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BIOCHEMICAL STUDIES ON THE INTERACTION BETWEEN NON-STEROIDAL ANTI-INFLAMMATORY AND ANTI-TUBERCULOSIS DRUGS IN RATS.

A Thesis

Submitted for the Partial fulfillment of the

M.Sc. Degree (In Physiology)

By

HEBA MOHAMMED HUSSEIN

(B.Sc.)

National Organization for Drug Control and Research

(NODCAR)

Department of Zoology

Faculty of Science,

Cairo University.

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Title of the M.Sc. Thesis

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Name of Candidate

Heba Mohammed Hussein Hassan

B.Sc., Faculty of Science

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Submitted to

Zoology Department

Faculty of Science, Cairo University

Supervisors Committee:

1- **Prof. Dr. Mohamed Marzouk Mohamed** M. Marzouk

Prof. of Physiology

Zoology Department

Faculty of Science, Cairo University

2- **Prof. Dr. Hany Alfons Abdo Samaan** Hany Alfons

Prof. of Pharmacology

Toxicology Department

National Organization of Drug Control & Research

Head of Zoology Department

Faculty of Science, Cairo University

K. S. Abouelala

Prof. Dr. Kawther Sayed Abou El-Ala

FACULTY OF SCIENCE
ZOOLOGY DEPARTMENT

TO WHOM IT MAY CONCERN

This is to certify that **Heba Mohammed Hussein** has attended and passed successfully the following Postgraduate Courses as a Partial Fulfillment of the requirements of the degree of Master of Science (**Comparative Physiology, 2001**).

1- Biochemistry
2- Haematology and blood chemistry
3- Ethology
4- Instrumental and microanalysis
5- Biochemistry of hormones
6- Biological Analysis
7- Genotoxicology
8- Xenobiotic metabolism and biochemical pharmacology
9- Minerals metabolism
10-Physiology of nervous and muscular systems
11-Neurophysiology
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14-Avian Physiology
15-Immunology
16-Radiobiology
17-Biostatistics
18-Cardiovascular Physiology
19-Pollution
20-Respiration
21-Computer Science
22-Biostatistics
23-German Language.

This Certificate is issued at his own request.

Date of Birth : 22/3/1978
Place of Birth : Giza

Controller
Mona Sharkawy
Prof. Dr. Mona Sharkawy Aly

Head of Zoology Department
K. S. Aboudala
Prof. Dr. Kawther S. Abou El Ala

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INTRODUCTION

INTRODUCTION

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. However, inflammation is sometimes inappropriately triggered by an innocuous agent, such as pollen, or by an autoimmune response, as in asthma or rheumatoid arthritis. In such cases, the defense reactions themselves may cause progressive tissue injury and anti-inflammatory or immunosuppressive drugs may be required to modulate the inflammatory process **(Mycek *et al.*, 2000).**

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of chemically dissimilar agents that differ in their antipyretic, analgesic and anti-inflammatory activities and they act primarily by inhibiting the cyclooxygenase enzymes **(Brooks and Day, 2000).** There are two forms of cyclooxygenase, termed cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). The first one is a constitutive isoform found in almost all tissues, blood vessels, stomach and kidney, while Cox-2 is induced in settings of inflammation by cytokines and inflammatory mediators **(Jackson and Hawkey, 2000).** NSAIDs have been prescribed extensively throughout the world **(Thabet *et al.*, 2002)**. The most commonly ingested NSAIDs have few toxic effects even when taken in significant quantities **(Ellenhorn. 1997). Rostom *et al* (2005)** reported that nonsteroidal anti-inflammatory drugs might cause hepatic side effects, but the frequency of these laboratory and clinical side effects is uncertain. The most tenable hypothesis to explain the anti-inflammatory action of NSAIDs is that they exert their effects through inhibition of prostaglandin synthesis. Inhibition of prostaglandin synthesis may account for certain toxicities that are common to certain NSAIDs **(Montini *et al.*, 2000).**

Rofecoxib (Rhuma-cure) is a member of a newest class of NSAIDs that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models **(Colburn and Flores, 2000).**

