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Posters

Shikha Agnihotry et al., Toxicol Open Access 2018, Volume 4
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Roles of *ATP7B* gene to maintain the copper-transporting ATPase in a HepG2 cell line against excess copper toxicity

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Wilson disease (WD) is an autosomal recessive disorder of copper transport with a worldwide frequency of ~1 in 30000. Wilson's disease is characterized by chronic liver and neurological disease and also reported in kidney. Hepatic copper levels vary among normal individuals and WD patients depending upon on dietary copper intake and bioavailability, as well as genetic factors. In this study we examined that abnormal copper accumulation in human hepatocarcinoma (HepG2) cell line. Copper chloride ($CuCl_2$) caused dose dependent cell viability reduction of human hepatocarcinoma (HepG2) cell line which was measured through MTT assay. We used different concentration of $CuCl_2$ in their log doses but maximum cell viability reduction was recorded at 15 µg/ml. It also induces cell cycle arrest and DNA damage due to intracellular ROS generation. $CuCl_2$ induces Ca^{2+} release from endoplasmic reticulum (ER) and leads to apoptotic cell death. It causes the up-regulation of WD stress marker genes *ATP7B* and Cyp1A1, Cyp1A2 at transcription levels. The similar response of *ATP7B* and Cyp1A1, Cyp1A2 proteins was recorded at translation levels. Heavy dietary intake of $CuCl_2$ induces mitochondria and reduced the mitochondrial membrane potential analyzed through JC-1 staining. It further increases Bax/Bcl2 ratio and promotes the release of cytochrome C, finally leads to caspase-dependent apoptosis. Up-regulation of APAF1 in $CuCl_2$ treated cells supports the mitochondrial-mediated apoptotic cell death. The results support the involvement of ER and mitochondria in ROS mediated $CuCl_2$ toxicity. Therefore, the heavy dietary intake of $CuCl_2$ in food products may be deleterious to users.

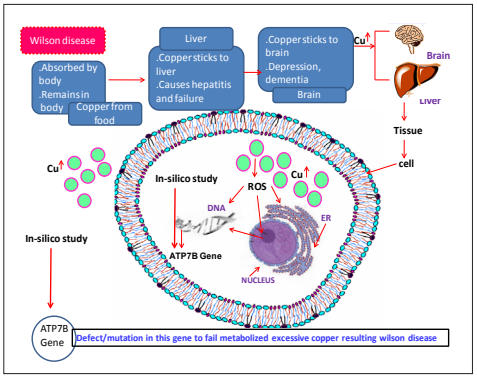

Figure-1: *Graphical abstract of copper toxicity*

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Biography

Shikha Agnihotry has been working as Research Assistant at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow of ICMR since 2013. She has been involved in training biomedical research scholars in the field of bioinformatics and has also assisted as Research Assistant under an ICMR-funded project.

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Yumiko Nitta, Toxicol Open Access 2018, Volume 4
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Circulation of zinc and cadmium in the sea and land environment of west Japan

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The Hiroshima-Oyster has bearded the Setouchi local cuisine culture. Its commercial share expanded to all over Japan after the great earthquake of eastern Japan in 2011. In order to evaluate the sanitary environment around Hiroshima Bay area, we collected wild oysters (*Crassostrea gigas*) and mud from gulf of Hiroshima, Kurashiki and Kagoshima, and measured their zinc (Zn) and cadmium (Cd) in their meat, shell and the mud. The mud at the gulf of Hiroshima contained Zn and Cd with amounts of 188.0 and 0.53 mg/kg mg/kg, respectively. Concentration ratios of Zn in the oysters were higher as the concentrations of it in mud were lower. The concentration ratio of Zn in the shell/whole oyster (meat plus shell) was constant among the three groups with the value of 0.019. This finding made us available to estimate the Zn concentration ratio of the meat from that of the shell. The formula is b=c•a, where b is concentration ratio in meat, c is constant (46.4) and a concentration ratio in shell. Concentration of Cd in the shell/whole oyster was constant among the three groups (0.26~0.42). For the monitoring of the cultivation environment of Hiroshima Bay area, the seawater temperature, salinity concentration and plankton amount were recorded weekly, while the content of moisture, protein, total lipid, minerals, Zn was measured monthly for mature and immature oysters. Measuring the concentration of Cd in shells and mud is very informative to estimate the amounts of metals we consume through seafood, vegetables and poultry, as the shell has been recycled for fertilizer of vegetables or food of poultry in Japan.

Figure 1. Concentrationof zinc (Zn) and cadmium (Cd).

	Zn			Cd		
	Kurashiki	Hiroshima	Kagoshima	Kurashiki	Hiroshima	Kagoshima
mud	39.3± 9.2	166.0±86.1	310.0±103.6 *	0.13±0.09	0.50±0.18 *	1.43±0.80 *
meat	354.8±39.8	467.5±48.3 *	721.0±143.6 *	0.41±0.05	0.25±0.04	0.30±0.04
shell	9.6± 3.4	8.9± 4.1	15.1± 9.5	0.16±0.05	0.16±0.08	0.20±0.03

*: P<0.05 by t-test (when compared to Kurashiki).

Figure 2. Concentration ratio of zinc (Zn) and cadmium (Cd).

	Zn			Cd		
	Kurashiki	Hiroshima	Kagoshima	Kurashiki	Hiroshima	Kagoshima
mud	1	1	1	1	1	1
meat	9.30±1.73	3.63±2.10 **	2.58±1.23 **	4.44±4.10	0.70±0.40	0.20±0.10
shell	0.26±0.11	0.07±0.06 *	0.05±0.03 *	1.93±1.29	0.29±0.06 *	0.16±0.07
meat plus shell	9.56±1.72	3.71±2.16	2.61±1.23	6.37±5.92	0.99±0.36	0.36±0.20
shell/meat plus shell	0.03±0.01	0.02±0.01	0.02±0.02	0.25±0.06	0.30±0.15	0.46±0.04

*: P<0.05 by t-test (when compared to Kurashiki); **: P<0.01 by t-test (when co,pared to Kurashiki).

Figure-1: *Concentration of zinc (Zn) and cadmium (Cd); concentration ratio of zinc (Zn) and cadmium (Cd)*

Recent Publications

1. Harada T, Nitta Y, et al. (2017) Epidemiological Study of Eating Habit of Middle-Aged and Elderly Women: Mihara and Hiroshima Questionnaire Study. *International Medical Journal*; 24: 214 -218.
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Biography

Yumiko Nitta has completed her PhD from Hiroshima University. She started her occupation as the Research Assistance at Research Institute of Radiation Biology and Medicine in Hiroshima University, where she examined effects of radiations on mammalian genome. Then, she obtained the position of Associate Professor at Suzugamine Women's College, where she analyzed data of human health monitoring. Presently she is a Professor at the Department of Nutrition, Faculty of Health Science of Hiroshima Shudo University, where she concerns about nutrition epidemiology.

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The antioxidant effect of resveratrol in cisplatin induced oxidative stress

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Statement of the Problem: Cisplatin is one of the most used cytostatic with a broad antitumor spectrum. The uses of different cytostatic are followed by release of reactive oxygen species (ROS) responsible for the adverse effect of the chemotherapy. The purpose of this study was to determine if the resveratrol administration can reduce the cisplatin induced oxidative stress.

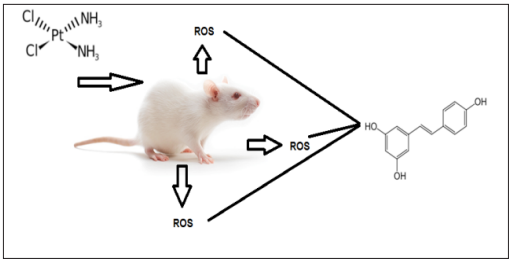

Figure-1: *Schematic reaction of the cisplatin administration, production of reactive oxygen species and resveratrol.*

Methodology: The study was conducted on 24 Wistar rats divided in four groups: C - the control group receiving 1 ml of physiological saline I.P., CR - control blank group receiving 20 mg/kg resveratrol I.P., CP - receiving cisplatin 10 mg/kg I.P. and CP+R receiving combination of 10 mg/kg cisplatin and 20 mg/kg resveratrol I.P. At the end of experiment were analyzed the biomarkers of oxidative stress enzymes: Glutathione (GSH), glutathione reductase (GSH-r), glutathione peroxidase (GSH-px), catalase (CAT), superoxide dismutase (SOD) and malondialdehyde (MDA).

Findings: Administration of cisplatin was followed by significant decrease of GSH (-29.44%, $p<0.01$), GSH-r (-31.88%, $p<0.0001$), CAT (-52.28%, $p<0.0001$) and increase of GSH-Px (+31.25%, $p<0.001$), SOD (+11.27%, $p>0.05$) and (+24.05%, $p<0.05$) comparative to control group. In case of cisplatin combined with resveratrol administration, the majority of biomarker enzymes of oxidative stress presented not significant ($p>0.05$) differences comparative to control group (GSH: -4.04%, GSH-r: -1.96%, GSH-px: +1.97%, SOD: -1.92%, MDA: +10.31%), exception in case of CAT which remains significantly lower than control (-21.62%, $p<0.01$).

