Libyan Journal of Medical and Applied Sciences LJMAS
Online ISSN: 3006-1113
Volume 3, Issue 4, 2025, Page No: 73-78
Website: https://ljmas.com/index.php/journal/index

Use of Wild Thyme Plant Extracts as Natural Ligands for the Synthesis of Metal Complexes and Evaluation of Their Efficacy as Inhibitors of Tumor-Associated Enzymes

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Received: September 02, 2025 Accepted: October 30, 2025 Published: November 04, 2025

Cite this article as: A, Y, Alnaas., A, F, zawia., H, K. Ibrahim. (2025). Use of Wild Thyme Plant Extracts as Natural Ligands for the Synthesis of Metal Complexes and Evaluation of Their Efficacy as Inhibitors of Tumor-Associated Enzymes. Libyan Journal of Medical and Applied Sciences (LJMAS). 2025;3(4):73-78.

Abstract

The present investigation explores the utilization of wild thyme (*Thymus vulgaris*) plant extracts as natural ligands for synthesizing novel metal complexes and evaluating their potential as inhibitors of tumor-associated enzymes. Three distinct metal complexes were synthesized using Cu (II), Zn (II), and Co (II) salts with ethanolic extracts of wild thyme, which contain phenolic compounds such as thymol, carvacrol, and rosmarinic acid. The synthesized complexes were characterized through various spectroscopic techniques including FT-IR, UV-Visible spectroscopy, ^{1}H NMR, ESI-MS, and thermogravimetric analysis. Physicochemical properties revealed successful coordination of thyme constituents to metal centers, with molar conductivity values indicating non-electrolytic nature. The biological evaluation focused on inhibitory activities against tyrosinase and carbonic anhydrase IX, both crucial enzymes in tumor progression and metastasis. Results demonstrated that the Cu (II)-thyme complex exhibited the highest inhibitory activity against tyrosinase with an IC_{50} value of 12.3 µM, while the Zn (II)-thyme complex showed superior carbonic anhydrase IX inhibition (IC_{50} = 8.7 µM). These findings suggest that metal complexation enhances the bioactivity of natural thyme constituents, providing a promising avenue for developing novel anticancer agents based on bioinorganic chemistry principles.

Keywords: Wild Thyme, Metal Complexes, Bioinorganic Chemistry, Tyrosinase Inhibition, Carbonic Anhydrase, Tumor-Associated Enzymes, Natural Ligands.

استخدام مستخلصات نبات الزعتر البري كليغاندات طبيعية في تحضير معقدات معدنية وتقييم فعاليتها كمثبّطات للإنزيمات المرتبطة بالأورام

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الملخص

تستكشف الدراسة الحالية استخدام المستخلصات النباتية من الزعتر البري (Thymus vulgaris) كليغاندات طبيعية في تحضير معقدات معدنية جديدة وتقييم فعاليتها المحتملة كمثبّطات للإنزيمات المرتبطة بالأورام. تم تحضير ثلاث معقدات معدنية مميزة باستخدام أملاح النحاس (II)، والزنك (II)، والكوبالت (II) مع المستخلص الكحولي للزعتر البري، الذي يحتوي على مركبات فينولية مثل الثيمول، والكارفاكرول، وحمض الروزمارينيك. وقد تم توصيف هذه المعقدات المحضَّرة باستخدام تقنيات طيفية متنوعة، شملت مطيافية الأشعة تحت الحمراء Fourier Transform (FT-IR)، ومطيافية الأشعة فوق البنفسجية-المرئية (UV-Visible)، ورنين مغناطيسي نووي البروتون (^{1}H NMR)، وتحليل الطيف الكتلي المُشَتَّت كهربائيًّا (ESI-MS)، إضافةً إلى التحليل الحراري الوزني (TGA). وأظهرت الخصائص الفيزيوكيميائية نجاح ارتباط مكونات الزعتر بمراكز المعادن، حيث أشارت قيم التوصيل المولاري إلى الطبيعة غير الإلكتروليتية لهذه المعقدات.

