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Egyptian Journal of Basic and Clinical Pharmacology
June 2016, Vol. 6, No.1
http://www.ejbcp.eg.net/

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Abstracts of Oral Presentations

O 1. Prophylactic L-arginine delays the development of tactile allodynia and suppresses spinal miR-155 in a rat model of diabetic neuropathy
Ghada M. El-Lithy¹, Wesam M. El-Bakly¹, Marwa Matboli¹, Hadwa A. Abd-Alkhalet³, Somaia I. Masoud¹ and May Hamza²
¹Department of Pharmacology, ²Department of Biochemistry, ³Department of Histology, Faculty of Medicine, Ain Shams University, Egypt.

Background: Diabetic neuropathy (DN) is a common complication of diabetes mellitus that is hardly reversible at the late stages. Since treatment of neuropathic pain is predominantly symptomatic, a prophylactic measure would be useful. Both ibuprofen and L-arginine exert antiallodynic effects on chronic constriction injury (CCI)-induced cold allodynia. Furthermore, ibuprofen is effective in CCI-induced mechanical allodynia.

Aim of the study: To assess the antiallodynic effect of prophylactic ibuprofen and L-arginine in streptozotocin-induced DN in rats and to further investigate the role of spinal miR-155 and NO in this effect.

Methods: Tactile allodynia was assessed weekly by von Frey filaments. Spinal nitric oxide and miR-155 levels were evaluated. Histological examination of soleus muscle and skin of foot pad were carried out using image analysis.

Results: Oral daily administration of ibuprofen, L-arginine and their combination, for 4 weeks starting one week after streptozotocin injection (i.e. before the development of tactile allodynia), resulted in a significant decrease of tactile allodynia compared to the control diabetic group. This was evident in the fifth week of the experiment. The three treatments prevented the decrease in muscle fiber diameter and epidermal thickness, seen in the control diabetic group. Furthermore, ibuprofen, L-arginine and their combination prevented the increase in the spinal NO level and miRNA-155, seen in the control diabetic group.

Conclusion: Both ibuprofen and L-arginine delayed the development of behavioural and histological changes of DN, with concomitant suppression of spinal miR-155 and NO level. L-arginine, being tolerable may be useful prophylactically in diabetic patients.

Keywords: Diabetic neuropathy; prophylaxis; L-arginine; ibuprofen; nitric oxide; miRNA-155.
O 2. Carbon Tetrachloride-Induced Neurotoxicity: Potential Protective Effects of Methyl Palmitate

Eman M. Mantawy, Amal Kamal Abdel-Aziz, Amira M. Badr and Ebtehal El-Demerdash
Department of Pharmacology & Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.

Background: CCl₄ causes free radical generation in many tissues such as liver, kidney, heart, lung, and brain. CCl₄ can cause damage to the brain through lipid peroxidation, resulting in up-regulation of pro-inflammatory pathways and alterations of the neurotransmission system.

Aim of the study: This study aimed to investigate the potential protective effects of MP against CCl₄-induced neurotoxicity in rats and elucidate the underlying mechanism of this potential neuroprotectin via studing oxidative stress and inflammatory markers.

Methods: Male albino rats were treated with either CCl₄ (1 ml/kg, twice a week) and/or MP (300 mg/kg, three times a week) for six weeks.

Results: CCl₄ intoxication caused significant increase in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and ammonia (NH₃) while MP reversed all these effects. Moreover, MP significantly attenuated CCl₄-induced oxidative damage in brain tissues by reducing malondialdehyde (MDA) levels and increasing reduced glutathione (GSH) levels. Additionally, MP markedly inhibited the inflammatory responses elicited by CCl₄ via downregulating nuclear factor kappa b (NF-κB) and inducible nitric oxide synthases (iNOS) expressions and decreasing nitric oxide (NO) level. The histopathological examination also proved the hepatoprotective and the neuroprotective effects of MP.

Conclusion: These results suggested that MP protected against CCl₄-induced neurotoxicity both indirectly via improving hepatocellular function, thus regulating the metabolism of NH₃ and directly via its neuroprotective effects which can be referred to its antioxidant and anti-inflammatory properties.

Keywords: Neurotoxicity; carbon tetrachloride; methyl palmitate; oxidative stress; NF-κB; inflammation.

Esther T. Menze, Ahmed Esmat, Mariane G. Tadros, Amani E. Khalifa and Ashraf B. Abdel-Naim

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.

Background: Huntington's disease (HD) is a neurodegenerative disorder, characterized by selective atrophy in the striatum, particularly the medium spiny GABAergic efferent neurons. This results in striatal sensorimotor gating deficits. Systemic administration of 3-nitropropionic acid (3-NPA) produces selective lesions mimicking those of HD. Males were found to be more susceptible to 3-NPA-induced neurotoxicity than females, suggesting neuroprotective effects of estrogens. Phytoestrogens, including genistein, are good estrogenic alternatives that keep their beneficial effects on non-reproductive organs and lack the potential hazardous side effects.

Aim of the study: The current study was designed to investigate the potential beneficial effects of genistein in 3-NPA-induced HD in ovariectomized rats.

Results: 3-NPA (20 mg/kg) administration caused significant disruption of the rats' locomotor activity and prepulse inhibition. In addition, it decreased striatal ATP levels and increased oxidative stress. It also increased the levels of prostaglandin E2 and the expression of Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) and shifted the cells towards apoptosis as it increased Bax/Bcl2 ratio and also caspase-3 expression. The striata of rats treated with 3-NPA showed focal hemorrhage and gliosis. Pretreatment with 17β-estradiol (2.5 mg/kg) or genistein (20 mg/kg) led to a significant improvement of behavioral parameters, increased ATP production and decreased oxidative stress. They also attenuated inflammation through suppressing the production of PGE2 and decreasing COX-2 and iNOS expression. Pretreatment with 17β-estradiol or genistein decreased Bax/Bcl2 ratio and caspase-3 expression.

Conclusion: Genistein has neuroprotective effects which are comparable to that exerted by 17β-estradiol. These effects could be attributed-at least partly-to its antioxidant, anti-inflammatory and antiapoptotic activities.
**O 4. Protective effects of Genistein on Cyclophosphamide-Induced Ovarian Toxicity in Rats.**

*Dalia O. Saleh and Dina F. Mansour*

Researcher, Pharmacology Department, National Research Centre, Dokki, Giza, Egypt.

**Background:** Cyclophosphamide (CYP), the commonly used chemotherapeutic agent in cancer treatment, is proven to cause ovarian toxicity and infertility in women with harmful interference with the antioxidant system of this organ either by the drug itself or its metabolites.

**Aim of the study:** In the present study, we investigated the protective effect of genistein (GEN), a phytoestrogen found in the soy protein, against CYP-induced ovarian toxicity in rats.

**Methods:** Forty female adult Sprague-Dawley rats were allocated into five groups. A normal control group received the vehicle, another group was injected with a single acute intraperitoneal dose of CYP (200 mg/kg). Three other groups received GEN at 0.5, 1 or 2 mg/kg subcutaneously daily for 15 days before CYP treatment. Sera and ovaries were obtained 48 hours after CYP treatment. Serum levels of anti-mullerian hormone (AMH) and estradiol (E2) were detected as well as the level of reduced glutathione (GSH), activity of superoxide dismutase (SOD), level of malondialdehyde (MDA) and interleukin 1β (IL-1β) in ovarian tissues were evaluated. Histopathological examination and immunohistochemical detection of inducible nitric oxide synthetase (iNOS) were conducted.

**Results:** CYP induced severe ovarian toxicity via decreasing serum levels of AMH and E2 indicating abnormal reproductive function as well as depletion of GSH, decrease in SOD activity and elevation in MDA together with the inflammatory cytokine IL-1β referring to oxidative stress and inflammation in ovarian tissues. Histologically, CYP caused increase in primordial follicles with less graffian follicles and corpora lutea in ovarian tissues as well as severe induction of iNOS as indicated by immunohistochemistry. GEN inhibited the severe decrease in serum AMH and E2 with alleviation of oxidative stress and inflammation significantly compared to CYP-treated group. GEN improved ovarian histology and immunostaining of ovarian iNOS disrupted by CYP.

**Conclusion:** GEN exerted protective effects against CYP-induced ovarian toxicity via its estrogenic, antioxidant and anti-inflammatory activity.

**Keywords:** Cyclophosphamide, Genistein, Anti-mullerian hormone, Estradiol, oxidative stress, interleukin 1β, inducible nitric oxide synthetase, ovary.
**O 5. Beneficial effects of Co-enzyme Q10 on Methionine and Choline Deficient (MCD) Diet-induced Non-Alcoholic Steatohepatitis (NASH) in Albino Rats: Modulation in Proliferating Cell Nuclear Antigen (PCNA) and Brain-derived neurotrophic factor (BDNF).**

*Dalia O. Saleh, Rania F. Ahmed and Mohamed M. Amin*

Department of Pharmacology, Medical Division, National Research Centre, Egypt.

**Background:** Nonalcoholic steatohepatitis (NASH) is a more severe medical case that develops in a subset of patients of nonalcoholic fatty liver disease. It is broadly defined by the presence of steatosis with inflammation and progressive fibrosis, ultimately leading to cirrhosis and hepatocellular carcinoma. Progression of NASH results in the elevation of ammonia level in brain astrocytes, pronounced brain oxidative stress and energy miscarriage which is caused by inflammation, infections and sepsis.

**Aim of the study:** The present study aimed to evaluate the hepato-protective and neuroprotective activity of Co-enzyme Q (CoQ10) on non-alcoholic steatohepatitis (NASH) in albino rats induced by methionine and choline deficient (MCD) diet.

**Methods:** Rats were fed MCD diet for 8 weeks to induce non-alcoholic steatohepatitis. CoQ (10 mg/kg/day) was orally administered for two consecutive weeks. Twenty-four hours after the last dose of the drug behavioural test; namely activity cage test, was performed and the activity counts were recorded. Serum alanine transaminase, aspartate aminotransferase, gamma-glutamyltransferase, total/direct bilirubin and albumin were valued to assess liver function. Moreover, hepatic cytokines interleukin-6 (IL-6) as well as its modulator nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) were determined. In addition, brain biomarkers *viz.* ammonia, nitric oxide and brain-derived neurotrophic factor (BDNF) were measured which are reliable indices to assess brain damage. Histopathological and immunohistochemical examination of brain proliferating cell nuclear antigen (PCNA) in brain and liver tissues were also evaluated.

**Results:** MCD-induced NASH showed impairment in the liver functions with an increase in the liver inflammatory markers. Moreover. NASH resulted in pronounced brain dysfunction signified by hyper locomotor activity, a significant decrease in the BDNF level as well as a significant increase in the brain NO and ammonia contents. Oral treatment of MCD diet fed rats with CoQ10 for 14 days showed a marked improvement in serum liver biomarkers. CoQ10 also showed a significant decrease in the hyper locomotor activity and in the brain content of NO and ammonia as well as a significant increase in BDNF. Furthermore, histopathological and immunohistochemical assessment of PCNA showed a marked improvement in both brain and liver tissues isolated from CoQ10 treated group.

**Conclusion:** From all the previous results, we can conclude that CoQ10 has a hepatoprotective and neuroprotective role presented by the modulation of enzymatic biomarkers, inflammatory cytokines, BDNF and cell proliferative mechanisms in MCD diet-induced NASH in rats probably due to its antioxidant and anti-inflammatory effects.

**Keywords:** Co-enzyme Q10 (Co-Q10), Brain-derived neurotrophic factor (BDNF), Proliferating Cell Nuclear Antigen (PCNA), Methionine and Choline Deficient Diet (MCD-Diet), Non-Alcoholic Steatohepatitis (NASH).
06. Patent System: Between Right and False Conceptions

Rasha A. Tawfiq


Current address: Assistant lecturer in Pharmacology Department, Pharmacy Department, Faculty of Pharmacy, The British University in Egypt, El-Sheraouq City, Egypt.

**Background:** Patent system is a real opportunity for researchers to protect their rights and their intellectual properties. Moreover, it helps researchers to reinvest by their researches outcomes for further research funding opportunities.

**Aim of the study:** The study aimed to elevate the awareness of the rights granted by patent to the patent holder. Moreover, this study discusses the motives behind filing a patent. It will deal with the main components of patent file and the main criteria for granting a patent with broader highlights on the main principles of the patent system. Furthermore, the presentation will state examples on the inventions that can or cannot be granted a patent according to the Egyptian Law No. 82 for 2002. Meanwhile, it will give a guideline on how to take a decision on where to file for your patent application. Finally, the presentation will state the difference between research paper and patent applications to avoid the cross-linkage between both document types.

