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Chronotherapeutic analgesic effect of Urtica dioica and Indomethacin in Mice

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ABSTRACT

The primary goal of the study was to examine how to lessen indomethacin's negative effects while boosting its analgesic and anti-inflammatory properties.
The yield of methanolic *Urtica dioica* extract during thirteen siphons was 250 gm ±2.68% per 5 gm *Urtica dioica* .
In sixty male mice, control given five was dosed, *Urtica dioica* given five was dosed with 10,20,40,60, and 80, and indomethacin given five subgroups was dosed with 10, 15, 25,30, and 35 mg.
The nociceptive stimulus was realized with analgesia and anti-inflammatory parameters. This study aimed to evaluate the *Urtica dioica* and indomethacin as an analgesic and anti-inflammatory efficacy and referenced free-form indomethacin in mice.

Introduction

Indomethacin is a common analgesic drug used widely in the world and broadly for the treatment of unpleasant pain, The systemic have serious adverse effect increasing the risk of serious dose-related gastrointestinal tract, cardiovascular, and renal effects, and exposing life to jeopardy through dried inhibit cyclooxygenase-PGs pathway and draw multiple line deleterious effect on tissues. (1).
On the other hand, synergism effect is the way of reducing unwanted effects. Prepare a *Urtica dioica* is developed to incorporate virgin plant extracts water or organic soluble one specific active extracted, purified constituent like flavonoids named flavorsome (2).
The objective is Indomethacin with maximal analgesic anti-inflammatory effect via synergetic with *Urtica dioica* to achieve safeness of function and high efficacy.
Chronotherapeutics studies of pharmacological maneuvers of synergetic with *Urtica dioica* - Indomethacin at setting time for increased efficacy and potency of the drug as well as predicted avoid adverse effect of indomethacin (3).

Materials and Methods

The study was carried out at the College of Veterinary Medicine and the University of Baghdad's Department of Physiology, Biochemistry, and Pharmacology. The ethical

database of experimental protocols was based on the authority of the animal ethical report regulations of (4) as entitled "Standardized Guidelines for the Careful Utilize Laboratory Animals in Research of Iraq."

First experimental

The first experimental Ɪ the *Urtica dioica* – indomethacin dose analgesic relation (dose-response curve) The 60 mice six groups according to therapeutic type

1-Group:-control 10 mice

2-Group:-indomethacin 25 mice

3-group:-*Urtica dioica* 25 mice

Second experimental

The synergy was divided into four groups according to the synergy protocol

ED_{20} indomethacin 5 mice & ED_{20} *Urtica dioica* 5 mice

ED_{50} indomethacin 5 mice & ED_{20} *Urtica dioica* 5 mice

ED_{20} indomethacin 5 mice & ED_{50} *Urtica dioica* 5 mice

ED_{50} indomethacin 5 mice & ED_{50} *Urtica dioica* 5 mice

Third experimental

The chronotherapeutics was divided into two groups according to the chronotherapeutic protocol

Control groups 5 mice

ED_{50} indomethacin 5 mice & ED_{50} *Urtica dioica* 5 mice

preparation *Urtica dioica* some Indomethacin protocal

Crude *Urtica dioica* extraction:

The dried *Urtica dioica* leaves 250g were ground by the electric grinder and extracted by methanol 400ml (99%) using soxhlet at 40 C° for 11 hours (13 siphon cycles) for three patches.

The extract was filtrated by Wattman filter paper (mesh 1000 µm) and concentrated by rotary evaporation conducted with a vacuum pump at 40 C°. The yield percentage and concentrations of *Urtica dioica* extract were estimated at three-time (5).

Indomethacin preparation:

Indomethacin 0.250 g was added (10ml phosphate buffer) and was added *Urtica dioica* vortex for 30 minutes and *Urtica dioica* Indomethacin was formed (6).

Animals

Male albino adult mice, 2.5–3 months old, weighing 20–35 g. The mice were kept in the animal housing of the College of Veterinary Medicine at the University of Baghdad at a constant room temperature of 25±2 °C and a 12-hour cycle of light and dark. For a week, the mice were confined in a shoebox for adaption, and they were given concentrate food and water to add libido (7).