Conclusion: Analyzing the dynamic of enzymes biomarkers of oxidative stress we can say that administration of resveratrol can reduce the ROS formation and has a good effect as antioxidant in case of cisplatin administration.

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Biography

Florin Muselin has his expertise in heavy metals reproductive toxicology, oxidative stress and medicinal and poisonous plants. He is an Associate Professor at Faculty of Veterinary Medicine from BUASMV Timisoaara, Romania.

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The anti-proliferative activity of *Coriandrum sativum* alcoholic extract on HCT-116 and MCF-7 cell lines

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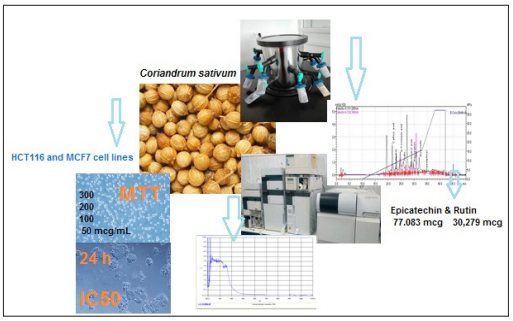
Statement of the Problem: It is known that vegetal extracts can generate positive responses in stages of several patho-processes. The anti-oxidant; protection against DNA damage and cancer activities of *Coriandrum sativum* were intensely studied in the last decade. Our research envisaged the polyphenolic compounds' structure and the anti-proliferative biologic activity of *C. sativum* 10% alcoholic extract against HCT-116 and MCF-7 cell lines.



Methodology: The *C. sativum* extract was obtained respecting the Romanian Pharmacopoeia 10th edition, the plant being lyophilized (with Ilshin Kryptonstraat 11, 6718WR EBE lyophilisator to -55 oC, 5 mTorr pressure and 24 hours lyophilization time). The polyphenols were determined by LC-MS and the *in vitro* evaluation effects by the MTT proliferation test, using HCT116 (colorectal carcinoma) and MCF7 (mammary adenocarcinoma). The cells were seed as: 2×10^4 (MCF7) and 1×10^4 (HCT) in 96 well plates. The lyophilized extracts were suspended in specific culture medium being obtained a 300 mg/mL *C. sativum* stock solution. From this, different test concentrations were prepared by dilution (300, 200, 100 and respectively 50 mcg/mL).

Result & Conclusion: As a following, after 24 hours from the exposure, using HCT-116 and MCF-7 cell lines it was observed that the cellular proliferation reduced, this being correlated to dose and the alterations of cell morphology to the groups studied; to great extract doses, apoptotic and necrotic alterations were observed, both for HCT and MCF cells; the IC50, representing concentration to which a marker substance is reducing the tissues viability with 50% after a fixed time exposure period wasn't observed for the cell lines used in this test; the chromatographic analysis of *C. sativum* alcoholic extract evidenced the presence of the polyphenolic compounds, the greatest concentrations were ascertained for epicatechin (77.083 mcg/mL) and rutin (30.279 mcg/mL), substances with known hard anti-oxidant proprieties.

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Biography

Eugenia Dumitrescu has her expertise in the veterinary field, reproductive toxicology, heavy metals, phyto-therapy and oxidative stress in animals. She is an Associate Professor at the Faculty of Veterinary Medicine at Banat's University of Agriculture and Veterinary Medicine, Romania.

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The evaluation of hypoglycemic effects of some plants extract on induced diabetes in mice

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Statement of the Problem: Diabetes mellitus is a chronic disease that is characterized by a relative or absolute lack of insulin, resulting in hyperglycemia, being one of the most frequent diseases. The purpose of this study was to determine the hypoglycemic effect of some plats extract on Streptozotocin induced diabetes in mice.

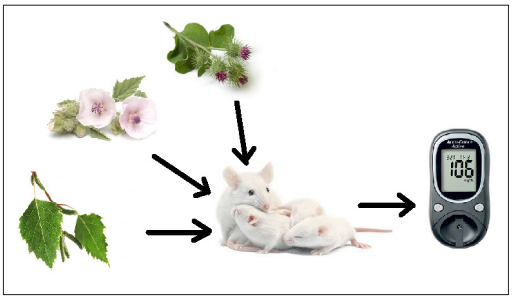

Figure-1: *Schematic exposure of different plants on diabetic mice glycaemia*

Methodology: The study was conducted on 35 BALB/c mice divided in five groups: C- control group receiving distillated water, DC - diabetic control receiving distillated water, E1 – diabetic mice receiving 10% *Arctium lappa* extract, E2 - diabetic mice receiving 1% *Betula pendula* lyophilizate extract, E3 - diabetic mice receiving 5% *Althaea officinalis* extract. The diabetes was induced by I.P. administration of 200 mg/kg bw Streptozotocin is single dose, mice with glycaemia over 150 mg/dl were considered diabetic and those with over 200 mg/dl were considered to have severe diabetes.

Findings: In diabetic rats we observed a significantly ($p<0.05$) increase of body weight comparative to control and also we observed a significant ($p<0.05$) increase of water consumption in diabetic rats in the first 24 hours, followed by a decrease of these possible due to the change in taste especially in E2 group. Administration of plants extract in groups E1, E2 and E3, decreased significantly ($p<0.05$) the glycaemia comparative to DC group reaching the values to C group. The decrease of glycaemia in groups that received plants extract was graduated started after 24 hours after exposure until 120 hours after exposure: E1/DC 72 hours: -27.52%; E1/DC 120 hours: -41.02%; E2/DC 72 hours: -32.58%; E2.DC 120 hours: -43.07%; E3/DC 72 hours: -34.83%; E3/DC 120 hours: -37.43%.

Conclusion: Administration of studied plants extract proven to have a good hypoglycemic effect and could be recommended for the control of glycaemia.

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Biography

Alexandru Octavian Doma is pursuing his PhD in Faculty of Veterinary Medicine from Banat's University of Agricultural Sciences and Veterinary Medicine, King Michael I of Romania from Timisoara. He has built his experience in research, evaluation, teaching during the PhD period. He is the Secretary of Romanian Society for Trace Elements in Medicine.

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Evaluation of oxidative stress effect for *in vitro* maturated cow oocytes through gene expression quantification

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In the current assisted reproductive practice in cows the IVF technique is used in increasing proportion. However, the used methods are not always standardized and are needed to be improved. The first challenge in optimization of IVF techniques is obtaining mature oocytes by growing them in culture media and by this to preserve their high fertilization quality. A crucial factor in improving IVF results is the prevention of oocytes from *in vitro* cultivation stress effects. In the presented study the beneficial effect of antioxidant supplementation in maturation culture media of cow oocytes was evaluated by apoptotic genes expression quantification. The oocytes were cultivated for 24 hours on conventional (control variant), supplemented with rosmarinic acid (RA variant) and ascorbic acid (C variant), maturation media. The oocytes were classified in three quality classes by morphological observation from which the total RNA was isolated. Quantitative PCR technique was used for quantification of BAX and BCL2 apoptotic genes expression. Results of qPCR were interpreted by Δ (ΔCt) method. The ratio BCL2/BAX was considered as an indicator of maturated oocytes homeostasis. Antioxidants culture media supplementation resulted in a better expansion of cumulus cells. The level of expression of the BAX gene has an increasing trend in all COC's, inversely proportional to oocyte quality, indicating the overcoming of cell adaptation process for the inferior class. Regarding the BCL2 gene, significantly higher expression levels can be observed in class I oocytes supplemented with antioxidants. The level of maintenance of cell homeostasis, as reflected by the ratio of BAX/BCL-2, with a value above 7, indicates that apoptotic processes have been installed in all class III oocytes. Supplementation with antioxidants exerts a beneficial effect on inferior class cells, which have a high stress level, to some extent assuring their protection, indicating the effectiveness of administering this supplement.

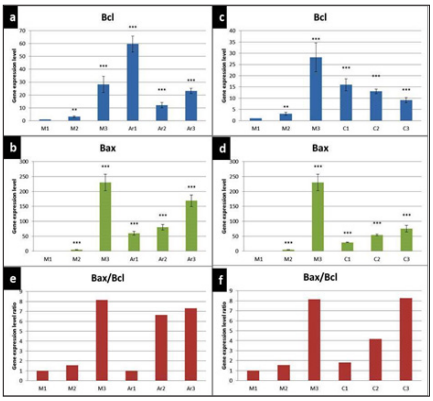

Figure-1: *BAX and BCL2 gene expression maturated oocytes. a- BCL2 gene expression for AR samples; b - BAX gene expression for AR samples; c - BCL2 gene expression for C samples; b - BAX gene expression for C samples; e - BAX/BCL2 genes expression ratio for AR samples; d - BAX/BCL2 genes expression ratio for C samples.*

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Biography

Camelia Tulcan is an Assistant Professor at Biochemistry Department, Faculty of Veterinary Medicine, Timisoara and Coordinator of Antioxidant Research Lab-Horia Cernescu Research Unit. She has expertise in oxidative stress evaluation in different physiological or pathological condition and was involved in management team of research infrastructure project and in implementation of quality management systems.