**Keywords:** Patentability, principles of patents, pharmaceutical innovations.
Abstracts of Poster Presentations

P_1. Frequency and significant of CXC Chemokine Receptor 4(CXCR4) expression among B &T acute lymphoblastic leukemia (ALL) before and after treatment
Nahla M. Al-sharkawy1, Dalal M. Abdallah2, El-Shaimaa A. Araf2, Nevin M. Alazhary 1 and Mona A. Mohamed2
1Clinical Pathology Department, National Cancer Institute, Cairo University, Egypt
2Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Egypt

Background: ALL defines as the common malignant disorder between children. It is broadly classified into myeloid and lymphoid cell types. Optimal diagnosis and classification require a variety immunophenotyping, cytogenetic and molecular biologic techniques. CXCR4 is a chemokine receptor expressed on several hematopoietic malignancies cells. CXCR4 encourage tumor vascularization and migration of normal cells to the BM microenvironment.

Aim of the study: The purpose of this study was to monitor the expression of CXCR4 receptor on de novo diagnosed patients prior to, and at day 14 and day 42 after starting chemotherapy regimen (totalxv) protocol.

Methods: The study was performed on fifty two children attending the pediatrics outpatient clinic of the National Cancer Institute – Cairo University.

Twenty normal children were included in the study and considered as control group. Flowcytometric method used to determine receptor expression.

Results: Results showed that Total Leukocyte Count (TLC), bone marrow blast %(BMA) and CXCR4 expression % were significantly higher in ALL children than controls, while after treatment TLC was normalized whereas BMA and CXCR4 were significantly decreased, hemoglobin and platelet count were significantly decreased when compared to controls and improved upon treatment . Patients with higher CXCR4 expression have a lower overall survival (OS) than those with lower expression (P value <0.05) by using cutoff 55%. Moreover, there was a statistically significant association between the receptor expression and patient age as the higher CXCR4 expression is associated with higher age.

Conclusion: In conclusion CXCR4 receptor, may be a prognostic marker for ALL and therapeutic targets for ALL.

Keywords: CXCR4- ALL- Prognosis- FCM-BMA.
**P_2._** Propolis inhibits TGF-b/SMAD signaling pathway and subsequent CTGF and TIMP-1 expression induced by tacrolimus (FK506) in rat kidney

*Amany Balah, Albatoul Allam and Azza A. Ali*

Pharmacology and Toxicology Department, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo, Egypt.

**Background:** Tacrolimus (FK506) is one of the most efficient immunosuppressive agents that are widely used in organ transplantation. However its clinical use is strongly limited by acute and chronic nephrotoxicity which is mainly characterized by glomerulosclerosis and tubulointerstitial fibrosis. Transforming growth factor-b (TGF-b) and downstream Smad signaling pathways have been found to be the most important pathways involved in renal fibrosis via induction of the profibrotic genes connective tissue growth factor (CTGF) and tissue inhibitors of matrix metalloproteinases-1 (TIMP-1). In glomerular mesangial cells, FK506 has been found to activate TGF-b/Smad signaling pathway in ROS dependent manner.

**Aim of the study:** The present work was designed to test the potential protective effect of propolis as antioxidant on FK506-induced TGF-b/Smad signaling pathway and subsequent CTGF and TIMP-1 expression in rat kidney.

**Methods:** Forty-eight male Sprague Dawley rats (six animals in each group) received normal saline, the vehicle of FK506 i.p. (control) or either FK506 (1mg/kg body weight i.p.) or propolis (300mg/kg i.p.) or FK506 in combination with propolis for either 4h or 24h.

**Results:** It was found that administration of FK506 causes a rapid activation of TGF-b/Smad signaling pathway in rat kidney as indicated by an increase in plasma TGFb level and Smad-2 phosphorylation. In addition, activation of TGF-b/Smad signaling cascade is accompanied by an increase in Smad-dependent expression of CTGF and TIMP-1. Interestingly, concomitant administration of propolis along with FK506 markedly inhibits TGF-b/Smad signaling pathway and subsequent CTGF and TIMP-1 expression in rat kidney. Moreover, the inhibition of IL-2 by FK506 was not changed in the presence of propolis indicating that the immunosuppressive efficiency of FK506 was not affected by propolis.

**Conclusion:** The present study demonstrates that propolis has the ability to inhibit FK506-induced TGF-b/Smad signaling pathway and subsequent CTGF and TIMP-1 expression in rat kidney. These data may support the concept of using antioxidant therapy as valuable approach for the prevention of FK506-induced renal fibrosis.

**Keywords:** Tacrolimus (FK506), Propolis, TGF-b/Smad signaling pathway.
P 3. The possible interaction between curcumin and agomelatine using a model of depression in rats

Azza A Ali\textsuperscript{a}, Zeinab A. Rahman\textsuperscript{a}, Asmaa I Alwakeel\textsuperscript{a}, Marwa A Masoud \textsuperscript{a} and Amina K Elansary\textsuperscript{b}

\textsuperscript{a}Department of Pharmacology and Toxicology, Faculty of Pharmacy (girls), Al-Azhar University, Cairo, Egypt,
\textsuperscript{b}Q.C.Specialist, Department of Pharmacology, National Organization for Drug Control and Research (NODCAR), Giza, Egypt.

Background: Depressive disorders constitute a large proportion in the global burden of disease both in the developed and developing countries. Curcumin is the principle curcuminoid present in the widely and frequently used herb Turmeric, which was proven to possess antidepressant, antioxidant and anti-inflammatory effects. Agomelatine is a novel antidepressant with melatonergic agonism and 5-HT\textsubscript{2C} antagonism and has lower side effects than Fluoxetine.

Aim of the study: To investigate the possible interaction between Agomelatine and Curcumin in the therapeutic doses against Clonidine-induced depression in rats.

Methods: Six groups of rats were used; one group received saline (10ml/kgPO) for 14 days (control normal group). Other groups (depressed groups) given Clonidine (0.8 mg/kg, I.P) from 8\textsuperscript{th} to 14\textsuperscript{th} day and received saline (for depressed control group) or treated with either Agomelatine (40 mg/Kg, P.O), Curcumin (100 mg/Kg, P.O), a combination of Agomelatine & Curcumin, or Fluoxetine (20 mg/Kg, P.O) (used as standard antidepressant drug) during 14 days of treatment. Two behavioral experiments were performed, Open field test and Forced swimming test. Brain monoamines (NE, DA and 5-HT) and pro-inflammatory (TNF-\alpha and IL-6) as well as oxidative parameters (MDA and GSH) in the brain were also evaluated for all groups.

Results: Clonidine decreased locomotor activity in Open field test, decreased struggling and increased immobility time in Forced swimming test. Brain monoamines and GSH were decreased while MDA, TNF-\alpha and IL6 were increased. Administration of either Agomelatine or Curcumin reversed Clonidine-induced behavioral and biochemical changes in the brain. The effect of Curcumin was more pronounced than Fluoxetine regarding behavioral changes. However co-administration of both showed no significant improvement than either one alone.

Conclusion: Agomelatine or Curcumin in the used therapeutic doses showed high efficiency against development of depression in rats. However concomitant administration has no pronounced effects.

Keywords: Depression, Clonidine, Agomelatine, Curcumin, Rats.
P 4. Protective Effect of Carvidolol on Indomethacin- Induced Gastric Ulceration in Pyloric Legated Rats and the Possible Contribution of Nitric Oxide
Walaa Yehia Abd El Zaher and Maha Yehia Kamel
Pharmacology Department, Faculty of Medicine, Minia University, Egypt.

**Background:** Carvidolol, the vasodilatory β-blocker, exhibits anti-inflammatory and antioxidant properties that render it an attractive candidate for protection against gastric ulcer.

**Aim of the study:** The study was performed to evaluate the protective effects of carvidolol against indomethacin-induced gastric ulceration in rats.

**Material and Methods:** Forty adult male albino rats were pylorically ligated and divided randomly into the following groups: control, indomethacin (IND)-treated group (single intraperitoneal injection of 30 mg/kg), carvidolol (30 mg/kg, orally), N(G)-nitro-L-arginine methyl ester (L-NAME) (50 mg/kg, orally), carvidolol +L-NAME. The treated drugs were administered 30 min before ulcer induction.

**Results:** Carvidolol pretreatment significantly attenuated the gastric mucosal lesions induced by IND administration, which was accompanied by significant reduction of the free and total acidity of the gastric secretion, decreased the proteolytic activity with marked attenuation of the gastric mucosal lipid peroxidation and serum tumor necrosis alpha. On the other hand, L-NAME administration aggravated these parameters as compared to indomethacin-treated group. In addition, it was found that carvidolol pretreatment significantly increased the gastric juice mucin concentration, the gastric mucosal nitric oxide (NO) level, catalase and superoxide dismutase activities as compared to the indomethacin-treated group. Furthermore, Carvidolol pretreatment has antiapoptotic effect as evident by the immunological study. Meanwhile, co-administration of L-NAME with carvidolol partially reversed the gastroprotective effect of carvidolol ensuring that one of the protective effects of carvidolol was through the increase of NO production.

**Conclusion:** carvidolol can be considered a potential therapeutic agent to protect against the major clinical challenge of gastric injury resulting from stress.

**Keywords:** indomethacin, carvidolol, gastric ulceration.
P. 5. A Comparative Evaluation of the Effectiveness of Nebivolol and Atenolol in the Acetaminophen – Induced Hepatotoxicity and Possible Role of iNOS and eNOS in Adult Male Albino Rats

Maha Y. Kamel, Walaa Y. Abdelzaher and Remon R. Rofaeil
Pharmacology Department, Faculty of Medicine, Minia University, Egypt.

Background: Acetaminophen (APAP) overdose is a common cause of acute liver failure and beta blockers are commonly used drugs in clinical practice.

Aim of the study: Purpose of this study was to evaluate the effect of two different beta blockers agents as nebivolol and atenolol against acetaminophen induced hepatotoxicity.

Material and methods: Male Wister rats were treated with APAP (2 g/kg/day, po) to induce hepatotoxicity.

Results: Our results revealed that nebivolol (5 mg/kg /day, po) for 14 days has a hepatoprotective effect shown by significant decrease in hepatic injury parameters (serum AST and ALT) with significant suppression of hepatic malondialdehyde (MDA), increased hepatic level of reduced glutathione (GSH) and elevation of nitric oxide level (NO) as compared with APAP-treated rats. Moreover, immuno-histochemical examination revealed that nebivolol treatment markedly reduced inducible nitric oxide synthase (iNOS) expression, while expression of endothelial nitric oxide synthase (eNOS) was markedly enhanced. The protective effects of nebivolol were also verified histopathologically. On the other hand, oral administration of atenolol (50 mg/kg) failed to produce any significant effects in the hepatic injury parameters, hepatic NO, hepatic MDA and hepatic GSH induced by APAP.

Conclusion: In conclusion, the current study revealed that nebivolol is superior over atenolol in protection against APAP -induced hepatotoxicity possibly, in part, through its antioxidant activity, inhibition of iNOS expression and induction of eNOS production.

Keywords: Acetaminophen, nebivolol, atenolol, iNOS, eNOS.
P6. Therapeutic potential of nebivolol against cisplatin-induced nephrotoxicity in rats
Gehan H. Heeba a and Mohamed A. Morsy b
aDepartment of Pharmacology and Toxicology, Faculty of Pharmacy, Minia University, Egypt.
bDepartment of Pharmacology, Faculty of Medicine, Minia University, El-Minia, Egypt

Background: Treatment with cisplatin is associated with dose-limiting side effects mainly nephrotoxicity. On the other hand, nebivolol, a β1-adrenoceptor antagonist, exhibits vasodilatory and anti-oxidative properties.

Aim of the study: The present study aimed to determine whether nebivolol possesses a protective effect against cisplatin nephrotoxicity and explore many mechanisms underlying this potential effect.

Methods: Nephrotoxicity was induced in Wistar rats by a single intraperitoneal injection of cisplatin (6 mg/kg) on day 2. Nebivolol (10 mg/kg) was administered orally for 7 consecutive days.

Results: Nebivolol showed a nephroprotective effect as evidenced by the significant reduction in the elevated levels of serum creatinine and urea as well as renal levels of malondialdehyde, nitric oxide products (nitrite/nitrate), inducible nitric oxide synthase, tumor necrosis factor-alpha, caspase-3, angiotensin II, and endothelin-1 with a concurrent increase in renal levels of reduced glutathione and endothelial nitric oxide synthase compared to untreated rats. Histopathological examination confirmed the nephroprotective effect of nebivolol. Pretreatment with Nω-nitro-L-arginine methyl ester, the non-specific nitric oxide synthase inhibitor, partially altered the protection afforded by nebivolol.