Results and Discussion

***Urtica dioica* extraction and yield**

Table 1: The yield percentage of the *Urtica dioica* leaves extraction process for two patches was 5g in each 250 g of *Urtica dioica* after 13 siphons (total 26 cycles).

Table 1 yield percent of *Urtica dioica* extract.

***Urtica dioica* Row g**	**Extract Yield G**	**Number of Siphon Cycles 40° C**	**Siphon time Hour**
250g	5g	13	1 hour

The *Urtica dioica*, 250 grams of produced 5 grams extract yield (Table 1). This result coincided with (8), which suggested that several variables could affect the amount of *Urtica dioica* extract produced, including extraction time, temperature, type of organic solvent, and dryness.

Analgesic effect of *Urtica dioica* by Hot Plate test

The analgesic result of the time score in the hot plate test represented an inhibitor percent of pain than *Urtica dioica* at all dosed groups significantly ($P \leq 0.05$). The response behavior was dose-dependent and increased direct significantly ($p \leq 0.05$).

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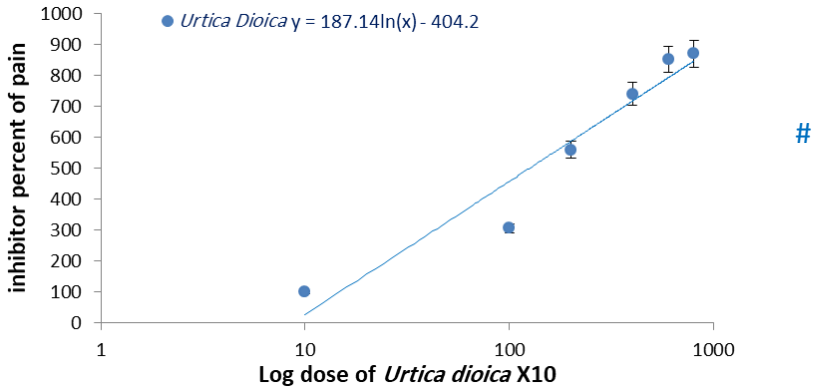

Figure 1: The inhibitor percent of pain as an analgesic effect of *Urtica dioica* by the hot plate in mice intraperitoneally. The data is displayed as mean ±SE, and discrepancies are indicated by blue-denoted differences between dosed groups significantly at ($p \leq 0.05$)

Anti-inflammatory of indomethacin

Preemptive analgesia can minimize inflammation and pain, which helps to lessen both peripheral and central sensitization. Pre-doses of different indomethacin may stop and diminish the pain signaling pathway, which would support the conventional preemptive analgesia.

The preemptive analgesia caused by indomethacin may be the result of arachidonic acid competing or rivaling with it for cyclo-enzyme oxygenase's binding, hence lowering prostaglandin production (9). No difference between delayed indomethacin treatment and preemptive analgesia of indomethacin was found in animal pain, according to (10,11). However, the study's findings concur with (11,12).

Demonstrate how indomethacin-based preemptive analgesics effectively reduced delayed pain in an animal that was being subjected to pain induction.

Analgesic result of the time score in the hot plate test represented in Figure 2 an inhibitor percent of pain .indomethacin at all dosed groups significantly ($p \leq 0.05$). The response behavior was dose-dependent and increased direct significantly ($p \leq 0.05$).

