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**Gender-dependent effect of prenatal immune challenge on adult hippocampal neurogenesis.**

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**Introduction:**

Early life psychological stress alters neurogenesis during adulthood in male progeny. The impact of early life challenges on female had received less attention. In the current study, we explored the long lasting impact of an immune challenge during pregnancy on hippocampal neurogenesis in male and female adult progeny. Since serotonin has been shown to promote neurogenesis, we also explored the impact of prenatal immune stress on hippocampal serotonin (5HT) and its transporter.

**Methods:**

Pregnant Sprague Dawley rats were given either lipopolysaccharide (LPS, 100 µg/kg i.p.) or saline on gestation days 15, 17 & 19. Hippocampal neurogenesis was monitored male and female offspring using immunofluorescent detection of doublecortin (DCX), a marker of newly born neurons. Expression levels of 5HT (raphé nucleus) and 5HT-transporter (hippocampus) were assessed using immunofluorescence and western blot respectively.

**Results:**

We observed no significant effect of prenatal LPS on hippocampal neurogenesis in one-month-old male and female rats. However, the expression of 5HT transporter was higher in male offspring when compared to that seen in female offspring regardless of early life challenge. There was no apparent effect of prenatal exposure to LPS on serotonin in the raphé nucleus. Interestingly, prenatal exposure to LPS significantly reduced hippocampal neurogenesis in the two-month-old female offspring. Such effect was not observed in the male offspring. Moreover, prenatal immune challenge significantly increased the expression levels of 5HT transporter within the hippocampus of both male and female rat offspring.

**Conclusions:**

Collectively, these data suggest that prenatal immune challenge selectively alters hippocampal neurogenesis in female offspring, an effect that was accompanied by an increase in the levels of 5HT transporter in the hippocampus. Future studies will explore this gender biased effect of early life immune stress.

*Key Words: Fetal programming; Serotonin; Neurogenesis;*



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### Antibacterial and antiproliferative activity of novel triazolyl oxazolidinones

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#### Introduction:

Oxazolidinones exhibit biological actions such as antibacterial, anticancer, and MAO inhibition. The presence of H-bond donor or acceptor group at C4 position of the phenyloxazolidinone pharmacophore gave derivatives with potent antibacterial activity due to enhanced binding to 50S ribosomal subunit. Some 5-triazolylmethyl-oxazolidinone derivatives have been shown to exhibit antiproliferative effect against cancer cell lines. We now investigate antibacterial and anticancer activity of some novel oxazolidinones.

#### Methods:

Selected oxazolidinone derivatives were synthesized and analyzed by spectroscopic and other analytical methods. Antibacterial activity was tested against standard reference Gram-positive and -negative bacterial strains. Minimum inhibitory concentrations (MIC's, ug/ml) were determined by agar dilution method on Mueller Hinton agar. Cell viability was determined cancer lines using MTT assay. UV-Vis and CD spectra of the substances in the presence of increased concentrations of ctDNA were measured. Inhibition of topoisomerase I and II were investigated.

#### Results:

PH-145, -181, -189 and -193 exerted superior activity against selected Gram-positive bacteria compared with linezolid. In the 1,4-dihydro-1,8-naphthyridine derivatives, the glyciny containing compound SA-20-15 showed superior antibacterial activity compared with SA-12-15 and linezolid against *S. epidermidis* and *E. faecalis*. The 5-nitrofuoyl derivatives exhibited cytotoxicity against sensitive and cisplatin-resistant ovarian cancer cells. These results showed that PH-145 and -189 may act on tumor cells selectively. Moreover, CD spectra of ctDNA with increased concentrations of the compounds did not show any remarkable change with the exception of compound SA-20-15. Electrophoretic separation proved that none of these compounds inhibits topoisomerases.

#### Conclusions:

Compounds showed strong antibacterial and some anticancer activities. Anticancer activity was not due to interaction with DNA. Kuwait University, Research Sector, General Facilities Grants GS01/03 & GS01/05 and VEGA Grant Agency of the Ministry of Education of the Slovak Republic No. 1/0790/14 & 1/0007/17.

