Pharmacology and Therapeutics Department:

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| Journal/Periodical Name | Basic & clinical Pharmacology & Toxicology |
| Publishing Info | 108(4) 263-273, (2011) |
| Research Title | A Novel COX-2 Inhibitor Pyrazole Derivative Proven Effective as an Anti-Inflammatory and Analgesic Drug |
| Research Abstract | The introduction of new COX-2 inhibitors with high efficacy and enhanced safety profile would be a great achievement in the development of anti-inflammatory drugs. This study was designed to screen and assess the anti-inflammatory and analgesic activities as well as some of the expected side effects of some pyrazole derivatives, newly synthesized as potential COX-2 inhibitors at the Faculty of Pharmacy, Alexandria University and compared to indomethacin and celecoxib. Twelve compounds were screened for their anti-inflammatory activity using carrageenan-induced paw oedema and cotton pellet granuloma tests. On the basis of their apparent anti-inflammatory activity, four compounds with different substitutions were selected for the evaluation of their analgesic activity using the formalin-induced hyperalgesia and hot-plate tests. Compound AD 532, ((4-((3-(4-Methylphenyl)-4-cyano-1H-pyrazol-1-yl)benzenesulfonamide)), showed very promising results. In the single-dose and subchronic toxicity studies, compound AD 532 showed no ulcerogenic effect and produced minimal effects on renal function. Furthermore, compound AD 532 was a less potent inhibitor of COX-2 in vitro than celecoxib, which may indicate lower potential cardiovascular toxicity. It is concluded that compound AD 532 appears to be a promising and safe option for the management of chronic inflammatory conditions. This study recommends more in-depth investigation into the therapeutic effects and toxicity profile of this compound including its cardiovascular toxicity.
### Author
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Issa I, Soubra O, and Soubra L

### Journal/Periodical Name
*Digestive Diseases and Sciences*

### Publishing Info
Vol. 57 No. 10 pp.: 2633-41, 2012

### Research Title
Variables associated with stress ulcer prophylaxis misuse: a retrospective analysis.

### Research Abstract
**BACKGROUND:**
Stress ulcer prophylaxis (SUP) is commonly used in hospitals. Although its indications are better delineated for the ICU patients, its use in non-ICU settings is somewhat arbitrary and based on judgment. Despite the availability of previous publications, data about factors governing misuse of acid suppression therapy (AST) is still scarce in the non-ICU setting.

**OBJECTIVE:**
We attempted to assess the extent of SUP overuse in our hospital. We also carefully collected and analyzed several variables to detect associations governing this flawed behavior. Finally, we attempted an assessment of the financial burden this inappropriateness carries on the hospital budget.

**MATERIALS AND METHODS:**
We retrospectively analyzed charts of patients admitted to the medical floor of a tertiary referral university hospital over a 1 year period. All adult patients admitted to the medical ward who received at least one dose of SUP were included and their charts reviewed for a multitude of variables in addition to the appropriateness of AST with regard to the preset rules and regulations available and previously published. Statistical analysis was performed to identify factors that may have impacted the decision to initiate SUP wrongly.

**RESULTS:**
We included 320 charts that were reviewed for our objectives. We found that 92% of patients admitted through that period were not eligible for SUP. The
total inappropriateness of SUP was noted to be 58% (p=0.015). Increasing age and male gender were found to be significant variables in AST misuse (p=0.045 and p=0.010). In addition, duration of hospital stay was discovered to be significantly different between the 2 groups (p=0.008). Co-morbidities was also found to be a defining variable that apparently pushed physicians for AST overuse (OR=3.27). Patients with two or more minor risk factors were also subjected to SUP inappropriately (OR=3.53). We proceeded to stratify the inappropriate AST according to medical departments and documented that some specialties were more associated with such a behavior (Neurology, Infectious Diseases ...). Our calculated financial burden was more than 23,000$ per year for the medical floor.

CONCLUSION:
This retrospective study confirmed the growing suspicion that SUP misuse is evident on the medical floors. We also delineated several factors and variables associated with and affecting SUP overuse. This stresses the necessity for new and updated guidelines and for hospitals to initiate their own policy for orders and prescriptions control as well as programs for physicians’ education.

