ABSTRACTS

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Abstracts of the Plenary Lectures

L1. The Future of Medicine and the role of Nanotechnology and Biotechnology in certain medical disorders. – *Key Note Lecture*

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Although there have been some advances in cancer treatment over the past several decades, current diagnostic and therapeutic approaches rely predominantly on invasive (i.e. random biopsies, surgery) and crude, non-specific techniques such as irradiation and chemotherapeutic agents. Thus, cancer continues to be almost uniformly fatal, and current therapeutic modalities have yet to significantly improve the dismal prognosis of this disease. Over the past few years, evidence from the scientific and medical communities has demonstrated that nanotechnology and nanomedicine have tremendous potential to profoundly impact numerous aspects of cancer diagnosis and treatment. The utilization of nanotechnology for the development of new nano-carrier systems has the potential to offer improved chemotherapeutic delivery through increased solubility and sustained retention times. One of the major advantages of this cuttingedge technology is its unique multifunctional characteristics. Targeted delivery of drug incorporated nanoparticles, through conjugation of tumor-specific cell surface markers, such as tumor-specific antibodies or ligands can not only enhance the efficacy of the anticancer drug but also reduce the unwanted toxicity of the drug. Additionally, multifunctional characteristics of the nano-carrier system would allow for simultaneous imaging of tumor mass, targeted drug delivery and monitoring. A summary of recent progress in nanotechnology as it relates specifically to nanoparticles and anticancer drug delivery will be reviewed. Nano Nutraceuticals using combination of various natural products provide a great potential in thalassemia and sickle cell anemia management. Additionally, various Nanomedicine approaches for the detection and treatment of various types of clots organ specific delivery, vascular targeting, and vaccine will be briefly discussed.

Learning Objectives:
Highlight the Role of Nanobiotechnology and other enabling technologies in the followings:

1. Targeted Drug Delivery
2. Early detection (Imaging)
3. Management of Hematological, vascular, and blood disorders
4. Cancer Treatment

L 2. Use of Monoclonal Antibodies in Organ Transplantation

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Background: Intervention in the alloimmune response with antibodies.
In 1899, was the first use of rabbit immune serum to remove leukocytes from human blood. Nowadays, polyclonal rabbit antithymocyte globulin (ATG) is still commonly used to prevent and treat allograft rejection. The formation of anti-rabbit antibodies and development of serum sickness diminishes its clinical use. Where polyclonal antibodies target a broad range of molecules, monoclonal antibodies have a single molecular target.

Aim of the study: Monoclonal antibodies are applied in various settings in organ transplantation.

Results: The first monoclonal antibody approved for use in human renal transplantation was muromonab anti-CD3. Depleting T-cell MABs are used for treatment of steroid-resistant acute rejection and as induction therapy to reduce the intensity of concomitant immunosuppressive drug therapy.
Induction therapy with the non-depleting IL-2 receptor antagonists basiliximab and daclizumab (anti- CD25), added to cyclosporine-based regimens, reduces the incidence of acute rejection without side effects.
The B-cell-targeting antibody rituximab: chimeric human–mouse anti-CD20 is used in blood group ABO-incompatible transplantation, in desensitization protocols, and for treatment of antibody-mediated rejection.
Eculizumab: humanized (mouse) anti-C5 interrupts the complement protein C5 pathway and is a promising tool for the treatment of antibody-mediated rejection which is accompanied by activation of the complement system. and post-transplant hemolytic–uremic syndrome.
Alemtuzumab: (humanized-rat; anti-CD52). CD52 is expressed on T cells, B cells, NK cells, monocytes, macrophages and dendritic cells. Depleting anti-CD52 antibodies (Campath-1) as induction therapy in renal transplantation showed effective lymphocyte depletion with reduced incidence of acute rejection, but with immunogenicity and also an increased incidence of infections.

Conclusion: Future options are monoclonal antibodies with new molecular targets that can be used for maintenance immunosuppression in order to avoid the toxicity of existing drugs. Challenges in transplantation that are not yet met are long-term toxicities associated with current regimens, and immune targets that are not affected by the current drugs. Ultimately, the induction of donor-specific tolerance remains the holy grail.

Keywords: Organ transplantation; antithymocyte globulin (ATG); muromonab anti-CD3; basiliximab and daclizumab: (anti- CD25); rituximab: chimeric human–mouse anti-CD20; Eculizumab: humanized (mouse) anti-C5; Alemtuzumab: (humanized-rat; anti-CD52)

L 3. Excellence in Pharmacovigilance

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Pharmacovigilance

With the increasing and ever- more stringent regulations in pharmacovigilance, the regulatory authorities face greater demands for patient welfare and safety, which become prominent especially after the Thalidomide disaster. These in turn necessitate standard levels of monitoring and data analysis that ensure safe drug delivery. This can be only attained by well-structured pharmacovigilance centres backed-up with a robust legal framework and clear guidelines. Pharmacovigilance has been defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

The Post-marketing context

PV help monitoring medicines in the real life use thus, overcome the well-known limitations of the clinical trials. International standards agreed on the importance of implementation in all countries worldwide and for all medicines. This global initiative is being organized by the WHO via its collaborating center; Uppsala Monitoring Center (UMC). Egypt collaborate with another 131 member countries in this program which enables drug regulators to have a worldwide safety view filed alongside with the local national safety view field for all marketed medicinal products.

Situation in the Arab region

In the context of the Arab world, Egypt, Saudi Arabia and Jordan already have strong regulations in pharmacovigilance based in their drug regulatory authorities which are addressed to marketing authorization holders (MAHs). These regulations require important documents to be present in registration dossiers and follow-up procedures to be done post-marketing; this can be described collectively as 'regulatory pharmacovigilance'. These three countries also have activities directed towards health care practitioners (HCPs). Morocco and Tunisia have pharmacovigilance centres located outside drug regulatory authorities and which do not assess registration dossiers and marketing authorization holders' obligations. United Arab Emirates, Oman, Kuwait, Iraq, Sudan and Syria are at early stages in this sphere.

Adapting the EU models

The robust regulations that are present in Egypt, Saudi Arabia and Jordan were mainly adopted from the volume 9A of the European Medicine Agency (EMA). The routine activities covered by standard regulations included the monitoring and assessment of:
(1) Marketing Authorization Holders' infrastructure, described in a document 'Detailed Description of Pharmacovigilance System' (DDPS)
(2) Qualified Person for Pharmacovigilance (QPPV)
(3) Periodic Safety Update Reports (PSURs)
(4) Individual Safety Case report (ICSRs)
(5) Reported new signals.
Additional pharmacovigilance activities included:
(1) Risk Management Plans (RMPs)
(2) Dear Healthcare Professional Communication (DHCPC)
(3) Post-Authorization Safety Studies (PASS).

Recent developments

However, new advances in the world of regulatory pharmacovigilance emerged:

- Moving from assessment of whether MAHs have infrastructures or not (described in Detailed Description of Pharmacovigilance System (DDPS)), to the concept of assessing the intelligence of such infrastructures (described now in Pharmacovigilance system master file (PSMF)).
- Moving from assessing only Periodic Safety (described in PSURs), to assessing Benefit/Risk ratio (described in Periodic Benefit Risk Evaluation reports (PBRER)).
- From assessing only submitted documents, to performing pharmacovigilance audits and inspections.
- From relying on Standard Operating Procedure (SOPs) of performance, to assessing quality systems as a whole.
- From depending only on Dear Dr Letters (DDL) for urgent safety evaluation to make use of recent revolution of internet connections.
- From acting reactively to acting proactively by adding more weight to Risk Management Plans (RMPs) and risk minimization activities.
- Adding more weight on Public participation and international co-operation.

Moves by the Arab League

In order to cope with these changes and to unify guidelines and performance across the Arab world, Arab ministers of health came to a common decree (number 7) in their 37th regular meeting in March 2012. Under the umbrella of the Arab League 'The Higher Technical Committee for Medicines' was established with representatives from all Arab countries, to create common Arab guidelines in pharmacovigilance, and in bioequivalence. This committee elected Dr. Amr Saad, head of the Egyptian centre, to lead the committee across all its rounds. The committee has finished the final drafts of the two common guidelines which were submitted to the 38th regular ministers meeting, and which has been approved by them.

Guidelines adopted

The new Common Arab guidelines is mainly adapted from the newly-established international Good Pharmacovigilance Practice (GVP), composed of 16 different modules together with some product/population specific considerations, as well as annexes and templates of submission. The Guidelines were published in March 2014 and the effective date will be 1st July 2015. It is expected that these guidelines will significantly influence pharmacovigilance practice in general in the whole Arab world, and will increase such activities including reporting rates and signal detection in that part of the world. It will also help some Arab countries to develop in the area of 'Regulatory Pharmacovigilance'.

L 4. Estrogen/estrogen receptor-induced Metabolic reprogramming in endometrial cells

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Proliferating cells encounter a profound metabolic challenge of increased bioenergetics and biosynthetic demands that must be met before cells start to proliferate. Therefore, In response to growth factor stimulus, proliferating cells adopt a distinctive metabolic phenotype characterized by enhanced glucose uptake and shifting glucose metabolism from oxidative phosphorylation (OXPH) into aerobic glycolysis and the pentose phosphate pathway (PPP) (Warburg-like effect). This metabolic phenotype imparts several growth advantages for the cells. It supports the production of the energy, anabolic precursors, and NADPH required for the de novo synthesis of structural macromolecules (proteins, lipids, and nucleic acids), and combats reactive oxygen species (ROS) produced during cell proliferation. Furthermore, certain intermediary metabolites from aerobic glycolysis influence the transcriptional factors, the chromatin structure, and the epigenetic circuits to establish a milieu conducive for cell proliferation. Estradiol-17β (E2) plays an indispensable role in the pathophysiological proliferation of endometrium by activating multiple signaling pathways. Yet, whether E2 reprograms cellular metabolism to support proliferation of human primary endometrial stromal cells (hESCs) and the molecular basis of this reprogramming are not well understood. In this session, we will show how hESCs alter their glucose metabolism in response to E2 treatment. We will present our recent findings that E2 induces a Warburg-like glucose metabolism in hESCs by upregulating c-Myc–hnRNP-PKM axis. We will also illustrate the molecular bases of E2-induced preferential splicing of Pyruvate kinase M (PKM) and causes its oxidation, phosphorylation, and nuclear translocation. In addition, we will depict the reciprocal biochemical interactions between nuclear PKM2 and estrogen receptor-α (ERα) and its implications in the pathophysiology of endometrium.

L 5. Novel Gene Therapy in Pancreatic Cancer

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Background: Pancreatic cancer (PaCa) is one of the most aggressive, apoptosis-resistant, lethal human cancers and is currently incurable. Pancreatic ductal adenocarcinoma (PDAC), the most common form of PaCa, is characterized by extensive local tumor invasion, metastasis, early systemic dissemination, poorest prognosis with dismal 5-year survival rates of 2-3%, and ~6 months median survival with therapy. Thus, finding novel targets for PaCa therapy are urgently needed. RNA interference (RNAi), a process of sequence-specific gene knockdown, has emerged as an important strategy for gene-activity manipulation and has been a critical cornerstone towards the development of gene-silencing therapies in cancer. Eukaryotic elongation factor-2 kinase (eEF-2K) is an atypical kinase that is highly up-regulated in PaCa cells. However, its role in PaCa survival remains largely unknown.

