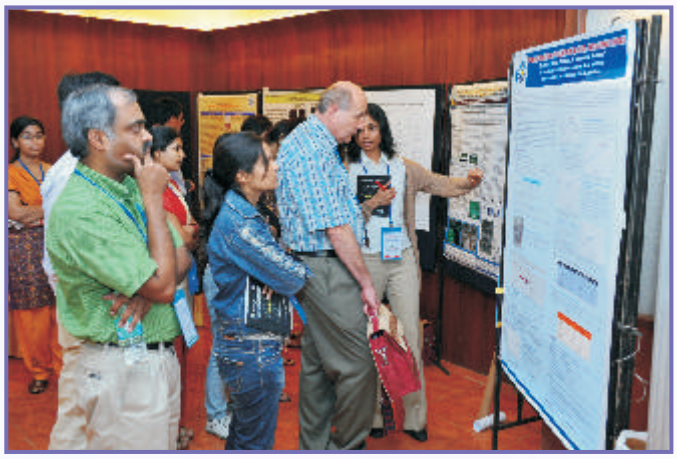
directions of R&D on alternate animal models on basic and applied research pertaining to environmental safety and human health. The valedictory function marked the end of three day international symposium. Dr. Ravi Ram, Joint convener of the symposium, summarized the proceedings of the symposium. The valedictory address was given by Prof. BS Srivastava, Emeritus Scientist, Central Drug Research Institute, India and function was chaired by Dr. TK Chakraborty, Director, Central Drug Research Institute, India.



Poster session in progress

Interactive session with the students

IITR RESEARCH HIGHLIGHTS

Nimesulide aggravates redox imbalance and calcium dependent mitochondrial permeability transition leading to dysfunction in vitro.

[Singh BK, Tripathi M, Pandey PK, Kakkar P. Toxicology. 2010 Sep 10;275(1-3):1-9.]

Nimesulide (selective cyclooxygenase-2 inhibitor) is a nonsteroidal anti-inflammatory drug for the symptomatic treatment of painful conditions like osteoarthritis, spondilitis and primary dysmenorrhoea. Nimesulide induced liver damage is a serious side effect of this otherwise popular drug. The mechanism involved in nimesulide induced hepatotoxicity is still not fully elucidated. However, both mitochondrial dysfunction and oxidative stress have been implicated in contributing to liver injury in susceptible patients. Mitochondria besides being the primary source of energy, act as a hub of signals responsible for initiating cell death, irrespective of the pathway, i.e. apoptosis or necrosis. The present study was aimed to explore the role of compounding stress, i.e. Ca(2+) overload and GSH depletion in nimesulide induced mitochondrial toxicity and dysfunction. Our study showed that, nimesulide (100 microM) treatment resulted into rapid depletion of GSH (60%) in isolated rat liver mitochondria and significant Ca(2+) dependent MPT changed. Enhanced ROS generation (DCF fluorescence) was also observed in mitochondria treated with nimesulide. An important finding was that the concentration at which nimesulide oxidized reduced pyridine nucleotides (autofluorescence of NAD(P)H), it affected mitochondrial electron flow (MTT activity decreased by 75%) and enhanced mitochondrial depolarization significantly as assessed by Rhodamine 123 fluorescent probe. Therefore, nimesulide was found to aggravate redox imbalance and affect Ca(2+) dependent mitochondrial membrane permeability transition leading to dysfunction and ultimately cell death.

Accumulation and translocation of heavy metals in soil and plants from fly ash contaminated area.

[Singh R, Singh DP, Kumar N, Bhargava SK, Barman SC. J Environ Biol. 2010 Jul;31(4):421-30.]

The present investigation deals with the accumulation of heavy metals in fields contaminated with fly ash from a thermal power plant and subsequent uptake in different parts of naturally grown plants. Results revealed that in the contaminated site, the mean level of all the metals (Cd, Zn, Cr, Pb, Cu, Ni, Mn and Fe) in soil and different parts (root and shoots) of plant species were found to be significantly ($p<0.01$) higher than the uncontaminated site. The enrichment factor (EF) of these metals in

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contaminated soil was found to be in the sequence of Cd (2.33) > Fe (1.88) > Ni (1.58) > Pb (1.42) > Zn (1.31) > Mn (1.27) > Cr (1.11) > Cu (1.10). Whereas, enrichment factor of metals in root and shoot parts, were found to be in the order of Cd (7.56) > Fe (4.75) > Zn (2.79) > Ni (2.22) > Cu (1.69) > Mn (1.53) > Pb (1.31) > Cr (1.02) and Cd (6.06) approximately equal Fe (6.06) > Zn (2.65) > Ni (2.57) > Mn (2.19) > Cu (1.58) > Pb (1.37) > Cr (1.01) respectively. In contaminated site, translocation factor (TF) of metals from root to shoot was found to be in the order of Mn (1.38) > Fe (1.27) > Pb (1.03) > Ni (0.94) > Zn (0.85) > Cd (0.82) > Cr (0.73) and that of the metals Cd with Cr, Cu, Mn, Fe; Cr with Pb, Mn, Fe and Pb with Fe were found to be significantly correlated. The present findings provide us a clue for the selection of plant species, which show natural resistance against toxic metals and are efficient metal accumulators.

Quantitative evaluation of benzene, toluene, and xylene in the larvae of *Drosophila melanogaster* by solid-phase microextraction/gas chromatography/mass spectrometry for potential use in toxicological studies.

[Mudiam MK, Singh MP, Chowdhuri DK, Murthy RC. J AOAC Int. 2010 Sep-Oct;93(5):1595-9.]

A simple, rapid, and solvent-free method for quantitative determination of benzene, toluene, and Xylene in exposed Drosophila larvae was developed using headspace solid-phase microextraction (HS-SPME) coupled to GC/MS. Larvae fed on standard Drosophila food mixed with benzene, toluene, and Xylene for 48 h were homogenized in Milli-Q water. Extraction of benzene, toluene, and Xylene was performed at 65^{0}C for 30 min on the SPME fiber (silica-fused). Subsequently, the fiber was desorbed in the GC injection port, followed by GC/MS analysis in the selected-ion monitoring mode. An external calibration curve was used for the quantification of benzene, toluene, and Xylene in the exposed organism. Recoveries were in the range of 78-82% (intraday) and 76-81% (interday) in larvae, and 91-96% (intraday) and 87-92% (interday) in the diet. LOD with an S/N of 3:1 and LOQ with an S/N of 10:1 were in the range of 0.01-0.023 and 0.034-0.077 µg/L, respectively. Percent RSD values for benzene, toluene, and Xylene were in the range of 0.50-0.81 (intraday) and 0.89-1.23 (interday) for retention time, and 2.16--3.85 (intraday) and 2.99-4.95 (interday) for peak concentration, showing good repeatability. This method was sensitive enough to quantitate benzene, toluene, and Xylene in small exposed organisms like Drosophila larvae. The SPME/GC/MS method developed may have wider applications in various in vivo toxicological studies.

Colorimetric detection of nucleic acid signature of shiga toxin producing *Escherichia* coli using gold nanoparticles.

[Jyoti A, Pandey P, Singh SP, Jain SK, Shanker R. J Nanosci Nanotechnol. 2010 Jul;10(7):4154-8.]

Enterohemorrhagic *E. coil* (EHEC) serotype O157:H7 is one of the major pathogens, responsible for the severe disease outbreaks. EHEC causes diseases in humans through production of shiga-like toxin leading to bloody diarrhea. The toxin is encoded by stx2 gene in *E. coli.* The current methodology for detection of EHEC relies on fluorogenic-substrate based culture media or nucleic acid amplification based Real-Time Polymerase Chain Reaction assays that are either time consuming or need expensive instrumentation. In this study, the optical properties of gold nanoparticles (GNPs) have been exploited for detection of nucleic acid of *Escherichia coli* O157:H7. The stx2 gene representing EHEC signature has been targeted using the gold nanoparticle probes. Gold nanoparticles (GNPs) of 20 +/- 0.2 nm were synthesised by citrate reduction method and characterised by spectroscopy and transmission electron microscopy. The GNPs were functionalised with 19 and 22 bp of thiolated single stranded DNA complementary to target highly conserved 149 bp region of stx2 gene. Transmission Electron Microscopy revealed the hybridization, aggregation and reduction in the interparticle distances of the GNP probes in the presence of target DNA. The aggregation and the spectral shift in the plasmon band observed with $10^{(6)}$ copies of target DNA indicates feasibility of a simple and quick colorimetric 'spot and read' test in contrast to amplification based detection methods.

ROS-mediated genotoxicity induced by titanium dioxide nanoparticles in human epidermal cells.

[Shukla RK, Sharma V, Pandey AK, Singh S, Sultana S, Dhawan A. Toxicol In Vitro. 2011 Feb;25(1):231-41.]

Titanium dioxide nanoparticles ($TiO_{(2)}$ NPs) are among the top five NPs used in consumer products, paints and pharmaceutical preparations. Since, exposure to such nanoparticles is mainly through the skin and inhalation, the present study was conducted in the human epidermal cells (A431). A mild cytotoxic response of $TiO_{(2)}$ NPs was observed as evident by the MTT and NR uptake assays after 48 h of exposure. However, a statistically significant ($p<0.05$) induction in the DNA damage was observed by the Fpg-modified Comet assay in cells exposed to 0.8 µg/ml $TiO_{(2)}$ NPs (2.20±0.26 vs. control 1.24±0.04) and higher concentrations for 6 h. A significant ($p<0.05$) induction in micronucleus

formation was also observed at the above concentration (14.67±1.20 vs. control 9.33±1.00). $TiO_{(2)}$ NPs elicited a significant ($p<0.05$) reduction in glutathione (15.76%) with a concomitant increase in lipid hydroperoxide (60.51%; $p<0.05$) and reactive oxygen species (ROS) generation (49.2%; $p<0.05$) after 6h exposure. Our data demonstrate that $TiO_{(2)}$ NPs have a mild cytotoxic potential. However, they induce ROS and oxidative stress leading to oxidative DNA damage and micronucleus formation, a probable mechanism of genotoxicity. This is perhaps the first study on human skin cells demonstrating the cytotoxic and genotoxic potential of $TiO_{(2)}$ NPs.

Transcriptome analysis provides insights for understanding the adverse effects of endosulfan in *Drosophila melanogaster.*

[Sharma A, Mishra M, Ram KR, Kumar R, Abdin MZ, Chowdhuri DK. Chemosphere. 2011 Jan;82(3):370-6.]

Indiscriminate use of agrochemicals worldwide, particularly, persistent organic pollutants (POPs), is of concern. Endosulfan, a POP, is used by various developing/developed nations and is known to adversely affect the development and the hormonal profiles of humans and animals. However, little is known about the molecular players/pathways underlying the adverse effects of endosulfan. We therefore analyzed the global gene expression changes and subsequent adverse effects of endosulfan using Drosophila. We used *Drosophila melanogaster* keeping in view of its well annotated genome and the wealth of genetic/molecular reagents available for this model organism. We exposed third instar larvae of *D. melanogaster* to endosulfan (2.0 µg mL(-1)) for 24 h and using microarray, we identified differential expression of 256 genes in exposed organisms compared to controls. These genes are associated with cellular processes such as development, stress and immune response and metabolism. Microarray results were validated through quantitative PCR and biochemical assay on a subset of genes/proteins. Taking cues from microarray data, we analyzed the effect of endosulfan on development, emergence and survival of the organism. In exposed organisms, we observed deformities in hind-legs, reminiscent of those observed in higher organisms exposed to endosulfan. In addition, we observed delayed and/or reduced emergence in exposed organisms when compared to their respective controls. Together, our studies not only highlight the adverse effects of endosulfan on the organism but also provide an insight into the possible genetic perturbations underlying these effects, which might have potential implications to higher organisms.

Expression and inducibility of endosulfan metabolizing gene in Rhodococcus strain isolated from earthworm gut microflora for its application in bioremediation.

[Verma A, Ali D, Farooq M, Pant AB, Ray RS, Hans RK. Bioresour Technol. 2011;102(3):2979-84.]

The metabolizing potential of a bacterial strain Rhodococcus MTCC 6716, isolated from the gut of an Indian earthworm *(Metaphire posthuma)* was studied for endosulfan bioremediation. In the present work, the optimum conditions for the maximum growth, kinetic of endosulfan degradation, regression equation, half life and correlation coefficient were studied. Endosulfan induced alterations in the expression of mRNA and protein of specific endosulfan metabolizing marker gene (Esd) was studied. Maximum growth of bacteria was observed at pH 7.0, 30°C and 0.085M sodium chloride concentration in a liquid culture medium. Endosulfan was degraded by Rhodococcus strain up to 97.23% within 15days without producing toxic metabolite and with strong correlation coefficient (-0.728) and half life 5.99days. Endosulfan degradation was mediated through gene(s) present in genomic DNA. Expression of marker gene was found endosulfan concentration dependent. The results suggest that this novel strain (Rhodococcus) may be utilized for bioremediation of endosulfan.

Caspase cascade regulated mitochondria mediated apoptosis in monocrotophos exposed PC12 cells.

[Kashyap MP, Singh AK, Siddiqui MA, Kumar V, Tripathi VK, Khanna VK, Yadav S, Jain SK, Pant AB. Chem Res Toxicol. 2010 Nov 15;23(11):1663-72.]

Monocrotophos (MCP) is a commonly used organophosphorus (OP) pesticide. We studied apoptotic changes in PC12 cells exposed to MCP. A significant induction in reactive oxygen species (ROS), lipid peroxide (LPO), and the ratio of glutathione disulfide (GSSG)/reduced glutathione (GSH) was observed in cells exposed to selected doses of MCP. Following the exposure of PC12 cells to MCP, the levels of protein and mRNA expressions of Caspase-3, Caspase-9, Bax, p53, P(21), Puma, and cytochrome-c were significantly upregulated, whereas the levels of Bcl(2), Bcl(w), and Mcl1 were downregulated. TUNEL assay, DNA laddering, and micronuclei induction show that long-term exposure of PC12 cells to MCP at higher concentration (10(-5) M) decreases the number of apoptotic events due to an increase in the number of necrotic cells. MCP-induced translocation of Bax and cytochrome-c proteins between the cytoplasm and

mitochondria confirmed the role of p53 and Puma in mitochondrial membrane permeability. Mitochondria mediated apoptosis induction was confirmed by the increased activity of caspase cascade. We believe that this is the first report showing MCP-induced apoptosis in PC12 cells, which is mitochondria mediated and regulated through the caspase cascade. Our data demonstrates that MCP induced the apoptotic cell death in neuronal cells and identifies the possible cellular and molecular mechanisms of organophosphate pesticide-induced apoptosis in neuronal cells.

Novel drug targets based on metallobiology of Alzheimer's disease.

[Bandyopadhyay S, Huang X, Lahiri DK, Rogers JT. Expert Opin Ther Targets. 2010 Nov;14(11):1177-97.]

Increased localization of Zn, Fe, Cu and Al within the senile plaques (SP) exacerbates amyloid beta (Aβ)-mediated oxidative damage, and acts as catalyst for Aβ aggregation in Alzheimer's disease (AD). Thus, disruption of aberrant metal-peptide interactions via chelation therapy holds considerable promise as a rational therapeutic strategy against Alzheimer's amyloid pathogenesis. The complexities of metal-induced genesis of SP are reviewed. The recent advances in the molecular mechanism of action of metal chelating agents are discussed with critical assessment of their potential to become drugs. Taking into consideration the interaction of metals with the metal-responsive elements on the Alzheimer's amyloid precursor protein (APP), readers will gain understanding of several points to bear in mind when developing a screening campaign for AD-therapeutics. A functional iron-responsive element (IRE) RNA stem loop in the 5' untranslated region (UTR) of the APP transcript regulates neural APP translation. Desferrioxamine, clioquinol, tetrathiolmolybdate, dimercaptopropanol, VK-28, and natural antioxidants, such as curcumin and ginko biloba need critical evaluation as AD therapeutics. There is a necessity for novel screens (related to metallobiology) to identify therapeutics effective in AD.