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Treatment of cigarette smoke condensate accelerates nonalcoholic steatohepatitis *in vitro*

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It has been well known that Cigarette Smoke (CS) is a leading cause of various diseases worldwide. Recently, cumulative evidence has suggested that exposure to CS detrimentally affects the pathogenesis of several chronic liver diseases, including nonalcoholic fatty liver disease (NAFLD). Nonalcoholic steatohepatitis (NASH), more severe stage of NAFLD, is characterized by steatosis, hepatocellular ballooning degeneration and lobular inflammation. Relationship between CS exposure and progression of NASH has not been fully understood. Therefore, the purpose of this study was to evaluate the effects of CS extract (CSE) or CS condensate (CSC) on the *in vitro* NASH model using mouse primary hepatocytes (HPs) treated with palmitic acid (PA) or PA plus LPS. Increased hepatocellular damage was observed in PA-treated HPs with CSC or CSE treatment, but increased triglyceride level was only observed in PA-treated HPs with high concentration CSC. Also, expression levels of NASH-related genes such as inflammation, oxidative stress and lipogenesis were significantly increased by treatment of CS. In order to more clearly demonstrate the effects of CSE or CSC, we used trans-well co-culture system of HPs and Kupffer cells (KCs) under the same condition of above mentioned. The levels of inflammatory cytokines and oxidative stress-related gene were markedly increased in co-cultured KCs with treatment of CSE or CSC. Furthermore, treatment of CSC or CSE significantly augmented the expression levels of KC activation markers including CD14 and CD68. Interestingly, each type of CS could not affect HPs apoptosis when only HPs were cultured; however, CS increased PA-induced HPs apoptosis when HPs were co-cultured with KCs. Overall, our current findings indicate that *in vitro* treatment of CSE or CSC differentially contributes to the severity of NASH by modulating NASH-related hepatocellular lipotoxicity and inflammation. These effects might be caused by KCs activation, subsequently inducing HPs apoptosis.

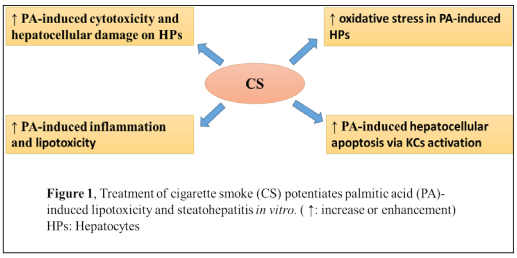

Figure 1, Treatment of cigarette smoke (CS) potentiates palmitic acid (PA)-induced lipotoxicity and steatohepatitis *in vitro*. (↑: increase or enhancement) HPs: Hepatocytes

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Biography

Zixiong Zhou has received his BS degree in 2014 from Southwest Minzu University of China and obtained MS degree from Chonbuk National University, South Korea in 2017. Currently he is pursuing his Doctoral degree at Chonbuk National University. He is focusing on various research topics including effects of cigarette smoke components to liver disease and Acetaminophen induced hepato-toxicology.

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Cigarette smoke exacerbates Acetaminophen-induced liver injury by modulating oxidative stress and inflammation via JNK signal pathway in mice

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Acetaminophen (APAP) overdose induces inflammation and oxidative stress that can lead to severe liver injury. Cigarette smoking is considered to be a crucial modifiable risk factor for disease and death worldwide. Our previous data revealed that cigarette 3R4F aggravated APAP-induced liver injury in a dose-dependent manner. This study aimed to investigate the effects of commercial cigarette A on the progression of APAP-induced acute liver injury. Seven-week-old C57BL/6 mice were exposed to cigarette A (300, 600 μg/L) or standard cigarette 3R4F (600 μg/L) or fresh air for 2 hours once daily and 5 days per week. After 4 weeks, mice were intra-peritoneally injected with PBS or APAP (500 mg/kg). Eight hours later the mice were euthanized and blood and tissues were collected for analysis. The results showed that cigarette smoke exposure significantly increased APAP-induced liver injury by increasing serum ALT and AST levels, exacerbated hepatic pathological damages with inflammatory cell infiltration and hepatocellular apoptosis and accompanied by up-regulated inflammatory mediators including tumor necrosis factor (TNF-α) and interleukin (IL)-1β. Cigarette smoke could increase the expressions of cytochrome P450 (CYP) 2E1 and 1A2 which could metabolize a large number of compounds in liver and lead to the down-regulation of antioxidant such as glutathione peroxidase (GSH-Px) and heme oxygenase-1 (HO-1) in APAP treated mice. Furthermore, cigarette smoke exposure obviously increased the activation of c-Jun N-terminal kinases (JNK) signal induced by APAP. Mice exposed to commercial cigarette A had no significant difference between those exposed to standard cigarette 3R4F after APAP injection. Overall, these findings suggested that cigarette smoke exposure could exacerbate APAP-induced hepatotoxicity and possible mechanism might be associated with the activation of JNK signal pathway.

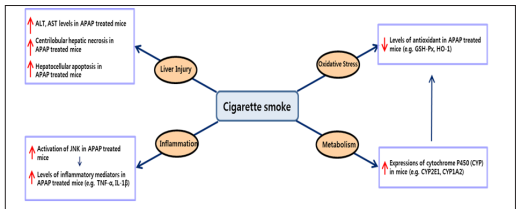

Figure 1: Effects of cigarette smoke on APAP-induced liver injury. (↑: increase or enhancement; ↓ decrease or deterioration)

References

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Biography

Jing Zhao is currently a Doctoral student of Veterinary Pathology in Chonbuk National University of South Korea and has received her Master's degree of Veterinary Medicine in China in July 2015. Her experiments focus on the liver diseases and damages in mice, including Acetaminophen-induced liver injury and Concanavalin A-induced liver injury.

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Yuki Mukai et al., Toxicol Open Access 2018, Volume 4
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Development of a screening kit for detecting synthetic cathinones

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In recent years, abuse of illicit drug has been a very important problem. Significant amount of unknown illicit substances are sized by law enforcement and boarder protection agencies. Synthetic cannabinoids and cathinones have a psychoactive effect on our bodies. The identification of these drugs is important not only for the proof of the crime, but also human health. Generally, to identify the illicit drugs, we use the techniques such as gas chromatography-mass spectrometry (GC-MS) and high performance liquid chromatography-mass spectrometry (HPLC-MS). These instruments, however, are not always convenient owing to their high cost of running, the need for trained personnel, lengthy analysis times, etc. Screening kits for detecting drugs, therefore, are required at the scene of crime and the development of them is desired. In this study, we have designed the screening kit for cathinones to provide easily an indication of the presence or absence of cathinones in a test sample. This kit consists of a glass tube enclosed reagents which react with them (named "cathinone detector tube"). This kit utilizes the reaction of cathinons with neocuproine and copper(II) to give a colored copper(I)-neocuproine complex. The presumptive color test method for the detection of synthetic cathinones by Morgan Philip, et al. is applied to the development of this screening kit. They describe that nepcuproine color test displays good selectivity to cathinone analogs. To improve operativity and preservation of our kit, three aqueous solutions were coated on silica gel particle and then the powders have been enclosed in a single glass tube. The reagent in the tube colored orange from light blue in the presence of cathinones. In consequence, this kit had very high sensitivity for detecting cathinones. The limit of detection of α-PVP, for example, was 5 μg (absolute amount, 100 μL of 50 μg/mL solution).

Figure-1: *Cathinone detector tube. Approximately 100 uL of a test solution is sucked into the detector tube. Upper one is positive control. Orange color appeared in the presence of cathinones.*

References

1. Morgan Philip, Ronald Shimmon, Mark Tahtouh, Shanlin Fu (2016) Development and validation of a presumptive color test method for the detection synthetic cathinones in seized illicit materials. *Forensic Chem*; 1: 39-50.

Biography

Yuki Mukai is currently a Masters student at University of Tsukuba, Japan. She belongs to Department of Legal Medicine and interested in drug abuse that is social problem in the world, especially in synthetic cannabinoids and cathinones. She has recently developed a screening kit for detecting synthetic cathinones.

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Deependra Prasad Sarraf et al., Toxicol Open Access 2018, Volume 4
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Effect of honey on rate of healing of socket after tooth extraction in rabbits

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Statement of the Problem: Honey is the worlds' oldest known wound dressing. Its wound healing properties is not fully established till today. Concerns about antibiotic resistance and a renewed interest in natural remedies, have prompted resurgence in the antimicrobial and wound healing properties of honey. Evidence from animal studies and some trials has suggested that honey may accelerate wound healing in burns, infected wounds and open wounds. None of these reports have documented the effect of honey on healing of socket after tooth extraction. Therefore, the present experimental study was planned to evaluate the efficacy of honey on the healing of socket after tooth extraction in rabbits.

