Effect Of Paracetamol On The Liver And Kidney Of Albino Rat A Histological And Histochemical Study

THESIS
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BY

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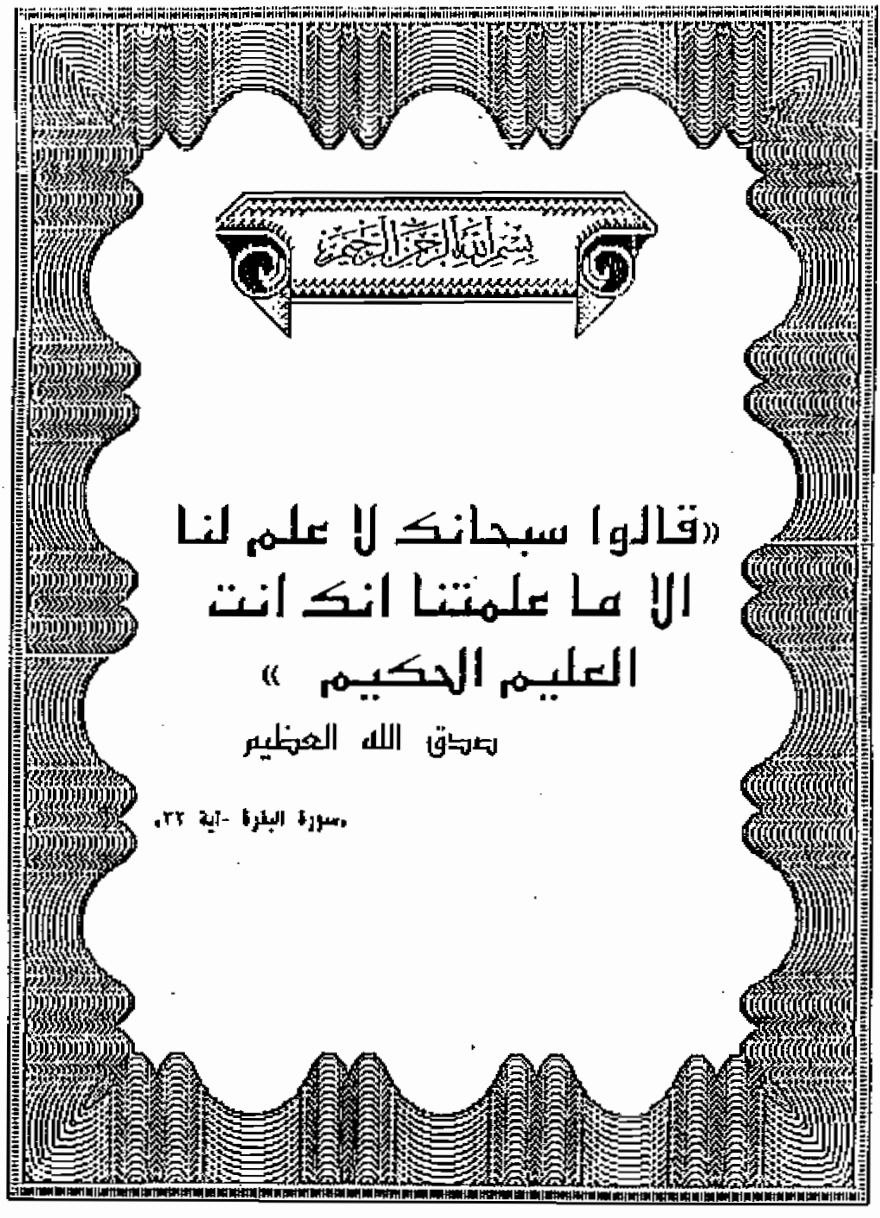
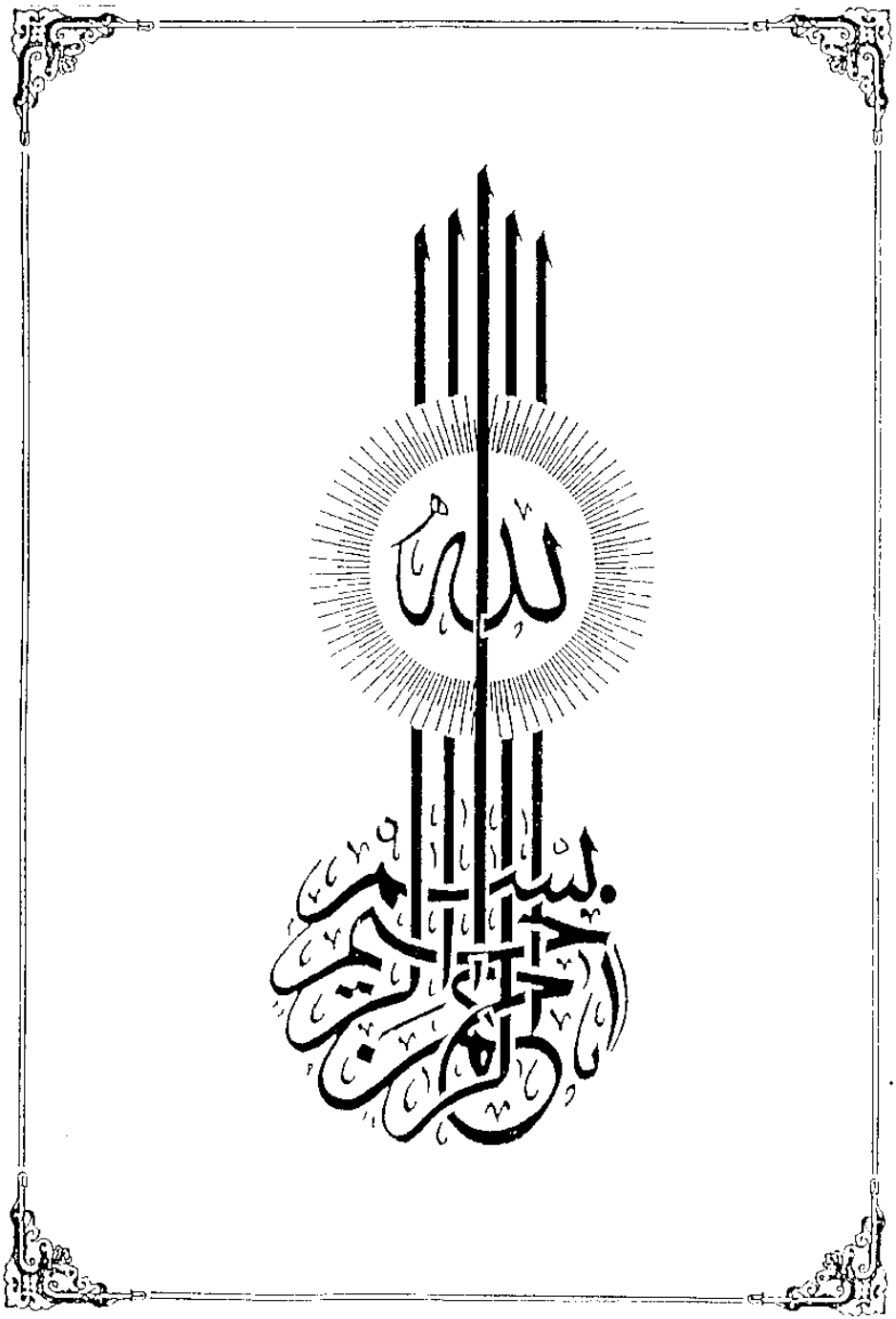