Bioaccumulation of copper and toxic effects on feeding, growth, fecundity and development of pond snail *Lymnaea luteola L.*

[Das S, Khangarot BS. J Hazard Mater. 2011 Jan 15;185(1):295-305.]

We studied the bioaccumulation and the toxic effects of Cu on survival, number of eggs and eggmasses laying, embryo development, growth, and food consumption in an Indian pond snail, *Lymnaea luteola* L. exposed for 7 weeks. Copper caused loss of chemoreception, locomotion and inhibited food consumption significantly during 7 weeks of exposure. Food consumption in Cu exposed snails significantly decreased and at 56 and 100 µg $L^{(-1)}$, snail stopped feeding activity. Mean number of eggmasses or eggs significantly decreased in Cu concentrations during the 7 week study. The percentage hatching decreased in Cu concentrations but there was more than 95% hatched in control in 10-11 days after spawning. Egg development was completely inhibited at 100 µg $L^{(-1)}$, while abnormal embryonic development observed at 32 and 56 µg $L^{(-1)}$ of Cu. The Cu concentration in tissues increased in Cu treated snails and bioaccumulation factor ranged from 2.3 to 18.7. Snail growth at 5.6 and 10 µg $L^{(-1)}$ was reduced by 6.2% and 16.9%, respectively. The study revealed that snail embryos and adults could be used as in vivo test models for ecotoxicological studies. Findings of present study are helpful for advancing water quality guidelines for protecting aquatic biota.

Maneb and paraquat-induced modulation of toxicant responsive genes in the rat liver: comparison with polymorphonuclear leukocytes.

[Ahmad I, Shukla S, Kumar A, Singh BK, Patel DK, Pandey HP, Singh C. Chem Biol Interact. 2010 Dec 5;188(3):566-79.]

Experimental studies have shown that toxicant responsive genes, cytochrome P450s (CYPs) and glutathione S-transferases (GSTs) play a critical role in pesticide-induced toxicity. CYPs play pro-oxidant role and GSTs offer protection in maneb (MB) and paraquat (PQ)-induced brain and lung toxicities. The present study aimed to investigate the effect of repeated exposures of MB and/or PQ on lipid peroxidation (LPO), glutathione content (GSH) and toxicant responsive genes, i.e., CYP1A1, 1A2, 2E1, GSTA4-4, GSTA1-1 and GSTA3-3 in the liver and to correlate the same with polymorphonuclear leukocytes (PMNs). A significant augmentation in LPO and reduction in GSH content was observed in a time of exposure dependent manner in the liver and PMNs of MB and/or PQ treated animals. The expression and catalytic activity of CYP2E1 and GSTA4-4 were significantly increased following MB and/or PQ exposure both in the liver and PMNs. Although the expression of GSTA3-3 was increased, the expression of GSTA1-1 was unaltered after MB and/or PQ treatment in both the liver and PMNs. MB augmented the expression and catalytic activity of CYP1A1 in the liver, however, CYP1A2 was unaffected. PQ, on the other hand, significantly increased hepatic CYP1A2 expression and catalytic activity. MB and/or PQ did not

produce any significant changes in CYP1A1 and CYP1A2 in PMNs. The results of the study thus demonstrate that MB and PQ differentially regulate hepatic CYP1A1 and CYP1A2 while LPO, GSH, CYP2E1, GSTA4-4 and GSTA3-3 are modulated in the similar fashions both in the liver and PMNs.

Face mask application as a tool to diminish the particulate matter mediated heavy metal exposure among citizens of Lucknow, India.

[Singh MP, Singh VK, Patel DK, Tandon PK, Gaur JS, Behari JR, Yadav S. Sci Total Environ. 2010 Nov 1;408(23):5723-8.]

Traffic related fine particulate emissions, enriched in metal contents, are directly linked to respiratory disorders in human subjects. In view of the growing traffic related emissions in India, the present study was undertaken to estimate the heavy metal exposure among non-occupationally exposed two vehicle riders of Lucknow City and related health effects via application of face masks (FMs) fitted with cellulose nitrate filters and measuring the peak respiratory flow rate (PEFR). Carefully selected 200 volunteers (asymptomatic n=154 and symptomatic n=46) were advised to use FMs during their deriving time for 30 days and PEFR test was conducted on each subject at the beginning, i.e. 0 day, and at end of the study period, i.e. 30 days. On completion of the prescribed study period, filters from the used FMs were collected, acid leached and analyzed for Fe, Mn, Cu, Zn, Pb, Ni, Cr and Cd. Asymptomatic and symptomatic subject groups were further divided into two age groups of 15-40 years and 41-68. Pb, Cu and Cd were significantly higher in lower age group (15-40) of symptomatic group and Cr was in asymptomatic group. Negative associations were observed between metals viz. Pb ($r=-0.39$, $p<0.001$), Cd ($r=-0.26$, $p<0.001$), Fe ($r=-0.37$, $p<0.001$), Mn ($r=-0.15$, $p<0.05$) and the lung functioning. 30 days PEFR of all subjects were higher by nearly 10% than 0 day in all 200 samples irrespective of age and symptomatic nature of the subject. The improvement could also be due to metals and other organic species, not analyzed herein. Nevertheless the results indicate that FM usage has a role to play for immediate, if not ultimate, improvement in public health and need further studies.

Pineapple bromelain induces autophagy, facilitating apoptotic response in mammary carcinoma cells.

[Bhui K, Tyagi S, Prakash B, Shukla Y. Biofactors. 2010 Nov-Dec;36(6):474-82.]

Bromelain, from pineapple, possesses potent anticancer effects. We investigated autophagic phenomenon in mammary carcinoma cells (estrogen receptor positive and negative) under bromelain treatment and also illustrated the relationship between autophagy and apoptosis in MCF-7 cells. MCF-7 cells exposed to bromelain showed delayed growth inhibitory response and induction of autophagy, identified by monodansylcadaverine localization. It was succeeded by apoptotic cell death, evident by sub-G1 cell fraction and apoptotic features like chromatin condensation and nuclear cleavage. 3-Methyladenine (MA, autophagy inhibitor) pretreatment reduced the bromelain-induced autophagic level, also leading to decline in apoptotic population, indicating that here autophagy facilitates apoptosis. However, addition of caspase-9 inhibitor Z-LEHD-FMK augmented the autophagy levels, inhibited morphological apoptosis but did not prevent cell death. Next, we found that bromelain downregulated the phosphorylation of extracellular signal-regulated kinase ½ (ERK½), whereas that of c-jun N-terminal kinase (JNK) and p38 kinase were upregulated. Also, MA had no influence on bromelain-suppressed ERK½ activation, yet, it downregulated JNK and p38 activation. Also, addition of mitogen-activated protein kinase (MAPK) inhibitors enhanced the autophagic ratios, which suggested the role of MAP kinases in bromelain-induced autophagy. All three MAPKs were seen to be constantly activated over the time. Bromelain was seen to induce the expressions of autophagy-related proteins, light chain 3 protein B II (LC3BII), and beclin-1. Using ERK½ inhibitor, expressions of LC3BII and beclin-1 increased, whereas p38 and JNK inhibitors decreased this protein expression, indicating that bromelain-induced autophagy was positively regulated by p38 and JNK but negatively regulated by ERK½. Autophagy-inducing property of bromelain can be further exploited in breast cancer therapy.

Induction of blood lymphocyte cytochrome P450 2E1 in early stage alcoholic liver cirrhosis.

[Khan AJ, Sharma A, Choudhuri G, Parmar D. Alcohol. 2011 Feb;45(1):81-7.]

To validate the induction of blood lymphocyte cytochrome P450 2E1 (CYP2E1) expression in alcoholic liver cirrhosis and mRNA and protein expression of CYP2E1 in freshly prepared blood lymphocytes of alcoholic liver cirrhotic (ACP), nonalcoholic cirrhotic patients (NACP), alcoholic controls (ACs), and nonalcoholic controls (NACs) were investigated. Registered ACP and NACP patients at Sanjay Gandhi Postgraduate Institute of Medical Science, Lucknow, India along with NACs and ACs were included in the

study. Real time polymerase chain reaction, enzyme-linked immunosorbent assay, and CYP2E1-dependent enzyme activity were determined in blood lymphocytes isolated from cases and controls. Significant increases in CYP2E1 mRNA and protein expression were observed in freshly prepared blood lymphocytes isolated from ACs and ACP patients as compared with respective NACs or NACP patients. A concomitant increase in N-nitrosodimethyamine demethylase activity was evident in the blood lymphocytes of ACs and ACP patients. Interestingly, the comparative increase observed in CYP2E1 expression was of greater magnitude in the blood lymphocytes isolated from ACP patients, although they abstained from alcohol drinking. Findings suggest that significant increase in the CYP2E1 mRNA and protein expression in the blood lymphocytes, isolated from early stage ACP patients, can be used to predict alcohol-induced toxicity.

UVA-induced cytotoxicity and DNA damaging potential of benz (e) acephenanthrylene.

[Ali D, Ray RS, Hans RK. Toxicol Lett. 2010 Nov 30;199(2):193-200.]

The toxicity of benz (e) acephenanthrylene (BeA) has been studied earlier with regard to the carcinogenicity of its metabolites, but its photo-genotoxicity is not well understood. Present study aimed to analyze the photodynamic response of BeA in human skin cell line (A375) under ambient environmental intensity of UVA (1.40 mW/cm$^{(2)}$). Kinetic of BeA showed that the highest intracellular uptake of BeA occurred after 24h of incubation. Cell viability, generation of reactive oxygen species (ROS), oxidative stress and DNA damage induced by BeA under UVA irradiation were assessed. BeA generates singlet oxygen ($^{(1)}O_{(2)}$), superoxide anion radical ($.O_{(2)}^{-}$) and hydroxyl radical (.OH) in a concentration-dependent manner. It was observed that glutathione reduced (GSH) and catalase activity were decreased while DNA damage and cell death were induced significantly (P>0.01) as concentration of BeA increased. Thus our results suggest that BeA may be phototoxic as well as photogenotoxic under UVA irradiation.

Characterization of developmental neurotoxicity of As, Cd, and Pb mixture: synergistic action of metal mixture in glial and neuronal functions.

[Rai A, Maurya SK, Khare P, Srivastava A, Bandyopadhyay S. Toxicol Sci. 2010 Dec;118(2):586-601.]

Neurotoxicity of individual metals is well investigated but that of metal mixture (MM), an environmental reality, in the developing brain is relatively obscure. We investigated the combinatorial effect of arsenic (As), cadmium (Cd), and lead (Pb) on rat brain development, spanning in utero to postnatal development. MM was administered by gavage to pregnant and lactating rats, and to postweaning pups till 2 months. The pups exhibited behavioral disturbances characterized by hyperlocomotion, increased grip strength, and learning-memory deficit. Disruption of the blood-brain barrier (BBB) was associated with dose-dependent increase in deposition of the metals in developing brain. Astrocytes were affected by MM treatment as evident from their reduced density, area, perimeter, compactness, and number of processes, and increased apoptosis in cerebral cortex and cerebellum. The metals induced synergistic reduction in glial fibrillary acidic protein (GFAP) expression during brain development; however, postweaning withdrawal of MM partially restored the levels of GFAP in adults. To characterize the toxic mechanism, we treated rat primary astrocytes with MM at concentrations ranging from lethal concentration (LC)(10) to LC(75) of the metals. We observed synergistic downregulation in viability and increase in apoptosis of the astrocytes, which were induced by proximal activation of extra cellular signal-regulated kinase (ERK) signaling and downstream activation of Jun N-terminal kinase (JNK) pathway. Furthermore, rise in intracellular calcium ion ($[Ca^{(2+)}](i)$) and reactive oxygen species generation promoted apoptosis in the astrocytes. Taken together, these observations are the first to show that mixture of As, Cd, and Pb has the capacity to induce synergistic toxicity in astrocytes that may compromise the BBB and may cause behavioral dysfunction in developing rats.

Isolation and characterization of a Pseudomonas sp. strain IITR01 capable of degrading a-endosulfan and endosulfan sulfate.

[Bajaj A, Pathak A, Mudiam MR, Mayilraj S, Manickam N. J Appl Microbiol. 2010 Dec;109(6):2135-43.]

A Pseudomonas sp. strain IITR01 capable of degrading α-ES and toxic ES sulfate was isolated using technical-ES through enrichment culture techniques. No growth and no degradation were observed using β-ES. Thin-layer chromatography and gas chromatography-mass spectrum analysis revealed the disappearance of both α-ES and ES sulfate and the formation of hydroxylated products ES diol, ether and lactone. We show here for the first time the formation of aforementioned metabolites in contrast to ES hemisulfate yielded by an

Arthrobacter sp. Metabolism of α-ES and endosulfate was also observed using the crude cell extract of IITR01. The molecular mass of protein induced during the degradation of α-ES and sulfate as substrate was found to be approximately 150 kDa as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). characterization of bacterium capable of degrading α-ES and ES sulfate but not β-ES was described. Genetic investigation suggests that a gene nonhomologous to the reported esd may be present in the strain IITR01. This study describes toxic ES degradation by a Pseudomonas species that may be utilized for the bioremediation of the industrial soils contaminated with ES residues.

Nrf2-ARE stress response mechanism: a control point in oxidative stress-mediated dysfunctions and chronic inflammatory diseases.

[Singh S, Vrishni S, Singh BK, Rahman I, Kakkar P. Free Radic Res. 2010 Nov;44(11):1267-88.]

Nrf2, a redox sensitive transcription factor, plays a pivotal role in redox homeostasis during oxidative stress. Nrf2 is sequestered in cytosol by an inhibitory protein Keap1 which causes its proteasomal degradation. In response to electrophilic and oxidative stress, Nrf2 is activated, translocates to nucleus, binds to antioxidant response element (ARE), thus upregulates a battery of antioxidant and detoxifying genes. This function of Nrf2 can be significant in the treatment of diseases, such as cancer, neurodegenerative, cardiovascular and pulmonary complications, where oxidative stress causes Nrf2 derangement. Nrf2 upregulating potential of phytochemicals has been explored, in facilitating cure for various ailments while, in cancer cells, Nrf2 upregulation causes chemoresistance. Therefore, Nrf2 emerges as a key regulator in oxidative stress-mediated diseases and Nrf2 silencing can open avenues in cancer treatment. This review summarizes Nrf2-ARE stress response mechanism and its role as a control point in oxidative stress-induced cellular dysfunctions including chronic inflammatory diseases.

Effects of cypermethrin on monoamine transporters, xenobiotic metabolizing enzymes and lipid peroxidation in the rat nigrostriatal system.

[Tiwari MN, Singh AK, Ahmad I, Upadhyay G, Singh D, Patel DK, Singh C, Prakash O, Singh MP. Free Radic Res. 2010 Dec;44(12):1416-24.]

Long-term exposure to cypermethrin induces the nigrostriatal dopaminergic neurodegeneration in adult rats and its pre-exposure in the critical periods of brain development enhances the susceptibility during adulthood. Monoamine transporters, xenobiotic metabolizing enzymes and oxidative stress play critical roles in the nigrostriatal dopaminergic neurodegeneration. The study was undertaken to investigate the effects of cypermethrin on DAT, VMAT 2, CYP2E1, GST Ya, GST Yc and GSTA4-4 expressions, CYP2E1 and GST activities and lipid peroxidation in the nigrostriatal system of adult rats with/without post-natal exposure to cypermethrin. Cypermethrin reduced VMAT 2 and increased CYP2E1 expressions without causing significant change in DAT. Although GSTA4-4 mRNA expression and lipid peroxidation were increased, no significant changes were observed in GST Ya and GST Yc expressions and total GST activity. The results obtained demonstrate that long-term exposure to cypermethrin modulates VMAT 2, CYP2E1, GSTA4-4 expressions and lipid peroxidation, which could contribute to the nigrostriatal dopaminergic neurodegeneration.

New protocol for oligonucleotide microarray fabrication using SU-8-coated glass microslides.