ركّز التقييم البيولوجي على النشاط التثبيطي ضد إنزيمي التيروسيناز وأنهيدراز الكربونيك IX، وهما إنزيمان حاسمان في تقدُّم الورم وانتشاره. أظهرت النتائج أن معقد النحاس (II)-الزعتر كان الأعلى فعالية في تثبيط إنزيم التيروسيناز، إذ بلغت

قيمته نصف القصوى للتثبيط 12.3 (IC_{50}) ميكرومولاًر، في حين تفوّق معقد الزنك (II)-الزعتر في تثبيط إنزيم أنهيدراز الكربونيك IX (IC_{50} = 8.7 ميكرومولاًر).
تشير هذه النتائج إلى أن تكوين المعقدات المعدنية يعزز الفعالية البيولوجية لمكونات الزعتر الطبيعية، مما يفتح آفاقًا واعدة لتطوير عوامل مضادة للسرطان مبنية على مبادئ الكيمياء الحيوية غير العضوية.

الكلمات المفتاحية: الزعتر البري، معقدات معدنية، كيمياء حيوية غير عضوية، تثبيط إنزيم التيروسيناز، أنهيدراز الكربونيك، إنزيمات مرتبطة بالأورام، ليغاندات طبيعية.

Introduction

The intersection of inorganic chemistry and biological systems has emerged as a fascinating field that continues to yield innovative therapeutic approaches for various diseases, particularly cancer. Metal complexes have garnered significant attention in medicinal chemistry due to their unique properties, including variable oxidation states, diverse coordination geometries, and the ability to interact with biological targets through multiple mechanisms [1]. The success of platinum-based anticancer drugs such as cisplatin has paved the way for exploring other transition metals and their complexes as potential therapeutic agents.

In recent years, there has been a growing interest in developing metal complexes using natural products as ligands, combining the benefits of traditional medicine with modern coordination chemistry. This approach addresses several limitations associated with synthetic drugs, including toxicity, resistance, and limited selectivity [2]. Natural products possess inherent bioactivity and often exhibit lower toxicity profiles compared to purely synthetic compounds, making them attractive candidates for drug development.

Wild thyme (*Thymus vulgaris*) represents one of the most extensively studied medicinal plants, belonging to the Lamiaceae family. This aromatic herb has been traditionally used for its antimicrobial, antioxidant, and anti-inflammatory properties across various cultures. The phytochemical composition of wild thyme is particularly rich in phenolic compounds, including thymol (2-isopropyl-5-methylphenol), carvacrol (5-isopropyl-2-methylphenol), rosmarinic acid, and various flavonoids such as apigenin and luteolin [3]. These compounds possess multiple functional groups, including hydroxyl, carboxyl, and aromatic systems, which can serve as potential coordination sites for metal ions.

The phenolic nature of thyme constituents is particularly significant from a coordination chemistry perspective. Phenolic compounds can act as chelating ligands through their hydroxyl groups, forming stable complexes with transition metals. The presence of extended π-conjugated systems in these molecules also enables additional interactions through π-π stacking and metal-π bonding, potentially enhancing the stability and biological activity of the resulting complexes [4].

Cancer remains one of the leading causes of mortality worldwide, with tumor progression involving complex enzymatic pathways. Among the various enzymes associated with tumorigenesis, tyrosinase and carbonic anhydrase IX (CA-IX) have emerged as significant therapeutic targets. Tyrosinase, a copper-containing oxidase, plays a crucial role in melanin biosynthesis and is overexpressed in melanoma cells. Beyond its role in pigmentation, tyrosinase is involved in tumor progression, angiogenesis, and metastasis through various signaling pathways [5].

Carbonic anhydrase IX represents another important target in cancer therapy. This enzyme is highly expressed in hypoxic tumor environments and contributes to pH regulation, tumor cell survival, invasion, and metastasis. CA-IX catalyzes the reversible hydration of carbon dioxide to bicarbonate and protons, thereby maintaining the acidic extracellular environment that favors tumor growth and progression. The selective expression of CA-IX in tumor tissues, with minimal expression in normal tissues, makes it an attractive target for anticancer drug development [6].

The rational design of metal complexes as enzyme inhibitors involves understanding the coordination preferences of different metal ions and their interaction mechanisms with target enzymes. Copper (II) complexes are particularly relevant for tyrosinase inhibition due to the presence of copper in the enzyme's active site, potentially allowing for competitive inhibition or allosteric modulation. Zinc (II) and cobalt (II) complexes have shown promise as carbonic anhydrase inhibitors, often through coordination to the zinc ion in the enzyme's active site or through alternative binding mechanisms [7].

Despite the growing interest in natural product-metal complexes, there remains a significant gap in understanding the structure-activity relationships governing their biological activities. Most studies have focused on isolated natural compounds or simple synthetic ligands, with limited exploration of crude plant extracts as ligand sources. The use of plant extracts offers the advantage of synergistic effects between multiple bioactive compounds, potentially leading to enhanced therapeutic efficacy and reduced resistance development.

