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HOSSAM MAGHRABY

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# التوثيق الالكتروني والميكروفيلم

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# COMPARATIVE STUDY ON EFFECTS OF DILTIAZEM VERSUS N-ACETYL CYSTEINE IN ACUTE ACETAMINOPHEN INTOXICATION IN MICE



**Thesis**

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**Forensic Medicine and Toxicology**

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# LIST OF ABBREVIATIONS

| ABB. | Words |
|---|---|
| PG | Prostaglandin |
| NAPQI | N-acetyl-p-benzoquinoneimine |
| NAC | N-acetyl cysteine |
| BZQ | 1,4 benzoquinoneimine |
| CYS | Cysteine |
| GSH | Glutathione |
| PGE2 | Prostaglandin E2 |
| PGI2 | Prostaglandin I2 |
| APAP | Acetaminophen |
| LSD | Least significant difference |

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# INTRODUCTION

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Acetaminophen (Paracetamol, N-acetyl-p-aminophenol, APAP) is one of the most commonly used non- narcotic, analgesic-antipyretic agents. It has only weak anti-inflammatory activity[1].

Acetaminophen nowadays is a common household analgesic because it is well tolerated, lacks many of the side effects of aspirin and is available without prescription. However, acute overdose causes fatal hepatic damage and the attempts of suicide with acetaminophen have grown alarming in the recent years[2].

## HISTORY:

Acetanilide is the parent of the group of acetaminophen. It was introduced into medicine in 1886 under the name antifebin by Cohin and Hepp, who had accidentally discovered its antipyretic action[2]. However, acetanilide was proved to be excessively toxic and it has been replaced by safer analgesics[3].

In the search for less toxic compounds, para-aminophenol was tried, in the belief that the body oxidizes acetanilide to this compound. However, toxicity was not lessened, a number of chemical derivatives of para- aminophenol were then tested[2].

One of the more satisfactory compounds of the group was phenacetin. It was introduced as a therapeutic agent in 1887[2] and was extensively employed in analgesic mixtures until it was implicated in analgesic abuse nephropathy[2, 4].

Acetaminophen was firstly used in medicine by Von Mering in 1893[2]. However, it has gained popularity only since 1949 after its recognition as the major active metabolite of both acetanilide and phenacetin[2](Fig. 1). It was firstly marketed for use as drug in the UK in 1956 and since then it has become popular with the

medical profession and the general public as a safe alternative to aspirin[5].

## PHARMACOLOGICAL EFFECTS:

Acetaminophen has analgesic and antipyretic effects that do not differ significantly from those of aspirin. However, it has only weak anti-inflammatory effects[6,7]. It appears to be an inhibitor of prostaglandin synthesis in the brain[1].

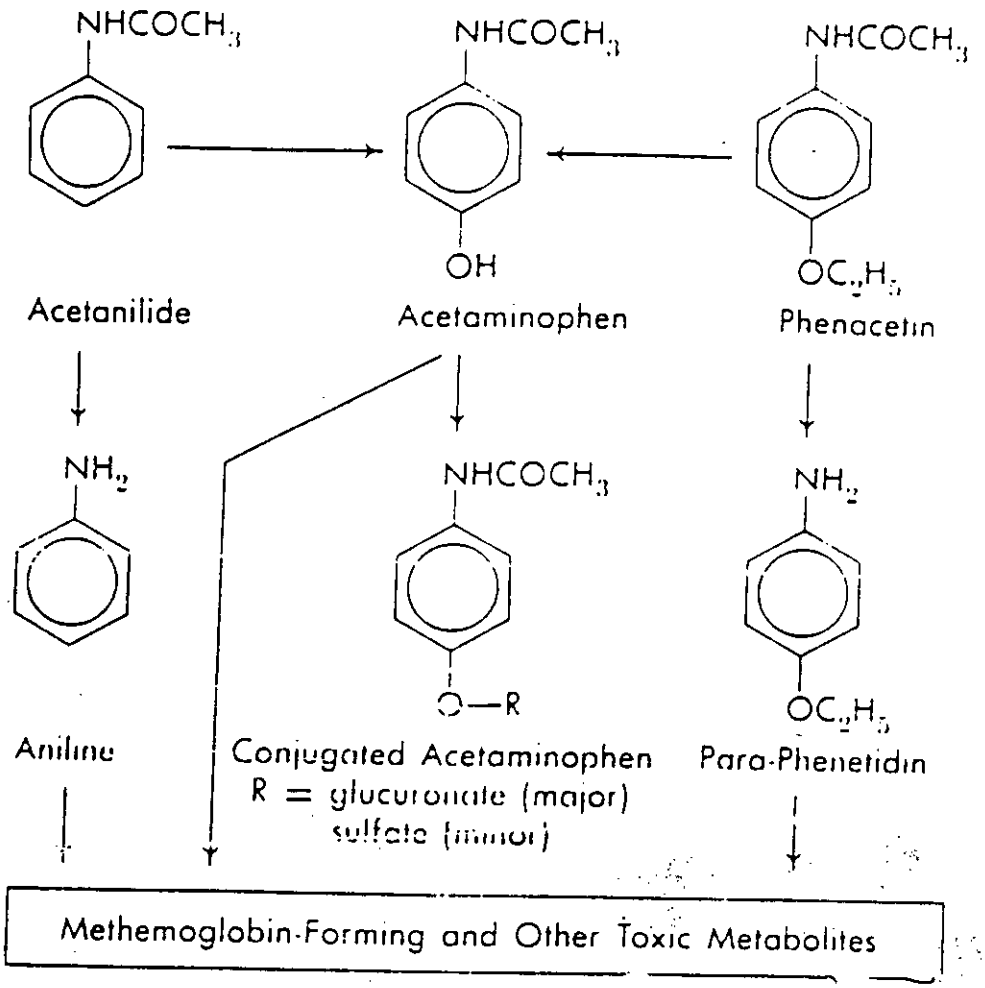


**Fig. (1):** Structural formulae of major para- aminophenol derivatives[2].

**1- Antipyretic effects[1]:**

Normal body temperature is regulated by a center in the hypothalamus and involves a sensitive control of the balance between heat loss and heat production . Fever occurs when there is a disturbance of the function of this hypothalamic regulation leading to the set-point of body to temperature being raised.

During any inflammatory reaction, bacterial endotoxins cause the release of a pyrogen from macrophages, which is probably interleukin-1 (IL-1). There is some evidence that this pyrogen causes the generation of prostaglandins (PG) of the E series in the hypothalamus leading to the elevation of the set-point for the temperature. So the antipyretic effect of acetaminophen could be explained as being due to its inhibition of prostaglandin synthesis. Once there have been a return to the normal set-point, the temperature-regulating mechanisms then operate to reduce temperature. Normal temperature is not affected by acetaminophen[1].

**2- Analgesic effect[1]:**

Several prostaglandins sensitize noticeptive afferent nerve terminals to mediators such as bradykinin. Thus, in the presence of $PGE_1$ or $PGE_2$ pain will be felt even with concentrations of anti-inflammatory mediators such as 5-hydroxytryptamine or bradykinin, which are too low to cause pain on their own. Acetaminophen is therefore mainly effective against types of pain in which prostaglandins amplify the basic pain mechanism. Hence, it will be effective in cases of pain associated with inflammatory processes[1].

They are useful against pain of mild to moderate intensity, particularly that due to bursitis or arthritis and pain of muscular or