Methodology & Theoretical Orientation: An experimental study was conducted in six New Zealand white rabbits. Extraction of first premolar tooth on both sides of lower jaw was done under anesthesia produced by ketamine and xylazine followed by application of honey on one socket (test group) and normal saline (control group) in the opposite socket. The intervention was continued for two more days. On 7th day, biopsy was taken from the extraction site and histo-pathological examination was done. Student's t-test was used for comparison between the groups and differences were considered to be statistically significant at p value less than 0.05.

Findings: There was a significant difference between control group and test group in terms of fibroblast proliferation (p=0.0019) and bony trabeculae formation (p=0.0003). Inflammatory cells were also observed in both groups and it was not significant (p=1.0). Overlying epithelium was hyperplastic in both the groups.

Conclusion & Significance: The study showed that local application of honey promoted the rapid healing process particularly by increasing fibroblast proliferation and bony trabeculae.

Recent Publications

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2. A Misra, DP Sarraf, GP Rauniar (2013) Prescribing Pattern of Antimicrobials in the In-Patients Department of Obstetrics and Gynaecology at A Tertiary Care Teaching Hospital at Nepal. International Journal of Pharmaceutical & Biological Archives; 4(5): 893–898.

Biography

Deependra Prasad Sarraf has his expertise in *in vivo* studies of natural herbs and medicinal foods. He is also involved in undergraduate and postgraduate medical students' teaching, thesis guidance and mentoring.

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Jong-Hoon Kim et al., Toxicol Open Access 2018, Volume 4
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Korean red ginseng increased the immune cell activity of splenocyte *in vitro* and *in vivo*

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Korean red ginseng is a pharmacological plant that is traditionally used to improve the body's immune functions and ameliorate the symptoms of various diseases. However, the splenocyte activity of Korean red ginseng and its underlying molecular and cellular mechanisms are not fully understood. In this study, *in vitro* and *in vivo* immune cell activities of Korean red ginseng were explored. Also, Korean red ginseng was assessed for its efficacy to act as an adjuvant for the immune response of splenocytes. The porcines were treated with different concentrations of Korean red ginseng, orally for 4 weeks. The splenocytes isolated from Korean red ginseng-treated group showed enhanced immune cell-activities in a dose dependent manner when compared to untreated group. Further, the intracellular levels of perforin and NKp46 were found to be significantly increased in translational level as revealed by western blot analysis, respectively. In addition, we compared the cytotoxic activity of Korean red ginseng-treated splenocytes against target cell such as K-562 cell for 4 weeks. The Korean red ginseng-treated splenocytes were incubated with K-562 in a ratio of dose-dependent manner for 4 hours. Korean red ginseng-treated splenocytes showed a significantly increased cytotoxicity in dose-dependent manner. In other hand, Korean red ginseng-untreated splenocytes showed a less immune cell activity. Finally, Korean red ginseng exhibited *in vivo* immune activities in the animal model by increasing the intracellular levels of perforin and NKp46 without changing the animal body weight. These results suggest that Korean red ginseng is capable of tumor cell suppression via different molecular and cellular mechanisms, including induction of activation of immune cells.

Biography

Jong-Hoon Kim has completed his PhD from Konkuk University, Seoul, Republic of Korea and Postdoctoral studies from Konkuk University, School of Veterinary Medicine. He is the Director for Department of Veterinary Physiology, a premier immunotherapy research lab. He has published more than 50 papers in reputed journals and has been serving as an Editorial Board Member of *Journal of Ginseng Research*.

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Influence of immune modulation by tumor cell-derived soluble compound

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Cancer has been viewed as a disease consisting of transformed cells, of hyper proliferative, invasive and immortal nature. Accordingly, the anti-cancer strategies are also focused on tumor cells only. In the present study, the gastric cancer cell (SNU-484) soluble compounds have been evaluated for its immunosuppression properties. The proteins present in the SNU-484 soluble compounds (SC) were identified with human cytokine array. The effect of SC on rat splenocytes has been studied with special emphasis on NK cell activity. In results, the addition of various concentration of SC did not show any significant apoptotic or proliferation changes when compared to untreated control splenocytes. Further the incubation of splenocytes with SC reduced the expression of NK cell markers at the transcription level. The same scenario was observed with the *in vivo* study following 2 days of treatment. Incubation of splenocytes with SC for a longer period reduced the cytotoxic ability, further this observation was strengthened by the reduction of $CD161^{+}CD3^{-}$(NK) cells in SC treatment. In addition tests were performed to check whether SC can influence tumor formation in allogenic tumor model. The B16F10 melanoma cells-injected animals developed tumor in 3 weeks, whilst the SC injected animals along B16F10 cells aggravates tumor formation, by increasing the PI3K/AKT levels. These findings clearly demonstrate that the presence of SC can modulate immune system response that favors the tumor formation.

Biography

Mohammad Amjad Hossain has completed his graduation from University of Development Alternative, Bangladesh and currently studying MS in Veterinary Medicine from Chonbuk National University School of Veterinary Medicine, South Korea. He has published 2 papers in reputed journals.

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Jing Qi et al., Toxicol Open Access 2018, Volume 4
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Nicotine attenuates concanavalin A-induced hepatic injury by regulating Kupffer cells in mice

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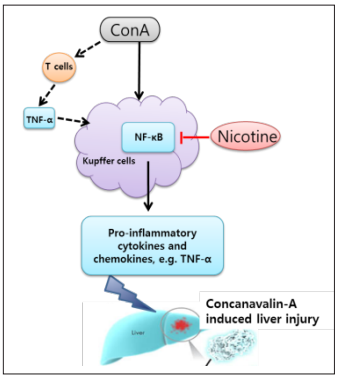
Nicotine, a major constituent of cigarette smoke, is a potent parasympathomimetic alkaloid found in the nightshade family of plants. Acute liver failure (ALF), known as a rapid and severe clinical syndrome, can induce multiple organ dysfunction and failure. This study aimed to investigate the effects of nicotine on concanavalin A (Con A) induced autoimmune hepatitis in mice and to elucidate its underlying molecular mechanisms. Autoimmune hepatitis was induced by the intravenous administration of Con A (15 mg/kg) to healthy BALB/c male mice and nicotine (0.5 mg/kg and 1 mg/kg) was intra-peritoneally injected before the challenge with Con A. Eight hours later the mice were euthanized and blood and tissues were collected for analysis. The present study showed that nicotine pretreatment significantly decreased the elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and ameliorated hepatic pathological damage and necrosis. In addition, nicotine treatment markedly suppressed the secretion of pro-inflammatory cytokines and chemokines including tumor necrosis factor-a (TNF-a), interferon (IFN)-γ and interleukin (IL)-4. Furthermore, nicotine down-regulated the activation of NF-kB signal in Con A-treated mouse livers. Since Kupffer cells have been known as a crucial component in the initial part of pathogenesis of ALF, our present study confirmed that depletion of Kupffer cells by liposomal clodronate abolished the protective effects of nicotine against Con A-induced hepatitis, as shown by the similar levels of serum aminotransferase levels and pro-inflammatory cytokines with or without nicotine treatment in Con A treated mouse livers. In the primary Kupffer cells, nicotine ameliorated inflammatory cytokines and regulated the expression of NF-kB signal. Consistent with the above findings, this study suggested that nicotine could attenuate Con A-induced autoimmune hepatitis and possible mechanism might be associated with the inhibition of Kupffer cells activation through NF-kB signal pathway.



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1. Park S, Kim JW, Yun H, Kim B (2016) Mainstream cigarette smoke accelerates the progression of nonalcoholic steatohepatitis by modulating Kupffer cell-mediated hepatocellular apoptosis in adolescent mice. *Toxicology Letters*; 256: 53-63.
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Biography

Jing Qi is a currently pursuing MBBS in Veterinary Pathology from Chonbuk National University of South Korea and has completed her Master's degree of Veterinary Medicine in China in June 2016. She is mainly researching on hepatotoxicity induced by medicine or metabolism in the mouse model.