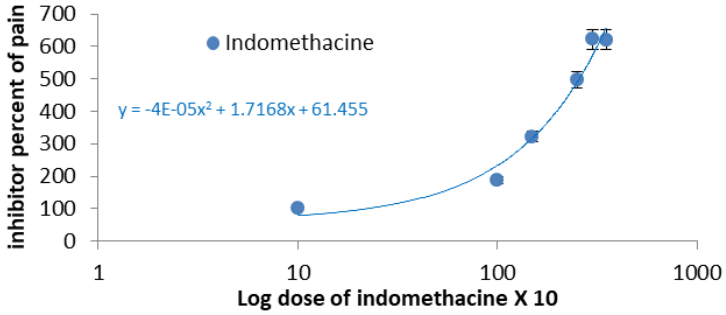

Figure 2: The inhibitor percent of the pain of analgesic effect of indomethacin by the hot plate in mice intraperitoneally. The data is displayed as mean ±SE, and discrepancies are indicated by blue-denoted differences between dosed groups significantly at ($p \leq 0.05$)

Table 2: concentration of ED_{50} and ED_{20}

	Indomethacin	***Urtica dioica***
ED_{50}	21.96	38.20
ED_{20}	9.90	10.74

Hot plate challenge test of synergism between EDs of indomethacin and *Urtica dioica*

The results of the synergism of the ED_{50} and ED_{20} of indomethacin and *Urtica dioica* (Figure 3) demonstrated that the ED_{50} indomethacin-ED_{50} of *Urtica dioica* extract and other ED_{20} indomethacin-ED_{20} of *Urtica dioica* extract, ED_{20} indomethacin-ED_{50} of *Urtica dioica* extract, and ED_{50} indomethacin-ED_{20} extract of *Urtica dioica* was less effect significantly ($P \leq 0.05$).

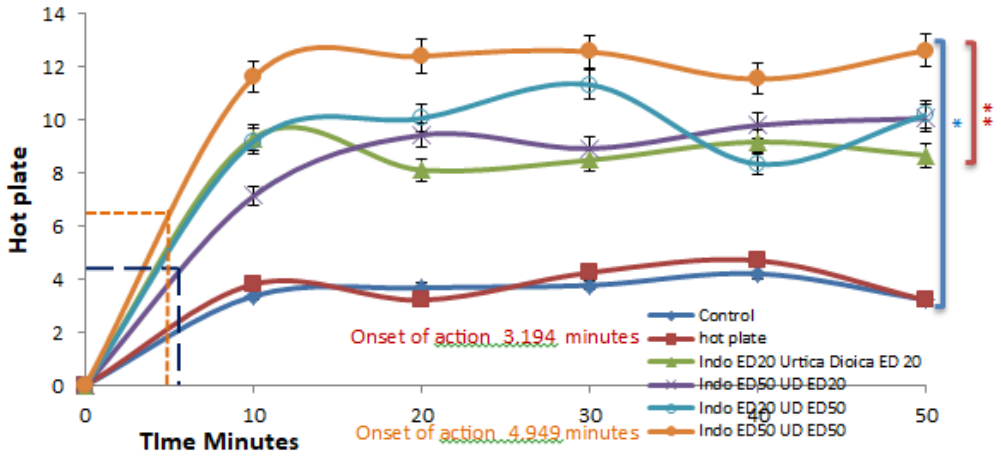

Figure 3: Timeline of the exploratory analgesic effects of indomethacin and *Urtica dioica* following a Hot plate challenge test in mice intraperitoneally.

The various stars indicated the difference between the treatment groups ($P \leq 0.05$), and the data were reported as mean ±SE. UD stands for *Urtica dioica*, and indo for Indomethacin provides preemptive antinociceptive effects in thermally produced pain, according to the study that gave birth to its dosage.

The hot plate test measures the antinociceptive effects of supraspinal analgesics and reflects activity in thermally sensitive afferent neural fibers as well as A and C fiber activity (13). The findings show that conventional Indomethacin and *Urtica dioica* have a thermal delay time that peaks at 30% Indomethacin concentration 21.96 and 60% *Urtica dioica* concentration 10.74 .

The indomethacin and *Urtica dioica* developed analgesia higher than the ordinary indomethacin form and increased both efficacy and potency expressed in values of ED_{50}, so it can lessen the incidence of adverse effects. Additionally, the withdrawal of the analgesic effect was delayed in synergism form than in Ordinary indomethacin.