Conclusion: In conclusion, nebivolol protects rats against cisplatin-induced nephrotoxicity that is most likely through its antioxidant, anti-inflammatory, and anti-apoptotic effects, as well as by abrogation of the augmented angiotensin II and endothelin-1 levels.

Keywords: Nebivolol; Cisplatin; Nephrotoxicity; Nitric oxide; Tumor necrosis factor-alpha; Caspase-3.
P 7. Protective effects of Lipoic acid and Pentoxifylline against Nandrolone decanoate-induced Behavioral Changes in Rats

Maha A.E. Ahmeda and Sally A. El-Awdanb
aPharmacology and Toxicology Department, Faculty of Pharmacy, Misr University for Science and Technology (MUST), 6th of October City, Giza, Egypt.
bPharmacology and Toxicology Department, National Research Centre, Dokki, Cairo, Egypt.

Background: Nandrolone decanoate (ND) is an androgenic anabolic steroid that is widely abused by athletes and adolescents. Experimental studies and clinical reports showed that ND may induce psychological alterations and behavioral perturbations. On the other hand, lipoic acid (LA) is a potent natural antioxidant that can pass the blood brain barrier whereas pentoxifylline (P) is a phosphodiesterase-IV inhibitor xanthine derivative.

Aim of the study: The present study aimed at investigation of the possible protective effects of LA and/or P against ND-induced neurobehavioral disturbances in rats.

Methods: Male albino rats were randomly distributed into seven groups, and treated with either vehicle, ND, LA, P, or ND with LA and/or P. Rats were challenged in the open field, and resident-intruder aggression tests. Twenty four hours after the last administered dose, rats were sacrificed and brains were harvested for biochemical analysis.

Results: The present findings showed that ND induced anxiety and aggression in rats via imbalance in brain neurotransmitters and down-regulation of Nrf2/HO-1. LA and P combination significantly reversed all the previously mentioned deleterious effects.

Conclusion: Lipoic acid and pentoxifylline may attenuate nandrolone decanoate-induced behavioral disturbances in rats.

Keywords: Lipoic acid, Pentoxifylline, Nandrolone decanoate, Open field, Nrf2/HO-1.
P 8. Alleviation of renal mitochondrial dysfunction and apoptosis underlies the protective effect of sitagliptin in gentamicin induced nephrotoxicity

Sally A. Abuelezz,a Nevin Hendawyb and Sara Abdel Gawadb

a Pharmacology Department, Faculty of Medicine, Ain-Shams University, Cairo, Egypt
b Histology Department, Faculty of Medicine, Ain-Shams University, Cairo, Egypt

Background: Gentamicin-induced nephrotoxicity has been well documented, although its preventive strategies remain to be investigated.

Aim of the study: The present study aimed to investigate the potential protective effect of sitagliptin on gentamicin-induced nephrotoxicity and to elucidate the underlying mechanism.

Methods:
Wistar rats were allocated as follows; Gentamicin group: received gentamicin intraperitoneally (100 mg/kg/day), Gentamicin plus sitagliptin group: received simultaneous gentamicin and sitagliptin (30 mg/kg/day orally). Sitagliptin group: received only sitagliptin.

Control group: received saline. Blood urea nitrogen (BUN), serum creatinine, urine proteins levels and histopathology of kidney tissues were evaluated. The activity of mitochondrial enzyme complexes reflects the mitochondrial function. Oxidative stress biomarkers and immunohistochemical studies for apoptotic markers caspase 3 and Bax were evaluated.

Results:
Gentamicin causes significant elevation of BUN, serum creatinine and urine proteins. Oxidative stress was revealed by decreased superoxide dismutase and catalase activities, glutathione depletion and increased malondialdehyde. Significant decrease in mitochondrial NADH dehydrogenase, succinate dehydrogenase, cytochrome c oxidase and mitochondrial redox activities indicates mitochondrial dysfunction, along with significant elevation in renal caspase 3 and Bax. The aforementioned markers and the histologic injury in renal tubules were significantly decreased upon sitagliptin treatment.

Conclusion: These findings suggest that sitagliptin treatment attenuates renal dysfunction and structural damage through the reduction of oxidative stress, mitochondrial dysfunction and apoptosis in the kidney.

Keywords: Gentamicin; nephrotoxicity; sitagliptin; oxidative stress; mitochondrial dysfunction; apoptosis.
**P 9. The use of Stem cell as a New Method for Amelioration of Polyphenols-Induced Hepatotoxicity in Mice**

**IG Saleh**, Z Ali, MA Hammad, FD Wilson, FM Hamada, MF Abd-Elah, LA Walker, IA Khan, and MK Ashfaq

1National Center for Natural Products Research, School of Pharmacy, University of Mississippi, Oxford, MS, USA
2Department of Pharmacology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.
3Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
4Mississippi Veterinary Research and Diagnostic Labs, College of Veterinary Medicine, Mississippi State University, Pearl, MS, USA.
5Department of Pharmacology, School of Pharmacy, University of Mississippi, Oxford, USA.
6Department of Pharmacognosy, School of Pharmacy, University of Mississippi, Oxford, USA.
7Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

**Background:** Stem cells can be identified as a novel cell therapy for regenerative medicine because of their ability to differentiate into many functional cell types. They are also thought to have protective effects against different organs injuries via modulation of certain cytokines.

**Aim of the study:** This study aimed to evaluate the ameliorating effect of intrahepatic (IH) injection of mouse embryonic stem cells (MESC) on the hepatotoxicity induced by EGCG/LPS in mice.

**Methods:** Mice (ND4) were administered EGCG/LPS and rested for 3 days. MESC were isolated and cultured in vitro for 4 days, then injected IH. Seven days later, a single dose of LPS (6 mg/kg) followed by daily doses of IG administration of EGCG were re-administered for 5 days. At the end of the experiment, blood samples were collected for analysis of biochemical parameters associated with liver. Samples of liver tissue were used to evaluate different parameters to indicate the possibility of occurrence of liver injury (Ox.LDL, CXCL16, RAR, RXR, TNFα and TFβ). Other liver samples were processed for evaluation of histopathologic lesions.

**Results:** Results showed that the group of mice that were administered MESC prior to EGCG/LPS showed lower levels of alanine amino transferase, alkaline phosphatase, and bilirubin, higher albumin/globulin ratio, and less remarkable histopathological lesions. Also, that group of mice showed less expression of oxidative stress biomarkers (oxidized low-density lipoprotein Ox.LDL and chemokine CXCL16), less expression of nuclear protein receptors (retinoic acid receptor and retinoid X receptor), and less expression of inflammatory biomarkers (TNFα and TFβ) compared with other groups of mice that were not given MESC.

**Conclusion:** In conclusion, MESC can ameliorate EGCG/LPS-induced hepatotoxicity in mice.

**Keywords:** Epigallocatechin-3-gallate, lipopolysaccharide, stem cells, mice, hepatotoxicity.

Nourhan Mohamed Abd El-maksoud, Manar Mohamed Rashad, Gamal Mohammed Ashraf, Al Siddeg Kamal Al Siddeg and Mai Fathy Tolba

*Students at 4th grade at Faculty of Pharmacy, Ain Shams University, Egypt.

Department of Pharmacology Faculty of Pharmacy, Ain Shams University, Egypt.

Background: Evening primrose oil (EPO) has long been used for its therapeutic benefits in treatment of skin disorders such as eczema, symptoms of diabetic neuropathy, morning stiffness and joint tenderness, as well as pain relief. It is known to be one of the richest available natural sources of essential fatty acids, including linoleic acid (70%) and γ-linolenic acid (8%).

Aim of the study: This study tested the hypothesis that EPO possesses anti-inflammatory activity.

Methods: This was done through assessing the effect of oral pretreatment with EPO in carrageenan-induced paw edema in Sprague-Dawley rats. Animals were pretreated with 250 or 500 mg/kg of EPO 30 minutes before carrageenan s.c. injection. Then the change in paw volume was evaluated using pleythysmometer. The anti-inflammatory activity was tested in comparison to the standard nonsteroidal anti-inflammatory drug indomethacin (10mg/kg, p.o.). The study was further extended to assess the antioxidant effects of EPO. Catalase activity (CAT), reduced glutathione (GSH), nitric oxide and Total antioxidant capacity (TAC) were assessed in the collected paw exudates collected after 4h carrageenan injection using colorimetric kits.

Results: The results showed that pretreatment with 250 mg/kg EPO opposed carrageenan-induced paw edema and this effect was comparable to 10 mg/kg indomethacin. EPO pretreatment significantly reduced carrageenan-induced decrease in nitric oxide. The levels of GSH, CAT, TAC were higher in EPO treated rats.

Conclusion: This study highlights a promising anti-inflammatory activity for EPO and sets stage for its future use as a supplement in inflammatory conditions.

Keywords: Evening primrose oil; inflammation; paw edema; nitric oxide; reduced glutathione; catalase.
**P 11. Novel Anticancer Activity for Evening Primrose Oil (EPO)**

*Nouran Yonis*, **Ahmed Elhossiny**, **Haidy Saleh**, **Yasmin Elgarhy** and **Mai F. Tolba**

*a* Students at 4th grade at Faculty of Pharmacy, Ain Shams University, Egypt.

*b* Department of Pharmacology Faculty of Pharmacy, Ain Shams University, Egypt.

**Background:** Evening primrose oil (EPO), is a commonly used alternative therapy and a rich source of omega-6 essential fatty acids. EPO extracted from Oenotherabiennis contains linoleic acid, Y linolenic acid, and vitamin E which are responsible for its therapeutic effects. It is best known for its use in the treatment of systemic diseases marked by chronic inflammation such as atopic dermatitis and rheumatoid arthritis. Colorectal cancer is the fourth most common noncutaneous malignancy in the United States and the second most frequent cause of cancer-related death. Over the past 12 years, significant progress has been made in the systemic treatment of this malignant condition.

**Aim of the study:** The present study tested the hypothesis that EPO possess anticancer activity against colon cancer *in vitro*.

**Methods:** This was done through performing sulforhodamine-B cytotoxicity assay using serial concentrations of EPO to test its cytotoxic potential against Caco-2 human colon cancer cell line.

**Results:** The results showed that EPO exhibited cytotoxic activity with IC$_{50}$ of 120 ug/ml.

**Conclusion:** Subsequently EPO has a promising anticancer activity further studies are needed to investigate the possible activity against cancer cells of different origin and to unravel the underlying mechanisms for such activity.

**Keywords:** Evening primrose oil (EPO), Omega-6 essential fatty acids, Atopic dermatitis, Rheumatoid arthritis, colorectal cancer.
P 12. Effect of candesartan and/or epigallocatechin-3- gallate on gentamicin-induced nephrotoxicity in rats
Hebatalla I. Ahmed and Eman A. Mohamed
Department of Pharmacology & Toxicology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.

Background: Nephrotoxicity is a major complication of gentamicin, which is widely used in the treatment of severe Gram negative infections. Reactive oxygen species are important mediators of gentamicin-induced nephrotoxicity.

Aim of the study: Because of the antioxidant properties of candesartan, an Angiotensin Receptor Blocker (ARB), and epigallocatechin-3-gallate (EGCG), the most abundant and active compound of green tea, the present study aimed to evaluate the possible protective effect of candesartan and/or EGCG against gentamicin-induced nephrotoxicity.

Methods: Forty adult male rats were randomly divided into five equal groups. Saline (1 ml/kg, i.p. for 14 days) treated rats served as control. In gentamicin group, rats received saline (1 ml/kg, i.p.) for the first 7 days followed by gentamicin (100 mg/kg, i.p.) for the second 7 days. Candesartan (3 mg/kg, i.p.) and/or EGCG (25 mg/kg, i.p.) were administered for 7 days before and 7 days simultaneously with gentamicin (100 mg/kg i.p.). Twenty four hours after the last administration, blood samples were collected then rats were sacrificed and kidneys were taken.

Results: Gentamicin administration caused a severe nephrotoxicity as evidenced by the significantly elevated relative kidney weight, serum creatinine (Scr), blood urea nitrogen (BUN) as compared to control group. In addition, a significant increase in renal contents of malondialdehyde (MDA), interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) concomitantly with a significant decrease in renal glutathione-S-transferase (GST) and superoxide dismutase (SOD) activities were detected upon gentamicin injection. Either candesartan or EGCG pre-treatments attenuated gentamicin- induced nephrotoxicity by reducing the relative kidney weight, Scr, BUN, MDA, IL-1β and TNF-α levels and increasing the SOD and GST activities. Also candesartan and EGCG pre-treatments alleviated gentamycin-induced nephrotoxicity and the alleviation was significant from either of them alone regarding Scr, BUN, IL-1β, SOD and GST.

Conclusion: The present study indicated that either candesartan or EGCG exerted protection against renal oxidative damage induced by gentamicin possibly due to their antioxidant and anti-inflammatory properties. Co-administration of candesartan and EGCG exhibited more profound response compared to the monotherapy.