*Key Words: antibacterial; antiproliferative; triazolyl-oxazolidinones;*



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**Atraumatic splenic Rupture in adult patient with chickenpox**

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**CASE REPORT**

**Background:** Chickenpox is a commonly encountered infection in children. It is usually a self-limiting infection. However, in adult population, chickenpox is much less common and may lead to serious complications and death. Serious complications include severe skin infections, pneumonia, septicaemi and meningitis. In extremely rare occasions spontaneous splenic rupture may occur.

**Case summary:**

Thirty-seven years old healthy female came to Jahra hospital casualty with one-day history of sudden onset left sided abdominal pain and vomiting. Four days ago, she noticed eruption of similar rash as her five years daughter had two weeks ago. No history of trauma. On examination, the patient was alert with pale skin and lips. Vitals were Pulse 88, Bp 85/40 and temp 37.9 C. There was generalized papulovesicular rash over the body. There was left sided abdominal tenderness but no ecchymosis, rigidity or guarding. Investigations revealed Hb (10.3 gm/dL), WBC 8 (\*10<sup>9</sup>/L) and platelets 127 (\*10<sup>9</sup>/L). Fast scan found intraperitoneal fluid with no solid organ damage. The patient was resuscitated with crystalloid fluids and started on vasopressor (norepinephrine). After initial resuscitation and stabilization, CT scan abdomen with contrast done and showed anterior splenic wall rupture with hemoperitoneum. No Active contrast leakage detected. Afterward, the patient was shifted to the ICU for close observation and conservative management. However, on the third day, she had worsening abdominal pain, vital signs were unstable and hemoglobin dropping. Thus, she had urgent blood transfusions and shifted to the theatre. Intra-operatively, active bleeding was seen near the hilum of the spleen with splenectomy successfully followed.

**Conclusion:**

Adult chickenpox may impose life-threatening surgical emergency to patients' life. Splenic rupture after chickenpox infection is extremely rare. This complication may initially be missed. Thus, immediate attention, suspicion and, if necessary, surgical intervention is required.

**Key Words:** Splenic; rupture; chickenpox;



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*Medical Microbiology*

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**Live recombinant *Mycobacterium smegmatis* as an antigen delivery system for the induction of antigen-specific and protective cellular immune responses in mice.**

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**Introduction:**

The identification of major *Mycobacterium tuberculosis*-specific antigens has paved the way to study their role in inducing protective immunity against tuberculosis and identify the antigens that could be used to protect against other immunological diseases, e.g. asthma. However, the delivery of these antigens is an important issue. In the past, non-living adjuvants have been tried with limited success. In contrast, the living adjuvants may provide better alternative. The aim of this study was to test live *M. smegmatis*, a non-pathogenic mycobacterium, as a delivery system for a dominant *M. tuberculosis*-specific antigen Rv3619.

**Methods:**

The gene encoding Rv3619 was amplified from the genome of *M. tuberculosis* and cloned in a plasmid vector pDE22. The recombinant plasmids were electroporated into *M. smegmatis* and the expression of rv3619 in recombinant (r)*M. smegmatis* was determined by reverse-transcriptase (RT-PCR). Mice were immunized and boosted with r*M. smegmatis* and sacrificed two weeks after the last injection. The spleenocytes were stimulated *in vitro* with a mitogen and synthetic peptides covering the sequence of Rv3619. The culture supernatants were assayed for the protective Th1 cytokine IFN-gamma and the pathologic Th2 (IL-5) and Treg (IL-10) cytokines in ELISA. The responses were considered positive with E/C >2, where E and C are the concentration of cytokines in stimulated and control cultures, respectively.

**Results:**

RT-PCR showed that the rv3619 was expressed in r*M. smegmatis*. The immunized mice showed positive responses to the peptide pool in Th1 assays but not in Th2 and Treg assays. Furthermore, all individual peptides of Rv3619 showed positive responses in Th1 assays.

**Conclusions:**

*M. smegmatis* selectively induced broad-based Th1 responses to Rv3619. Hence, this delivery system could be useful for the induction of protective immune responses against intracellular pathogens and non-infectious diseases like asthma.

Supported by the College of Graduate Studies and the Research Sector Projects YM06/15 and SRUL02/13.