Author Prof. Dr. Hania Nakkash
Participants: N. Nuwayri-Salti, K. Knio, A. Jammoul, R. Fakhoury, and K. Sarhane
Journal/Periodical Name PLoS Neglected Tropical Diseases
Publishing Info Vol. 6 No. 8 pp.:e1782, 2012
Research Title Atypical Systemic Leishmaniasis to be Considered in The Differential of Patients Presenting with Depressed Immunity
Research Abstract Background
Systemic leishmaniasis has been known to present with prolonged fever, hepatosplenomegaly and wasting. Beside this classical form, a sub-clinical form has been identified. It is described with either one or two of the above symptoms missing; other findings have been reported instead, such as lymphadenopathy and
anemia. In this report, we reveal a third unsuspected form which we are referring to as “atypical”.

Methodology/Principal Findings
Patients suspected to be immune-deficient were referred to our immunology specialized laboratory to study some aspects of their immune functions (not normally covered in the general laboratory). Multiple specialized tests were performed, including microscopic examinations using appropriate stains, and mainly cultures of biopsies on several types of specialized media. 19.4% of 160 patients were found to have close to normal laboratory profiles, but exhibited dysfunctional macrophages laden with *Leishmania* parasites.

Conclusions/Significance
Findings such as the ones we obtained allowed us to uncover the presence of patients with an atypical form of systemic leishmaniasis. It presents with symptoms masquerading a condition in which the immune system is non functional. This predisposes patients to recurrent secondary infections resulting in clinical pictures with a great variety of signs and symptoms. These findings alerted us to the fact that systemic leishmaniasis presents with a much wider spectrum of signs and symptoms than so far suspected and is far more common than diagnosed to date. Furthermore, among these 31 patients was a number of adults. This proved that in our area systemic leishmaniasis is surely not limited to the pediatric age group. Our recommendation is to entertain the diagnosis of atypical systemic leishmaniasis in any patient with an unexplained depressed immunity state and in whom no obvious immunologic defect can be identified.

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<th>Author</th>
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<td>Participants</td>
<td>S. Noureddine, H. Fakhoury, and R. F. Makki</td>
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<td>Journal/Periodical Name</td>
<td><em>Annals of Thoracic Medicine</em></td>
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<td>Vol. 7 No. 3 pp.: 130–2, 2012</td>
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<td>Research Title</td>
<td>MMP1-1607 (1G&gt;2G) polymorphism and the risk of lung cancer in Lebanon.</td>
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<td>Research Abstract</td>
<td>CONTEXT: Matrix metalloproteinases (MMPs) are a</td>
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family of enzymes that degrade various components of the extracellular matrix and are involved in the development and progression of cancer. Lung cancer is the most commonly diagnosed cancer in Lebanon. MMP1 is responsible for degrading stromal collagens, which enhance the ability of neoplastic cells to cross basal membrane of both the endothelium and the vascular endothelium. A recent meta-analysis has suggested that the MMP1-1607 2G allele may be associated with an increased risk for certain types of cancers.

AIM: This study was undertaken to investigate the association between guanine insertion polymorphism in the MMP1 promoter and the susceptibility to lung cancer in the Lebanese population.

SETTINGS AND DESIGN: This case control study was conducted on 41 patients with lung cancer and 51 healthy controls, recruited from different regions of Lebanon.

METHODS: MMP1 -1607(1G>2G) polymorphism was studied using polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP).

RESULTS: No significant differences in allele or genotype frequencies for the MMP1 gene polymorphism between lung cancer patients and controls were found.

CONCLUSIONS: Our data shows that MMP1 promoter polymorphism is not associated with lung cancer susceptibility in the Lebanese population.
Dichloroacetonitrile induces oxidative stress and developmental apoptotic imbalance in mouse fetal brain.

