كلية الطب
الدراسات العليا والبحوث

محضر
اجتماع لجنة الحكم على الرسالة المقدمة من

الطبيب / ولاء عبد الفتاح عثمان

توطئة للحصول على درجة الماجستير / الدكتوراه

في الفارماكولوجي

تحت عنوان باللغة الإنجليزية :

Comparative study of the analgesic, anti-pyretic and anti-inflammatory activities of Extra virgin olive oil and Ibuprofen and their combination in different animal models in albino mice

باللغة العربية :

دراسة مقارنة لتقييم فعالية زيت الزيتون البكر الممتاز كمسكن للالم و خافض للحرارة و مضاد للالتهاب مقارنة بالايبوبروفين منفصلين و معا على نماذج تجريبية مختلفة مستحدثه في الفئران البيضاء

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عصام

Comparative Study of the Analgesic, Anti-Pyretic and Anti-Inflammatory Activities of Extra Virgin Olive Oil and Ibuprofen and Their Combination in Different Animal Models in Albino Mice

Thesis

Submitted for Partial Fulfilment of the M.D. Degree in
Medical Pharmacology

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ABSTRACT

Background: Inflammation is a complex series of physiological events designed to repair the damaged tissue caused by injury or infection. It is involved in the development of many diseases. Cardinal signs of inflammation as pain and fever are commonly treated with NSAIDs which have many adverse effects. Recently, there is a new trend towards the natural dietary anti-inflammatory agents which have potential therapeutic effects with less adverse events. Extra virgin olive oil (EVOO) has been documented nowadays to have diverse beneficial effects on human beings. Oleocanthal is a phenolic compound in olive oil which was proved to have similarity with ibuprofen (IBU).

Aim of the work: This work was designed to compare the analgesic, antipyretic and anti-inflammatory effects of EVOO with IBU and their combinations on different animal models in mice.

Methods: 140 adult healthy male Swiss albino mice were used in this study. The analgesic effect was assessed using acetic acid-induced writhing test. The antipyretic effect was evaluated by brewer's yeast induced pyrexia and the anti-inflammatory activity was investigated by two models; the carrageenan-induced paw edema and the carrageenan induced peritonitis in which the levels of total leucocytic count, neutrophil count, INF-γ and PGE2 were measured in the peritoneal exudate. Animals were allocated into groups as follows: The disease models groups that represent the positive control (group 1). They were injected with acetic acid intra- peritoneally in the writhing test (model for nociception), with brewer's yeast subcutaneously (model for pyrexia), and with carrageenan either intra plantar in the right hind paw of the mice or intra peritoneally in the carrageenan-induced paw edema test and carrageenan-induced peritonitis in mice, respectively. The other groups represent the treated groups which received drugs in a fixed regimen in all the four tests as follows: a single oral dose of IBU at its therapeutic dose (100mg/kg) in group 2 which represents the standard treatment, EVOO (8ml/kg) in group 3, the combination of EVOO (8ml/kg) with the therapeutic dose of IBU (100mg/kg) in group 4 and the combination of EVOO (8ml/kg) with a low dose of IBU (40mg/kg) in group 5. In the last two tests, group 0 was added which includes normal untreated animals (negative control) group.

Result: The results revealed that the group treated with the combination of EVOO with the therapeutic dose of IBU 100mg/kg showed the highest percentage of inhibition in acetic acid-induced writhing test and in carrageenan-induced paw edema and the lowest rectal temperature in the brewer's yeast induced pyrexia, followed by that using the standard treatment IBU (100mg/kg) separately. Meanwhile, using EVOO alone or in combination with the low dose of IBU (40mg/kg) showed significant results from the disease model (positive control) but their effects were less than the group treated with the standard drug (IBU 100mg/kg). In the carrageenan induced peritonitis, the results revealed that using the combination of EVOO either with the therapeutic dose of IBU (100mg/kg) or with its low dose (40mg/kg) showed the best results in a dose dependent manner, while using olive oil alone decreased significantly most of the measured parameters and its effects was insignificant from the standard treatment IBU (100mg/kg).