Aim of the study: The goal of this study was to investigate the role of eEF-2K in PaCa progression, apoptosis modulation, as well as the regulation of the invasive phenotype and promoting motility/migration of PaCa cells. Meanwhile, the study perspective was also designed to identify novel biomarkers of eEF-2K downstream molecular effects and to explore the molecular mechanisms associated with eEF-2K down-regulation and over-expression in PaCa cells.

Methods: PANC-1and MIAPaCa-2 pancreatic cancer cell lines were used to investigate the biological and molecular events associated with targeting eEF-2K. Small interfering RNA (siRNA) and lentiviral eEF-2K expression vector (pCDH-eEF-2K) were used to knockdown and overexpress eEF-2K, respectively. For analysis of apoptotic cell death, Annexin V assay and mitochondrial membrane potential, MMP ($\Delta\Psi m$) assay were employed. To determine the changes in the invasion/migration capacity of the cells, Matrigel invasion assay and Wound-Healing assay were performed. In addition, immuno-blotting and RT-PCR analysis were executed in order to investigate the underlying molecular mechanisms and to identify the downstream molecular effects associated with eEF-2K knockdown or over-expression.

Results: The targeted-silencing of eEF-2K, using siRNA, in PaCa cells induces intrinsic apoptosis, with dissipation of mitochondrial membrane potential ($\Delta\Psi m$), and stimulates extrinsic apoptosis with concomitant induction of TNF-related apoptosis inducing ligand (TRAIL) receptors, DR4 and DR5, with caspase-8 activation. AIF-dependent apoptosis was also activated. In addition, down-regulation of eEF-2K displays impairment of PaCa cells invasion/migration, and suppresses the epithelial-mesenchymal transition (EMT), an important driver for promoting cancer invasion and carcinomas metastasis. Such cellular events were accompanied with a significant decrease in the expression of tissue transglutaminase (TG2), the multifunctional enzyme implicated in regulation of cell attachment, motility apoptosis and survival. In addition, marked reductions in β1

integrin/uPAR/MMP-2 signaling as well as decrease in Src activity were observed. Importantly, eEF-2K over-expression, by lentivirus-based expression plasmid, increases PaCa cellular survival and potentiates cellular invasion/migration capability and correlated molecular events.

Conclusion: Collectively, these results indicate, for the first time, that the down-regulation of eEF-2K leads to induction of intrinsic, extrinsic as well as caspase-independent apoptosis in PaCa cells. Moreover, the data strongly suggests that eEF-2K is a central driver for PaCa progression, being involved in the regulation of the invasive phenotype of PaCa cells and the modulation of EMT regulators which modulate cancer cell motility and metastatic potential. The data establishes a mechanistic rationale for eEF-2K inhibition as a novel potential therapeutic target in pancreatic cancer.

Keywords: eEF-2K, Ca2+/calmodulin–dependent kinase III; siRNA; Tissue transglutaminase (TG2); β1 Integrin; Src; Matrix metalloproteinase-2 (MMP-2); Urokinase-type plasminogen activator receptor (uPAR); Extracellular matrix (ECM); Apoptosis; Invasion; Pancreatic cancer.

L 6. Monitoring cell signalling and drug profiling using a new microarray based technology

Dr. Abdullah Gibriel PhD
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Background: Biological processes in mammalian cells are driven by gene expression that is in turn regulated by transcription factors (TFs). The latter are controlled by a series of complex network of biochemical pathways that represent the core for cell signalling. There has been little success in monitoring cell signalling using traditional methods such as proteomics.

Aim of the study: In this report we demonstrate the possibility of deconvoluting such complexity using a multiplexed library of plasmids carrying a TF binding site upstream of a unique reporter sequence (UR). A microarray sensor platform was then used to monitor dynamic changes in cells by measuring UR expression levels.

Methods: HEK293 cells, treated with various drugs and inducers, were transfected with the multiplexed plasmid library. mRNA was then purified and reverse transcribed to produce first strand cDNA. The latter was then amplified by PCR using a universal fluorescently labelled primer. Purified PCR amplicons were then hybridized with antisense oligonucleotide captures at 53˚C. Epoxy slides were then washed and quantified using the ScanArray Express Scanner (Perkin Elmer).

Results: The microarray platform was optimized to detect down to 1 attomol with a maximal degree of specificity and a minimal probe volume of 2µl. This platform was able to detect changes in the TF activity following treatment of cells with dexamethazone, cadmium, forskolin and TPA and drugs such as cAMP analogues, cGMP analogues and PDEIs. The data was consistent with qPCR and western blot analysis.

Conclusion: The microarray platform was shown to be robust, sensitive and reproducible in monitoring dynamic changes in mammalian cells. The system could be used for early detection of desired therapeutic effects for new drugs and also for early prediction of their possible side effects. The system can be easily tailored to include transcription factors of interest to fit with the required purposes.

Keywords: Cell signalling; Drug profiling; Microarray; PCR.

L 7. Novel Targets for the treatment of GERD

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Background & Aims: Because the pathophysiology of GERD is not fully understood, presently used drugs target only one or more of the known underlying mechanisms but are not fully effective in all patients. Identifying novel targets may pave the way to develop more effective agents.

Methods: A surgical model of sub-chronic reflux esophagitis was developed. Wistar rats were pretreated for 7days with omeprazole (standard proton pump inhibitor) or STW5 (herbal preparation of established efficacy in gastro-intestinal disorders). Treatment was continued for 10days after surgery, rats were sacrificed and esophagi excised. Histological, proteomic and transcriptomic methods were applied to identify reflux induced changes and treatment responses.

Results: Protection against reflux induced inflammation was achieved by both test drugs. Both reduced macroscopic and microscopic lesions of the esophagi as well as most measured pro-inflammatory cytokines without significantly affecting NF-kB activity. Proteomic and transcriptomic analysis identified CINC1-3, MIP-1/3α, MIG, RANTES and IL-1β as highly relevant mediators in GERD. Other highly regulated genes were those of IL-6, CCL3, CCL7 and LOX-1. Many affected cyto-/chemokines were involved in the TREM-1 signaling pathway. The fatty acid receptor GPR84 was highly up-regulated in esophagitis but down-regulated by both drugs. This was confirmed by Western blot and immune-histochemical staining, showing for the first time expression of this receptor in esophageal tissue and its possible involvement in GERD.

Conclusion: STW5 and omeprazole target a broad spectrum of molecules involved in immunological and inflammatory processes, of which IL-8 (CINC1-3), TREM-1 pathway and GPR84 are proposed to be most promising novel targets for the treatment of GERD.

L 8. Developing new integrated curriculum of Pharmacology; Conceptual Learning in medical schools

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Pharmacology education considered the cornerstone in medical schools. Currently, pharmacology education in Egypt tended to follow specific approach that limited to procedural learning rather than conceptual one. Consequently, students couldn't blend the pharmacology with other sciences what interrelated to it. Indeed, the present teaching mode is away from problem-based, interactive learning and integrated model of pharmacology education. Undergraduate students may lose their interest and capabilities to deserve what they are learned plus practically studied. Accordingly, developing elective courses of pharmacology using the conceptual method for teaching and integrated learning across the different department may improve the student's capabilities and develop valuable skills.
This curriculum aims to provide precious interdisciplinary educational activities and research training through combination of core principles of biochemistry, structural biology, genetics, cellular and molecular biology within a context of physiology and disease pathophysiology, identification of drug targets and development of lead therapeutic compounds.
The integrated curriculum will declare blended of computational and modelling tactics in order to attain intellectual skills in problem solving. The curriculum will provide background for undergraduate students about new areas throughout their careers.
The course will advance a learning environment that promoted by independent thinking and individual analytical talent, while fostering the ability to work in collaborative and research environments by using active learning tools such as peer evaluation and diverse presentation formats. The new curriculum will develop the student's experiences to tackle important problems and cutting edge interactions across traditional disciplines.
In conclusion, this course may participate to modify the mind-set of the undergraduate students by incorporation the pharmacology concepts into different discipline and improve their career pathway.

Keywords: Pharmacology education, curriculum, conceptual learning, elective course.

L 9. The Egyptian Drug Market Surveillance

Dr. Osama Badary
Prof. of Clinical Pharmacy & Pharmacy Practice, Faculty of Pharmacy, Ain Shams University, Chairman of National Organization for Drug Control & Research (NODCAR) Ministry of Health & Population

By: Dr Hanan Amin Rizk, PhD
Head of Registration Unit
National Organization for Drug Control and Research (NODCAR)

The presentation includes:
Role of NODCAR
NODCAR Organization chart
NODCAR Distribution Units
Registration of Pharmaceutical Products
Conditions that require Re-registartion

Abstracts of Oral Presentations

O 1. Development of novel glycoengineering tools for the production of bioconjugate vaccines and humanized glycoproteins.

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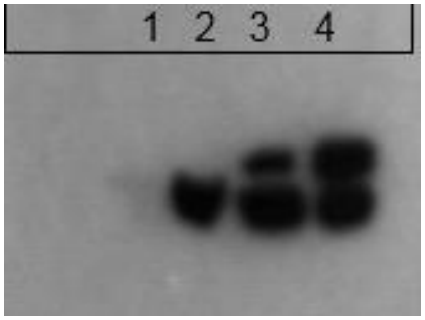
Background: Glycoengineering serves as a promising tool for the designing, tailoring and production of glycoconjugates. Protein glycan coupling can be done within an *E. coli* host through the transformation of three plasmids. The first coding for polysaccharide biosynthesis, the second coding for the acceptor protein and the third coding for the oligosaccharyltransferase (OSTase). This method suffers the complications of needing to select compatible origins of replications and antibiotic markers. At times, glycoconjugates can be produced in the natural host itself by transferring plasmids coding for the OSTase and the carrier protein, however, some organisms cannot maintain even these plasmids.

Aim of the study: We present a novel glycoengineering tool to overcome the above mentioned problems by introducing either the OSTase or the carrier protein into the chromosomal DNA of a chosen host.

