ISBN 978-9940-611-12-5

COAST
INTERNATIONAL CONFERENCE ON ADVANCES IN SCIENCE AND TECHNOLOGY

V INTERNATIONAL CONFERENCE ON
ADVANCES IN SCIENCE AND TECHNOLOGY

PROCEEDINGS COAST 2026

FACULTY OF MANAGEMENT HERCEG NOVI

HERCEG NOVI, MONTENEGRO

09 JUNE – 13 JUNE 2026

FAKULTET ZA MENADŽMENT
HERCEG NOVI

V INTERNATIONAL CONFERENCE ON
ADVANCES IN SCIENCE AND TECHNOLOGY

BOOK OF PROCEEDINGS

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Publisher:
Faculty of Management Herceg Novi

Editor-in-Chief:
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Editors:
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Design and Computer processing:
Zvonko Perušina, BSc

CIP - Каталогизација у публикацији
Национална библиотека Црне Горе, Цетиње

ISBN 978-9940-611-12-5
COBISS.CG-ID 39796484

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The authors have full responsibility for the originality and content of their own papers.

EFFECT OF SALVIA PRATENSIS AND LYTHRUM SALICARIA EXTRACTS ON INTERACTIONS WITH COPPER(II) AMINE COMPLEXES

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ABSTRACT:
The interactions of copper(II) complexes bearing ferrocenyl-containing amine ligands, together with natural extracts from Salvia pratensis root parts and Lythrum salicaria aerial, with human serum albumin (HSA) were investigated using fluorescence spectroscopy. Binding studies were performed in the presence and absence of site markers, ibuprofen and eosin Y, in order to evaluate binding affinity and identify potential binding sites on HSA. The copper(II) complex exhibited moderate interaction with HSA ($K_{sv} \approx 0.5 \times 10^5$ M^{-1}), while a significant increase in binding affinity was observed in the presence of plant extracts, with binding constants reaching $\approx 2.7 \times 10^5$ M^{-1} and up to $\approx 5.1 \times 10^5$ M^{-1}, corresponding to an enhancement of up to tenfold compared to the complex alone. The results obtained in the presence of site markers indicate that the copper(II) complex shows a slight preference for Sudlow site II, whereas in the presence of extracts, altered binding behavior involving alternative or multiple binding sites is observed. The combined systems, comprising the copper(II) complex and plant extracts, demonstrated enhanced and modified binding to HSA, suggesting that plant-derived compounds not only promote but also influence the interaction of the complex with the protein. These findings indicate that natural extracts may affect the transport and biodistribution of copper(II) complexes, highlighting their potential role in modulating the pharmacokinetic behavior of ferrocenyl-containing metal complexes.

Keywords: *copper(II) complex, human serum albumin, binding interactions, natural extract, fluorescence spectroscopy*

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1. INTRODUCTION

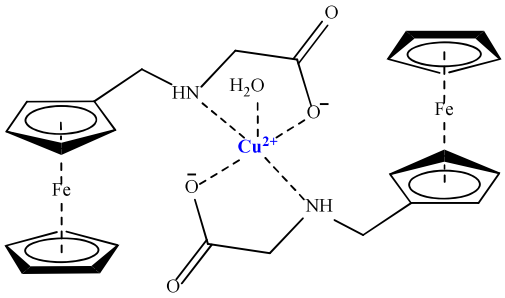
The design of metal-based therapeutic agents has long attracted attention in medicinal inorganic chemistry, as metal ions and their ligands offer a unique combination of coordination geometry, redox activity, and tunable kinetic properties that purely organic compounds cannot replicate.[1] A key factor governing the pharmacological behavior of such compounds is their interaction with human serum albumin (HSA), the most abundant transport protein in human plasma. Since HSA serves as the primary carrier for a wide variety of endogenous and exogenous molecules, understanding how a given compound binds to it is essential for predicting its bioavailability, distribution, and potential for drug-drug interactions.[2]

Among metal-based candidates, copper(II) complexes have emerged as particularly attractive due to their broad spectrum of biological activity, encompassing antibacterial, antifungal, and anticancer effects[3], [4]. The incorporation of a ferrocene unit into the ligand framework contributes favorable properties including chemical stability under physiological conditions, lipophilicity, low toxicity, and a well-defined reversible redox couple. These features have established ferrocene as a versatile platform in bioorganometallic chemistry, with ferrocifen and ferroquine standing as the most recognized examples of ferrocene-containing bioactive molecules targeting breast cancer and malaria, respectively.[5]