*Key Words:* Recombinant *M. smegmatis*; Rv3619; Cytokines;



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**Oncology**

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**Natural phenolic compounds enhance the lethality of the multi-kinase inhibitor Sorafenib in human hepatocellular cancer cells.**

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**Introduction:**

Drug resistance & the unenviable side-effects are major obstacles to successful chemotherapeutic treatment. Sorafenib (Sora), FDA approved multi-kinase inhibitor, with potent antiangiogenic & antitumor activities. Effective strategies to reduce the side-effects & enhance the activity of Sora are much required. In this study, we endeavored to investigate the effects of combination treatment with Sora & natural phenolic compounds (NPC), on human hepatocellular carcinoma (HCC) cell growth, & intracellular transduction pathways involved in cell cycle & apoptosis.

**Methods:**

MTT assay was used to monitor the cytotoxicity of 14 NPCs on fibroblast cells CRL1554 & to measure the lethality of Sora, NPC & their combinations on HCC cells; Hep3b & HepG2 using three different approaches; sequential, reverse sequential & simultaneous. Cell cycle was analyzed by flowcytometry. Apoptosis was assessed by; DNA fragmentation, Annexin V/PI double staining assay & mitochondrial membrane potential assay (MMP). Finally, gene expression of apoptosis & cell cycle proteins was evaluated by western blot analysis.

**Results:**

Four NPCs; curcumin (Cur), quercetin (Que), kaempferol (Kmf) & resveratrol (Rsv) were selected, for their %Cytotoxicity ( $0 \leq 20\%$ ) on CRL1554 cells. Combination treatments of Sora & the selected NPC against HCC cells proved to be cytotoxic in a dose & schedule dependent manner where; Cur ( $p < 0.0001$  &  $p < 0.002$ ) and Kmf ( $p < 0.024$ ). Cell cycle analysis showed that HCC cells growth arrest at the S & G2/M phases. DNA fragmentation depended on the dose & type of treatment. Annexin V assay, demonstrated a high percentages of cell displayed early & late apoptotic phenotypes. Furthermore, assessment of MMP revealed extensive membrane damage. Finally, western blot analysis showed that protein expression is altered in a dose-dependent manner.

**Conclusions:**

Results showed a marked enhancement of Sora efficacy on HCC cells. In vivo & clinical studies of the combination treatments are needed. College of Graduate Studies and Research Sector, Project No. YS01/15, Kuwait University.

*Key Words: Hepatocellular carcinoma; Sorafenib; Natural phenoli compounds;*



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*Anatomy*

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**Developmental vitamin D deficiency impairs spatial learning but has no effect on memory**

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**Introduction:**

Recent evidence suggests that Vitamin D deficiency (VDD) affects cognitive functions in adults but the effect of developmental vitamin D deficiency (DVDD) on brain development and cognitive functions has not been well-established. This study was conducted to explore the functional and structural effects of DVDD in rat pups.

**Methods:**

The effects of DVDD on spatial learning and memory in Wistar rats at postnatal day 24 (PND24; weaning) and PND45 were analyzed by Morris water maze (MWM) test. Rat pups were divided into four groups: C (control), dG (deficient during gestation), dL (deficient during lactation), dGL (deficient during gestation and lactation). We also measured cortical thickness after MWM test at PND63 at the level of hippocampus, and counted synapses in the hippocampus at PND32 and PND63.

**Results:**

Repeated measure ANOVA revealed that at PND24 and PND45 the dGL group learned significantly slower compared to all other groups ( $P < 0.05$ ). At PND45, also the dL learned significantly slower than the control groups ( $P < 0.05$ ). Probe test was performed after 2 days of learning sessions for Short term memory (STM) and after 10 days for long term memory (LTM). Neither STM nor LTM were affected by DVDD at both PND24 and PND45. The number of synapses at PND32 and PND63 were significantly lower in the DVDD groups than C group ( $P < 0.001$ ). All groups with DVDD showed significant reduction in cortical thickness compared to control group ( $P < 0.05$ ). No significant differences were observed among the different DVDD groups.

