



# The 9th International Electronic Conference on Medicinal Chemistry (ECMC 2023)

01–30 November 2023 | Online

## Phenolic Compounds as Potential Siderophores

Chaired by **Dr. Alfredo Berzal-Herranz**  
and **Prof. Dr. Maria Emília Sousa**



*pharmaceuticals*



**José R. A. Coelho**<sup>1,\*</sup>, **Maria José G. Fernandes**<sup>1</sup>, and **M. Sameiro T. Gonçalves**<sup>1</sup>

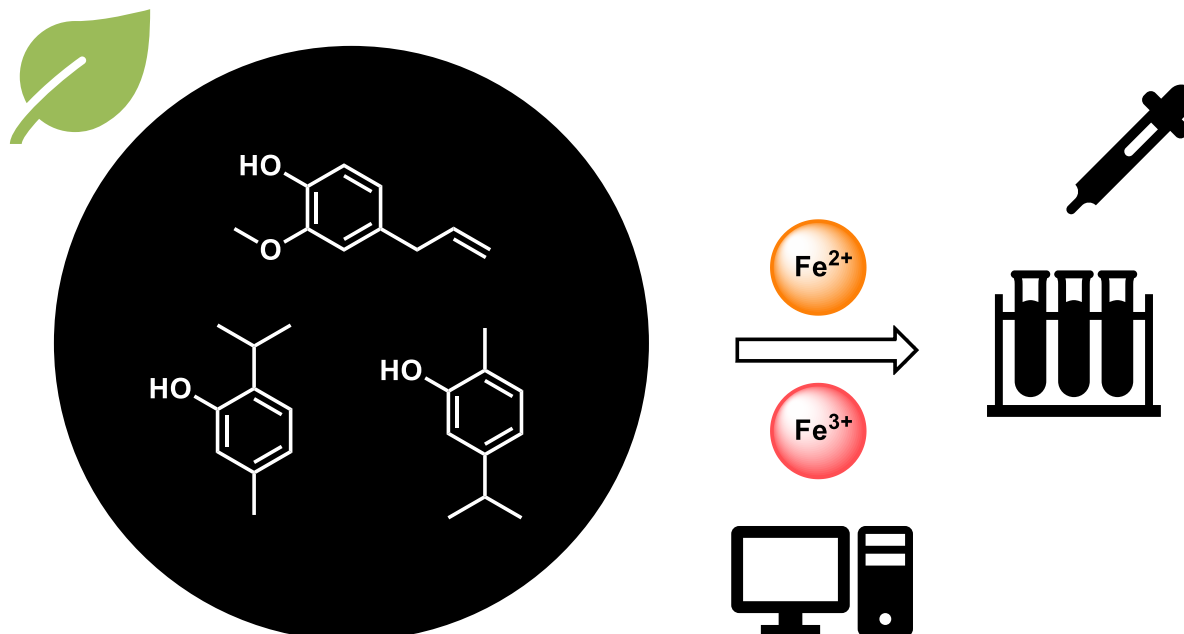
<sup>1</sup> Centre of Chemistry (CQ/UM), University of Minho, Campus of Gualtar, 4710-057 Braga, Portugal.

\* Corresponding author: [a85799@alunos.uminho.pt](mailto:a85799@alunos.uminho.pt)





## Phenolic Compounds as Potential Siderophores





## **Abstract:**

Natural products are a rich source for the design and construction of new biologically or analytically relevant molecules. Multidirectional activity of essential oils (EOs) is widely described in literature: among them antioxidants, antimutagenic, anticarcinogenic, anti-inflammatory, allelopathic, repellent, insecticidal, antiviral, antifungal and antibacterial properties are highlighted. EOs are widely used in food, cosmetic, and pharmaceutical industries. Many EOs are constituted by phenolic compounds, such as eugenol, thymol and carvacrol, where a presence of hydroxyl group makes them potential siderophores, as a small, high-affinity iron-chelating ligands. Iron acquisition through siderophores is a widely spread strategy among pathogens, in environmental research. For instance, siderophores function as biocontrols, biosensors, and bioremediation and chelation agents. Considering these facts, the chelation of some EOs are evaluated by UV-vis absorption spectroscopy in relation to various metal cations, as potential ligands.

**Keywords:** Essential Oils, Metals, Phenolic Compounds, Siderophores.



## Introduction

A **siderophore** is a small molecule or compound that is produced by microorganisms, such as bacteria and fungi, as well as some plants, to facilitate the uptake of iron from the environment [1,2].

