

RECOMMENDATION

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In view of the present results, the following can be recommended:

- 1- Further experiments should be carried out to study the gastroprotective effect of different combinations of the studied drugs.
- 2- Clinical trials are needed to establish that:
 - a. Rebamipide is a good choice to be given concurrently with ulcerogenic drugs like NSAIDs to guard against gastric insults.
 - b. *Oleum cinnamomi* should be advised to be added as a food supplement for patients with history of PUD.
 - c. Tianeptine, could be a good choice with particular importance for PUD patients who are under stress.

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REFERENCES

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PROTOCOL

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**A COMPARATIVE STUDY OF THE POSSIBLE PROTECTIVE
EFFECTS OF REBAMIPIDE, TIANEPTINE, OLEUM
CINNAMOMI ON ETHANOL-INDUCED AND
INDOMETHACIN-INDUCED GASTRIC ULCER IN RATS**

دراسة مقارنة للتأثير الوقائي المحتمل لأدوية الريبامبيد والتاينبتين وزيت القرفة على
قرحة المعدة المستحثة بالإيثانول والمستحثة بالإندوميثاسين في الجرذان

Protocol of a thesis submitted
to the Faculty of Medicine
University of Alexandria
In partial fulfillment of the
requirements of the degree of
Master of Clinical Pharmacology

خطة بحث مقدمة
لكلية الطب
جامعة الإسكندرية
إيفاء جزئياً
لشروط الحصول على درجة
الماجستير في الفارماكولوجيا الإكلينيكية

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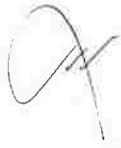
Shahrazad Abdulmagid Youssef Gazeti
MBBCh, EL-Zawia
Department of Clinical Pharmacology
Faculty of Medicine
University of Alexandria
2013

شهرزاد عبد المجيد يوسف القزيطي
بكالوريوس الطب والجراحة, الزاوية
قسم الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية
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عمر لعل

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صديقا



SUPERVISORS

المشرفون

Prof. Dr. Mervat Kamel Barakat
Professor of Clinical Pharmacology,
Faculty of Medicine,
University of Alexandria.

أ.د. مرفت كامل بركات
أستاذ الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية

Dr. Amr Abd-Elkader Okda
Assistant Professor of Clinical Pharmacology,
Faculty of Medicine,
University of Alexandria.

د. عمرو عبد القادر عقدة
أستاذ مساعد الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية

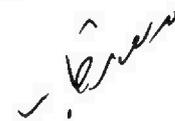
CO_SUPERVISOR

المشرف المشارك

Dr. Doaa Ali Abdelmonsif
Lecturer in Medical Biochemistry,
Faculty of Medicine,
University of Alexandria.
For her experience in the field of biochemical
analysis

د. دعاء علي عبد المنصف
مدرس كيمياء حيوية طبية
كلية الطب
جامعة الإسكندرية
وذلك لخبرتها في مجال الفحص
الكيميائي الحيوي





3.

ASSISTANT-RESEARCHER

الباحث المساعد

Joana Naji Ramzi Zaki Eid

جوانا ناجي رمزي زكي عيد

Third grade student,

طالبة بالفرقة الثالثة

Faculty of Medicine,

كلية الطب

University of Alexandria.

جامعة الاسكندرية

Mobile phone: 01227000260

E-mail: joananagi@yahoo.com

لجنته

دعواته

مدرسة

A

INTRODUCTION

Gastric ulcer is a multi-etiological chronic disease. Ulcerogenic factors impair the balance between aggressive mechanisms (e.g. increased acid secretion) and protective mechanisms (e.g. healthy mucosa and bicarbonate secretion). Such ulcerogenic factors include: stress, trauma, sepsis, hemorrhagic shock, burns, pulmonary and liver diseases, helicobacter pylori, use of cigarettes and alcohol, and steroidal and non steroidal anti-inflammatory drugs.^(1,2)

Moreover mucosal damage by oxygen free radicals has been associated with peptic ulcer and gastritis. The mechanism of damage involves lipid peroxidation, which destroys cell membranes with the release of intracellular components, such as lysosomal enzymes, leading to further tissue damage. These free radicals also promote mucosal damage by causing degradation of the epithelial basement membrane components, complete alteration of the cell metabolism and DNA damage.⁽³⁾

