# Abstracts of the Conference

## Problem-Based Learning Strategy in Pharmaceutical Education

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Problem-based learning (PBL) is both a teaching method and an approach to the curriculum. It consists of carefully designed problems that challenge students to use problem solving techniques, self-directed learning strategies, team participation skills, and disciplinary knowledge. PBL was initiated by medical schools in Canada in the 70's moving then slowly to the U.S. where it has been adopted mostly in medical, pharmaceutical and other professional schools. The University of Mississippi introduced PBL to its medical and pharmaceutical education in the 90's both to the Pharm. D. and graduate school programs. According to the formal definition, PBL is: "an instructional strategy in which students confront contextualized, ill-structured problems and strive to find meaningful solutions." In simpler terms PBL is learning from working with problems. Usually a class is divided into small groups (6-8 students) to work under the direction of a faculty facilitator. The problems or so called "cases" are distributed to students a week in advance to be discussed in problem-solving sessions. In keeping with a model of self-directed learning no specific textbooks are recommended, instead the reading list is provided including available electronic library sources and databases. Evaluation of students' work is based on their participation and performance during problem-solving sessions, seminars, and examinations.

The specific examples of PBL strategy of teaching in undergraduate and graduate program of the Department of Pharmacognosy in the School of Pharmacy at the University of Mississippi will be presented.

**Systemic drug delivery through different routes of administration**

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To discover, develop and bring a new drug to the market is estimated to cost one billion dollar. The drug toxicity profile, its mechanism of action, metabolism, potential teratogenicity and how age, sex, genetics, food, disease and other drugs can affect a new drug entity must all be investigated.

The food and drug administration evaluates the volume of data produced for each new drug when it weighs its safety and efficacy against its risk to the public before it gives approval for marketing. The detailed, time consuming studies required of each new drug are designed to minimize the risk to people from drugs that may do more harm than good. That protection comes with a cost, and that cost continues to increase as more is learned about what additional information is needed to prevent problems and make informed decisions about new drug entities.

The time and cost to develop a new drug makes it far more attractive (and far less costly) to develop new, more efficacious ways of delivering established drugs to their desired physiological site of action. New dosage forms are often developed to optimize bioavailability, minimize toxicity, reduce side effects and / or improve stability. Understanding how these systems work, when they are appropriate and justified and how or if they truly improve drug delivery is the focus of this presentation.

An appreciation for rational dosage form design requires an understanding of key physical-chemical parameters and certain biopharmaceutical characteristics of a drug formulation. It also requires some understanding of various physiological environments that are sites for drug administration, and how each site ultimately affects the drug formulation. The physical-chemical properties of a drug, its biopharmaceutical formulation and site of administration can have a tremendous impact on the amount of drug that reaches the blood, which in turn can affect drug efficacy and toxicity. Understanding these factors will enhance appreciation for differences between drug formulations and the appropriate selection and development of the optimum dosage form.

Examples are provided throughout this presentation to demonstrate key points related to rational drug design. The objective is to provide a thorough understanding of how drug design can and has played a key role in affecting the therapeutic efficacy of drugs.

## Current status of Pharmacy Education and Practice in Jordan

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In the last quarter of the 20$^{th}$ millennium, pharmacy education and practice witnessed massive changes in the role of pharmacist in the health care system that was accompanied by parallel changes in the education system worldwide. These changes included introduction of the concept of "Pharmaceutical Care" which emphasized the pharmacist role in patients' drug management, as opposed to his traditional role of drug manufacture and compounding. In Jordan these changes started to happen at the turn of the century, and some steps were taken in the direction of adopting the concepts of Pharmaceutical care. In this presentation we will take a quick look onto the current status of pharmacy practice and education and practice in Jordan. Problems facing pharmaceutical care application will be highlighted, which involves stakeholders in this process: pharmacists, physicians, and public.

## Recent Advances in Computer-Aided Drug Design and Discovery

**Prof. Dr. Mutasem O. Taha**
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Computer-aided drug design and discovery at the Faculty of Pharmacy-University of Jordan has witnessed significant advances over the past few years. These can be summarizing as follows: (i) Hybridizing pharmacophore and quantitative structure-activity relationship (QSAR) modeling for the identification of binding site flexibilities and multiple binding modes. (ii) Combining supervised or unsupervised pharmacophore modeling, QSAR analysis and *in silico* screening for the discovery of new biologically interesting leads. (iii) Combining docking methodologies and ligand-based QSAR methodologies as means to achieve the best possible docking/scoring settings for a particular case. Furthermore, we developed several novel structural databases that cover natural compounds, established drugs and agrochemicals, with the intension of using them for *in-silico* drug discovery purposes.

Most recently, we invented two new algorithms: (i) the Binding Interactions Locator (BIL), which is intended to help hybridizing structure-based approaches and pharmacophore modeling; and (ii) nonlinear QSARTool, which is intended to explore nonlinear QSAR models.
This presentation is intended to summarize the recent advances in computer-aided drug design and discovery carried out at the faculty of pharmacy-University of Jordan.

**Ocular Residence of Polymeric In-Situ gelling Systems: Evaluation Using Gamma Scintigraphy**

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Purpose:
In-situ gelling systems are polymeric formulations that can undergo a sol-to-gel transition due to change in temperature, ionic strength, and pH. They are of interest for ophthalmic applications as they can prolong the contact time with the ocular surface, hence increase ocular bioavailability. The purpose of this study was to investigate the ocular residence (contact time with the surface of the eye) of seven systems based on gellan gum, xanthan gum, carrageenan, alginate, HPMC, carbopol and chitosan using gamma scintigraphy.

Methods:
Six male New Zealand Albino Rabbits were used. 20µl of each formulation containing 5MBq 99mTc DTPA were instilled into both eyes. Ocular drainage was monitored using a XR GE gamma camera. Regions of Interest (ROIs) were created around the ocular surface and the nasolacrimal duct. Time versus activity curves were generated and two parameters were monitored: area under the 'percentage-activity-remaining-versus-time' profile ($AUC_{0\text{-}15min}$) and the percentage activity remaining in the precorneal area after 15 min ($a_{15min}$).

Results:
Drainage of the aqueous solution (control) was rapid with less than 40% radioactivity remaining in the precorneal ROI, while all of the in-situ gelling systems (apart from alginate and HPMC) remained in the precorneal region for a substantially longer time. Formulations based on gellan gum, xanthan gum, carrageenan, carbopol and chitosan were significantly different ($P<0.01$) from the control in terms of the $AUC_{0\text{-}15min}$ and ($a_{15min}$). The system based on xanthan gum achieved the best ocular retention, with both parameters being significantly different from the control, alginate and HPMC.

Conclusion:
In-situ gelling polymeric systems based on gellan, xantham gum and carrageenan are promising for improving ocular bioavailability due to their prolonged ocular retention.

**Investigation of the compatibility of the solid dispersions of drug nimesulide with the polyethylene glycols (PEG)**

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Solubility phenomenon is an area of particular importance. Increasing the water solubility of insoluble or slightly soluble compounds is of major concern for pharmaceutical researchers. There are many techniques employed to enhance the solubility of poorly water soluble drugs and one such technique is dispersion of the hydrophobic drug generally in a hydrophilic matrix, called solid dispersions, wherein the compatibility of the drug and hydrophilic matrix is very essential. In this study nimesulide was formulated as a solid dispersion with polyethylene glycols 4000 and 6000. The chemical integrity of nimesulide was assessed spectrophotometrically, where as physical interactions were studied by thermal analysis. Twelve formulations were prepared on the basis of eutectic mixture, temperature and solvent mediated solid dispersions. Thermal analysis was carried out by differential scanning calorimetry (DSC). Compatibility study was carried out after three months of storage in a stability chamber. The spectrophotometric analysis of the drug after being solid dispersed indicated no change in its chemical integrity as supported by more than 98% of drug assay value and there was no alteration in the spectrum while performing the thermal analysis. The nimesulide (pure drug) was subjected to DSC and the thermogram was obtained. The thermogram for nimesulide revealed one initial start up deflection at around $42^0$C, followed by the onset of the transition at $147.94^0$C which ended at $152.54^0$C, the peak being at $150.83^0$C. In this case the melting transition is one exothermic one. The decomposition took place at above $340^0$C. In case of the thermograms for solid dispersion samples the initial start-up deflection was similar at $42^0$C. A new peak appeared with the onset temperature of 45 to $94^0$C with varied peak values. This peak may be due to the process crystallization, which usually happens in case of polymeric material. Hence the additional phenomenon, if compared to the thermogram of the pure drug can be ascribed to the presence of the PEGs. In all the cases the peak transition for nimesulide has been highly affected as supported by a shift of the transition towards the left and with a very anomalous type of transition in all the cases of solid dispersions. This thermal study indicated a strong physical alteration due to the hydrophilic matrix as well as the process of preparing the solid dispersion without affecting the chemical integrity. Hence it can be concluded that compatibility study revealed a strong physical interaction, without affecting the structure of nimesulide. If correlated with the solubility data it can be suggested that the physical alterations contributed to the solubility in a positive manner.

**Nanopharmaeuticals As Antineopjastic Agents**

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Aim: The chemotherapy of neoplastic disease has become increasely important in recent years . An indication of this important is the establishment of a medical specially in nanotechnology.

Methods: Although this research has not yet produced an approval , many poly peptide amines have been design to prepared and tested as dendrimers as drug delivery system or biological active agents .

Conclusions: We concluded that nanodrugs are the future of health care and full of promise . New series of compounds were prepared .

## Bioanalytical Method Validation

**Rana Bustami**
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Bioanalysis employed for the quantitative determination of drugs and their metabolites in biological fluids, are the key determinants in generating reproducible and reliable data which in turn are used in the evaluation and interpretation of bioavailability, bioequivalence, and pharmacokinetic findings. It is essential to employ well-characterized and fully validated analytical method to yield reliable results which will be satisfactorily interpreted since the quality of the studies, which are often used to support regulatory filings, is directly related to the quality of the underlying bioanalytical data.

Bioanalytical method validation includes all of the procedures required to demonstrate that a particular bioanalytical method for the quantitative determination of the concentration of the analyte in a particular matrix, such as blood, plasma, serum, or urine is reliable for the intended application. The fundamental parameters for the validation include (1) accuracy, (2) precision, (3) selectivity, (4) sensitivity, (5) reproducibility, and (6) stability. Validation involves documenting through the use of specific laboratory investigations, that the performance characteristics of the method are suitable data corresponds directly to the criteria used to validate the method.

**Proton magnetic resonance, mass spectroscopy and Polarography of substituted phenyl bronate esters of chloramphenicol**

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P.m.r., m.s. and polarographic studies were described , the results shown in tables and figures for four substituted phenyl boronate esters of chloramphenicol , a marked similarity in the chemical shifts of the compounds was prepared , the fragmentation patterns are similar to that reported by Irwin et al (4) for the phenyl compound, the redox potential measurements are found to be around -0.6 volt which is similar to the redox potential of chloramphenicol base.

**Determination of atorvastatitin in human plasma by liquid chromatography-tandem mass spectrometry**

**Rana T. Bustami, Sewar Khasawneh*, Muhammad Al-Atoum**
*Pharmaceutical Research Unit, Amman – Jordan*

A rapid, sensitive, and highly selective liquid chromatography-tandem mass spectrometry method was developed and validated for determination of atorvastatin in human plasma. The analyte was analysed in plasma after precipitation of plasma proteins using acetonitrile. Atorvastatin was detected by tandem mass spectrometry using LC-MS/MS system (HPLC coupled with Triple Quadra pole mass spectrometry). The method has a lower limit of quantitation (LLOQ) of 0.20 ng/mL. The chromatographic run time was approximately 3.5 minutes. The standard calibration curve was linear over the concentration range of 0.199 - 22.087 ng/mL. The intra- and inter-day precisions determined for QC samples, expressed as the relative standard deviation, were less than 10.5%. The absolute recovery for QC samples was higher than 90%. The method was successfully applied for the evaluation of the pharmacokinetic parameter of atorvastain in a bioequivalence study after oral dose of 10 mg tablet.

**Protective effects of leave extract of Teucrium polium against oxidative stress of carbon tetrachloride in rats**

**AL-Kubaisy Khaled* and Al-Essa Luay Yousif****

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** Department of Pharmacy, Faculty of Pharmacy, Al-Zaytoonah University, Amman, Jordan.

The hepatoprotective effect of Teucrium polium leaves extract traditionally used in Jordan for the treatment of various disease states was evaluated in vivo using carbon tetrachloride ($CCl_4$) intoxicated rats as an experimental model.