The present study aims to bridge this knowledge gap by investigating the synthesis and characterization of metal complexes using wild thyme extracts as natural ligands. The specific objectives include: (1) extraction and preliminary characterization of bioactive compounds from wild thyme, (2) synthesis of Cu (II), Zn (II), and Co (II) complexes using thyme extracts, (3) comprehensive characterization of the synthesized complexes using spectroscopic and analytical techniques, and (4) evaluation of their inhibitory activities against tyrosinase and

carbonic anhydrase IX enzymes. This multidisciplinary approach combines principles of natural product chemistry, coordination chemistry, and enzymology to develop potential anticancer agents based on bioinorganic chemistry concepts.

Materials and Methods

Materials and Chemicals

Wild thyme (*Thymus vulgaris*) was collected from the Mediterranean region during the flowering season and authenticated by botanical experts. All metal salts including Cu $(NO_3)_2 \cdot 3H_2O$, Zn $(NO_3)_2 \cdot 6H_2O$, and Co $(NO_3)_2 \cdot 6H_2O$ were purchased from Sigma-Aldrich (≥99% purity). Ethanol, methanol, and dimethyl sulfoxide (DMSO) were obtained from Merck. Mushroom tyrosinase (EC 1.14.18.1), L-DOPA, carbonic anhydrase IX human recombinant enzyme, and 4-nitrophenyl acetate were procured from Sigma-Aldrich. All other reagents were of analytical grade and used without further purification.

Plant Extract Preparation

Dried wild thyme leaves (100 g) were ground to a fine powder and subjected to Soxhlet extraction using 95% ethanol (500 mL) for 8 hours at 78°C. The extract was concentrated under reduced pressure using a rotary evaporator at 40°C to yield a dark green residue. The concentrated extract was stored at -20°C until further use. Preliminary phytochemical screening confirmed the presence of phenolic compounds, flavonoids, and terpenoids using standard qualitative tests.

Synthesis of Metal Complexes

Metal complexes were synthesized using a modified method adapted from literature. For each complex, a 1:2 molar ratio of metal salt to extract (calculated based on average molecular weight of major phenolic constituents) was employed. The ethanolic thyme extract (0.5 g dissolved in 20 mL ethanol) was added dropwise to a stirred solution of the respective metal nitrate (0.2 mmol) in 15 mL distilled water. The pH was adjusted to 7-8 using dilute sodium hydroxide solution. The reaction mixture was refluxed for 4 hours at 80°C with continuous stirring. The resulting precipitate was filtered, washed with cold ethanol and distilled water, and dried in a vacuum oven at 60°C for 24 hours.

Characterization Techniques

Fourier Transform Infrared (FT-IR) spectra were recorded on a Perkin-Elmer Spectrum 100 spectrometer using KBr pellets in the range 4000-400 cm^{-1}. UV-Visible absorption spectra were obtained using a Shimadzu UV-2600 spectrophotometer in DMSO solution (1×10^{-4} M). ^1H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using DMSO-d_6 as solvent. Electrospray ionization mass spectrometry (ESI-MS) was performed on a Waters Micromass Q-TOF Premier instrument. Thermogravimetric analysis (TGA) was conducted using a TA Instruments Q500 analyzer under nitrogen atmosphere with a heating rate of 10°C/min from room temperature to 800°C. Molar conductivity measurements were performed using a Jenway 4510 conductivity meter in DMSO solution (1×10^{-3} M) at 25°C.

Enzyme Inhibition Assays

Tyrosinase inhibition activity was evaluated using L-DOPA as substrate according to the modified method of Pomerantz. The reaction mixture contained phosphate buffer (50 mM, pH 6.8), mushroom tyrosinase (100 units), test compound at various concentrations, and L-DOPA (2 mM). The formation of dopachrome was monitored spectrophotometrically at 475 nm for 5 minutes. Kojic acid was used as positive control.

Carbonic anhydrase IX inhibition was assessed using the esterase activity assay with 4-nitrophenyl acetate as substrate. The assay mixture contained Tris-HCl buffer (20 mM, pH 8.0), human recombinant CA-IX (0.1 μM), test compound, and substrate (1 mM). The hydrolysis of 4-nitrophenyl acetate was monitored at 405 nm. Acetazolamide served as the reference inhibitor. IC_{50} values were calculated using non-linear regression analysis.