Gastric mucosal damage can be induced experimentally by ethanol. Ethanol causes hemorrhage, hyperemia, and loss of epithelial cells in the gastric mucosa through increased lipid peroxidation.⁽⁴⁾

Also mucosal injury can be elicited by indomethacin. Indomethacin acts as a non-selective inhibitor of the enzyme cyclooxygenase. Cyclooxygenase catalyses the formation of prostaglandins and thromboxane from arachidonic acid, which itself is derived from the cellular phospholipid bilayer by phospholipase A₂. Indomethacin, through inhibition of the formation of gastroprotective prostaglandins, can induce several changes in the gastric microenvironment (e.g., reduced gastric blood flow, reduced mucus and bicarbonate secretion, decreased cell repair and replication).⁽⁵⁾

فردى
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There are several drugs available for treatment of gastric ulcer. However, they are frequently incompletely sufficient for controlling ulcer manifestations. Moreover, many of them are expensive and could have adverse effects not tolerated by all patients. Rebamipide, 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolin-4-yl] propionic acid, is a new drug acting as an antioxidant by inhibiting lipid peroxidation in the gastric mucosa; and it was found to increase gastric mucosal prostaglandins by stimulating the biosynthesis of prostaglandin E₂-like substances.^(6,7)

Many herbs and spices have been shown to impart antioxidant effects, the active principles are phenolics. Cinnamon is one of such traditional herbs that possess potent antioxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic, anti-tumour activities.⁽⁸⁾ Such chemoprotective properties of cinnamon appear helpful in gastric ulcer disease.

Experimental studies have shown that some antidepressant drugs could be beneficial in gastric ulcer. A study performed on rats showed that imipramine dose dependently prevented cold-stress-induced gastric lesions. Another study has shown that serotonin-reuptake inhibitors could prevent 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridin (MPTP)-induced duodenal ulcer in rats.^(9,10)

Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a redox-sensitive transcription factor that regulates the expression of a variety of antioxidant and detoxification genes through an antioxidant-response element. Nrf2 has been shown to protect several types of cells against the acute and chronic injury that accompanies oxidative stress.⁽¹¹⁾ Nrf2 could therefore be involved in some protective mechanisms of antiulcer agents.

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AIM OF THE WORK

The aim of the present work is to investigate the possible protective effects of Rebamipide (antioxidant), Tianeptine (antidepressant), *Oleum Cinnamomi* (herbal extract) on indomethacine- and ethanol-induced gastric ulcer in rats.

This will be conducted in view of correlation between these drugs and their effects on some oxidative stress parameters and the transcription factor Nrf2.

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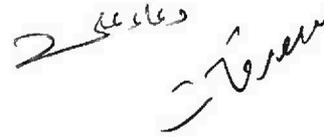
MATERIAL

The present work will be conducted on 72 male albino rats of body weight ranging from 160-180 gm.

The rats will be housed in animal cages, and will be kept under standard conditions of light and temperature with free access to food and water.

The following drugs will be used in the study.

- Rebamipide (antioxidant)
- Oleum Cinnamomi(herbal extract)
- Tianeptine(antidepressant)
- Indomethacin(ulcer inducer)
- Ethanol(ulcer inducer)



METHODS

Experimental groups and treatment:

Animals will be divided into 3 groups:

1. Group 1: Control group:8 rats:

These animals will receive 5 ml/kg body weight of 2% gum acacia orally daily for 7 days as vehicle control of the studied drugs.

2. Group 2:Ethanol induced gastric ulcer:

This group will be subdivided in to 4 groups each of 8 rats.

2a: Control group:

Animals will receive 5 ml/Kg body weight of 2% gum acacia orally daily for 7 days as vehicle control of the studied drugs. Then gastric lesion will be induced by oral administration of 1ml 50% ethanol for each rat on the 7th day .

2b: These animals will be treated with rebamipide 60 mg/kg body weight orally for 7 days and on the 7th day induction of ulcer will done by giving 1ml 50% ethanol orally

2c:These animals will be treated with *Oleum cinnamomi* 2.5 ml/kg body weight orally for 7 days and on the 7th day induction of ulcer is done by giving 1ml 50% ethanol orally.