**Conclusions:**

Early postnatal DVDD impairs learning, but once learning has occurred there is no significant effect on memory. Prenatal or pre-weaning VDD alone does not affect learning. Long-term effects of the DVDD-induced structural changes in the brain needs further investigation.  
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*Key Words: Developmental Vitamin D deficiency; Learning; Brain Development;*



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*Biochemistry*

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**Protective effects of GLP-1 analogues against cellular stress in glucose up-taking tissues under lipotoxic conditions**

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**Introduction:**

Increase in glucagon-like peptide-1 (GLP-1) activity has recently emerged as a useful therapeutic tool for the treatment of type 2 diabetes (T2D) by enhancing the glycemic control and also helping in maintaining or even decreasing body weight of most patients. The action of GLP-1 and its mimetics on pancreatic  $\beta$ -cells as well as on nervous and digestive systems are relatively well established. The effect of this peptide and its analogues in other tissues including adipose, muscles and liver, however, are still poorly defined. We therefore investigated the potential beneficial effects of GLP-1 mimetics on those peripheral tissues using established cell lines.

**Methods:**

Using cell lines from liver (HEPG2), muscle (L6) and adipose tissue (3T3-L1), we analysed the effect of GLP-1 mimetic (Exendin-4) on MAPKs in the presence of stressing amounts of palmitic acid (PA). Differential protein expression pattern was investigated using LC-MS/MS Orbitrap system and label-free quantification with a focus on the MAPKs. Results were validated using Western blotting, RT-PCR approaches. Cell viability assay was also performed.

**Results:**

In all used cell lines, Under lipotoxic conditions (400uM PA) a set of proteins related to lipid homeostasis were also modulated by GLP-1 analogues. We showed that JNK and ERK MAP- Kinases were among the proteins that were highly modulated by GLP-1 analogues both at the expression and phosphorylation levels which was validated by proteomic profiling, and mRNA and protein expression levels. Furthermore, cell viability assays have shown that exendin-4 alleviated the palmitate induced cell death.

**Conclusions:**

Our results suggest that GLP-1 mimetics alleviate the lipotoxicity-related cellular stress in peripheral cells and thus restoring their normal homeostasis

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*Key Words: GLP-1 analogues; ER stress; MAPKs;*



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*Pharmacy*

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**Economic Burden of Multiple sclerosis on Kuwait Health care system**

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**Introduction:**

This study aims to measure the cost of health resources utilization by multiple sclerosis (MS) patients and to examine the difference in utilization and its attributed costs among patients with different types of MS and expanded disability status scale (EDSS) scores.

**BACKGROUND**

Multiple sclerosis is a chronic neurological disease with heavy economic and social burdens resulting in significant disability and social dependence. The prevalence of MS is in an upward trend in Kuwait reaching 85.05 per 100,000 in 2011.

**Methods:**

A cross-sectional study using Kuwait National MS registry was conducted to estimate the costs of utilization of resources. Data of patient demographics, clinical features, and diagnostic / therapeutic utilizations between 2011 and 2015 were extracted. Kruskal-Wallis was used to examine the difference in costs between types of MS and EDSS scores.

**Results:**

By end of 2015, 1344 MS patients were included in the registry; of whom 75.9% were of relapsing remitting (RR) form, and 83.3% had EDSS scores  $\leq 3$ . The average annual cost per MS patient has increased from 4,532 KD in 2011 to 6,753 KD in 2015. Utilization of disease modifying therapies (DMTs) was the main driver of costs reaching 89.9% in 2015. The number of treated patients increased by 12.7% due to the availability of oral DMTs. Throughout the five-year period, relapse severity decreased as the proportion of relapses treated in ambulatory settings increased by 5.8% while hospitalizations decreased by 2.6%. There was a significant difference between the average cost per patient in different type of MS and different EDSS categories ( $p < 0.0001$ ), with patients with RR course and moderate EDSS score (3.5-6) having the highest average 7,144 KD and 10,544 KD respectively.

**Conclusions:**

Multiple sclerosis has a significant economic burden on the Kuwait healthcare system. Disease modifying therapies seem to be the main driver of cost.

*Key Words: Multiple Sclerosis; Economic burden; Kuwait;*