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# Copper-Drug Based Complexes: Antimicrobial, Antioxidant and Pharmacological Study

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## Introduction

The study on complexation of drug molecules with various metal ions is an important field of research in the chemical, biochemical, medicinal and pharmacological point of views [1]. Our body possesses a large number of metal ions for operating normal physiological activities and we also intake a number of metals as drug, dietary factor, drinks and we also come in close contact with different drugs. It's also well established that many pathological situations involve deregulation in the metabolism of metals: therapeutic responses are then necessary and although most drugs or compounds used in medicine are purely organic. The challenge is to enhance the properties of these drugs by complexing them and to study their interaction with the trace elements present in the human organism. In fact, the complexation offers the metal ion a multitude of coordination possibilities and a wide range of geometries. As a result, the metal complexes, due to their thermodynamic and kinetic properties, and in some cases their redox activities, offer novel mechanisms of action that organic compounds do not exhibit themselves so it's very important to control all these properties to obtain the desired therapeutic effect when a drug or a metal complex is introduced into the body or the cell [2-4].

The interest of this study is to examine the modifications that the metal can make to the properties of an organic molecule when the latter is coordinated to it. Copper complexes have attracted great deal of attention due to their therapeutic applications as antimicrobial and antioxidant so, we have been interested in the study of the complexation of this metal by some drug molecules such as Paracetamol, Indomethacin and Spiramycin. Few works report similar study [5-9].

## Discussion

### Antibacterial and antifungal activity (*in vitro*)

The results of our investigations (Table 1) show that some metal complexes are more toxic than their parent ligands against the same microorganism and under identical experimental conditions. This would suggest that chelation could facilitate the ability of the complex to cross a cell membrane. It's well established that the mode of action of antimicrobials may involve various targets in the microorganisms [10]. These targets include the following: the higher activity of the metal complexes may be due to the different properties of the metal ions upon complexation [11]. According to Overtone's concept [12] of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid-soluble materials, so lipophilicity is an important factor controlling the antifungal activity. On the other hand and upon Tweedy's chelation theory [13] the polarity of the metal ion will be reduced because of the partial sharing of the positive charge of the metal with the donor groups present in the ligand. Thus, chelation enhances the penetration of the complexes into lipid membranes. These results are corroborated by DFT calculations.

**Table 1:** Antibacterial study results.

| Target/ inhibition zone (cm) | Para. | Ind. | Spi. | CuP | CuI | CuS |
|---|---|---|---|---|---|---|
| *Escherichia coli* ATCC 25922 | - | - | 15 | 12 | 12 | 9 |
| *Pseudomonas aeruginosa* ATCC 27853 | - | 9 | 0 | 23 | 10 | 11 |
| *Staphylococcus aureus* ATCC 25923 | - | 10 | 32 | 9 | 9 | 30 |
| *Bacillus subtilis* ATCC 27853 | - | 12 | 31 | 15 | 0 | 28 |
| *Micrococcus luteus* CIP | - | 10 | 55 | 12 | 9 | 40 |
| *Cancida albicans* ATCC 21131 | - | 11 | 9 | 9 | 11 | 10 |

## Acute toxicity

**Table 2:** Acute toxicity study results.

| | Para. | Spi. | CuP | CuS |
|---|---|---|---|---|
| MTD (mg/Kg) | - | - | 1140.7 | 143.2 |
| $LD_{50}$ (mg/Kg) | 322 | 332 | 3172.57 | 557.82 |
| $LD_{100}$ (mg/Kg) | - | - | 8662.18 | 1630.12 |

The comparison of the LD50 values of the complexes with that of the free ligands shows formally that the complexes are less toxic with a much higher tolerance to the synthetic product. Some results of this investigation are given in Table 2.

## Subacute toxicity

**Table 3:** Results of subacute toxicity study of CuP.

| Lot | Dose (mg/Kg) | Number of dead mice | Mortality (%) | Mortality (%) |
|---|---|---|---|---|
| | | Male | Female | |
| 1 | 66.66 | 0 | 0 | 0 |
| 2 | 100 | 0 | 0 | 0 |
| 3 | 150 | 0 | 0 | 0 |
| 4 | 225 | 0 | 0 | 0 |
| 5 | 338 | 0 | 0 | 0 |
| 6 | 760.5 | 0 | 0 | 0 |
| 7 | 1140.7 | 0 | 0 | 0 |
| 8 | 1711.05 | 3 | 4 | 70 |
| 9 | 2566.57 | 3 | 5 | 80 |
| 10 | 8662.18 | 5 | 5 | 100 |
| Control | - | 0 | 0 | 0 |

As a result, we find that batches treated with CuP complex with doses lesser than 50% of determined lethal dose do not affect the weight evolution of the mice. Therefore, the results obtained suggest that CuP complex is fairly non-toxic (Table 3).