2d: These animals will be treated with 12 mg/kg body weight Tianeptin orally for 7 days and on the 7th day induction of ulcer is done by giving 1 ml 50% ethanol orally.

3. Group 3: Indomethacin induced gastric ulcer:

This group will be subdivided into 4 groups each of 8 rats.

3a: **Control group:** Animals will receive 5 ml/Kg body weight of 2% gum acacia orally daily for 7 days as vehicle control of the studied drugs.

عمر العزوي

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Then gastric lesion will be induced by giving 100 mg /kg indomethacin orally.

3b: These animals will be treated with rebamipide 60 mg/kg body weight orally for 7 days and on the 7th day induction of ulcer will be done by giving 100 mg/kg indomethacin orally.

3c: These animal will treated with *Oleum cinnamomi* 2.5 ml/kg orally for 7 days and on the 7th day induction of ulcer will be done by giving 100 mg/kg indomethacin orally.

3d: These animal will treated with 12 mg/kg body weight Tianeptin orally for 7 days and on the 7th day induction of ulcer will be done by giving 100 mg/kg indomethacin orally.

4 hours after ulcer induction, the animals will be sacrificed .

The ulcer index will be calculated: the stomach will be cut along the lesser curvature and the mucosa is washed with cold saline, mucosa is scrubbed and stored at 20⁰C until estimation of the chemical parameter.

The following parameters will be assessed:

1. Ulcer index and protective ratio. ⁽¹²⁾
2. Glutathione peroxidase in gastric mucosa. ⁽¹³⁾
3. Malondialdehyde in gastric mucosa. ⁽¹⁴⁾
4. Superoxide dismutase in gastric mucosa. ⁽¹⁵⁾
5. Nuclear factor erythroid related factor(Nrf2) in gastric mucosa. ⁽¹¹⁾

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RESULTS

The results of this study will be tabulated and analyzed with the use of appropriate statistical methods and appropriate figures and diagrams.

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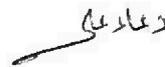
DISCUSSION

The results will be discussed in view of achievement of the aim, their significance and their comparison with previous related researchers.

دعوات
عبدالله بن محمد
عبدالله بن محمد

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ARABIC SUMMARY

الملخص العربي

تعد قرحة المعدة والاثني عشر هي المرض ذو التأثير الاكلينيكي الاكبر بين امراض هذا الجزء من القناة الهضمية. وتتمحور الفيزيولوجيا المرضية لقرحة المعدة حول عدم التوازن بين العوامل الضارة والعوامل الوقائية التي يتعرض لها الغشاء المخاطي، والطريقة الأكثر فاعلية للتغلب على هذه المشكلة هي استكشاف عوامل الخطر المرتبطة بها واستهدافها بالعلاج. في هذه الدراسة، تم استخدام نموذجي قرحة المعدة المستحدثة بالاندوميثاسين والايتانول في الجرذان لاختبار ومقارنة التأثيرات الوقائية لكل من الريبامبيد، التيانبتين وزيت القرفة في تطور قرحة المعدة.

أجريت هذه الدراسة على اثنين وسبعين من ذكور الجرذان البيضاء تراوحت اوزانها بين ١٦٠-١٨٠ جرام. تم تقسيم الحيوانات عشوائيا إلى ثلاث مجموعات على النحو التالي:

١. المجموعة ١: مجموعة ضابطة: ٨ جرذان:

هذه الحيوانات تلقت ٥ مل / كجم وزن جسم ٢٪ من معلق الصمغ العربي عن طريق الفم يوميا لمدة ٧ أيام كأداة حاملة للأدوية محل الدراسة.

٢. المجموعة ٢: مجموعة قرحة المعدة المستحدثة بالايتانول (٣٢ جرذ):

تم تقسيم هذه المجموعة إلى أربع مجموعات فرعية في كل مجموعة ثمانية جرذان.

أ) مجموعة القرحة المعدية المستحدثة بالايتانول و غير المعالجة:

تلقت الحيوانات ٥ مل / كجم وزن جسم ٢٪ من معلق الصمغ العربي عن طريق الفم يوميا لمدة ٧ أيام كأداة حاملة للأدوية التي شملتها الدراسة، ثم تم في اليوم السابع استحداث قرحة المعدة بجرعة مفردة عن طريق الفم بمقدار ٧٠٪ ١ مل ايتانول لكل جرذ.