بسم الله الرحمن الرحيم
«قالوا سبحانك لا علم لنا
الا ما علمتنا انك انت
العليم الحكيم »
صدق الله العظيم
«سورة البقرة -آية ٣٢»



TO.....

MY MOTHER

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Non-steroidal anti-inflammatory drugs, NSAID, which are non narcotic analgesics and anti rheumatics, are mostly orally-active and weak analgesics, with or without anti-inflammatory and anti-pyretic actions. Serious dependence does not occur with this group.

The drugs are classified according to their combined analgesic and anti-inflammatory properties seen at their therapeutic doses. They vary from paracetamol, which is an analgesic with negligible anti-inflammatory properties, to indomethacin, which is a potent anti-inflammatory drug with little analgesic effect.

The drugs with the least anti-inflammatory action tend to be the least toxic. At the same time, those with the most anti-inflammatory action cause more serious adverse reactions.

For relief of many pains as headaches, dysmenorrhoea, and toothache, paracetamol or low doses of aspirin will be effective.

Therefore, NSAID may be classified as the following:

1. Drugs with analgesic but with negligible anti-inflammatory actions: Aniline derivative, paracetamol, is the principal member of this group now used. Phenacetin is obsolescent.

2. Drugs with analgesic and mild to moderate anti-inflammatory actions:

a) Propionic acid derivatives e.g. ketoprofen, naproxsen, fenoprofen.

b) Anthranilic acid derivatives e.g. mefenamic acid.

c) Arylacetic acid derivatives e.g. fenclofenac.

3. Drugs with analgesic and marked anti-inflammatory actions:

a) Salicylates and their derivatives e.g. aspirin, aloxiprin, diflunisal, salsalate.

b) Pyrazolone derivatives e.g. phenyl butazone, feprazone.

c) Indole derivatives e.g. indomethacin.

As regards the mode of action of NSAID, it is known that inflammation is accompanied by pain, oedema, erythema, and fever. The mechanisms of the inflammatory process are complex and involve mediators including: histamine, 5-hydroxytreptamine, slow reacting substance of anaphylaxis, bradykinin, lymphokines, and others. Some mediators may play a more prominent role than others in particular types of inflammation. It has recently been observed that prostaglandins are intimately concerned with the inflammatory process. Thus, in case of pain and possibly other aspects of inflammation, prostaglandins act as modulators being capable of increasing or decreasing the response rather than actual mediators.

The understanding of how the NSAID act was increased enormously when it was found that they are capable of preventing the synthesis of prostaglandins (Laurence and Bennett, 1980).

Paracetamol (acetaminophen, N-acetyl-P-aminophenol) is an aniline derivative and one of the non steroidal anti-inflammatory drugs (NSAID). It has analgesic, antipyretic, and negligible anti-inflammatory actions (Laurence and Bennett, 1980).

Paracetamol, like its analogues, phenacetin (acetophenetidin) and acetanilide, was introduced into clinical medicine as an antipyretic agent in the late 19th century (Woodbury and Fingl, 1975).

It was found by chance that acetanilide, a derivative of aniline, possesses antipyretic activities. It was introduced for treatment of fever in 1866, but was proved to be toxic. Attention was then directed towards other derivatives of aniline such as phenacetin and paracetamol. Phenacetin was marketed in 1887 but also was found to cause serious side-effects. These effects, including haemolytic anaemia, met-haemoglobin formation, as well as nephrotoxicity, were tied to its long term ingestion (Brodie and Axelrod, 1949).

In 1899, aspirin was introduced into clinical practice. Although paracetamol had already been synthesized by that time, yet its medicinal properties remained unknown. Little interest was given to the drug, until in 1948, when Flinn and Brodie demonstrated that paracetamol was the metabolite of phenacetin and acetanilide (aniline derivatives). It was also found responsible for the analgesic and antipyretic properties of these two compounds. By that time, paracetamol started to be widely used instead of acetanilide and phenacetin.

Paracetamol was marketed in 1950 in the U.S.A., as a substitute of phenacetin, in an analgesic mixture. After a few case reports of blood dyscrasias, the manufacturer recalled the drug in 1951. It was, again, made available in the market in the following year, only on prescription. In 1955, it became freely available without prescription. In the U.K., it was marketed in 1956. Since then it became accepted as an alternative to aspirin, avoiding aspirin's side effects as gut intolerance, bleeding tendency, or allergy (Meredith and Goulding, 1980). They studied, as well paracetamol metabolism and found it to be carried out mostly in the liver. As a result of this, it can lead to liver cell injury or damage following overdosage or abuse.

In this work, we chose paracetamol as it is one of the most commonly used NSAIDs. Hazards of paracetamol abuse are still a problem for the clinical practice, due to its availability in many countries over the counter without prescription.