Intraperitoneal pretreatment of rats with Teucrium polium leaves extract significantly reduced the elevation of serum hepatic markers (AST, ALT, GGT, and bilirubin) levels and significantly increased serum albumin and total protein levels induced by $CCl_4$-induced intoxication. Histopathological examination showed a damaging effect of liver cells after $CCl_4$ administration, with marked improvement was seen after Teucrium polium leaves extract treatment supported the biochemical results.

In conclusion, Teucrium polium leaves extract has protective effect and is able to minimize the toxic effect of $CCl_4$ on hepatocellular injury.

**Discovery of New Cholesteryl Ester Transfer Protein Inhibitors via Ligand-based Pharmacophore Modeling and QSAR Analysis Followed by In-Silico Screening**

**Reema Abu-kalaf**
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Atherosclerosis describes the underlying progression in arterial dysfunction and remodeling that restricts blood flow to vessels in the peripheral vasculature and is ultimately manifested as coronary artery disease (CAD). Several epidemiological studies have demonstrated an inverse relationship between serum high-density lipoprotein cholesterol (HDLc) levels and the incidence of ischemic heart disease.

Cholesteryl ester transfer protein (CETP), a 476-residue glycoprotein, binds to HDL and is involved in the transfer of lipoprotein particles and neutral lipids, including cholesteryl ester (CE), phospholipids, and triglyceride.

The pharmacophoric space of CETP was explored using three diverse sets of known inhibitors. Subsequently, genetic algorithm and multiple linear regression analysis were employed to select an optimal combination of pharmacophoric models and physicochemical descriptors that access self-consistent quantitative structure-activity relationship (QSAR) ($r^2$ = 0.800, n=96, F = 72.1, $r^2_{LOO}$ = 0.775, $r^2_{PRESS}$ against 22 external test inhibitors = 0.707). Two orthogonal pharmacophores (of cross-correlation $r^2$ =0.533) emerged in the QSAR equation suggesting the existence of at least two distinct binding modes accessible to ligands within CETP binding pocket.

The validity of the QSAR equation and the associated pharmacophore models was experimentally established by the identification of several promising new CETP inhibitors retrieved via *in silico* search of the NCI and drug databases. One of the excellent hits is NSC 40331 ($IC_{50}$=6.54 μM), which can serve as excellent lead for optimization.

**Iminopropadienones from dioxanediones, isoxazolopyrimidinones, pyridopyrimidinones, and pyridopyrimidinium olates.**

**Dr Majed Shtaiwi**
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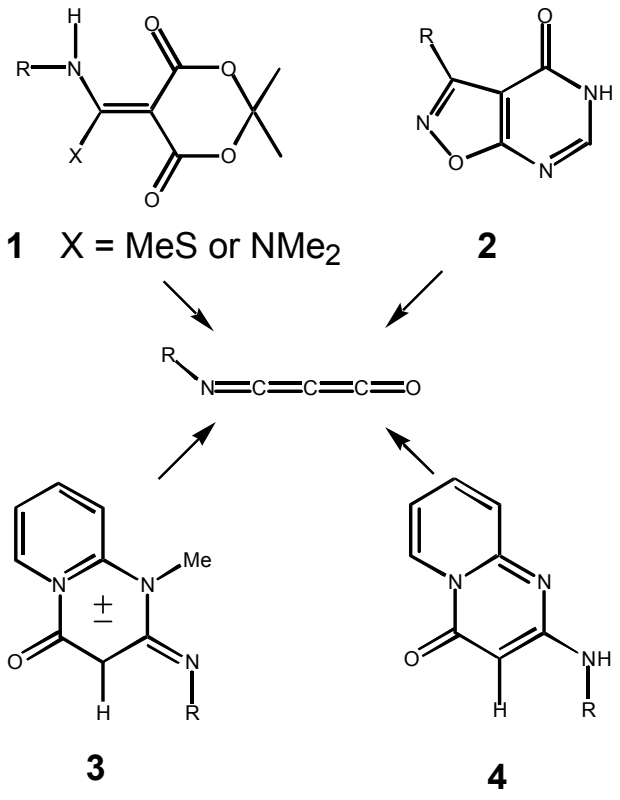
Iminopropadienones, RN=C=C=C=O, can be generated from four different types of precursors in flash vacuum thermolysis reactions: 1,3-dioxane-4,6-diones **1** , isoxazolopyrimidinones **2**, pyridopyrimidinium olates **3**, and pyridopyrimidinones **4**.
The iminopropadienones have been directly observed by Ar matrix IR spectroscopy in one or more of these reactions.

Nucleophilic addition of amines affords the malonic amidoamidines. Addition of 1,2-dimethylhydrazine produces pyrazolinones. Addition of N,N'-dimethyldiaminoethane and -propane gives diazepine and diazocine respectively (X-ray structures of these cyclic compounds available). The mesoionic pyridopyrimidinium olates are obtained by addition of 2-(methylamino)pyridine (X-ray structure is available). Primary 2-aminopyridines afford the pyridopyrimidininones and 2-aminopyrimidines and 2-aminopyrazine afford pyrimidopyrimidinones and pyrazinopyrimidinones.

(*o-tert*-Butylphenylimino)propadienones was found to be stable at room temperatureare reported.



**The Effects of Oral Antioxidant Drugs During Radiotherapy in Women with Breast Cancer.**

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Radiotherapy involves production of reactive oxygen species and induces oxidative stress mainly attributed to the impairment of antioxidant defense mechanisms in the body. This study was designed to evaluate the possible role of antioxidant drugs (vitamins C and E, allopurinol, aspirin and melatonin) in the protection against oxidative stress induced damage during exposure to radiotherapy.
95 women were involved in this study, 20 healthy control women and 75 had breast cancer and were allocated into 5 subgroups:

**Group (A):** Include 15 patients maintained on radiotherapy and did not given any antioxidant.

**Group (B):** Include 15 patients maintained on radiotherapy given vitamin C and E (vitamin C 500 mg / day and vitamin E 100 mg/day) during radiotherapy.

**Group (C):** Include 15 patients maintained on radiotherapy given allopurinol (100 mg/ day) during radiotherapy.

**Group (D):** Include 15 patients maintained on radiotherapy given aspirin (100 mg/ day) during radiotherapy.

**Group (E):** Include 15 patients maintained on radiotherapy given melatonin (3 mg/ day) during radiotherapy.

Malondialdehyde and glutathione in both erythrocytes and plasma, biochemical parameters (total plasma proteins, plasma albumin, uric acid and plasma calcium) levels, and hematological parameters (hemoglobin, white blood cell counts, platelets counts) all parameters were measured pre- and post radiotherapy for 4 weeks.
The results of this study showed an increase in the oxidative stress parameters in women with breast cancer and increases during radiotherapy (increased Malondialdehyde and decrease glutathione levels) which is improved by antioxidant drugs, however melatonin showed a more potent action as antioxidant effect than other.
Antioxidant drugs produced significant elevation in total plasma protein, in addition vitamins (C and E), and melatonin show a significant elevation in plasma albumin levels also.
The elevated plasma uric acid value in cancer patients did not show any changes with antioxidants.
All antioxidant drugs treatment reduces plasma calcium level compared with pre treatment levels.
The results also showed no effect on hematological parameters after treatment with antioxidant drugs except for aspirin, in which it improves hemoglobin levels, meanwhile allopurinol and melatonin increase white blood cell counts previously reduced after exposure to radiation.
In conclusion, radiation therapy initiates ionization leading to free radicals formation which affects the antioxidants defense mechanisms of the body, increases the oxidative stress status of the body and the antioxidant drugs in this study may limit the side effects of radiation in women with breast cancer .

**The impact of pharmaceutical care on drug related problems in hospitalized internal medicine patients.**

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Background and Objective:
For most diseases, drug therapy will enhance health- related quality of life; however, inappropriate use of drugs may be harmful and could evoke new symptoms. Drug related problems (DRPs) have often been addressed through studies on databases. The clinical approach—bedside evaluation of patients' DRPs—has rarely been applied. More importantly only few randomized controlled trials of the effect of pharmaceutical care on DRPs in hospitalized patients were done. The primary aim of this study was to investigate the impact of providing pharmaceutical care on DRPs in hospitalized internal medicine patients.

Design: The study was a prospective randomized controlled trial. 152 patients were included and randomly divided between intervention and control . The research team composed of 10 clinical pharmacists. Group differences (intervention, control) groups were examined using independent sample t-test.

Setting: The study was carried out at the internal medicine wards at a teaching hospital in Jordan
Main outcome measures

1. Outcomes of pharmaceutical care recommendations during hospitalization. These were measured in term of the number of recommendations accepted and implemented
2. Outcomes of DRPs during hospitalization. These were measured in term of the number of DRPs resolved, prevented and improved
3. Number of DRPs upon discharge in the intervention group compared to the control group.

Results: The average number of the identified DRPs was eight. Ninety-five percent of the submitted recommendations were accepted by physicians. However, only 67% of these recommendations were actually implemented. Tow third of DRPs in the intervention group were either resolved, improved or their morbidity were prevented, while it was only 14% in the control group ($p < 0.005$). The mean number of DRPs upon discharge for intervention and control group were 1.61 and 6.25 respectively. This represent a three times decrease in the number of DRPs in the intervention group compared to the control (relative risk reduction).

Conclusions: The number of DRPs in internal medicine hospitalized patients is high. Clinical pharmacists were able to identify these problems and resolve them or decrease the associated morbidity. The high acceptance rate by physicians indicates the importance and high quality of the recommendations and that physicians are starting to accept the role pharmacist as a health care provider in Jordan.

**An integrated pharmaceutical care intervention for patients with type 2 diabetes**

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Glycaemic goals are often not achieved despite the availability of many effective treatments and the documented benefits of glycaemic control. Several studies have established the important positive impact of pharmacist-led management on achieving glycemic control and other clinical outcomes in diabetic patients. The aim of the present study was to evaluate, in a randomised, controlled trial, the impact of an integrated pharmaceutical care intervention programme on a range of clinical and humanistic outcomes in type 2 diabetic patients. Patients attending an outpatient clinic for type 2 diabetes were randomly assigned to intervention and control group. Intervention patients had face-to-face objective-directed medication and lifestyle counseling at baseline and at 6 months follow-up plus 8-weekly telephone assessments and provision of other educational material. The main outcome measure was change in HbA1c. A total of 123 patients participated in the study. Significant improvements in the key biomedical variables from baseline were achieved in the intervention patients ($n$=61) when compared with the control patients ($n$=62) at the 12 month assessment for HbA1c (8.6% [IQR=1.3]; 8.3 [IQR=1.0]) vs. (7.9 [IQR=1.6]; 8.4 [IQR=1.8]) ($P$ < 0.05), fasting blood glucose (12.1 [7.6]; 10.9 [7.2]) vs. (10 [4.5]; 12.3 [5]) ($P$ < 0.05), systolic (128 [20]; 130 [20]) vs. (126 [15]; 130 [20]) ($P$ < 0.05) and diastolic (80 [20]; 70 [10] vs. (71 [10]; 80 [13]) ($P$ < 0.05) blood pressure, total cholesterol (4.08 [1.3]; 4.15 [1.2]) vs. (3.75 [1.25]; 4.19 [1.1]) ($P$ < 0.05) and LDL (1.9 [0.95]; 2.0 [1.13]) vs. (1.75 [0.7]; 2.0 [0.8]) ($P$ < 0.05). Intervention patients showed also significant improvements in all aspects of diabetes knowledge, self-reported medication adherence ($P$ < 0.05), different self-care activities and health-related quality of life ($P$ < 0.05). The enhanced patient outcomes as a result of the disease management programme in the present study therefore clearly demonstrates the value of an enhanced clinical pharmacy service in achieving the desired therapeutic outcomes for type 2 diabetic patients.