ب) مجموعة القرحة المعدية المستحدثة بالايتانول، بعد العلاج بالريبامبيد:

تم علاج الحيوانات باستخدام ريبامبيد ٦٠ مجم/كجم وزن جسم عن طريق الفم ولمدة ٧ أيام قبل استحداث القرحة بالايتانول.

ج) مجموعة القرحة المعدية المستحدثة بالايتانول، بعد العلاج بالتيانبتين:

تم علاج الحيوانات باستخدام تيانبتين ١٢ مجم/كجم وزن جسم عن طريق الفم ولمدة ٧ أيام قبل استحداث القرحة بالايتانول.

د) مجموعة القرحة المعدية المستحدثة بالايتانول، بعدالعلاج بزيت القرفة:

تم علاج الحيوانات باستخدام زيت القرفة ٢.٥ مجم/كجم وزن جسم عن طريق الفم ولمدة ٧ أيام قبل استحداث القرحة بالايتانول.

٣) المجموعة ٣: القرحة المعدية المستحدثة بالاندوميثاسين (٣٢ جرذ):

تم تقسيم هذه المجموعة إلى ٤ مجموعات فردية كل واحدة تحتوى على ٨ جرذان.

أ) مجموعة القرحة المعدية المستحدثة بالاندوميثاسين وغير المعالجة:-

تلقت الحيوانات ٥ مل / كجم من وزن الجسم ٢٪ من معلق الصمغ العربي عن طريق الفم يوميا ولمدة ٧ ايام على اعتباره اداة حاملة للأدوية محل الدراسة، ومن ثم تم استحداث الاصابة المعدية بجرعة فردية من الاندوميثاسين عن طريق الفم مقدارها ١٠٠مجم/كجم.

بدأنا في دراسة تجريبية منفصلة مع جرعات صغيرة ٢٠ و ٣٠ و ٥٠ ملجم / كجم لكنها لم تعط التأثير، ثم قمنا بزيادة الجرعة، وحصلنا على تأثير بجرعة ١٠٠ ملجم / كجم.

ب) مجموعة قرحة المعدة المستحدثة بالاندوميثاسين، بعد العلاج بالريباميبايد:

تم علاج الحيوانات بريبياميبايد ٦٠ ملجم / كجم من وزن الجسم عن طريق الفم يوميا لمدة ٧ أيام قبل استحداث القرحة بالاندوميثاسين.

ج) مجموعة قرحة المعدة المستحدثة بالاندوميثاسين، بعد العلاج بالتيايبين:

تم علاج الحيوان بتيايبين ١٢ ملجم / كجم عن طريق الفم يوميا لمدة ٧ أيام قبل استحداث القرحة بالاندوميثاسين.

د) مجموعة القرحة المعدية المستحدثة بالاندوميثاسين، بعد العلاج بزيت القرقة:

تم علاج الحيوانات بزيت القرقة مقدار ٢.٥ ملجم/كجم عن طريق الفم يوميا لمدة سبعة ايام قبل استحداث القرحة بالاندوميثاسين.

في نهاية فترة التجربة تم تخدير الحيوانات واستئصال المعدة في كل منها الحيوانات ثم وضعت كل معدة في كوب مملوء بملح فسيولوجي ثلجي بارد، ومن ثم تم تجفيفه بعناية. فتحت المعدة على طول الانحناء الأكبر، ومن ثم تم تقييم مؤشر القرحة ونسبة الحماية على أساس قطر الاصابة ثم أزيل الغشاء المخاطي باستخدام شريحة زجاجية تمت مجانسته ثم وضع في جهاز الطرد المركزي ثم اخذت المادة الطافية وجمدت في درجة حرارة -٢٠ C وذلك لتقييم المعاملات التالية:

* السوبراوكسايد دسميوتيز.

* مالون داي الديهايد.

* جلوتاثيون بيروكسيديز.

* عامل Nrf2.

وكانت نتائج الدراسة كالاتي:

أ) تأثير كل من الريباميبايد، التيايبين، وزيت القرقة على القرحة المعدية المستحدثة بالاندوميثاسين في الجرذان:-

١- التأثير على مؤشر القرحة :

انخفض مؤشر القرحة بشكل ملحوظ في جميع المجموعات التي خضعت للعلاج بالادوية محل الدراسة بالمقارنة مع مجموعة الاندوميثاسين الضابطة.