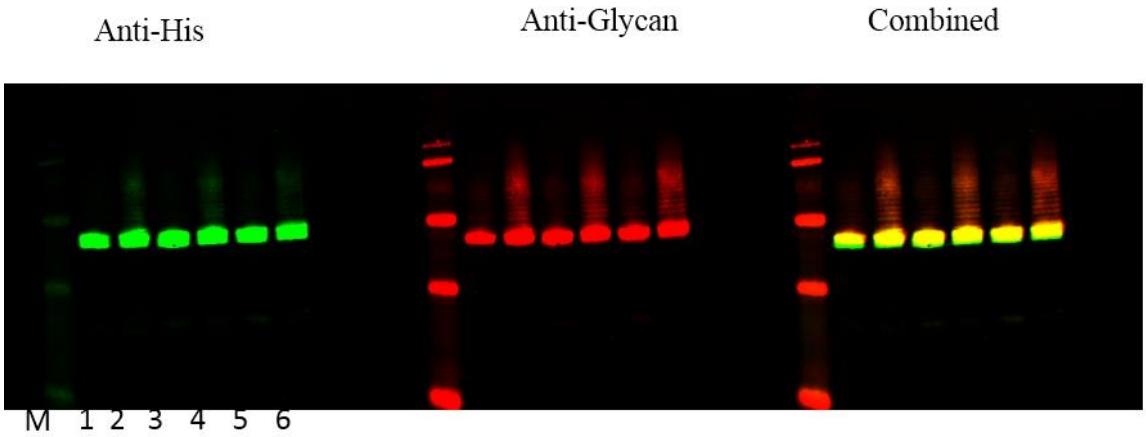
Methods: Insertional mutagenesis:
OSTase was transferred into the chromosome of *E.coli* W3110, *E.coli* O9:K30, *Citrobacter freundii* and *Burkholderia thialandensis* through overnight conjugation with the donor strain.
Affinity Chromatography purification:
Overnight cultures of the bacterial strains were subcultured in LB broth with the appropriate antibiotics. Protein expression was induced by IPTG at $O.D_{600}$ 0.4 and incubated overnight at 37^{o}c with shaking. Cells were harvested and lysed, whole cell lysate was incubated for an hour with Ni-NTA agarose (Qiagen) followed by 4 washes and eluted in 0.5 ml 4 times. Elutes were concentrated via Amicon with 30 kDa cut off, stored at 4^{o}c for further analysis.
Western blot:
Protein samples were run on 10% Bis-Tris SDS-PAGE for 1 hour. Transferred to nitrocellulose membrane (GE healthcare, UK), blocked for an hour in 2% skimmed milk followed by 3 washes, 5 minutes in PBS-0.1% Tween each and incubated with 1ry anti-his antibody (abcam, UK) for an hour. The membrane was then washed 3 times, 5 minutes each with PBS-0.1% Tween and incubated with the 2ndy antibody for 30 minutes followed by 2 washes, 5 minutes each in PBS-0.1% Tween and final wash in PBS only. Membranes was scanned using the LiCor Odyessey at wavelength 700 nm and 800 nm.

Results:



Anti- His Western blot, lane 1, *E.coli* O9:K30 wildtype ; lane 2, *E.coli* O9:K30 carrying pFel expressing Cj0114; lane 3, *E.coli* O9:K30 chormosomal insertion of the OSTASe and

carrying pFel expressing Cj0114 (colony 1) ; lane 4, , *E.coli* O9:K30 pJAN25 expressing OSTase and carrying pFel expressing Cj0114 (colony 2)



Anti –His Western blot of purified AcrA from *E.coli* W3110 carrying pGAB2
Lane 1,3,5, biological replicates pGVXN114 pglB , pMH5 expressing AcrA and pGAB2; lane 2,4,6, biological replicates chromosomal OSTase , pMH5 expressing AcrA and pGAB2

Conclusion: These novel glycoengineering tools prove that we can transfer OTases genes into the chromosomal DNA of a recipient organism efficiently. These tools could be useful in future glycoconjugate vaccines production. The tools also shows a greater yield of glycoprotein production compared to the conventional method. Herein, we present a versatile method that can be easily tailored for the development of bioconjugate vaccines and glycoproteins.

Keywords: Vaccine Development, Glycoengineering, Glycoproteins

O 2. Epigenetic effects of reactive oxygen species (ROS) in first trimester trophoblasts: impact on miRNA profile

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Background: Preeclampsia (PE) is a major contributor to maternal and neonatal mortality and morbidity. It is a pregnancy-specific syndrome characterized by new-onset hypertension (blood pressure ≥140/90 mm Hg in previously normotensive women after the 20th week of pregnancy) and proteinuria (300 mg/24 h urine collection). The exact cause of PE is still unclear. However, oxidative stress seems to play a significant role as it can trigger widespread endothelial dysfunction and vasoconstriction. Hydrogen peroxide (H2O2) is a terminal oxidative stress metabolite and previous reports indicated that the circulating levels of H2O2 are increased in women with PE. Furthermore, the levels of H2O2 are also higher in placental tissues from preeclamptic pregnancies. MicroRNA (miRNA), a class of small and non-coding RNAs that transcriptionally or post-transcriptionally modulate the expression of their target genes, has been implicated as critical regulatory molecules in many diseases. A multitude of studies indicated differential alterations in miRNA profile in placentas from women suffering PE versus normotensive pregnancies.

Aim of the study: The current work aimed at investigating the effect of increased ROS on miRNA profile in placental trophoblasts.

Methods: First trimester trophoblast cells were exposed to H2O2 level equivalent to a fraction of its half-maximal inhibitory concentration (IC50) at 4 hours and then determining the effect on the expression of 1008 miRNAs using the human miRNome PCR array (Qiagen).

Results: A panel of miRNAs was found to be differentially altered in the H2O2 challenged cells versus untreated controls. TAM analysis indicated that these miRNAs belong to several pathways that affect critical cellular processes including apoptosis, cell cycle progession, angiogenesis, inflammation, and oncogenesis.

Conclusion: Short-term exposure of villous first trimester trophoblasts to H2O2 resulted in significant alterations in miRNA expression profile.

Key words: Oxidative stress, trophoblasts, epigenetics, miRNA, mRNA

Abstracts of Poster Presentations

P 1. Possible Role of Resveratrol Targeting Estradiol and Neprilysin Pathways in Lipopolysacharide induced Alzheimer's Disease Model

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Background: Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative brain disease that slowly destroys memory and thinking skills. It is the most common cause of dementia among older people. One of the most important hallmarks of AD is the presence of amyloid beta (Aβ) peptide in the brain that suggests being the primary trigger for neuronal loss. One of the most important amyloid degrading enzymes is neprilysin (NEP), which plays a major role in degrading Aβ, and mainly affected by estrogen.

Aim: The aim of the present study is to investigate the possible role of resveratrol (RSV) (a phytoestrogen) in lipopolysaccharide model of AD and it's implication role in regulating the estradiol and neprilysin pathways.

Methods: Mice were divided into four groups: Control group (0.9% saline), LPS group (0.8 mg/kg i.p once) , Treatment group with RSV (mice were once injected with LPS then after 30 minutes given a dose of {4 mg/kg} RSV for 7 days) and RSV group only (mice received 4 mg/kg i.p for 7 days only). After 7 days mice were subjected to different behavioral tests using Y-maze, object recognition test and open field tests. Estradiol and NEP level were measured using ELISA kits.

Results: LPS significantly reduced mean alternation percentage, discrimination ratio object recognition test and locomotor activity. LPS significantly decreased estradiol and NEP level. On the other hand, RSV significantly improved these LPS induced cognitive functions and locomotor activity impairment. RSV (4 mg/kg) significantly increased estradiol and NEP levels. Moreover, administration of RSV (4 mg/kg for 7 days alone) significantly improved cognitive functions, locomotor activity and significantly increased estradiol and NEP level in healthy mice (non LPS treated mice).

Conclusion: The present study demonstrates the beneficial *in vivo* effects of RSV by improving learning, memory and locomotor activity in a model of chronic neuroinflammation. These effects were accompanied by significant increase in estradiol and NEP level, which might suggest RSV as a potential promising treatment for AD.

P 2. Folic acid and vitamin B complex improves quality of life in hepatitis C infected patients treated with Peginterferon and Ribavirin: A randomized controlled trial

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Background/Aims: Pegylated-interferon α-2a and ribavirin (PIFN/RBV), the current standard treatment for hepatitis C virus (HCV) infection in Egypt, is frequently associated with hematological adverse effects, leading to high treatment discontinuation rates. The objective of the present study is to explore the effectiveness of intervening with folic acid (F) and/or vitamin B complex (B) compared with placebo (C) in HCV-treatment Egyptian patients for the management of treatment-induced deterioration of health related quality of life (HRQOL) as well as hematological parameter.

Methods: In a randomized controlled trial, one hundred and sixty subjects were randomly assigned to receive PIFN/RBV in addition to BF, B, F, or C. Blood samples were collected at different time points during 48 weeks and at 12 and 24 weeks post treatment for complete blood count and for HCV RNA real time PCR. Short form SF 36V2 questionnaire were used to assess HRQOL at various time during and post treatment.

Results: Egyptian HCV patients treated with PIFN/RBV showed deterioration of HRQOL which were correlated with deterioration in the measured hematological parameter. Supplementation with vitamin B complex plus folic acid significantly ($P<0.001$) decreased the deterioration observed in physical and mental health as well as complete blood count. Supplementation with either vitamin B complex or folic acid were also effective but with lower potency than their combination.

Conclusion: BF supplementation can reduce adverse effects of PIFN/RBV therapy in chronic hepatitis C patients, which may improve patients' HRQOL and their adherence to combination antiviral therapy.

Keywords: Hepatitis C virus, Quality of life, Side effects, Folic acid, Vitamin B complex, Peginterferon, Ribavirin

P 3. Transplanted Wharton's Jelly-Derived MSCs Combined with PZQ Treatment Ameliorate *S. mansoni*-Induced Liver Fibrosis in Mice

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Background: One of the most serious consequences of *Schistosoma* (*S.*) *mansoni* infection is hepatic schistosomiasis or periportal fibrosis. Treatment with praziquantel (PZQ) remains the mainstay of schistosomiasis control. Stem cells and their possible use in cell therapy have drawn much attention recently, due to their potential for self-renewal and differentiation.

Aim of the study: The present study aimed to investigate the feasibility of liver damage repair using Wharton's jelly-derived mesenchymal stem cells (WJMSCs; the major umbilical cord stem cell population) combined with PZQ to treat *S. mansoni*-induced liver fibrosis at both acute and chronic stages by monitoring transplanted stem cell differentiation into hepatocyte-like cells and assessing *S. mansoni*-induced liver fibrosis.

Methods: *S. mansoni*-infected mice (60±10 cercariae/mouse, s.c.) received early (8th week post infection) and late (16th week post infection) intra-hepatic injection of WJMSCs ($1.5x10^6$ cells/mouse), alone or combined with oral PZQ (500 mg/kg/day, for 2 days, seven weeks post infection), to investigate the efficacy on both acute and chronic stages of liver fibrosis, respectively. At the 10th month post infection, histopathological, morphometric, and immunohistochemical analysis for human-specific alpha fetoprotein, alpha smooth muscle actin, Hep par-1, cytokeratin-18, vimentin, and β2-globulin, were performed. Relative mRNA expression of albumin, alpha fetoprotein, alpha smooth muscle actin, collagen I, and interleukin 13 was measured by real time reverse transcription polymerase chain reaction (RT-PCR). Gelatin zymographic analysis for matrix metalloproteinase (MMP)-2 and -9 was also performed.

Results: Histopathological and morphometric findings showed a regression in fibrosis in WJMSCs-treated groups and better results were obtained when PZQ was combined to stem cell therapy. Immunohistochemical and RT-PCR findings showed positive expression for hepatocyte-specific markers in transplanted groups and an amelioration of fibrosis-related markers. Differentiation of transplanted WJMSCs into hepatocyte-like cells was found to be enhanced in transplanted groups which received PZQ. Gelatin zymography results showed an elevation of the enzymatic activity of MMP-2 and -9 in WJMSCs-treated groups. Meanwhile, PZQ caused a reduction in the activity of both enzymes. Combined treatment, however, caused no or little change.

Conclusion: PZQ enhanced the differentiation potential of transplanted WJMSCs into functioning hepatocyte-like cells in the livers of *S. mansoni*-infected mice contributing to partial repair of liver fibrosis at both acute and chronic stages.