**The Safety Profile of Single Daily Dose of Aminoglycosides in comparison with Multiple Daily Dose.**

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To overcome the problems which associated with the standard multiple daily doses (MDD) of aminoglycosides (AGs) like high incidence of toxicity(nephrotoxicity, ototoxicity)(5-25%) and high cost, an alternative approach was developed which was single daily dose (SDD).This new regimen was designed to maximize bacterial killing by optimizing the peak concentration/minimum inhibitory concentration(MIC)ratio and to reduce the potential for toxicity. The study includes 75 patients selected randomly, 50 of them received SDD regimen of age range of 17-79 years and the remaining received MDD regimen of age range of 13-71 years. The study was designed to evaluate the safety of SDD regimen in comparison with MDD regimen. All the patients in SDD group received a constant dose of 5-mg/kg/day of gentamicin and 20mg/kg/day of amikacin with a drug administration interval based on estimated creatinine clearance(CLcr): if ≥60 ml//min every 24 hrs (q24h), 59- 40 ml/ min every 36hrs and 39- 30 ml/min every 48 hrs.The calculated dose was diluted with 0.9% normal saline or 5% dextrose to 50-100 ml and given as intravenous infusion over 30-60 minutes. In SDD group , the mean length of therapy was 6.4±1.73 days .Gentamicin accounted for 96% of the aminoglycoside use, and the majority(58%) of patients received the drug every 24 hrs.The 36- and -48 hrs intervals were used for 34 and 8% of the population, respectively.While in MDD group , the mean length of therapy was 5.0±0.91 days. Gentamicin accounted for all (100%) of aminoglycoside use, and all of the patients received the drug every 8 hrs.

No clinically apparent ototoxicity and nephrotoxicity were observed in the patients in the SDD group, in contrast to the patients in MDD group, in whom 4 patients (16%) were developed nephrotoxicity and 1 patient (4%) was developed ototoxicity. The obtained results indicate that SDD regimen was safer through decreasing the incidence of both nephrotoxicity and ototoxicity.For statistical analysis, Fisher and t-test were used with $P<0.01$.Each mean was expressed as mean±SEM(Standard Error of Mean).Key words=Aminoglycosides, Single Daily Dose, Nephrotoxicityand Ototoxicity.

**New Therapeutical Potential in Histaminergic Receptors**

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*Al- Fujairah Campus*

Histamine release has been implicated in the pathogenesis of various inflammatory reactions. Also, this autacoid plays an important pathophysiologic role in the mediation of type 1 hypersensitivity reactions such as urticaria, hay fever and seasonal rhinitis angioneurotic edema, which is treated with H1-receptor antagonists. The second major pathophysiological role is the stimulation of gastric acid secretion, which is treated with H2-receptor antagonists. Really histamine has more pathophysiologic roles, histamine H3 receptors are involved in arousal disorders (eg attention deficit hyperactivity disorder - ADHD) and conditions associated with reduced cognition (eg Alzheimer's disease and schizophrenia. Because of its ability to modulate other neurotransmitters in the CNS such as serotonin, Noradrenalin, Ach and other neurotransmitters, H3 receptor are being investigated for the treatment of numerous neurological conditions, including obesity (because of the histamine/Anorexgenic system interaction)movement disorders (because of H3 receptor-modulation of dopamine and GABA in the basal ganglia), schizophrenia ADHD.

H3-receptor Antagonists. Abbott's H3 histamine receptor antagonist, ABT-239, a candidate treatment of cognitive disorders, ADHD, Alzheimer's and schizophrenia. Indeed, it has been found that about half the patients classified as suffering from schizophrenia have low histamine levels. H3 receptor ligands could be useful in modulating wakefulness (because of effects on noradrenaline, glutamate and histamine blood. Indeed, This receptor is a target for treating sleep disorders.

Pathophysiologic roles of histamine H4 receptors are involved in asthma and allergy, inhibiting the H4 receptor, asthma and allergy may be treated. Interestingly, patients with multiple sclerosis are deficient in histamine; in MS, the myelin of the CNS and spinal cord is destroyed. Histamine, which stimulates repair by increasing the production of myelin, is greatly reduced in MS patients. Various histamine patches and replacement therapies have been developed due to this information. Further, Research has shown that histamine is released as part of the human orgasm from mast cells in the genitals. If this response is lacking this may be a sign of histapenia (histamine deficiency). In such cases, may take diet supplements with folic acid and niacin (which used in conjunction can increase blood histamine levels and histamine release), or L-histidine. Conversely, men with high histamine levels may suffer from premature ejaculations. Indeed, Studies have shown that histamine deficiency leads to poor folic acid status

In conclusion, it is thought of interest to direct the attention of researchers on the following points.

Relationship between the histaminergic receptors & cardio vascular disease, Epileptic & histaminergic receptors histaminergic receptors, Sexual performance problems & histaminergic receptors. Obesity & histaminergic receptors Learning problem & attention and histaminergic receptors.

Asthma and H4 receptors.

The results of the new studies suggest a dramatic alteration in the distribution of histamine receptors in colon cancer. These findings raise the perspective of targeted pharmacological studies with selective histamine receptor antagonists or agonists in the therapy of colorectal tumours. Histamine Receptors & multiple sclerosis, Histamine Receptors & Sexual performance.

## The role of topical and oral melatonin in management of melasma patients

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**** College of pharmacy/University of Baghdad. ****Dermatologist /Alkarama teaching hospital /Baghdad*

Melasma is an acquired symmetric hypermelanosis characterized by irregular light- to gray-brown patches on sun -exposed areas. Many therapeutic agents are available but are unsatisfactory. Recently, it has been demonstrated that the generation of oxygen free radicals in response of skin exposure to the sun light is involved in the pathogenesis of melasma. The administration of antioxidants may decrease the effects of oxidative damage induced by ultraviolet (UV) radiation on skin pigmentation.

Melatonin is a hormone with multiple functions in human, synthesized and secreted by the pineal gland in response to changes in the darkness and light environment of the human. It is a powerful antioxidant and the most potent free radical scavenger known.

This novel study was designed to evaluate the possible effects of topically formulated melatonin cream alone or in combination with sunscreen and oral melatonin for the management of melasma patients in comparison with hydroquinone as a standard therapy.

In a double blind manner, this preliminary clinical study was performed on 36 patients with epidermal melasma and 10 healthy subjects as control. They were diagnosed as having melasma and they were under dermatologist supervision during the entire period of treatment. The patients were allocated into four groups (A, B, C, and D), and treated with topical melatonin only, topical melatonin and sunscreen, topical and oral melatonin, and 4% hydroquinone cream, respectively for a period of 90 days followed by 30 days treatment with placebo.

The severity of melasma was evaluated using the Melasma Area & Severity Index (MASI) before starting treatment and after each 15 days for 120 days. To evaluate the oxidative stress status, malondialdehyde (MDA) and glutathione (GSH) levels in plasma were measured before starting treatment and after 45, 90, and 120 days of treatment.

At the end of treatment period (90 days); all melasma patients demonstrated significant reduction in MASI score in different levels. In all groups, the plasma MDA levels were decreased and plasma GSH levels were increased in different scales after 90 days of treatment.

The overall results of this study suggested that topical melatonin could be used as a hypopigmenting agent in treatment of melasma, and this effect is augmented by the oral administration of the drug and the use of sunscreen, possibly by its antioxidant activity or by other mechanisms unrelated to antioxidant effect.

**المؤسسة العامة للغذاء و الدواء**
**أ. د. محمد رواشده**

**نشأتها :**

أنشأت المؤسسة العامة للغذاء والدواء بقانون مؤقت رقم( 31 )لسنة 2003 و تتمتع وفقه بشخصية اعتبارية ذات استقلال مالي وإداري :- حيث تعتمد ايرادات المؤسسة بالكامل على الرسوم وبدل الخدمات التي تتقاضاها بموجب التشريعات النافذة المتعلقة بالغذاء والدواء ولا يتم رصد اية مخصصات لها في الموازنة العامة .كما أن للمؤسسة مديراً عاماً يرأس اللجنة العليا للغذاء واللجنة العليا للدواء،وهو ايضا نائب رئيس مجلس ادارة المؤسسة والتي يرأسها معالي وزير الصحة وأعضاء من القطاعين العام والخاص.

**الاسباب الموجبة لانشائها:**

من أهم الاسباب الملحة لانشاء المؤسسة ؛ تزايد الاهتمام الرسمي والوعي الشعبي باهمية سلامة الغذاء وفاعلية الدواء ,عولمة التجارة , مواكبة الالتزامات الخارجية للاردن , انتشار ظاهرة التزوير والتهريب والتسوق الالكتروني والافراط في استخدام التقنيات الحديثة في الغذاء كالاغذية المحورة جينيا والدواء. ونظرا لضرورة وجود سلطة وطنية مركزية مختصة بالرقابة على ذاء و الدواء تعمل على رفع كفاءة وفاعلية النشاطات الرقابية وتقوم بتنسيق العمل الرقابي دون ازدواجية او ثغرات وتعمل على تحديد صلاحية جهات الرقابة الرسمية بالاضافة الى ضبط و اعتماد القواعد و الاسس العلمية لاجراءات الرقابة و تطويرمفاهيم واساليب حديثة للرقابة.

**التشريعات الضابطة لعمل المؤسسة:**

تتولى المؤسسة العامة للغذاء و الدواء المهام والصلاحيات المنوطة بها بمقتضى قانون الرقابة على الغذاء و الدواء بالاضافة الى الاستناد لمجموعة من القوانين السارية ذات العلاقة بالغذاء والدواء وهي :-

- قانون المؤسسة العامة للغذاء والدواء رقم (41)لسنة 2008
- قانون الدواء والصيدلة رقم (80)لسنة 2001
- قانون الدراسات الدوائية
- قانون المخدرات والمؤثرات العقلية
- قانون الرقابة على الغذاء رقم (79)لسنة 2001
- قانون الصحة العامة رقم ( 54) لعام 2002

**المؤسسة العامة للغذاء و الدواء (رؤيتها و أهدافها و مهامها ):**

تحقيقا لرؤى جلالة الملك عبد الله الثاني المعظم في خطاب العرش السامي في افتتاح الدورة العادية الاولى لمجلس الامة الخامس عشر وضعت المؤسسة نصب عينيها تحقيق الاهداف الوطنية و المتمثلة في أولا: تأمين كل مواطن بمستوى جيّد من الخدمات الحياتيّة والأساسية. ثانيا :تعزيز تنافسية اقتصادنا الوطني. و لانجاز هذة الاهداف تم تحديد مهام وواجبات المؤسسة على النحو التالي:-

**- مديرية الدواء:**

تتلخص مهام مديرية الدواء بمسؤوليتها عن إجازتة الدواء منذ بدايتة كمادة خام وحتى الحصول عليه كمستحضر جاهز لاستعماله من قبل المريض و ذلك لضمان سلامة وجودة وفاعلية الدواء (سواء المصنع محليا أو المستورد) وتوفيره للمواطن بسعر مناسب. وتقوم مديرية الدواء باداء العديد من المهام من خلال أقسامها الادارية و الفنية الاحد عشر بالاضافة الى اثنتي عشرة لجنة فنية و من هذه المهام :-

تقوم بمراقبة الاتجار المشروع بالمخدرات والمؤثرات العقلية والسلائف الكيماوية و منح التراخيص للمتعاملين بها ومتابعة استيرادها واستلامها ومراقبة التوزيع الداخلي لها , تسجيل و اجازة وتسعير جميع الادوية و المستحضرات وبشكل مستمر وفق الأسس والمعايير المتعلقة بذلك ومنها تسعير الأدوية الأصيلة (Originators) تسعير الأدوية الجنيسة (Generics) , الرقابة والتفتيش على كافة المؤسسات الصيدلانية من صيدليات ومستودعات ومصانع ادوية ( محلية أو خارجية) و المؤسسات الغير صيدلانية وتتبع الادوية المزورة, إجراء دراسات حيوية أو دراسات التكافؤ و تقييم البروتوكولات الخاصة بها , تشجيع و تسهيل تصدير واستيراد الادوية حسب المعايير العالمية , متابعة و تشجيع الاستهلاك الرشيد للأدوية.

**- مديرية الرقابة على الغذاء:**

تتلخص مهام مديرية الرقابة على الغذاء في النهوض بمستوى الرقابة الصحية على الغذاء إلى أعلى مستوى ممكن ضمن الإمكانيات المتاحة من خلال التخطيط الجيد لبرامج الرقابة الصحية على الأغذية والإشراف الفعال على هذه البرامج وإدارة الإمكانيات المتاحة بكفاءة و فاعلية, وتطوير مفاهيم واساليب حديثة للرقابة على الغذاء. وتقوم مديرية الرقابة على الغذاء باداء مهامها الرئيسية من خلال أقسامها الادارية و الفنية التسعة و بالتزامن مع وجود سبعة لجان ادارية وفنية و من هذة المهام :-

اعتماد مفاهيم وقيم رقابية حديثة منها نظام الرقابة على الأغذية المبني على درجة الخطورة الصحية , الرقابة الشاملة على سلسلة الغذاء من المادة الخام وحتى وصوله الى المستهلك , نظام تصنيف الاغذية الى ثلاث مسارب , دراسات وبرامج الرصد وتحليل المخاطر الخاصة بالاغذية و مكوناتها كمتبقيات المبيدات والمعادن الثقيلة و الملوثات الجرثومية و الكيماوية وغيرها , مفهوم الرقابة المتكامل ( تطبيق التشريعات وبرامج الرقابة الذاتية و توعية المستهلك) , الشراكة و التنسيق مع الجهات الرقابية الأخرى من خلال توقيع مذكرات التفاهم , مراجعة المواصفات الغذائية و تعليمات الرقابة على الغذاء و تحديثها و هذا يشمل الغذاء المتداول محليا في الاسواق و المستورد عبر المراكز الجمركية.