This is possible because the indomethacin and *Urtica dioica* reduced the indomethacin clearance, which increased residence in blood circulation

The Caraginan challenge test of synergism between EDs of indomethacin and *Urtica dioica*

The results of the synergism of ED_{50} indomethacin-ED_{50} of *Urtica dioica* extract and others ED_{20} indomethacin-ED_{20} of *Urtica dioica* extract, ED_{20} indomethacin-ED_{50} of *Urtica dioica* extract, and ED_{50} indomethacin-ED_{20} of *Urtica dioica* extract were significantly less effective in ($p \leq 0.05$). then the other combinations (Figure 4).

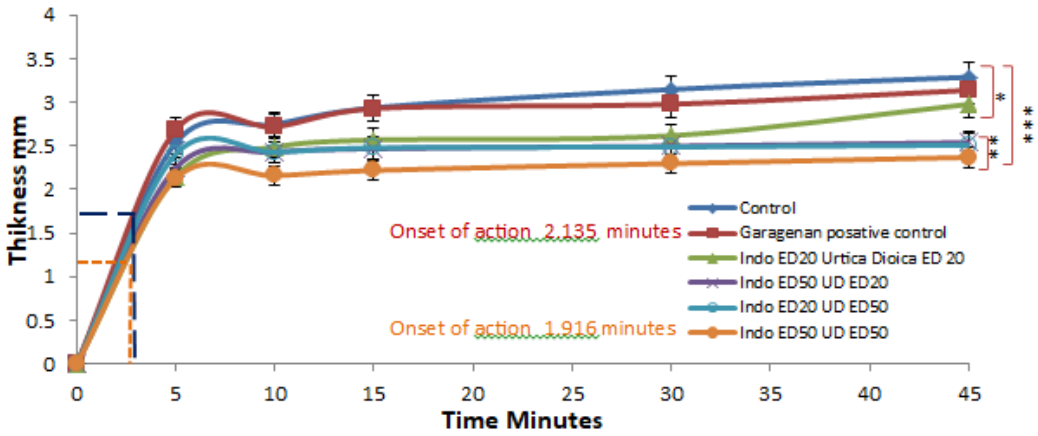

Figure 4: A timeline showing the anti-inflammatory effects of indomethacin and *Urtica dioica* EDs after the Garaginan challenge test on mice's paws. The data are provided as mean ∓standard error, and the various stars indicate differences between treatment groups (p≤ 0.05). stands for *Urtica dioica*, and indo for indomethacin.

This test is appropriate for evaluating the anti-inflammatory impact of medications because it uses an accurate and effective way to determine the amount of pathologically artificially produced paw edema (14). Indomethacin- *Urtica dioica* injections reduced carrageenan-induced edema in a dose-dependent manner.

The improvement in the therapeutic efficacy of Indomethacin and *Urtica dioica* can be correlated with the ability of the delivery system in positive alteration of Indomethacin biopharmacological characterization, according to the ED_{50} od Carrageenan test values in (Figure 4), Improved solubility and absorption of indomethacin via the lymphatic transport system, and protective properties of the *Urtica dioica* that reduce the adverse effects of drug metabolism (15).

Serotonin and histamine act as mediators to cause acute inflammatory reactions in mice, whereas kinins and PGs act as mediators to cause chronic delayed-onset responses (16). The lower paw edema volume at the delay phase of the carrageenan-induced paw edema test indicates the anti-inflammatory action;

This may be because Indomethacin primarily inhibits the COX-I and COX-II enzymes, which are in charge of producing PGs (16). When compared to conventional indomethacin, *Urtica dioica* and indomethacin had a greater anti-inflammatory effect, indicating that in raising indomethacin's efficacy value and therapeutic effectiveness (17).

The Tail Flick challenge test of synergism between EDs of indomethacin and *Urtica dioica*

The results of ED_{50} indomethacin-ED_{50} of *Urtica dioica* extract and others ED_{20} indomethacin-ED_{20} of *Urtica dioica* extract, ED_{20} indomethacin-ED_{50} of *Urtica dioica* extract, and ED_{50} indomethacin-ED_{20} of *Urtica dioica* extract were less substantially effective ($p \leq 0.05$).