• وكان المتوسط \pm الخطأ المعياري لمؤشر القرحة في مجموعة الاندوميثاسين الضابطة $13 \pm$ و $1,02$ بينما في المجموعة السابق علاجها بالريباميبايد، التيايبين وزيت القرقة كان $3,5 \pm$ و $0,71$ ، $9,88 \pm 0,64$ و $0,93 \pm 7$ مع نسب حماية 74% ، 25% و 46% على التوالي.

٢-التأثير على السوبراوكسايد دسميوتيز:

كانت هناك زيادة كبيرة في نشاط السوبراوكسايد دسميوتيز في جميع المجموعات المعالجة السابق علاجها بالمقارنة مع مجموعة الاندوميثاسين الضابطة. كان المتوسط \pm الخطأ المعياري في المجموعات السابق علاجها بالريباميبايد، التيايبين وزيت القرقة كان $0,96 \pm 0,27$ ، $0,23 \pm 0,65$ و $4,72 \pm 0,43$ وحدة / جم على التوالي مقابل $3,06 \pm 0,62$ وحدة/ جم في مجموعة الاندوميثاسين الضابطة.

٣-التأثير على مالون داي الدهياد:

كان هناك انخفاض في محتوى مالون داي الدهياد في المجموعات السابق علاجها بالتينابنتين وزيت القرفة مقارنة مع مجموعة الاندوميثاسين الضابطة. وكان المتوسط \pm الخطأ المعياري $238,38 \pm 21,71$ و $217,66 \pm 12,21$ نانومول/ جم على التوالي مقابل $388,00 \pm 27,22$ نانومول / جم في مجموعة الاندوميثاسين الضابطة ، في حين كانت هناك تغييرات ضئيلة في المجموعة السابق علاجها بالريباميبايد.

٤- التأثير على الجلوتاثيون بيروكسيداز:

كانت هناك زيادة كبيرة في نشاط جلوتاثيون بيروكسيداز بالغشاء المخاطي بالمعدة في كل المجموعات المعالجة مقارنة بمجموعة الاندوميثاسين الضابطة. المتوسط \pm الخطأ المعياري كان في المجموعات المعالجة بالريباميبايد، التينابنتين وزيت القرفة هو : $66,75 \pm 5,95$ ، $51,63 \pm 2,89$ و $45,81 \pm 3,63$ وحدة / جم على التوالي مقابل $16,35 \pm 1,01$ وحدة / جم في مجموعة الاندوميثاسين الضابطة.

٥- التأثير على عامل (Nrf2):

لوحظ انخفاض كبير في مستوي عامل Nrf2 بالغشاء المخاطي بالمعدة مقارنة بمجموعة الاندوميثاسين الضابطة. كان المتوسط \pm الخطأ المعياري في المجموعات المعالجة بالريباميبايد، التينابنتين وزيت القرفة $126,58 \pm 10,96$ ، $117,50 \pm 4,82$ و $112,54 \pm 11,19$ نانوجرام / مل على التوالي مقابل $206,13 \pm 11,49$ نانوجرام / مل في مجموعة الاندوميثاسين الضابطة.

(ب) تأثير الريباميبايد والتينابنتين وزيت القرفة على القرحة المعدية المستحدثة بالايثانول في الجرذان:-

(١) التأثير على مؤشر القرحة :

كان هناك انخفاض كبير في مؤشر القرحة في كل المجموعات التي خضعت للعلاج بالادوية محل الدراسة مقارنة بمجموعة الايثانول الضابطة.

وكان المتوسط \pm الخطأ المعياري لمؤشر القرحة في مجموعة الايثانول الضابطة $26,88 \pm 2,29$ بينما في المجموعة المعالجة تمهيدا بالريباميبايد، التينابنتين وزيت القرفة: $7,75 \pm 0,65$ ، $13,50 \pm 0,98$ و $10,75 \pm 1,0$ مع نسب وقائية من 72% ، 48% و 60% على التوالي.

٢- التأثير على السوبر اوكسايد دسميوتيز:

كانت هناك زيادة كبيرة في نشاط السوبراوكسايد دسميوتيز في المجموعة السابق علاجها بزيت القرفة وكان المتوسط \pm الخطأ المعياري هو $6,63 \pm 0,94$ وحدة / جم في مقابل $2,69 \pm 0,73$ وحدة / جم في مجموعة الايثانول الضابطة.