Iron is an essential nutrient for many living organisms because it plays a critical role in various biological processes, including oxygen transport, energy production, and DNA synthesis.

**Siderophores** are specialized molecules that can bind to iron (preferentially  $\text{Fe}^{3+}$ ) and form a complex that is more soluble and can be easily taken up by the organism. This allows the microorganism to acquire the iron it needs for growth and metabolic processes [3].

[1] Ahmed, E; Holmström, S. J. *Microb Biotechnol.* **2014**, *7*, 196–208.

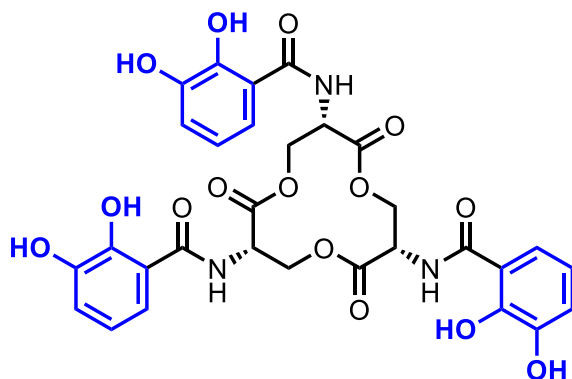
[2] Roskova, Z.; Skarohlid, R.; McGachy, L. *Sci Total Environ.* **2022**, *819*, 153144.

[3] Kurth, C.; Kage, H.; Nett, M. *Org Biomol Chem.* **2016**, *14*, 8212– 8227.

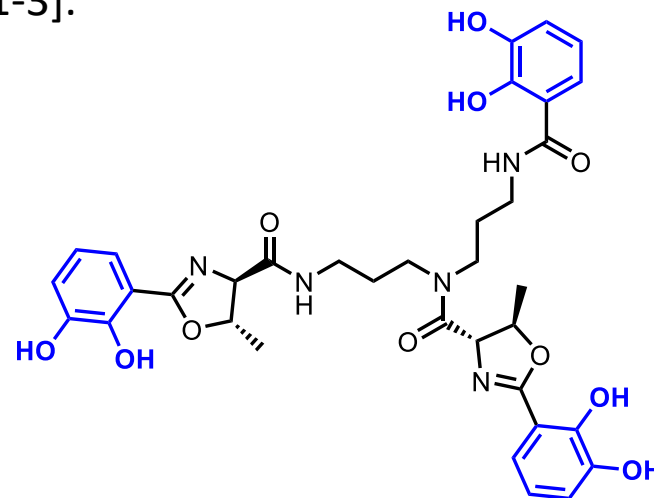


## Introduction

**Siderophores** usually form a stable complex preferentially with  $\text{Fe}^{3+}$  ion. The most effective siderophores are those that have three bidentate ligands per molecule, forming a hexadentate complex. They are usually classified by the ligands used to chelate the ferric iron, where one major groups include phenolic compounds (catechol nucleus) [1-3].



**Enterobactin**  
*Escherichia coli*



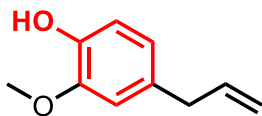
**Vibriobactin**  
*Vibrio cholerae*

- [1] Ahmed, E; Holmström, S. J. *Microb Biotechnol.* **2014**, *7*, 196–208.  
[2] Roskova, Z.; Skarohlid, R.; McGachy, L. *Sci Total Environ.* **2022**, *819*, 153144.  
[3] Kurth, C.; Kage, H.; Nett, M. *Org Biomol Chem.* **2016**, *14*, 8212– 8227.

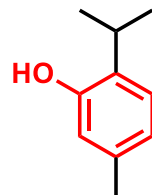


## Introduction

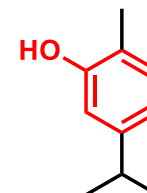
**Essential oils** (EOs) are complex and synergetic mixtures that have promising antioxidant activities, mainly due to the presence of **phenolic compounds** which are gaining interest as natural alternatives to synthetic antioxidants in food and cosmetic industries [4,5].