[Sethi D, Kumar A, Gandhi RP, Kumar P, Gupta KC. Bioconjug Chem. 2010 Sep 15;21(9):1703-8.]

Microarray technology has become an important tool for detection and analysis of nucleic acid targets. Immobilization of modified and unmodified oligonucleotides on epoxy-functionalized glass surfaces is often used in microarray fabrication. Here, we demonstrate a protocol that employs coating of SU-8 (glycidyl ether of bisphenol A) onto glass microslides to obtain high density of epoxy functions for efficient immobilization of aminoalkyl-, thiophosphoryl-, and phosphorylated oligonucleotides with uniform spot morphology. The resulting microarrays exhibited high immobilization (65%) and hybridization efficiency (30-36%) and were sufficiently stable over a range of temperature and pH conditions. The prominent feature of the protocol is that spots can be visualized distinctly at 0.05 μM probe (a 20-mer oligonucleotide) concentration. The constructed microarrays were subsequently used for detection of base mismatches and bacterial diseases (meningitis and typhoid).

Environmental reservoirs for enteroto-xigenic *Escherichia coli* in south Asian Gangetic riverine system.

[Singh G, Vajpayee P, Ram S, Shanker R. Environ Sci Technol. 2010 Aug 15;44(16):6475-80.]

IITR RESEARCH HIGHLIGHTS

Forecasting diarrheagenic *E. coli* contamination of aquatic resources to prevent outbreaks largely depends on rapid and accurate diagnostic testing in a few hours. Real-time PCR is widely used for quick culture-free quantitative enumeration of pathogenic bacteria in environmental samples. In this study, real-time PCR in molecular beacon format was used for detection and culture-free quantitative enumeration of enterotoxigenic *Escherichia coli* (ETEC) harboring LT1 gene in a sewage-impacted south Asian Gangetic riverine system. The quantitative budget for ETEC in surface water was observed to vary significantly (DMRT, $p < 0.05$) among the sites. Aquatic flora *(Eichhornia crassipes, Potamogeton crispus, Potamogeton pectinatus, Ranunculus sceleratus, Polygonum glabrum, Pontederia cordata, Najas indica* and strands of Spirogyra spp.) collected between sites 1 and 9 exhibited significant high levels of ETEC in comparison to their representatives collected from pristine area. The level of ETEC harboring LT1 gene observed in leafy vegetables cultivated along the banks was in the following order: mint leaves > coriander > spinach > methi leaves. The study suggests that the aquatic flora and cultivated leafy vegetables in the south Asian Gangetic riverine system are environmental reservoirs for enterotoxigenic *Escherichia coli.*

Potentiation of tumour promotion by topical application of argemone oil/isolated sanguinarine alkaloid in a model of mouse skin carcinogenesis.

[Ansari KM, Das M. Chem Biol Interact. 2010 Dec 5;188(3):591-7.]

Several incidences of adverse effects on human health have been reported in many countries, due to consumption of edible oil adulterated with argemone oil (AO). The clinical manifestation of the disease is commonly referred to as epidemic dropsy. Our prior studies have shown that AO and isolated sanguinarine alkaloid (SANG) possess genotoxic and tumour initiating activity. In this study, the effect of AO/SANG was investigated on the development of tumour formation in mice using 7,12-dimethylbenz (a) anthracene (DMBA) initiated followed by tetradecanoyl phorbol acetate (TPA)-promoted skin tumour protocol. Single application of AO (300µl) or SANG (4.5µmol) when used during initiation phase in DMBA/TPA group did not reveal substantial difference in tumourigenic response. However, twice weekly application of AO (100µl) or SANG (1.5µmol) during promotion phase (25 weeks) resulted in enhanced tumourigenic response by ≥30% in DMBA/TPA treated group along with significant decrease in dermal tyrosinase (45-49%), histidase (30-32%), superoxide dismutase (53-56%), catalase (41%), GSH reductase (37-40%) and GSH-peroxidase activity (29-33%) compared to control. Furthermore, significant decrease of epidermal GSH (64-66%) content and enhanced formation of lipid peroxides (96-121%) was noticed following AO or SANG treatment during promotion phase to DMBA/TPA induced animals indicating the modified pro-oxidant status in skin. Although dermal biochemical parameters were also altered by AO or SANG when used during initiation phase in DMBA/TPA treated animals, nonetheless, the response in these parameters were relatively more when AO or SANG were used during promotion phase in DMBA/TPA treated animals. These results clearly suggest that AO and SANG have the ability to enhance the tumourigenic response, which may have relevance to its carcinogenic potential.

Genotoxic and carcinogenic risks associated with the dietary consumption of repeatedly heated coconut oil.

[Srivastava S, Singh M, George J, Bhui K, Murari Saxena A, Shukla Y. Br J Nutr. 2010 Nov;104(9):1343-52.]

Repeated heating of vegetable oils at high temperatures during cooking is a very common cooking practice. Repeated heating of edible oils can generate a number of compounds, including polycyclic aromatic hydrocarbons (PAH), some of which have been reported to have carcinogenic potential. Consumption of these repeatedly heated oils can pose a serious health hazard. The objectives of the present study were to evaluate the genotoxic and carcinogenic risks associated with the consumption of repeatedly heated coconut oil (RCO), which is one of the commonly consumed cooking and frying medium. The PAH were analysed using HPLC in fresh CO, single-heated CO (SCO) and RCO. Results revealed the presence of certain PAH, known to possess carcinogenic potential, in RCO when compared with SCO. Oral intake of RCO in Wistar rats resulted in a significant induction of aberrant cells ($P<0{\cdot}05$) and micronuclei ($P<0{\cdot}05$) in a dose-dependent manner. Oxidative stress analysis showed a significant ($P<0{\cdot}05$) decrease in the levels of antioxidant enzymes such as superoxide dismutase and catalase with a concurrent increase in reactive oxygen species and lipid peroxidation in the liver. In addition, RCO given alone and along with diethylnitrosamine for 12 weeks induced altered hepatic foci as noticed by alteration in positive (γ-glutamyl transpeptidase and glutathione-S-transferase) and negative (adenosine triphosphatase, alkaline phosphatase and glucose-6-phosphatase) hepatospecific biomarkers. A significant decrease in the relative and absolute hepatic weight of RCO-

supplemented rats was recorded (P<0·05). In conclusion, dietary consumption of RCO can cause a genotoxic and preneoplastic change in the liver.

Suppression of oxidative stress and pro-inflammatory mediators by Cymbopogon citratus *D. Stapf* extract in lipopolysaccharide stimulated murine alveolar macrophages.

[Tiwari M, Dwivedi UN, Kakkar P. Food Chem Toxicol. 2010 Oct;48(10):2913-9.]

Exploration of antioxidants of plant origin and their scientific validation for their immense pharmacological potential is emerging as an issue of intense research now-a-days.The effect of Cymbopogon citratus extract was seen on cell viability, oxidative stress markers i.e. ROS production, SOD activity, lipid peroxidation and GSH content of murine alveolar macrophages stressed with lipopolysaccharide. Modulation in release of NO and pro-inflammatory cytokine TNF-α along with alterations in mitochondrial membrane potential under stress were compared with known plant derived antioxidant quercetin. The extract was not found to be cytotoxic at any of the selected doses. At 5 and 10 µg the extract showed significant increase in SOD activity, GSH content (p<0.001), decrease in ROS production as seen by fluorescent dye DCFH-DA and also MDA formation (lipid peroxidation marker) significantly. The extract also showed reduction in the release of pro-inflammatory mediators TNF-α and NO significantly indicating an anti-inflammatory effect. The extract was able to restore mitochondrial membrane potential as estimated by spectrofluorimetry using the fluorescent dye Rhodamine 123. The results suggest potential use of the cytoprotective, antioxidant and anti-inflammatory property of *C. citratus* in the form of dietary component and also in formulations against lung inflammatory diseases where oxidative stress plays an important role.

Polo-like kinase1 (Plk1) knockdown enhances cisplatin chemosensitivity via up-regulation of p73α in p53 mutant human epidermoid squamous carcinoma cells.

[Tyagi S, Bhui K, Singh R, Singh M, Raisuddin S, Shukla Y. Biochem Pharmacol. 2010 Nov 1;80(9):1326-34.]

Polo-like kinase 1 (Plk1), a critical regulator of mitotic entry, progression and exit, has been shown to be involved in a variety of cancers and thus is becoming an attractive target for cancer management. In case of DNA damage, Plk1 not only inhibits p53 independent apoptosis by dysfunctioning p73α but also allows cells to recover from growth arrest. Here, we showed the effects of knocking down plk1 gene through small interference RNA (siRNA) on cell cycle progression, proliferation and chemosensitivity of p53 mutant A431 cells to cisplatin (CDDP). The expression of Plk1 was measured by RT-PCR and Western blotting. Anti-proliferative response accompanied with cell cycle arrest in G(2)/M phase and induction of cell death was recorded following Plk1 knockdown. Furthermore, cells following knockdown of Plk1, which induced increase of Cyclin B1, p-Cdc2 and p73α with a decrease in p-Cdc25C, were more sensitive to CDDP. CDDP treatment induced nuclear translocation and co-localization of Plk1 with p73α whereas combination of CDDP and Plk1siRNA upregulated the expression of p73α protein in a synergistic manner thereby leading to an increase up to 5 folds in CDDP-induced cell death. The increase in caspase-3 activity indicated apoptosis as a contributor in the total cell death. Conclusively, plk1 gene silencing can enhance the sensitivity of A431 cells to low doses of CDDP by upregulating p73α expression and thus can be a revolutionary approach in cancer chemotherapy.

Bioaccumulation and toxic effects of cadmium on feeding and growth of an Indian pond snail *Lymnaea luteola* L. under laboratory conditions.

[Das S, Khangarot BS. J Hazard Mater. 2010 Oct 15;182(1-3):763-70.]

Effects of dissolved cadmium exposure on the survival, feeding, growth rates and accumulation in Indian pond snails *Lymnaea luteola* L. were examined for a period of 7 weeks. The concentrations of cadmium tested were 0, 10, 32, 100, 320, 560, and 1000 µg $l^{(-1)}$. Cadmium exposure significantly inhibited the feeding and growth rates. At higher Cd concentrations snails refused to consume food offered as plant Marsilia sp. leaves. Cadmium mainly accumulated in soft tissues in a dose-dependent manner. After 4 and 7 weeks of exposure, the no observed effect concentration (NOEC) of Cd was 10 µg $l^{(-1)}$ and the lowest observed effect concentration (LOEC) was 32 µg $l^{(-1)}$. Reduction of growth (decrease in wet weight) was noticed followed by a high mortality in higher Cd concentrations. Significant reduction in food consumption and growth rates was found at 32 µg $l^{(-1)}$ and above Cd concentration. A significant relationship between Cd exposure and growth and feeding rates was noticed. The results obtained with these key aquatic organisms in the food chains complement those obtained with other aquatic organisms and gastropod snails. The findings of the present study and those of earlier studies suggested that Indian pond snail *L. luteola* are useful test organisms for ecotoxicology bioassays.

IITR RESEARCH HIGHLIGHTS

Nanotoxicity of pure silica mediated through oxidant generation rather than glutathione depletion in human lung epithelial cells.

[Akhtar MJ, Ahamed M, Kumar S, Siddiqui H, Patil G, Ashquin M, Ahmad I. Toxicology. 2010 Oct 9;276(2):95-102.]

Though, oxidative stress has been implicated in silica nanoparticles induced toxicity both *in vitro* and *in vivo,* but no similarities exist regarding dose-response relationship. This discrepancy may, partly, be due to associated impurities of trace metals that may present in varying amounts. Here, cytotoxicity and oxidative stress parameters of two sizes (10 nm and 80 nm) of pure silica nanoparticles was determined in human lung epithelial cells (A549 cells). Both sizes of silica nanoparticles induced dose-dependent cytotoxicity as measured by MTT [3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide] and lactate dehydrogenase (LDH) assays. Silica nanoparticles were also found to induce oxidative stress in dose-dependent manner indicated by induction of reactive oxygen species (ROS) generation, and membrane lipid peroxidation (LPO). However, both sizes of silica nanoparticles had little effect on intracellular glutathione (GSH) level and the activities of glutathione metabolizing enzymes; glutathione reductase (GR) and glutathione peroxidase (GPx). Buthionine-[S,R]-sulfoximine (BSO) plus silica nanoparticles did not result in significant GSH depletion than that caused by BSO alone nor N-acetyl cysteine (NAC) afforded significant protection from ROS and LPO induced by silica nanoparticles. The rather unaltered level of GSH is also supported by finding no appreciable alteration in the level of GR and GPx. Our data suggest that the silica nanoparticles exert toxicity in A549 cells through the oxidant generation (ROS and LPO) rather than the depletion of GSH.

Toxicity assessment of nanomaterials: methods and challenges.

[Dhawan A, Sharma V. Anal Bioanal Chem. 2010 Sep;398(2):589-605.]

The increasing use of nanomaterials in consumer and industrial products has aroused global concern regarding their fate in biological systems, resulting in a demand for parallel risk assessment. A number of studies on the effects of nanoparticles in *in vitro* and *in vivo* systems have been published. However, there is still a need for further studies that conclusively establish their safety/toxicity, due to the many experimental challenges and issues encountered when assessing the toxicity of nanomaterials. Most of the methods used for toxicity assessment were designed and standardized with chemical toxicology in mind. However, nanoparticles display several unique physicochemical properties that can interfere with or pose challenges to classical toxicity assays. Recently, some new methods and modified versions of pre-existing methods have been developed for assessing the toxicity of nanomaterials. This review is an attempt to highlight some important methods employed in nanomaterial toxicology and to provide a critical analysis of the major issues/challenges faced in this emerging field.

Metabolic profiles and phylogenetic diversity of microbial communities from chlorinated pesticides contaminated sites of different geographical habitats of India.

[Manickam N, Pathak A, Saini HS, Mayilraj S, Shanker R. J Appl Microbiol. 2010 Oct;109(4):1458-68.]

Aim of the this work was to study the microbial communities in three sites contaminated with chlorinated pesticides and evaluation of dehydrodechlorinase (linA) gene variants involved in gamma-hexachlorocyclohexane (γ-HCH, lindane) degradation., 16S rRNA genes were amplified from microbial communities occurring in contaminated soils using a culture-independent method. From 375 clone libraries analysed, 55 different restriction fragment length polymorphism phylotypes were obtained. Dehydrodechlorinase (linA) gene, which initiates the γ-HCH degradation, was directly amplified by PCR from the DNA extracted from soils. Deduced amino acid sequences of eight variant genotypes of linA showed few amino acid changes. All the variants of linA had mutations of F151L and S154T, and one of the genotype carried 12 amino acid changes when compared to a linA of Sphingomonas sp. reported from the same soil. The microbial communities displayed complex and diverse groups similar to bacteria involved in biodegradation. The presence of biodegradative genes like linA indicates the presence of communities with capacity to biodegrade the persistent pesticide HCH. This study provides insights to evaluate the presence of catabolic genes and assessing the bioremediation potential of the industrial soils contaminated by chlorinated pesticides.

Chlorpyrifos induces apoptosis and DNA damage in Drosophila through generation of reactive oxygen species.

[Gupta SC, Mishra M, Sharma A, Deepak Balaji TG, Kumar R, Mishra RK, Chowdhuri DK. Ecotoxicol Environ Saf. 2010 Sep;73(6):1415-23.]

The present study investigated the apoptosis and DNA damage inducing potential of chlorpyrifos (CP) in

Drosophila melanogaster. Third instar larvae of Drosophila were treated with different concentrations of CP (0.015-15.0 microg/L) for 2-48 h. Reactive oxygen species (ROS) generation, oxidative stress markers, DNA damage and apoptotic cell death end points were measured in them. A significant increase in DNA damage was concomitant with apoptotic mode of cell death in 15.0 µg/L CP-treated organisms for 24 and 48 h. Depolarization in mitochondrial membrane potential and increased casapase-3 and caspase-9 activities in these organisms indicated both as potential targets of CP. A significant positive correlation was observed among ROS generation, apoptosis and DNA damage. The study suggests that (i) ROS may be involved in inducing apoptosis and DNA damage in the CP-exposed larvae of Drosophila and (ii) *D. melanogaster* may be used as an alternative *in vivo* animal model for xenobiotics hazard assessment.