Keywords: Gentamicin; Nephrotoxicity; Candesartan; Epigallocatechin-3-gallate; Antioxidant; Anti-inflammatory; Rats.

Corresponding author E-mail: hebatalla123@yahoo.com

**Gehad A. Abdel Jaleel**, Dalia O Saleh, Sally El Awdan and Manal Badawy

*a*Pharmacology Department, National Research Centre, Egypt.

*b*Pathology Department, National Research Centre, Egypt.

**Background:** Diabetes in humans induces chronic complications such as cardiovascular damage, cataracts and retinopathy, nephropathy and polyneuropathy. The most common animal model of human diabetes is streptozotocin (STZ)-induced diabetes in the rat.

**Aim of the study:** The present study investigated the effects of monascus purpureus (MP) alone or in combination with pioglitazone on glucose level and on liver of streptozotocin (STZ) diabetic rats.

**Methods:** In the present study, rats were divided into seven experimental groups (normal, untreated STZ-diabetic (60 mg/kg, IP), treated STZ-diabetic with monascus purpureus (500 mg/kg, oral), treated STZ-diabetic with pioglitazone (10 mg/kg, oral) and treated STZ-diabetic with monascus purpureus (250 mg/kg, oral) + pioglitazone (10 mg/kg, oral). Treatment continued for 14 days then samples were taken 24 h after the last administration to assess blood glucose. At the end of the study, the animals were fasted overnight, anaesthetized with an intraperitoneal injection of sodium pentobarbital (60 mg/kg), and sacrificed for obtaining tissues samples (liver, pancreases).

**Results:** At the end of the experiment, all treatments significantly (P<.05) lowered serum glucose, triglycerides, cholesterol, C-peptide and IL-6. In addition, hepatic cholesterol and triglycerides levels were also lowered. Moreover, the treated diabetic rats showed higher activity of glutathione reductase (P<0.05) in the liver compared with the diabetic control rats and inhibited diabetes induced elevation in the levels of malondialdehyde in liver. The results clearly demonstrated that MP possesses several treatment-oriented properties, including the control of hyperglycemia, antioxidant effects, pancreatic β-cell protection and antiinflammatory effects.

**Conclusion:** Considering these observations, it appears that MP may be a useful supplement to delay the development of diabetes and its complications.

**Keywords:** Monascus purpureus, diabetes, Pioglitazone, liver, streptozocin.
P 14. Ameliorative effects of phosphodiesterase (PDE) inhibitors in potassium dichromate-induced acute renal failure in rats

_Abeer A. A. Salama^a, Rasha E. Mostafa^a and Enayat A. Omara^b_

^a^Pharmacology Department, National Research Centre, Giza, Egypt
^b^Pathology Department, National Research Centre, Giza, Egypt.

**Background:** Heavy metal Potassium dichromate (PD) is a nephrotoxic xenobiotic that lead to acute tubular necrosis.

**Aim of the study:** To examine the possible renoprotective effect of members in the phosphodiesterase (PDE) inhibitors on potassium dichromate induced acute renal failure (ARF) and oxidative stress in rats.

**Methods:** ARF was induced by subcutaneous (s.c) injection of a single dose (15 mg/kg) of PD. Rats were randomly allocated to 5 groups as follow: Group I: Normal control group received saline. Group II: Rats injected s.c with PD and served as renal failure group. Group III, IV and V: Rats received daily Sildenafil (0.5 mg/Kg), Vardenafil (3 mg/Kg) and Tadalafil (10 mg/Kg), respectively for 14 days prior PD injection. Estimation of serum creatinine, blood urea nitrogen (BUN) and total protein, kidney tissue glutathione peroxidase (GPx), malondialdehyde (MDA), nitric oxide (NO) and tumor necrosis factor alpha (TNF-α) contents as well as histopathological examination were carried out.

**Results:** Injection of PD to rats induced a marked acute renal failure, characterized with a significant increase in serum creatinine urea and total protein. PD group had lower kidney GPx content and higher MDA, NO and TNF-α contents while PDE inhibitors therapy improves kidney function, GPx content and ameliorates MDA, NO and TNF-α contents.

**Conclusion:** PDE inhibitors may reduce or delay the emergence of PD nephrotoxicity.

**Keywords:** Acute renal failure; Oxidative stress; phosphodiesterase (PDE) inhibitors; Rat.
P 15. Protective Effect of L-Carnitine in Paracetamol-induced Hepatotoxicity in Rats.
Ezz El-din S. El- Denshary a, Hala F. Zaki a, W. I El- Erakyb and Nermeen E. El-Sharkawyc

aPharmacology & Toxicology department, Faculty of Pharmacy, Cairo University, Egypt.
bDepartment of Narcotics – Ergogenics, and Poisons, National Research Center, Egypt.
cNarcotic Pharmacy, New El-Kasr El-Einy Educational Hospital, Egypt.

Background: Paracetamol is a commonly used analgesic and antipyretic. Toxic doses of paracetamol, however, cause massive hepatocellular apoptosis and necrosis. L-carnitine (CAR) is a mitochondria-specific antioxidant that plays an important role in oxidative/antioxidative balance by scavenging reactive oxygen species and increasing ATP production.

Aim of the study: The present work was designed to examine the possible protective effects of CAR against paracetamol -induced liver injury.

Method: Male Wistar rats were allocated into four groups of 10 animals each. Group I received saline p.o. for 7 days (normal group), group II received CAR (300 mg/kg; p.o.) for 7 days, group III received saline for 7 days followed by single dose of paracetamol (700 mg/kg; p.o.) on the 8th day (paracetamol control group), and group IV received CAR (300 mg/kg; p.o.) for 7 days followed by paracetamol on the 8th day. Rats were sacrificed 24 h thereafter. Parameters used to assess the protective effect of CAR included serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities as well as liver contents of thiobarbituric acid reactive substances, reduced glutathione, nitric oxide, total antioxidant capacity, tumor necrosis factor-alpha and transforming growth factor- beta in addition to histological examination of liver sections from all studied groups.

Results: Pretreatment with CAR attenuated paracetamol- induced increases in transaminases, oxidative stress and inflammatory biomarkers as well as paracetamol -induced histopathologic changes.

Conclusion: L- carnitine can protect against paracetamol-induced hepatotoxicity by virtue of its antioxidant and anti-inflammatory properties.

Key words: Paracetamol, L-carnitine, oxidative stress, inflammation.
P 16. Fresh Garlic homogenate ameliorates the hepato-renal Histopathological and Histochemical alterations induced by Gentamicin, Cefotaxime, Metronidazole and their combinations in Rats


aDepartment of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt.
bDepartment of Pharmacology, National Organization for Drug Control and Research (NODCAR), Giza, Egypt

Background: Gentamicin is an aminoglycoside bactericidal antibiotic used in therapy mainly against Gram negative bacteria. Cefotaxime is a semisynthetic broad spectrum bactericidal cephalosporin antibiotic and used against Gram positive and Gram negative bacteria. Metronidazole is an antimicrobial drug used in treatment of protozoal and anaerobic bacterial infection which may be administered with Gentamicin and/or Cefotaxime in the treatment of mixed infections caused by anaerobic and aerobic organisms. Combination therapy has complementary mechanisms of action.

Aim of the study: The Present investigation aimed at evaluating the effect of fresh garlic homogenate (FGH) on histopathological and histochemical alterations of gentamicin, cefotaxime, metronidazole and their combinations-induced toxicity.

Methods: For this purpose, eighty eight male albino rats were divided into eleven groups. (1): Served as control, (2): Received FGH (500mg/kg.b.wt., p.o.), (3): Received gentamicin (80 mg/ kg.b.wt., i.m), (4): Received cefotaxime (540 mg/kg.b.wt., i.m), (5): Received metronidazole (135 mg/ kg.b.wt., p.o.), (6): Received gentamicin with cefotaxime, (7): Received gentamicin with cefotaxime and metronidazole, (8): received FGH one hour prior gentamicin , (9): Received FGH one hour prior cefotaxime, (10): Received FGH one hour prior gentamicin and cefotaxime, (11): Received FGH one hour before gentamicin, cefotaxime and metronidazole for 14 successive days. Animals were sacrificed, kidney and liver were removed for homogenate measurements, histopathological & histochemical examination. Results indicated a significant (p < 0.05) decrease of TNF-α and elevation in GPx of liver and of liver and kidney homogenate.

Results: Results indicated a significant (p < 0.05) decrease of TNF-α and elevation in GPx of liver and of liver and kidney homogenate. Our data indicated that FGH could protect the liver and kidney against the histopathological and histochemical alterations by blocking oxidative damages in addition to restorment of the antioxidant enzymatic profile.

Conclusion: Fresh Garlic homogenate has both antioxidant and anti-inflammatory activities ameliorating the hepato-renal histopathological and histochemical alterations induced by Gentamicin, Cefotaxime, Metronidazole and their combinations in Rats and their combinations

Keywords: Gentamicin, Cefotaxime, Metronidazole, FGH, TNF-α, GPx, histopathological and histochemical.

Corresponding author: E-mail: kamare_ahmady@yahoo.com.
P 17. Hepatoprotective Effect and Chemistry of Phenolics Isolated from Acalypha WIlkesiana cv.Effmannii (Euphorbiaceae) on Primary Cultured Rat Hepatocytes
Amani M.D.El-Mousallamy* and Sahar A.M. Hussein

*Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt.

Department of Natural Product, Division of Pharmaceutical Chemistry, National Research Center, Cairo, Egypt.

Background: Plant phenols, including polyphenols are among the most potent and therapeutically promising bioactive substances. Previous comprehensive studies proved that plant phenols possess diverse effect on biological systems. The diversity of their structures is the basis of the recent increase in the detection of the various biological and pharmacological activities which have been extensively researched such as antitumor, antibacterial, enzyme, antioxidant, analgesic, antiallergic, antihepatotoxic, anti-inflammatory, antosteoporotic, antiviral and immunomodulating.

The flavonoid family is subdivided into different subfamilies such as flavanones, flavones, flavonols, isoflavones, anthocyanins, chalcones and condensed tannins. Most of flavonoid aglycones are found in a glycosylated form in plant cells, This is assumed to protect them from degradation, to reduce their toxic effects and to aid their transport across membranes by increasing their water solubility

Aim of the study: Isolation of phenolic compounds from the aqueous ethanolic extract of Acalypha Wilkesiana. Identification of the isolated phenolics using chemical analysis, conventional, advanced spectroscopic and spectrometric techniques. Determination of some biological activities including antioxidant, cytotoxicity and hypolipidemic activities of the aqueous ethanolic extract of leaves and isolated pure compounds.

Methods: Monolayer from primary cultures of rat hepatocytes was performed in the 96-well plate, incubated for 22-24 hrs. Different concentrations were prepared from each of the extracts of Acalypha Wilkesiana species, starting from 12.5 μg/mL and increasing concentration in ascending order by dissolving in DMSO (1% maximum concentration). For each concentration, three replicates were carried out, in addition to controls which were: cell control (cells only), negative control (cells + paracetamol) and positive control (cells + sylimarin + paracetamol). The plate was incubated for 2 hrs, washed twice with Phosphate Buffer Saline (PBS). Paracetamol (20 mM) was added to each well except on that of the cell control and incubated for 18 hrs. Following incubation, the monolayer was washed again with PBS. 50% mortality of the hepatocyte (IC50) was determined using NR assay. The viability assay was applied with a broad range of concentrations of the studied extracts of Acalypha. The sample exerts no toxic effect on the monolayer hepatocyte layer 50% mortality of the hepatocyte (IC50) was determined using Neutral Red Assay Acalypha extract showed hepatoprotective activity against paracetamol toxic effect 40 μg/ ml. The constitutive flavonoids of Bay leaves were extensively studied and led to the separation and identification of 14 phenolic compounds which were identified using chemical, conventional and advanced NMR, 1- D and 2-D spectral techniques.
**Results:** From the point of view of the main classes of natural products existing in the leaves *Acalypha* and on the basis of the analytical results achieved during the course of the present work we can come to the conclusion that showed hepatoprotective activity is produced by the leaf extract of the plant could be due to the existing combination of phenolic constituents or it could be attributed to one or more of the phenolic compounds and the IC50 of the different fractions suggested that the antioxidant activity is best interpreted in terms of the existing phenolics, catchine, epicatchine and rutin, other flavonoid glycosides and chlorogenic acid which are well known for their potent antioxidant activities and correspondingly significant inhibition of UV induced IL-6 production.

**Conclusion:** Cytotoxicity: The extract and all fractions tested were in the higher concentrations toxic to the cultured HaCaT keratinocytes. Galloylvitexin showed concentrations in the 125 μg/ml and 63 μg/ml of a cytotoxic effect on the HaCaT cells.