Keywords: Liver fibrosis; *S. mansoni*; Wharton's jelly; mesenchymal stem cells; praziquantel

P 4. Modulation of resistance to sorafenib in human hepatocellular carcinoma cell line

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Background: Sorafenib is the only therapeutic agent approved for the treatment of advanced hepatocellular carcinoma (HCC); however, survival rates were modest. Indole-3-carbinol (I3C) is a promising chemopreventive agent with multiple anti-tumor activities.

Aim of the study: The present study investigated the possible modulatory effects of I3C on the resistance to sorafenib in the human HCC cell line, HepG2, as well as the possible mechanisms underlying this modulation.

Methods: HepG2 cells were treated with sorafenib and I3C, alone and in combination. From fitted survival curves, the concentration of I3C that inhibited 5% of the cells was selected to be used in combination with sorafenib. The effect of the combination on the expression of apoptotic and signal transduction biomarkers was assessed. Moreover, the cell cycle was investigated using flowcytometry.

Results: I3C significantly enhanced sorafenib cytotoxicity in HepG2 cells. The combination induced the apoptotic machinery as demonstrated by increased expression of active caspase-3 and active caspase-8. The expression of phosphorylated ERK was significantly reduced. I3C caused the accumulation of HepG2 cells in the G0/G1 phase.

Conclusion: I3C chemosensitized the HepG2 cell line to sorafenib. This modulatory effect could be partially attributed to the up-regulation of caspase-3 and caspase-8 activity as well as the down-regulation of phosphorylated ERK. Nevertheless, further studies are needed to explain the efficacy and safety profile of such combination.

Keywords: Sorafenib; Indole-3-carbinol; Hepatocellular carcinoma; Apoptosis

P 5. In vitro studies on the potential hepatoprotective and antioxidant effects of *Dietes bicolor* leaf extract

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Background: Over the past two centuries, natural products have played an invaluable role in drug discovery contributing enormously to the development of therapeutic agents currently used in modern medicine. *Dietes bicolor (D. bicolor)*, commonly known as Yellow Wild Iris, Peacock Flower or Butterfly Iris is a rhizomatous perennial herb belonging to family Iridaceae. The phytochemical and pharmacological properties of this genus have never been reported.

Aim: The current study was designed to investigate the potential hepatoprotective activity of *D. bicolor* leaf extract.

Methodology: The aqueous methanolic extract of *D. bicolor leaves was subjected to* sequential liquid-liquid extraction *using n-hexane, dichloromethane and n-butanol*. The total leaf extract and its fractions were examined for possible hepatoprotective activity. This was achieved *in vitro* using HepG2 cell line challenged with carbon tetrachloride (CCl-4) as a model. The biologically active fraction was subjected to further phytochemical analysis utilizing several chromatographic techniques. The major compound was isolated and its structure was elucidated using various spectroscopic techniques.

Results: *D. bicolor* leaf extract and fractions exhibited a promising hepatoprotective activity against CCl-4-induced damage in HepG2 cells as evidenced by reduced leakage of alanine transaminase (ALT) and aspartate transaminase (AST) in the culture medium. Furthermore, the extract exhibited significant increase in reduced glutathione (GSH) levels as well as superoxide dismutase (SOD) activity. A flavone C-glycoside was isolated from the biologically active fraction which may contribute to the observed biological activity.

Conclusion: *D. bicolor* exhibited a promising cytoprotective and antioxidant activity in vitro. The flavonoid content of *D. bicolor* might at least partly contribute to the possible biological effects of the extract.

Keywords:
Dietes bicolor; Iridaceae; hepatoprotection; GSH; SOD

P 6. Neuroprotective Potential of Pregabalin through Anti-oxidant, Anti-inflammatory and Anti-apoptotic Mechanisms against Transient Ischemic/Reperfusion Injury in Diabetic Rats

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Background: stroke and diabetes mellitus are two separate conditions which share multiple common threads. Pregabalin is clinically considered as the gold standard for the treatment of painful diabetic neuropathy in human being.

Aim of the study: interest was raised to investigate the neuroprotective effects of pregabalin against transient ischemia/reperfusion (I/R) injury in diabetic rats targeting mainly the oxidative-inflammatory-apoptotic cascade which has been previously addressed as co-conspirators in this insult.

Methods: forebrain ischemia was induced in streptozotocin-diabetic rats by bicommon carotid occlusion for 15 min followed by 1h reperfusion. Pregabalin (10 mg/kg; p.o) was administered daily for 2 weeks prior to I/R.

Results: the drug alleviated hippocampal injury inflicted by diabetes and/or I/R injury where it suppressed nuclear factor kappa NF-κB, and consequently the downstream inflammatory cytokines tumor necrosis factor-α and interleukin-6. In parallel, the anti-inflammatory cytokine interleukin-10 was elevated. Antioxidant potential of pregabalin was depicted, where it reduced neutrophil infiltration, lipid peroxides, nitric oxide associated with replenished reduced glutathione. Decline of excitatory amino acid glutamate content is a main finding which is probably mediated by the NF□B signaling pathway as well as improved oxidant status. Pregabalin exerted an anti-apoptotic effect as reflected by the reduction of the cytosolic cytochrome c and the key downstream executioner caspase-3.

Conclusion: pregabalin is gifted with neuroprotective properties which are probably mediated by its antioxidant, anti-inflammatory, and anti-apoptotic mechanisms hence may provide a successful agent for the management of ischemic stroke.

Keywords: Diabetes; Ischemia/reperfusion; Pregabalin; Nuclear factor kappa B; Caspase 3; Hippocampus.

P 7. A novel role for ursodeoxycholic acid in inhibiting rotenone induced apoptotic cascade *via* preservation of mitochondrial function

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Background: The recent emergence of ursodeoxycholic acid (UDCA) as a contender in modifying neurotoxicity in human dopaminergic cells as well as its recognized antiapoptotic and anti-inflammatory potentials in various hepatic pathologies raised impetus in investigating its neuroprotective capacity against Parkinson's disease (PD).

Aim of the study: This study was conducted to examine the antiparkinsonian effect of UDCA in rotenone-induced PD model in rats.

Methods: Rats received 11 injections of rotenone every other day (1.5 mg/kg, s.c.) to induce PD-like symptoms; meanwhile, UDCA (50 mg/kg, i.p.) was administered daily for 3 weeks. 24 h after the last injection of rotenone, rats were screened for motor impairment; they were thereafter, euthanized and striatal tissues were used for estimation of dopamine, ATP along with inflammatory and apoptotic biomarkers. Moreover, transmission electron microscopic examination of striata was performed.

Results: UDCA improved motor performance in open field test and halted the decline in the striatal dopamine content. Meanwhile, it improved mitochondrial function as verified by elevation of ATP associated with preservation of mitochondrial integrity as portrayed in the electron microscope examination. In addition, through its anti-inflammatory potential, UDCA reduced rotenone-induced nuclear factor-κB expression and tumor necrosis factor-α level. Furthermore, UDCA amended alterations in Bax, Bcl-2, and reduced the activities of caspases- 8, 9, 3 indicating that it suppressed rotenone-induced apoptosis *via* modulating both intrinsic and extrinsic pathways.

Conclusion: UDCA can be introduced as a novel approach for the management of PD *via* antiapoptotic and anti-inflammatory mechanisms. These effects are probably linked to dopamine synthesis and mitochondrial regulation.

Keywords: Ursodeoxycholic acid; Rotenone; Caspases; Dopamine; Nuclear factor-κB; ATP

P 8. Thymoquinone protects against myocardial ischemia-reperfusion injury *via* modulation of oxidant generation and nuclear factor-kappaB-mediated responses

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Background: Ischemia-reperfusion injury (IRI) remains among the most serious problems in cardiac surgery. Understanding the mechanisms of natural compounds in modulating disease has moved to the forefront of cardiovascular research. Thymoquinone (TQ), a constituent of the volatile oil derived from Nigella sativa seeds, possesses antioxidant, anti-inflammatory, and vasodilating properties. TQ has demonstrated promising effects against IRI of different organs; however, the mechanism of TQ action on myocardial IRI has not been delineated.

Aim of the study: The aim of the present study was to investigate the effects and possible underlying mechanisms of TQ on myocardial IRI.

Methods: Rat hearts were either subjected to 30 min of global ischemia followed by 120 min of reperfusion using a Langendorff system, or to 30 min of left anterior descending coronary artery ligation followed by 24 h of reperfusion. TQ was infused *ex-vivo* for 10 min either pre- or post-ischemia or IP-injected for ten days prior to the surgery.

Results: TQ significantly reduced reactive oxygen species (ROS) generation, infarct size and apoptosis, and markedly enhanced coronary flow and ventricular function of the ischemic hearts. TQ attenuated the IR-induced up-regulation of SAPK/JNK, myocardial nuclear factor (NF)-kappaB, TNF-α, and P38-MAPK expression and increased the Bcl-2/Bax ratio.

Conclusion: The data indicate that TQ inhibited ROS generation-induced NF-kB which led to inhibition of pro-inflammatory cytokines and apoptosis, protecting the heart against IR injury. This study presents a new molecular mechanism of action and efficacy of TQ with promise as a natural compound in the management of myocardial IRI.

Keywords: Ischemia/reperfusion, oxidative stress, apoptosis and NF-kB

P 9. Thymol and Carvacrol prevent cisplatin-induced nephrotoxicity by abrogation of oxidative stress, inflammation and apoptosis in rats.

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Background: Chemotherapy with cisplatin (CP) is accompanied with nephrotoxicity.

Aim of the study: The current study aimed to evaluate thymol and/or carvacrol (CAR) as antioxidant, anti-inflammatory and anti-apoptotic agent against CP-induced-renal toxicity.

Methods: Seventy-two male adult Swiss albino rats were allocated into nine groups (eight rats / each group). The animals in groups 1-5 received saline (as control), corn oil (as solvent), thymol (20 mg/kg, p.o.), CAR (15 mg/kg, p.o.) and combination of thymol & CAR, respectively for 21 days. The animals in group 6 received CP in a single dose of 6 mg/kg, i.p.. Groups 7-9 were treated with thymol (20 mg/kg, p.o.), CAR (15 mg/kg, p.o.) and combination of thymol & CAR, respectively for 14 days before CP injection and for 7 days after CP administration. Finally, the animals were sacrificed at day 7 from CP injection and blood samples were collected. Kidneys were removed, weighed and histopathological investigation was done.

Results: A single dose of CP produced significant increases in serum urea, creatinine and tumor necrosis factor alpha levels. It also increased kidney contents of malondialdehyde and caspase-3 activity with significant reduction in serum albumin, kidney content of reduced glutathione as well as catalase and superoxide dismutase activity as compared to that of the control group. In contrast, administration of thymol and / or CAR restored the kidney function and the oxidative stress parameters. The histopathological findings demonstrated that administration of CP induced various degenerative changes in kidney cells. In contrast, pretreatment with thymol and / or CAR obviously mitigated the histopathological changes induced by CP.

Conclusion: Thymol was more effective as a nephroprotective agent than CAR. Moreover, combination of thymol and CAR had a synergistic nephroprotective effect that might be attributed to antioxidant, anti-inflammatory and anti-apoptotic activities.

Keywords: Cisplatin; Nephrotoxicity; Thymol; Carvacrol; Anti-oxidant; Anti-inflammatory; Anti-apoptotic.

P 10. Protective effects of red wine polyphenols and grape-seed proanthocyanidin extract on acetaminophen-induced liver injury

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Background: Severe liver injury as a result of overdose or chronic use of acetaminophen remains a significant clinical problem, accounting for 40% of acute liver failure cases.