Results

Physicochemical Properties

Table 1: Physicochemical properties of synthesized metal complexes with wild thyme extract

Physicochemical properties	complex		
	Cu-Thyme	Zn-Thyme	Co-Thyme
Yield (%)	73.2	68.7	71.8
M.P. (°C)	248-252	235-239	258-262
Color	Dark green	Light yellow	Brownish-red

Solubility	DMSO, DMF	DMSO, MeOH	DMSO, DMF
Proposed Formula	$[Cu(L)_2(H_2O)_2]$	$[Zn(L)_2(H_2O)_2]$	$[Co(L)_2(H_2O)_2]$
Molar Conductivity (S·cm2·mol-1)	18.4	15.2	16.9

The synthesized complexes exhibited moderate to good yields with distinct colors characteristic of their respective metal centers. Low molar conductivity values indicate non-electrolytic behavior, suggesting coordination of the ligands to metal centers. The proposed molecular formulas assume bidentate coordination of the major phenolic constituents (L = deprotonated phenolic ligand). All complexes showed limited solubility in polar protic solvents but good solubility in polar aprotic solvents.

Spectroscopic Characterization

Table 2: Spectroscopic characterization data of metal complexes

Spectroscopic Characterization	Complex		
	Cu-Thyme	**Zn-Thyme**	**Co-Thyme**
FT-IR (cm^{-1})	3425 (O-H), 1598 (C=C), 1385 (C-O), 521 (M-O)	3441 (O-H), 1605 (C=C), 1378 (C-O), 498 (M-O)	3438 (O-H), 1592 (C=C), 1382 (C-O), 512 (M-O)
UV-Vis λ_{max} (nm)	285, 324, 598	278, 318, 365	282, 326, 485, 652
^{1}H NMR (δ, ppm)	6.78-7.42 (Ar-H), 2.28 (CH3), 1.18 ($CH(CH_3)_2$)	6.82-7.38 (Ar-H), 2.31 (CH3), 1.21 ($CH(CH_3)_2$)	6.75-7.45 (Ar-H), 2.26 (CH_3), 1.16 ($CH(CH_3)_2$)
ESI-MS $[M+H]^+$	542.2	548.3	541.8

FT-IR spectra confirmed successful coordination through shifts in O-H and C-O stretching frequencies compared to free ligand. The appearance of new bands in the 498-521 cm^{-1} region indicates M-O bond formation. UV-Visible spectra showed characteristic d-d transitions for Cu (II) and Co (II) complexes, while the Zn (II) complex exhibited only ligand-to-metal charge transfer bands. ^{1}H NMR data revealed slight downfield shifts of aromatic protons upon complexation, consistent with coordination through phenolic oxygen atoms. ESI-MS confirmed the proposed molecular compositions.

Enzyme Inhibition Studies

Table 3: Enzyme inhibitory activities of metal complexes

Compound	Tyrosinase IC50 (µM)	CA-IX IC50 (µM)	Selectivity Index*
Free Extract	45.6 ± 3.2	38.7 ± 2.8	1.18
Cu-Thyme	12.3 ± 1.1	15.4 ± 1.3	0.8
Zn-Thyme	28.9 ± 2.4	8.7 ± 0.9	3.32
Co-Thyme	21.7 ± 1.8	18.2 ± 1.6	1.19
Kojic acid	16.8 ± 1.4	-	-
Acetazolamide	-	12.1 ± 1.0	-

*Selectivity Index = IC_{50} (CA-IX)/IC_{50} (Tyrosinase). Values represent mean ± standard deviation (n=3). The Cu-Thyme complex demonstrated superior tyrosinase inhibition, showing 3.7-fold enhancement compared to the free extract. The Zn-Thyme complex exhibited the highest potency against CA-IX with excellent selectivity. All metal complexes showed improved inhibitory activities compared to the free plant extract, indicating successful enhancement of bioactivity through metal coordination. The Co-Thyme complex displayed balanced inhibition against both enzymes.

Discussion

The successful synthesis and characterization of metal complexes using wild thyme extracts represent a significant advancement in the field of bioinorganic medicinal chemistry. The physicochemical properties of the synthesized

complexes align well with previous reports on phenolic-metal coordination compounds, though the use of crude plant extracts introduces additional complexity compared to studies utilizing pure compounds [8].

The spectroscopic characterization data provide compelling evidence for successful coordination of thyme constituents to the metal centers. The FT-IR spectral changes, particularly the shifts in O-H stretching frequencies from approximately 3550 cm-1 in the free extract to 3425-3441 cm-1 in the complexes, suggest coordination through phenolic hydroxyl groups. This observation is consistent with the coordination behavior of similar phenolic compounds reported by [9], who observed comparable shifts in plant extract-metal complexes.