Partial characterization of red gram *(Cajanus cajan* L. Millsp) polypeptides recognized by patients exhibiting rhinitis and bronchial asthma.

[Misra A, Kumar R, Mishra V, Chaudhari BP, Tripathi A, Das M, Dwivedi PD. Food Chem Toxicol. 2010 Oct;48(10):2725-36.]

We sought to assess the allergenic potential of red gram by identifying and characterizing the responsible proteins. Immunoblotting was performed to detect IgE binding proteins. Identities of these proteins were confirmed by mass spectrometry. To evaluate allergenic potential, BALB/c mice were sensitized with red gram proteins and levels of specific immunoglobulins, histamine, Th2 cytokines were measured. Allergenic response was evident by significant increase in specific IgE, IgG1, histamine and Th2 cytokine levels. Prominent anaphylactic symptoms, discernible histopathological responses and down regulation of IFN-gamma levels give strong support towards allergenicity of red gram proteins. IgE immunoblot detected five proteins; one of 66 kDa, three of 45 kDa (pI of approximately 5.3, 5.9 and 6.6) and one of 30 kDa. All these proteins showed homology to known allergens of soybean (different subunits of beta-conglycinin), lentil (Len c1 and Len c2), peanut (Ara h1) and pea (vicilin). In conclusion, five novel IgE binding proteins (namely Caj c1, Caj c2, Caj c3, Caj c4 and Caj c5) were identified as putative clinically relevant allergens.

Artemisia vulgaris-derived mesoporous honeycomb-shaped activated carbon for ibuprofen adsorption

[Dubey SP, Dwivedi AD, Gopal K, Sillanpää M. Chemical Engineering Journal,165,537-544, 2010]

The purpose of the present work was to synthesize a novel mesoporous activated carbon from an invasive weed to investigate its potential application for removal of the emerging organic contaminants in waters. The worldwide highly consumable non-steroidal anti-inflammatory drug (NSAID); ibuprofen (Ibu), was chosen for the study due to its toxicity and global occurrence in waters. Keeping this in mind, *Artemisia vulgaris* (common name: Mugwort) leaves were processed by physical and chemical activation to obtain the mesoporous honeycomb-structured activated carbon (MAC) to mitigate Ibu. To understand the activity of the activated carbon towards contaminant, adsorption batch mode process was investigated for the solid–liquid phase characteristics of Ibu–water system. Both kinetic and equilibrium models were evaluated over a wide range of conditions to determine the rate laws and maximum Ibu uptake capacity. A decisive reliance of adsorption capacity on pH was observed in pH range from 2 to 9. The high surface area (358.20 m^2/g), mesoporosity (2.46 nm) and surface functionality of MAC played significant role in Ibu uptake. Plausible mechanistic findings for adsorptive mitigation were substantiated by spectroscopic techniques viz. SEM, FTIR, EDX and ζ potentiometry.

Biosynthesis of silver and gold nanoparticles using *Chenopodium album* leaf extract

[Dwivedi AD, Gopal K, *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 369, 27-33, 2010*

This paper reports a facile and rapid biosynthesis of silver and gold nanoparticles from *Chenopodium album,* an obnoxious weed. The aqueous leaf extract of the herb was used as mild reducing agent for silver and gold nanoparticles (SNPs and GNPs) synthesis from their salt solutions in single-pot process. Quasi-spherical shapes were observed for biosynthesized SNPs and GNPs within range of 10–30 nm, respectively. The UV–VIS spectra gave surface plasmon resonance (SPR) for SNPs and GNPs at 460 and 540 nm, respectively. Influence of leaf extract quantities, metal concentrations, contact time, reaction temperature and pH were evaluated to find their effects on NPs synthesis. The produced nanocrystals of silver and gold were analyzed with transmission electron microscopy (TEM), X-ray diffraction (XRD), energy dispersive X-ray (EDX)

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and fourier transform infrared spectroscopy (FTIR). The stability of NPs was evaluated at different pH with zeta potentiometer without adding any stabilizing agents.

Fig. *Chenopodium album*

TOPIC OF INTEREST

Neurotoxicology Research in India

Azadirachtin poisoning: a case report.

[Iyyadurai R, Surekha V, Sathyendra S, Paul Wilson B, Gopinath KG. Clin Toxicol (Phila). 2010 Oct;48(8):857-8]

The use of neem-based products is widespread in the Indian Subcontinent. Neem-based pesticides obtained from neem kernels are considered natural and safe. The toxic effects of ingestion and overdose of this pesticide in adults have not been described in this literature. We report the case of a 35-year-old lady who had consumed Azadirachtin in an attempt of deliberate self-harm. The patient had features of neurotoxicity because of Azadirachtin requiring intensive medical care with mechanical ventilation. The patient survived the overdose with no long-lasting side effects of the toxin.

Characterization of developmental neurotoxicity of As, Cd, and Pb mixture: synergistic action of metal mixture in glial and neuronal functions.

[Rai A, Maurya SK, Khare P, Srivastava A, Bandyopadhyay S. Toxicol Sci. 2010 Dec;118(2):586-601.]

Neurotoxicity of individual metals is well investigated but that of metal mixture (MM), an environmental reality, in the developing brain is relatively obscure. We investigated the combinatorial effect of arsenic (As), cadmium (Cd), and lead (Pb) on rat brain development, spanning in utero to postnatal development. MM was administered by gavage to pregnant and lactating rats, and to postweaning pups till 2 months. The pups exhibited behavioral disturbances characterized by hyperlocomotion, increased grip strength, and learning-memory deficit. Disruption of the blood-brain barrier (BBB) was associated with dose-dependent increase in deposition of the metals in developing brain. Astrocytes were affected by MM treatment as evident from their reduced density, area, perimeter, compactness, and number of processes, and increased apoptosis in cerebral cortex and cerebellum. The metals induced synergistic reduction in glial fibrillary acidic protein (GFAP) expression during brain development; however, postweaning withdrawal of MM partially restored the levels of GFAP in adults. To characterize the toxic mechanism, we treated rat primary astrocytes with MM at concentrations ranging from lethal concentration LC (10) to LC(75) of the metals. We observed synergistic downregulation in viability and increase in apoptosis of the astrocytes, which were induced by proximal activation of extra cellular signal-regulated kinase (ERK) signaling and downstream activation of Jun N-terminal kinase (JNK) pathway. Furthermore, rise in intracellular calcium ion ([Ca(2+)](i)) and reactive oxygen species generation promoted apoptosis in the astrocytes. Taken together, these observations are the first to show that mixture of As, Cd, and Pb has the capacity to induce

synergistic toxicity in astrocytes that may compromise the BBB and may cause behavioral dysfunction in developing rats.

Protective effect of montelukast against quinolinic acid/malonic acid induced neurotoxicity: possible behavioral, biochemical, mitochondrial and tumor necrosis factor-α level alterations in rats.

[Kalonia H, Kumar P, Kumar A, Nehru B. Neuroscience. 2010 Nov 24;171(1):284-99.]

The present study has been designed to explore the protective effect of montelukast (leukotriene receptor antagonist) against intrastriatal quinolinic acid (QA; 300 nmol) and malonic acid (MA; 6 µmol) induced Huntington's like symptoms in rats. Quinolinic acid has been reported to induce excitotoxicity by stimulating the N-methyl-D-aspartate receptor, causing calcium overload which in turn leads to the neurodegeneration. On the other hand, MA, being a reversible inhibitor of mitochondrial enzyme complex-II, leads to energy crisis and free radical generation. Recent studies have reported the therapeutic potential of leukotriene receptor antagonists in different neurodegenerative disorders. However, their exact role is yet to be established. The present study accordingly, is an attempt to investigate the effect of montelukast against QA and MA induced behavioral, biochemical and molecular alterations in rat striatum. Oxidative stress, mitochondrial enzyme complex and tumor necrosis factor-alpha (TNF-α) were evaluated on day 21st and 14th post intrastriatal QA and MA treatment, respectively. Findings of the present study demonstrate significant alteration in the locomotor activity and motor coordination as well as oxidative burden (increased lipid peroxidation, nitrite concentration and decreased endogenous antioxidants), mitochondrial enzyme complex (I, II and IV) activities and TNF-α level, in both intrastriatal QA and MA treated animals. Further, montelukast (0.4, 0.8 mg/kg p.o.) treatment for 21 and 14 days respectively, attenuated the behavioral alterations, oxidative stress, mitochondrial dysfunction and TNF-α level in these models of Huntington's disease in a significant manner. In conclusion, the present study emphasizes the neuroprotective potential of montelukast in the therapeutic management of Huntington like symptoms.

Neurotoxic activity of a Topoisomerase-I inhibitor, camptothecin, in cultured cerebellar granule neurons.

[Uday Bhanu M, Kondapi AK. Neurotoxicology. 2010 Dec;31(6):730-7.]

DNA Topoisomerase-I (Topo-I) is an enzyme involved in DNA rearrangements, transcription and replication and is a potential target for cancer chemotherapy. Camptothecin is one of the chemotherapeutic agents inhibiting the catalytic activity of Topo-I through the formation of single-strand protein-DNA cross-links. Here, we show that camptothecin is toxic to primary cerebellar granule neurons (CGNs), and camptothecin-induced toxicity is not solely due to the inhibition of Topo-I. An analysis of the effect of camptothecin on CGNs in culture showed that camptothecin inhibits the viability of CGNs. The observed inhibition of cell viability is through the induction of a pro-apoptotic pathway that leads to neuronal degeneration. Furthermore, results show that camptothecin inhibits both protein synthesis and the neuritic outgrowth of CGNs. To determine if the observed neurotoxicity was due to inhibition of Topo-I alone, siRNA-mediated Topo-I-downregulated CGNs were analyzed for cell viability, apoptosis, protein synthesis and neurite outgrowth. The results of these experiments demonstrate that Topo-I downregulation affects only neurite outgrowth and has no significant effect on viability, apoptosis and protein synthesis in granule neurons. In conclusion, camptothecin-induced neurotoxicity may be due to the induction of protein-DNA cross-links and other unknown drug-related interactions rather than the inhibition of Topo-I activity alone.

The Ayurvedic drug, Ksheerabala, ameliorates quinolinic acid-induced oxidative stress in rat brain.

[Swathy SS, Indira M. Int J Ayurveda Res. 2010 Jan;1(1):4-9.]

One of the mechanisms of neurotoxicity is the induction of oxidative stress. There is hardly any cure for neurotoxicity in modern medicine, whereas many drugs in Ayurveda possess neuroprotective effects; however, there is no scientific validation for these drugs. Ksheerabala is an ayurvedic drug which is used to treat central nervous system disorders, arthritis, and insomnia. The aim of our study was to evaluate the effect of Ksheerabala on quinolinic acid-induced toxicity in rat brain. The optimal dose of Ksheerabala was found from a dose escalation study, wherein it was found that Ksheerabala showed maximum protection against quinolinic acid-induced neurotoxicity at a dose of 15 microL/100 g body weight/day, which was selected for further experiments. Four groups of female albino rats were maintained for 21 days as follows: 1. Control group, 2. Quinolinic acid (55 microg/100 g body weight), 3. Ksheerabala (15 microL/100 g body weight), 4. Ksheerabala (15 microL/100 g body weight) + Quinolinic

acid (55 microg/100 g body weight). At the end of the experimental period, levels of lipid peroxidation products, protein carbonyls, and activities of scavenging enzymes were analyzed. The results revealed that quinolinic acid intake caused enhanced lipid and protein peroxidation as evidenced by increased levels of peroxidation products such as malondialdehyde, hydroperoxide, conjugated dienes, and protein carbonyls. On the other hand, the activities of scavenging enzymes such as catalase, superoxide dismutase (SOD), glutathione peroxidase, and glutathione reductase as well as the concentration of glutathione were reduced. On coadminstration of Ksheerabala along with quinolinic acid, the levels of all the biochemical parameters were restored to near-normal levels, indicating the protective effect of the drug. These results were reinforced by histopathological studies.

Scientific basis for the use of Indian ayurvedic medicinal plants in the treatment of neurodegenerative disorders: ashwagandha.

[Ven Murthy MR, Ranjekar PK, Ramassamy C, Deshpande M. Cent Nerv Syst Agents Med Chem. 2010 Sep 1;10(3):238-46.]

Ayurveda is a Sanskrit word, which means "the scripture for longevity". It represents an ancient system of traditional medicine prevalent in India and in several other south Asian countries. It is based on a holistic view of treatment which is believed to cure human diseases through establishment of equilibrium in the different elements of human life, the body, the mind, the intellect and the soul. Ayurveda dates back to the period of the Indus Valley civilization (about 3000 B.C) and has been passed on through generations of oral tradition, like the other four sacred texts (Rigveda, Yajurveda, Samaveda and Atharvanaveda) which were composed between 12(th) and 7(th) century B.C. References to the herbal medicines of Ayurveda are found in all of the other four Vedas, suggesting that Ayurveda predates the other Vedas by at least several centuries. It was already in full practice at the time of Buddha (6(th) century B.C) and had produced two of the greatest physicians of ancient India, Charaka and Shushrutha who composed the basic texts of their trade, the Samhitas. By this time, Ayurveda had already developed eight different subspecialties of medical treatment, named Ashtanga, which included surgery, internal medicine, ENT, pediatrics, toxicology, health and longevity, and spiritual healing. Ayurvedic medicine was mainly composed of herbal preparations which were occasionally combined with different levels of other compounds, as supplements . In the Ayurvedic system, the herbs used for medicinal purposes are classed as brain tonics or rejuvenators. Among the plants most often used in Ayurveda are, in the descending order of importance: (a) Ashwagandha, (b) Brahmi, (c) Jatamansi, (d) Jyotishmati, (e) Mandukparni, (f) Shankhapushpi, and (g) Vacha. Ashwagandha (*Withania somnifera,* WS), also commonly known, in different parts of the world, as Indian ginseng, Winter cherry, Ajagandha, Kanaje Hindi and Samm Al Ferakh, is a plant belonging to the Solanaceae family. It is also known in different linguistic areas in India by its local vernacular names. It grows prolifically in dry regions of South Asia, Central Asia and Africa, particularly in India, Pakistan, Bangladesh, Sri Lanka, Afghanistan, South Africa, Egypt, Morocco, Congo and Jordon. In India, it is cultivated, on a commercial scale, in the states of Madhya Pradesh, Uttar Pradesh, Punjab, Gujarat and Rajasthan. In Sanskrit, ashwagandha, the Indian name for WS, means "odor of the horse", probably originating from the odor of its root which resembles that of a sweaty horse. The name"somnifera" in Latin means "sleep-inducer" which probably refers to its extensive use as a remedy against stress from a variety of daily chores. Some herbalists refer to ashwagandha as Indian ginseng, since it is used in India, in a way similar to how ginseng is used in traditional Chinese medicine to treat a large variety of human diseases. Ashwagandha is a shrub whose various parts (berries, leaves and roots) have been used by Ayurvedic practitioners as folk remedies, or as aphrodisiacs and diuretics. The fresh roots are sometimes boiled in milk, in order to leach out undesirable constituents. The berries are sometimes used as a substitute to coagulate milk in cheese making. In Ayurveda, the herbal preparation is referred to as a "rasayana", an elixir that works, in a nonspecific, global fashion, to increase human health and longevity. It is also considered an adaptogen, a nontoxic medication that normalizes physiological functions, disturbed by chronic stress, through correction of imbalances in the neuroendocrine and immune systems. The scientific research that has been carried out on Ashwagandha and other ayurvedic herbal medicines may be classified into three major categories, taking into consideration the endogenous or exogenous phenomena that are known to cause physiological disequilibrium leading to the pathological state; (A) pharmacological and therapeutic effects of extracts, purified compounds or multi-herbal mixtures on specific non-neurological diseases; (B) pharmacological and therapeutic effects of extracts, purified compounds or multi-herbal mixtures on neurodegenerative disorders; and (C) biochemical, physiological and genetic studies on the herbal plants themselves, in order to distinguish between those

originating from different habitats, or to improve the known medicinal quality of the indigenous plant. Some of the major points on its use in the treatment of neurodegenerative disorders are described in the present study.