Aim of the study: The present study was designed to examine the potential protective effects of red wine polyphenols (RWPs) and grape seed proanthocyanidin extract (GSPE) against acetaminophen-induced hepatotoxicity.

Methods: Sixty-four male adult rats were divided into eight groups (eight rats / each group). The animals in groups 1-4 received saline + 10% cremophor EL (as control), silymarin (100 mg/kg, p.o.), RWPs (40 mg/kg, p.o.) and GSPE (100 mg/kg, p.o.), respectively for 15 days. The animals in group 5 received acetaminophen in a single dose of 800 mg/kg, i.p.. Groups 6-8 were treated with silymarin, RWPs and GSPE, respectively for 15 days before acetaminophen administration. Silymarin was used as a standard reference hepatoprotective agent. Finally, the animals were sacrificed 24 h after acetaminophen administration and blood samples were collected. Livers were removed, weighed and histopathological investigation was done.

Results: Administration of acetaminophen to rats, caused a significant increase in serum ALT, AST, alkaline phosphatase (ALP), bilirubin, total cholesterol (TC), triglycerides(TG), tumor necrosis factor alpha (TNF-α) and liver contents of malondialdehyde (MDA) and nitric oxide (NO) with significant decrease in serum albumin, HDL cholesterol, reduced glutathione (GSH) and hepatic activities of catalase (CAT), superoxide dismutase (SOD) and caspase-3 in liver tissue as compared with the control group. On the other hand, administration of each of GSPE, RWPs and silymarin for 15 consecutive days significantly ameliorated the liver injury; observations that were confirmed by histopathological examination.

Conclusion: In summary, RWPs and GSPE show protective effects against acetaminophen hepatotoxicity; most probably through their antioxidant, anti-inflammatory and anti-apoptotic effects.

Keywords: Acetaminophen; Hepatotoxicity; Red wine polyphenols; Grape seed proanthocyanidin extract.

P 11. Effect of Green tea and EGCG on Liver *: in vivo* and *in vitro* Study

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Background: Epigallocatechin 3-gallate (EGCG), the principal component of green tea (GT), is well known for its beneficial effects. However, high doses of EGCG may cause liver toxicity.

Aim of the study: studied the effect of GT and EGCG in vivo and in vitro. In the in vivo study, we examined the potential hepatotoxicity of high doses of EGCG under febrile conditions induced by lipopolysaccharide (LPS).

Methods: In the *in vivo* study, EGCG was given intra gastric (IG) or intraperitoneal (IP), while LPS was given IP to mice (ND4). Plasma ALT levels were determined and liver histopathology was performed.
In the *in vitro* study, HepG2 cells were treated with different concentrations of GT and EGCG with and without pre-sensitization with LPS**.** TGFβ1, RXRα and cell viability were assessed using immunofluorescence imaging and analysis.

Results: *In vivo* results suggested that administration of high doses of EGCG can lead to mild liver toxicity. However, under febrile conditions (induced by LPS), this liver toxicity could become severe. *In vitro* results suggested that at lower concentrations of GT or EGCG, cell viability was increased regardless of pre-sensitization with LPS. However, at higher concentrations, both GT and EGCG decreased cell viability, especially, in cells that were presensitized with LPS. Furthermore, TGFß1 and RXRα were also over-expressed in HepG2 cells that were pre-sensitized with LPS and treated with high concentration of EGCG.

Conclusion: The *in vitro* results lend support to the *in vivo* results indicating that EGCG probably acts as an anti-oxidant at lower doses but at higher doses, specially under the influence of inflammatory conditions, it may cause hepatotoxicity possibly due to its pro-oxidant activity.

Keywords: Green tea, EGCG, LPS, Immunofluorescence, hepatotoxicity, Inflammation.

P 12. Cigarette smoke extract causes endothelial nitric oxide synthase dysfunction through stimulation of ubiquitin proteasome system

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Background: Cigarette smoking (CS) is a major risk factor for endothelial dysfunction (ED), a prognostic predictor for the risk of future cardiovascular events. Endothelial nitric oxide synthase (eNOS) dysfunction has been linked to CS-induced ED; however, the exact mechanism is not fully understood.

Aim of the study:
To investigate the possible role of the ubiquitin proteasome system (UPS) in CS- induced eNOS dysfunction and and consequently, ED.

Methods:
HPLC analysis of BH4: BAECs were exposed to various concentration of CSE for 4 hours with or without pre-incubation with 100 nM MG132 for 1 hour. The total cell lysate was filtered. Then 20 µl were injected to The HPLC
Western Blot Analysis: Whole cellular protein extracts were obtained, separated in a reducing graded polyacrylamide gel and blotted against different antibodies
Superoxide Detection: BAEC were exposed to CSE, with or without L-NAME or SOD_m, for 20 minutes, stained with DHE. DAPI was used as a counter stain and sections were imaged with confocal microscopy.
EPR spectroscopy: NO generated from BAECs were trapped using Fe-MGD spin trap followed by NO measurement using a Bruker (EMXplus) EPR spectrometer.

Results: Exposure of bovine aortic endothelial cells (BAECs) to cigarette smoke extract (CSE) resulted in a concentration-dependent decrease in nitric oxide (NO) production, accompanied by an increase in superoxide generation and formation of 4-hydroxy-2-nonenal protein adducts. CSE depleted tetrahydrobiopterin (BH_4), total biopterin, and decreased the expression of eNOS and guanosine triphosphate cyclohydrolase-1 (GTPCH-1). More importantly, exposure of BAECs to CSE led to accumulation of ubiqutinylated protein and increased the 26S proteasomal activity in a concentration-and time-dependent manner. Pre-treatment of BAECs with MG132, an inhibitor of 26S proteasome, restored the levels of eNOS, BH_4, GTPCH-1, and enhanced NO production in BAECs following CS exposure.

Conclusion: Our data reveal that CS-induced stimulation of the UPS resulted in degradation of eNOS and GTPCH-1 that led to eNOS dysfunction and uncoupling. Thus, controlled interference with the UPS pathway could be a novel modality in the prevention of CS-induced ED.

Keywords: Cigarette smoking, Endothelial dysfunction, Ubiquitin proteasome system.

P 13. Effect of dexmedetomidine and cold stress on chronic constriction injury (CCI) of the sciatic nerve as a model of neuropathic pain in rats

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Background: The sympathetic nervous system plays an essential role in the pathophysiologic mechanisms of neuropathic pain and cold stress. Dexmedetomidine (DEX), a recent α2 adrenoceptor agonist achieves an effective antinociception and sedative effect in the intensive care unit.

Aim of the study: The present study was designed to investigate the effect of DEX or repeated cold stress (RCS) alone and in combination with chronic constriction injury (CCI) of the sciatic nerve as a model of neuropathic pain in rats.

Methods: Following unilateral ligation of the left sciatic nerve, the effect of intraperitoneal (i.p.) dexmedetomidine (5μg/kg) and RCS on blood pressure, heart rate, and mechanical hyperalgesia were studied.

Results: The sham-operated rats and un-operated hind paw (right paw) press normally on the floor reproduced by a weighted pain score of 0. Behavioral and mechanical tests confirmed the development of neuropathic pain after CCI. Dexmedetomidine did not produce any sedation/motor impairment ($P > 0.05$). Repeated cold stress increased the systolic blood pressure and dexmedetomidine decreased the systolic (SBP), diastolic (DBP) and mean blood pressure (MBP). Repeated cold stress also induces significant mechanical hyperalgesia. Chronic constriction injury of the sciatic nerve caused a significant increase in SBP, DBP and MBP compared to sham group values. Administration of Dex and exposure to RCS with CCI demonstrated a significant decrease in heart rate.

Conclusion: Chronic constriction injury may be a useful model to study the mechanisms linking stress and pain and be a useful approach for uncovering new therapeutic targets for the treatment of pain and stress-related disorders.

Keywords: Allodynia, chronic constriction injury, cold stress, dexmedetomidine, hyperalgesia, rat.

P 14. Effects of Glue Inhalation on Dopamine and Serotonin Levels in rat Brain

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Background: Inhalant abuse is still a significant worldwide health problem among both young and adolescent segments of societies. In Egypt, kolla, a kind of glue, is commonly abused by street children. Previous chemical analysis showed that the main constituent of kolla is the volatile solvent toluene, therefore it was used as a standard solvent inhalant in this study.

Aim of the study: This work was devoted to evaluate the effects of acute and subchronic inhalation of kolla on few brain transmitters' levels. Besides, the changes in some liver and kidney function parameters were studied in rats.

Methods: The effect of single (30 minutes exposure) as well as subchronic inhalation (30 min/day for 10 days) for two concentrations of kolla and toleune were tested. Dopamine and serotonin levels were assigned spectrofluorometrically. Serum alanine aminotransferase (ALT/GPT), aspartate aminotransferase (AST/GOT) and serum alkaline phosphatase (ALP) levels were studied using assay kits. Moreover, serum urea and creatinine levels were also measured, using assay kits as well.

Results: Single as well as repeated daily inhalation of the two concentrations of kolla and toleune increased the level of dopamine in rat's brain. Brain serotonin level increased following single inhalation of the high concentrations of both susbstances of interest. Serotonin level was also increased after repeated daily inhalation of all of the four tested concentrations. Liver and kidney function tests showed an increase in serum liver enzymes' levels as well as in both serum urea and creatinine levels following single and repeated daily inhalation.

Conclusion: glue inhalation leads to remarkable changes in some brain neurotransmitters and deleterious effects on liver and kidneys.

Keywords: Kolla, glue, inhalant abuse, dopamine and serotonin

P 15. Rosmarinic acid alleviates cisplatin-induced nephrotoxicity in mice without compromising its anti-tumour activity

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Background: Cisplatin is an effective anticancer drug; however, its clinical use is usually associated with nephrotoxicity as a dose-limiting side effect.

Aim of the study: The aim of this study was to explore the potential nephroprotective effect of rosmarinic acid; a natural phenolic acid found in Lamiaceae family, and the possible mechanisms underlying this protection *in vivo*.

Methods & Results: Pre-treatment with rosmarinic acid (200 mg/kg, p.o., for 7 days) significantly ($p<0.05$) mitigated cisplatin-induced elevation of blood urea nitrogen and serum creatinine levels. Moreover, the elevated malondialdehyde (MDA) and tumor necrosis factor-alpha (TNF-α) in kidney tissues were significantly ($p<0.05$) reversed. Additionally, rosmarinic acid significantly abrogated cisplatin-induced reduction in reduced glutathione level (GSH). The kidney tissues histopathological examination emphasized the obtained results. On the other hand, administration of rosmarinic acid(100, 200 mg/kg, p.o., for 14 days) did not modulate the antitumor activity of cisplatin as evidenced by the percent survival and mean survival time of EAC-bearing mice.

Conclusion: In conclusion, rosmarinic acid ameliorates cisplatin-induced renal injury in mice, an action which could be attributed to inhibition of oxidative stress and inflammation produced by the former.

Keywords: Cisplatin, rosmarinic acid, nephrotoxicity, antitumor, malondialdehyde, tumor necrosis factor- alpha

P 16. Attenuating Effects of Coenzyme Q10 and Amlodipine in Ulcerative Colitis Model in Rats.