## Anti-inflammatory assay

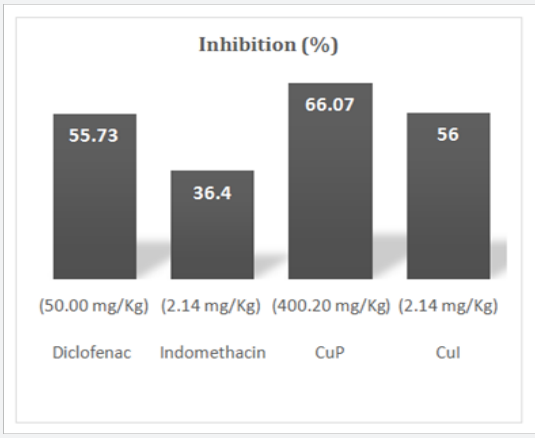


**Figure 1:** Anti-inflammatory assay study.

The injection of Carrageenan induces the liberation of bradykinin, which later induces the biosynthesis of prostaglandin and other autacoids, which are responsible for the formation of the inflammatory exudates [14-16]. The study of the acute anti-inflammatory tests showed that copper complexes produced a significant (P=0.028) reduction at 6h in Carrageenan induced paw edema when compared to the positive control group (Diclofenac at 50mg/Kg-body weight). Some results are gathered in Figure 1. These results suggest that the complexation of indomethacin increases its anti-inflammatory effect and that of paracetamol confers anti-inflammatory activity.

## Antioxidant assay

The antioxidant activity of Cu(II) complexes was measured in terms of their hydrogen donating or radical scavenging ability by UV–vis spectrophotometer using the stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) (DPPH: 18H12N5O6). For illustrating this study, we give here the results corresponding to CuP tests. Radical scavenging activity of paracetamol and CuP complex as well as the standard was increased in a dose-dependent manner; nevertheless, paracetamol and CuP complex showed less good activities as a radical scavenger compared to that of ascorbic acid, which was used as a standard. However, they exhibit appreciable activity with 80% in percentage scavenging in from a concentration of 300µg/mL.

## Electronic properties

The electronic structures of the studied compounds have been investigated by the quantum chemical parameters like energy of the highest occupied molecular orbital ($E_{HOMO}$), energy of the lowest unoccupied molecular orbital ($E_{LUMO}$), LUMO-HOMO energy gap (ΔE) and natural atomic charges calculated by natural population analysis. The HOMO and the LUMO are important parameters in organ metallic chemistry especially in chemical reactivity. ΔE is an important stability index helping to characterize the chemical reactivity and kinetic stability of the compound [17].

**Table 4:** Frontier orbital's energies.

| Compound | E HOMO (Hartree) | ELUMO (Hartree) | ΔE (Hartree) |
|---|---|---|---|
| Para. | -0.203539 | -0.014882 | 0.188657 |
| Indo. | -0.204289 | -0.06498 | 0.139309 |
| CuP | α: -0.219543<br>β: -0.219501 | α: -0.024034<br>β: -0.154801 | 0.0647 |
| CuI | α: -0.213538<br>β: -0.213533 | α: -0.072461<br>β: -0.146490 | 0.067043 |

In the copper complexes, the $E_{HOMO}$ and $E_{LUMO}$ are negative (Table 4) which indicates their stability. The complexes have the smallest energy gap (beta), so they are more reactive than the parent ligands since they easily offer electrons to an acceptor.


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## Conclusion

Microbial studies suggested that the copper complexes showed importantly raised antibacterial and antifungal activities and presented higher antimicrobial activity than the corresponding free ligand.

Based on the results of the toxicological study, the acute toxicity of the complexes tested on mice of NMRI strain revealed that the copper - drug complex is generally not toxic. The anti-inflammatory assay study shows that the copper-ligand binding induced an anti-inflammatory effect to the drug molecule, which thus changes the therapeutic class. These experimental tests are corroborated by the DFT study which shows the higher reactivity of the complex with respect to the free ligand.

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