Antiperoxidative and antiinflammatory effect of *Sida cordifolia* Linn. On quinolinic acid induced neurotoxicity.

[Swathy SS, Panicker S, Nithya RS, Anuja MM, Rejitha S, Indira M. Neurochem Res. 2010 Sep;35(9):1361-7.]

Sida cordifolia is a plant belonging to the Malvaceae family used in many ayurvedic preparations. This study aimed at assessing the effects of ethanolic extract of *Sida cordifolia* root on quinolinic acid (QUIN) induced neurotoxicity and to compare its effect with the standard drug deprenyl in rat brain. Rats were divided into six groups: (1) control group (2) QUIN (55 microg/100 g bwt/day) (3) 50% ethanolic plant extract treated group (50 mg/100 g bwt/day) (4) Deprenyl (100 microg/100 g bwt/day) (5) QUIN (55 microg/100 g bwt/day) + 50% ethanolic plant extract treated group (50 mg/100 g bwt/day) (6) QUIN (55 microg/100 g bwt/day) + Deprenyl (100 microg/100 g bwt/day). At the end of the experimental period a status of lipid peroxidation products, protein peroxidation product, activities of the scavenging enzymes and the activities of the inflammatory markers were analyzed. Results revealed that the lipid peroxidation products decreased and the activities of the scavenging enzymes increased significantly in the brain of the plant extract treated group, deprenyl treated group and also in the coadminstered groups. The activities of markers of inflammatory responses such as cyclooxygenase and lipoxygenase were found to be significantly increased in the QUIN treated rats and this was decreased upon the administration of plant extract and deprenyl. In short, the study revealed that 50% ethanolic extract of *Sida cordifolia* has got potent antioxidant and antiinflammatory activity and the activity is comparable with the standard drug deprenyl.

Neuroprotective effect of curcumin in arsenic-induced neurotoxicity in rats.

[Yadav RS, Shukla RK, Sankhwar ML, Patel DK, Ansari RW, Pant AB, Islam F, Khanna VK. Neurotoxicology. 2010 Sep;31(5):533-9.]

Our recent studies have shown that arsenic-induced neurobehavioral toxicity is protected by curcumin by modulating oxidative stress and dopaminergic functions in rats. In addition, the neuroprotective effect of curcumin has been investigated on arsenic-induced alterations in biogenic amines, their metabolites and nitric oxide (NO), which play an important role in neurotransmission process. Decrease in the levels of dopamine (DA, 28%), norepinephrine (NE, 54%), epinephrine (EPN, 46%), serotonin (5-HT, 44%), 3,4-dihydroxyphenylacetic acid (DOPAC, 20%) and homovanillic acid (HVA, 31%) in corpus striatum; DA (51%), NE (22%), EPN (47%), 5-HT (25%), DOPAC (34%) and HVA (41%) in frontal cortex and DA (35%), NE (35%), EPN (29%), 5-HT (54%), DOPAC (37%) and HVA (46%) in hippocampus, observed in arsenic (sodium arsenite, 20 mg/kg body weight, p.o., 28 days) treated rats exhibited a trend of recovery in rats simultaneously treated with arsenic and curcumin (100 mg/kg body weight, p.o., 28 days). Increased levels of NO in corpus striatum (2.4-fold), frontal cortex (6.1-fold) and hippocampus (6.2-fold) in arsenic-treated rats were found decreased in rats simultaneously treated with arsenic and curcumin. It is evident that curcumin modulates levels of brain biogenic amines and NO in arsenic-exposed rats and these results further strengthen its neuroprotective efficacy.

Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients.

[Kesavan R, Narayan SK, Adithan C. Eur J Clin Pharmacol. 2010 Jul;66(7):689-96.]

Cytochrome P450 2C9 and 2C19 (CYP2C9 and CYP2C19, respectively) genetic polymorphisms play an important role in phenytoin (PHT) metabolism. We have evaluated whether these genetic polymorphisms have an effect on PHT-induced neurological toxicity in Tamilian (ethnic group native to southern India) patients with epilepsy. We studied 292 Tamilian patients who were taking PHT for the treatment of various epileptic seizures. PHT toxicity was defined on the basis of neurological signs of toxicity and further sub-classified into mild, moderate, and severe toxicity based on clinical severity. Genomic DNA was extracted from peripheral leukocytes and genotyped for CYP2C9*2, *3 and CYP2C19*2, *3 by PCR-restriction fragment length polymorphism analysis.

Of the 292 patients in the patient cohort, 58 were clinically diagnosed to have PHT toxicity. When risk ratios were calculated for each mutant CYP2C9 genotype separately, the adjusted odds ratio for CYP2C9*1/*3 was found to be 15.3 (95% confidence interval 5.8-40.3, P<0.0001) for the cases compared to controls. When the four single nucleotide polymorphisms of CYP2C9 and CYP2C19 were analyzed using a haplotype approach, significant difference in the distribution of the C-C-G-G haplotype

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was observed between the cases and controls. Our results show that CYP2C9 genetic polymorphisms (particularly the *3 allele) were associated with high risk of epileptic patients developing PHT-induced neurological toxicity.

A study to correlate rotenone induced biochemical changes and cerebral damage in brain areas with neuromuscular coordination in rats.

[Swarnkar S, Singh S, Mathur R, Patro IK, Nath C. Toxicology. 2010 Jun 4;272(1-3):17-22.]

Rotenone induces neurotoxicity but its correlation with biochemical and cerebral changes in rat brain regions are not well defined. In the present study rotenone was administered (3, 6 and12mug/mul) intranigrally in adult male SD rats and its effect was assessed on neuromuscular coordination and in different brain areas viz. striatum (STR), mid-brain (MB), frontal cortex (FC) and hippocampus (HP) cerebral and biochemical changes on 1st and 7th day after treatment. All the doses of rotenone significantly impaired neuromuscular coordination performance on Rota rod test on 1st and 7th day. TTC staining showed significant increase in cerebral injury volume on 1st and 7th day after rotenone treatment indicating mitochondrial enzyme deficiency but increase after 7th day was less that after 1st day. Rotenone treated rats showed significant decrease in GSH and increase in MDA in different brain regions though the pattern was varied. After 1 day of rotenone (6 and 12mug) treatment significant decrease in GSH was observed in STR and MB while MDA was significantly increased only in MB. The maximal effect on GSH and MDA was obtained in STR and MB on 7th day after treatment with 12mug dose of rotenone. Thus, based on the occurrence of changes, it may be suggested that impairment of neuromuscular coordination is inked to oxidative stress rather than mitochondrial enzyme deficiency, all the processes are correlated with each other with the progression of time. MB appeared as most sensitive brain area towards rotenone toxicity.

Melatonin protection on mercury-exerted brain toxicity in the rat.

[Rao MV, Purohit A, Patel T. Drug Chem Toxicol. 2010 Apr;33(2):209-16.]

The effect of melatonin on the neurotoxicity induced by mercuric chloride was studied. Adult rats were fed orally with two different doses of mercuric chloride (2 mg; 4 mg/kg body weight) to evaluate brain toxicity with respect to cerebral hemisphere, cerebellum, and medulla oblongata regions for 60 days with or without supplementation with melatonin (5 mg/kg body weight) intraperitoneally. The results suggest that the graded doses of mercury elicit the depletion of enzymatic activities, such as adenosine triphosphatase, succinate dehydrogenase, phosphorylase, alkaline phosphatase, acid phosphatase, altered glycogen, total protein, and lipid peroxidation levels in the cerebral hemisphere, cerebellum, and medulla oblongata of the brain, thereby affecting their respective functions. Blood glucose and mercury levels increased, followed by a reduction in body and organ weights. All these effects seemed to be severe in the cerebral hemisphere of the brain. Further affected indices were, to some extent, maintained in the brain of animals cotreated with melatonin, showing its protective role against mercury-exerted neurotoxicity.

Nicotine- and caffeine-mediated changes in gene expression patterns of MPTP-lesioned mouse striatum: Implications in neuroprotection mechanism.

[Singh K, Singh S, Singhal NK, Sharma A, Parmar D, Singh MP. Chem Biol Interact. 2010 Apr 29;185(2):81-93.]

Exposure to 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) induces dopaminergic neurodegeneration in the nigrostriatal pathway and nicotine and caffeine ameliorate neurodegenerative changes in MPTP-lesioned mouse model of Parkinson's disease (PD). The present study was undertaken to investigate the effect of nicotine and caffeine on the expression patterns of genes in the striatum of control and MPTP-treated mice to identify the differentially expressed transcripts and to assess their possible implications in neuroprotection. Mice were treated intraperitoneally with caffeine (20mg/kg) or nicotine (1mg/kg), daily, for the first 8 weeks followed by MPTP (20mg/kg) co-treatment for further 4 weeks along with respective controls. RNA was isolated from the striatum of control and treated mice; reverse transcribed separately into labeled cDNA and a mixture of equal quantities of labeled cDNA was hybridized with mouse 15k array. The expression levels of toll-interleukin-1 receptor domain-containing adaptor protein, nuclear protein-1, cathepsin B, interleukin-4 receptor, caspase 9, complement component-1, heat shock protein-1 and cytochrome c-oxidase-VIIc were validated by quantitative real-time polymerase chain reaction (qRT-PCR). MPTP differentially regulated the expression of many genes involved in apoptotic cell death, oxidative stress, cell cycle regulation, protein modification and mitochondrial dysfunction. The expression patterns of many of these transcripts were significantly restored in

caffeine- and nicotine-treated mice. The results demonstrate the involvement of multiple molecular events in MPTP-induced toxicity and nicotine or caffeine-mediated neuroprotection.

Toxic neuropathies.

[Misra UK, Kalita J. Neurol India. 2009 Nov-Dec;57(6):697-705.]

Toxic neuropathies generally result in length dependent axonal neuropathy with the exception of diphtheria and a few toxic neuropathies. In spite of occurrence of diphtheria in India there is paucity of published reports on diphtheritic neuropathy. Arsenic neuropathy commonly occurs in Bengal and Bangladesh because of ground water contamination whereas in Punjab it is due to contamination of opium. Lead neuropathy is rare and has been reported in battery workers and silver refining workers. It produces motor neuropathy resulting in foot drop and wrist drop. Organophosphates are used as pesticides, industrial chemicals and food adulterant. Certain organophosphates such as triorthocresyl phosphate used for or oil adulteration inhibit neurotoxic esterase and result in a delayed type of axonal neuropathy. Alcohol related neuropathy is a controversial issue whether it is due to alcohol related toxicity or due to nutritional deficiencies. Indian studies have revealed that neuropathy occurs both in alcoholic and non-alcoholic cirrhosis. Hexane neuropathy is reported in screen printers and these cases highlight the need for better preventive and occupational measures. Iatrogenic toxic neuropathies have been reported with cisplatin and vincristine. Because of geographical, occupational and health related conditions toxic neuropathies are likely to be more common than reported and greater awareness is needed.

Refractory status epilepticus: a developing country perspective.

[Sinha S, Prashantha DK, Thennarasu K, Umamaheshwara Rao GS, Satishchandra P. J Neurol Sci. 2010 Mar 15;290(1-2):60-5.]

To analyse the underlying causes, therapeutic response and outcomes of convulsive refractory status epilepticus (RSE). This retrospective analysis was carried on 98 patients with RSE (age: 16.9+/-14.5 years). All had received a combination of parenteral benzodiazepine and phenytoin or phenobarbitone followed by other anti-epileptic drugs (AEDs). The clinical, EEG, imaging features of convulsive RSE and long-term seizure outcome were analysed. Seventy six patients had de novo RSE for the first time in life. The mean duration of RSE, before and during NICU admission was 3.4+/-3.2 days and 2.9+/-2.4 days respectively. The mean duration of NICU stay and mechanical ventilation was 17.4+/-14.5 was 14.4+/-12.8 days respectively. The precipitating factors included viral fever - 13, AEDs stoppage - 7 and alcohol - 1. EEG was abnormal in 81.5% of patients. CT and MRI were abnormal in 63.4% and 82.3% respectively. Thirty-four patients died and compared to those surviving, patients were older, had lesser duration of NICU stay and elevated CSF protein. Dependence for activities of daily living (ADL) at discharge was: recovered - 29, mild to moderate - 13 and severe - 22. Seizure outcome in 64 patients after 43.5+/-58.2 weeks were - seizure-free: 65.6%, one seizure: 21.8%, >1 seizure/month: 14.1%, and seizure recurrence requiring admission: 1.5%. After six and twelve months of follow up, the long-term seizure outcome were: seizure-free: 48.3% and 28.6%; one seizure: 27.6% and 38.1%; >1 seizure/month: 20.7% and 28.6%; and seizure recurrence requiring admission: 3.4% and 4.7% respectively. Among those survived 49 de novo RSE, about one-third developed post-SE symptomatic seizures after 30.1+/-54.4 weeks. Seizures could still be controlled in two-thirds of patients with convulsive RSE. About 30% of patients achieved long-term seizure freedom.

Potentiation of neurotoxicity of *Lathyrus sativus* by manganese: alterations in blood-brain barrier permeability.

[Mishra G, Shukla R, Hasan M, Khanna SK, Das M. Toxicol Mech Methods. 2009 May;19(4):318-26.]

Environmental factors have been speculated to play an important role in potentiating the neurotoxicity of *Lathyrus sativus* (LS). Hence, blood-brain barrier permeability and neurotoxicity studies were carried out in manganese- and LS-exposed animals. Dietary feeding of LS (80%) plus Mn (0.4 mg/100 g diet) for 90 days to guinea pigs showed significant ($p < 0.05$) decrease in brain nucleotidase and ATPase activities when compared to control or LS alone treated groups. Combined treatment of LS and Mn showed a significant ($p < 0.05$) decrease in neuronal aryl hydrocarbon hydroxylase (36-40%), ethoxyresorufin-O-deethylase (40-45%), glutathione-S-transferase (27-31%), and quinone reductase (24-25%) activities when compared to control and LS alone treated animals. Lipid peroxidation, a marker for membrane damage, was found to be relatively more enhanced (58-141%) along with significant ($p < 0.05$) depletion of GSH levels in LS+Mn-treated animals when compared to control, Mn alone, and LS alone treated groups. The neuronal catalase activity of lathyrus plus Mn-treated animals showed a pronounced decrease (37-49%) when compared to control, Mn, and lathyrus alone treated

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groups. On the contrary, glutathione peroxidase in brain of Mn and lathyrus alone treated animals indicated a respective increase ($p < 0.05$) of 18% and 20%, while the combined effect of lathyrus plus Mn exhibited an increase of almost 50% when compared to control guinea pigs. Single parenteral administration of Mn (15 mg/kg b.wt) to guinea pigs followed by single oral intubation of beta-N-oxalyl-L-alpha, beta-diamino propionic acid (ODAP, 75 mg/guinea pig) resulted in a significant increase (143%) in neuronal ODAP content. ODAP (50 mg/kg,iv) treatment to mice pretreated with MnCl2 (10 mg/kg b.wt for 3 days or 40 mg/kg b.wt for 1 day), caused an enhancement in blood-brain barrier (BBB) permeability (129-196%), while ODAP and Mn alone showed relatively less enhancement (66-87%). The lumbar region of LS+Mn showed a number of vacuolated areas of variegated size and chromatolytic neurons, along with a few degenerated neurons. These results suggest that Mn may potentiate the neurotoxicity of lathyrus/ODAP by altering the BBB permeability.

Neuroprotective efficacy of *Bacopa monnieri* against rotenone induced oxidative stress and neurotoxicity in *Drosophila melanogaster.*

[Hosamani R, Muralidhara. Neurotoxicology. 2009 Nov;30(6):977-85.]