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Background: Ulcerative colitis is a chronic inflammatory bowel disease driven through altered immune responses with production of proinflammatory cytokines.

Aim of the study: The aim of the present study was to evaluate the possible protective effects of CoQ10, amlodipine and their combination on ulcerative colitis.

Methods: Colitis was induced in rats by intracolonic injection of 2 ml 3% acetic acid. CoQ10 (10 mg/kg), amlodipine (3 mg/kg) and their combination were administered for 8 consecutive days before induction of colitis. The colonic mucosal injury was assessed by macroscopic scoring and histological examination. Moreover colon tissue superoxide dismutase (SOD) activity, malondialdehyde (MDA), adenosine-5'-triphosphate (ATP), tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-10 (IL-10), myeloperoxidase (MPO), prostaglandin E2 (PGE2) and heat shock protein (HSP-70) levels were assessed.

Results: All parameters were altered by acetic acid-induced colitis compared to normal control group. However, they were improved by pre-treatment with either CoQ10 or amlodipine revealing a decrease in the colon peroxidative and inflammatory damage. Co-administration of CoQ10 and amlodipine was found to be more effective in all parameters, acting in an additive manner in most of them.

Conclusion: Our results indicate the protective effect of CoQ10, amlodipine and their combination against acetic acid-induced colitis in rats, via their antioxidant, anti-inflammatory and energy restoration properties.

Keywords: Ulcerative colitis, CoQ10, Amlodipine, Inflammation, Oxidative stress.

P 17. Pomegranate Extract Protects against Cerebral Ischemia/Reperfusion Injury and Preserves Brain DNA Integrity in Rats *via* antioxidant, anti-inflammatory, anti-apoptotic and ATP-replenishing effects

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Background: Stroke is a primary cause of disability and mortality in many countries. The brain is constantly demanding energy supply to maintain its high metabolic requirements. Therefore, interruptions to blood flow causes ischemia and infarction of brain tissues with subsequent neuronal damage and brain dysfunction. On the other hand, pomegranate extract showed antioxidant and anti-inflammatory activities in various *in-vitro* and *in-vivo* experimental models. Notably, pomegranate extract contains active compounds that are well tolerated and may be consumed safely in high amounts. Therefore, many investigators assume that flavonoid-enriched extracts from natural sources should be given strong consideration as novel therapies for the treatment of neurodegenerative disorders.

Aim of the study: This study was performed to investigate whether pomegranate extract could offer a significant protection against cerebral ischemia/reperfusion injury in rats, and to elucidate the underlying mechanisms.

Methods: To achieve the aim of the current study, rats were orally administered two dose levels of pomegranate extract (250, 500 mg/kg) before exposure to cerebral I/R. Brain homogenate was used to determine the levels and/or activities of MDA, NO, SOD, GPX, GRD, NF-ķB, TNF-α, caspase-3, IL-10, ATP, and comet assay.

Results: The results of the present study showed that pre-administration of a standardized pomegranate extract (250, 500 mg/kg, orally) to rats can offer a significant dose-dependent neuroprotective activity against cerebral ischemia/reperfusion (I/R). The current data shows reduction in brain malondialdehyde (MDA), nitric oxide (NO), and enhancement of superoxide dismutase (SOD), glutathione peroxidase (GPX), and glutathione reductase (GRD) activities, in rats treated with pomegranate extract before cerebral I/R. Moreover, pomegranate extract suppressed cerebral I/R-induced inflammation, and apoptosis as evidenced by decreased brain levels of NF-ķB, TNF-α, caspase-3 and increased levels of the anti-inflammatory cytokine IL-10. Moreover pomegranate extract administration preserved cerebral ATP production in rats with I/R. Interestingly, the comet assay showed less brain DNA damage in I/R exposed rats pre-treated with pomegranate extract.

Conclusion: The present study revealed that pomegranate extract administration can protect against ischemia/reperfusion-induced brain injury and preserve cerebral DNA integrity *via* antioxidant, anti-inflammatory, anti-apoptotic and ATP-replenishing effects.

Keywords: Pomegranate extract; cerebral ischemia/reperfusion**;** MDA, NO, SOD, GPX, GRD, NF-ķB, TNF-α, caspase-3, IL-10, ATP, and comet assay.

P 18. Ursodeoxycholic acid dose-dependently attenuated thioacetamide-induced liver fibrosis in rats.

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Background: Liver diseases are associated with significant morbidity and mortality due to hepatic fibrosis that can progress to liver cirrhosis, ultimately leading to organ failure and death. Ursodeoxycholic acid (UDCA); a hydrophilic bile acid, is increasingly used in treatment of cholestatic disorders.

Aim of the study: To investigate possible antifibrotic effects of UDCA in non-cholestatic thioacetamide (TA)-induced liver fibrosis in rats.

Methods: Animals were injected with TA (50 mg/kg twice weekly for 6 weeks, i.p.). Separate groups were treated with UDCA (25 or 50 mg/kg/day orally for 6 weeks), with or without TA.

Results: UDCA, in both doses, succeeded in improving liver function after TA-intoxication, as it significantly decreased the levels of serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Both dosages also improved oxidative stress, possessed anti-nitrosative and anti-apoptotic effects, as well as attenuated TA-induced fibrosis, evident by significant decrease in hepatic malondialdehyde (MDA) level, down-regulation of inducible nitric oxide synthase (iNOS) and caspase 3 expression, with significant decrease in fibrotic score by Masson trichrome staining, respectively. Interestingly, both dosages of UDCA did not improve superoxide dismutase (SOD) activity after TA challenge. UDCA dose-dependently improved TA-induced fibrosis, shown by the down-regulation of a well-known fibrogenic indicator, namely tissue inhibitor of metalloproteinase (TIMP)-1. It was noteworthy that UDCA only at higher dose significantly decreased liver/body weight index and hepatic nitric oxide level, as well as improved the score of histopathological picture.

Conclusion: UDCA, especially at high dose, successfully reversed TA-induced liver fibrosis, through antioxidant, antinitrosative, anti-inflammatory, anti-apoptotic and anti-fibrotic mechanisms.

Keywords: Ursodeoxycholic acid, thioacetamide, liver fibrosis, iNOS, TIMP-1.

P 19. Renal Protection of Diacerein against Cisplatin-induced Nephrotoxicity in Rats

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Background: Cisplatin is one of the most effective chemotherapeutics. However, its clinical use is hampered by its severe nephrotoxicity, whose mechanisms are not fully understood.

Aim of the study: To investigate possible protection conferred by diacerein; a powerful antioxidant drug, against cisplatin-induced renal damage.

Methods: To assess its reno-protective effect, diacerein was administered orally in two doses of 50 and 100 mg/kg for 14 days. At day 11 of the experiment, cisplatin (5 mg/kg, i.p.) was given with or without diacerein pre-treatments. Assessment of renal function was performed via measuring serum creatinine, urea and sodium levels, as well as determining micro-albuminurea and creatinine clearance. Kidney damage was further evaluated histopathologically, and oxidative stress assessed *via* renal tissue malondialdehyde level, reduced glutathione concentration and catalase activity.

Results: Cisplatin caused distortion in normal renal histological structure, with significant increase in serum urea and creatinine levels, as well as fractional excretion of sodium and albuminurea, with decrease in creatinine clearance compared to control group. Cisplatin also disrupted normal tissue oxidation processes, as it significantly decreased reduced glutathione concentration and catalase activity, as well as increased malondialdehyde level compared to control group. On the other hand, pre-treatment with both diacerein doses significantly restored renal functional parameters as well as histological structures. Moreover, cisplatin/diacerein groups exhibited significant improvement in oxidative stress measures, compared to cisplatin-treated group.

Conclusion: Diacerein, through antioxidant mechanisms, exhibited nephro-protection against cisplatin-induced renal toxicity, and might be a successful adjuvant during cancer chemotherapy.

Keywords: Diacerein, cisplatin, nephrotoxicity, antioxidant

P 20. Fucoidan ameliorates hepatic and metabolic disorders in high-fat diet-induced non-alcoholic fatty liver disease in rats

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Background: Fucoidan, a sulfated polysaccharide derived from brown seaweeds, possesses a wide range of pharmacological properties.

Aim of the study: In the present study, we investigated the therapeutic effect of fucoidan against hepatic and metabolic disorders in high-fat diet (HFD)-induced non-alcoholic fatty liver disease (NAFLD) in rats with the use of metformin as a standard drug.

Methods: Rats were fed HFD for 12 weeks to induce NAFLD. Oral administrations of fucoidan (100 mg/kg, orally), metformin (200 mg/kg, orally) or vehicle were started in the last four weeks.

Results: Results showed that chronic administration of fucoidan for 4 weeks attenuated the development of NAFLD as evidenced by significant decrease in liver index, serum liver enzymes activities, serum total cholesterol and triglycerides, fasting serum glucose, insulin, insulin resistance, and body composition index. Further, fucoidan inhibited hepatic malondialdehyde as well as nitric oxide concentrations, and concomitantly increased hepatic reduced glutathione level. In addition, the effect of fucoidan was accompanied with significant decrease in hepatic mRNA expressions of tumor necrosis factor-α, interleukins-1β and matrix metalloproteinase-2. Moreover, the effect of fucoidan was confirmed by histopathological examination.

Conclusion: In conclusion, the present study shows the ameliorative effect of fucoidan on HFD-induced NAFLD in rats that may partly be correlated with its hypolipidemic, insulin sensitizing, antioxidant and anti-inflammatory mechanisms.

Keywords: NAFLD, High-fat diet, Fucoidan, Metformin, Oxidative stress, Inflammatory cytokines

P 21. Spironolactone ameliorates endothelial dysfunction in streptozotocin-induced diabetic rats.

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Background: Endothelial dysfunction is a critical initiator for developing diabetic vascular complications. Substantial clinical and experimental evidence suggest that aldosterone plays a crucial role in its pathogenesis

Aim of the study: The present study aimed to investigate effect of the mineralocorticoid receptor (MR) blocker, spironolactone on diabetes-associated endothelial dysfunction and address the underlying mechanism(s) involved in this setting

Methods: Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) to rats and spironolactone was orally administered (50 mg/kg/day)

Results: Our results showed a marked increase in aortic malondialdehyde (MDA) level and upregulation the catalytic NADPH oxidase subunit, NOX2 gene expression alongside reducing catalase enzyme capacity and the serum nitric oxide (NO) bioavailability in diabetic rats. This was associated with a significant reduction in endothelial nitric oxide synthase (eNOS) immunoreactivity and gene expression in diabetic aorta. The transforming growth factor-β (TGF-β) protein and the MR gene expression levels were significantly increased in diabetic rat aorta. Moreover, the diabetic aorta showed a marked impairment in acetylcholine–mediated endothelial dependent relaxation. Additionally, spironolactone significantly inhibited the elevated MDA, TGF-β, NOX2 and MR levels alongside correcting the dysregulated eNOS expression and the defective antioxidant function. Spironolactone markedly reversed the impaired endothelial function in the diabetic aorta.

Conclusion: Collectively, our study demonstrates that spironolactone ameliorated the vascular dysfunction of diabetic aorta, at least partially *via* its anti-inflammatory and anti-oxidative effects alongside correcting the dysregulated eNOS and TGF-β expression. Thus, blockade of MR may represent a useful therapeutic approach against diabetic vasculopathy.