**دراسات الجدوى الإقتصادية:**
**الصيدلي: زياد عبدالحميد سنقرط**

- ضرورة عمل دراسة الجدوى للمشاريع الإقتصادية.
- طبيعة عمل المشروع ، صناعي، زراعي، تجاري، عقاري، أم خدماتي.
- التأهيل لعمل دراسات الجدوى الإقتصادية.

مشاريع الصناعة الدوائية:

- خصوصية المشروع، وأسلوب عمله.
- الموقع والظروف الإقتصادية والإجتماعية المحيطة بالمشروع.
- الأسواق المستهدفة، وإمكانيات التوسع فيها.
- توفر الخبرات والمعرفة الفنية.
- مصادر الأيدي العاملة، والإمكانيات التدريبية.
- الأصناف المزمع إنتاجها.
- أعمال البحث والتطوير اللازمة، وتحديد المواصفات.
- عمل دراسات التكافؤ الحيوي.
- طرق التصنيع والتعبئة والتغليف.
- الآلات والأجهزة اللازمة للإنتاج ورقابة الجودة.
- المواد الأولية والمواد المساعدة اللازمة ومواصفاتها.
- أساليب الرقابة النوعية على مدخلات الإنتاج والمنتج النهائي.
- نظام متكامل لضبط الجودة.
- العمالة اللازمة آنيا ومستقبليا.
- مساحات الأراضي والمباني اللازمة لتحقيق الأهداف الحالية والإستراتيجية.
- المتطلبات البيئية المتعلقة بالمشروع.
- التمويل اللازم لنجاح المشروع.
- المدة الزمنية اللازمة لإنجاز الدراسات الهندسية للمشروع والمباشرة بالعمل.
- المدة الزمنية اللازمة لإنجاز وإستلام مباني المشروع والمباشرة بتركيب الماكنات.
- وضع البرنامج الزمني الأنسب لإنجاز عمليات التأهيل للماكنات، وعمليات التحقق للمعادلات الإنتاجية.
- مصاريف ما قبل التشغيل.
- مصاريف ما قبل طرح المنتج في الأسواق.
- دراسة الكلف التسويقية، وتحديد الأسلوب التسويقي الملائم.
- تحليل البيانات وإحتساب الربحية، والزمن اللازم لإسترداد رأس المال.

**Drug Promotion**.

**Adi Nuseirat**
*Head of Rational Drug Use Department*
*JFDA*

This lecture is aimed to give the audience an idea about the new guidelines that launched from Jordan Food and Drug Administration to control drug promotion.

Drug Promotion is any activity undertaken, organized or sponsored by a pharmaceutical company, or with its authority, which promotes the prescription, supply, sale, administration or consumption of its medicinal product.The physician's main sources of pharmaceutical information are the pharmaceutical industry through: Face to face meetings, Lectures, Samples, Brochures. Studies consistently show that promotion increases prescribing; Increased prescribing with increased contact; more costly prescribing; more non-rational prescribing; new drug prescribing; decreased use of generic drugs. Studies also show that physicians do not believe that promotion affects prescribing.

JFDA newly launched guidelines (code of ethics) to ensure that pharmaceutical companies conduct their promotion in a truthful manner avoiding deceptive practices.
These codes cover all methods of promotion including: oral and written promotional activities and communications, journal and direct mail advertising, the activities of medical sales representatives:
**International events** – No meeting outside of home country of prescribers unless appropriate or justified (security, diverse nationalities…)
**Company sponsorship of prescribers** – Unconditional, no payment for time spent; no sponsorship of accompanying guests
**Payment of reasonable fees** for speaker allowed on the basis of a written contract
**Hospitality** – no stand alone entertainment
**Gifts** - these must be inexpensive and relevant to the practice of the professional. ban on cash gifts; reminders & gifts of medical utility allowed; cultural courtesy gifts allowed if defined.
**SAMPLES** - a limited number may be supplied to healthcare professionals who are qualified to prescribe that medicinal product in order to familiarize them with the product (No more than 10 samples of a particular medicine may be provided to an individual health professional in one year). Companies must have adequate systems of control and accountability for samples which they distribute and for all medicines handled by its representatives. Each sample shall be no larger than the smallest presentation on the market. Each sample must be marked ‘free medical sample– not for resale’ or words to that effect. No samples of medicinal products which contain substances defined as psychotropic or narcotic.
**Company representative visits –** Representatives must have adequate training and sufficient scientific knowledge to enable them to provide full and accurate information about the medicines they promote. Representatives must not make claims or comparisons which are inaccurate, misleading, disparaging, in poor taste or which are outside the terms of the marketing authorisation (e.g.: an unlicensed indication). They must be able to provide a Summary of Product Characteristics (SPC) for the medicines they are promoting on request.

# The actual and the Clinical Studies Law in Jordan

**Saleem Al-Mahrouq, M.Sc. Clinical Pharmacy**
**CTU-JFDA**

The Hashemite Kingdom of Jordan is considered one of the pioneers in the field of clinical trials as it is the only Arab country in the region that has a law for the clinical trials which is the lax of Clinical Studies, Provisional Lax No. (67) For the year 2001.

As the safety and wellbeing of the participants in the clinical studies being held in Jordan are the tow major considerations of the Jordan Food and Drug Administration, the Clinical Trials Unit was established Within JDFA in August 2004.

A committee is formed at the Administration called (clinical Studies committee) and chaired by the Director General and the membership of specialists form the JFDA, the Director of pharmacy at the Royal Medical Services and five members representing universities and private sector who are specialized in the fields of kinetic, analytical pharmacy, biostatistics, clinical pharmacy, pharmacology.

Clinical studies are in general divided into:

a) Therapeutic clinical studies: Any clinical study performed on sick or healthy volunteers.

b) Non- Therapeutic clinical studies: Any study performed on healthy volunteers in terms of effectiveness, kinetics, bioequivalence. A clinical studies will not be performed on a human being without his/her written approval(signed consent form) and after undergoing the medical tests necessary for his/her safety.

Clinical studies can't be conducted unless the performing body has obtained an authorization from the Minister of Health upon a recommendation from the Clinical Studies Committee Clinical studies are executed at hospitals that possess technical to provide the required and intensive care in addition to laboratory that carries out clinical tests. University academic institutions, specialized scientific research institutions and pharmaceutical manufacturing companies, which have the required technical potentials, are also included.

Another committee is formed within the conducting authority called (The Institutional Review Board committee) consisting of at least five members from both sexes with enough experience and quite competent provided that one of them should be legal advisor in addition to a representative from the local community.

Both the Clinical Studies Committee and the CTU in the JFDA assume certain responsibilities and powers.

## الملف المكتمل الوثائق لغايات التسجيل

**Pharm Hakima Ibraheem Hoseh**
Head of regestration unit, registration department, JFDA

ن قسم التسجيل وهو القسم المعني باستلام الملفات وتدقيقها وعرضها على اللجان المعنية لدراستها ومن ثم تسجيلها او اجازة تداولها سواء كان ملفا لموقع تصنيعي لشركة منتجة او لمستحضر دوائي او مستحضر طب نووي او عشبي او فيتامين او مستحضر تجميلي اومستلزم طبي. وللتنوع الكبير في المتطلبات تم تخصيص شعب لمتابعة جميع المعاملات الخاصة بكل مستحضر وتم إصدار اسس خاصة لكل نوع من انواع المستحضرات لتتم عملية التسجيل او الاجازة بناء على اسس واضحة لكلا الطرفين وتسهيل الحصول على المتطلبات واذكر هنا توفر هذه المتطلبات على موقع المؤسسة الالكتروني www.jfda.jo.

وحيث انني رئيسة شعبة التسجيل سأتحدث عن الأدوية الجديدة والتي لها مثيل مسجل وبعض الملاحظات التي تؤدي الى عدم اكتمال الوثائق حيث يشترط لتسجيل الدواء التأكد من أن الملف مكتمل الوثائق تحقيقا. للمادة التاسعة – ا من اسس التسجيل والتي تنص على انه : "تبت اللجنة في أي طلب تسجيل للأدوية الجديدة والأدوية التي لها مثيل مسجل يرد إليها خلال مدة لا تزيد عن مائة وثمانين يوما(180) من تاريخ تقديم الطلب المكتمل الوثائق لدى المديرية ".

تبدأ عملية التسجيل لاي مستحضر بالترتيب لاخذ موعد لتسليم الوثائق اللازمة وهي عملية مرتبطة بكيفية تقديم الوثائق ومدى معرفة مقدم الوثائق بمحتواها وتحقيق شرط أن الملف مكتمل الوثائق حيث تنص الاسس على انه " يقدم طلب تسجيل الدواء الجديد والدواء الذي له مثيل مسجل لدى المديرية من قبل الصيدلي المسؤول في المستودع أو المدير الفني في مصنع الأدوية المحلي مرفق به الملف المكتمل الوثائق حسب المتطلبات المذكورة في الملحق رقم (1) من الاسس."

أما تعريف الملف المكتمل الوثائق فهو ملف مستحضر لموقع وخط إنتاج معتمد واثبت مأمونية استعماله وفعاليته عن طريق الدراسات السريرية ودراسات التوافر أو التكافؤ الحيوي واثبت جودته عن طريق دراسات الثبات المتسارعة والحقيقة .

فهل يتم تقديم ملفات مكتملة الوثائق ؟؟؟وما اسباب تأخر عملية التسجيل في بعض الاحيان ؟؟؟؟

واذكر هنا بعض الاسباب :

1. عدم معرفة الصيدلي المسؤول في المستودع او الشركة للقوانين واسس التسجيل المعتمدة في مديرية الدواء وقسم التسجيل .
2. عدم وجود برنامج تدريبي خاص للصيادلة المختصة في انظمة التسجيل وقوانين التسجيل قبل البدء بتقديم الملفات
3. أن يكون الموقع التصنيعي أو خطالإنتاج غير معتمد لنفس الشكل الصيدلاني للمستحضر خاصة ان كان المستحضر بيولوجيا يجب اعتماد خط المستحضر نفسه وليس خط الإنتاج
4. عدم نجاح دراسة التكافؤ او دراسة الذائبية او الدراسات السريرية بسبب عدم توافق الدراسة مع المتطلبات الحديثة

وفي اغلب الاحيان تكون نواقص الملفات كالتالي:

- عدم احضار شهادة الممارسة الطبية الجيدة او شهادة التحليل الجيد
- عدم احضار دراسة الذائبية المقارنة لغايات التكافؤ
- عدم التقيد بقواعد التحليل الاحصائي
- عدم احضار شهادات التحليل للمستحضرات
- عدم اجراء الدراسات المطلوبة والتي تتناسب مع الشكل الصيدلاني للمستحضر

5. عدم معرفة ان المستحضر مستثنى من تقديم دراسات التكافؤ
6. عدم التقيد بتقديم الوثائق المطلوبة حسب قائمة محتويات ملف المستحضر المعتمدة في المؤسسة ومراعاة المحدثة باستمرار
7. عدم الانتباه لمدة صلاحية الشهادات ومراجعة تاريخها قبل تقديمها والتاكد من تصديقها اصوليا وذلك بختم كل صفحة من الصحة والسفارة و الخارجية او ان تكون مختومة بشكل كلي ال
8. عدم التأكد من المستحضر مباع في بلد المنشأ وبنفس التركيبة او احضار الشهادات البديلة .
9. عدم التأكد من تشابه نشرة المستحضر الذي له مثيل بنشرة المستحضر الاصيل.
10. عدم احضار دراسات الثبات المطلوبة بحيث تغطي في حدها الادنى ستة اشهر متسارعة واثني عشر شهرا للدراسات الحقيقة واحضار الرسوم الاستشرابية لأحد التشغيلات على الأقل والتي تغطي نقطة البداية ونقطة النهاية للدراسة المقدمة
11. عدم احضار الدراسات التثلتية لطرق التحليل مع الرسوم الاستشرابية كاملة لها
12. عدم مراعاة تقديم دراسات الثبات التي تتوافق مع أن الأردن ضمن المنطقة المناخية الثالثة والتي تتطلب تقديم دراسات ثبات الحقيقية على درجة حرارة 30 درجة منوية ورطوبة 60% إلا إذا اقتضى المستحضر غير ذلك.
13. عدم إجراء دراسات الثبات الخاصة بالاستخدام مثل دراسة ثبات بعد الحل ، او دراسة ثبات الوضع للحقن وغيرها
14. عدم احضار التبرير العلمي من الشركة الصانعة في حال عدم الالتزام باي من المتطلبا ت او وجود أي اختلاف عنها .
15. عدم التقيد بمتطلبات العبوات خاصة فيما يتعلق بذكر ظروف التخزين اوتوافقها مع دراسات الثبات
16. عدم الانتباه الى الاسم التجاري بحيث لا يتشابه مع الاسم العلمي والتركيز على تسويق اسم الشركة الصانعة او ماشابه
17. عدم التقيد بتقديم احدث تقرير مأمونية وعدم التقيد بالاسس الخاصة به وموافقة النشرة مع ما به من معلومات .
18. عدم متابعة التعاميم التي تصدر اما لتحديث المعلومات او لتوضيحها .