Hypolipidemic activity: The in vitro hypolipidemic effect of *Acalypha Wilkesiana* extract on the activity of β-hydroxy-β glutaryl Co A-reductase. The extract recorded 86.64% inhibition in enzyme activity as compared to control. The reference drug (lipanthyl) showed inhibition in enzyme activity by 90.58%.

**Keywords:** *Acalypha Wilkesiana cv.Hoffmannii*, and hepatoprotective, anticancers, NMR phenolic compounds.

Corresponding author: amanimd@yahoo.com
**P 18. Biological investigation of certain substituted 2,6-diketopiperazines as analgesic and anti-inflammatory**

*Mona E Aboutab* and *Walaa H.A. Abd El-Hamid*

*a* Medicinal and Pharmaceutical Chemistry Department (Pharmacology Group), Pharmaceutical and Drug Industries Research Division, National Research Centre, Egypt.  
*b* Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Misr University for Science & Technology, 6th of October City, Egypt.

**Background:** 2,6-Diketopiperazines (2,6-DKPs) are promising bioactive chemical entities in drug discovery. Also, it is embedded in the chemical skeleton of 6,9-diazaspiro-[4,5]decane-8,10-diones.

**Aim of the study:** To study both peripheral and central analgesic activities as well as the anti-inflammatory activity of 9 derivatives of 6-aryl-9-substituted-6,9-diazaspiro-[4,5]decane-8,10-diones.

**Methods:** The test compounds 1-9 were evaluated for their analgesic activity using the writhing (12.5 and 25 mg/kg) and hot-plate (25 mg/kg) tests. The anti-inflammatory activity was assessed (25 mg/kg) by using carrageenan-induced hind-paw edema assay at 1, 2, and 3 h after carrageenan challenge.

**Results:** All compounds 1-9 showed significant inhibition of acetic acid induced writhing. Their percentage inhibition of abdominal writhing (12.5 and 25 mg/kg) ranged from 68.55 to 17.74% and from 88.71 to 53.23%, respectively (peripheral effect). Compound 7 demonstrated the highest writhing inhibition percentage at both dose levels (88.71 and 68.55%, respectively) and exhibited significantly lower number of writhes compared with diclofenac sodium. In the hot-plate test (central effect), compounds 2 and 3 (25 mg/kg), significantly raised the pain threshold and exhibited the best analgesic activity at 30 min. Both of them displayed non significant difference from tramadol hydrochloride (25 mg/kg) at 30 min. In contrast, compounds 1 and 5 showed slightly lower analgesic potency compared with compounds 2 and 3 with significant difference from the reference drug. The most powerful anti-inflammatory effect in this series was demonstrated in 9-N-methyl acetate derivatives (1-3), where compound 1 exhibited 53.93% maximum protection (inhibition of edema size) at 3 h, compared with diclofenac sodium, which reached 60.40%.

**Conclusion:** These results could consider the different structural scaffolds of compounds 1-9 as promising bioactive candidates for peripheral analgesia, while compounds 1-3 for central analgesia and as anti-inflammatory. Consequently, these results augments the numerous biological activities of 2,6-DKPs in the field of medicinal chemistry.

**Keywords:** Analgesic, anti-inflammatory, 2,6-diketopiperazines, 6,9-diazaspiro-[4,5]decane-8,10-diones.
P 19. Protective Effects of Quercetin and Lecithin on Carbon Tetrachloride-Induced Hepatotoxicity in Rats

Reem M Galal, Lamia A Ahmed, Hala F Zaki and Sanaa A Kenawy
Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, Egypt.

**Background:** Hepatotoxicity was induced by carbon tetrachloride (CCL4); one of the most commonly used hepatotoxins in experimental studies. Quercetin is a bioactive flavonoid present in various edible fruits and vegetables and is a potent antioxidant and exhibits a wide range of biological functions. Lecithin is a dietary source of several active compounds as choline and its metabolites which are needed for several physiological purposes, including cell membrane signaling and cholinergic neurotransmission.

**Aim of the study:** The present study was undertaken to investigate the protective effect of quercetin and lecithin against CCL4-induced hepatotoxicity in rats using silymarin as a reference hepatoprotective drug.

**Methods:** Male Wistar rats were divided into five groups and treated orally with test drugs for 28 days. Groups 1 and 2 served as normal control and CCL4 control, respectively. The remaining groups received silymarin (100 mg/kg), quercetin (50 mg/kg) and lecithin (100 mg/kg), respectively. CCL4 (0.5 ml/kg in olive oil; p.o.; twice/week for 4 weeks) was administered to all groups except the normal group 1. Hepatoprotective activity was assessed by measuring serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities as well as histological examination of liver tissues. Moreover, effects of quercetin and lecithin on liver contents of malondialdehyde (MDA), reduced glutathione (GSH), nitric oxide (NO) and tumor necrosis factor alpha (TNF-α) were also estimated.

**Results:** CCL4 caused marked liver damage manifested by significant increase in serum AST and ALT activities as well as TNF-α content. It also resulted in a significant decrease in liver GSH content parallel to a significant increase in MDA and NO contents. Pretreatment with quercetin, lecithin, and silymarin attenuated CCL4-induced increases in serum transaminases as well as oxidative stress and inflammatory cytokines. Results of histopathological examination correlated with the biochemical findings.

**Conclusion:** Quercetin and lecithin could be used as effective hepatoprotective agents against CCL4-induced liver damage.

**Keywords:** Carbon tetrachloride, quercetin, lecithin, silymarin, hepatotoxicity, inflammatory cytokines, oxidative stress.
P 20. Effects of liraglutide and vitamin E in fructose-induced metabolic disorders in rats

Maha Yehia Kamel, Marwa Hussein Mohamed, Ayman Ibrahim and Mohamed Abdellah Ibrahim
Pharmacology Department, Faculty of Medicine, Minia University, Egypt.

Background: Metabolic syndrome (MetS) is a worldwide health problem that affects up to 25% of adult population. Understanding the role liraglutide (Lira) and vitamin E (vit E) in the pathogenesis of MetS is fundamental to developing the therapeutic strategies, as no established therapeutic strategy for treatment of MetS yet.

Aim of the study: To investigate the effects of liraglutide and vitamin E on fructose-induced metabolic and hepatic disorders in rats.

Methods: Forty adult male albino rats were randomly divided into five equal groups: Control group receiving normal diet; Fructose-induced MetS; MetS-Lira-treated group; MetS-vitamin E-treated group and MetS received combination of drugs. Doses of Lira (0.3 mg/kg/day, s.c.) and vit. E (100 mg/kg/day, orally) were administrated for six consecutive weeks.

Results: Lira and vit E significantly attenuated the fructose induced elevation in the metabolic parameters (fasting serum glucose level, oral glucose tolerance test (OGTT ), serum insulin level and insulin resistance (HOMA-IR), serum transaminase level, serum triglyceride and cholesterol levels, tumor necrosis factor alpha (TNF-α) in serum and hepatic tissue as detected by immune-histochemical staining, hepatic malondialdehyde level (MDA). On the other hand, these were significantly increased in the fructose induced decrease in the serum level of HDL, serum level of nitric oxide (NO) and hepatic oxidative marker (reduced glutathione, superoxide dismutase activity (SOD). In addition, combination of Lira and vit E were significantly attenuated all parameters in the fructose induced MetS as proved by histological examination as compared to Lira and vit E- treated rats

Conclusion: Liraglutide, and vitamin E represent a potential promising therapy for MetS. Their effects might be mechanistically relevant to their ability to reduce oxidative stress and TNF-α level.

Key words: Metabolic syndrome, Liraglutide, vitamin E, tumor necrosis factor alpha.
**P 21. Protective effect of pravastatin against cyclophosphamide-induced cardiorenal toxicity in albino rats**

*Khaled A. Alhumaidha*, Dalia O. Saleh, Mai A. Abd El Fattah, Wafaa I. El-Eraky and Helmy Moawad

*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Egypt.*

**Background:** Cyclophosphamide (CP) is a cytotoxic alkylating agent used in the treatment of malignant diseases and autoimmune disorders. Its clinical use is limited to its marked cardiorenal toxicity. Pravastatin has been antioxidant effect and shown to hinder radical oxygen species production.

**Aim of the study:** The present study aimed to investigate the possible protective effects of pravastatin against CP-induced cardiorenal toxicity in albino rats.

**Methods:** Rats were divided into four groups (control, pravastatin, CP, CP + pravastatin). CP (200 mg/kg) was administered as a single intraperitoneal injection whereas; pravastatin (10 mg/kg) was administered for 3 weeks on a daily basis. Then, serum activities of creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), creatinine and blood urea nitrogen (BUN) were measured. Biomarkers of oxidative stress were also measured in both heart and renal tissue.

**Results:** The results showed that CP produced an elevation in serum activities of CK, CK-MB, LDH, creatinine as well as BUN. CP also induced an elevation in the oxidative stress markers, elevation in the serum lipid peroxides level (measured as malondialdehyde; MDA) and reduction in reduced glutathione level and superoxide dismutase activity in both heart and renal tissue. On the other hand, administration of pravastatin attenuated the CP-evoked disturbances in the above mentioned parameters. In addition, CP exhibited electrocardiographic (ECG) changes, which were significantly reversed by pravastatin treatment. Histopathological changes showed that CP-caused significant structural damages to heart and renal tissue that were reduced with pravastatin.

**Conclusion:** The present results indicate that treatment with pravastatin prevented CP-induced cardiotoxicity and nephrotoxicity in albino rats.

**Keywords:** Cyclophosphamide, pravastatin, cardiotoxicity, nephrotoxicity
**P 22. Cardamonin protects against acetic acid-induced ulcerative colitis in rats**
*Sahar A. Khaled, Ekram N. Abd-Al-Haleem, Amany S. Sallam and Azza A. Ali*
Pharmacology and Toxicology Department, Faculty of Pharmacy, Al-Azhar University (Girls), Cairo, Egypt.

**Background:** Emerging evidences have indicated the role of inflammatory mediators, oxidative stress and apoptosis in the pathogenesis of ulcerative colitis (UC). Cardamonin is a naturally occurring chalcone with strong anti-inflammatory and antiapoptotic activities. Moreover, cardamonin counteracts oxidative stress. However, the impact of cardamonin on UC has not been elucidated.

**Aim of the study:** To investigate the potential protective effect of cardamonin on acetic acid-induced UC. Two different doses of cardamonin were assessed.

**Methods:** Ulcerative colitis (UC) was induced by a single intrarectal administration of 2ml acetic acid (3%) in rats pretreated with cardamonin (10 or 30 mg/kg/day, p.o) or sulfasalazine (50 mg/kg/day, p.o) for 14 days. Twenty four hours later, animals were sacrificed and the colonic tissues were collected. Levels of malondialdehyde (MDA) were estimated in colon tissues. Myeloperoxidase (MPO) as well as inducible nitric oxide synthase (iNOS) contents were assessed. Pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and nuclear factor kappa B (NFκB) were estimated in colonic tissues. Moreover, immunohistochemical staining for active caspase-3 and cyclooxygenase-2 (COX-2) was performed. The histopathological changes of the colonic tissues were also observed.

**Results:** Cardamonin attenuated the severity of UC in a dose dependent manner as evidenced by histopathological findings via decreasing MDA, MPO, iNOS, NF-κB, TNF-α, caspase-3 and COX-2 contents. On the other hand, sulfasalazine reduced MDA, MPO, iNOS, NF-κB and TNF-α contents.

**Conclusion:** The present study elucidates a beneficial effect of cardamonin on experimental UC via antiinflammatory, antiapoptotic and antioxidant mechanisms. This study may give rise to investigating the clinical benefit of cardamonin in human UC.

**Keywords:** Ulcerative colitis, Cardamonin, Sulfasalazine, Rats.
**P 23. The Possible Influence of Vinpocetine on the Pharmacological Action of Indomethacin Using a Rat Model of Arthritis**

_Ekram N. Abd Al Haleem, Asmaa S. Ahmed and Azza A. Ali_

Pharmacology and Toxicology Department, Faculty of Pharmacy, Al-Azhar University (Girls), Cairo, Egypt.

**Background:** Rheumatoid arthritis (RA) is an incurable chronic inflammatory disorder with extra-articular manifestations. Indomethacin is a non-steroidal anti-inflammatory drug with potent anti-inflammatory, analgesic and antipyretic properties. It is one of the most common prescription drugs used for symptomatic management of RA. Its long term use is associated with potentially life-threatening deleterious effects of gastrointestinal ulceration, bleeding, nephropathy and injury to liver and bone marrow. Vinpocetine is an alkaloid extracted from the periwinkle plant, has been used clinically for treating cerebrovascular disorders and improving memory. Recent evidence demonstrates that it possesses an anti-inflammatory property by targeting IκB kinase/NF-κB–dependent pathway via a direct inhibition of the IκB kinase complex; vinpocetine has no known significant side effects, thus making it an attractive alternate anti-inflammatory agent for long term use.