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Nanofiber sheets using small intestinal sub-mucosa for skin wound healing

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Currently, various wound healing agents are being developed. The patch-type therapeutic agent for skin wound healing has almost no side effects and the drug is delivered to the body at a constant rate, it is a new concept drug treatment that can be applied directly. Most of the conventional patch type therapeutic agents have limitations in that the drug is not well controlled due to the structure of the film, so that the drug is not smoothly absorbed into the skin and the secondary infection is a concern due to poor ventilation and sterilization. In this work, nanofiber sheets (NS) as patch-type therapeutic agent using small intestinal sub-mucosa (SIS) prepared by electro-spinning. Nano-fibers have a large surface area and high porosity. The large surface area not only sufficiently constitutes the wet state but also has a three-dimensional structure similar to the extracellular matrix structure (ECM), so that drug release is facilitated at the wound site and effective for skin regeneration. Also, SIS, a natural material, has excellent biocompatibility and is an ECM with signaling bio-active molecules, cytokines and many other factors, so it has the advantage of controlling cell function. In this experiment, the nanofiber morphology of the SIS-NS was evaluated by SEM. The absorbability of SIS-NS was evaluated by contact angle test. The cytotoxicity of SIS-NS was evaluated and the wound healing effect was confirmed *in vitro*. Also, the skin wound healing effects of SIS-NS was evaluated by *in vivo* experiments such as incision and staining for 3 weeks. In conclusion, these results indicate that SIS-NS is effective for skin wound healing and SIS-NS can be applied as a therapeutic agent for various types of skin wound healing effects.

Biography

Minju Kim is currently studying at Regenerative Medicine Laboratory in Ajou University. Her main research interests are drug delivery system.

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Jiyoung Seo, Toxicol Open Access 2018, Volume 4
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Hyaluronic acid hydrogel as drug carrier for rheumatoid arthritis treatment

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Patients with rheumatoid arthritis-related diseases show an increasing trend. Although many drugs for rheumatoid arthritis (RA) have been appeared in the market, the drugs have some disadvantages; short half-life *in vivo*, inconvenience of taking drugs for a long period of time and drug toxicity in oral administration. Thus, a study of formulations that can continuously release the drug is being required. Recently, injectable drug carriers into the joints as a treatment for RA have been suggested as a very effective treatment. Therefore, in this study, we have developed the effective drug carrier via hyaluronic acid (HA), which has a high bioavailability, for RA treatment. The cross-linking agent was introduced into HA having a molecular weight of 1,000,000 to improve the physical properties of the HA hydrogel and control the pore size of each HA hydrogel for continuous drug release. We also investigated cell viability and inflammation test by using Alamar blue assay and enzyme-linked immune-sorbent assay (ELISA) about RAW264.7 cells and SW 982 cells. By near-infrared (NIR) fluorescence imaging, we confirmed the local release of NIR from the depot injected into the articular joint over an extended period. The effect of HA hydrogel as a RA drug delivery depot was evaluated *in vivo* experiments through extraction and staining over 1 week, 3 weeks and 6 weeks. Collectively, these results indicated that the drug depot formed after intra-articular injection of methotrexate loaded cross-linked HA hydrogel induced long-lasting drug release and allowed to result in enhanced RA repair.

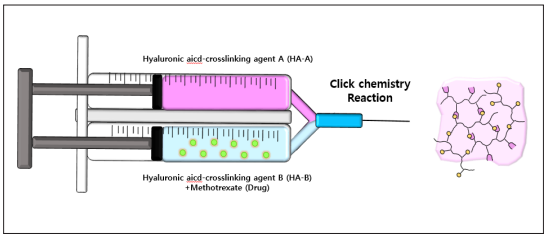

Figure-1: *Hydrogel loaded dual syringe. Hyaluronic acid hydrogel (HA, each introducing crosslinking agent) loaded in dual syringe. The HA including Methotrexate is cross-linked through the needle of a syringe. The hydrogel becomes a better viscous drug carrier for treatment of Rhematoid arthritis.*

Biography

Jiyoung Seo majored in Applied Chemistry and Biotechnology at Ajou University and obtained a Bachelor of Science (BS) in Engineering (2017). She was selected as the Research Director of the program sponsored by the Ministry of Science and ICT and Korea Research Foundation. In the program, she studied the delivery of rheumatoid arthritis medications. She is currently pursuing Master's degree in the Ajou University Regenerative Medicine Laboratory.

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Anti-photoaging effects of ammonium glycyrrhizate in UVB-irradiated HaCaT keratinocytes and UVA-irradiated human dermal fibroblasts

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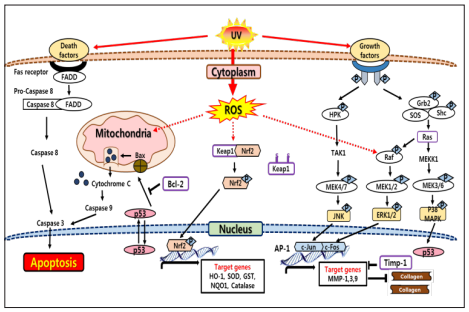

Among many environmental factors, solar ultraviolet irradiation is considered the main cause of skin aging in humans. In this study, the protective effect of ammonium glycyrrhizate (AG), an active component of Licorice root, on UVA- and UVB-induced photo-toxicity was investigated. The antioxidant phytochemical AG has been reported to have various pharmacological properties including cardio-protective, anti-inflammatory and soothing effects on sensitive skin. Despite the known therapeutic effect of AG, the molecular mechanisms related to the photo-protection of AG against UV-induced oxidative cell damage has not yet been determined. In UVB-irradiated HaCaT keratinocytes, AG inhibited both oxidative stress and the apoptosis signaling pathway. In addition, AG promoted the activities of the antioxidant enzymes heme oxygenase-1 (HO-1), glutathione peroxidase 1/2 (Gpx1/2) and superoxide dismutase 2 (SOD2) by translocating nuclear factor (erythroid-derived 2)-like 2 (Nrf2) in the nucleus. In UVA-irradiated human dermal fibroblasts, AG suppressed the expression of secreted matrix metalloproteinase (MMP)-1 and -9 by inhibiting the activator protein-1 (AP-1) transcription factor. Furthermore, AG remarkably increased the synthesis of pro-collagen in human dermal fibroblasts (HDF). These results suggest that AG has protective effects against UVA and UVB-induced photoaging and should be considered a potential therapeutic agent against photo-toxicity in skin.

Recent Publications

1. Kyu-Bong Kim, Young Woo Kim, Seong Kwang Lim, Tae Hyun Roh, Du Yeon Bang, Chang Won Park, Hyung Sik Kim, Byung-Mu Lee (2017) Toxicological and risk assessment of zinc oxide nanoparticles, a cosmetic ingredient used as a UV filter in sunscreens. *J. Toxicol Environ Health Part B.;* 20(3): 155-182.
2. Min Ji Kim, Seung Jun Kwack, Seong Kwang Lim, Yeon Joo Kim, Tae Hyun Roh, Seul Min Choi, Hyung Sik Kima, Byung Mu Lee (2015) Toxicological evaluation of isopropylparaben and isobutylparaben mixture in Sprague-Dawley rats following 28 days of dermal exposure. *Regul. Toxicol. Pharmacol.*; 73(2): 544-51.

Biography

Byung-Mu Lee has his expertise in development of anti-aging and anti-inflammation agents. He is also interested in chemoprevention and risk assessment. He is an Associate Editor of the *Journal of Toxicology and Environmental Health A, Food and Chemical Toxicology* and Editorial Review Board of *Environmental Health Perspectives* (EHP) and Advisory Editor of *Archives of Toxicology*. He was the Vice President of International Association of Environmental Mutagenesis and Genomics Society (IAEMGS) and Vice President of the Asia Society of Toxicology (ASIATOX).

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Zangroniz Calvo Bertha et al., Toxicol Open Access 2018, Volume 4
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The consumption of psychopharmacs, a problem of pharmaceutical care

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Reports made by the World Health Organization (WHO), indicate that 12% of the global burden of diseases is due to mental and behavioral disorders and that only a minority of those affected even in the developed world receive treatment basic, adequate and prescribed by a doctor. The misuse and abuse of psychotropic drugs can lead to serious health problems, not only by altering brain activity, but also by being responsible for drug dependence, with its consequent somatic, psychic and social reactions. The problem of the inadequate use of psychotropic drugs is currently associated with an increase in intoxications and addictions. A retrospective descriptive study was carried out, using as sample the cases of intoxicated by psychopharmacs reported to CENATOX through the telephone information service of urgency, in the years 2013-2017, the reports of intoxication reports by psycho-pharmaceuticals were reviewed during the years of study with a work universe of 8448 cases intoxicated by drugs, of which 3988 intoxicated by psychotropic drugs, took into account month and year of occurrence, sex and age group of all patients intoxicated by psychotropic drugs. The circumstances of the intoxication were studied and a nominal dichotomous scale was established in intentional and accidental. It can be concluded that psychotropic drugs generate 48.44% of drug intoxications. The female sex of 13-19 years was the most affected by acute poisonings by consumption of psychotropic drugs and the male sex between 15-25 years, was the most affected by addictive behaviors. The poly-drug use of psychotropic drugs was the cause of higher incidence, followed by the consumption of Carbamazepine in the ages comprised between 13-19 years. The most commonly used drugs were anxiolytics, in particular chlorodiazephoxide and diazepam.

Biography

Zangroniz Calvo Bertha works in BioCubaFarma, Cuba. She has conducted research related to drug poisonings. She works in the Cuban Biopharmaceutical industry.

