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Preparation, spectroscopic, thermal, antihepatotoxicity, hematological parameters and liver antioxidant capacity characterizations of Cd(II), Hg(II), and Pb(II) mononuclear complexes of paracetamol anti-inflammatory drug

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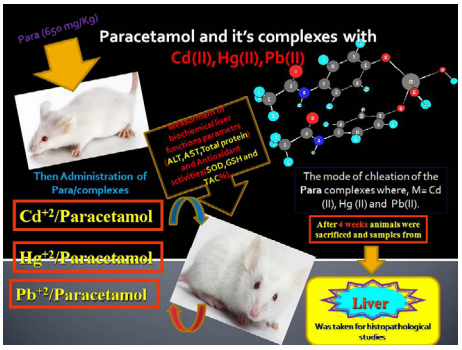
HIGHLIGHTS

- The Cd(II), Hg(II), and Pb(II) complexes of paracetamol have been synthesized.
- The general formula of complexes is $[M(\mathbf{Para})_2(H_2O)_2]\cdot nH_2O$.
- In vivo the antihepatotoxicity effect were measured.
- The Cd^{2+} + **Para** complex has succeeded in improvement of the antioxidant capacities.

GRAPHICAL ABSTRACT



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ABSTRACT

Keeping in view that some metal complexes are found to be more potent than their parent drugs, therefore, our present paper aimed to synthesized Cd(II), Hg(II) and Pb(II) complexes of paracetamol (**Para**) anti-inflammatory drug. Paracetamol complexes with general formula $[M(\mathbf{Para})_2(H_2O)_2]\cdot nH_2O$ have been synthesized and characterized on the basis of elemental analysis, conductivity, IR and thermal (TG/DTG), ^1H NMR, electronic spectral studies. The conductivity data of these complexes have non-electrolytic nature. Comparative antimicrobial (bacteria and fungi) behaviors and molecular weights of paracetamol with their complexes have been studied. In vivo the antihepatotoxicity effect and some liver function parameters levels (serum total protein, ALT, AST, and LDH) were measured. Hematological parameters and liver antioxidant capacities of both **Para** and their complexes were performed. The Cd^{2+} + **Para** complex was recorded amelioration of antioxidant capacities in liver homogenates compared to other **Para** complexes treated groups.

Introduction

Paracetamol (**Para**; Fig. 1) was a widely used as analgesic and antipyretic drug [1–6], also, it was known to be hepatotoxic in

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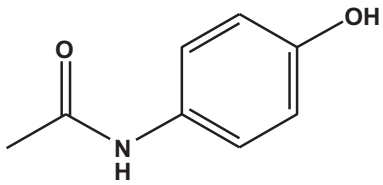

Fig. 1. Paracetamol (**Para**) drug structure.

man and various experimental animals upon overdose [7–9]. Taking the presumed molecular mechanisms of analgesic activity as well as of the hepatotoxicity of paracetamol into consideration, there have been several efforts to improve its analgesic activity while preventing its toxicity by modifying its structure [10–13]. In an attempt to improve the analgesic activity of paracetamol by mono-substitution ortho to the hydroxyl group, Harvison et al. [11] showed that 3-methyl paracetamol was equipotent to paracetamol with respect to analgesic activity in mice. Unfortunately however, hepatotoxicity was also equal, the hepatotoxicity of paracetamol was decreased by 2-methyl substitution (meta to the hydroxyl group), however, the analgesic activity was also decreased. N-methyl paracetamol was found to be completely devoid of hepatotoxicity but also of analgesic activity [14]. In addition to mono-substitution, it has been shown that dialkyl-substitution at the 3- and 5-positions of the aromatic nucleus of paracetamol did not reduce the analgesic activity [15]. A toxicological study showed that the in vivo hepatotoxicity of the 3,5-dialkylated analogs was reduced almost completely [16]. Recently, it was reported that aromatic ring-substitution by one or two fluorines decreased the analgesic activity of paracetamolacetamol in mice [17]. It was also shown that these modifications decreased the in vivo toxicity [18]. The formation of complexes of paracetamol and Zn(II) was studied in aqueous media at pH 7.2 by polarography and spectroscopy [19]. The stoichiometry of the Zn(II)-paracetamol complex was 1:1. Analgesic studies on the drug and its metal complex have been performed in albino mice. Revealing the complex to be more potent in analgesic activity compared to the paracetamol alone drug.