Bacopa monnieri, Linn. (Brahmi, BM), traditionally used to improve mental health in Indian ayurvedic system of medicine is known to possess various neuropharmacolgical properties. In the recent past, Drosophila has been widely used as a model to study various neurodegenerative diseases. Environmental toxins like rotenone, a specific inhibitor of complex I is employed to increase oxidative stress mediated neuropathology and sporadic Parkinson's disease. In this study, we examined the neuroprotective properties of BM against rotenone induced oxidative damage and neurotoxicity. Flies (Oregon K strain, adult males) exposed to a standardized BM powder for 7 days in the diet exhibited significant diminution in the levels of endogenous oxidative markers viz., malondialdehyde, hydroperoxide and protein carbonyl content. Further, BM offered complete protection against rotenone (500 microM) induced oxidative stress and markedly inhibited dopamine depletion (head region, 33%; body region, 44%) in flies. Flies exposed to rotenone+BM exhibited a lower incidence of mortality (40-66% protection) and performed better in a negative geotaxis assay (45-65%) both suggesting the neuroprotective potential of BM. Interestingly, BM also conferred significant resistance (43-54% protection) in a paraquat oxidative stress bioassay. The neuroprotective effects of BM were highly comparable to those of a commercially available Brahmi preparation. Although the precise mechanism/s underlying the neuroprotective efficacy of BM are not clear, it is hypothesized that it is wholly or in part related to its ability to mitigate rotenone induced oxidative stress. Further, our approach confirms the utility of the Drosophila model in screening putative neuroprotective phytomedicines prior to their use in mammalian models.

Attenuation of arsenic neurotoxicity by curcumin in rats.

[Yadav RS, Sankhwar ML, Shukla RK, Chandra R, Pant AB, Islam F, Khanna VK. Toxicol Appl Pharmacol. 2009 Nov 1;240(3):367-76.]

In view of continued exposure to arsenic and associated human health risk including neurotoxicity, neuroprotective efficacy of curcumin, a polyphenolic antioxidant, has been investigated in rats. A significant decrease in locomotor activity, grip strength (26%) and rota-rod performance (82%) was observed in rats treated with arsenic (sodium arsenite, 20 mg/kg body weight, p.o., 28 days) as compared to controls. The arsenic treated rats also exhibited a decrease in the binding of striatal dopamine receptors (32%) and tyrosine hydroxylase (TH) immunoreactivity (19%) in striatum. Increased arsenic levels in corpus striatum (6.5 fold), frontal cortex (6.3 fold) and hippocampus (7.0 fold) associated with enhanced oxidative stress in these brain regions, as evident by an increase in lipid perioxidation, protein carbonyl and a decrease in the levels of glutathione and activity of superoxide dismutase, catalase and glutathione peroxidase with differential effects were observed in arsenic treated rats compared to controls. Simultaneous treatment with arsenic (sodium arsenite, 20 mg/kg body weight, p.o., 28 days) and curcumin (100 mg/kg body weight, p.o., 28 days) caused an increase in locomotor activity and grip strength and improved the rota-rod performance in comparison to arsenic treated rats. Binding of striatal dopamine receptors and TH expression increased while arsenic levels and oxidative stress decreased in these brain regions in co-treated rats as compared to those treated with arsenic alone. No significant effect on any of these parameters was observed in rats treated with curcumin (100 mg/kg body weight, p.o., 28 days) alone compared to controls. A significant protection in behavioral, neurochemical and immunohistochemical parameters in rats simultaneously treated with arsenic and curcumin suggest the neuroprotective efficacy of curcumin.

Aluminium neurotoxicity: neurobehavioural and oxidative aspects.

[Kumar V, Gill KD. Arch Toxicol. 2009 Nov;83(11):965-78.]

Aluminium is the most widely distributed metal in the environment and is extensively used in daily life that provides easy exposure to human beings. The exposure to this toxic metal occurs through air, food and water. However, there is no known physiological role for aluminium within the body and hence this metal may produce adverse physiological effects. Chronic exposure of animals to aluminium is associated with behavioural, neuropathological and neurochemical changes. Among them, deficits of learning and behavioural functions are most evident. Some epidemiological studies have shown poor performance in cognitive tests and a higher abundance of neurological symptoms for workers occupationally exposed to aluminium. However, in contrast to well established neurotoxic effects, neurobehavioural studies of aluminium in rodents have generally not produced consistent results. Current researches show that any impairment in mitochondrial functions may play a major role in many human disorders including neurodegenerative disorders. Being involved in the production of reactive oxygen species, aluminium may cause impairments in mitochondrial bioenergetics and may lead to the generation of oxidative stress which may lead to a gradual accumulation of oxidatively modified cellular proteins. In this review, the neuropathologies associated with aluminium exposure in terms of neurobehavioural changes have been discussed. In addition, the impact of aluminium on the mitochondrial functions has also been highlighted.

Neurology of acute organophosphate poisoning.

Singh G, Khurana D. Neurol India. 2009 Mar-Apr;57(2):119-25.

Acute organophosphate (OP) poisoning is one of the most common poisonings in emergency medicine and toxicological practice in some of the less-developed nations in South Asia. Traditionally, OP poisoning comes under the domain of emergency physicians, internists, intensivists, and toxicologists. However, some of the complications following OP poisoning are neurological and involve neurologists. The pathophysiological basis for the clinical manifestations of OP poisoning is inactivation of the enzyme, acetylcholinesterase at the peripheral nicotinic and muscarinic and central nervous system (CNS) nerve terminals and junctions. Nicotinic manifestations occur in severe cases and late in the course; these comprise of fasciculations and neuromuscular paralysis. There is a good correlation between the electrophysiological abnormalities and the severity of the clinical manifestations. Neurophysiological abnormalities characteristic of nicotinic junctions (mainly neuromuscular junction) dysfunction include: (1) single, supramaximal electrical-stimulus-induced repetitive response/s, (2) decrement-increment response to high frequency (30 Hz) repetitive nerve stimulation (RNS), and (3) decremental response to high frequency (30 Hz) RNS. Atropine ameliorates muscarinic manifestations. Therapeutic agents that can ameliorate nicotinic manifestations, mainly neuromuscular, are oximes. However, the evidence for this effect is inconclusive. This may be due to the fact that there are several factors that determine the therapeutic effect of oximes. These factors include: The OP compound responsible for poisoning, duration of poisoning, severity of poisoning, and route of exposure. There is also a need to study the effect of oximes on the neurophysiological abnormalities.

Curcumin attenuates aluminium-induced functional neurotoxicity in rats.

[Sethi P, Jyoti A, Hussain E, Sharma D. Pharmacol Biochem Behav. 2009 Jul;93(1):31-9.]

Curcumin is a polyphenol extracted from the rhizome of *Curcuma longa* and well known as a multi-functional drug with antioxidative, anti-cancerous and anti-inflammatory activities. Curcumin's antiaging and neuroprotective potential is widely reported. In the present study, effect of curcumin treatment dose 30 mg kg(-1) day(-1) was investigated against aluminium neurotoxicity in young and old animals. Direct and indirect intakes of aluminium have been reported to be involved in the etiology of several neurodegenerative disorders like Alzheimer's and Parkinson's diseases. Long term Al was administered through drinking water at a dose of 50 mg/kg/day for 6 months in both young (4 months) and old (18 months) male Wistar rats. Result obtained demonstrates that curcumin treatment attenuates the Al-induced alterations at biochemical, behavioral and ultrastructural levels which was well reflected in the electrophysiological recordings. Our results indicate that curcumin's ability to bind redox active metals and cross the blood-brain barrier could be playing crucial role in preventing against Al-induced neurotoxicity.

Delayed-onset encephalopathy and coma in acute organophosphate poisoning in humans.

[Peter JV, Prabhakar AT, Pichamuthu K. Neurotoxicology. 2008 Mar;29(2):335-42.]

The objective of the study was to describe the clinical

TOPIC OF INTEREST

characteristics and course of delayed-onset organophosphate (OP) poisoning. In our clinical experience, we have noticed patients with onset of deep coma 4-7 days after hospital admission, clinical features that have not been previously described. We set up a prospective observational study over 1 year to formally characterize this observation. Thirty-five patients admitted to the intensive care unit (ICU) with severe OP poisoning and treated with atropine and supportive therapy were followed up. Oximes were not administered. Three patients developed delayed-onset coma after presenting with normal or near normal Glasgow coma score (GCS). They developed altered conscious state rapidly progressing to deep coma, 5.0+/-1.0 (mean+/-S.D.) days after OP ingestion. The GCS persisted at 2T for 4.3+/-2.1 days despite the cessation of sedative drugs at the onset of coma. During this period, the patients had miosed non-reacting pupils and no clinically detectable cortical or brainstem activity. Computed tomography of the brain and cerebrospinal fluid analysis were normal. Electroencephalogram showed bihemispheric slow wave disturbances. Two patients required atropine during this period to maintain heart rate and reduce secretions. In all three patients, no metabolic, infective or non-infective cause of altered conscious state was identified. With supportive therapy the GCS improved to 10T in 8.0+/-2.0 days. All patients survived to hospital discharge. Three other patients who developed a reduction in GCS (3T-7T) by 4.7+/-1.2 days but not progressing to coma and recovering (GCS 10T) in 3.3+/-0.6 days may have manifested delayed-onset encephalopathy. Delayed-onset coma appears to have a distinct clinical profile and course with complete resolution of symptoms with supportive therapy. Although persistent cholinesterase inhibition is likely to have contributed to the manifestations, the mechanism of coma and encephalopathy need to be explored in further trials. The good outcomes in these patients suggest that therapy should not be limited in OP-poisoned patients developing profound coma or encephalopathy during hospitalization.

RESEARCH DIGEST

A Greener Way to Make Plastic

[http://news.sciencemag.org/sciencenow/2010/11/a-greener-way-to-make-plastic.html]

A portable biorefinery for pyrolysis oil production.

Chemical refineries are great at converting petroleum into gasoline and the building blocks of plastics and other consumer goods. But when it comes to sustainable starting materials, such as wood chips, corn stalks, or other plant "biomass," refineries are too inefficient to make the process commercially viable. Researchers have now given that efficiency a major boost, perhaps enough of one to allow us to leave petroleum behind. There are plenty of ways to convert biomass into useful fuels and chemicals. But each has drawbacks. Yeast and other microbes can ferment plant sugars into ethanol, a gasoline additive. But only moderate amounts of ethanol can be added to gasoline without requiring engine modifications. Algae readily produce bio-oils, but the technology remains costly and requires too much land and fresh water to make an impact on the market. A third route, known as pyrolysis, heats dried and ground biomass to about 550°C in an oxygen-depleted chamber (so the biomass doesn't burn), producing a mixture of gases, liquids, and a gray, carbon-rich solid called coke. When the gases cool and condense, they combine with the liquids to form a mixture of oils. These oils are cheap: It costs only $1 to make oil through pyrolysis that has the same energy content as a gallon of gasoline. But they must be further chopped into smaller hydrocarbons before they are suitable for industrial use. In addition, oxygen-rich acids in the oil make it corrosive, so it can't be used in conventional engines and storage containers.

Engineers have worked to tackle these problems with pyrolysis oils by adding a second treatment step, where the oils react with hydrogen over catalysts called zeolites. The hydrogen replaces oxygen in the acids and other compounds in the bio-oils and makes them less corrosive, and the zeolites break the large hydrocarbons into compounds such as toluene and benzene that are

commonly used building blocks for a large number of industrial chemicals. The problem is that coke and other substances made by pyrolysis can gum up zeolites. Only 20% of the pyrolysis oils are converted to useful chemicals. Most of the rest winds up as coke, carbon monoxide, and carbon dioxide. In hopes of improving the efficiency, George Huber, a chemical engineer at the University of Massachusetts, Amherst, and colleagues tested several combinations of zeolites (hundreds are known) and reaction conditions and found one standout. They split the second treatment step in two. First, they reacted their pyrolysis oils with hydrogen over a ruthenium and platinum catalyst, which stripped out much of the oxygen from the acids and added hydrogen. This made a mix of stable compounds that were less likely to form coke when they were processed in the second step over the zeolites. It also allowed the zeolites to convert 60% of the longer hydrocarbon chains into five key chemical starting materials: benzene, toluene, xylene, propylene, and ethylene. Together, these compounds represent five of the seven key starting materials (the others are methanol and 1,3-butadiene) that form the basis of the $400-billion-a-year petrochemical industry. The process can also be tailored to produce more of individual chemical building blocks, which in the future could allow chemical companies to produce the most valuable building blocks at any given time. Robert Brown, who directs the Bioeconomy Institute at Iowa State University, Ames, says the new work is noteworthy because chemical companies have many decades of experience in using heat and catalysts to convert petroleum into a wide variety of commodity chemicals. "There is a notion that thermochemical processing is a mature technology," with little room for improvements, Brown says. "Huber's work demonstrates that there is potential for many advances," as the technology is applied to biomass, he says. Huber says he has formed a start-up company, Anellotech, that plans to commercialize the technology, first with a small pilot plant, followed by a commercial demonstration facility.

Bisphenol A goes through the skin: Till receipts are a potential source of exposure to the controversial chemical.

[Nature | 4 November 2010 | doi:10.1038/news.2010.581]

Thermal paper used in till receipts are a source of BPA

Two studies have thrown the controversial compound bisphenol A (BPA) back into the limelight. One study found that the chemical is readily absorbed through the skin, while a second study found that people who routinely touch BPA-laden till receipts have higher than

average levels of the chemical in their bodies. Taken together, the findings strengthen calls for tougher regulation of the chemical, which is widely used in plastics manufacturing. BPA is detectable in most people in Western countries. Animal studies have confirmed that high doses are harmful, but some evidence that it may also be harmful at low doses has yet to convince regulators to take decisive action against the compound. The chemical mimics the effects of oestrogen in the body, so health concerns are especially pressing for pregnant women and some scientists also advise against the use of babies' bottles that contain BPA. BPA is commonly used in food and drink packaging, where the molecule is usually locked in as part of a complex polymer. However, concerns have also been raised over its presence in the thermal paper used mainly in till receipts. In thermal paper the compound exists as a free monomer, which makes it easier for the body to absorb than other forms found in food packaging. Daniel Zalko, a toxicologist at the French National Institute for Agricultural Research in Paris, and his colleagues have shown that free BPA can indeed be 'efficiently' absorbed through the skin. The findings, published in *Chemosphere,* could help to explain why BPA levels in the general population appear to be higher than doses theoretically received through food and drink. To investigate levels of skin exposure, the researchers took radioactively labelled BPA and observed the movement of radioactivity through pig ear skin — a widely used model for human skin. They repeated their experiments with smaller samples of human skin. In the pig model, about 65% of the BPA diffused through the skin. For human skin around 46% diffused through. Both types of tissue were also able to metabolize BPA. The findings suggest that till receipts should be handled with caution, says Zalko. "In the same way we advise people not to use polycarbonate-based baby bottles, it would be smart to advise pregnant women to avoid or wash their hands after touching these sorts of papers."

Problem on paper

Zalko and his team's findings are supported by another study that took a contrasting approach. Joe Braun, an epidemiologist at Harvard University in Boston, Massachusetts, and his group looked at the urine

RESEARCH DIGEST

concentrations of BPA in 389 pregnant women, and broke these data down by occupation Cashiers — who handle far more receipts than the general population — had the highest prenatal BPA concentrations in their urine at 2.8 micrograms per gram. By contrast, teachers had 1.8 micrograms per gram and industrial workers had 1.2 micrograms per gram. Previous studies in factory workers exposed to BPA found even higher levels. One study linking BPA exposure to reduced sexual function in men found that one-quarter of workers had levels above 467 micrograms per gram. Although there were only 17 cashiers in his sample, Braun says that he is "pretty confident" of the finding, not least because of Zalko's work. "It's reasonable to assume BPA can be absorbed through the skin," he says. Braun notes that for people who handle only a couple of receipts a day, thermal paper is unlikely to be a major source of exposure. Pregnant women working as cashiers should be careful though, he suggests. "I would err on the side of caution and avoid exposure we think might be harmful."