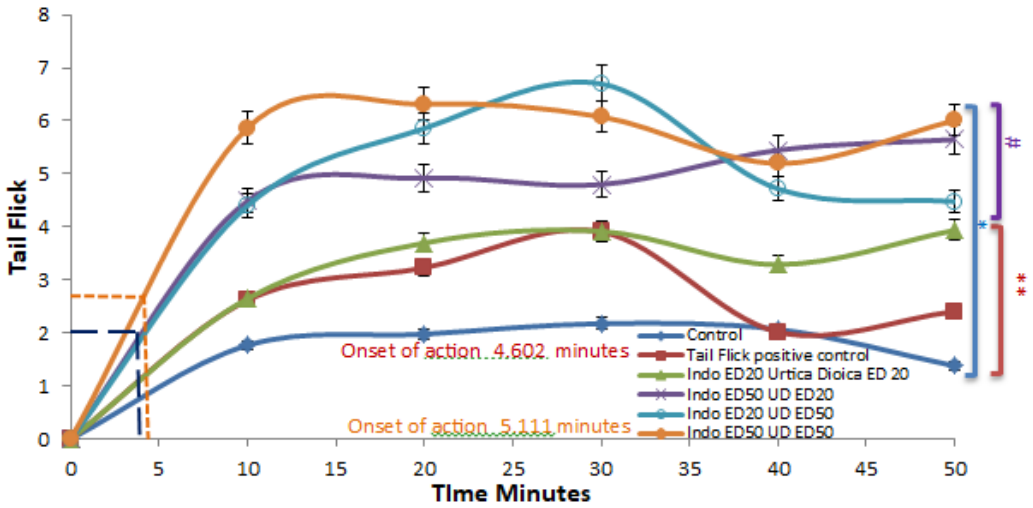

Figure 5: the timing of the *Urtica dioica* and indomethacin Tail Flick effects after mice were given both drugs intraperitoneally. The various stars indicated the difference between the treatment groups ($p \leq 0.05$), and the data were reported as mean ±SE. stands for *Urtica dioica*, and indo for indomethacin.

The *Urtica dioica* extract and indomethacin, as well as the *Urtica dioica*, indomethacin, and the control group all demonstrated a significant difference (increasing) in withdrawal time per (second), as shown in (Figure 5). The *Urtica dioica* had strong anti-nociceptive activity in our investigation, which was consistent with earlier research by (18).

It is generally accepted that analgesic efficacy is dependent on the nociceptive stimulus and that chemical stimulation (like the formalin experiment) is more sensitive than thermic one like the tail-flick experiment test. This is unlikely to be secondary to its non-specialized muscle relaxant, specific and/or non-specific tranquilizer central effects.

The Formalin challenge test of synergism between EDs of indomethacin and *Urtica dioica*

The results of the synergism of the ED_{50} and ED_{20} of indomethacin and *Urtica dioica* (Figure 6) demonstrated that the ED_{50} indomethacin-ED_{50} of *Urtica dioica* extract and other ED_{20} indomethacin-ED_{20} of *Urtica dioica* extract, ED_{20} indomethacin-ED_{50} of *Urtica dioica* extract, and ED_{50} indomethacin-ED_{20} extract of *Urtica dioica* was less effect significantly ($P \leq 0.05$).