Dichloroacetonitrile (DCAN) is one of the disinfection by-products of chlorination of drinking water. Limited mechanistic studies exist on the developmental toxicity of haloacetonitriles (HANs). The present study was designed to investigate the potential adverse effects of maternal exposure to DCAN on mouse fetal brain. Based on initial dose–response experiment, DCAN (14 mg/kg/day) was administered orally to pregnant mice at gestation day (GD) 6, till GD 15. Maternal exposure to DCAN resulted in redox imbalance in fetal cortex and cerebellum, characterized by significant decrease in reduced glutathione (GSH), and elevation of malondialdehyde (MDA) level and superoxide dismutase (SOD) activity. Further, DCAN-induced apoptosis indicated by significant enhancement of DNA fragmentation and active caspase-3 level in fetal cortex and cerebellum. Neuronal degeneration was indicated by positive cupric silver staining. In conclusion, maternal exposure to DCAN adversely affects mouse fetal brain as
evidenced by induction of oxidative stress, apoptotic imbalance and neurodegeneration.

Author: Ass. Prof. Asser Ghoneim
Participants: Eldahshan OA
Journal/Periodical Name: J Pharm Pharmacol
Publishing Info: 2012 Mar;64(3):430-438
DOI: http://dx.doi.org/10.1111/j.2042-7158.2011.01418.x
Research Title: Anti-apoptotic effects of tamarind leaves against ethanol-induced rat liver injury.

Research Abstract: Objectives: The leaf decoctions of Tamarindus indica (TI) have long been traditionally used in liver ailments. The aim of this study was to investigate the anti-apoptotic activity of TI leaf extract against acute ethanol (EtOH)-induced liver injury. The major constituents of the extract were also examined for standardization purposes. Methods: Rats (n = 5–7) were orally pretreated with TI leaf extract (25, 50 and 100 mg/kg) for seven days. Silymarin was used as a positive control. Liver tissue biochemical assays included key markers of apoptosis and its redox signalling. Serum enzyme levels were also determined. Key findings: All graded doses of TI leaf extract mitigated the EtOH-induced liver caspase-3 activation (42, 57 and 64%) as well as DNA fragmentation (32, 47 and 50%), respectively. The highest dose of the extract demonstrated membrane-stabilizing (38%) in addition to glutathione-replenishing (88%) effects. Also, the leaves improved the
liver histopathological alterations. Moreover, major plant bioactive polyphenolics, that might be responsible for the extract’s observed effects, were isolated and identified.

Conclusions: TI leaf extract demonstrated promising anti-apoptotic hepatoprotective effects in rats. The use of TI leaves in different liver diseases, having apoptosis as the underlying pathology, hence warrants further clinical investigation.

Author: Ass. Prof. Asser Ghoneim
Participants: Allam RM, Selim DA, Ghoneim Al, Radwan MM, Nofal SM, Khalifa AE, Sharaf OA, Toaima SM, Asaad AM, El-Sebakhy NA

Journal/Periodical Name: *Chin J Nat Med*
Research Title: Hepatoprotective effects of Astragalus kahiricus root extract against ethanol-induced liver apoptosis in rats

Research Abstract: The hepatoprotective activity of the ethanol extract of Astragalus kahiricus (Fabaceae) roots against ethanol-induced liver apoptosis was evaluated and it showed very promising hepatoprotective actions through different mechanisms. The extract counteracted the ethanol-induced liver enzymes leakage and glutathione depletion. In addition, it demonstrated anti-apoptotic effects against caspase-3 activation and DNA fragmentation that were confirmed by liver histopathological examination. Moreover, the phytochemical study of this extract led to the isolation of four cycloartane-type triterpenes identified as astrasieversianin II (1), astramembranin II (2), astrasieversianin XIV (3), and cycloastragenol (4). The structures of these isolates were established by HRESI-MS and 1D and 2D NMR experiments. The antimicrobial, antimalarial, and cytotoxic activities of the isolates were further evaluated, but none of them showed any activity.
Phytochemicals and amino acids have long been considered as important inducers of cell death. However, many of these natural compounds have been demonstrating dual action effects on cell death through inhibition as well as induction. Clinical applications may require dosage adjustment and determination of selectively vulnerable cells, either normal or cancer cells. Indeed, the opposing actions and controversial uses as cytoprotective and/or cytotoxic agents, in different tissues and diseases, need further scrutiny. The potential usefulness of these natural compounds as combined chemoprotectants for cancer chemotherapy should also be taken into consideration. Special emphasis will be placed on curcumin and Astragalus constituents as potential phytochemicals. Relevant amino acids include the excitatory and branched-chain ones, as well as glycine and cysteine.