The therapeutic relevance of plant-derived extracts has gained increasing recognition, particularly when considered in combination with synthetic metal complexes. Salvia pratensis L., a meadow sage species that has received considerably less scientific attention than Salvia officinalis, has nonetheless proven to be a rich source of biologically active polyphenolic compounds.[6], [7], [8] Its root extract in particular has shown pronounced antimicrobial, antioxidant, and cytotoxic activities, attributable to a high content of phenolic acids including rosmarinic, caffeic, and salvianolic acids.[9] The combination of such extracts with metal complexes may give rise to synergistic interactions that favorably modulate protein binding and broaden therapeutic applicability. This study therefore investigates the binding of a novel ferrocene-based copper(II) complex (Cu1) and its combinations with aqueous root extract of *Salvia pratensis* (SPR) and aerial extracts of *Lythrum salicaria* (LSA) to HSA, with the aim of identifying specific binding sites and assessing the potential of these systems for further pharmacological development.

2. MATERIALS AND METHODS

The effect of aqueous root extract of *Salvia pratensis* (SPR) and aqueous aerial extract of *Lythrum salicaria* (LSA) on the interaction of the tested complex Cu1 (Fig. 1) with human serum albumin (HSA) was studied by fluorescence spectroscopy.[10]



Cu1

Fig. 1. Structural formula of copper(II) complex with ferrocene-based amine ligand

A copper(II) complex with a ferrocene-based amine ligand was synthesized as follows. The amine ligand was prepared from ferrocenecarbaldehyde and aminoester hydrochlorides. The resulting imine was subsequently reduced to an amine using sodium borohydride. The novel copper(II) complex was obtained by stirring a methanolic solution containing 1 mol of $(CH_3COO)_2Cu \cdot H_2O$ and 2 mol of the ligand, followed by overnight reflux.

Interactions between the complex in the presence of each natural extract and human serum albumin (HSA) were investigated using fluorescence spectroscopy. The excitation wavelength was set at 295 nm to selectively excite tryptophan residues, while fluorescence spectra were recorded in the range of 300-500 nm. The examined complex was added to the HSA solution (2 μM) in increasing concentrations (0-4 μM), and fluorescence spectra were recorded after each addition. Fluorescence titration was performed for three systems: (i) the Cu1 complex alone; (ii) the Cu1 complex combined with SPR; and (iii) the Cu1 complex combined with LSA, with the concentration of both extracts being up to 20 μg/L. Additionally, binding affinity experiments were performed in the presence of site marker molecules (ibuprofen and eosin Y) to identify potential binding sites and mechanisms. The Stern-Volmer constant (K_{sv}) values were calculated from the linear relationship between I_0/I and [Q] using the Stern-Volmer equation, serving as a measure of binding affinity.

2.1. RESULTS AND DISCUSSION

This study investigated the effect of aqueous extracts from *S. pratensis* root parts (SPR) and *L. salicaria* aerial (LSA) on the interaction of the copper(II) amine complex Cu1 with human serum albumin (HSA). Fluorescence titration experiments revealed a concentration-dependent reduction in fluorescence intensity upon incremental addition of the complex to the HSA solution. This reduction in fluorescence intensity is attributed to alterations in the tertiary structure of the protein, induced by changes in the microenvironment surrounding the tryptophan residue upon binding of the complex.

The fluorescence emission spectra resulting from the interaction of the Cu1 complex, SPR and LSA extracts, and their respective combinations (Cu1-SPR and Cu1-LSA systems) with HSA were recorded and presented in Fig. 2, while the corresponding binding constants (K_{sv}) derived from Stern-Volmer analysis are listed in Table 1. The Cu1 complex alone exhibited moderate binding affinity toward HSA ($K_{sv} = 0.58 \times 10^5$ M^{-1}). When combined with the SPR extract, the binding affinity increased significantly to 2.7×10^5 M^{-1}, and an even more pronounced enhancement was observed for the Cu1-LSA system, which reached 5.1×10^5 M^{-1}. These results indicate that both plant extracts markedly improve the interaction of the copper(II) complex with HSA, with the *L. salicaria* aerial extract exerting a stronger effect.

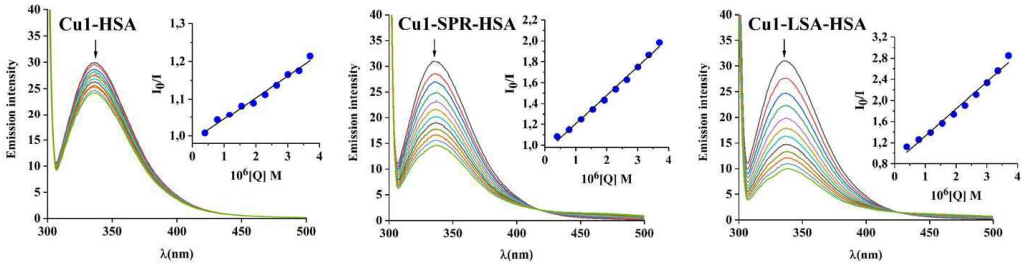


Fig. 2. Emission spectra of HSA in the presence of the Cu1 complex and natural extracts SPR and LSA

