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# SYNERGIC ANTI-INFLAMMATORY COMBINATION OF THYMOQUINONE AND ACETYLPROLINE

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**Introduction.** Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used drugs that help reduce inflammation, fever and pain in patients. NSAIDs have cyclooxygenases 2 (COX-2) inhibitors, which suppresses prostaglandins E2 synthesis but do not influence leukotriene B4 or C4. Prostaglandins play a crucial yet partial role in the development of edema in the inflammation process. COX-2 inhibitors only work on prostaglandins, limiting their effectiveness to fight inflammation. Combining this with the fact that COX-2 inhibitors have a saturation dose/effect relationship means that COX-2 inhibitors are not effective anti-inflammatory combination drugs. Thymoquinone has also been shown to have anti-inflammatory effects by COX-2 inhibition. While Thymoquinone blocks prostaglandin E2 synthesis as well, it has been shown to also block interleukin-6, interleukin-1-β as well as tumor necrotic factor-α and interferon-γ. It was found that the use of repair inducers, specifically Acetylproline (N-acetyl-L-proline) helps in controlling the degenerative process. They also suppress cellular infiltration and inhibit inflammatory tissue destruction. They also lack the antipyretic and gastro-toxic properties characteristic of NSAIDs and cyclooxygenase inhibitors.

**Aim:** to determine if synergism exists between combinations of Thymoquinone and Acetylproline at different doses.

**Materials and methods.** 84 lab mice were obtained and divided into 12 groups containing 6 mice each, with the last 12 mice in placebo group. The groups were-Thymoquinone: 2mg/kg, 5mg/kg, 10mg/kg, Acetylproline: 100mg/kg, 200mg/kg, 400mg/kg, 800mg/kg, 4 different doses of Thymoquinone and Acetylproline combinations with ratio 1:20, respectively: 1mg/kg and 20mg/kg, 2mg/kg and 40mg/kg, 5mg/kg and 100mg/kg and finally 10mg/kg and 200mg/kg. As a reference NSAID we used Meloxicam in dose 5mg/kg. The mice were injected with inflammation inducing 0.03ml of 1% carrageenan gel into their right paws. After 1 hour, the different drugs were administered- Meloxicam and Acetylproline were introduced orally, while Thymoquinone was introduced peritoneally. Using a thickness gauge, we measured the degree of inflammation in the mice's paws for every hour for 5 hours, and then again after 24 hours from carrageenan.

**Results and their discussion.** Meloxicam reduced acute stage paw inflammation by 44±3%. Thymoquinone and Acetylproline anti-inflammatory effect was dependent on dose. Using regression analysis, we calculated estimated values of effective doses. For Acetylproline, $ED_{50}$=440mg/kg, for Thymoquinone, $ED_{50}$=8mg/kg. Acetylproline and Thymoquinone combinations at 20:1 ratio in doses of 20+1, 40+2, 100+5 and 200+10, anti-inflammatory effect was respectively 38±8%, 31±5%, 28±4% and 37±11%. We then calculated the results using the J.Webb method to estimate synergy, we found that aforementioned doses of Acetylproline and Thymoquinone resulted in increased activity, while higher doses resulted in antagonism.

**Conclusion.** In regard to Thymoquinone and Acetylproline combination in ratio 1:20, synergism was found in small doses. Quick saturation of effect was observed. The maximal dose used in our experiment was not synergetic. The combination of drugs resulted in increased activity, but effectivity did not increase. It's possible to achieve desired synergetic effect at small doses, which can limit the appearance of side effects in patients taking anti-inflammatory drugs.