واخيرا هذه بعض الملاحظات والتي تتكرر باستمرار واعتقد بداية ضرورة عمل برنامج تدريبي للصيادلة المسؤولين لمراجعة قسم التسجيل قبل البدء بذلك، واصدار شهادات تاهيل لهم بحيث يصبح الصيدلي المسؤول مؤهلا Qualified Person وذلك اون المؤسسة مع جميع المؤسسات ذات العلاقة بدأ بالجامعات بتخصيص محاضرات خاصة بالقوانين التي تحكم عملية التسجيل محليا وعالميا ونقابة الصيادلة واتحاد منتجي الادوية وجمعيات المستودعات.

## Good Manufacturing Practice

**Dr Soumah Al-Qutob**
Head of factories section / Inspection and monitoring department
Jordan Food and Drug Administration

This lecture will focus on Good Manufacturing Practice (GMP): what is GMP, how does it apply, why is GMP important, what are the essential parts of GMP.
GMP is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by Marketing Authorization or product specifications.

GMP covers all aspects of production, from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product.

There must be systems to provide documents proof that correct procedures are consistently followed at each step in the manufacturing process-every time a product is

The essential parts of GMP are:
Organization and Personnel
Building and Facilities
Equipment
Control of components and drug product, containers and closures
Production and process controls
Holding and distribution
Packaging and labeling controls
Laboratory control
Records and Reports
Returned Drug Products
Analytical Method Validation.
Good Practices means less findings which leads to compliance.

## The Role of Food and Drug Administration on Narcotic and Psychotropic Substance Control

**Heyam Wahbeh**
*HEAD OF NARCOTIC AND PSYCHOTROPIC CONTROL DEPARTMENT*

Food and Drug Administration is the responsible authority on the licit trade control of narcotic and psychotropic substances and controlled chemical precursors in Jordan through the narcotic and psychotropic substance control department in Drug Directorate to ensure the availability of these substances for medical & scientific purposes and prevention of its diversion from licit International Trade into illicit Channels.

Narcotic and psychotropic substances have been classified internationally according to its susceptibility to abuse and addiction into four schedules for narcotic and four schedules for psychotropic substances.

The control of these substances based on the provisions of the international conventions and Jordan laws acts and Regulations. It is Includes both the International control system like Issuing import & export licenses, reporting the annual quarterly statistical reports in addition to the assessment of annual medical & scientific requirement and the national control system like issuing special licenses for physicians, pharmacists and scientific Institutions also distribution control between the whole sailors and retailers.

The latest stage of control is the Inspection system on the manufacturers, exporters, importers, wholesale distributors, retail distributors and the medical scientific institutions that use these substances to monitor the application of control measures required by the law regulation.

So that we notice that the control of narcotic and psychotropic substances, starts from it's the import, distribution ending its use**.**

## Human Resource Management: A Vital Function in Organizations

**Yara K. Abu Taleb, MSc Pharmacist, Diana T. Blokh, MSc Pharmacist,**

The Royal Medical Servies, Jordan

Human resource management (HRM) is a vital function in organizations; it engages everyone and it take time. Managing human resources effectively requires that the special expertise of HR professionals in the HR department be used by, and in partnership with, line managers and other employees. It involves attending to the concerns of the moment while keeping a longer-term perspective in mind. It also involves continuously improving and changing activities that take time to put in place and produce results. Consequently, HRM includes:

1. The people managing activities, policies, and practices that firms can use to compete effectively now, and

2. The many changing forces (e.g., new competitors, new technology, business restructuring, legal, and social concerns) that organizations need to understand and respond to in order to ensure they are positioned to compete effectively over the longer term.

HRM involves all management decisions and actions that affect the nature of the relationship between the organization and employees its human resources. And it encompasses the development of all aspects of an organizational context, so that they will encourage and even direct managerial behaviour with regard to people. HRM is organizational in its compass, it involves all managerial personnel, it regards people as the most important single asset of the organization and it seeks to enhance company performance, employee needs and societal well-being. It comprises a broad area of focus and carries with it the ideal of increasing the sum of human satisfaction at a variety of levels.

Moreover, other than the links with strategic management from a disciplinary standpoint, it synthesizes elements from international business, organizational behaviour, personnel management and industrial relations. Moreover, its diverse parent disciplines include various relevant themes from occupational psychology, labour economics and industrial sociology.

**Exploring practices and theories governing regulatory affairs profession and clarifying its important impact on pharmaceutical organizations and on the pharmacist as an employee.**

**Lubna Rshaidat; Asma Al-Khateeb**

Methods:

- Direct interaction with various health authorities all over the world.
- Direct interaction with regulatory affairs professionals all over the world.
- Practical experience in regulatory affairs field.
- Reputable web sites of regulatory affairs oriented magazines and publications.

Regulations governing the pharmaceutical fields are very strict, and they are not limited to the pharmaceutical industry sector but they extend to govern all pharmaceutical sectors practices like control or direct all pharmaceutical product life cycle according to rules, guidelines , or laws for drug from its being a chemical entity molecule through its journey being formulated and produced , its approval phase and launching into market then its post marketing rules, guidelines , or laws. Nowadays; calls for stricter regulations are coming from governmental concerns as well as the medical community at large. Although this direction started from the developed countries; increased regulation is being globally implemented.

Long gone are days when the, Regulatory affairs professional's role focused largely on regulatory submissions (registration). In 30 years, Regulatory affairs transformed from that little known job function into a vital, recognized profession, at the core of the health product lifecycle.

Regulatory affairs professional's role can encompass a wide range of responsibilities, from developing regulatory strategy – at a certain health authority- to qualifying manufacturing facilities or clinical sites, coordinating and or writing regulatory submissions, overseeing the Quality assurance functions, working on licensing deals and even filing. Consequently; the demand for regulatory affairs professionals is growing among all types of organizations, industry, government, research & clinical institutions and academia. So, don't be surprised if you know that many professionals form scientific, clinical and engineering are transitioning into regulatory affairs.

Results:

The trend toward more aggressive regulations is increasing. Regulatory affairs is the job function that puts those regulations and deals with them, and regulatory affairs professionals are those who have the limitless role in all phases from research and development through post market advertising and promotion.

Conclusion:

- RA is a very important field of which global attention is getting dramatically increased.
- Having Professional RAs in the pharmaceutical organization is a major need for organizational success.
- Working in RA field is a major added value and way to career success for the pharmacist's benefit.
- Importance and global trend of getting benefits from experts in RA translated into collaborative work between Health Authorities RAs and Pharmaceutical institutes RAs to put and implement rules, guidelines , or laws for Drug products
- One of the tools for exchanging information and maintaining RA professionalism is getting benefits from experts of RAs within same sector and RAs within all over the world Pharmaceutical institutes.
- It is recommended to put and implement action plans raising the caliber of RAs in Jordan and Arab world.

**The Role of Oxidative Stress in the Long Term Neurotoxicity of TCDD**

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The University of Toledo
College of Pharmacy
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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is one of the most toxic environmental pollutants known. Accidental acute human exposure to high concentrations of the compound occurred in several areas of the world and resulted in several human diseases, with the liver considered as one of the main target organs for the toxicity. Several mechanisms have been proposed for the acute toxicity of the compound, including oxidative stress. We have studied the involvement of oxidative stress in the TCDD-induced hepatotoxicity after chronic exposure to low environmental concentrations of the compound in rats. We also assessed the role of oxidative stress in the long term neurotoxicity of the compound by studying the induction of this mechanism in the brains of animals and compared the results with those of the liver. Our results indicated that oxidative stress, including production of reactive oxygen species and oxidative tissue damage indicated by the production of lipid peroxidation and DNA damage is significantly induced in the livers and brains of animals after chronic exposure to environmental concentrations of the compound. The results also indicated that the cerebral cortex and the hippocampus were the most affected regions of the brains and that those effects were associated with changes in the distribution of the biogenic amines in different brain regions. Our results were considered to be the first to indicate the brain as another target organ for the long term toxicity of TCDD.

## Stability of drugs in postmortem

**Ph. Bayan Al-Awaisheh**
*Master Analytical toxicology*

Ministry of health. Stability of drugs in biological samples stored under different conditions, is regarded a nightmare for toxicologists, especially after along time lapses before sample analysis.

There is a shortage of data regarding the stability of drugs of forensic interest in human postmortem blood, especially when the postmortem tissue samples has been subject to variable degree of putrefaction, or in some cases, acquisition by the laboratory to perform a full drug screen is after a few months of storage due to a requirement for new evidence.

Therefore it is necessary to establish whether these drugs are stable over a period of time under different storage conditions.

Toxicological analysis of poisons causing death is a complicated process because of the normal chemical changes that occur during decomposition of poisons or drugs.

The toxicological analysis should be started as soon as possible after death because the natural enzymatic and non enzymatic processes of decomposition and microbial metabolism may destroy a poison initially present at death, or may produce substances or compounds with chemical and physical properties similar to those of commonly encountered poisons.

**Factors affecting blood pressure and quality of life in out-patients with hypertension: focus on drug related problems**

**AbuRuz S., Abu Farha R**
Department of Clinical Pharmacy, *Faculty of Pharmacy, The University of Jordan, Amman, Jordan*

Unawareness and poor control of hypertension remain important national health concerns. Although factors such as decreased access to medical care and financial barriers contribute to lower control, blood pressure control is poor even in patients who can receive pharmacological treatment. As a consequence, improving care and, in particular, resolving and preventing drug related problems could increase disease control. The effect of drug related problems on blood pressure was not previously investigated in the literature. Also the factors affecting blood pressure in Jordanian population was not previously investigated. Identifying these factors is very important in order to improve blood pressure control rate in Jordan. The primary aim of this study was to investigate the effect of the presence of drug related problems on blood pressure control and quality of life in out-patients with hypertension. Two hundred patients were recruited during the study period. The major end result of this cross sectional trial is that the presence of drug related problems is considered one of the most important determinants of blood pressure control and quality of life in out-patients with hypertension. We also identified other factors that significantly affect blood pressure and quality of life in Jordanian hypertensive patients.

# Effects of Low Doses of Captopril or Losartan in Improving Glycemic Control by Oral Hypoglycemic Agents in Type 2 DM Patients

**Saad Abdul-Rehman Hussain [1] (B.Sc., M.Sc., Ph.D.),**
**Nesren Shaban Mohammed [2] (B.Sc., M.Sc., Ph.D.),**
**Esam Noori Al-Karwi [3] (MBChB, FIBM)**

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Background and Objective:
Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Cross-talk between the rennin-angiotensin system (RAS) and insulin signaling has been demonstrated. The rennin angiotensin system (RAS) may regulate pancreatic islet blood flow, oxygen tension, and islet (pro) insulin biosynthesis. The present study was designed to evaluate the effect of low doses captopril and losartan, as adjunct treatment in uncontrolled type 2 DM patients treated with oral hypoglycemic agents alone.

Methods: This double-blind placebo-controlled clinical trial was conducted on 75 patients with uncontrolled type 2 diabetes mellitus; they are randomized into three groups:
Group A: includes (25) patients treated with placebo formula containing lactose only for 4 months; group B: includes (25) patients treated with 12.5 mg captopril given once daily at bed time, for 4 months; group C: includes (25) patients treated with 25 mg losartan given as a single daily dose at bed time for 4 months; all patients take the test drugs in addition to the routinely administered oral hypoglycemic drugs (glibneclamide and metformin). After 12 hours fasting, blood samples were collected from all patients to measure fasting plasma sugar (FPS), glycated hemoglobin ($HbA_1c$), C-peptide, triglyceride (TG), total cholesterol, low density lipoproten (LDL), high density lipoprotein (HDL), serum urea and creatinin, microalbuminuria (MAU), C-reactive protein, alanine transaminase, aspartat transaminase, alkaline phosphatase (ALP) and gamma glutamine transferees(GGT), before starting drug treatment (as zero time sample) and then after 4 months of treatment to follow the changes in the studied parameters.