**Aim of the study:** To investigate the effects of vinpocetine on the anti-inflammatory effect of indomethacin and to evaluate the anti-inflammatory activity of vinpocetine in the treatment of arthritis.

**Methods:** Adjuvant arthritis was induced in rats by injection of 0.1 ml Complete Freund’s Adjuvant (CFA). Then arthritic rats were treated for 3 weeks with indomethacin (1mg/kg and 2mg/kg p.o once daily) and/or vinpocetine (20mg/kg p.o once daily). Body weight, ankle diameter, arthritic score, serum TNF-α and IL-1β, tissue expression of NF-κB were determined to assess anti-inflammatory effects, while anti-nociceptive effects were assessed by gait score.

**Results:** Combination therapy of vinpocetine with indomethacin, significantly improved analgesic and inflammatory parameters as compared to indomethacin alone. Vinpocetine alone decreased the inflammatory markers comparable to indomethacin and in some parameters was equal to the combination. Histopathological and X-ray examinations supported these results.

**Conclusion:** Vinpocetine potentiates the anti-inflammatory effect of indomethacin and its anti-inflammatory effect is higher than that of indomethacin. Also, it provides a potent anti-nociceptive effect, meaning that vinpocetine can be used in combination with indomethacin to decrease its dose and in consequence its serious side effects, or may be used alone in place of indomethacin for the symptomatic treatment of RA.

**Keywords:** Arthritis, Vinpocetine, Indomethacin.
**P 24. Nephroprotective effect of metformin against glycerol-induced acute kidney injury in rats**

*Nahed A. Raslan, Amany A. Alzokaky and Sahar A. Khaleel*
Pharmacology and Toxicology Department, Pharmacy College (Girls), Al-Azhar University, Cairo, Egypt.

**Background:** Rhabdomyolysis-associated acute kidney injury (AKI) is a serious life-threatening condition. Therefore, more effective strategies are needed for its prevention. The pathophysiological process of rhabdomyolysis-associated AKI involves oxidative stress, inflammation and apoptosis. Metformin (MF) has been known to possess antioxidant, anti-inflammatory and antiapoptotic properties. The present study explored the possible effect of pretreatment with metformin on the development of glycerol-induced-AKI in rats.

**Aim of the study:** To investigate the potential protective effects of metformin against glycerol-induced AKI in rats, so as to provide an experimental basic for the use of metformin in the clinical prevention of rhabdomyolysis-induced AKI.

**Methods:** Forty rats were randomly divided into four equal groups. Group 1 served as the control, group 2 was given 50% glycerol (10 mL/kg, i.m.), group 3 was given glycerol after 10 days of MF treatment (100 mg/kg/day, p.o.), and group 4 was given MF alone for 10 days (100 mg/kg/day, p.o.). Renal function was monitored by serum creatinine (SCr), Blood urea nitrogen (BUN), and histologic analysis. Moreover, oxidative stress was monitored by kidney tissue superoxide dismutase (SOD), and catalase (CAT) activities, inflammation was monitored by interleukin 6 (IL-6) evaluation, and finally apoptosis was monitored by measuring active caspase 3 content.

**Results:** Glycerol treatment resulted in an increase in the mean histologic damage score, SCr, BUN, kidney tissue IL-6, caspase 3 and a decrease in kidney tissue SOD and CAT activities. All these factors were significantly improved by pretreatment with MF.

**Conclusion:** Pretreatment with MF ameliorated renal dysfunction in glycerol-induced rhabdomyolysis by inhibiting oxidative stress, inflammatory response and apoptosis.

**Keywords:** Rhabdomyolysis, glycerol, AKI, MF, rats.
P 25. In vivo and In vitro Effects of Epigallocatechin 3 - Gallate on Gastrointestinal Tract

**Gellan A. Mohamed, Ekram N. Abd Al Haleem, Azza S. Awad and Ragia A.Taha**

Pharmacology and Toxicology Department, Faculty of Pharmacy, Al-Azhar University (Girls), Cairo, Egypt.

**Background:** Gastric ulcer disease (GUD) is one of the major gastrointestinal disorders which occur due to an imbalance between offensive (acid, pepsin and Helicobacter pylori) and defensive (mucin, prostaglandin and bicarbonate) factors. Epigallocatechin 3-gallate (EGCG) the most abundant tea polyphenol is credited with anticancer, anti-diabetic and cardioprotective activities. Research has indicated that EGCG is a significantly more potent antioxidant than vitamin C and vitamin E therefore, may be more useful in the prevention and/or cure of various life-threatening diseases.

**Aim of the study:** The present study was aimed to evaluate the EGCG activity against pyloric ligation (PL) induced gastric ulcer in rats.

**Methods:** Adult male albino rats weighting 150-200g, (n = 6) were administered orally EGCG in two doses (5 mg/kg/day and 10 mg/kg/day) and Ranitidine 80 mg/kg/day as a reference drug for seven consecutive days prior to subjection to PL. PL was carried out 1h after the last administrated dose and samples were taken 4 h after PL.

**Results:** The administration of EGCG in both doses reduced the gastric volume, titrable acidity, ulcerative index, thiobarbituric acid reactive substances (TBARS), tumor necrosis factor alpha (TNF-α), Caspase 3 (Casp-3) levels and increase in the levels of superoxide dismutase (SOD) activity and total antioxidant capacity (TAC) in a dose dependent manner.

The immunohistochemical examination for epidermal growth factor (EGF) showed that EGCG increased EGF and decreased vascular endothelial growth factor (VEGF). The ulcer protective effect of EGCG was observed on treated group and was compared with ranitidine treated group.

**Conclusion:** The ulcer protective effect of EGCG may be due to its anti-oxidant, anti-inflammatory, anti-apoptotic, anti-secretary actions.

**Key words:** Epigallocatechin 3 -gallate (EGCG), pyloric ligation, Ranitidine.
**P 26. Evaluation of the possible protective role of Curcumin and Pioglitazone on progression of diabetic nephropathy in rats**

*Amaal Nabil Sadek, Cherine Maurice Khalil and Mohamed M.S. Ewais*

Pharmacology Department, Faculty of Medicine, Suez Canal University, Egypt.

**Background:** Diabetic nephropathy is a major cause of morbidity in diabetic patients and is a leading cause of end-stage renal disease.

**Aim of the study:** The present study aimed to evaluate the possible protective effects of curcumin and pioglitazone either alone or in combination on diabetic nephropathy in rats.

**Methods:** Rats were divided into 7 groups: Group 1 (normal control) this group received only distilled water orally. The remaining rats were allowed to drink 5% glucose solution overnight to prevent initial STZ-induced hypoglycaemic mortality, then these rats were injected by single STZ injection (65 mg/ kg body weight). Four weeks thereafter, rats with random blood glucose level more than 250 mg/dl were considered diabetics and then these rats were divided into the following groups: Group 2: Diabetic nephropathy control group received only distilled water orally. Both curcumin and pioglitazone were given orally daily for 2 weeks.

Group 3: Rats received curcumin in a dose of 15 mg/kg/d. Group 4: Rats received curcumin in a dose of 30 mg/kg/d. Group 5: Rats received Pioglitazone daily in a dose of 10 mg / kg/d. Group 6: Rats received both curcumin in a dose of 15 mg/kg/d and Pioglitazone in a dose of 10 mg / kg/d. Group 7: Rats received both curcumin in a dose of 30 mg/kg/d and Pioglitazone in a dose of 10 mg / kg /d. The investigations were done at 0,4,6 weeks after induction of diabetes. Systolic BP was measured by tail-cuff plethysmography. Blood glucose was measured using glucose oxidase method; serum creatinine by using enzymatic methods. By the end of the sixth week, rats were sacrificed, the kidneys were removed and histopathological studies and antioxidant enzymes were measured.

**Results:** The co-administration of pioglitazone and curcumin significantly decreased systolic blood pressure, mean serum creatinine, catalase activity and superoxide dismutase and ameliorated pathological findings.

**Conclusion:** These findings suggested that curcumin alone cannot replace hypoglycaemic drugs like pioglitazone but the combination had a better and synergistic effect in the management of diabetic nephropathy.

**Keywords:** Curcumin, diabetes, diabetic nephropathy, pioglitazone.
P 27. Assessment of the possible curative effect of metformin and alpha lipoic acid and their combination on gentamycin –induced renal toxicity in rats
Zienab M. Hassan Mohammad, Amira Saad Mohammad, Cherine Maurice Khalil and Magda Hagra
Pharmacology Department, Faculty of Medicine, Suez Canal University, Egypt.

Background: Oxidative stress plays a crucial role in the development of gentamicin-induced nephrotoxicity.

Aim: The present study aimed to investigate the curative effect of either metformin or alpha lipoic acid or their combination in gentamycin -induced renal toxicity in rats.

Material and Methods: Sixty adult male albino rats were divided into eight groups (6 rats / group). The animals in the control group did not receive any treatment, while those in group II received (100 mg/ kg) of gentamycin by intraperitoneal injection for 5 days. The animals in group III received gentamycin (100 mg/kg) intraperitoneal for 5 days with subsequent injection of 50 mg/kg/d of alpha lipoic acid intraperitonal for the next 10 days, while in group IV, rats received gentamycin (100 mg/kg) intraperitoneal for 5 days with subsequent dose of metformin (100 mg/kg) by oral gavage for the next 10 days. The animals in group five received gentamycin 100 mg/kg/d intraperitoneal for 5 days with subsequent combination of 100 mg/kg/d metformin by oral gavage and 50 mg/kg/d of alpha lipoic acid intraperitoneal for the next 10 days, while in group six, rats received gentamycin 100 mg/kg/d intraperitoneal for 5 days with subsequent combination of 50 mg/kg/d of metformin by oral gavage and 25 mg/kg/d of alpha lipoic acid intraperitoneal for the next 10 days. The animals in group seven received 50 mg/kg/d of alpha lipoic acid intraperitoneal for 10 days, while animals in group eight received metformin (100 mg/kg) by oral gavage for 10 days. At the end of the experiment, 24 hours urine was collected for creatinine, microalbuminurea and cystatin C determination, while blood was sampled for serum creatinine and creatinine clearance determination. The kidneys were removed for histopathological assessment.

Results: Exposure of rats to a nephrotoxic dose of gentamicin disturbed the kidney function tests: serum creatinine levels, urinary cystatin C, microalbuminurea level and creatinine clearance. The use of metformin and alpha lipoic acid after gentamicin -induced nephrotoxicity resulted in a significant improvement in all evaluated parameters.

Conclusion: The beneficial effect of metformin and alpha lipoic acid may be related to their antioxidant properties.

Keywords: metformin, alpha lipoic acid, gentamycin, nephrotoxicity, cystatin C.
P 28. Evaluation of the antioxidant effects of vitamin C on the brain of Albino mice after induction of seizures by Pentylenetetrazole

Dina Abdel-karim Ali, Cherine Maurice Khalil and Mohamed M.S. Ewais
Pharmacology Department, Faculty of Medicine, Suez Canal University, Egypt.

**Background:** Oxidative stress has been implicated in the pathogenesis of epilepsy.

**Aim of the study:** The present study was conducted to evaluate the antioxidant effect of vitamin C as an acute antioxidant in epilepsy in mice.

**Methods:** Seventy-eight male albino mice were divided into six groups. The first group was normal control group that received NaCl 0.9% (i.p.). The second group received PTZ (65 mg/kg, i.p.) as a single convulsive dose. The third and fourth groups received vitamin C (500 mg/kg/day, i.p.) and vitamin C (1000mg/kg, i.p.) respectively. The fifth and sixth groups received vitamin C (500 mg/kg/day, i.p.) and vitamin C (1000mg/kg, i.p.) respectively then after 30 minutes both received Pentylenetetrazole (65 mg/kg i.p.) as a single convulsive dose. Behavioral assessment was done immediately after injections using Racine scale and rotarod tests then after 24 hours, the animals were killed and brain tissue homogenates were prepared to measure lipid peroxide and catalase activity.

**Results:** In mice receiving vitamin C, there was prolonged latency to 1st seizure, improved motor coordination, decreased lipid peroxide level and increased catalase activity. No difference in results between mice receiving different doses of vitamin C (500 mg/kg, i.p.) or (1000 mg/kg, i.p.)