٣-التأثير على مالون داي الدهياد:

كان هناك انخفاض كبير في محتوى مالون داي الدهياد في كل المجموعات السابق علاجها بالادوية محل الدراسة مقارنة بمجموعة الايثانول الضابطة. كان المتوسط \pm الخطأ المعياري في المجموعات المعالجة بالريباميبايد، التينابنتين وزيت القرفة في هو $143,63 \pm 7,84$ ، $163,75 \pm$

٩,٠١ و ١٨٣,٩١ ± ٣٧,٥٦ نانومول / جم على التوالي مقابل ٣٢١,٢٥ ± ١٢,٠٢ نانومول / جم في مجموعة التحكم بالايثانول.

٤-التأثير على الجلوتاثيون بيروكسيديز:

كانت هناك زيادة كبيرة في نشاط جلوتاثيون بيروكسيديز في المجموعات السابق علاجها بالريبيامبيد والتيانيبين - مقارنة بمجموعة الايثانول الضابطة. وكان المتوسط ± الخطأ المعياري في المجموعات السابق علاجها بالريبيامبيد والتيانيبين هو : ٤,٨٤ ± ٧٥,٦٩ و ٥,٣٢ ± ٦٥,٦٦ وحدة/جم على التوالي مقابل ١٨,٤٩ ± ٢,٧٦ وحدة / جم في مجموعة الايثانول الضابطة. من ناحية أخرى، لم يلاحظ اي تغييرات ذات قيمة معنوية في المجموعة السابق علاجها بزيت القرقة.

٥-التأثير على عامل (Nrf2):

بالغشاء المخاطي للمعدة في كل المجموعات السابق Nrf2 لوحظ وجود انخفاض كبير في مستوي علاجها بالادوية محل الدراسة مقارنة بمجموعة الايثانول الضابطة. وكان المتوسط ± الخطأ المعياري في المجموعات السابق علاجها بالريبيامبيد، التيانيبين وزيت القرقة هو ٧٠,١٣ ± ٦,٤٣ ، ٧٤,٥٩ ± ٣,٣١ و ٩٣,٤٦ ± ٣,١٠ نانوجرام / مل على التوالي مقابل ١٦٥,١١ ± ١١,١١ نانوجرام / مل في مجموعة الايثانول الضابطة.

الملخص العربي

لجنة الإشراف

.....
أ.د. مرفت كامل بركات
أستاذ الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية

.....
د. عمرو عبد القادر عقدة
أستاذ مساعد الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية

.....
مشرف مشارك
د. دعاء علي عبد المنصف
مدرس كيمياء حيوية طبية
كلية الطب
جامعة الإسكندرية

دراسة مقارنة للتأثير الوقائي المحتمل لأدوية الريباميبايد والتاينبتين وزيت القرفة على قرحة المعدة المستحدثة بالإيثانول والمستحدثة بالإندوميثاسين في الجرذان

مقدمة من

شهرزاد عبد المجيد يوسف القزيطي

بكالوريوس الطب والجراحة - جامعة الزاوية

للحصول على درجة

الماجستير

في

الفارماكولوجيا الإكلينيكية

موافقون

لجنة المناقشة والحكم على الرسالة

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أ. د / مصطفى عبد العزيز محمد
أستاذ الفارماكولوجيا
كلية الطب البيطري
جامعة كفر الشيخ

.....

أ. د / ميرفت كامل بركات
أستاذ الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية

.....

د / إناس السيد درويش
أستاذ مساعد الفارماكولوجيا الإكلينيكية
كلية الطب
جامعة الإسكندرية

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رسالة

مقدمة الي الفارماكولوجيا الإكلينيكية - كلية الطب - جامعة الإسكندرية
إستيفاء للدراسات المقررة للحصول على درجة

الماجستير

في

الفارماكولوجيا الإكلينيكية

مقدمة من

شهرزاد عبد المجيد يوسف القريطي

بكالوريوس في الطب والجراحة- كلية الطب- جامعة الزاوية

قسم الفارماكولوجيا الإكلينيكية - كلية الطب

جامعة الإسكندرية

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