Results:Adjuvant use of low doses of captopril or losartan with the currently used oral hypoglycemic agents (glibneclamide and metformin) results in significant reduction in FPS and $Hb_{A1c}$ levels associated with increase in C-peptide level compared to those treated with the oral hypoglycemic agents and placebo; additionally, lipid profile, MAU, renal and liver functions were significantly improved after 4 months of treatment.

Conclusion:Inhibition of RAS by ACEIs or AT1 antagonists (ARBs) increases insulin sensitivity and improves insulin secretion, where treatment of poorly controlled type 2 DM patients with captopril or losartan resulted in improving the response of target tissues to glibneclamide and metformin.

**Precipitating factors for hemolytic anemia among glucose-6-phosphate dehydrogenase deficient patients in North Jordan.**

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**[2] Mohammad J. Al-Ajlony, MD.**
**[1] Sayer I. Al-Azzam, Pharm D., MSc.**
**[1] Abeer Ayoub, MSc.**
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*[2] Department of Pediatrics, Princess Rahma Teaching hospital, Irbid, Jordan.*

Background:
Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common human enzyme deficiencies. In children, a potentially life-threatening hemolytic anemia can result from the ingestion of fava beans by persons with G-6-PD enzyme deficiency.

Purpose:
This study aims to investigate the precipitating factors for hemolytic crisis in G6PD deficient pediatric patients in northen Jordan .

Methods:
Retrospectively & prospectively a total of 284 pediatric patients (218 males and 66 females) were studied. Data was obtained from the medical records of patients admitted to *Princess Rahma Teaching hospital* in Northern Jordan between the period of January 2001 to April 2007 & from parents of newly admitted patients during the study . Patients included in this study were G6PD deficient children who were admitted to the hospital secondary to a hemolytic anemia episode.

Results:
Out of 258 pediatric patients included, 244patients (94.2%) had developed hemolytic episode secondary to ingestion of fava beans. The remaining 15 children (5.8%) developed hemolytic episode triggered by other factors including drugs (Non-steroidal anti-inflammatory drugs "NSAIDs" and co-trimoxazole) and upper respiratory infections & 1 child from those develops hemolysis after breast feeding. Amongst the studied sample (n=284), 278 (98.6 %) were jaundiced on admission, while the rest (1.4%) did not show clinical jaundice.

Conclusion:
Fava bean ingestion was the major precipitating factor for hemolytic anemia episode amongst G6PD enzyme deficient children. Other minor triggers like infections, drug use &breast feeding were noticed to induce hemolysis in sample studied.

**Novel Synthesis of Macrocyclic Bisbenzylisoquinoline Models With One Ether Linkage Utilizing Lithiation-Alkylation Approach**

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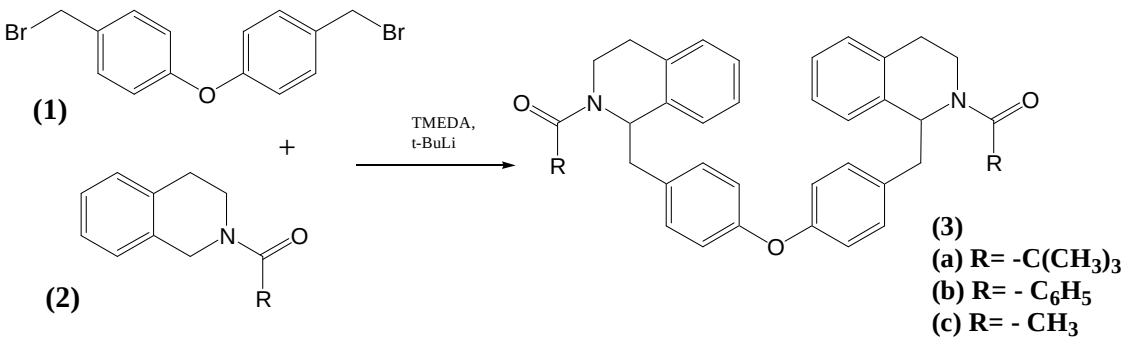
Bisbenzyltetrahydroisoquinolines (BBIQs) are naturally occurring alkaloids with broad spectrum of biological activity. Although more than 400 members were reported, their synthesizes are long and low yielding. As a result, there have been no systematic attempts at exploitation of the potential therapeutic applications.

This research aims at using N-acyl-BBIQs as a new approach to prepare models, new substituted and naturally occurring one ether BBIQs (**3**). The idea involves preparing novel models of the N-acylated tetrahydroisoquinoline heads (**2**) followed by coupling with substituted-(dibromomethyl)diphenyl ether tail unit ((**1**). Acylating the 1,2,3,4-tetrahydroisoquinoline nucleus with the proper acyl chloride furnished the N-acetyl, N-benzoyl and N-pivaloyl derivatives with high yields. The N-acylated head of each type was coupled through lithiation reaction to produce the colored anion, then followed by alkylation with the target diphenyl ether tail. Although n-BuLi and DPA were used for lithiation of the head, best coupling conditions were obtained with N-pivaloyl head. Employing t-BuLi, TMEDA in THF at –78 ºC, furnished more than 85 % yield of the pivaloyl derivatives (**3a**) with non-detectable side products. Lower yields were obtained with the N-acetyl and the N-benzoyl derivatives. The final products were easily purified by Chromatography and crystallization, characterized by NMR, IR, EA and MS techniques.Such procedure can be good start to prepare new or natural candidates for further biological activity screening.

**Graphical abstaract**



**Pharmaceutical Effects of Cadmium Toxicity on the Cellular Ultra Structure**

**Hussain. A. Shareiff* and Aliaa H. Ahmed**
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The toxic effect of heavy metal (Cadmium) was investigated using a species of freshwater aquatic insect-nymph of Ephemeroptera, Cloen dipterum (L). This heavy metal was found to have a significant pharmaceutical effect on the fine structure of the cells in proportion to the concentration of cadmium used (0.1, 0.5 and 1 ppm). The results were supported by ultra structural observation on different types of the gill cell organelles (gill lamella, nucleus, mitochondria, endoplasmic reticulum and other parts of the cell). Transmission electron microscopy has revealed the disruption and the damage for the normal cellular organization of the lymph gill cells when the animal exposed for 36 hours in the pollutant media. Most of the freshwater pollution scientist thought that this kind of aquatic insects can be used as biological monitors of heavy metal pollution.

The aim of the present study is to investigate the poisoning pharmaceutical effects of this heavy metal on the mortality caused by ultra structural damage which is standing behind the death of the animal and human being from one hand and to explain that the removal of free sulphydryl groups by a combination with some heavy metals had an acceleration of respiration and at high concentration the metal become attached to the enzyme molecules themselves and made inhibition of oxygen uptakes follows, from the other hand. This fact may stand behind the cell death as an accessory reason which is added to the organelles damage happening when heavy metal poisoning takes place.

**Prescribing Pattern of NSAIDs in outpatient clinics in Royal Rehabilitation Center**

**Kholoud Z. Qoul MSc clin. Pharm, Ikbal N. Thuheerat* MSc clin. Pharm,**
*Royal Medical Services.*

Objectives:
Analyzing prescribing pattern of NSAIDs in OPC at RRC and studying the correlation between the use of selective COX-2 inhibition and the use of conventional NSAIDs.

Methodology:
A total number of 25,692 prescriptions from OPC were collected, which constitute all prescriptions during the period of September to December 2007. Data collected includes: percentage of each type of NSAIDs, dosage form, percentage share for each selective and non-selective NSAID, and concomitant therapy with gastroprotective agent. Additional information that was collected includes age, sex, indication for use, and average number of drugs per prescription. The study was approved by the ethical committee at RMS.

Results:
52% of the collected prescriptions contain NSAIDs. 76% of the prescriptions are for women and 24% are for men. Age of patients included in the prescription ranges between 16 and 81 years, with a mean of 59.3± 15.8 years.
The results of the study show that indications for NSAIDs are 58.3% for osteoarthritis, 12.1% rheumatoid arthritis, and 20.1% orthopedics pain. Also, 96.4% prescriptions are for traditional NSAIDs, while 3.6% prescriptions are for the newer selective COX-2 inhibitors. Additionally, the results of the study indicate that diclofenac is at the top of the list with 83.74% of prescriptions of NSAIDs.

Concomitant therapy with gastroprotective agents was seen in 71.2% of prescriptions. Famotidine is the most prescribed gastroprotective agents followed by antacid and omprazole

Conclusions and recommendations:
The study concludes that diclofenac is the top of the list because of its relative low price and availability in different dosage forms, and traditional NSAIDs combined with a gastroprotective agent is the most appropriate first-line NSAID therapy in many patients. The study recommends to use NICE guidance when starting a new patient on NSAIDs or after an existing patients reported a side effect with a NSAIDs.

**Liver enzyme abnormalities induce by Methotrexate in patients with rheumatoid arthritis.**

**Kholoud. Z. Qoul. B. Sc. pharmacy, M.S. Clinical pharmacy*.**

*Royal Medical Services.*

Back ground:
Methotrexate has been the most frequent used DMARD in the treatment of rheumatoid arthritis, but the possibility of hepatotoxicity continues to represent a major problem with tolerance and prolonged use of this drug.

Objective:
Evaluates the frequency of significant hepatotoxicity (liver enzyme abnormalities) in MTX treated patients with rheumatoid arthritis in relation of the age and other DMARD combined drugs.

Methodology:
Eighty- four patients diagnosed with RA. Evaluate liver enzymes serum transaminase (ALT, AST) base line and every visit to clinic (monthly then periodically) after starting MTX.

Result:
The ratio of men to women is 1 to 2.26. Age of participants ranges between 25 and 60 years, with a mean of 35.27± 11.32 years. The median duration of patients' disease is six years .mean cumulative dose of MTX was 350±18mg. seven patients (8.33%) on MTX developed abnormal liver enzymes.

Conclusion:
The incidence of liver enzyme abnormality was significant in old patients with rheumatoid arthritis and the duration of therapy.

## *Terminalia bellerica* (Belliric Myrobalan) stimulates the secretion and action of insulin and inhibits starch digestion and protein glycation

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Traditional plant treatments have been used throughout the world for the therapy of diabetes mellitus. The aim of this study was to investigate the efficacy and mode of action of *Terminalia bellerica* used traditionally for treatment of diabetes in India. *T. bellerica* aqueous extract stimulated basal insulin output and potentiated glucose-stimulated insulin secretion concentration-dependently in the clonal pancreatic beta cell line, BRIN-BD11 ($p<0.001$). The insulin secretory activity of plant extract was abolished in the absence of extracellular $Ca^{2+}$ and by inhibitors of cellular $Ca^{2+}$ uptake, diazoxide and verapamil, ($P<0.001$, $n=8$). Furthermore, the extract did not increase insulin secretion in depolarised cells and did not further augment insulin secretion triggered by IBMX, tolbutamide or glibenclamide. *T. bellerica* extract also displayed insulin mimetic activity and enhanced insulin-stimulated glucose uptake in 3T3 L1 adipocytes by 300%. At higher concentrations, the extract also produced 10-50 % ($P<0.001$) decrease in starch digestion *in vitro* and inhibited protein glycation ($p<0.001$). This study has revealed that components in *T bellerica* extract stimulate insulin secretion, enhance insulin action and inhibit both protein glycation and starch digestion. The former actions are dependent on the active principle(s) in the plant being absorbed intact. Future work assessing the use of *Terminalia bellerica* as dietary adjunct or as a source of active antidiabetic agents may provide new opportunities for the treatment of diabetes.