Conclusion: Using EVOO in combination with the therapeutic dose of ibuprofen showed synergistic effect in controlling the cardinal signs of acute inflammation rather than using ibuprofen or EVOO individually.

Keywords: EVOO, Ibuprofen, Anti-inflammatory, Anti-pyretic, Analgesic.

LIST OF ABBREVIATIONS

AA	:	Arachidonic acid.
ANOVA	:	Analysis of variance.
ARE	:	Antioxidant responsive elements
B.C	:	Before Christ.
b.w	:	Body weight.
cPGEs	:	Cytosolic prostaglandin E2 synthase.
COX	:	Cyclooxygenase enzyme.
DAG	:	Diacylglycerols.
DAMPs	:	Damage-associated molecular patterns.
DNA	:	Deoxyribonucleic Acid.
ELISA	:	Enzyme-linked immunoabsorbant assay.
EP	:	Prostaglandin E2 receptor.
FFA	:	Free fatty acid.
FMF	:	Familial Mediterranean Fever.
G1 phase	:	The first growth period of cell cycle.
HCAs	:	Heterocyclic amines.
HIF-1α	:	Hypoxia-induced factor-1α.
H2O2	:	Hydrogen peroxide.
IBU	:	Ibuprofen.
ICAM-1	:	Intercellular adhesion molecule-1.
IκB	:	Inhibitor of nuclear factor kappa B.
IκK	:	Inhibitor of kappa B kinase.
IL-1β	:	Interleukin-1beta.
IL-6	:	Interleukin-6.
ILs	:	Interleukins.
INF-γ	:	Interferon gamma.
iNO	:	Inducible nitric oxide.
i.p	:	Intra peritoneal injection.
Keap1	:	Kelch-like ECH-associating protein 1.
KOH	:	Potassium hydroxide.
LDL	:	Low density lipoprotein.

LOX	:	Lipooxygenase enzyme.
LPS	:	Lipopolysaccharide.
LRP1	:	Lipoprotein receptor-related protein 1.
MAG	:	Monoacylglycerols.
MCP-1	:	Monocyte Chemoattractant Protein-1.
MHC	:	Major histocompatibility complex.
MMP	:	Matrix Metalloproteinase.
mPGEs	:	Microsomal prostaglandin E2 synthases.
µM	:	Micro molar.
µl	:	Micro liter.
MPO	:	Myloperoxidase enzyme.
MUFA	:	Monounsaturated fatty acid.
NaOH	:	Sodium hydroxide.
NF-κB	:	Nuclear factor-kappa B.
NK cell	:	Natural killer cell.
NO	:	Nitric oxide.
Nrf2	:	Nuclear factor erythroid -related factor 2.
NSAIDs	:	Non-steroidal anti-inflammatory drugs.
$O2^{-}$	:	Superoxide anion.
$^{1}O2$	:	Singlet oxygen.
O.D	:	Optical density.
Ops	:	Olive oil phenols.
PAMPs	:	Pathogen-associated molecular patterns.
PBS	:	Phosphate Buffered Saline**.**
PGs	:	Prostaglandins.
PGE2	:	Prostaglandin E2.
PGEs	:	Prostaglandin E2 synthases.
Pg/ml	:	Picogram per milliliter.
PLA2	:	Phospholipase A2.
PRRs	:	Pattern recognition receptors.
PUFA	:	Polyunsaturated fatty acid.
RNS	:	Reactive nitrogen species.
RONS	:	Reactive Oxygen/Nitrogen Species.

ROS	:	Reactive oxygen species.
RT	:	Rectal temperature.
SAT	:	Saturated fatty acid.
S.C	:	Subcutaneous.
SD	:	Standard deviation.
TAG	:	Triacylglycerols.
TBS	:	Tris-buffered saline.
TCR	:	T-cell receptor.
TLC	:	Total leucocytic count.
TMB	:	Tetramethylbenzidine.
TNF-α	:	Tumor necrosis factor –alpha.
VCAM-1	:	Vascular cell adhesions molecule-1 .
v/v	:	Volume to volume.
w/v	:	Weight to volume.
λ	:	Lambda.

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INTRODUCTION