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Hanayuki Okura et al., Toxicol Open Access 2018, Volume 4
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Bridging the MOA and the POC for clinical application: A case study

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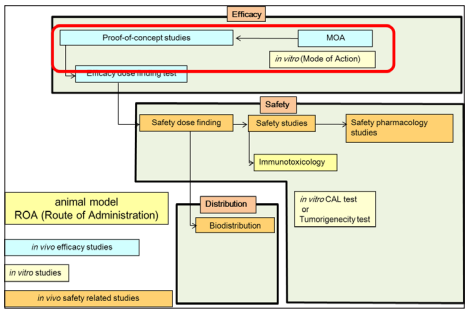

Once the manufactured cells were assigned for cell-based medicinal products, non-clinical studies shall be conducted. In the constructed non-clinical study package including *in vitro* and/or *in vivo* studies: (1) the mode of action (MOA) should be shown, (2) the proof of concept (POC) to be acquired and (3) safety of the candidates be examined. In this presentation, we will focus on MOA and POC and bridge these two concepts, in which adipose tissue-derived multi-lineage progenitor cells (ADMPCs) would be developed as cell-based medicinal products for liver fibrosis. To treat the patients with the liver cirrhosis, the pathogenesis and pathophysiology should be concerned to the MOA. Liver fibrosis is characterized by excessive accumulation of extracellular matrix with inflammatory status *in situ*, therefore, in the developing cell-based medicinal products, anti-inflammatory cytokines and fibrinolytic enzyme secretion is anticipated as MOA. After showing the appropriate MOA, the MOA and the POC should be bridges and the key issues are what kind of animal models should be selected. In the case of the developing cell-based products, MOA is that the cells act as vehicle for the delivery of anti-inflammatory cytokines and MMPs. Tetra carbon chloride (CCl_4)-chronic induction evolved radicals, followed by inflammation, resulted in fibrosis of the parenchyma. So, the expected mode could be applicable in this animal model. To acquire the POC after bridging to MOA, the appropriate route of administration (ROA) should be concerned. In the case study, the POC of the developing cell-based products by the improvement of liver fibrosis, function by systemic administration of ADMPC. In conclusion it can be said that: (1) MOA should be planned from the pathophysiology of the target diseases, (2) the POC-study should be designed to bridge to the MOA and (3) the applicable limitation should be concerned in clinical use for the patients of the disease.

Recent Publications

1. Okura H, Morita M, Fujita M, Naba K, Takada N, Takagaki Y, Suzuki O, Matsuyama A (2017) Therapeutic potential of adipose tissue-derived multi-lineage progenitor cell-sheets on liver fibrosis. *Journal of Translational Science*; 4: 1-6.
2. Negoro T, Okura H, Matsuyama A (2017) Induced Pluripotent Stem Cells: Global Research Trends. *Biores Open Access*; 6: 63-73.

Biography

Hanayuki Okura has completed her PhD degree from Osaka University Graduate School of Medicine. She was Research Fellowship for Young Scientists of Japan Society for the Promotion of Science in her graduate school student years. She is currently the Deputy Director of Center for Rare Diseases Research, National Institutes of Biomedical Innovation, Health and Nutrition, Japan.

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AFLATOX: A biotechnological approach for the development of new antifungal compounds to protect the environment and the human health

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The aim of the Aflatox project (www.aflatox.it) is the development of an innovative biotechnological multi-step approach to design and test new compounds with a biological activity on fungi. The full-experimental database that we have been creating constitutes a powerful source of data to identify important requirements to be taken into account for the development of new generation pesticides, responding to "greener" and environmentally sustainable agricultural strategies. In particular, the compounds must be active against phytopathogenic genera contaminating cereals and food/feed derivatives, with a particular focus on aflatoxigenic species. The requirements to become a good candidate, are not only the high effectiveness in preventing fungal proliferation and mycotoxin biosynthesis, but also the non-toxicity for the environment and the human health. The project has been divided into three different sections: the first is the design and synthesis of some parent compounds from natural molecules, the second is the study of their biological effect and cytotoxicity, and the third is the chemical modification of the most active compounds in order to study the mechanism of action and to improve the biological activity. In particular, in this last stage of the project, the compounds which had shown good results were modified not only in their chemical scaffold, but also used as chelating agents for bio-metal ions like zinc, copper or iron. At present, we have managed to create a database containing a panel of 162 compounds which have been synthesized, characterised and tested for antifungal and antimicotoxigenic properties. Toxicological and genotoxicological evaluation were conducted on normal human cell lines and A. cepa root apex. All these data have been collected in a database that will allow us to produce Q-SAR (Quantitative structure-activity relationship) evaluation profiles.

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Biography

Annamaria Buschini is a genotoxicologist. Her main research interests are environmental mutagenicity and the study of the toxicological profile of drugs/phytochemicals. From the beginning of her research career, she worked on eukaryotic model-systems to study the interaction between xenobiotics (environmental pollutants, drugs, etc) and the cellular environment. One of the goals of this long-term project was to build up and validate screening systems able to detect different mutagenic events at the molecular level for a quantitative/qualitative evaluation of the "genetic hazard". In recent years, she has been involved in epigenotoxicological studies.

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Yoshimasa Takahashi et al., Toxicol Open Access 2018, Volume 4
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Active QSAR modeling for environmental toxicity prediction by partial least squares

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QSAR models obtained from a data set that consists of structurally diverse compounds often give us poor results for the prediction. In the previous work, we proposed a technique of active QSAR modeling that is based on active sampling of a temporary training set. In the method, structurally similar compounds are explored and collected as a training set to make a local model around the query. The result suggested that the approach would often give us better prediction performance than that obtained by the ordinal QSAR modeling. In this paper, we applied the PLS method to QSAR modeling for fish toxicity prediction. We used topological fragment spectra (TFS) to describe structural features of individual compounds. TFS is a digitization of the chemical structure information described in a multidimensional numerical vector. We used a dataset of fish 96h-LC50 for 330 chemicals. The toxicity data were taken from the results of eco-toxicity tests by Ministry of the Environment, Japan. Those toxicity were converted from units of milligrams per litre to moles per litre (mol/L) and then to the corresponding logarithmic values. The TFS-based PLS model obtained with a single latent variable gave us an approximation of R=0.931, R2=0.866, RMSE=0.341 to the experimental values. But, leave-one-out testing for the data set resulted with the RMSE=0.886, unfortunately.

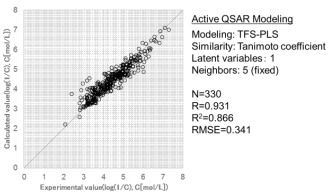

Fig.1 Correlation plot between calculated values and experimental values

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Biography

Yoshimasa Takahashi has received his PhD in chemometrics at Kyoto University in 1984. He was awarded the Niwa Memorial Award for studies on information management and computer-aided design system for chemical research in 1988, presented by Japan Information Center of Science and Technology (JICST). He was also a past chair of Division of Structure-Activity Studies, Pharmaceutical Society of Japan. His current research interest center on intelligent information processing based on structural similarity.

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Ming Ju Hsieh et al., Toxicol Open Access 2018, Volume 4
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Celastrol induces apoptosis-mediated cell death in multi-drug resistance human nasopharyngeal cancer cells

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Nasopharyngeal carcinoma (NPC) belongs to squamous cell carcinoma that occurs in the epithelial lining of the nasopharynx. Because of the anatomical position close to the cervical lymph node, some patients have a distant metastasis at the time of diagnosis that leads to treatment failure. Although early stages have a high curability and excellent prognosis, advanced NPC urgently requires new drugs developed to reinforce the effectiveness of therapy without noticeable side effects. Celastrol, a chemical compound isolated from the root extracts of *Tripterygium wilfordii* (thunder god vine) and *Celastrus regelii* has been reported to possess anticancer potential. The aim of the present study was to determine the anticancer activity of celastrol and further elucidate the underlying molecular mechanisms. In this study, we first demonstrated that celastrol potently suppressed cell viability in MDR-NPC cell lines. Treatment of cells with celastrol induced G2/M arrest and apoptosis. Further studies showed that celastrol increased the expression of cleaved caspase-3, -8, -9 and subsequently activated apoptosis. Moreover, we found that celastrol-induced activation of bax, bim and t-Bid involved in the apoptosis. The expression of anti-apoptotic proteins Bcl-2 was significantly reduced, but expression of Bcl-XL was no significantly change after treatment of celastrol. Celastrol treatment also increased the expression of Fas, DcR2, DR5, RIP and TRADD. The cytotoxic effect of celastrol on NPC cells is mainly due to apoptosis, mediated by Fas-Fas ligand and mitochondrial pathway. These results suggested that celastrol could be a potential anticancer agent for NPC.

Recent Publications

1. Lin H F, Hsieh M J, Hsi Y T, Lo Y S, Chuang Y C, Chen M K, Chien S Y (2017) Celastrol-induced apoptosis in human nasopharyngeal carcinoma is associated with the activation of the death receptor and the mitochondrial pathway. ***Oncol Lett***; 14(2): 1683-1690.
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Biography

Ming Ju Hsieh is a Biochemistry Doctor, specializing in biochemistry, biotechnology, tumor metastasis, apoptosis and other research areas. He has considerable experience in research results in the hospital and research units.