**Predictors of "Worsening Renal Function" in Hospitalized Patients.**

**Dr. Waleed Sweileh**
*Al-Najah University*
*Palesitine*

Aim: The aim of this study was to identify predictors of worsening renal function (WRF) among hospitalized patients. Settings and Design: A one-year, hospital-based prospective study. Methods and Material: This study was carried out at the internal medicine department of Al-Watani governmental hospital, Palestine. Inclusion criteria were: hospitalization for at least 48 hours and availability of at least three serum creatinine (Scr) measurements. WRF was defined as an elevation in Scr of ≥0.5 mg/dL from baseline value if baseline Scr value was < 3mg/ dL and 1mg/dL if the baseline value was ≥ 3mg/dL. Statistical Analysis: Regression analysis was carried out on two sets of variables: non-medication variables (Model I) and medication variables (Model II). Statistics was performed using SPSS version 15. Results: Three hundred and sixty one patients were included in this study. The prevalence of WRF was 40.2%. In the majority of cases, WRF started within the first 48 hrs of admission. Analysis of data indicated that eight variables were significantly associated with WRF: renal dysfunction (P< 0.0001), diabetes mellitus (P= 0.005), hypertension (P< 0.0001), congestive heart failure (P= 0.021), age (P= 0.003), number of diagnosis (P< 0.001), furosemide (P = 0.001) and calcium channel blockers (P= 0.01) administration at admission. Regression analysis indicated that HTN (P =0.033) and renal dysfunction (P= 0.007) were predictors of WRF in model I, while furosemide administration (P= 0.01) was the only predictor of WRF in model II. Conclusion: hypertension, renal dysfunction and furosemide administration at hospital admission are predictors of WRF among hospitalized patients.

**Evaluation of Angiotensin-Converting Enzyme Inhibitors Dose in Patients with Chronic Heart Failure**

**Ansam Sawalha**
*Al-Najah University*
*Palesitine*

Objective: To describe the usage and dosing patterns of angiotensin converting enzyme inhibitors (ACE-I) among patients with chronic heart failure (CHF), and to review evidence regarding the utilization of optimum dose.

Methodology: A cross-sectional analytical study of the medications for patients diagnosed with CHF. The study was carried out between September 2006 and August 2007 at Al-Watani governmental hospital/ Palestine. The focus was on whether patients were using ACE-I, and if the dosing was appropriate. Doses shown to be effective in randomized clinical trials in reducing mortality among patients with CHF were considered optimum while lesser doses were considered sub-optimum. Patients with known cautions or contraindications to the use of ACE-I were excluded from the analysis.

Results: Of the 165 patients surveyed, 17% had identifiable contraindication to the use of ACE-I, while 83% (137) had no identifiable contraindication. Of those patients who had no contraindication for ACE-I use, 70.1% were using the ACE-I. Of those patients who were using ACE-I, 51% were given an optimum dose while 49% were given a sub-optimum dose. Patients given sub-optimum doses of ACE-I had no identifiable caution/ contraindication to receiving a higher dose. Of all patients with CHF studied, 64.2% were either receiving no ACE-I or a sub-optimum dose in the absence of contraindication. Only the presence of hypertension was significantly associated with the administration of ACE-I ($P = 0.009$, $OR = 2.7$). The use of optimum dose ACE-I was not significantly associated with any of the tested factors but was found to be more likely among patients <65 years, patients with creatinine clearance >60 ml/ min and patients with diabetes mellitus. Analysis of the specific doses of prescribed ACE-I agents indicated that enalapril was used more often at the optimum dose than captopril.

Conclusion: There is an abundance of evidence in favor of using high doses of ACE-I in the management of patients with CHF. There is a need for physicians to be educated regarding the role of optimum doses of ACE-I in the management of CHF. It is likely that a change in prescribing patterns would provide many benefits, like decreasing the possibility of re-hospitalization, for patients with CHF.

# Posters

## Cytotoxic effect of Maillard reaction products from whey on *in vitro* cancer cell lines

**Abdulmajeed H. Al-Samaraie*, Nahi Y. Yaseen**, Luma A. Altai***, Luay Y. Al-Essa******
** Department of Food Science and Biotechnology, College of Agriculture, University of Baghdad*
*** Iraqi Center for Cancer and Medical Genetic Research, University of Al-Mustansiriyah*
**** Department of Biology, College of Education, Ibn Al-Haithem University*
***** Faculty of Pharmacy, Al-Zaytoonah University.*

Maillard reaction products correspond to modified protein derivatives that are initially generated by non-enzymatic glycation between amino acids and reducing sugars in heat-treated foods, and some of them are blamed to be carcinogens. This work is to evaluate the anti-cancer activity of these products. Lyophilized whey was dissolved in water (1%) at pH (9) and boiled for 1, 3, or 5 hours to get Maillard reaction compounds. Their cytotoxic effect on some cancer cell lines (human larynx epidermoid carcinoma-Hep-2 and mouse mammary adenocarcinoma-AMN-3) was studied. Different concentrations (0.625, 1.25, 2.5 and 5 mg/ml) of whey solution was added to the cells and incubated for 24, 48 and 72 hours. Genotoxic effect increased with the increasing of whey concentration, boiling period and incubation time with cells. The cytotoxic effect on Hep-2 was noticed after 72 hours of incubation with 5 mg/ml solution boiled for 1, 3 or 5 hours. The inhibition ratios were 81.9, 92.2 and 83.5 for the three boiling periods respectively, whereas AMN-3 cell lines were inhibited by lower concentrations. Maximal inhibitions (85.4, 85.1 and 86.5) were noticed when 5 mg/ml concentration of the whey solution was used for the same boiling and incubation periods. In conclusion, Maillard reaction products have cytotoxic effect against malignant cells.

**Multiple Displacement amplification as a method of whole genome amplification for comparative genome hybridisation**

**Ammar Al Naimi, Soha Tashkandi, Stavros Glentis, Thalia Mamas, Souraya Jaroudi, Joyce Harper and Sioban SenGupta**

Comparative genomic hybridization (CGH) allows detection of chromosomal imbalances in the entire genome in a single experiment without cell culture. Single cell CGH has been applied in both clinical and research preimplantation genetics. In preimplantation genetic diagnosis (PGD) the scarcity of the genetic material from a single blastomere limits the application of CGH especially in combination with other molecular tests. Multiple displacement amplification (MDA) is a whole genome amplification method that uses Φ29 polymerase.

DNA from normal male, normal female, fibroblast cell lines with known trisomies, and clumps of ten male and female lymphocytes were amplified using MDA. DNA concentration following MDA ranged from 1.2µg/ml to 2.1µg/ml regardless of the concentration of DNA prior to MDA. With a starting DNA template from 10 cells, 1µg of MDA product was sufficient for interpretable metaphase CGH analysis. Several CGH experiments and haplotype analysis could be performed using a single MDA product. Unlike genomic DNA, MDA products showed under-representation of the repetitive centromeric sequences and further amplification bias against repetitive sequences at 1p, 16p, and on chromosomes 19 and 22 .

Although further optimisation is required for single cell analysis, MDA may broaden the scope of PGD to include CGH and haplotyping.

## *In vitro* anti-amoebic and anti-giardial activity of *Aloe vera* L. crude extract.

**Ammar Bader [1], Ibrahim Mosleh[2]**

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According WHO Diarrhea is the passage of 3 or more loose or liquid stools per day, It is usually a symptom of gastrointestinal infection, which can be caused by a variety of microorganism, parasites or viruses. Infection can be transmitted through contaminated food or drinking-water, or from person to person as a result of poor hygiene. Severe diarrhea leads to fluid loss, and may be life-threatening. Among the causative agents of Diarrhea are the anaerobic parasitic protozoan *Entamoeba histolytica* and *Giardia intestinalis*.

Human infection with Amoebiasis and giardiasis is conventionally treated with metronidazole, tinidazole or nitazoxanide. Although Metronidazole is the current first line therapy, it is mutagenic in bacteria and carcinogenic in mice, so should be avoided during pregnancy it has also Metallic taste and could cause nausea; vomiting; dizziness; headache; neutropenia. These parasite became recently multidrug resistant, so the finding of new synthetic or natural drugs is of great necessity.
In this work we have tested the crude extract of *Aloe vera* L. the extract showed a degree of inhibition effect against *Entamoeba histolytica* and *Giardia intestinalis.* The extract was not toxic to hep 2 and vero cells at the IC50 concentrations. Results were compared also with Metronidazole.

**Synthesis and Antiviral-Anticancer Activity Studies of Phosphonate Derivatives of Conventional Nucleosides and Acyclic Nucleosides**

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Conventional or classical nucleosides and acyclic nucleosides are known in their clinical applications in the prophylaxis and /or in the treatment of several viral diseases. Acyclic nucleoside phosphonates (ANPs) class have been shown to possess broad-spectrum antiviral activity against DNA viruses and retroviruses and, recently, some of them have been approved from FDA in the treatment of chronic hepatitis and AIDS. We report here the synthesis of new generations of compounds that combined the phosphonate side-chain of some of ANPs with the sugar portion of some of the conventional nucleosides and acyclic nucleosides in order to study the effect of the sugar increment by the attachment of an additional acyclic sugar portion which contains phosphonate group, on the phosphorylation process and how, finally, it affects the antiviral and anticancer activity.

Phosphonates of Zidovudine (AZT) (**1**), Lamivudine (3TC) (**2**) and of Acyclovir (ACV) (**3**) were prepared by coupling reaction between AZT, 3TC, and ACV with (diisopropylphosphonomethoxy)ethyltosylate in DMF in the presence of sodium hydride followed by deprotection of the phosphonate esters with TMSBr. *In vitro* studies of compounds **1**, **2**, and **3** are running to evaluate their antiviral and anticancer activities and they will be reported and discussed.

**Effects of *Ballota undulata* on spermatogenesis and fertility of male albino rats**

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Objective: The aims of this study to know the effects of Ballota undulata (70% EtOH) on the reproductive system and fertility on adult male albino rats.

Material and method: 20 albino rats were involved in this study and were divided into two groups. Group (A) a vehicle-treated control group (B) a treated group with Ballota undulata. at a dose of 250 mg/kg body weight for 60 days.

Results: Ballota undulata induce a significant decrease in the weight of reproductive organs as compared to control animals ($P<0.01$). The sperm motility and count in cauda epidydimides and testicular ducts were significantly decreased ($P<0.01$). Spermatogenesis was decreased at primary &secondary spermatocyte stages. Epididymides showed decreased number of spermatozoa. Lumen of vas deferentia were arrested of sperms. The secretary activities of seminal vesicle and ventricular prostate were also decreased. A significant decrease ($P<0.01$) in spermatogenesis activity was observed in semniferous tubule. Treated rats testicular cell population showed a decrease in number of spermatocytes and spermatids ($P<0.001$) when compared to control animals. Decreased in number female rats impregnated by males receiving treatment was also observed and ($P<0.01$).
Conclusion: the aqueous extracts of Ballota undulata have increased spermatogenesis of male albino rats.

**Development and validation of HPLC method for the determination of lamotrigine in formulations**

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Simple, fast and sensitive HPLC method was developed and validated for determination of lamotrigine. The HPLC separation was achieved on a C18-Bond pack column (250 mm× 4.6 mm) using a mobile phase of acetonitrile–monobasic potassium phosphate solution (35:65, v/v) containing orthophosphoric acid to adjust pH to 7.0 at a flow rate of 1.5 ml/min. The UV detector was operated at 210 nm, and column temperature was adjusted at 40 $^{o}$C. The method was validated for specificity, linearity, precision, accuracy, robustness and limit of quantitation. The linearity of the calibration curves, the percent recoveries, the limit of detection and quantitation, were determined. The method was found to be simple, specific, precise, accurate, and reproducible.

**Formulation and stability studies of Diloxanide furoate suspension**

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Diloxanide furoate (DF), a poorly water soluble drug which is used in treatment of intestinal amebiasis (luminal amebicide) has been formulated as suspension several times.
In order to obtain the most acceptable, stable and effective suspension, the suspending agents, additives and pH were changed.
The formula that possesses the optimum properties and stability was chosen for further studies which include rheology, preservative efficacy, expiration date and clinical evaluation. The results of this study indicated that suspension formula containing xanthan gum as a suspending agent and the chelating agent EDTA together with the antioxidant sodium metabisulfite, sorbitol (sweetening agent) and paraben (preservative) and pH of 4 gave the best suspension of DF, the calculated expiration date was 4.3 years.
The preliminary clinical study of this formula suggested the validity and effectiveness of this formula in treatment of cyst-passer amebiasis.