The aim of this work is to demonstrate early and late histopathological changes in the liver and kidney tissues, after paracetamol oral administration in various doses and for different periods. Recovery was also detected.

Eighty adult female albino Wistar rats (150-200 gm) were divided into groups including a control group and treatment groups. Treatment groups were given paracetamol orally and were divided into subgroups according to the dose and duration of the treatment. The liver and kidney tissues were investigated using histological, histochemical, and electron microscopic techniques.

Review of Literature

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Many pathological conditions were caused by exposure to toxic agents. It was important to understand the toxic effects as well as the metabolism of the compounds to which the living beings were exposed.

Nowadays drugs are recognized as often potent compounds. In many cases, their toxicities as well as their actions resulted from a chemical reaction between the drug (or metabolite) and structures (receptors), within the cell. Most foreign compounds undergo chemical transformations in the body, including oxidation, reduction, hydrolysis, and synthesis. The transformations were demonstrated to be generally catalyzed by enzymes and mostly occurring in the liver. The type of chemical changes which occurred was found to be depending on the structure of the foreign compound. Other factors, such as species, diet, pre-treatment with drugs, hormones, or other compounds, and route of administration were shown to be important. The resultant metabolites and unchanged materials were usually excreted through the kidney or bile duct (Williams, 1959).

Hepatic necrosis resulting from paracetamol overdosage was first reported in rats by Boyd and Bereczky (1966).

Toghill, Williams, Stephens and Carroll (1969) reported an increase in cases with paracetamol toxicity.

In the same year, Rose, reported cases of paracetamol overdosage in his hospital. Their postmortem findings showed extensive liver affection, as well as acute tubular necrosis.

Proudfoot, and Wright in 1970 stated that the kidneys were the next most frequently damaged organs after the liver. They concluded also that in adults, the consumption of less than 10 gm of acetaminophen might be associated with hepatic damage. A dose of 25 gm or more might result in death from hepatic failure.

However, Prescott, Wright, Roscoe and Brown in 1971 gave a dose of 7.5 gm paracetamol and observed a striking elevation of SGOT and SGPT with little or no changes in alkaline phosphatase or creatine-kinase activities. Prothrombin time was prolonged in every patient, irrespective of signs of liver damage. They also stated that renal failure was not certainly accompanied by hepatic failure.

In the same year, Boyer and Rouff showed that moderate to severe renal impairment might occur in patients with little evidence of hepatic injury.

Furthermore, investigations were done by Edwards, Edwards, Huskison and Taylor in 1971, where they assessed renal function in 18 rheumatology patients consuming paracetamol over varying periods. They reported no significant impairment of renal function. There was no relation between any impairment and the quantity of paracetamol ingested.

As regards minor metabolites of acetaminophen, Koch-Weser and Sellers showed in 1971 that they were formed by

hydroxylation and deacetylation. These metabolites were highly affected by inducers and inhibitors of metabolism.

As regards the mode of action, in 1972, Feldberg, Gupta, Milton, and Wendlandt, stated that the possession of antipyretic properties by aspirin and paracetamol was the result of their ability to inhibit the biosynthesis of prostaglandins and other substances from the anterior hypothalamus.

Further studies were performed on the rat in which Potter, Davis, Mitchell, Jollow, Gillette, and Brodie (1973) demonstrated the relation between acetaminophen and hepatic glutathione in rats. They found out that the activity of the mixed function oxidase system was lowered in the rat more than in other species. They also detected that pre treatment with phenobarbitone increased hepatotoxicity of paracetamol while microsomal enzyme inhibitor decreased it.

Goulding (1973) showed that the extensive availability of acetaminophen increased the probability of accidental ingestion of toxic quantities by infants and children.

In the same year, Wright and Prescott confirmed that ingestion of alcohol and barbiturates augmented the toxic effect of acetaminophen.

Master and Krikler (1973) reported four cases of analgesic nephropathy associated with the chronic ingestion of large quantities of paracetamol. These results were verified by Clark, Borirakchanyavat, Davidson, Thompson, Widdop, Goulding, And Williams (1973 a). They reported acute tubular necrosis together