Changes caused by smoking block tumour-fighting genes

[New Scientist 12 October 2010]

The first direct evidence has been found linking smoking to epigenetic changes in genes that help fight cancer. Reversing these changes may one day provide a new route to treating cancer. Women with cervical cancer are known to have higher levels of epigenetic modifications – methyl groups attached to particular sites on their DNA – affecting a gene called p16, which is known to be involved in suppressing tumours. To find out more, Yuk Ting Ma at the University of Birmingham, UK, re-analysed samples from a series of cervical smear tests taken over four years from 1075 women. Ma found evidence of p16 methylation in the cervical cells of 37 per cent of smokers compared to 9.3 per cent of non-smokers. Women who started smoking during the study were 3.7 times more likely to acquire p16 methylation than non-smokers. In two-thirds of the 19 smokers with p16 methylation who gave up smoking during the trial, the methylation disappeared. This suggests not only that smoking caused the changes, but also that it might be possible to reverse them before they lead to cancer.

Traffic Trouble: Study Links Diabetes to Vehicular Pollution

[Environmental Health Perspectives volume 118 | number 9 | September 2010 A 399]

There is a well-documented relationship between exposure to particulate matter (PM) in ambient air pollution and risk of developing cardiovascular disease. Subclinical or low-grade inflammation, believed to serve as an intermediary between air pollution and cardiovascular/metabolic health risks, is associated with impaired glucose metabolism, but few studies to date have examined the relationship between air pollution and diabetes. For the first time, a prospective study provides evidence linking exposure to traffic-related air pollution with an increase in the risk of developing type 2 diabetes in women [EHP 118(9):1273–1279; Krämer et al.]. In the current study, researchers investigated the relationship between air pollution exposure and new-onset incident type 2 diabetes using information from the prospective Study on the Influence of Air Pollution on Lung, Inflammation, and Aging (SALIA). The authors also assessed whether baseline inflammation was associated with pollution exposure. The SALIA cohort is composed of 1,775 women aged 54–55 years without diabetes at enrollment. The women lived in the highly industrialized Ruhr district of Germany or in rural, nonindustrial towns nearby. Using data obtained from cross-sectional surveys administered in 1985–1994 and a follow-up interview in 2006, the investigators analyzed the incidence of type 2 diabetes over 1990–2006. They also collected information on symptoms and diagnoses of respiratory disease, home and occupational exposure to air pollution, smoking status, and socioeconomic status. They took initial height and weight measurements, and collected nonfasting blood serum samples to measure complement factor C3c, a blood protein that served as a marker for subclinical inflammation. They estimated exposure to nitrogen dioxide (NO_2) and PM, the major components of traffic emissions, by applying land-use regression models.

Between 1990 and 2006, 187 participants (10.5%) were diagnosed with type 2 diabetes. Exposure to traffic-related air pollution and higher levels of C3c in the blood at baseline were both associated with increased diabetes risk. Living within 100 m of a busy roadway was

A portable biorefinery for pyrolysis oil production.

associated with more than double the risk of diabetes for women with a lower education level compared with women in the same group who did not live near a busy roadway; women with higher education who lived near busy roads had no altered risk. Overall, the researchers observed significant associations with PM and NO_2 exposure. The slightly stronger associations of risk with NO_2 exposure than with PM exposure further support a link between traffic-related air pollution exposure and diabetes, since most sources of NO_2 are traffic-related

Green machine: Tackling the plastic menace

[New Scientist June 2010]

Plastic can take hundreds of years to degrade, so bottles and bags can be a danger to wildlife, strangling birds, mammals and fish, and soaking up toxic chemicals from seawater that can poison any creatures that swallow them. What's more, plastic is expensive to recycle and requires a significant energy outlay, particularly in sorting and separating the different polymers that may be present. Now Vilas Ganpat Pol at the Argonne National Laboratory in Illinois has developed a technique to convert a mixture of waste plastics into micro-spheres of a form of carbon called carbon black. The micro-spheres can be used in paints, lubricants and tyres, and even incorporated into the anodes of lithium-ion batteries. To create the spheres, Pol melted a mixture of plastics in a reactor at 700 °C. At this temperature, the pressure in the reactor reaches 34 atmospheres, helping to break down the bonds between the hydrogen and carbon atoms in the polymer chains. The hydrogen gas is siphoned off, leaving behind carbon micro-spheres up to 10 micrometres in diameter (Environmental Science and Technology, DOI: 10.1021/es100243u). Pol recently used a similar process to convert plastic waste into carbon nanotubes. However, this required the use of a relatively costly cobalt acetate catalyst, which could make the process prohibitively expensive if scaled up. The new technique requires no catalyst at all, says Pol. Geoffrey Mitchell, a material scientist at the University of Reading in the UK, says the fact that the process uses no catalyst is a major plus, and if the technique can be used to recycle the growing mountain of low-value, mixed plastic waste, it could have a rosy future.

Meanwhile, Scott Phillips and Wanji Seo at Pennsylvania State University in University Park have developed self-destructing plastics that could lead to packaging that is more easily recycled and friendlier to wildlife. Working with the polymer poly(phthalaldehyde), the team attached one of two chemical end groups, or "triggers" – either a silyl ether or an allyl ether – to each phthalaldehyde building block. When a square of the polymer was exposed at room temperature to fluoride ions, the central section, where molecules were capped with the silyl ether, underwent rapid depolymerisation and broke down. Those sections capped with the allyl ether remained unchanged (Journal of the American Chemical Society, DOI: 10.1021/ja104420k). The technique could be modified to develop plastic products that quickly degrade when exposed to triggers in the environment, he says. If a bag made of the right plastic reaches the ocean, for example, microbial enzymes in the water would make the material depolymerise and "the bag just disappears", Phillips says. By capping all the polymer sections with an end group that responds to a certain chemical, the technique could also be used as a low-energy method for recycling plastic waste, says Phillips. The resulting monomers would have to be re-polymerised to create a new plastic, but this may prove cheaper than separating different polymers before recycling can begin, he says.

So far the team has developed polymers with end groups that react with fluoride ions, palladium and hydrogen peroxide, and they are also hoping to develop polymers that respond to enzymes, he says. The team cautions that the research is still at the proof-of-concept stage. Work remains to be done to find polymers that break down into substances that are more environmentally friendly than phthalaldehyde. Another problem is that the polymers they have so far made are sensitive to acidity and need to be more stable to be usable.

A portable biorefinery for pyrolysis oil production.

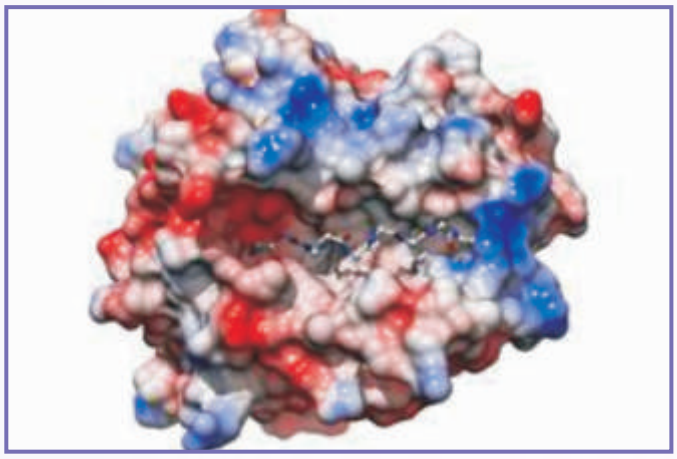
HIV immunity is all in the amino acids

Worldwide study implicates structural changes in a protein binding site

[Nature |4 November 2010 | doi:10.1038/news.2010.582]

Why do some people who are infected with HIV not go on to develop AIDS? A large-scale genetic analysis

RESEARCH DIGEST



suggests that the answer lies in tiny changes in the structure of a protein that helps the immune system to recognize and destroy infected cells. Most people who contract HIV eventually end up with full-blown AIDS as the virus replicates in their cells, reaching very high levels and damaging their immune systems. However, the virus does not progress to this stage in about 1 out of every 300 infected people. These 'HIV controllers' do not require treatment, because their bodies suppress the replication of the virus. Bruce Walker, an immunologist and director of the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology and Harvard University in Charlestown, first thought of carrying out the study when he recognized the clinical value of such HIV controllers. "I realized that we could create a cohort by going directly to physicians around the world, and I thought we should figure out what is genetically unique about people who do well compared with people who do badly," he says.

Walker and his colleagues sampled the DNA of more than 900 HIV controllers. They compared it with the genetic code of 2,600 individuals with normal HIV infections, using a technique called a genome-wide association study (GWAS). The GWAS tested single nucleotide polymorphism (SNP) variations — changes in one letter of DNA — at a million points in the genomes of these individuals, and found more than 300 sites that were statistically associated with control of HIV. All the sites identified are in a region of the genome that codes for proteins involved in immune response, called HLA proteins. The researchers used regression analyses to narrow their search down to the four sites most strongly linked to HIV immunity. “This will help us induce better responses to HIV, because we now know what it is that we're trying to induce.” It isn't possible to tell from the statistics alone whether these sites cause HIV immunity themselves or are simply closely associated with others that do. But using a detailed map of the HLA regions of the genome, created as part of an earlier diabetes study, the team pinpointed specific amino acids in the protein HLA-B that differed between controllers and people with normal infections. These amino acids seemed to be behind the ability to control the virus. "Out of the three billion nucleotides [that make up the human genome], we narrowed it down to a handful of amino acids that define the difference, each coded for by just three nucleotides," says Walker.

HLA-B plays an important part in the body's immune response to viral attack. When viruses infect the body, they hijack host cells to produce viral proteins. HLA-B grabs peptides — short fragments of these viral proteins — and carries them to the cell membrane, where they act as markers to flag the cell for destruction by the immune system. Five of six amino acids that differed between controllers and non-controllers are found in the lining of the structural pocket used by HLA-B to bind those viral proteins. A smaller study in South Africa had already implicated HLA-B in HIV immunity, but "this confirms that HLA-B is the most important protein", says Rodney Phillips, an immunologist and co-director of the Institute of Emerging Infections at the University of Oxford, UK.

The mechanics of immunity

Changes in the amino acids identified by Walker's team alter how HLA-B presents viral peptides from HIV to the immune system, but how this process differs between controllers and people with normal HIV infections remains unclear. "We're trying to define the precise mechanism and figure out exactly what this thing is doing, so there is clearly more work to be done," says Walker. Studies of immune responses to other diseases have also implicated amino acids in the binding pocket of HLA proteins, says Phillips. "If you've got a slightly different structure to the groove, you may be able to bind peptides in a slightly different sequence, or at a slightly different [protein-folding] conformation, and that might evoke a better immune response," he says. However, it will be a long time before this work gives rise to treatments or vaccines. "We're a long way from translating this, but the exciting part is that this GWAS led us to an immune response. That has to be good news for vaccines, because they manipulate the immune response," says Walker. "We're cautiously optimistic that this will help us develop ways of inducing better responses, because we now know what it is that we're trying to induce."

FORTH COMING CONFERENCE

International Workshop on Dilemmas of Choice: Responsibility in Nanotechnology Development

Rovigo, Italy, June 6-7, 2011
Website :www.ciga.unipd.it or ciga@unipd.it

Alternatives for Developmental Neurotoxicity Testing

Varese, Italy, May 10-13, 2011
Website:http://ihcp.jrc.ec.europa.eu/dnt3conference/index.htm

6th International Scientific Conference on Bioaerosols, Fungi, Bacteria, Mycotoxins in Indoor and Outdoor Environments and Human Health

Saratoga Springs, New York, USA, September 6 - 9, 2011
Website:http://www.bioaerosol.org/

51st Annual Meeting of the Teratology Society: Translational Research in Birth Defects: From Mechanism to Epidemiology

Coronado, California, USA, June 25-29, 2011
Website:http://teratology.org/meetings/2011/general_information.asp

8th World Congress on Alternatives and Animal Use in the Life Sciences

Montréal, Canada, August 21-25, 2011.
Website:http://www.wc8.ccac.ca/pages/welcome

31st Annual Meeting of the Academic of Environment Biology and National Symposium on "Sustainable Development, Environment & Socio economic Challenges" Bundelkhand University, Jhansi U.P., India 14-16 October, 2011.

हिन्दी भाषा खण्ड

भारतीय विषविज्ञान अनुसंधान संस्थान में हिंदी सप्ताह का आयोजन किया गया

भारतीय विषविज्ञान अनुसंधान संस्थान (आई.आई.टी.आर.) लखनऊ के प्रेक्षागृह में दिनांक 14.09.2010 को सांय 4:00 बजे हिंदी सप्ताह 14 से 20 सितम्बर, 2010 के उद्घाटन समारोह का आयोजन किया गया। इस अवसर पर मुख्य अतिथि प्रो. मनोज कुमार मिश्रा, कुलपति, लखनऊ विश्वविद्यालय थे। मुख्य अतिथि को संस्थान के निदेशक डॉ. के.सी. गुप्ता ने स्मृति चिन्ह भेंट किया। निदेशक ने मुख्य अतिथि का परिचय देते हुए कहा कि प्रो. मिश्रा किसी परिचय के मोहताज नहीं है। आपको हम आई.आई.टी.आर. परिवार का अभिन्न अंग मानते हैं। आपको जब भी हमने संस्थान में आमंत्रित किया आपने हमें निराश नहीं किया है। मैं आपकी उपस्थिति में गौरवान्वित महसूस कर रहा हूँ। एक वैज्ञानिक जिन पुरस्कारों को प्राप्त करने का इच्छुक रहता है वे सभी प्रो. मिश्रा को प्राप्त हैं। मुख्य अतिथि ने अपने संदेश में कहा कि जब मुझे आमंत्रित किया गया तो मैं सोचने लगा कि हिंदी दिवस पर क्या बोलूँगा। मुझे लखनऊ विश्वविद्यालय आकर हर्ष हुआ कि यहाँ मेरा हिंदी प्रेम प्रस्फुटित होने लगा है। अपनी सभ्यता के प्रति प्रेम को अंगीकार करना चाहिए। हमारी संस्कृति किसी भी प्रकार से कम नहीं है। हिंदी भाषा का बहुत समृद्ध साहित्य है। संस्थान के निदेशक, डॉ. के.सी. गुप्ता ने अध्यक्षीय संबोधन में कहा कि हमारे शोध संस्थानों से अनुरोध है अपने शोध पत्र को सामान्य लोगों हेतु हिंदी में भी प्रकाशित करें। पहली बार हमारा पिछला वार्षिक प्रतिवेदन पूर्णतया द्विभाषी प्रकाशित हुआ हमारे संस्थान की वेबसाइट 60 प्रतिशत द्विभाषी है और शीघ्र ही इसे पूर्णतया द्विभाषी कर दिया जाएगा। श्री प्रदीप कुमार, अनुभाग अधिकारी ने कार्यक्रम का संचालन किया और सभी के प्रति आभार व्यक्त किया। दिनांक 20.09.2010 को अपराह्न 3:00 बजे हिंदी सप्ताह 14 से 20 सितंबर, 2010 के पुरस्कार वितरण एवं समापन समारोह का आयोजन हुआ। इस अवसर पर संस्थान के निदेशक, डॉ. के.सी. गुप्ता ने कहा कि हिंदी सप्ताह के दौरान आप लोगों ने बढ़-चढ़ कर हिस्सा लिया यह आपार हर्ष की बात है। हिंदी में काम करना कोई मुश्किल नहीं है। हिंदी में ज्यादा से ज्यादा कार्य करने का प्रयास किया जाना चाहिए। उन्होंने बताया कि आई.आई.टी.आर. में हिंदी का स्तर काफी अच्छा है। हिंदी में जब ज्यादा से ज्यादा कार्य किया जाएगा तभी हिंदी अपने उचित स्थान को प्राप्त कर पाएगी। उन्होंने इस अवसर पर सप्ताह के दौरान आयोजित वाद-विवाद, आशुभाषण, लेख, टिप्पण व मसौदा लेखन, हिंदीतर भाषी का हिंदी ज्ञान, हिंदी टंकण, अनुवाद एवं क्विज प्रतियागिताओं में विजयी प्रतिभागियों को प्रथम, द्वितीय व तृतीय पुरस्कार एवं प्रमाण-पत्र प्रदान किया। इसके अलावा हिंदी में कार्य करने की प्रोत्साहन योजना के अन्तर्गत विजयी प्रतिभागियों को दो प्रथम, तीन द्वितीय और पाँच तृतीय और प्रमाण-पत्र भी प्रदान किए गए। श्री मुकुन्द सहाय, प्रशासनिक अधिकारी ने धन्यवाद प्रस्ताव दिया। कार्यक्रम का आयोजन श्री प्रदीप कुमार, अनुभाग अधिकारी ने किया।