**Pharmacological Evaluation of Selected Novel Amides as Potential Antiarrythmic and Cardioprotective agents**

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In the search for new potential and safer anti-arrhythmic and cardioprotective agents, the present study focuses in the pharmacological effects of selected novel amides as anti-arrhythmic and cardioprotective agents. The effects of selected novel amides *N*-(4-acetylphenyl)-1-ethyl-1*H*-indole-2-carboxamide (C1), *N*-(4-benzoylphenyl)-1-ethyl-1*H*-indole-2-carboxamide (C2) and 1-Ethyl-N-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-1*H*-indole-2-carboxamide (compound 3) were investigated on ischaemia and reperfusion-induced arrhythmias and on the infarction size. The study was carried out in Langendorff perfused rat hearts (n=5) subjected to coronary artery occlusion by using silk suture, Mersilk 3/0, threaded through a polythene guide in which the severity of arrhythmias, coronary flow, heart rate and percentage of infarction were measured. The %incidence of reperfusion-induced ventricular fibrillation was completely abolished in compounds 1 and 2, and significantly reduced in compound 3 (83% in control vs. 0%, 0% and 83% at 1.6 μM compounds 1, 2 and 3 respectively, $p<0.05$). Further more the occluded zone was significantly reduced from 43.1±3.3 in control hearts to 23.0±4.2, 7.4±2.2 and 11.4±0.8 in compound 1, 2 and 3, respectively ($p<0.05$). In conclusion, compound 2 was the only compound to completely abolish the incidence of ischaemia and reperfusion-induced arrhythmias and has the most beneficial effects as a cardioprotective agent. This later effects may be due to $Na^+$ channel blockade since it contains the same functional group; the amide group as some of class I antiarrhythmic agents.

**Synthesis of New Organic Derivatives of 1,3-Dimethylbarbituric Acid.**

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New organic derivatives of 1,3-dimethylbarbituric acid were prepared by novel methods and classified into salts, ylides and sulfides compounds. The salts derivatives were obtained by reaction of 1,3-dimethylbarbituric acid with strong ylide type bases.

The ylide compounds were obtained by nucleophilic attack of imidazole carbene and triphenylphosphine at the methylene 1,3-dimethylbarbituric acid to produce zwitterionic derivatives in good yields. Bis[1,3-dimethylbarbituryl(5)]sulfide ($[BarbH]_2S$, BarbH = 1,3-dimethylbarbitur-5-yl) was obtained from 1,3-dimethylbarbituric acid and $SCl_2$ or $SO_2Cl_2$. X-ray diffraction analysis and spectroscopic techniques were used to confirm the chemical structures.

**Effect of crystal habit and surfactants on the dissolution rate of mefenamic acid**

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Purpose: The effect of crystal habit and surfactants on the characteristics and dissolution of mefenamic acid (MA) crystals.

Method: The surfactants used were namely, anionic sodium lauryl sulphate (SLS), cationic cetrimide and non-ionic (Tween-80). Various techniques were used for characterization including: scanning electron microscope (SEM), differential scanning calorimetry (DSC), fourier transform infrared (FTIR) spectroscopy and X-ray diffractometry (XRD). Dissolution profiles for the starting material and crystals were also constructed. The mechanism of enhancement and the effect of crystal habit of mefenamic acid on dissolution were also discussed.

Results: It was found that the starting material was mainly of polymorph (I), the stable one. Recrystallization using different types of aqueous surfactants yielded different crystal habits. The enhancement of dissolution rates of mefenemic acid crystals prepared with the above mentioned aqueous surfactants were found to be in the order of tween 80> cetrimide> SLS.

Conclusion: Crystal habit has a profound effect on the dissolution rate of mefenamic acid.

**Effects of *Ballota undulata* on Blood Biochemical Parameters and Insulin in Albino Rats.**

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Objective: To study the effect of *Ballota undulata* (70% EtOH) extract on blood biochemical parameters and Insulin in Albino rats.

Material and Method: The plant extract was orally administered to the albino Rats. At dose of 300 mg/kg body weight for 7 days by Albino rats (n=10) was investigated to study its effects on glucose, total cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), troponin I (TnI), serum creatine kinase (CK), total protein, total bilirubin and blood urea. *Ballota undulata* extract caused a significant decrease in blood glucose, total serum cholesterol and CK levels. Blood levels of TnI, AST, ALT, triglycerides, total bilirubin, total protein and blood urea were unchanged.

Results: The hypoglycemic effect of *Ballota undulata* extract on Albino rats was further investigated by conducting a glucose tolerance test intraperitoneally (IPGTT). Healthy rats that were fasting for 18 hours followed by administration of a dose of 400 mg/kg body weight of the crude extract of *Ballota undulata*, orally. A significant decrease in blood glucose levels (after 15, 30, and 45 minutes) with a significant increase in serum insulin level (after 15 and 30 minute) was noted. These results suggest that, the crude extract of *Ballota undulata* have hypoglycemic, insulin-releasing and cholesterol lowering effects in rats.

Conclusion : the crude extract of *Ballota undulata* have hypoglycemic, insulin-releasing and cholesterol lowering effects in rats.

**The aqueous seed extract of *Carica papaya* Linn. lowers blood glucose and lipids in rats**

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The present study investigates the hypoglycemic, hypolipidemic and cardioprotective effects of 100-400 mg/kg/day/oral route of the aqueous seed extract of *Carica papaya* Linn. (*CPASE*) in normal male Wistar rats for 30 days. Rats, divided into groups I - V of six rats each, were orally administered with 10 ml/kg/day of distilled water, 10 mg/kg/day of glibenclamide, 100, 200, and 400 mg/kg/day of extract respectively, for 30 days. In addition, the acute oral toxicity using OECD guidelines [1] and phytochemical analyses of the extract were conducted. On day 31, after an overnight fast, blood samples were obtained by cardiac puncture under inhaled diethyl ether anesthesia for the determination of the fasting blood glucose (FBS), serum triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c), and high density cholesterol (HDL-c). The atherogenic (AI) and coronary artery (CAI) indices were also calculated. Results showed that *CPASE* significantly and progressively ($p<0.05$, $p<0.01$ and $p<0.001$) lowered the FBS, TG, TC, LDL-c, and VLDL-c dose-dependently, while significantly ($p<0.05$, $p<0.01$, $p<0.001$) causing dose-related elevation in HDL-c concentration when compared to the untreated control and glibenclamide treated rats. The extract also significantly ($p<0.05$, $p<0.01$ and $p<0.001$) lowered the AI and CAI indices dose-dependently. The acute oral toxicity showed the extract to be safe. Phytochemical analyses revealed the presence of alkaloids, flavonoids, saponins, tannins, anthraquinones, anthocyansides and reducing sugars. Thus, lending support to previous reports on the blood glucose and lipid-lowering effects of the plant [2, 3] and its folkloric use in the management of suspected type 2 diabetic patients.

**Expression of tumor rejection antigen (Gp96) in breast cancer cell lines and its potential use as a therapeutic vaccine**

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Breast cancer is the most common cancer in most parts of the world and is a leading cause of death among women. Even though the incidence of the disease is increasing each year, early detection and improved treatments have increased the survival rates. Currently, only a few markers are used for either early diagnosis, treatment response or for survival of breast cancer. In this study, two-dimensional gel electrophoresis (2DGE) was used in the quest for new potential biomarkers for the disease. MCF-7 and MDA-MB-231 breast cancer cell lines and MCF-10A normal breast cell line were used. PDQuest 7.3 software was applied to analyze the gels, after which several protein spots of interest were excised and analyzed using MALDI-TOF spectrometer. Tumor rejection antigen (gp96), HSP 90α, nucleosome assembly protein 1-like1 were found to be up-regulated in breast cancer cell lines and opioid-binding cell adhesion molecule precursor was found to be down-regulated in breast cancer cell lines when compared to the normal breast cell line. Among those proteins, gp96 is used as a potential vaccine in melanoma treatment and it was also found to over-expressed in breast cancer tissues, thus it can has the potential to be used as a therapeutic vaccine for breast cancer.

## Conformational Changes of Chitosan Oligomers

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The effects of molecular weight, concentration, and ionic strength on the configuration of chitosan oligomers in solution state were analyzed. A series of chitosan oligmers with various molecular weights was prepared. The indirect method of analysis included surface tension, particle size, zeta-potential, viscosity, and determination of PKa values. The amino groups in chitosan have pKa value of about 6.5, thus, chitosan is positively charged and soluble in acidic to neutral solution with a charge density dependent on pH and the DDA values.The results of surface tension measurements showed that the surface tension increases in water after addition of chitosan oligomers, this suggest that the oligomer perform good intermolecular forces with water and stays in the bulk. On the other hand, surface tension decreases slightly with increasing chitosan concentration in the high dilution, which was explained with concentration-induced conformational transformation. All explanations were correlated to zeta potential, particle size, and Pka values. Ionic strength was proved to affect the conformation and solution properties of the oligomers.

**Water-Soluble Palladium(II) Catalysts for the Preparation of Polyketones: from Aqueous to Emulsion Polymerization.**

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The replacement of organic solvents for water as a reaction medium for the synthesis of polyketones is among the most important development in this field in the last decade. This is due to several exceptional scientific and economic advantages of water. In comparison to traditional free radical polymerization of polyketones, water-soluble palladium(II) catalysts allow fine-tuning of the microstructure of the produced polyketones. This article reviews the design and synthesis of water-soluble palladium(II) catalysts that control the properties of polyketones in aqueous phase. Furthermore, this review will discuss the progress in design of new water-soluble palladium(II) catalysts that permits the achievement of stable colloidal latices of polyketone polymers (emulsion products) with high solid content, high molecular weight, and typical particle size and glass temperature.

**Effects of antioxidant vitamins on glutathione depletion and lipid peroxidation induced by restraint stress in rat liver**

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Stress as a cofactor is reportedly known to affect the progression and severity of several diseases. Influence of stress on liver is of interest from the clinical point of view as stress plays a potential role in aggravating liver diseases in general and hepatic inflammation in particular probably through generation of reactive oxygen species. The present study was undertaken to investigate the potential of antioxidant vitamins A, E and C individually and in combination (Vitamin E+C) in modulating restraint stress induced oxidative changes in terms of measurement of hepatic free radical scavenging enzymes like Superoxide dismutase (SOD), Catalase, the levels of Reduced Glutathione (GSH) contents and Malondialdehyde (MDA). Six hours of immobilization stress caused a decrease in the liver levels of SOD, catalase and GSH while the levels of MDA were enhanced when compared to non-stressed control rats. Both pre-vitamin stress and post-vitamin stress treatments either alone or in combination resulted in an alteration of these parameters towards their control values with a relative dominance by the later (post-vitamin stress treatment). Vitamin E and C individually were found more effective in restoring the inherent antioxidant system than vitamin A. Though, the combined vitamins (E+C) post-stress treatment was found to be effective but not additive in combating hepatic oxidative stress.
Thus vitamins E or C alone or in combination can be given as prophylactic / therapeutic supplements for scavenging free radicals generated in the liver tissues in order to reduce oxidative stress caused by various diseases like cirrhosis.

**CpG-Oligodeoxynucleotide (ODN): Breaking Down the Barriers to Cancer Immunotherapy**

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The toll like receptors (TLRs) are mammalian type I transmembrane protein that play an essential role in the activation and regulation of innate and adaptive immunity through the recognition of specific molecular patterns of pathogens .In humans, ten TLRs (TLR1–10) have been identified. Among these, oligodeoxynucleotides (ODNs) with unmethylated deoxycytosine-deoxyguanosine (CpG) motifs are recognised by Toll-like receptor (TLR)9 expressed in specialised cell subsets of the human immune system, B cells and plasmacytoid dendritic cells. CpG-ODN is thought to affect the Toll-like receptor 9 (TLR9) signaling pathway which can induce upregulation of immunologically relevant surface markers, increased proliferation and cytokine release. The immune stimulatory effects of CpG-ODN are being exploited as a novel therapeutic approach to treatment of human diseases and tumors. In cancer, the combination of CpG-ODN with tumor antigens, monoclonal antibodies or dendritic cells were promising. The immunostimulatory CpG-ODN can be used alone to activate locally the innate immunity leading to a tumour-specific response that would overcome the need to identify the tumoral antigen.

Several B cell malignancies have been shown to express TLR9 and to respond to CpG ODN**.** In preliminary experiments done in our lab, using ex vivo tumour B cells and cell lines, the apparent expression of TLR9 was seen by monoclonal antibody staining and flow cytometry, and was also seen in a range of non-haematological tumour cell lines, including epithelial cancers and melanomas. The aims of this project are to investigate whether TLR9 is expressed in malignant tumors by a range of methods and to address the relationship between TLR9 expression and response to CpG ODN in both haematological and non-haematological cancer cells. The studies will provide valuable information on the response of tumour cells, as opposed to cells of the immune system, to CpG ODN as a potential immunotherapeutic agent. In addition, they should shed new light on the mechanisms of action of CpG activation of TLR9 signaling in immune and non-immune cells.