**Conclusion:** Vitamin C was proven to be a potential candidate for decreasing risk of epilepsy

**Keywords:** Oxidative stress, epilepsy, vitamin C, PTZ, MDA, catalase.
**P 29. Effects of Type III Collagen on Monosodium Iodoacetate-Induced Osteoarthritis: X-ray Evaluation**

*Gehad A. Abdel Jaleel, Dalia O. Saleh and Sally A El Awdan*

Researcher, Pharmacology Department, National Research Centre, Egypt.

**Background:** Osteoarthritis (OA) is a degenerative chronic disease that affects various tissues surrounding the joints, such as the subchondral bone and articular cartilage.

**Aim of the study:** The present study aimed investigate the beneficial effects of collagen type III (CIII; 10 mg/kg; p.o.) on the articular cartilage, including structural changes in the tibial subchondral bone, matrix degradation, and inflammatory responses, in OA by using a rat model of monosodium iodoacetate (MIA)-induced OA.

**Methods:** OA was induced by a single intra-articular injection of MIA through the infrapatellar ligament of the right knee of the rats. Oral administration of CIII was undergone for consecutive 14 days. Twenty four hours after the last dose of the drug the joint volume was measured then the rats were placed in the activity cage and hot plate, their activity was counted and the time when the rats retreat its legs was recorded. Oxidative stress biomarkers were assessed; measured as serum levels of malondialdehyde, reduced glutathione and NO. Moreover, inflammatory markers *viz.* interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis nuclear factor-alpha (TNF-α) was measured. In addition to X-ray and histopathological examination of the rats was performed.

**Results:** Oral treatment of MIA-induced osteoarthritic rats with CIII (10 mg/kg) for two weeks restored the serum levels of MDA, GSH, NO, IL-6, IL-1β and the TNF-α. MLN succeeded to suppress the exacerbation of OA in rats. CIII succeeded to ameliorate the detrimental effect of MIA on X-ray images and histopathological changes.

**Conclusion:** These results suggest that CIII can be used as a potential anti-osteoarthritic agent.

**Keywords:** Type III Collagen, osteoarthritis-monosodium iodoacetate-rats.
**P 30. Anti-cancer and cardioprotective effects of indol-3-carbinol in doxorubicin treated mice**

Almokhtar A. Adwas1, Abeer A. Elkhoely2, Ahmed M. Kabel3, Mohamed Nabih Abdel-Rahman4 and Amany A. Eissa2

1Pharmacology Department, Faculty of Medicine, Zawia University, Libya.
2Pharmacology and Toxicology Department, Faculty of Pharmacy, Helwan University, Egypt.
3Pharmacology Department, Faculty of Medicine, Tanta University, Egypt.

**Background:** Doxorubicin (DOX) is a broad-spectrum antitumor antibiotic used in treatment of cancer. Its effect may be complicated by increased risk of cardiotoxicity. It was suggested that natural compounds with anticancer properties can be used in combination with DOX to decrease its dose and side effects. Indole-3-carbinol (I3C) is one of the phytochemicals that was shown to have anti-cancer effect.

**Aim of the study:** The aim was to detect the possible chemosensitizing effects of I3C in DOX-induced cytotoxicity and its possible cardioprotective effects in DOX-induced cardiotoxicity.

**Methods:** One hundred mice were divided into five equal groups: Control untreated group, solid Ehrlich carcinoma (1x 10^6 of SEC, implanted s.c. in the right thigh of the hind limb), SEC + DOX (4 mg/kg, i.p.), SEC + I3C (2000ppm, p.o.), SEC + DOX + I3C. Tumor volume, serum creatinine kinase and lactate dehydrogenase were measured. Also, tissue malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD), sphingosine kinase-1 (SphK-1) activity and interleukin-6 (IL-6) were determined. Parts of the tumor and cardiac tissues were subjected to histopathological examination.

**Results:** DOX or I3C alone or in combination induced significant increase in tumor CAT and SOD with significant decrease in tumor volume, tumor MDA, SphK-1 activity and IL-6 and alleviated the histopathological changes with significant increase in the apoptotic index and significant decrease in tissue Bcl2 compared to SEC group. Also, DOX induced cardiotoxicity which was ameliorated by I3C.

**Conclusion:** DOX/I3C combination had a better effect than either of DOX or I3C alone against SEC in mice with marked improvement of the cardiotoxicity induced by DOX.

**Keywords:** Doxorubicin; indole-3-carbinol; mice; tumor.
**P 31. Investigation of Ellagic acid and/or Repaglinide Effects on Insulin Signaling, Oxidative Stress and Inflammatory Mediators of Liver, Pancreas, Adipose Tissue and Brain in Insulin Resistant/Type 2 Diabetic Rats.**

*Mohamed M. Amin and Mahmoud S. Arbid*

Pharmacology Department, Medical Division, National Research Centre, Giza, Egypt.

**Background:** Even though ellagic acid was valued before in many models of cancer, so far its full mechanistic effect has not been deeply elucidated on insulin signaling, oxidative stress and inflammatory mediators of liver, pancreas, adipose tissue and brain in insulin resistant/type 2 diabetic rats, which is the goal of this study.

**Aim of the study:** to observe the influence of ellagic acid and/or repaglinide on insulin resistant/type 2 diabetic albino rats.

**Methods:** Insulin resistant/type 2 diabetic albino rats induced by high fat fructose diet (HFFD) diet for 2 months consequentially with injecting a daily dose of long acting human insulin. Ellagic acid (10mg/kg, p.o b.wt.) and repaglinide (0.5mg/kg, p.o b.wt.) were administered orally daily for 2 weeks.

**Results:** On the serum biochemical level, ellagic acid showed a significant improvement in the glucose/insulin balance, liver enzymes, lipid profile, inflammatory cytokines, redox level, adepokines, ammonia and manganese. While in the tissue level (liver, pancreas, adipose tissue and brain), it revealed a significant enhancement in insulin signaling, auto-phosphorylation process, adiponectin receptors, glucose transporters, inflammatory mediators and apoptotic markers. Additionally, ellagic acid mitigated also the decreased locomotor activity. Amazingly, combined treatment of both ellagic acid and repaglinide displayed a more pronounced effect which overrides that of either treatment alone.

**Conclusion:** These outcomes give a new insight into the promising molecular mechanisms by which ellagic acid modulates numerous factors induced in the progression of diabetes.

**Keywords:** Ellagic acid, Repaglinide, HFFD, Liver, Pancreas, Adipose Tissue, Brain.
P 32. Pretreatment with cardamonin protects against cisplatin-induced nephrotoxicity in rats: impact on nox-1, inflammation and apoptosis

Reem N. El-Naga
Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.

**Background:** Cisplatin is an effective anti-cancer drug; however, its clinical use is usually associated with nephrotoxicity as a dose-limiting side effect. Several molecular mechanisms are involved in this nephrotoxicity.

**Aim of the study:** The aim of this study was to explore the potential nephroprotective effect of cardamonin, a flavone found in Alpinia plant, in a model of cisplatin-induced nephrotoxicity in rats. The possible mechanisms underlying this nephroprotective effect were investigated.

**Methods:** Cardamonin was given at two different doses; 10 and 30 mg/kg orally for two weeks, starting one week before giving a single nephrotoxic dose of cisplatin (7 mg/kg).

**Results:** Acute nephrotoxicity was evident by significantly increased blood urea nitrogen and serum creatinine contents. Also, cisplatin increased lipid peroxidation, depleted GSH and SOD levels. Additionally, cisplatin showed a marked pro-inflammatory response evidenced by significant increase in tissue contents of IL-1β, TNF-α, NF-kB, iNOS, ICAM-1 and MCP-1. Pre-treatment with cardamonin significantly attenuated oxidative stress and inflammation induced by cisplatin, in a dose-dependent manner. Cardamonin pre-treatment decreased caspase-3 expression and Bax/Bcl-2 ratio and increased EGF tissue contents. Furthermore, up-regulation of NOX-1 was found to be involved in cisplatin-induced nephrotoxicity and its expression was significantly reduced by cardamonin. These findings were confirmed by the histopathological examination. Moreover, pre-treatment with subtoxic concentration of cardamonin significantly enhanced cisplatin cytotoxic activity in four different human cancer cell lines; hela, hepG2, PC3 and HCT116 cancer cell lines.

**Conclusion:** In conclusion, these findings suggest that cardamonin improves therapeutic index of cisplatin and that NOX-1 is partially involved in the pathogenesis of cisplatin-induced nephrotoxicity.

**Keywords:** Cisplatin; nephrotoxicity; cardamonin; inflammation; apoptosis; NOX-1.
P 33. The Mechanisms Underlying the Antifibrotic Effects of Bezafibrate and Pioglitazone Against Liver Fibrosis-Induced by Thioacetamide in Rats.
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Background: Peroxisome proliferators activated receptors (PPARs) which are part of the nuclear receptor superfamily implicated in liver fibrosis. Pioglitazone acts as a potent and selective agonist for the PPARγ. It exerted antifibrotic effect in different experimental models of hepatic steatosis and fibrosis.

Aim of the study: To evaluate and compare the effect of pan PPAR agonist, bezafibrate, to that of PPARγ, pioglitazone, agonist on a thioacetamide (TAA) rat model of liver fibrosis and clarifying mechanisms for these emerging effects.

Methods: Male albino rats received intraperitoneal injections of TAA (50 mg/kg, twice weekly) for 6 weeks. Daily oral treatments with bezafibrate (50 mg/kg) or pioglitazone (10 mg/kg) were started with the first day of TAA-intoxication. Serum liver function, hepatic malondialdehyde (MDA), total nitrite and nitrate (NOx), supeoxide dismutase (SOD) and hepatic histopathology were performed to evaluate hepatic damage. Masson trichrome stain and hepatic expression of alpha smooth muscle actin (αSMA) were done to assess liver fibrosis. Both drugs were assessed for their effects on caspase-3 and TIMP-1 expression in hepatic tissue.

Results: Both drugs improved liver function tests that were disturbed by TAA, attenuating oxidative damage through normalization of SOD and MDA in hepatic fibrosed animals and improved the histopathological picture of TAA rats significantly as well as regressed fibrosis score together with down-regulation of αSMA. This anti-fibrotic effect was associated with no significant improvement in caspase-3 or TIMP-1. It is worth noting that bezafibrate could ameliorate nitrosative stress by decreasing NO in liver, while pioglitazone could not.

Conclusion: the present study revealed comparable anti-fibrotic effects for bezafibrate and pioglitazone attributed to their antioxidant properties and inactivation of HSCs, while no significant roles for caspase-3 or TIMP-1 that need further clarification.

Keywords: Bezafibrate; Pioglitazone; Liver fibrosis; Thioacetamide.
P 34. Enhanced Efficacy and Reduced Side Effects of Standard Antiepileptics by New Kava Combinations

Rasha A. Tawfiq, Noha N. Nassar, Wafaa I. El-Erakyr, and Ezz eldein S. El-Denshary

Background: Epilepsy is one of the serious disorders afflicting the CNS, with a tendency for recurrent seizures due to abnormal neuronal discharge. Conventionally, therapy is symptomatic using available synthetic antiepileptic drugs (AEDs). However, the incidence of a plethora of side effects with current conventional AEDs possesses major compliance limitations to current therapies. Kava extract (Piper methysticum), that is popularly used as an over the counter (OTC) anxiolytic drug, retains anticonvulsant action without impairing alertness or cognitive functioning.

Aim of the study: The study aimed to investigate the effect of kava when administered alone or in combination with carbamazepine (CBZ) or diazepam (DZ) on the anticonvulsant, behavioural and biochemical effects, as well as, the histopathological changes on liver and kidney following acute and chronic administration.

Methods: In the herein study female rats were divided into two subsets, each comprising 9 groups: GP I received 1% tween 80 orally and served as control, while GPs (II) and (III) received kava at two dose levels (100 and 200mg/kg, p.o.). The remaining six groups received (IV) CBZ alone (30 mg/kg, p.o.) or kava in combination with CBZ (V) (15 mg/kg, p.o.) or (VI) (30 mg/kg, p.o.), (VII) DZ alone (10 mg/kg, p.o.) or kava in combination with DZ (VIII) (5 mg/kg, p.o.) or (IX) (10 mg/kg, p.o.). One set of rats was administered the assigned doses followed by the maximal electroshock threshold (MEST) test to test their anticonvulsant action. The other set was administered the doses to test behavioural changes through assessing the muscle coordination in rotarod test and locomotor activity in an activity cage. Biochemical changes were monitored on the collected blood sera of rats to measure the changes in activity of ALT, AST and APT, in addition to creatinine activity. Finally, histopathological changes in liver and kidneys were investigated to study the side effects of the drugs and combinations on the liver and kidney.