**Eugenol**  
*Syzygium aromaticum*



**Thymol**  
*Thymus vulgaris*



**Carvacrol**  
*Origanum vulgare*

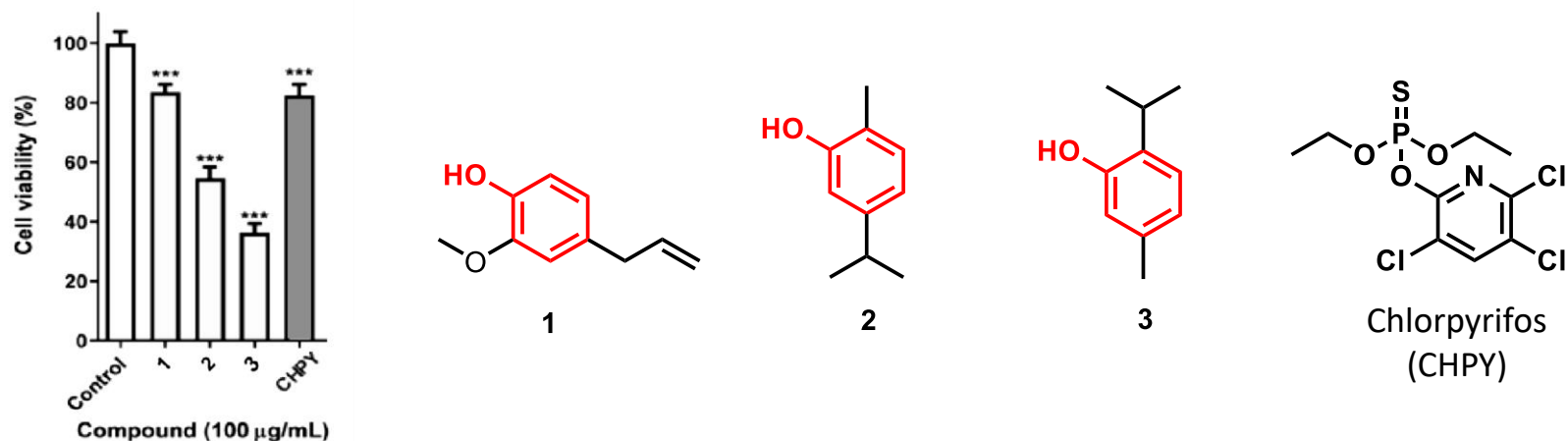
[4] Hassoun, A.; Çoban, Ö. E. *Trends Food Sci. Technol.* **2017**, *68*, 26–36.

[5] Singh, A.; Sheikh, J. *ACS Omega*, **2023**, *8*, 10214–10224.



## Introduction

In previous studies, the selected essential oils were tested on *Sf9* cell line [6].



**Figure 1.** Viability of *Sf9* insect cells exposed to the molecules under study 1–3 and CHPY (100 µg/mL), or medium (control). \*\*\*  $p < 0.001$ .

Phenolic compounds from EOs could be a good starting point for building siderophores. The presence of the hydroxyl group represents an excellent ligand for coordinating with the ferric ion.