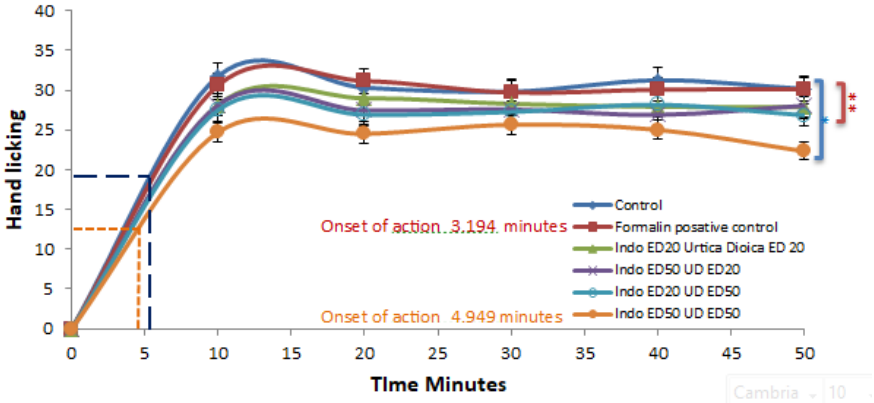

Figure 6: Timeline of the exploratory analgesic effects of indomethacin and *Urtica dioica* following a formalin challenge test in mice paws. The various stars indicated the difference between the treatment groups ($P \leq 0.05$), and the data were reported as mean ±SE. stands for *Urtica dioica*, and indo for indomethacin.

This helps identify whether peripheral or central pathways are involved in triggering the nociceptive pain reaction. The formalin test technique's two stages, each expressing a different type of pain, were notable for this.

While the latter or delay phase indicates pain from inflammation, the earlier or primary phase reflects a direct formalin impact on the pain sensory receptor of nociception (19). When compared to the control groups in the late phase (15–30 minutes), the dosed with Ordinary Indomethacin and *Urtica dioica* Indomethacin demonstrated a substantial anti-inflammatory effect with a decrease in licking duration and quantity.

This outcome pointed to an inflammatory response that was in the delaying phase and may have been blocked by indomethacin. Indomethacin that was in *Urtica dioica* had a larger anti-inflammation impact % during the delay phase than the groups who received several doses of indomethacin. By bettering indomethacin distribution to the target site and facilitating the solubility of indomethacin by *Urtica dioica*, the Urtica dioica was likely able to boost the efficacy of indomethacin therapeutic effects (20).

Additionally, as indicated above, *Urtica dioica* has antioxidant and anti-inflammatory properties that support anti-inflammatory pathways.

The Acetic acid challenge test of synergism between EDs of indomethacin and *Urtica dioica*

The results of the synergism of the ED_{50} and ED_{20} of indomethacin and *Urtica dioica* (Figure 7) demonstrated that the ED_{50} indomethacin-ED_{50} of *Urtica dioica* extract and other ED_{20} indomethacin ED_{20} of *Urtica dioica* extract, ED_{20} indomethacin-ED_{50} of *Urtica dioica* extract, and ED_{50} indomethacin-ED_{20} of *Urtica Dioica* extract of *Urtica dioica* was less effect significantly ($P \leq 0.05$).

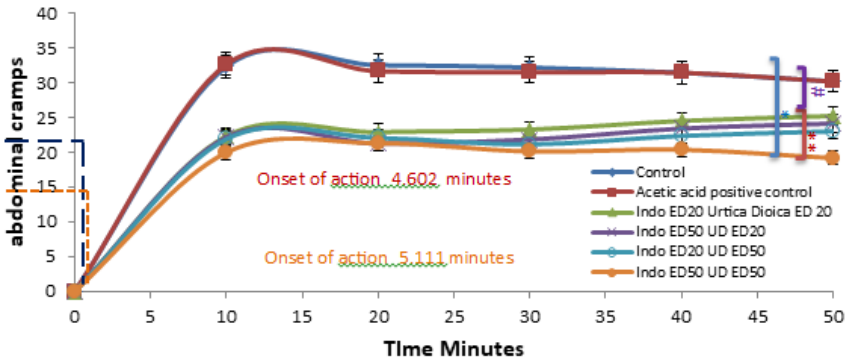

Figure 7: Timeline of the induction of writhing in mice after intraperitoneal administration of indomethacin and *Urtica dioica* EDs. The data are provided as mean ±standard error, and the various stars indicate differences between treatment groups ($P \leq 0.05$). stands for *Urtica dioica*, and indo for indomethacin.

According to (21), The test is a sensitive screening method often employed to investigate both peripheral and central antinociceptive responses. While inflammatory pain, also known as the late phase, is defined by pain response brought on by the release of algogenic chemicals from wounded tissues, the former is characterized by direct activation of nociceptors in the paw (22).