Table 1. Interaction constants for the examined complex Cu1 with HSA and site markers in the presence of natural extract *Salvia pratensis* and *Lythrum salicaria*

System	HSA 10^5 K_{sv} [M^{-1}]	HSA-eosine Y 10^5 K_{sv} [M^{-1}]	HSA-ibuprofen 10^5 K_{sv} [M^{-1}]
Cu1	0.58±0.1	0.58±0.1	0.44±0.1
Cu1 - SPR	2.7±0.1	2.6±0.1	2.7±0.1
Cu1 - LSA	5.1±0.1	4.5±0.1	4.3±0.1

To elucidate the binding mechanisms and identify specific binding sites on HSA, fluorescence titration experiments were performed in the presence of site marker molecules eosin Y (Fig.3) and ibuprofen (Fig.4). The results revealed differential binding behavior depending on the site marker used. In the presence of eosin Y, a Site I marker (subdomain IIA), the binding affinity of Cu1 remained unchanged, suggesting that Cu1 does not interact with Site I (subdomain IIA). However, in the presence of ibuprofen, a Site II marker (subdomain IIIA), the binding affinity decreased, indicating that Cu1 preferentially binds at Site II (subdomain IIIA) of HSA, and that ibuprofen competes for the same binding region.

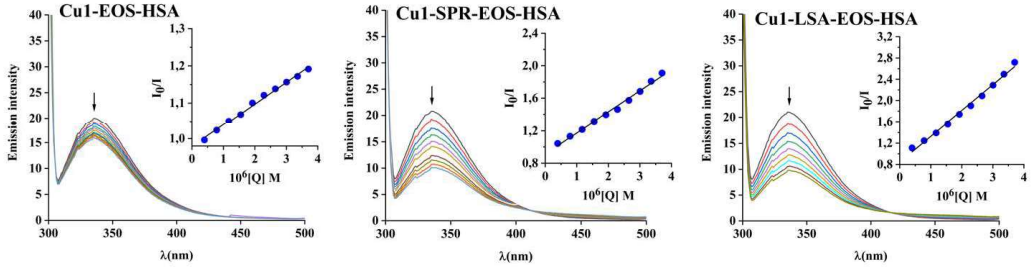


Fig. 3. Emission spectra of HSA and eosin Y in the presence of the Cu1 complex and natural extract SPR and LSA

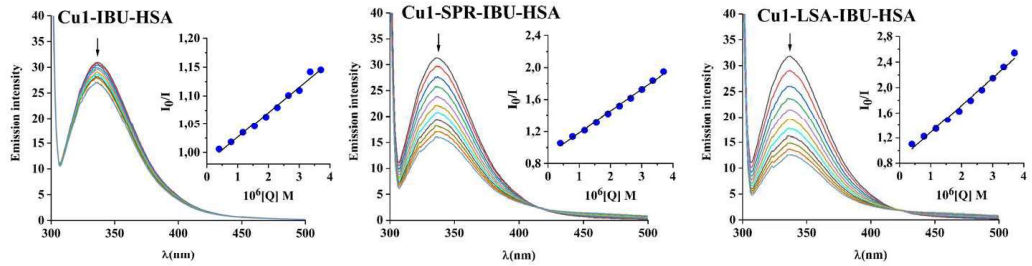


Fig. 4. Emission spectra of HSA and ibuprofen in the presence of the Cu1 complex and natural extract SPA and LSR

For the Cu1-SPR system, the binding affinity remained consistently high across all three systems, with only marginal variations in the presence of either site marker. This suggests that the combination of Cu4 with the SPR extract results in a binding mode that is largely independent of both Site I and Site II, possibly indicating multiple simultaneous binding interactions or a dominant binding mode driven by the bioactive compounds present in the extract.

Notably, the Cu1-LSA system exhibited the highest binding affinities overall. The progressive decrease in binding affinity in the presence of both site markers suggests partial involvement of both Site I (subdomain IIA) and Site II (subdomain IIIA) in the binding of the Cu1-LSA system. These findings indicate that the LSA extract significantly enhances the interaction between the Cu1 complex and HSA, likely through a combination of complementary binding at multiple protein subdomains and conformational changes induced by the bioactive constituents of the extract, resulting in a markedly stronger and broader binding profile compared to Cu1 alone or the Cu1-SPR combination.