Keywords: Spironolactone, diabetes, endothelial dysfunction, oxidative stress

P 22. Evaluation of the anti-inflammatory, analgesic and anti-ulcerogenic potentials of *Achillea fragrantissima* (Forssk.)

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Background: *Achillea fragrantissima* is a perennial herb grown in Egypt and traditionally employed medicinally for its anti-inflammatory and analgesic properties among Sinai inhabitants. Non-polar and polar extracts were obtained by successive foliar extraction with dichloromethane and aqueous methanol, respectively. Solvent extracts were assayed in a rodent system for anti- inflammatory, anti-ulcerogenic and analgesic activities.

Aim of the study: The present study aims to evaluate the anti- inflammatory and analgesic activities together with the anti-ulcerogenic potential of both extracts in rodents at two oral dose levels (200 and 400 mg/kg).

Methods: Acute toxicity of non-polar and polar extracts of *A. fragrantissima* was evaluated in mice. Anti-inflammatory activity was assessed in carrageenan-induced rat-paw edema test while analgesic activity was explored centrally and peripherally using hot plate and writhing tests, respectively. In addition, anti-ulcerogenic activity was assayed in colon and gastric tissues.

Results: Foliar extracts of *A. fragrantissima* exhibited anti-inflammatory, central and peripheral analgesic activities. Moreover, both non-polar and polar fractions revealed protective effects against rat ulcerative colitis and gastric ulcers.

Conclusion: *A. fragrantissima* extracts possess anti-inflammatory, central and peripheral analgesic activities in addition to protective properties in colonic and gastric tissue.

Keywords: *Achillea fragrantissima*, anti- inflammatory, analgesic, anti-ulcerogenic, Egyptian Folk Medicine.

P 23. Phenolic Constituents Isolated from Punica Granatum L. (Punicaceae) and Evaluation of Antioxidant, Anti-cancers, Antiestrogens Activities

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Background: In recent years, there has been an increasing interest in the field of natural phenolics. That interest apparently arises from the growing awareness and concern at all levels of society of the importance of natural products in general, but specifically on natural phenolics.

Aim of the study: Plant phenolics, especially flavonoids, are currently of growing interest owing to their supposed functional properties in promoting human health.As a part of our continuing search among medicinal plants cultivated in Egypt for flavonoid constituents, which might possess biological activity.

Methods: All structures were determined by conventional method of analysis and confirmed by FT-MS and NMR studies. Interpretation of the data of 1-D ^{1}H and ^{13}C NMR, together with 2D-homo- and hetero-nuclear chemical shift correlation NMR is discussed to confirm the configuration and conformation of the sugar core of each compound.

Results: Isolation of the compounds 3,6–*O*–Hexahydroxy-diphenoly -(α/β)-$^{1}C_{4}$ -glucopyranose;1-mono -*O*-galloy-3,6-*O*-Hexahydroxydiphenoly-(β)-$B_{1,4}$-glucopyranose;1,4-di-*O*-galloy-3,6-*O*-Hexahydroxy -diphenoly - (β) - $B_{1,4}$ – glucopyranose ; 1,2,4-tri-*O*-galloy-3,6-*O*-Hexahydroxy- diphenoly - (β)-$B_{1,4}$-glucopyranose were isolated from the leaves of *Punica granatum.*

Conclusion: The efficacy for preventing and remediating cancers including breast and prostate cancers by oral administration of the juice, seed oil, and peel extract is still believed to be true. In this review, target components of pomegranate such as antioxidants, anti-cancers, antiestrogens and ethnomedical components were analyzed and discussed along with examining its pharmaceutical efficacy and prescription to postmenopausal lesion, cardiosclerosis, cosmetic beautification, viral and allergic symptoms, and diabetes mellitus, etc….
This could be recognized from the fact that although a surprisingly several natural phenolics have interesting pharmacological properties, yet the number of commercially successful phenolic drugs from natural resources remains small.

Keywords: NMR, *Punica granatum*, antioxidants, anti-cancers, antiestrogens and ethnomedical components.

P 24. Chemistry and hepatoprotective effect of Phenolics isolated from *Acalypha Wilkesiana cv.Hoffmannii* (Euphorbiaceae) on primary cultured rat hepatocytes

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Background: Throughout the ages, human has relied on nature to get the essentials of life, e.g. food, medicines, clothes, flavors and fragrances, fertilizers, means of transportation and some raw materials needed to satisfy all his requirements. During the last decades, there has been an increasingly search for active compounds from many sources which have been termed "natural products" to use them either as drugs or for industrial purposes.

Materials and methods: Monolayer from primary cultures of rat hepatocytes was performed in the 96-well plate, incubated for 22-24 hrs.Different concentrations were prepared from each of the extracts of Acalypha wilkesiana species, starting from 12.5 µg/mL and increasing concentration in ascending order by dissolving in DMSO (1% maximum concentration). For each concentration, three replicates were carried out, in addition to controls which were: cell control (cells only), negative control (cells + paracetamol) and positive control (reference) (cells + sylimarin + paracetamol). The plate was incubated for 2 hrs, washed twice with Phosphate Buffer Saline (PBS). Paracetamol (20 mM) was added to each well except on that of the cell control and incubated for 18 hrs. Following incubation, the monolayer was washed again with PBS.50% mortality of the hepatocyte (IC50) was determined using NR assay.

Result: The viability assay was applied with a broad range of concentrations of the studied extracts of Acalypha. The sample exerts no toxic effect on the monolayer hepatocyte layer 50% mortality of the hepatocyte (IC_{50}) was determined using Neutral Red Assay Acalypha extract showed hepatoprotective activity against paracetamol toxic effect 40 µg/ ml. The constitutive flavonoids of Bay leaves were extensively studied and led to the separation and identification of 14 phenolic compounds which were identified using chemical, conventional and advanced NMR,1- D and 2-D spectral techniques.

Conclusion: From the point of view of the main classes of natural products existing in the leaves Acalypha and on the basis of the analytical results achieved during the course of the present work we can come to the conclusion that showed hepatoprotective activity is produced by the leaf extract of the plant could be due to the existing combination of phenolic constituents or it could be attributed to one or more of the phenolic compounds and the IC50 of the different fractions suggested that the antioxidant activity is best interpreted in terms of the existing phenolics, catchine, epicatchine and rutin, other flavonoid glycosides and chlorogenic acid which are well known for their potent antioxidant activities and correspondingly significant inhibition of UV induced IL-6 production .

P 25. Assessment of Anti-inflammatory, Antinociceptive, Immunomodulatory and Antioxidant Activities of *Cajanus cajan* L. Seeds Growing in Egypt and its Phytochemical Composition

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Background: *Cajanus cajan* (L) known as Pigeon pea is a perennial member of the family Fabaceae. It is widely used in traditional medicine as diuretic tea for inflammation and blood disorders. It is also used as expectorant, sedative, to arrest bleeding, relieve pain, kill worms, and in treating hepatitis and measles.

Aim of the study: The present study was designed to identify the phytochemical composition of hexane and butanol extracts of the seeds of *Cajanus cajan* L. growing in Egypt. The hexane extract was evaluated for anti-inflammatory, immunomodulatory, antinociceptive, activities. Moreover, the antioxidant effect was examined in the butanolic fraction.

Methods: Unsaponifiable matter and fatty acids were separated from the hexane extract and analyzed by gas chromatography/mass spectrometry. The flavonoidal compounds in the *n*-BuOH fraction containing were identified by spectroscopy techniques. Adult male Albino rats were treated with *Cajanus cajan* (hexane fraction) at doses of 200 and 400 mg/kg for evaluation of their pharmacological effects. The anti-inflammatory activity was evaluated using the carrageenan-induced rat paw edema. Measurements of rat paw thickness were carried out at 1, 2, and 3 hours post-carrageenan injection. The serum IgG and inflammatory markers (tumor necrosis factor-alpha and Interleukin-6) levels were detected by enzyme linked immunosorbent assay technique. The antinociceptive activity was determined by adopting the writhing test in mice. The *in vitro* antioxidant assays: DPPH radical scavenging, total reduction capability and inhibition of lipid peroxidation were determined.

Results: Twenty one unsaponifiable compounds and twelve fatty acids were identified in the hexane extract of *Cajanus cajan* L. seeds. Phytol, 2,6-di-(t-butyl) -4-hydroxy-4-methyl-2,5-cyclohexadiene-1-one and steroidal compounds as β-sitosterol, stigmasterol and campsterol were the main compounds in the unsaponifiable fraction. 9,12-octadecadienoic acid and palmitic acid were the major fatty acids identified. The *n*-BuOH fraction contains seven flavonoidal compounds; quercetin-3-O-β-D-glucopyranoside, orientin, vitexin, quercetin, luteolin, apigenin and isorhamnetin. *Cajanus cajan* hexane extract inhibited the inflammation induced by carrageenan by 85% and 95% for rats treated with 200 and 400 mg/kg of the extract at 3 hours post-carrageenan challenge. This was accompanied by a decrease in the inflammatory biomarkers TNF-α and IL-6. In addition, it significantly decreased the IgG serum levels in carrageenan-induced inflammation. Moreover, hexane extract exhibited a potent antinociceptive effect in acetic-acid induced pain at the dose of 400 mg/kg. In addition, the butanol fraction exhibited antioxidant activities more than L-ascorbic and butylated hydroytoluene.

Conclusion: *Cajanus cajan* seeds possess anti-inflammatory, antinociceptive and immunomodulatory as well as antioxidant activities which could play a potential role in the pharmacological management of inflammatory and pain conditions.

Key words:
Cajanus cajan seeds, lipoidal matter, flavonoids, anti-inflammatory, IL6, TNFα, IgG, antinociceptive, antioxidant.

P 26. Alleviation of haloperidol induced oxidative stress: Effects of sucrose vs grape seed extract

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Background: Haloperidol (HP) is a classic antipsychotic drug known for its propensity to cause extrapyramidal side effects. HP is known to induce oxidative stress due to increased turnover of dopamine.

Aim of the study: The aim of the present study was to investigate the effect of sucrose and grape seed extract on the oxidative stress induced in rats by HP

Methods: Oxidative stress was induced by concurrent injection of HP with the sucrose (1 and 5 mg/kg) and grape seed extract (GSE; 100, 200 and 400 mg/kg). Both drugs were administered orally once per day for 14 consecutive days and their effects were evaluated 24 h after the administration of the last dose. Liver and brain levels of malondialdehyde (MDA), reduced glutathione (GSH), nitric oxide (nitrite) levels were determined in the brain and liver.

Results: Results of the present study revealed that HP-treated rats showed elevated levels of NO in the brain and MDA in the brain and liver. HP- treated rats showed also a decreased levels of NO level in the liver and GSH in the brain and liver. Treatment of HP-treated rats with GSE reversed all the oxidative stress markers in both the brain and liver due to its potent antioxidant property. On the hand, treatment of HP-treated rats with sucrose attenuates the level of NO in the brain and liver and the brain levels of MDA and GSH.

Conclusion: It can be concluded that both GSE and sucrose have a beneficial effect on oxidative stress induced in the brain and the liver of rats by HP.

Keywords: Haloperidol, oxidative stress, MDA, GSH, sucrose and grape seed extract

P 27. Beneficial effect of artichoke leaf extract on ethylene glycol-induced urolithiasis in rats

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Background: Urolithiasis is one of the most painful ailments of the urinary tract disorders found in humans.