The present work was built on the study of the interactions between paracetamol drug and some of heavy metal ions like Cd(II), Hg(II), and Pb(II). The elemental analysis, conductivity, IR and, thermal (TG/DTG), ^{1}H NMR, electronic spectral studies of these complexes were discussed and deduced the suggested structure which associated via deprotonation of —OH hydroxyl group. The antihepatotoxicity, hematological parameters and antioxidant effects of the **Para** complexes were investigated on the treated rats upon the calculations of liver function parameters levels (serum total protein, ALT, AST, and LDH), SOD, GST and TAC.

Experimental

Materials and preparations

Analytical grade of chemicals used were purchased from Aldrich and Merck chemical companies. Paracetamol drug was received from Egyptian International Pharmaceutical Industrial Company (EIPICo.). The **Para** complexes were prepared by mixing twice amount of **Para** (2 mmol) and 1 mmol of metal(II) nitrates (Cd(II), Hg(II) and Pb(II)) in MeOH/H_2O (50/50, w/w; 40 cm^3) solvent, then pH of the mixtures was adjusted to 7–8 using 5% alcoholic ammonia solution. The reaction mixtures were stirred at 60 °C for 2 h and left to stand overnight. The precipitated complexes were filtered off, washed with MeOH/H_2O and dried in *vacuum* at room temperature over anhydrous $CaCl_2$.

Physical measurements

Carbon, hydrogen and nitrogen contents were determined using a Perkin–Elmer CHN 2400. The metal content was determined by atomic absorption spectrometer model PYE-UNICAM SP 1900 and the corresponding lamps were used for this purpose. Infrared spectra were recorded on Bruker FTIR Spectrophotometer (4000–400 cm^{-1}) in KBr pellets. The UV–Vis spectra were studied in the DMSO solvent with a concentration of 1.0×10^{-3} M for the **Para** and their complexes using Jenway 6405 Spectrophotometer with 1 cm quartz cell, in the range 800–200 nm. Molar conductance's of the freshly prepared solutions of the **Para** complexes with 1.0×10^{-3} M in DMSO were measured using Jenway 4010 conductivity meter. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using DMSO-d_6 as solvent. Thermogravimetric analyses (TG/DTG) were carried out in a dynamic nitrogen atmosphere (30 mL/min) with a heating rate of 10 °C/min using a Shimadzu TGA-50H thermal analyzer.

Antimicrobial activities

According to Gupta et al. [20], the antimicrobial tests were done. The investigated isolates of bacteria were seeded in tubes with nutrient broth (NB). The seeded NB (1 cm^3) was homogenized in the tubes with 9 cm^3 of melted (45 °C) nutrient agar (NA). The homogeneous suspensions were poured into Petri dishes. The holes (diameter, 4 mm) were done in the cool medium. After cooling, 2×10^{-3} dm^3 of the investigated compounds were applied using a micropipette. After incubation for 24 h in a thermostat at 25–27 °C, the inhibition (sterile) zone diameters (including disc) were measured and expressed in mm. An inhibition zone diameter of over 7 mm indicates that the tested compound is active against the bacteria under investigation. The antibacterial activities of the investigated compounds were tested against *Escherichia coli* (Gram, −ve), *Bacillus subtilis* (Gram, +ve) and antifungal (*Asperagillus oryzae*, *Asperagillus niger*, and *Asperagillus flavus).*

Experimental animals

Antihepatotoxicity effect in male albino rats

The present study was carried out at Zoology Department, Faculty of Science-Zagazig University, Egypt using fifty clinically healthy mature adult male *albino* rats. The animals were obtained from the animal House of Faculty of Veterinary Medicine, Zagazig University, Egypt. Their weights ranged from (200–250 g). The animals were housed in standard conditions, where the animals were housed in metal cages and bedded with wood shavings and kept under standard laboratory conditions of aeration and room temperature at about 25 °C. The animals were allowed to free access of standard diet and water ad-libtum, We have followed the European community Directive (86/609/EEC) and national rules on animal care. The animals were accommodated to the laboratory conditions for 2 weeks before being experimented, adaptation and 10 rats were placed into each cage. Six groups were established in the study as follows.

The present study was undertaken to assess the effects of single or multiple-dose administration of **Para** and it is complexes in normal treated rats. All experiments were performed during the same time of day, between 10 am and 1 pm to avoid variations due to diurnal rhythms.

Experimental design

– Test compounds; **Para**, Cd^{2+}/**Para**, Hg^{2+}/**Para**, and Pb^{2+}/**Para**.

Animal groups

Treatment schedule (each group comprises 10 rats): In order to optimize **Para** drug absorption, all animals were starved overnight