3. CONCLUSION

The results of this study demonstrate that the copper(II) complex Cu1 exhibits moderate binding affinity toward HSA on its own, with site marker experiments indicating a preferential interaction with Site II (subdomain IIIA), as evidenced by the decreased binding affinity observed in the presence of ibuprofen and the unchanged affinity in the presence of eosin Y. The combination of Cu1 with the aqueous root extract of *Salvia*

pratensis (SPR) markedly enhances its interaction with HSA, indicating an apparent synergistic effect, while the binding mode shifts toward a site-independent profile, suggesting the involvement of multiple binding interactions driven by the bioactive constituents of the extract. Most notably, the Cu1-LSA system exhibited the highest binding affinities among all investigated systems, with a progressive decrease in the presence of both site markers pointing to partial involvement of both Site I (subdomain IIA) and Site II (subdomain IIIA), indicative of a broader and more complex binding mechanism. These findings highlight the important role of plant-derived bioactive components in modulating metal complex-protein interactions, demonstrating that different plant extracts can distinctly influence both the strength and the mode of binding between copper complexes and HSA. The pronounced enhancement of HSA binding affinity observed particularly in the Cu1-LSA system suggests that combining metal-based therapeutics with natural plant extracts may represent a promising strategy for tuning their pharmacokinetic and biological properties. Future studies should focus on evaluating the potential antimicrobial and anticancer properties of the Cu1-SPR and Cu1-LSA systems, as well as further elucidating the molecular mechanisms underlying the observed synergistic effects.

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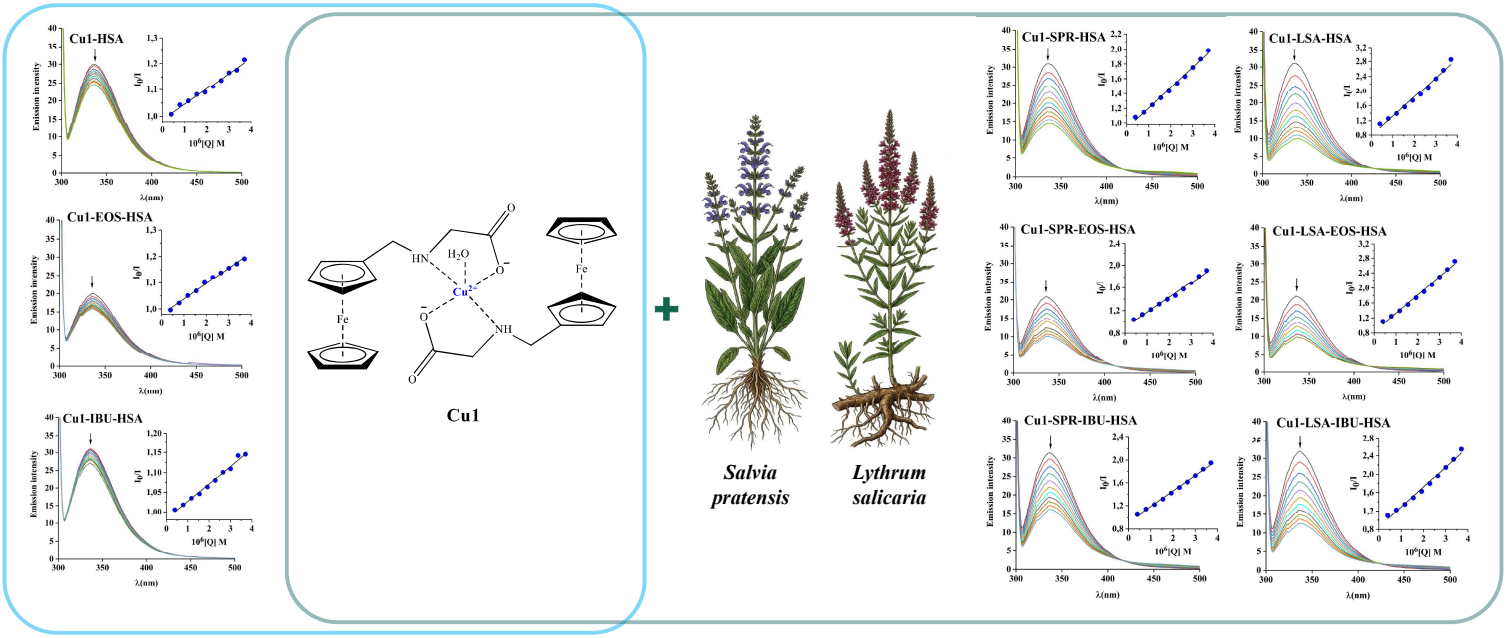

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Zahvalnica

Rad je podržalo Ministarstvo za nauku, tehnološki razvoj i inovacije Republike Srbije (Ugovori br. 451-03-33/2026-03/ 200122 i 451-03-34/2026-03/ 200122).