कुछ जानकारियां :-

स्टीविया चबाओ, मधुमेह भगाओ

विश्व स्वास्थ्य संगठन की रिपोर्ट के अनुसार देश में लगभग दो करोड़ दस लाख लोग मधुमेह की बीमारी से पीड़ित है। संगठन का यह भी अनुमान है कि वर्ष 2020 में भारत का हर पांचवां व्यक्ति मधुमेह से पीड़ित होगा। जम्मू-कश्मीर राज्य में भी मधुमेह की बीमारी महामारी का रूप जा रही है। इसके बचाव व नियंत्रण के लिए वैसे तो कई उपाय हैं, लेकिन एक आयुर्वेदिक पौधा ऐसा है तो इस खतरनाक बीमारी से राहत दिलाने में अहम भूमिका निभा रहा है। इस आयुर्वेदिक पौधे का

नाम है स्टीविया। सर्वे के अनुसार डायबिटीज के मरीजो के लिए मीठा खाना जहर नहीं बनेगा बशर्ते वह मीठा खाने के तुरंत बाद आयुर्वेदिक पौधे स्टीविया की कुछ पत्तियों को चबा लें। गन्ने से तीन सौ गुणा अधिक मीठा होने के बावजूद स्टीविया पौधे फैट व शुगर

से फ्री है। इतना अधिक मीठा होने के बावजूद यह शुगर को कम तो करता ही है साथ ही इसे रोकने में भी सहायक है। खाना खाने में बीस मिनट पहले स्टीविया की पत्तियों का सेवन अत्यधिक फायदेमंद होता है। अद्भुत गुणों का संगम आयुर्वेदिक पौधा घर में भी लगाया जा सकता है। एक बार लगाया गया पौधा पांच वर्ष तक प्रयोग में लाया जा सकता है। पौधे के गुणों को देखते हुए कई आयुर्वेदिक कंपनियों ने इससे संबंधित उत्पाद तैयार करना शुरू कर दिए हैं। पिछले पंद्रह सौ वर्षो से स्टीविया का स्वीटनर और मेडिसिनल के रूप में प्रयोग किया जा रहा है। 1920 में स्टीविया को जापान ने शुगर के प्रमुख अल्टरनेटिव के रूप में शुरू किया था। स्टीविया के सुरक्षित प्रयोग का न केवल लंबा इतिहास है बल्कि इस पर लगभग 150 स्टडीज हो चुकी हैं। विश्व के लगभग 20 देशों की सरकारे इसे मान्यता भी दे चुकी हैं। डोना गेट्स की स्टीविया कुक बुक के सह लेखक डाक्टर रे शाहलीयन (एमडी) ने स्टीविया को शुगर का अद्भुत अल्टरनेटिव होने के अलावा शुगर के मरीजों के लिए एकमात्र ऐसा आर्टिफिशियल स्वीटनर बताया है। स्टीविया पैंक्रियाज से इंसुलिन को रिलीज करने में अहम भूमिका निभाता है। डिपार्टमेंट आफ एंडोक्रिनोलाजी एंड मेटाबालिज्म आर्थोस यूनिवार्सिटी हास्पिटल डेनमार्क, आयुर्वेद फार टोटल हेल्थ के संपादक डाक्टर अनूप गक्खड़ अनुसार स्टीविया एक हर्बल प्लांट है। यह शुगर के मरीजों के लिए वरदान है। आयुर्वेदिक विशेषज्ञों के अनुसार स्टीविया न केवल शुगर बल्कि ब्लड प्रेशर, हाईपरटेशन, दांतों, वजन कम करने, गैस, पेट की जलन, दिल की बीमारी, चमड़ी रोग और चेहरे की झुर्रिया की बीमारी में भी कामगार हैं।

कब जागोगे

एक वर्ष के दौरान स्कूली बच्चों द्वारा जटरोफा के बीज खाकर बीमार होने की सौ से अधिक घटनाएं हो चुकी हैं परन्तु इतना होने के बाद भी शिक्षा एवं स्वस्थ्य विभाग की उदासीनता वास्तव में शर्मनाक है। ताजा घटना में हरियाणा कृषि विश्वविद्यालय में स्थित राजकीय प्राथमिक पाठशाला के 50 बच्चे बीमार हो गए और उन्हें सामान्य अस्पताल के आपातकालीन वार्ड में दाखिल होना पड़ा। एड्स जागरूकता अभियानों में स्कूलों के मासूम बच्चों को झोंक दिया जाता है, जबकि अधिकतर बच्चे एड्स का मतलब भी नहीं जानते। क्षयरोग, पोलियो, हेपेटाइटिस, एनीमिया आदि रोगों के खिलाफ स्वास्थ्य विभाग आवश्यकता से अधिक जागरुक दिखाई पड़ता है। हर गांव-कस्बे व शहर में हर दिन रैली, प्रदर्शनी, सेमिनार, वाद-विवाद प्रतियागिताओं की भरमार होती है जिसमें औपचारिकता अधिक और व्यावहारिकता कम दिखाई देती है। पिछले तीन साल से जटरोफा बच्चों पर कहर ढा रहा है परन्तु किसी भी शहर, कस्बे या गांव में एक भी आयोजन नहीं हुआ जिसमें इस पौधे व बीज के बारे में जागरूकता का संदेश दिया गया हो। पानीपत, जीद, हिसार, फतेहाबाद और सिरसा तक की बेल्ट में ही जटरोफा का सर्वाधिक विस्तार है। बात ध्यान देने योग्य है कि जटरोफा के विस्तार में सरकार ही जिम्मेदार है। चार वर्ष पहले सरकारी तत्र द्वारा जोर-शोर से प्रचार किया गया था कि अधिक से अधिक संख्या में जटरोफा के पौधे लगाए जाएं क्योंकि इसके बीज से डीजल-पेट्रोल जैसा तेल निकाला जा सकता है।

स्कूलों-सामुदायिक केंद्रों के आसपास खाली पड़ी जमीन पर इसके पौधे लगाए गए जो सरकारी विभागों द्वारा ही उपलब्ध कराए गए थे। स्वयंसेवी संगठनों के अलावा स्कूली छात्रों, अध्यापकों को भी जटरोफा उगाओ अभियान में बड़ी संख्या में शामिल किया गया था। अंजाम से बेखबर सरकार ने आगाज तो धुंआधार कर दिया पर न तो इन पौधों की देखभाल हुई और तेल निकालने की योजना भी तुगलकी साबित हुई। विभिन्न जिलों में ये पौधे मुसीबत के दूत बन कर खड़े हैं। मौसम आते ही इन पर बीज लगते हैं, वे बच्चों को आकर्षित करते हैं और फिर खबर आती है उनके बीमार पड़ने की। क्या सरकार अपनी इस गलती पर प्रायश्चित नहीं करना चाहती, क्या जिला शिक्षा, स्वास्थ्य, कृषि एवं वन्य अधिकारी तब जागेंगे जब कोई बड़ा हादसा होगा। अन्य अभियानों के लिए तो बजट का प्रावधान है पर बच्चों के स्वास्थ्य पर कुठाराघात करने वाले जटरोफा पर नियंत्रण के लिए फूटी कौड़ी तक का भी प्रबंध नहीं किया गया।

हिन्दी भाषा खण्ड

भारतीय विषविज्ञान अनुसंधान संस्थान (आई.आई.टी.आर.) लखनऊ के प्रेक्षागृह में दिनांक 14.09.2010 को सांय 4:00 बजे हिंदी सप्ताह 14 से 20 सितम्बर, 2010 के उद्घाटन समारोह का आयोजन किया गया। इस अवसर पर मुख्य अतिथि प्रो. मनोज कुमार मिश्रा, कुलपति, लखनऊ विश्वविद्यालय थे। मुख्य अतिथि को संस्थान के निदेशक डॉ. के.सी. गुप्ता ने स्मृति चिन्ह भेंट किया। निदेशक ने मुख्य अतिथि का परिचय देते हुए कहा कि प्रो. मिश्रा किसी परिचय के मोहताज नहीं है। आपको हम आई.आई.टी.आर. परिवार का अभिन्न अंग मानते हैं। आपको जब भी हमने संस्थान में आमंत्रित किया आपने हमें निराश नहीं किया है। मैं आपकी उपस्थिति में गौरवान्वित महसूस कर रहा हूँ। एक वैज्ञानिक जिन पुरस्कारों को प्राप्त करने का इच्छुक रहता है वे सभी प्रो. मिश्रा को प्राप्त हैं। मुख्य अतिथि ने अपने संदेश में कहा कि जब मुझे आमंत्रित किया गया तो मैं सोचने लगा कि हिंदी दिवस पर क्या बोलूँगा। मुझे लखनऊ विश्वविद्यालय आकर हर्ष हुआ कि यहाँ मेरा हिंदी प्रेम प्रस्फुटित होने लगा है। अपनी सभ्यता के प्रति प्रेम को अंगीकार करना चाहिए। हमारी संस्कृति किसी भी प्रकार से कम नहीं है। हिंदी भाषा का बहुत समृद्ध साहित्य है। संस्थान के निदेशक, डॉ. के.सी. गुप्ता ने अध्यक्षीय संबोधन में कहा कि हमारे शोध संस्थानों से अनुरोध है अपने शोध पत्र को सामान्य लोगों हेतु हिंदी में भी प्रकाशित करें। पहली बार हमारा पिछला वार्षिक प्रतिवेदन पूर्णतया द्विभाषी प्रकाशित हुआ हमारे संस्थान की वेबसाइट 60 प्रतिशत द्विभाषी है और शीघ्र ही इसे पूर्णतया द्विभाषी कर दिया जाएगा। श्री प्रदीप कुमार, अनुभाग अधिकारी ने कार्यक्रम का संचालन किया और सभी के प्रति आभार व्यक्त किया। दिनांक 20.09.2010 को अपराह्न 3:00 बजे हिंदी सप्ताह 14 से 20 सितंबर, 2010 के पुरस्कार वितरण एवं समापन समारोह का आयोजन हुआ। इस अवसर पर संस्थान के निदेशक, डॉ. के.सी. गुप्ता ने कहा कि हिंदी सप्ताह के दौरान आप लोगों ने बढ़-चढ़ कर हिस्सा लिया यह आपार हर्ष की बात है। हिंदी में काम करना कोई मुश्किल नहीं है। हिंदी में ज्यादा से ज्यादा कार्य करने का प्रयास किया जाना चाहिए। उन्होंने बताया कि आई.आई.टी.आर. में हिंदी का स्तर काफी अच्छा है। हिंदी में जब ज्यादा से ज्यादा कार्य किया जाएगा तभी हिंदी अपने उचित स्थान को प्राप्त कर पाएगी। उन्होंने इस अवसर पर सप्ताह के दौरान आयोजित वाद-विवाद, आशुभाषण, लेख, टिप्पण व मसौदा लेखन,

हिंदीतर भाषी का हिंदी ज्ञान, हिंदी टंकण, अनुवाद एवं क्विज प्रतियागिताओं में विजयी प्रतिभागियों को प्रथम, द्वितीय व तृतीय पुरस्कार एवं प्रमाण-पत्र प्रदान किया। इसके अलावा हिंदी में कार्य करने की प्रोत्साहन योजना के अन्तर्गत विजयी प्रतिभागियों को दो प्रथम, तीन द्वितीय और पाँच तृतीय और प्रमाण-पत्र भी प्रदान किए गए। श्री मुकुन्द सहाय, प्रशासनिक अधिकारी ने धन्यवाद प्रस्ताव दिया। कार्यक्रम का आयोजन श्री प्रदीप कुमार, अनुभाग अधिकारी ने किया।

विश्व स्वास्थ्य संगठन की रिपोर्ट के अनुसार देश में लगभग दो करोड़ दस लाख लोग मधुमेह की बीमारी से पीड़ित है। संगठन का यह भी अनुमान है कि वर्ष 2020 में भारत का हर पांचवां व्यक्ति मधुमेह से पीड़ित होगा। जम्मू-कश्मीर राज्य में भी मधुमेह की बीमारी महामारी का रूप जा रही है। इसके बचाव व नियंत्रण के लिए वैसे तो कई उपाय हैं, लेकिन एक आयुर्वेदिक पौधा ऐसा है तो इस खतरनाक बीमारी से राहत दिलाने में अहम भूमिका निभा रहा है। इस आयुर्वेदिक पौधे का नाम है स्टीविया। सर्वे के अनुसार डायबिटीज के मरीजो के लिए मीठा खाना जहर नहीं बनेगा बशर्ते वह मीठा खाने के तुरंत बाद आयुर्वेदिक पौधे स्टीविया की कुछ पत्तियों को चबा लें। गन्ने से तीन सौ गुणा अधिक मीठा होने के बावजूद स्टीविया पौधे फैट व शुगर से फ्री है। इतना अधिक मीठा होने

के बावजूद यह शुगर को कम तो करता ही है साथ ही इसे रोकने में भी सहायक है। खाना खाने में बीस मिनट पहले स्टीविया की पत्तियों का सेवन अत्यधिक फायदेमंद होता है। अद्भुत गुणों का संगम आयुर्वेदिक पौधा घर में भी लगाया जा सकता है। एक बार लगाया गया पौधा पांच वर्ष तक प्रयोग में लाया जा सकता है। पौधे के गुणों को देखते हुए कई आयुर्वेदिक कंपनियों ने इससे संबंधित उत्पाद तैयार करना शुरू कर दिए हैं। पिछले पंद्रह सौ वर्षो से स्टीविया का स्वीटनर और मेडिसिनल के रूप में प्रयोग किया जा रहा है। 1920 में स्टीविया को जापान ने शुगर के प्रमुख अल्टरनेटिव के रूप में शुरू किया था। स्टीविया के सुरक्षित प्रयोग का न केवल लंबा इतिहास है बल्कि इस पर लगभग 150 स्टडीज हो चुकी हैं। विश्व के लगभग 20 देशों की सरकारे इसे मान्यता भी दे चुकी हैं। डोना गेट्स की स्टीविया कुक बुक के सह लेखक डाक्टर रे शाहलीयन (एमडी) ने स्टीविया को शुगर का अद्भुत अल्टरनेटिव होने के अलावा शुगर के मरीजों के लिए एकमात्र ऐसा आर्टिफिशियल स्वीटनर बताया है। स्टीविया पैंक्रियाज से इंसुलिन को रिलीज करने में अहम भूमिका निभाता है। डिपार्टमेंट आफ एंडोक्रिनोलाजी एंड मेटाबालिज्म आर्थोस यूनिवार्सिटी हास्पिटल डेनमार्क, आयुर्वेद फार टोटल हेल्थ के संपादक डाक्टर अनूप गक्खड़ अनुसार स्टीविया एक हर्बल प्लांट है। यह शुगर के मरीजों के लिए

वरदान है। आयुर्वेदिक विशेषज्ञों के अनुसार स्टीविया न केवल शुगर बल्कि ब्लड प्रेशर, हाईपरटेशन, दांतों, वजन कम करने, गैस, पेट की जलन, दिल की बीमारी, चमड़ी रोग और चेहरे की झुर्रिया की बीमारी में भी कामगार हैं।

कब जागोगे

एक वर्ष के दौरान स्कूली बच्चों द्वारा जटरोफा के बीज खाकर

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Any feedback on this publication is welcome

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