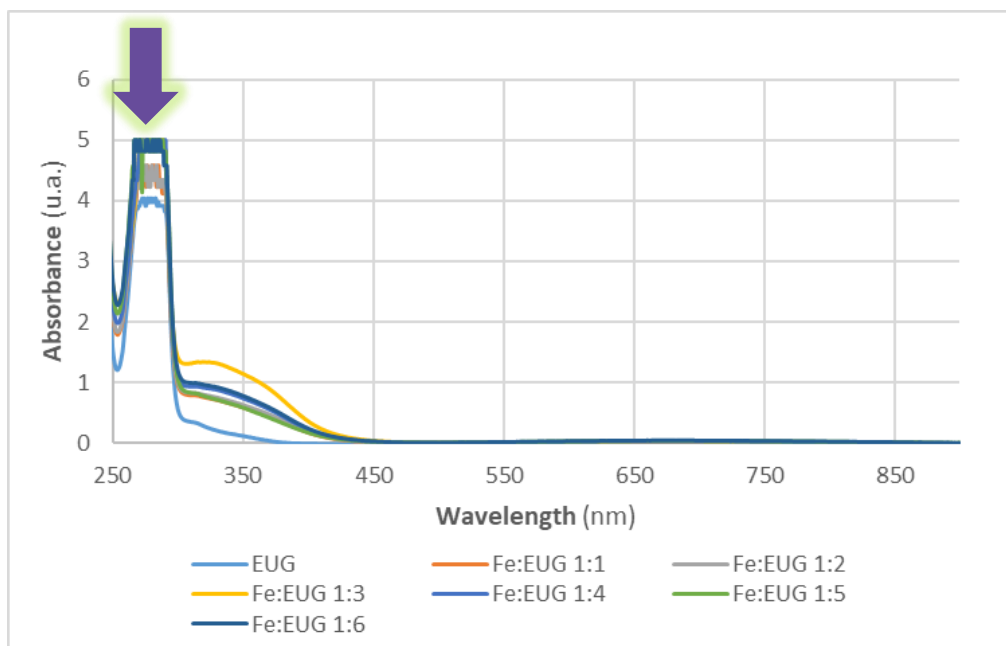




## Results and discussion

### *UV-vis Spectroscopy*

The UV–vis spectra of eugenol and different systems iron(II)–eugenol (Fe:EUG) obtained in EtOH are show in Figure 1.



One characteristic electronic transition of phenolic compounds ( $\pi \rightarrow \pi^*$ ) can be observed in the near UV region at 270 nm.

[EUG] = 1.5 mM

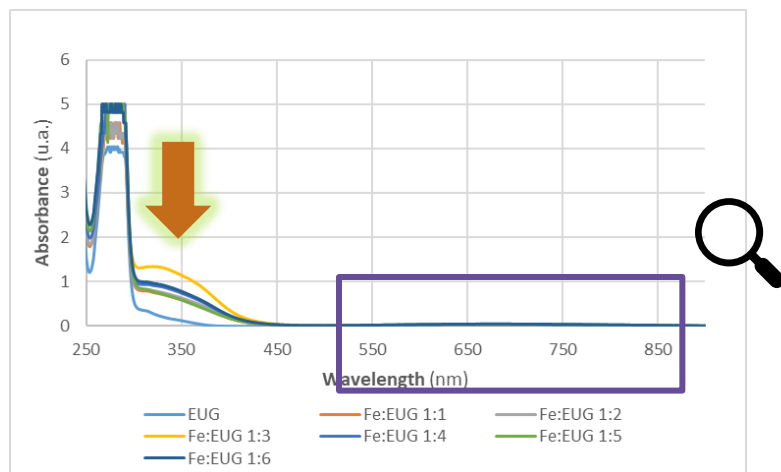
**Figure 2.** Absorption spectra of interaction between Fe(II) ions and eugenol.





## Results and discussion

### UV-vis Spectroscopy



In the absorption spectra, in the range from 520 to 870 nm, a broad and intense band appears in the eugenol spectrum (Figure 2) with  $\lambda_{\max}$  at 680 nm.