Rofecoxib is eliminated predominantly by hepatic metabolism with a terminal half-life of approximately 17 h during steady state **(Ahuja *et al.*, 2003)**. Rofecoxib is one of the first selective cyclooxygenase-2 inhibitors approved for the treatment of pain and inflammation in osteoarthritis, and has been described to provide advantages over acetaminophen and celecoxib **(Geba *et al.*, 2002)**. There is a lack of clear dose effect relationship concerning rofecoxib clinical analgestic and also its anti-inflammatory efficacy **(Truitt *et al.*, 2001)**. It was pointed that rofecoxib causes a relatively strong sodium and water retention **(Whelton *et al.*, 2001 and Niederberger *et al.*, 2003)**. **Laudanno *et al.*, (2001)** concluded in a study on rats that rofecoxib aggravated and complicated gastric ulcers as well as necrosis in the small intestine and consequently restricting their clinical use. Again **Thabet *et al.*, (2002)** suggested significant increase in hepatic malonaldehyde production accompanied by a significant reduction in glutathione activity in liver of albino mice treated by rofecoxib.

Tuberculosis continues to be a serious disease worldwide and is believed to be present in about one third of the world's population **(Sahbazian and Weis, 2005). Fernandez-Villar *et al.*, (2004)** reported that hepatotoxicity is one of the most serious adverse effects of anti-tuberculosis drugs. The most common mode that leads to liver injuries is anti-tuberculosis drugs induced hepatitis **(Rana *et al.*, 2006)**. The severity of drug induced liver injury varies from minor non-specific changes to fulminate hepatic failure **(Hussawi *et al.*, 2003)**. **Yee *et al.*, (2003)** reported that major adverse reactions to anti-tuberculosis drugs can cause significant morbidity, and compromise treatment regimens for tuberculosis. There may be considerable morbidity, even mortality, particularly with drug-induced hepatitis **(Schaberg *et al.*, 1996).**

Rimactazid is a drug for all forms of pulmonary and extra-pulmonary tuberculosis, one tablet of rimactazid containing 300 mg rifampicin and 150 mg of isoniazid (INH). According to **William and Petri (2001),** rifampicin and isoniazid are the most effective drugs available for the treatment of

tuberculosis. It has been well documented that INH can cause adverse effects on the liver, ranging from mild transient elevations in aminotransferases, to overt hepatitis, occurring much more rarely **(Nolan *et al.*, 1999)**. Rifampicin is an effective antibiotic against gram-positive bacteria including mycobacteria, being frequently used currently in the chemotherapy of tuberculosis along with isoniazid **(Davies and Yew, 2003 and Mitchison, 2005)**. Rifampicin has been used extensively in clinical studies as a prototypical inducer of drug-metabolizing enzymes and transporters, due not only to autoinduction by itself or induction by other drugs and food stuffs, but also its broad effects on drug-drug interactions **(Chen and Raymond, 2006)**. However rifampicin has been reported as causing hepatitis in patients being treated for tuberculosis **(Prince *et al.*, 2002)**. Isoniazid (INH) is still an integral part of both the treatment of active and latent infections of *Mycobacterium* tuberculosis **(Fountain *et al.*, 2005)**. Many earlier reviews have discussed different aspects of rifampicin metabolism and its effects on the actions of other drugs **(Borcherding and Baciewicz, 1992; Yew, 2002 and Niemi *et al.*, 2003)**. According to **Attri *et al.* (2000)**, the oxidative injury induced by isoniazid and rifampicin can be prevented by supporting the cellular antioxidant defense mechanism by N-acetylcysteine. **Prabakan *et al.*, (2000)** reported that oral treatment with ethanol extract of *Hemidesmus indicus* roots (100 mg/kg, for 15 days) significantly prevent rifampicin and isoniazid induced hepatotoxicity in rats. **Labana *et al.*, (2002)** reported that co-administration of isoniazid and rifampicin encapsulated in specific stealth liposomes at one third of their recommended dose has a chemotherapeutic efficacy in infected mice.

Mepacure is one of drugs which protects the liver cells during administration of drugs hazardous to the liver by acting as a cell membrane stabilizer by blocking the entrance of harmful toxins and helps to remove these toxins from the liver cells. In addition, Mepacure is used for the treatment of chronic hepatitis, cirrhosis and fatty degeneration. Each Mepacure capsule contains 30 mg Dimethyl Biphenyl Dicarboxylate (D.D.B) and 50 mg Silymarin.