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Rochelle R Pamaran, Toxicol Open Access 2018, Volume 4
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The demographic, clinical and psychosocial profile of pediatric acute poisoning cases in a tertiary hospital: A 5 year retrospective study

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Introduction: Poisoning is a major cause of morbidity and mortality worldwide and represents a major public health threat in children according to World Health Organization.

Objective: To determine the profile of acute poisoning cases in the pediatric population in a tertiary hospital from 2012 to 2016.

Design: The study is a retrospective cross-sectional study on acute poisoning cases among the pediatric population. Review of hospital records was done upon approval of Ethics Review Board.

Patients/Participants: Random sampling was done among acute poisoning cases and 128 cases were included.

Results: The prevalence rate of acute poisoning was 0.56%. Majority were adolescents. Females were more affected. A greater number of cases had intentional poisoning with adolescents and females being more affected. Unintentional poisoning/ accidental poisoning was observed more among children aged less than years old. The toxicants more commonly ingested were therapeutics drugs mostly over the counter drugs, organophosphates, caustic chemicals and herbicides. There were three mortalities, one from nitrite poisoning and two from paraquat poisoning. Most of the cases were classified as C3 and D and they represent the population with lower economic status. Most patients with intentional poisoning were diagnosed to have adjustment disorder with depress mood. The association of age, sex and medical social classification with the nature of incident is not statistically significant, but percentage shows that intentional poisoning is more common among adolescents and unintentional poisoning occurred more among younger age group.

Conclusion: Acute poisoning is indeed one of the health problems at present because of the increasing availability of toxic agents as product of modern innovations in pharmacotherapy and chemical use in the environment. It is recommended to concerned agencies to strengthen existing rules and regulations in usage, distribution and marketing of commonly encountered toxicants that caused mortality, including those that are banned.

Biography

Rochelle R Pamaran has received the degree of Doctor of Medicine at Cagayan State University, Cagayan, Philippines and passed the Physician Licensure Examination in 2007. She has worked as a Clinical Coordinator under the Asian Foundation for Tropical Medicine in collaboration with the Research Institute for Tropical Medicine for the Influenza Surveillance.

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Lei Zhang, Toxicol Open Access 2018, Volume 4
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HZ-6d targeted HERC5 to regulate p53 ISGylation in human hepatocellular carcinoma

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Manipulating the posttranslational modulator of p53 is central in the regulation of its activity and function. ISGylated p53 can be degraded by the 20S proteasome. During this process, HERC5/Ceb1, an IFN-induced HECT-type E3 ligase, mediated p53 ISGylation. In this study, we indicated that HERC5 was over-expressed in both HCC tissue samples and cell lines. Knockdown of HERC5 significantly induced the expression of p53, p21 and Bax/Bcl-2 in HCC cells, resulting in apoptosis augment. Whereas, opposite results were obtained by using HERC5 over-expression. On this basis, we screened a 7, 11-disubstituted quinazoline derivative HZ-6d that could bind to the HERC5 G-rich sequence *in vitro*. Interestingly, HZ-6d injection effectively delayed the growth of xenografts in nude mice. *In vitro*, HZ-6d significantly inhibited cell growth, suppressed cell migration, induced apoptosis in HCC cells. Further studies demonstrated the anti-cancer effect of HZ-6d was associated with down-regulation of HERC5 and accumulation of p53. Collectively, we demonstrated that HZ6d is a HERC5 G-quadruplex ligand with anti-tumor properties, an action that may offer an attractive idea for restoration of p53 function in cancers.

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Accepted Abstracts

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Molecular modeling a tool for postulating the mechanism of drug interaction: Glimepiride alters the pharmacokinetics of Sildenafil Citrate in diabetic nephropathy animals

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The present study evaluates the possible drug interaction between glimepiride (GLIM) and sildenafil citrate (SIL) in streptozotocin (STZ) induced in diabetic nephropathic (DN) animals and also postulates the possible mechanism of interaction by molecular modeling studies. Diabetic nephropathy was induced by single dose of STZ (60 mg/kg, IP) and confirms it by assessing the blood and urine biochemical parameters on 28th day of its induction. Selected DN animals were used for the drug interaction between GLIM (0.5 mg/kg, P.O.) and SIL (2.5 mg/kg, P.O.) after 29th and 70th day of protocol. Drug interactions were assessed by evaluating the plasma drug concentration using HPLC-UV and also determine the change in the biochemical parameter in blood and urine. Mechanism of the interaction was postulated by molecular modeling study using Maestro module of Schrodinger software. DN was confirmed as there was significant alteration in the blood and urine biochemical parameter in STZ treated groups. The concentration of SIL increased significantly ($p<0.001$) in rat plasma when co administered with GLIM after 70th day of protocol. Molecular modeling study revealed few important interactions with rat serum albumin and CYP2C9. GLIM has strong hydrophobic interaction with binding site residues of rat serum albumin compared to SIL, whereas, for CYP2C9, GLIM has strong hydrogen bond with polar contact and hydrophobic interactions than SIL. Present study concludes that bioavailability of SIL increases when co-administered chronically with GLIM in the management of DN animals and mechanism has been supported by molecular modeling studies.

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Development of solid phase extraction and HPLC method for simultaneous estimation Ilaprazole and Glimepiride in rat plasma: Application to pharmacokinetic studies

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A novel, simple and MS compatible high-performance liquid chromatography (HPLC) method is reported for the simultaneous estimation of ilaprazole (ILA) and glimepiride (GLM) in rat plasma. The bio-analytical procedure involves extraction of ILA, GLM and internal standard (IS) from rat plasma with a solid phase extraction (SPE) process. The chromatographic analysis was performed on Waters-600 system using a isocratic mobile phase comprising methanol:water (80:20 % v/v) with pH of water modified to 3 using formic acid at a flow rate of 1.0 mL/min and Kinetex C_{18} column maintained at 30±1 °C. The signals were monitored using a PDA detector set at 225 nm. IS, ilaprazole and glimepiride eluted at 2.04, 4.7 and 7.4 min respectively and the total run time was 10 min. Method validation was performed as per US Food and Drug Administration guidelines and the results met the acceptance criteria. The calibration curve was linear over a concentration range of 10-600 ng/mL (r_2=0.999). The intra- and inter-day precisions for ILA and GLM were (%RSD values) in the range of 1.52-9.74 and 1.52-11.76%, respectively, in rat plasma. The method was successfully applied in pharmacokinetic studies followed by oral administration of GLM and ILA in rats.

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Anti-photoaging effect of Crocin: Its molecular mechanism in UVB-irradiated keratinocytes and human dermal fibroblasts

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Solar ultraviolet (UV) radiation, particularly UVB radiation, is the major cause of photoaging, the most damaging effect of which is skin carcinogenesis. UVB-induced oxidative stress plays a crucial role in initiating and promoting cell signaling involved in aging. Specifically, photoaging results from the up-regulation of metalloproteinases (MMPs) via the activation of activator protein-1 (AP-1) and subsequent collagen breakdown in the skin. This study demonstrates the protective effect of Crocin, an active carotenoid component of *Crocus sativus* L and *Gardenia jasminoides* E, on UVB-induced photoaging. Using HaCaT human keratinocytes and human dermal fibroblasts (HDFs), we evaluated Crocin's anti-photoaging effect by conducting 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays, western blots, enzyme assays and fluorescence-activated cell sorting. In keratinocytes, crocin significantly inhibited UVB-induced oxidative stress and apoptosis by suppressing reactive oxygen species (ROS) generation. Furthermore, it significantly increased the activity of antioxidant enzymes regulated by the transcription factor, Nrf2. In fibroblasts, Crocin significantly attenuated UVB-enhanced MMP expression by inhibiting AP-1 activity in a dose-dependent manner. In addition, it significantly promoted the synthesis of collagen and elastin in HDF cells. Taken together, these results suggest that Crocin prevents UVB-induced photoaging in keratinocytes and fibroblasts by suppressing ROS generation and regulating gene expression.

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Risk assessment of N-nitrosodiethylamine (NDEA) and N-nitrosodiethanolamine (NDELA) in cosmetics

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N-nitrosamine (N-nitrosodiethanolamine (NDELA), N-nitrosodiethylamine (NDEA)) and amine (triethanolamine (TEA), diethanolamine (DEA)) levels in cosmetics were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) procedures. The impact of N-nitrosamine formation on the levels of TEA, DEA, nitrite and other nitrosating agents was also studied. N-nitrosamine concentrations correlated with the number of nitrosating agents and nitrite concentrations. Risk assessments, including the margin of exposure (MOE) and lifetime cancer risk (LCR) for N-nitrosamines and the margin of safety (MOS) for amines, were calculated using product type, use pattern and concentrations. Exposure to maximum amounts of NDELA and NDEA resulted in MOE>10,000 (based on the benchmark dose lower confidence limit 10%) and LCR<1×10^{-5}, respectively. Additionally, TEA and DEA in the cosmetic samples resulted in MOS values>100. Therefore, no safety concerns were associated with cosmetic products containing NDELA, NDEA, TEA and DEA in this study. However, since amines and nitrosating agents produce carcinogenic nitrosamines, their use in cosmetics should be minimized to levels as low as technically feasible.