Fe:EUG 1:1 Fe:EUG 1:2 Fe:EUG 1:3 Fe:EUG 1:4 Fe:EUG 1:5 Fe:EUG 1:6

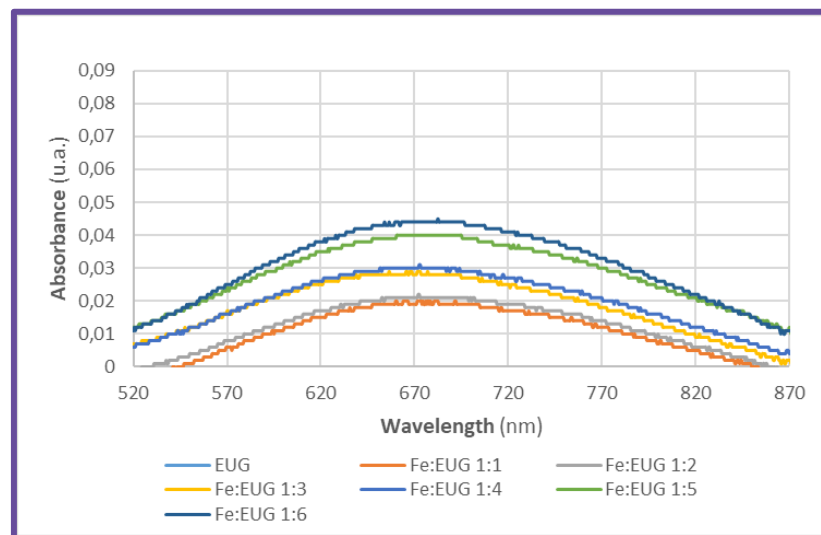
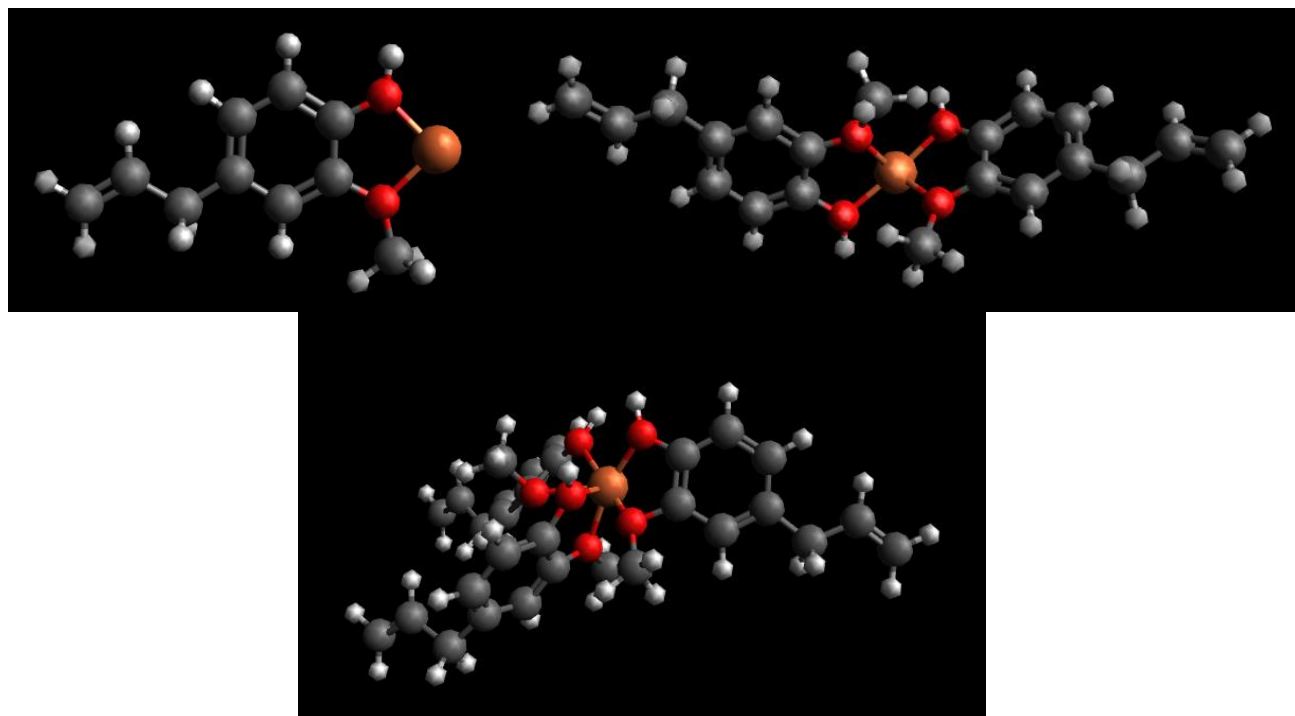


Figure 3. *d-d* transition of  $d^6$  complex Fe-EUG.



## Results and discussion

### *Computational Analysis*



**Figure 4.** Optimized structure of iron complexes with eugenol in *Avogadro*<sup>®</sup>.



## Results and discussion

### *Computational Analysis*

Density functional calculations were performed using the hybrid B3LYP functional. The CBSB7 atomic basis is well-known for computing fully accurate energies of the organic and inorganic compounds, was used for all the atoms.

The theoretical models were built considering the direct interactions between iron(II) and iron(III) ions with different numbers of carvacrol, thymol and eugenol ligands ( $x$ ). The final charge of the complex formed depends on the oxidation state of the metal center ( $n$ ).

The electronic bonding energies of the optimized coordinated iron complexes, named here in as  $\Delta E_{bond}$ , were obtained in the gas and solution phase through following equation:

$$\Delta E_{bond} = [E([FeL_x]^{n+}) - (E(L) + E([FeL_{x-1}]^{n+}))]$$



## Results and discussion

### *Computational Analysis*

The zero-point energy corrections were calculated using the harmonic approximation at the B3LYP/CBSB7 level of theory. All calculations were performed with Gaussian 09W program.

The main results of the stable complex of Fe(II) and Fe(III) and their bonding energies are show in Table 2.