Both conventional indomethacin and *Urtica dioica* and indomethacin demonstrated dose-dependent pain response inhibitory bio-activities in the obtained data, which were distinguished by a substantial ($p \leq 0.05$) reduction in the writhing effect. Certainly, A remedy's effectiveness in indomethacin ED50 will be considerably increased by encapsulating with other NSAIDs, allowing for the use of lower dosages while still minimizing side effects. (23,24)

Chronotherapeutics

Chronobiology and chronotherapeutics are making it more and more clear that the precise moment that patients take their prescription may be much more important than previously thought. The custom of giving medicine at regular times throughout the day to maintain steady drug levels throughout 24 hours, may change as researchers report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms.

Table 3: *Urtica dioica* and Indomethacin from Chronotherapeutics

(1) Control					
7Am 5 mice Hot plate	1pm 5 mice Hot plate	1Am 5 mice Hot plate	7Am 5 mice Caraginan	1pm 5 mice Caraginan	1Am 5 mice Caraginan
3.318	**3.712**	**4.058**	**3.260**	**2.860**	**3.464**
(2) *Urtica dioica* ED_{50} 38.20 / Indomethacin ED_{50} 21.96					
7Am 10 mice Hot plate	1pm 10 mice Hot plate	1Am 10 mice Hot plate	7Am 10 mice Caraginan	1pm 10 mice Caraginan	1Am 10 mice Caraginan
11.542	**12.170**	**12.758**	**2.476**	**2.302**	**2.638**

Chronotherapeutics is the practice of timing in vivo medication availability to coincide with the cycles of illness to maximize therapeutic results and reduce negative effects. It is based on the discovery that numerous medication pharmacokinetics, pharmacologic sensitivity, and peak-to-trough rhythmic activity in illness symptoms and risk factors are interdependent (3). As more continues to be learned about. The results in the table indicate that the best result and the best time is at 1 am

Conclusions

Successful of creation of phytosom *Urtica dioica* carry in indomethacin in degree stable form

1. *Urtica dioica* phytosome Indomethacin was improved the standard form of Indomethacin as an analgesic dosage form, increasing thermal tolerance in Hot plate test, formalin test, acetic acid test, and carrageenan test in *Urtica dioica* phytosome Indomethacin more than Indomethacin ordinary form.

2. *Urtica dioica* phytosome Indomethacin's duration of action was longer than that of Indomethacin; the more patent ED_{50} than other convenation indomethacin and *Urtica dioica*.

3. *Urtica dioica* in groups that received treatment, partially Indomethacin showed an anti-inflammatory effect that was superior to that of ordinary Indomethacin, and its ED_{50} value was lower than that of conventionl *Urtica dioica* phytosome Indomethacin.

4. The chronotherapeutic of phytosom *Urtica dioica* carry of indomethacin set time at night mode (1 am).

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التأثير العلاجي الزمني لمسكن الألم الإندوميثاسين و نبات القريص في الفئران

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الملخص

كان الهدف الرئيسي من الدراسة هو معرفة كيفية الحد من الآثار السلبية للإندوميثاسين مع تعزيز خصائصه المسكنة والمضادة للالتهابات. كان محصول مستخلص الميثانول من نبات القريص خلال ثلاث عشرة جلسة سحب كان 250 جم ± 2.68 جم من مستخلص نبات القريص

استخدم في الدراسة 60 ذكر فأر. قسمت الى ثلاث مجاميع ،مجموعة السيطرة قبل العلاج ، مجموعة الاندوميثاسين قسمت الى خمس مجاميع جرعت 35,30,25,15,10 .مجموعة القريص وقسمت الى خمس مجاميع جرعت 80,60,40,20,10. حققت معايير التسكين ومضادات الالم ضمن تحفيز الالم عن طريق الاختبارات الصفيحة الساخنة، الحمام المائي ، حقن حامض الخليك، الفورمالين ، الكاركينان.

أشارت نتائج العلاج الزمني الى ان افضل وقت وافضل نتائج اعطاه العلاج هو في الساعة 1 صباحآ.