Aim of the study: The present study aimed to investigate the anti-urolithiatic activity of artichoke leaf extract (ART) on ethylene glycol (EG)-induced urolithiasis in albino rats.

Methods: Urolithiasis was induced by adding ethylene glycol (0.75% v/v) to drinking water of rats for 28 consecutive days. Concurrently, ART (125, 250 and 500 mg/kg) were orally administrated either from the 1st day in the preventive regimen or from the 15th day in the curative regimen. A standard anti-urolithiatic drug, cystone (CST; 150 mg/kg; p.o.), was also used.

Results: The present study showed that EG-induced urolithiasis was accompanied by a decrease in the body weight and an increase in both the kidney weight and the relative kidney weight. Adding EG to drinking water for 28 days showed an increase in the serum levels of uric acid, urea, creatinine and calcium with an increase in protein concentration in urine as indicators of renal damage. Moreover, induction of urolithiasis was associated with an elevated renal levels of lipid peroxides (measured as malondialdehyde; MDA) and reduced glutathione (GSH) as reliable indices of oxidative stress. In both regimens, administration of ART (125, 250 and 500 mg/kg; p.o.) restored the body weight, the kidney weight and the relative kidney weight. Moreover, ART decreased the serum levels of uric acid, urea, creatinine and calcium and also decreased the protein concentration in urine in a dose dependent manner. It also attenuated the kidney levels of MDA and GSH. The histological findings also showed improvement after treatment with ART in both regimens.

Conclusion: From the previous results, it can be concluded that ART has a protective effect on the kidney functions in EG-induced urolithiasis in rats probably due to its potent anti-oxidant property.

P 28. Effect of levofloxacin prophylaxis on febrile neutropenia in acute myeloid leukemia patients : Episode resolution and bacterial culture

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Background: Fever neutropenia prophylaxis in patients with hematologic malignancies is controversial. This prophylaxis has been reported to decrease the infection related mortality, but emergence of resistance is a concern

Aim of the study: This study assess the effect of levofloxacin prophylaxis in hematologic patients verseus a control group that did not receive such prophylaxis.it measures the effect of prophylaxis on fever neutropenia resolution. the study assesses the presence or absence of fever. The study also measures the effect of prophylaxis on bacterial culture type (gram positive and gram negative)and compares it to the control group.it also investigates the presence of resistant microbial strains and their type in patients receiving prophylaxis and compares the results to those of the control group

Methods: Cohort retrospective analysis of levofloxacin prophylactic use in pediatric hematologic patients assessing:
1- the effect of prophylaxis on febrile neutropenia resolution which is defined as an auxiliary temperature>38 .0 C and a neutrophil count<500 cells/ul.
2- bacterial culture type (gram positive and gram negative) and compares it to the control
3- the presence of resistant microbial strains and their type and compares the results to those of the control group

Results: Comparing the prophylaxis versus the control group the following results were obtained:
No statistical significance was detected concerning the frequency or the depth of the fever neutropenia episodes
No statistical significance was detected concerning the type of bacterial cultures isolated
No statistical significance was detected concerning the type of bacterial resistance

Conclusion: The prophylactic use of levofloxacin in high risk AML patients has no treatment value that benefit the resolution of the fever neutropernia episodes postchemotherapy cycle nor it does affect the pattern of microbial resistance in those patients.

Keywords: Levofloxacin , prophylaxis ,fever neutropenia ,antimicrobial resistance.

P 29. Effect of Clarithromycin on pregnant Albino rat and their developing embryos

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Background: Clarithromycin is a member of the antibacterial macrolides group. Macrolide antibiotics have been used frequently to treat mild to-moderately severe upper and lower respiratory tract infections and some genitourinary infections. Clarithromycin provides better effect at the tissue level, especially for pneumonia, Asthma and *Helicobacter pylori* with fewer gastrointestinal side effects.

Aim of the study: This work studies the effect of Clarithromycin on pregnant female rats during different pregnancy phases.

Methods: In the present study four groups of pregnant animals were used. The first group received distilled water and used as control and sacrificed at 8th, 15th and 20th day of gestation. The other three treated groups are oral administered with 45 mg/kg. clarithromycin from 1st to 7th , 8th to 14th and from15th to 19th days of gestation and were scarified with its control group at 8th , 15th and 20th day of gestation.

Results: The obtained results showed a decrease in the maternal body weight gain, increase in the rate of abortion, resorption and growth retardation of fetuses and some morphological malformation. Milled and sever lack of ossification and some malformation in the skeletal system of groups treated with Clarithromycin.

Conclusion:
The results show that Clarithromycin produce morphological and skeletal anomalies in rats.

Keywords: Macrolides, Clarithromycin, teratology, rat and skeletal malformation.

P 30. A study of the possible healing effects of Portulaca oleracea on wounds in rats and its antioxidant effects on different organs

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Background: Portulaca oleracea (purslane) is a nutritious vegetable used fairly for human consumption.
Previous studies revealed that Purslane exhibits a wide range of biological effects such as antioxidant, anti-inflammatory and antidiabetic effects.

Aim of work : to study the effects of purslane in infected and non-infected wounds induced in rats with evaluation of its antioxidant effects of purslane on skin ,liver and kidney in addition to its possible anti-microbial effects *in vitro*.

Methods: Wounds are induced in three groups of rats; control, infected and noninfective. Fresh extract of whole plant was applied locally on skin and the rate of healing was recorded. In another set of rats, Purslane was administrated orally for four weeks. Histopathology of skin, kidney and brain was done in addition to measuring the antioxidants in tissue homogenates.

Results: Improved healing of wounds with good anti-infective effects *in vivo.* Histopathological changes were observed in different organs with obvious antioxidant potential for purslane. Antimicrobial sensitivity *in vitro* revealed a highest inhibition zone to staphylococcus aureus and Escherichia coli.

Conclusion: The present study showed that Portulaca oleracea is a promising plant in treating wounds with good anti- infective and antioxidant properties .

Keywords: Portulaca oleracea wound healing, antibacterial, antioxidant.

P 31. Ellagic Acid Anti-inflammatory and Anti-apoptotic Potential Mediate Renoprotection in Cisplatin Nephrotoxic Rats

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Background: The therapeutic benefit of the chemotherapeutic agent cisplatin is confined to its nephrotoxicity; however Ellagic acid (EA) renoprotective effect against cisplatin (CIS)-induced nephrotoxicity remains elusive.

Aim of the study: The potential protective effect of Ellagic acid (EA) on the renal dysfunction was investigated

Methods: Therefore, male Sprague–Dawley rats received CIS alone or EA (10 and 30 mg/kg, p.o.) for 5 days before and after CIS injection.

Results: CIS increased serum levels of blood urea nitrogen, creatinine, γ –glutamyl transferase, and reduced those of albumin and total protein. It also raised serum endothelin-1, as well as serum and renal nitric oxide, tumor necrosis factor-α, and monocyte chemoattractant protein-1. CIS enhanced the renal caspase-3, hemeoxygenase , nuclear factor κB, and inducible nitric oxide. EA hampered CIS-induced nephrotoxicity manifested by an enhancement of the glomerular filtration rate which was associated by the reduction of inflammatory mediators and the apoptotic marker in the serum and/or kidney.

Conclusion: The present study discloses that EA suppresses HO-1 and, its renoprotection is also linked to its anti-inflammatory and antiapoptotic properties, as well as the reduction of nitric oxide and endothelin-1.

Key words: Cisplatin; Ellagic Acid; Nephrotoxicity; Inflammation; Apoptosis

P 32. Comparative study of anti-fibrotic activity of some magnesium containing supplements on experimental liver toxicity (Molecular Study)

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Background: Liver fibrosis is the excessive accumulation of extracellular matrix (ECM) proteins including collagen that occurs in most types of chronic liver diseases.

Aim of the study: This study aimed to investigate and compare the therapeutic efficacy of different Mg containing supplements (Biomag, Spasmag and Caldin-C) on CCl_4 - induced liver fibrosis in rats.

Methods: Liver fibrosis was induced by intraperitoneal injection of rats with CCl_4 (1:1 in olive oil, 2 ml/kg, 3 times/week) for 4 weeks, then rats were orally treated with different Mg containing supplements (Biomag, Spasmag and Caldin-C) once daily for another one month. Liver fibrosis was quantified by evaluation of expression of collagen I, TGFβ1, PDGF-C, NF-κβ and measurement of hepatic collagen (hydroxyproline) level. Also, MDA, NO, GSH level, SOD and GST activities were estimated.

Results: CCl_4 administration significantly elevated the expression of the studied genes, hepatic hydroxyproline, MDA, NO levels and caused depletion of GSH level, SOD and GST activities when compared with that of their corresponding control, $P < 0.05$. All Mg supplements significantly inhibited the expression of all studied genes and attenuated the hepatic hydroxyproline level as compared with that of CCl_4- treated group; $P < 0.05$, for NF-κβ, the highest inhibition was by Spasmag and Caldin-C. Regarding collagen I, TGFβ1 and hepatic hydroxyproline content, the highest inhibition was by Caldin-C and Biomag revealed highest inhibition for PDGF-C. All Mg supplements revealed normalization of oxidant and antioxidants parameters. Histopathological examination supports the biochemical and molecular findings.

Conclusion: Mg supplements were effective in the treatment of hepatic CCl_4-induced fibrosis-rat model.

Keywords: liver fibrosis, carbon tetrachloride, TGFβ1, PDGF-C, Magnesium.

P 33. Effect of selective versus non selective cyclooxygenase inhibitors on ischemia-reperfusion-induced hepatic injury in rats

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Background: The role of cyclooxygenase (COX) enzymes in pathogenesis of Ischemia-reperfusion (IR) is not clear.

Aim: To evaluate the effect of selective cyclooxygenase-2 (COX-2) versus non selective COX inhibitors in hepatic IR in rats.

Methods: Rats were allocated into 4 groups: Sham (control) group, IR non-treated (positive control) group, Indomethacin (non selective COX inhibitor) + IR group, and Celecoxib (selective COX-2 inhibitor) + IR group. The measured parameters were: serum alanine aminotransferase (ALT) and hepatic glutathione peroxidase (GPx), super oxide dismutase (SOD), catalase, malondialdehyde (MDA), nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α). Histopathological examination of liver tissues and immunohistochemical assay of caspase-3, iNOS and eNOS were performed.

Results: IR caused hepatic injury as evidenced by high serum ALT level as well as by histopathological findings. Hepatic IR injury was associated with high hepatic levels of MDA, NO and TNF-α, GPx activity and expression of caspase-3 and iNOS along with low activities of both SOD and catalase as well as with low eNOS expression. Pretreatment with either indomethacin or celcoxib significantly reduced levels of MDA, NO, TNF-α and normalized activites of GPx, catalase and SOD enzymes. However celecoxib, but not indomethacin, pretreatment significantly reduced hepatic IR injury as indicated by reduced ALT level as well as by histopathological improvement. Such effect was associated with significant reduction in caspase-3 and iNOS expression along with elevated eNOS immunostaining in hepatic tissue.

Conclusion: Celecoxib (selective COX-2 inhibitor), but not indomethacin (non selective COX-inhibitor), has hepatoprotective effect against liver IR injury. The protective effect of celecoxib might be attributed to block of COX-1- eNOS pathway.

Keywords: Hepatic ischemia-reperfusion, Cyclooxygenase-ischemia-reperfuion.

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