**Table 1.** B3LYP/CBSB7 bonding energies  $\Delta E_{\text{bond}}$  in the gas-phase/water solution in kcal/mol.

Ligand number	Fe <sup>2+</sup>			Fe <sup>3+</sup>		
	Eugenol	Thymol	Carvacrol	Eugenol	Thymol	Carvacrol
1	-186.76/-17.20	-132.64/-7.01	-150.25/-8.98	-177.72/-8.52	-102.29/-6.23	-120.61/-8.11
2	-99.40/-15.04	-112.57/-5.28	-126.36/-6.18	-93.96/-6.08	-79.39/-4.31	-94.32/-5.22
3 <sup>a</sup>	-47.98/-8.76			-38.65/-4.43		
3 <sup>b</sup>	-56.64/-12.82			-27.09/-3.56		

<sup>a</sup>For distorted square pyramidal geometry.

<sup>b</sup>For distorted octahedral geometry.



## Results and discussion

### *Computational Analysis*

**Table 1.** B3LYP/CBSB7 bonding energies  $\Delta E_{\text{bond}}$  in the gas-phase/water solution in kcal/mol.

Ligand number	Fe <sup>2+</sup>			Fe <sup>3+</sup>		
	Eugenol	Thymol	Carvacrol	Eugenol	Thymol	Carvacrol
1	-186.76/-17.20	-132.64/-7.01	-150.25/-8.98	-177.72/-8.52	-102.29/-6.23	-120.61/-8.11
2	-99.40/-15.04	-112.57/-5.28	-126.36/-6.18	-93.96/-6.08	-79.39/-4.31	-94.32/-5.22
3 <sup>a</sup>	-47.98/-8.76			-38.65/-4.43		
3 <sup>b</sup>	-56.64/-12.82			-27.09/-3.56		

<sup>a</sup>For distorted square pyramidal geometry.

<sup>b</sup>For distorted octahedral geometry.

- ❑ Eugenol has a more favorable thermodynamic environment for the direct interaction of the Fe(II) and Fe(III) ions, because can act as a bidentate ligand and form chelates, compared to thymol and carvacrol.
- ❑ The presence of the methoxy group can justify the greater chelating activity of eugenol in comparison to remaining phenols.
- ❑ All the phenolic compounds studied tend to complex more easily with Fe(II) ions.



## Results and discussion

### *Computational Analysis*

**Table 1.** B3LYP/CBSB7 bonding energies  $\Delta E_{\text{bond}}$  in the gas-phase/water solution in kcal/mol.

Ligand number	Fe <sup>2+</sup>			Fe <sup>3+</sup>		
	Eugenol	Thymol	Carvacrol	Eugenol	Thymol	Carvacrol
1	-186.76/-17.20	-132.64/-7.01	-150.25/-8.98	-177.72/-8.52	-102.29/-6.23	-120.61/-8.11
2	-99.40/-15.04	-112.57/-5.28	-126.36/-6.18	-93.96/-6.08	-79.39/-4.31	-94.32/-5.22
3 <sup>a</sup>	-47.98/-8.76			-38.65/-4.43		
3 <sup>b</sup>	-56.64/-12.82			-27.09/-3.56		

<sup>a</sup>For distorted square pyramidal geometry.

<sup>b</sup>For distorted octahedral geometry.

- In the carvacrol and thymol cases, the third ligand was not able to coordinate with respective cations. This fact can be due to the steric effect (isopropyl chain), which makes the approximation of the third ligand more difficult.



## Conclusions

The absorption spectra of eugenol underwent strong changes after interaction with iron(II) ions. The Fe(II) complex with eugenol is blue in colour and has a  $\lambda_{\max}$  of 315 and 680 nm.

Based on the computational study carried out, eugenol tends to complex more easily with iron ions than thymol and carvacrol, because the complexes formed are thermodynamically more stable due to the chelate effect caused by the methoxyl group.

Studies of biological activity of iron complexes against the *Sf9* cell lines are being carried out to evaluate the potential insecticidal activity.





## Acknowledgments

The authors acknowledge to Foundation for Science and Technology (FCT, Portugal), and FEDER-COMPETE-QREN-EU for financial support to the research centres CQ-UM (UID/QUI/00686/2020) and REQUIMTE (UIDB/50006/2020). The NMR spectrometer Bruker Avance III 400 is part of the National NMR Network and was purchased within the framework of the National Program for Scientific Re-equipment, contract REDE/1517/RMN/2005 with funds from POCI 2010 (FEDER) and FCT.

