HEMATOLOGICAL SAFETY OF ANTIBACTERIAL FORMULATIONS WITH NATURAL COMPOUNDS: AN EXPERIMENTAL TOXICITY STUDY

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INTRODUCTION: Antimicrobial resistance is a public health concern that compromises the efficacy of widely used antibiotics. The development of innovative therapies that combine antimicrobial efficacy with toxicological safety is urgent. In this context, the association of conventional antibacterial agents with natural compounds emerges as a promising strategy, combining antimicrobial action with antioxidant properties. However, beyond efficacy, it is essential to ensure the non-toxicity of such formulations, especially through *in vivo* hematological analyses, which are sensitive to systemic toxic effects. OBJECTIVE: To evaluate, *in vivo*, the safety of antibiotic associations with natural antibacterial compounds through an oral repeated-dose toxicity study over 28 days (OECD 407). MATERIALS AND METHODS: Forty-eight Wistar rats (both males and females) were randomly assigned to four groups: control (C), nisin 1.25 mg/mL (N), nisin + curcumin 4 mg/mL (NC), and nisin + curcumin + sericin 1 mg/mL (NCS). Except for the control group, all groups also received amoxicillin (3 mg/mL) and 5% bacterial nanocellulose as a drug delivery system, administered orally by gavage (CEUA-Uniso 246/2024). A group receiving only amoxicillin was not included, as its safety profile is already established. At the end of the experiment, the animals were euthanized with ketamine, xylazine, and acepromazine administered intraperitoneally. Blood samples were collected, and hematological analysis was performed using an automated analyzer (Hematology XS 1000i WAS, Roche®). Data were subjected to statistical analysis (ANOVA, Tukey; $p<0.05$). RESULTS AND CONCLUSION: White and red blood cells, hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin showed no statistically significant differences between the treatment groups and the control. However, a significant reduction in mean corpuscular hemoglobin concentration was observed in the NC and NCS groups compared to the control, which may be related to the chelating effect of curcumin on iron metabolism. Additionally, the NCS group showed a significant decrease in platelet count compared to the C and NC groups, indicating a mild antiplatelet effect likely associated with the presence of sericin. Despite

these alterations, the results indicate an acceptable safety profile of the tested formulations, reinforcing the potential *in vivo* use of natural compounds in combination with conventional antibiotics.

Keywords: Antimicrobial resistance; natural compounds; experimental toxicology; hematological parameters.

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