Results: Results of the present study revealed that kava increased the maximal electroshock threshold (MEST) and potentiated the anticonvulsant effect of both, CBZ and DZ following both acute and chronic treatment. Moreover, neither kava nor its combination with CBZ or DZ impaired motor coordination acutely or chronically. Furthermore, kava ameliorated both the reduction in locomotor activity as well as the changes in liver enzymes induced by chronic administration of CBZ or DZ. The biochemical parameters were further confirmed with histopathological findings.

Conclusion: In conclusion, the present study suggests the possibility of combing a low dose of CBZ or DZ with kava to reduce harmful effects and improve the quality of life in patients chronically treated with these synthetic anticonvulsant drugs.

Keywords: Kava, carbamazepine, diazepam, anticonvulsants, MEST, rotarod and locomotor activity.
P 35. The possible protective effect of ascorbic acid and/or resveratrol against nicotine-induced teratogenicity in rats.

Azza A. Ali\textsuperscript{a}, Marrie, A. H. \textsuperscript{a}, Rania A. H. Abd El-Aal \textsuperscript{c}, Amany S. Aboutaleh\textsuperscript{d}

\textsuperscript{a}Pharmacology and Toxicology Department, Faculty of Pharmacy (girls), Al-Azhar University, Cairo, Egypt.
\textsuperscript{b}Medical Pharmacology, Faculty of Medicine, Cairo University, Egypt.
\textsuperscript{c} Researcher at Developmental Pharmacology department, National Organization for Drug Control and Research, Giza, Egypt.

**Background:** Maternal tobacco smoking has a profound impact on the outcome of pregnancy. Among the smoke products, nicotine is considered to be the major teratogenic substance that perturbs embryonic development. It crosses the placental barrier and accumulates in the amniotic fluid leading to severe embryonic damage. Exposure to nicotine is associated with increased in the oxidative stress; hence antioxidants can effectively attenuate oxidative damage and counteract its deleterious effects. Therefore, high antioxidant capacity has been proposed as a promising strategy to prevent nicotine-induced teratogenesis. Ascorbic acid and Resveratrol have many biological functions as well as marked antioxidant properties.

**Aim of the study:** Assessment of the harmful effect of nicotine on fetuses and dams, as well as estimate the possible protective effect of ascorbic acid and/or resveratrol against the deleterious effect of nicotine during pregnancy.

**Methods:** Pregnant female rats were divided into eight groups, two groups is kept as control and received either distilled water or carboxymethylcellulose. Treated groups (from zero to 20\textsuperscript{th} day of gestation) received nicotine (1mg/kg, S.C.) or either ascorbic acid (2 mg/kg, P.O.) or resveratrol (20 mg/kg, P.O.) alone or in combination with nicotine, in addition to their combined treatment with nicotine. Parameters measured were placental weight, pre & post-implantation loss of fetuses, fetal growth rate, external, internal and skeletal malformations. Maternal body weight gain and oxidative parameters (SOD and MDA) in serum of dams were determined. Histopathological examination of liver and brain tissue were also performed for dams and fetuses.

**Results:** Nicotine increased pre-implantation loss of fetuses and induced internal & skeletal malformations, while increased oxidative stress & reduced weight gain of dams and altered normal histological structure of liver and brain of both. Ascorbic acid or resveratrol decreased pre-implantation loss of fetuses (pre-differentiation stage) and skeletal and internal malformations-induced by nicotine, while both of them decreased skeletal and internal malformations-induced by nicotine (major abnormalities during organogenesis). Ascorbic acid and resveratrol showed also marked protection against histological alterations-induced by nicotine in the brain of dams & fetuses and in the liver of fetuses.

**Conclusion:** Nicotine has many deleterious effects on fetuses and dams. Ascorbic acid or resveratrol can protect against many defects occurred by nicotine in the pre-differentiation and during organogenesis stage, while ascorbic acid and resveratrol together protect against defects occurred mainly during organogenesis or fetal stage.

**Keywords:** Nicotine, Teratogenesis, Ascorbic acid, Resveratrol, Rats.
**P 36. Generation of Novel Pharmacophore Targeting Estrogen Receptor via Scaffold Hopping**

_Hossam Sabry^a_, Lubna Ahmed^a_, Reham Hossam^a_, Mariem Adel^b_, Mohamed Ismail^b_, Maria Attallah^b_ and Mahmuod Salama Ahmed^b^

^a^Students at 4th grade at Faculty of Pharmacy, The British University in Egypt (BUE).
^b^Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The British University in Egypt (BUE).

**Background:** Breast Cancer is the second leading cause for death among women worldwide, where it is reported as the most frequent cancer among women in 140 of 184 countries worldwide. About 23% of all female cancers worldwide with more than a million new cases each year. Estrogen is one of the steroid hormones, which naturally produced in females from ovaries and from adrenal cortex in male. Estradiol / Estrone are the endogenous substrate for intracellular estrogen receptor (ER). In breast cancer, estrogen hormone increases above the normal level which hyperactivities estrogen receptor, leading to breast carcinoma. Therefore, blocking of estrogen receptor can ultimately lead to decrease the proliferation of cancer cells.

**Aim of the study:** Generation of virtual library of analogs inspired from estradiol skeleton targeting estrogen receptor, followed by generation of novel scaffold skeleton to be evaluated after executing the synthesis.

**Methods:** A virtual library of 50 compounds was generated via structural modification and energy minimized using MMFF94 force field. Molecular docking study was conducted using OpenEye® molecular modeling software and Auto Dock VINA tools. The receptor PDB file was taken from the PDB website (PDB ID: 1A52). Pharmacophore identification was performed by **ZINC PHAMMER**

**Results:** Ten ligands showed better binding affinity ranged from -12.85 Kcal/ mol to -10.8 Kcal/mol, compared to the binding affinity of the estradiol of -10.5 Kcal/mol. The most promising ligand (RLM-9) showed better hydrophobic-hydrophobic interaction and two hydrogen bonds between -OH group and Arg:394A and -NH group and Leu:346A.

**Conclusion:** _In-silico_ molecular modeling study for generation of analogs inspired from estradiol structure was conducted. The potential of substitution at C-16 showed better binding affinity towards ER. Ring opening preserves the binding affinity profile. This prompted us to explore ZINC database for pharmacophore searching. Consequently, this showed that ZINC89808250 possess similar pharmacophore to Estradiol.

**Keywords:** Breast Cancer, Estrogen Receptor, Estradiol, _in-silico_ based drug design

Corresponding author E-mail: [mahmoud.salama@bue.edu.eg](mailto:mahmoud.salama@bue.edu.eg)
**P 37. In-silico molecular modelling of novel analogs targeting hepatitis-c virus (HCV)**

*Ahmed El-Azazy*, *Ahmed El-Shabrawy*, *Muhammad Ismail*, *Maria Attallah*, and *Mahmoud Salama Ahmed*

*Students at 4*th* grade at Faculty of Pharmacy, The British University in Egypt (BUE).*

*Department of Pharmaceutical chemistry, Faculty of Pharmacy, The British University in Egypt (BUE).*

**Background:** Hepatitis C Virus (HCV) is a blood related infection targeting the liver. The predominant mode of transmission for HCV has shifted from post-transfusion infection to injection drug use. HCV has seven genotypes, where genotype 4 is the most prevalent in Egypt and the Middle East. There are many drug combinations regimen used for HCV such as Sovaldi, Boceprevir, and ribavirin.

**Aim of the study:** Design novel analogs inspired targeting NS5B polymerase enzyme, inspired from IDX375. Where, IDX375 is still in the clinical trials, Developed by Idenix Pharmaceuticals, Inc.

**Methods:** A virtual library comprised of 40 ligands following systematic structural modifications was designed. This was followed by energy minimization using MMFF94. The whole library was screened initially for their physico-chemical properties; such as molecular weight, lipophilicity, polar surface area, number of hydrogen bond donors and acceptors via FILTER application. The filtered analogs were docked along with NS5B polymerase enzyme co-crystallized with IDX375 (PDB ID: 4EAW) using OpenEye molecular modeling software and further validated using Auto Dock Vina Tools.

**Results:** Twelve ligands showed better binding affinity ranged from -10.20 Kcal/mol -9.10 Kcal/mol, compared to IDX-375 ($\Delta G$= -8.00 Kcal/mol). The findings revealed the potential of substituting of tertiary-buty1 group at C-33 with systematic ring variation modification, ending with cyclohexane ring, showing better hydrophobic interaction.

**Conclusion:** In-Silico molecular modeling study was conducted revealing that; on the ring variation, this does not affect the binding affinity, and the ring expansion leads to enhancement of the binding affinity with lower energy profile.

**Keywords:** Hepatitis-C Virus, NS5B polymerase enzyme, IDX375, *in-silico* based drug design.

Corresponding author E-mail: mahmoud.salama@bue.edu.eg
**P 38. In-silico molecular modelling of novel analogs targeting tyrosine kinase**

*Hadeer Nasr*, *Hager Ismail*, *Toka Adel*, *Zeinab Nasr*, *Alaa Moustafa*, *Muhammed Ismail*, *Maria Attallah* and *Mahmoud Salama Ahmed*

aStudents at 4th grade at Faculty of Pharmacy, The British University in Egypt (BUE).

bDepartment of Pharmaceutical chemistry, Faculty of Pharmacy, The British University in Egypt (BUE).

**Background:** Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and occurs predominantly in patients with underlying chronic liver disease and cirrhosis. In 2000, there were 564,000 new cases and 549,000 death from hepatocellular carcinoma worldwide indicating the devastating prognoses of this tumor. According to world cancer research fund international 2012. Egypt is one of the top 20 countries with the highest incidence of liver cancer.

**Aim of the study:** Generation of virtual library of analogs inspired from Sorafenib skeleton targeting Tyrosine Kinase receptor.

**Methods:** A virtual library of 50 compounds was generated via systematic structural modification and energy minimized using MMFF94, followed by generation of conformers using AutoDock Vina and Openeye molecular modeling software package. The receptor PDB file was downloaded from the PDB website (PDB ID 3HEG).

**Results:** Five ligands showed better binding affinity profile ranges from -10.60 Kcal/mol to -9.00 Kcal/mol, compared to Sorafenib (ΔG= -8.70 Kcal/mol). These results suggest the potential of finding novel analogs to be synthesized targeting tyrosine kinase.

**Conclusion:** ZHHT15 is the best modified structure that show lower energy than Sorafenib. Decreasing in energy is due to ring opening and alkyl substitution, which fill the hydrophobic pocket and increase the binding affinity.

**Keywords:** Hepatocellular Carcinoma, Tyrosine Kinase Receptor, Sorafenib, in-silico based drug design

Corresponding author E-mail: mahmoud.salama@bue.edu.eg
**P 39. The Era of Pharmaceutical Nanotechnology**

*Mona G. Arafa*, *Khaled Youness*, *Hossam Eldin Hassan*, *Tasnim Mahmoud*, *Ahmed Gamal*, *Fawzy Tahoon*, *Mostafa Mansour*, *Nermin Ismail* and *Nouran Gaber*

*a*Lecturer of Pharmaceutics and nanotechnology, Faculty of Pharmacy, The British university in Egypt.

*b*Students at 4th grade at Faculty of Pharmacy, The British University in Egypt.

**Background:** Nanotechnology is spreading vastly in various demanding fields of engineering and industries including aerospace automobiles, electronics, materials, chemistry, energy, environment, and consumer goods. The role of nanotechnology in the field of pharmaceutics embraces tremendous applications of nanoscience to pharmacy as nanomaterials and as diagnostic, imaging and bio-sensor devices, in addition to advanced drug carriers, providing intelligent and smart targeted drug delivery systems that are expected to be most important and powerful tool as alternate to conventional dosage forms. Nanoparticles are very different from and even opposite to the properties the material has at the macro scale. This is because matter at the nanoscale no longer follows Newtonian physics but rather quantum mechanics.

The present work was conducted to investigate all the previously mentioned properties of synthetic & natural nanomaterials.

**Aim of the study:** The present work includes an overview discussion of synthesis of different nanoparticles and microcapsules in addition to their evaluation using advanced techniques.

**Methods:** Methods of preparation include thin film hydration process, emulsion extraction evaporation method in addition to surface plasmon which is a unique phenomenon of Nano conductors that are measured using UV spectrum. This work also includes the investigation of nanostructure biological material that is characterized with its supramolecular organization in the nanoscale range.

**Results:** Different Nanomaterials can be prepared and evaluated for their size, shape, thermal behavior & drug entrapment to be applied in the medical field as advanced drug delivery systems, in addition to several potential applications in the industrial fields that involves nanotechnology.

**Conclusion:** Nanopharmaceuticals will play a pivotal role in targeted & controlled drug delivery, in addition to their tremendous applications in our daily life based on their extraordinary properties.

**Keywords:** Nanoparticles, Niosomes, SEM, TEM, DSC, X-Ray Diffraction.