The UV-Visible spectroscopic data reveal interesting coordination chemistry insights. The Cu (II)-thyme complex exhibits a broad absorption band at 598 nm, characteristic of d-d transitions in octahedral Cu (II) complexes with some distortion. This wavelength is similar to that reported for Cu (II)-phenolic complexes by [10], suggesting similar coordination environments. The Co (II) complex shows two distinct d-d transition bands at 485 and 652 nm, indicating an octahedral geometry with some tetragonal distortion, consistent with the proposed structure containing two water molecules in axial positions.

The enzyme inhibition results demonstrate remarkable enhancement of biological activity upon metal complexation. The 3.7-fold improvement in tyrosinase inhibition observed for the Cu (II) complex compared to the free extract can be attributed to several factors. First, the presence of copper in both the inhibitor and the enzyme active site may facilitate competitive inhibition through metal-metal interactions. Second, the coordination of phenolic compounds to copper may enhance their binding affinity to the enzyme through additional coordination interactions, as suggested by the molecular docking studies conducted by [11] on similar systems.

The exceptional performance of the Zn (II)-thyme complex against carbonic anhydrase IX (IC50 = 8.7 μM) warrants particular attention. This potency approaches that of clinically used CA inhibitors and significantly exceeds the activity of the free extract. Zinc plays a crucial role in CA-IX catalytic activity, and the inhibition mechanism likely involves displacement of the catalytic zinc ion or coordination to alternative binding sites. The selectivity index of 3.32 for the Zn (II) complex suggests preferential inhibition of CA-IX over tyrosinase, which is advantageous for targeted anticancer therapy.

Comparing our results with recent literature, [12] reported IC50 values of 0.5-1.2 μM for various plant extract-metal complexes against tyrosinase, while our Cu (II)-thyme complex achieved 12.3 μM, indicating comparable activity. Similarly, the CA-IX inhibition data compares favorably with the study by [13], who reported IC50 values of 8-20 μM for plant-based enzyme inhibitors.

The structure-activity relationships observed in this study align with established principles in bioinorganic chemistry. The superior tyrosinase inhibition by the Cu (II) complex can be rationalized by the matching of metal ions between inhibitor and enzyme, facilitating more effective binding interactions. The enhanced CA-IX inhibition by the Zn (II) complex similarly reflects the zinc-dependent nature of the target enzyme. The Co (II) complex showed intermediate activity against both enzymes, which may be attributed to its ability to undergo ligand exchange reactions more readily than the other complexes.

The synergistic effects of multiple bioactive compounds present in the thyme extract likely contribute to the observed activities. Unlike studies using isolated compounds, the crude extract contains thymol, carvacrol, rosmarinic acid, and various flavonoids that can coordinate simultaneously or sequentially to the metal center, potentially creating a more complex and effective inhibitor structure. This multi-component approach aligns with the growing recognition of synergistic effects in natural product-based drug development [14]

The thermal stability data from TGA analysis (not shown in tables but mentioned in characterization) indicated that all complexes remain stable up to approximately 200°C, with gradual decomposition occurring at higher temperatures. This thermal stability suggests potential suitability for pharmaceutical formulation and storage, though more detailed stability studies would be required for clinical development.

Conclusion

This investigation successfully demonstrates the potential of wild thyme plant extracts as natural ligands for synthesizing bioactive metal complexes with enhanced tumor-associated enzyme inhibitory properties. The Cu (II), Zn (II), and Co (II) complexes were successfully synthesized and characterized, showing distinct improvements in biological activity compared to the free plant extract. The Cu (II)-thyme complex emerged as the most potent tyrosinase inhibitor (IC50 = 12.3 μM), while the Zn (II)-thyme complex exhibited superior carbonic anhydrase IX inhibition (IC50 = 8.7 μM) with excellent selectivity.

The spectroscopic characterization confirmed successful coordination of phenolic constituents through hydroxyl groups, resulting in stable, non-electrolytic complexes with appropriate geometries. The structure-activity relationships observed support the rational design approach, where matching metal ions between inhibitor and target enzyme enhances inhibitory potency.

These findings contribute significantly to the growing field of bioinorganic medicinal chemistry and suggest promising avenues for developing novel anticancer agents. Future research directions should include detailed

mechanistic studies, in vivo evaluation, toxicity assessment, and optimization of the extraction and synthesis procedures to maximize therapeutic potential while minimizing adverse effects.

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