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Amelioration of altered blood lipid level by imipramine in depressed rat

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Purpose: The study was conducted to investigate the effect of imipramine on blood lipid parameters in depressed rat.

Methods: Rats were subjected for 21 days social isolation; the rats displayed an increase in depression on force swim test and tail suspension test relative to control. Various blood lipid parameters i.e. cholesterol, triglyceride, LDL and HDL were determined.

Results: There was significant increase in the level of cholesterol, triglyceride, LDL and decrease in the levels of HDL after social isolation.

Conclusion: The result of the present investigation showed that with the increase in the levels of depression, there is increase in the blood lipid profile.

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Acute phosphide poisoning related deaths reported at Toxicology Unit of Tanta Emergency University Hospital: A retrospective study

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Background: Acute phosphide poisoning represents a worldwide problem due to its associated morbidity and mortality.

Aim: To determine the magnitude, pattern, trend and possible risk factors in acute phosphide poisoning related deaths.

Patients & Methods: A retrospective study reviewed data from death cases of acute poisoning admitted to Toxicology Unit, Tanta Emergency University Hospital, from 1st of January 2009 to 31st December 2013. Poisoning was diagnosed by history taking and clinical examination. Recorded data included age, gender, residence, phosphide type, manner, pre-hospitalization interval, clinical examination, results of ante mortem laboratory investigations and all received treatments.

Results: 17 phosphide poisoned cases died during the study duration (13 with aluminum and 4 with zinc phosphides), most cases were young (61.54%), females (69.23%), suicidal, from Kom Hamada (53.85%). Most cases received inadequate or improper first aid treatment either at home or primary health care units. The majority of cases (61.54%) did not require mechanical ventilation and most of deaths occurred during the first 6 hours from admission.

Conclusion: Intentional phosphide poisoning, particularly aluminum phosphide, had the first rank as a cause of death in poisonings referred to Tanta Toxicology Control Unit. Governmental regulation to ban the use of phosphide-based pesticides and proper training of physicians at primary health units are advocated to decrease the phosphide poisoning associated mortality.

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Tobacco smoking-induced toxicity in cardiomyocytes derived from human pluripotent stem cells

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Cigarette smoking is an important risk factor for heart disease. Mechanistically-relevant biomarkers could provide timely assessment of the toxicity of tobacco products, including new products that wish to make claims with reduced health risks. The goal of this study is to investigate toxic effects and identify biomarkers of harm in induced pluripotent stem cell (iPSC)-derived human cardiomyocytes. Two cigarette smoke condensate (CSC) concentrations were tested: Low (10 μg/ml) and high (30 μg/ml) following 1-30 day exposures. RNA was isolated at defined time points (1, 7, 14, 30 days) and global gene expression was analyzed using next-generation sequencing. Exposure of cardiomyocytes to CSCs resulted in significant changes to multiple transcripts. The Nrf2-mediated oxidative stress pathway was consistently up-regulated across all time points. Moreover, microRNA-34a, which is involved in the regulation of Nrf2, was down-regulated (two-fold) in CSC-treated cardiomyocytes as early as 24 hours. The high concentration caused the largest reduction in cell viability at the longest exposure time (30 days). Interestingly, induction of the DNA damage and repair pathways occurred only after 30-day exposure .Transcriptional regulation of the Nrf2 pathway may be involved in the underlying mechanism associated with smoking-induced cardio-toxicity. Significantly dysregulated transcripts, such as heme oxygenase 1, glutathione S-reductase and microRNA-34a, in this pathway are potential biomarkers of harm that may be useful as surrogate markers in epidemiological studies and clinical trials to evaluate new tobacco products.

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OEL values for new chemicals in 2017 in Poland

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Statement of the Problem: The aim of the studies is to support enterprises in the implementation of statutory obligations relating to health and safety by providing information on the risks posed by chemical substances on the basis of monographs developed occupational exposure limits. In Poland the system of setting hygienic standards was launched in 1983 by the minister of labor, wages and social affairs and the minister of health and social welfare who appointed the interdepartmental commission for maximum admissible concentrations and intensities for agents harmful to health in the working environment. In Poland in 2017, the OEL values were established for 6 new substances.

Methodology & Theoretical Orientation: The selection of substances to develop monograph of OEL values was taken into account, 3 substances classified as carcinogenic: Phenolphthalein, 2-nitroanisol, N-nitrosodimethylamine. Two active substances of anticancer drugs, i.e. etoposide and fluorouracil were also considered as part of the follow-up work on the development of occupational exposure limits for cytostatics. Considering the need to establish the normative value of 2,3,7,8-tetrachlorodibenzo-p-dioxine for which no OEL has been established yet, but it is a major hygienic problem in plants where chlorine-containing compounds are burned, e.g. in hazardous waste incineration plants.

Findings: On the basis of the available data in the literature on the health and biological effects caused by the selected substances have identified the effects and organs or critical systems of their toxic effects and have assessed the risk to the health of workers who are exposed to them. In the case of cytostatics, setting OELs protects medical staff mainly against the distal effects of exposure.

Conclusion & Significance: Establishing the OEL values for selected chemicals in the work environment will help to effectively manage the risks associated with exposure to them.

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Pattern of ocular toxicity in patients on antipsychotic drug therapy at Alexandria Main University Hospital

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Psychotic disorders are severe mental disorders that cause abnormal thinking and perceptions. Antipsychotic drug treatment is a key component of schizophrenia treatment first-generation antipsychotics, known as typical antipsychotics where second-generation drugs, known as atypical antipsychotics. All psychotropic medications have the potential to induce numerous and diverse unwanted ocular effects. The study aimed to assess the occurrence of ocular toxic effects of antipsychotic drugs and evaluate intraocular pressure in patients treated with psychiatric medications. Informed consent was taken from patients. The present study was conducted on 100 chronic psychotic patients attending the Alexandria main university hospital who on treatment of antipsychotic drugs for a period more than six months period with age group between18-45 years. 14% of those patients were on phenothiazine therapy, 16% on atypical anti-psychotic while 70% were on combined therapy. 2% of all cases had pigmentation of conjunctiva that was on phenothiazine therapy only. Corneal opacity was manifested on 5% of cases. The majority of them was on phenothiazine therapy only while 14% on combined therapy. 7% was suffered from lens opacity; six cases due to phenothiazine therapy only while one case due to combined therapy. Intraocular pressure was manifested in 11% of all cases. Optic examination revealed two cases had increased cup disc ratio who on phenothiazine therapy only. It was concluded that ocular toxicity was manifested mainly with phenothiazine therapy that affected by duration of treatment. The incidence of toxicity decreased with combination of typical and atypical. It is recommended that psychiatrists, ophthalmologists and patients need to be aware of and prepared for any medication-induced ocular toxic effect.

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The side effects of developmental treatment with maternal antiepileptic drugs

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Most women with epilepsy require one or more antiepileptic drugs (AEDs) throughout their entire pregnancy to control seizures. Long-term use of AEDs in epileptic mothers can elicit lasting side effects in their children. The mechanisms of anatomical and behavioral teratogenesis may well differ, because it appears that the highest risk of anatomical defects is from first-trimester, whereas the highest risk of behavioral defects appears to be from exposure during the third trimester. Proposed mechanisms underlying teratogenicity of AEDs include impaired folate, ischemia-hypoxia, neuronal suppression, reactive intermediates and AED-induced neuronal apoptosis. Disturbed folate metabolism during administration of AEDs, reduces neurogenesis, increases apoptosis. AEDs inhibit S-adenosyl methionine and dihydro folic acid reductase, so associated with disturbed folate metabolism and increases plasma homocysteine levels. AEDs depressed synthesis of the neurotrophins BDNF and NT-3 and reduced levels of the active phosphorylated forms of c-RAF, ERK1/2 and AKT. Suppression of synaptic neurotransmission is the common denominator in the action of AEDs, via block voltage-gated sodium channels enhance GABAergic inhibition, or block glutamate-mediated excitation, therefore major AEDs cause, sensitive neurons and apoptotic neuro-degeneration in the developing brain. Prostaglandin H synthase enzyme and lipoxygenase enzyme in the fetus are active, so they can convert AEDs to free radicals and cause anatomical defects. Findings suggest, the functional consequences of *in utero* AED exposure depend upon the type, dose and timing of treatment with AED that can induce long-lasting cognitive, behavioral and anatomical impairments and certain caution must be taken when prescribing these medications to pregnant or breastfeeding mothers.

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Notes: