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SOME MEDICAL PROPERTIES OF SYNTHETIC AND NATURAL BIOACTIVE SUBSTANCES

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Abstract

Thiosemicarbazone-based compounds have garnered significant interest due to their dual antiproliferative (APA) and antioxidant (AOA) properties, crucial for combating cancer progression and associated oxidative stress. Copper(II) coordination complexes demonstrate superior APA (IC_{50} ≤0.1 μM), often surpassing doxorubicin/cisplatin. Ni(II), Zn(II), Co(III), and Fe(III) derivatives offer improved selectivity indices, with N-heteroaromatic modifications further enhancing Cu(II) potency.

Iodinated isothiosemicarbazones (L^9·HI, L^{11}·HI, L^{13}·HI) exhibited exceptional activity (IC_{50} 0.01–1.5 μM), attributed to halogen bonding, increased lipophilicity, and covalent protein adduction. While metal coordination amplifies APA (Cu(II) > Ni(II) > Zn(II)), it often reduces AOA (Cr(III) > Mn(II)).

Bee products provide complementary natural antioxidants. Propolis proved most potent (IC_{50} ABTS = 0.08 mg/mL; DPPH = 0.13 mg/mL), ~2000× superior to honey (543 mg/mL), followed by bee bread (1.45 mg/mL), royal jelly (6.65 mg/mL), beeswax (9 mg/mL).

Keywords: anticancer activity; antioxidant activity; selectivity; synthetic compound; honey bee products; natural bioactive substance.

UNIILE PROPRIETĂȚI MEDICALE ALE SUBSTANȚELOR BIOACTIVE SINTETICE ȘI NATURALE

Rezumat

Compușii pe bază de tiosemicarbazonă au suscitat un interes deosebit datorită proprietăților lor duale antiproliferative (APA) și antioxidante (AOA), esențiale în combaterea progresiei cancerului și a stresului oxidativ asociat. Complexele de coordonare ale cuprului(II) manifestă o activitate antiproliferativă superioară (IC_{50} ≤0,1 μM), depășind frecvent eficacitatea doxorubicinei și cisplatinei. Derivații metalici de Ni(II), Zn(II), Co(III) și Fe(III) indică un profil selectiv îmbunătățit, iar modificările N-heteroaromatice sporesc suplimentar potența complexelor Cu(II).

Izotiosemicarbazonele iodate (L^9·HI, L^{11}·HI, L^{13}·HI) au evidențiat o activitate remarcabilă (IC_{50} între 0,01 și 1,5 μM), atribuibilă interacțiunilor halogenice, lipofilicității crescute și posibilei adducii covalente cu proteinele. În timp ce coordonarea metalelor amplifică efectul antiproliferativ în ordinea Cu(II) > Ni(II) > Zn(II), aceasta poate conduce adesea la o reducere a activității antioxidante, conform secvenței Cr(III) > Mn(II).

Produsele apicole constituie surse naturale complementare de antioxidanți. Dintre acestea, propolisul s-a dovedit cel mai activ (IC_{50} ABTS = 0,08 mg/mL; DPPH = 0,13 mg/mL), fiind de aproximativ 2000 ori mai eficient decât mierea (543 mg/mL), urmat de pâinea de albine (1,45 mg/mL), lăptișorul de matcă (6,65 mg/mL) și ceara de albine (9 mg/mL).

Cuvinte-cheie: activitate anticancerigenă, activitate antioxidantă, selectivitate, compus sintetic, produse apicole, substanță bioactivă naturală.

Introduction

Cancer remains one of the leading causes of death globally, with incidence rates rising across populations due to uncontrolled cell proliferation and metastasis. Conventional chemotherapeutics like doxorubicin and cisplatin demonstrate potent antiproliferative activity but suffer from severe toxicity (selectivity index 0.05–1.8), multi-organ damage, and resistance, necessitating novel selective agents [1-3].

Recent literature highlights metal coordination compounds as promising anticancer candidates. Thiosemicarbazones and isothiosemicarbazones, with their versatile S,N-donor atoms, form stable complexes with 3*d* transition metals (Cr(III), Mn(II), Fe(III), Co(III), Ni(II), Cu(II), Zn(II)). These exhibit dual antiproliferative (APA) and antioxidant (AOA) properties through DNA intercalation, apoptosis induction, ROS modulation, and cell cycle arrest [4-9]. Copper(II) complexes show particular promise due to elevated tumor copper levels and angiogenesis inhibition.

Bee products represent a complementary natural antioxidant source. Propolis (50% phenolics) exhibits superior radical scavenging (ABTS / DPPH), followed by bee bread, royal jelly, beeswax, and honey. These mitigate oxidative stress—a carcinogenesis driver—while providing antimicrobial protection.

This article aims to analyze APA/AOA of isothiosemicarbazone 3*d* metal complexes, elucidate structure-activity relationships, antioxidant capacity of bee products.

Materials and methods

Cell Lines and Culture Conditions

Cancer cell lines HeLa (cervical adenocarcinoma), RD (rhabdomyosarcoma), BxPC-3 (pancreatic adenocarcinoma), and normal MDCK (Madin-Darby canine kidney) cells were obtained from ATCC. Cells were maintained in DMEM supplemented with 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37°C in 5% CO_2. Exponential growth phase cells were used for assays.

Antiproliferative Activity (APA) Assays

MTT assay: Cells seeded at 5×10^3 cells/well (96-well plates) were incubated 24 h, then treated with compounds (0.001–100 µM, 24 h). MTT (0.5 mg/mL) added for 4 h; formazan dissolved in DMSO. Absorbance measured at 570 nm (BioTek Synergy H1). IC_{50} calculated via nonlinear regression.

Resazurin assay: Post-24 h treatment, resazurin (10 µM) added for 2–4 h. Fluorescence measured (λ_ex=530 nm, λ_em=590 nm). Cell viability expressed as % control. Selectivity index (SI) = IC_{50} MDCK/IC_{50} cancer line. Doxorubicin (DOXO), cisplatin (CDDP) as standards.

Antioxidant Activity (AOA) Assays

DPPH assay: DPPH (100 µM in MeOH) mixed with samples (0.01–100 mg/mL, 30 min dark, RT). Absorbance measured at 517 nm.

ABTS assay: ABTS generated (7 mM $ABTS^+$ 2.45 mM $K_2S_2O_8$, 12–16 h dark). Diluted to 0.70 ± 0.02 Abs (734 nm). Samples added (30 min, RT). % Inhibition calculated. Trolox as standard.

Sample Preparation

Synthetic compounds: Stock solutions (10 mM) in DMSO. Final DMSO ≤0.1%.

Bee products: Collected May 2025, Institute of Zoology apiary (Moldova). Honey: water-ethanol (1:1 v/v); others: 96% ethanol extracts. Incubated 25°C, 48 h. Filtered (0.22 µm). Tested 0.01–100 mg/mL.

Results and discussion

Anticancer and antioxidant properties of the synthetic compounds and the influence of structure on their activity

Antiproliferative and antioxidant activities in drug development

Antiproliferative activity (APA) and antioxidant activity (AOA) are two important parameters frequently used to evaluate the biological activity of compounds, particularly in drug development.

Oxidative DNA damage is a significant factor in carcinogenesis, aging, and neurodegeneration. Studies show it accumulates in cancerous tissues, with higher levels of oxidative base damage in lung cancer tissues compared to normal tissues. Markers such as 8-oxoG, 8-hydroxyadenine, and 2,6-diamino-4-hydroxy-5-formamidopyrimidine are significantly elevated in breast cancer tissues versus normal tissues. This accumulation correlates with increased cancer risk with age, suggesting cancer as a degenerative disease linked to aging. Evidence confirms oxidative DNA damage buildup with age, mainly via elevated 8-oxoG levels.

Antioxidant activity is the ability of compounds to neutralize free radicals and prevent oxidative cell damage. By donating electrons or hydrogen atoms, antioxidants reduce free radical reactivity, aiding cellular defense against oxidative stress. AOA is typically assessed using ABTS and DPPH methods, with Trolox as the standard (Table 1).

Anticancer activity is defined by the ability to inhibit cancer cell proliferation. Compounds with APA may induce cell cycle arrest, promote apoptosis, or alter growth-regulating signaling pathways. Some antioxidants indirectly influence APA by preventing DNA damage and reducing inflammation that promotes tumor growth. APA is evaluated via MTT and resazurin assays, using doxorubicin and cisplatin as standards (Table 1).

Studies indicate substances with high AOA may also possess anticancer properties, as antioxidants scavenge free radicals and mitigate oxidative stress—a cancer development factor. However, high AOA does not guarantee significant APA; some compounds neutralize radicals effectively but lack direct cellular impact or efficacy at high concentrations.

Comparing AOA and APA is essential for understanding therapeutic potential. Deeper analysis of their relationship could lead to drugs that protect against oxidative stress while inhibiting cancer cell growth. Development requires thorough property analysis, mechanism studies, and experimental validation.

High systemic toxicity and drug resistance remain major challenges in cancer treatment despite advances. Chemotherapy causes severe side effects by targeting normal cells, necessitating dose reduction or treatment cessation. Anticancer drugs must exhibit APA and cytotoxicity selectively in tumor cells without affecting normal tissues; the key need is discovering effective, safe agents.

Doxorubicin is a potent FDA-approved frontline chemotherapeutic but causes multi-organ toxicity, especially cardiotoxicity via mitochondrial damage in cardiomyocytes and induced oxidative stress.

Platinum-based drugs are key in treating malignancies but limited by nephrotoxicity, neurotoxicity, and resistance. This spurred research into endogenous metals; copper(II) coordination compounds are promising alternatives to platinum agents due to copper's biocompatibility and biological roles. Copper metabolism is altered in cancer cells, with higher levels in tumors than normal tissues; copper sequestration inhibits angiogenesis. Thus, cancer cells are selective targets for copper-based agents.

Recent reports highlight numerous synthetic copper(II) thiosemicarbazone complexes as pharmacological, anticancer agents active *in vitro* and *in vivo* [10-14].

Thiosemicarbazones are organic compounds with broad biological and medical properties, featuring donor atoms that form complexes with transition metals.

Anticancer screening primarily uses cancer cell lines. Studies by Acad. A. Gulea et al. from the Laboratory of Advanced Materials in Biopharmaceutics and Technics, Moldova State University Institute of Chemistry, demonstrated APA and AOA of thiosemicarbazones and their Cr(III), Mn(II), Fe(III), Co(III), Ni(II), Cu(II), Zn(II) complexes—valuable for preliminary oncology screening [15-17].

Many antitumor drugs induce DNA damage, effective in S-phase replication. Selectivity index used MDCK normal cells to assess cancer vs. non-cancer selectivity, aiding optimal dosing.

Results in Table 1 show doxorubicin and cisplatin's high toxicity (selectivity index 0.05–1.8). Both are effective against HeLa, RD, BxPC-3 lines, with doxorubicin superior to cisplatin. Both have AOA, doxorubicin exceeding Trolox. Correlation exists between AOA and anticancer activity for doxorubicin/cisplatin on HeLa and BxPC-3 lines.

Table 1. Antiproliferative activity of the standard drugs against HeLa, RD, and BxPC-3 cancer cell lines, as well as MDCK cell lines. $ABTS^{\bullet+}$ scavenging activity of DOXO, CDDP, and Trolox.

Compound	ABTS IC_{50} (μM)	SI	BxPC-3 IC_{50} (μM)	SI	RD IC_{50} (μM)	SI	HeLa IC_{50} (μM)	MDCK IC_{50} (μM)
DOXO	12.0	1.8	6.0	0.7	16.2	1.8	6.2	10.8
CDDP	43.0	0.1	11.2	0.3	4.6	0.05	30.9	1.5
Trolox	33.3	-	-	-	-	-	-	-

Average results of three experiments, SEM < ±3%.

Antiproliferative and antioxidant activities of isothiosemicarbazones

Isothiosemicarbazones represent a distinct group of organic derivatives synthesized through the condensation of isothiocyanates with hydrazines or related compounds. Unlike thiosemicarbazones, these isomers feature a unique >C=N-NH-C(S)- functional moiety with nitrogen positioning that alters their reactivity profile. Their general structure follows R_1R_2C=NNH-C(S)NH_2, where R_1 and R_2 denote various organic groups. The embedded isothiocyanate functionality confers exceptional reactivity, enabling diverse bond formations. These compounds readily engage in nucleophilic additions and substitution reactions, facilitated by the polarized C=N double bond .

Like their thiosemicarbazone counterparts, isothiosemicarbazones demonstrate antioxidant capabilities, effectively countering oxidative stress through free radical scavenging. Certain derivatives also show promising anticancer potential, suppressing tumor cell proliferation via apoptosis induction or cell cycle blockade. Consequently, isothiosemicarbazones emerge as a compelling chemical class, distinguished by specialized reactivity and pronounced bioactivity. Their utility spans medical applications as antioxidants, oncotherapeutic candidates, and antimicrobial agents, sustaining active investigation within organic synthesis and pharmacological sciences. Table 2 summarizes the antioxidant and antiproliferative potencies of tested isothiosemicarbazones, reported as IC_{50} values.

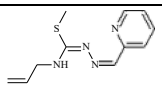
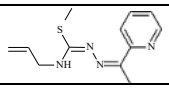
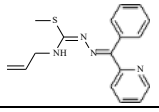
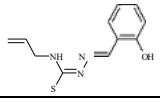
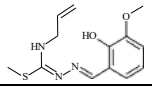
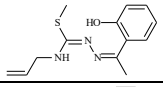
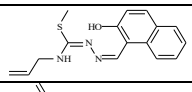
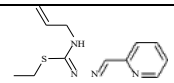
Notably selective APA was observed for ligands including methyl N-prop-2-en-1-yl-N'-[pyridin-2-ylmethylidene]carbamohydrazonothioate, methyl N'-[phenyl(pyridin-2-yl)methylidene]-N-prop-2-en-1-ylcarbamohydrazonothioate, methyl N'-[(2-hydroxy-3-methoxyphenyl)methylidene]-N-prop-2-en-1-ylcarbamohydrazonothioate, ethyl N-prop-2-en-1-yl-N'-[pyridin-2-ylmethylidene]carbamohydrazonothioate, ethyl N-prop-2-en-1-yl-N'-[1-(pyridin-2-yl)ethylidene]carbamohydrazonothioate, and phenyl N'-[(2-hydroxyphenyl)methylidene]-N-prop-2-en-1-ylcarbamohydrazonothioate. Modification with iodine hydriodide markedly amplified APA against examined cancer lines for ethyl N-prop-2-en-1-yl-N'-[1-(pyridin-2-yl)ethylidene]carbamohydrazonothioate (L^9), N'-[(2-hydroxy-3-methoxyphenyl)methylidene]-N-prop-2-en-1-ylcarbamohydrazonothioate (L^{11}), and N-prop-2-en-1-yl-N'-[1-(pyridin-2-yl)ethylidene]carbamohydrazonothioate (L^{13}) (Table 2) .

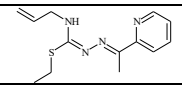
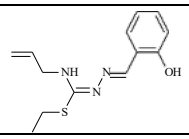
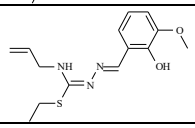
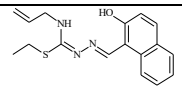
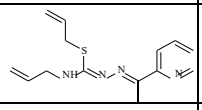
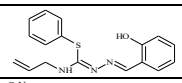
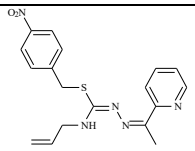
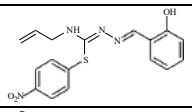
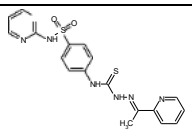
Among these, $L^9 \cdot HI$ proved most potent, achieving IC_{50} = 0.01 μM versus BxPC-3 and 0.7 μM versus RD cells. $L^{11} \cdot HI$ yielded IC_{50} = 0.4 μM (BxPC-3), 1.0 μM (RD), and 1.4 μM (HeLa). $L^{13} \cdot HI$ recorded IC_{50} = 0.5 μM (BxPC-3), 1.2 μM (RD), and 1.5 μM (HeLa) (Table 2). These values surpass corresponding potencies of doxorubicin and cisplatin standards .

This superiority likely stems from iodine's properties as a sizable, polarizable halogen capable of halogen bonding with biomolecular targets. Such interactions stabilize $L^{13} \cdot HI$ configurations, enhancing target affinity and selectivity for proliferation-related sites. Iodination boosts lipophilicity, promoting membrane permeation and intracellular access. Additionally, iodine modulates electron distribution, potentially activating key functional groups to heighten reactivity or binding precision .

Structural distinctions between isothiosemicarbazones and thiosemicarbazones thus underpin their divergent APA and AOA profiles. The former excel in antiproliferative action through optimized engagement with cellular machinery like enzymes and receptors. The isothiocyanate motif further enables covalent protein adduction, disrupting critical functions and curtailing proliferation .

Table 2. Antiproliferative activity of isothiosemicarbazones against HeLa, RD, and BxPC-3 cancer cell lines, as well as the MDCK normal cell line. $ABTS^{\bullet+}$ scavenging activity of the compounds.

	Formula	ABTS IC_{50} (μM)	BxPC-3 IC_{50} (μM)	RD IC_{50} (μM)	HeLa IC_{50} (μM)	MDCK IC_{50} (μM)
L^1		≥100	115.5	16.0	≥100	≥100
$L^1 \cdot HI$		≥100	≥100	20.2	≥100	≥100
L^2		≥100	1.4	≥100	47.5	13.0
L^3		-	0.9	30.1	≥100	18.0
L^4		-	≥100	70.6	≥100	≥100
$L^4 \cdot HI$			≥100	≥100	≥100	≥100
L^5		8.8	35.9	44.7	5.2	≥100
$L^5 \cdot HI$		7.7	72.7	126.3	4.0	≥100
$L^6 \cdot HI$		8.7	≥100	≥100	≥100	≥100
L^7		-	≥100	99.8	90	53
L^8		51.2	14.2	≥100	81.4	≥100

	Formula	ABTS IC_{50} (μM)	BxPC-3 IC_{50} (μM)	RD IC_{50} (μM)	HeLa IC_{50} (μM)	MDCK IC_{50} (μM)
L^9		≥100	15.5	≥100	≥100	≥100
L^9·HI		41.2	0.01	0.7	≥100	24
L^{10}·HI		13.7	88.0	≥100	≥100	≥100
L^{11}		6.9	≥100	≥100	≥100	≥100
L^{11}·HI		8.6	0.4	1.0	1.4	1.0
L^{12}·HI		6.2	≥100	≥100	≥100	≥100
L^{13}		≥100	13.5	13.71	13.2	11.9
L^{13}·HI		49.9	0.47	1.18	1.45	1.5
L^{14}		34.0	57.6	10.8	27.5	0.1
L^{15}		≥100	≥100	≥100	≥100	≥100
L^{15}·H Br		31.0	48.5	≥100	≥100	≥100
L^{16}		29.0	≥100	≥100	≥100	≥100

Average results of three experiments, SEM < ±3%.

The study of isothiosemicarbazones highlights a significant relationship between their structural characteristics and both APA and AOA. The findings reveal that specific functional groups, such as hydroxyl, methoxy, and halogen substituents like iodine, play a crucial role in modulating the biological activities of these compounds. Hydroxyl and methoxy groups enhance AOA by stabilizing free radicals through hydrogen donation, while the isothiocyanate functionality enables covalent interactions with cellular targets, thereby increasing APA. The incorporation of iodine not only improves the lipophilicity of these compounds but also boosts their binding affinity to biological targets, further amplifying their APA and AOA.

Antiproliferative and antioxidant activities of the 3d metal coordination compounds of isothiosemicarbazones

The comparative analysis of 3*d* metal coordination compounds of thiosemicarbazones and isothiosemicarbazones highlights the impact of different 3d metals on their antiproliferative and antioxidant activities. The study shows that the coordination of these ligands to metal centers generally enhances their antiproliferative properties but tends to reduce their antioxidant capabilities. Notably, a substantial number of these coordination compounds demonstrated antiproliferative activities exceeding those of well-known drugs like doxorubicin and cisplatin.

The study of 3*d* metal coordination compounds reveals a specific order of APA, Cu(II) complexes ≥ Ni(II) complexes ≥ Zn(II) complexes ≥ Co(III) complexes = Fe(III) complexes ≥ Cr(III) complexes, and AOA, Cr(III) complexes ≥ Mn(II) complexes = Fe(III) complexes ≥ Co(III) complexes = Ni(II) complexes = Cu(II) complexes = Zn(II) complexes (Table 3).

Table 3. Antiproliferative activity of the coordination compounds against HeLa, RD, and BxPC-3 cancer cell lines, as well as MDCK cell lines. $ABTS^{\bullet+}$ scavenging activity of the 3*d* metal coordination compound.

	Formula	ABTS IC_{50} (μM)	BxPC-3 IC_{50} (μM)	RD IC_{50} (μM)	HeLa IC_{50} (μM)	MDCK IC_{50} (μM)
1.1	$Cu(L_1)(NO_3)_2$	≥100	1.0	1.5	1.1	1.3
1.2	$Cu(L^1)Cl_2$	≥100	1.0	1.1	0.9	5
1.3	$Cu(L^1)Br_2$	≥100	0.3	0.6	1.2	1.5
1.4	$Cu(L^1)(ClO_4)_2$	≥100	1.3	1.3	1.4	5.5
1.5	$Cu(L^1\text{-}H)CH_3COO$	-	0.7	1.7	5.4	6.6
1.6	$Zn(L^1)_2I_2$	-	≥100	10.9	≥100	68
1.7	$Ni(L^1)_2I_2$	-	51.6	14.1	54	95
1.8	$Ni(L^1)_2(ClO_4)$	-	30.6	≥100	74.9	≥100
1.9	$Co(L^1\text{-}H)_2I$	≥100	≥100	≥100	≥100	≥100
1.10	$Co(L^1\text{-}H)_2Cl$	-	48.1	15.8	2.1	≥100
1.11	$Co(L^1\text{-}H)_2(NO_3)$	≥100	≥100	57.0	≥100	≥100
1.12	$Cu(L^1)SO_4$	≥100	≤0.1	0.7	2	2
2.2	$Cu(L^2)Cl_2$	≥100	≤0.1	0.1	3	1
2.3	$Cu(L^2)Br_2$	≥100	≤0.1	≤0.1	0.5	0.3
2.4	$Ni(L^2)_2(ClO_4)_2$	25.1	2.5	6.4	10.1	7.3
2.5	$Ni(L^2)_2(NO_3)_2$	21.5	16.4	≥100	25.5	≥100
2.6	$Co(L^2\text{-}H)_2NO_3$	≥100	12.9	7.5	12.8	18.5
2.7	$Co(L^2\text{-}H)_2I$	≥100	21.8	11.2	10.9	18.8
2.8	$Cu(L^2)(NO_3)_2$	≥100	≤0.1	0.1	1.0	0.7
2.9	$Fe(L^2\text{-}H)_2Br$	≥100	8.5	10.7	3.4	11.0
2.10	$Co(L^2\text{-}H)_2Cl$	≥100	≥100	12.6	92	42
3.1	$Cu(L^3)Br_2$	45.9	0.2	1.3	0.3	1.64
3.2	$Cu(L^3\text{-}H)(CH_3COO)$	≥100	2.8	2.5	1	3
3.3	$Cu(L^3)Cl_2$	≥100	≥100	13.4	≥100	36.3
3.4	$Ni(L^3)_2(NO_3)_2$	21.1	1.3	8.3	2.9	14.4
3.5	$Ni(L^3)_2(ClO_4)_2$	22.0	3.0	9.3	4.3	10.0
3.6	$Co(L^3\text{-}H)_2(CH_3COO)$	≥100	7.3	1.4	1	12.4
3.7	$Co(L^3\text{-}H)_2NO_3$	≥100	1.3	1.1	0.8	1.9
3.8	$Zn(L^3)I_2$	55.7	2.5	12.2	1.4	11.1
3.9	$Fe(L^3\text{-}H)_2NO_3$	10.0	≥100	0.9	15	75
4.2	$Co(L^4\text{-}H)_2NO_3$	7.1	≥100	49.3	≥100	≥100
4.3	$Co(L^4\text{-}H)_2Cl$	23.2	≥100	≥100	≥100	≥100

	Formula	ABTS IC_{50} (μM)	BxPC-3 IC_{50} (μM)	RD IC_{50} (μM)	HeLa IC_{50} (μM)	MDCK IC_{50} (μM)
4.4	$Co(L^4\text{-}H)_2I$	21.7	≥100	≥100	≥100	≥100
4.5	$Cr(L^4\text{-}H)_2NO_3$	1.2	≥100	≥100	≥100	≥100
4.6	$Ni(L^4)(L^4\text{-}H)ClO_4$	-	22.4	≥100	91.1	≥100
4.7	$Cu(L^4\text{-}H)CH_3COO$	-	0.4	11.1	3.1	13.1
4.8	$Cu(L^4\text{-}H)Br$	-	0.6	5.2	1.6	12.7
4.9	$Cu(L^4\text{-}H)Cl$	-	0.5	1.2	6.2	13.56
4.10	$Cu(Py)(L^4\text{-}H)NO_3$	46.6	1.28	11.4	5.0	12.2
4.11	$Cu(3\text{-}Pic)(L^4\text{-}H)NO_3$	53.1	0.7	13.8	9.4	16.9
4.12	$Cu(Im)(L^4\text{-}H)NO_3$	48.9	2.8	12.1	4.7	27.3
4.13	$Cu(3,4\text{-}Lut)(L^4\text{-}H)NO_3$	47.0	6.3	10.2	71.2	12.3
4.14	$Cu(1,10\text{-}Phen)(L^4\text{-}H)NO_3$	11.6	0.96	1.28	2.7	1.34
4.15	$Cu(L^4H)Cl$	20.9	0.4	1.2	1.0	1.3
5.2	$Cu(L^5\text{-}H)NO_3$	38.9	3.7	1.19	1.3	4
5.3	$Ni(L^5)(L^5\text{-}H)NO_3$	15.5	≥100	≥100	≥100	30
5.4	$Ni(L^5)(L^5\text{-}H)I$	8.3	15.4	9.7	4.3	12
5.5	$Co(L^5\text{-}H)_2NO_3$	20.9	≥100	≥100	≥100	≥100
5.6	$Co(L^5\text{-}H)_2I$	19.2	≥100	≥100	≥100	≥100
5.7	$Co(L^5\text{-}H)_2Cl$	23.1	≥100	≥100	≥100	≥100
5.8	$Fe(L^5\text{-}H)_2NO_3$	9.6	81.0	1.1	≥100	≥100
5.9	$Cu(L^5\text{-}H)Cl$	13.1	0.9	10.9	2.3	11.8
6.2	$Cu(L^6\text{-}H)NO_3$	12.2	2.5	12.5	14.5	12.2
6.3	$Cu(L^6\text{-}H)ClO_4$	16.3	1.2	3.2	6.6	13.3
6.4	$Cu(L^6\text{-}H)(CH_3COO)$	19.8	0.8	1.3	1.7	4.9
6.5	$Ni(L^6\text{-}H)_2$	6.0	78.3	≥100	≥100	≥100
6.6	$Co(L^6\text{-}H)_2NO_3$	14.5	8.5	≥100	23.8	≥100
6.7	$Co(L^6\text{-}H)_2Br$	7.5	5.0	10.7	≥100	27.2
6.8	$Co(L^6\text{-}H)_2I$	15.3	35.9	≥100	32.1	≥100
6.9	$Fe(L^6\text{-}H)_2NO_3$	2.1	34.1	≥100	28.3	≥100
7.1	$Cu(L^7\text{-}H)ClO_4$	11.9	1.3	12.5	3.9	14.7
7.2	$Ni(L^7)(L^7\text{-}H)ClO_4$	5.2	9.3	≥7	44.0	≥100
7.3	$Ni(L^7\text{-}H)_2$	8.6	0.72	9.8	3.5	12.6
7.4	$Co(L^7\text{-}H)_2NO_3$	16.5	44.3	≥100	≥100	≥100
7.5	$Co(L^7\text{-}H)_2I$	-	≥100	117.5	57.7	≥100
7.6	$Cr(L^7\text{-}H)_2NO_3$	1.4	≥100	≥100	≥100	≥100
8.1	$Cu(L^8\text{-}H)Cl$	108.0	≤0.1	≤0.1	1.5	0.4
8.2	$Co(L^8\text{-}H)_2I$	≥100	11.3	11.1	14.0	16.9
9.1	$Co(L^9\text{-}H)_2I$	≥100	4.1	1.2	1.9	5.6
9.2	$Ni(L^9)_2I_2$	16.7	5.2	≥100	6.4	≥100
9.3	$Cu(L^9)Cl_2$	-	≤0.01	0.2	0.5	1.4
9.4	$Cu(L^9)(NO_3)_2$	-	0.04	0.14	0.3	1.3
10.1	$Cu(L^{10}\text{-}H)NO_3$	27.9	1.0	5.5	13	1.6
10.2	$Cu(L^{10}\text{-}H)Br$	38.6	21.8	11.8	37.1	33.4
10.3	$Ni(L^{10})(L^{10}\text{-}H)ClO_4$	8.0	0.8	1.4	1.7	1.1
10.4	$Fe(L^{10}\text{-}H)_2NO_3$	12.5	1.3	≥100	2.2	≥100
10.5	$Co(L^{10}\text{-}H)_2NO_3$	19.3	≥100	≥100	≥100	≥100
10.6	$Cu(L^{10}\text{-}H)Cl$	13.7	≥100	12.6	14	12
10.7	$Ni(L^{10})(L^{10}\text{-}H)I$	6.2	69.0	56.7	82.6	≥100
10.8	$Co(L^{10}\text{-}H)_2I$	30.1	19.1	36.5	≥100	28.6
11.1	$Co(L^{11}\text{-}H)_2I$	19.0	≥100	≥100	≥100	≥100
11.2	$Ni(L^{11}\text{-}H)_2$	12.0	≥100	≥100	≥100	≥100

	Formula	ABTS IC_{50} (μM)	BxPC-3 IC_{50} (μM)	RD IC_{50} (μM)	HeLa IC_{50} (μM)	MDCK IC_{50} (μM)
11.3	$Co(L^{11}\text{-}H)_2Br$	17.9	≥100	≥100	≥100	≥100
11.4	$Co(L^{11}\text{-}H)_2(CH_3COO)$	23.2	≥100	≥100	≥100	≥100
11.5	$Co(L^{11}\text{-}H)_2NO_3$	21.7	≥100	≥100	≥100	≥100
11.6	$Fe(L^{11}\text{-}H)_2NO_3$	4.0	3.7	-	9.8	-
12.1	$Cu(L^{12}\text{-}H)Cl$	-	1.16	6.7	7.9	20.0
12.2	$Cu(L^{12}\text{-}H)NO_3$	-	0.9	18.8	9.3	12.7
12.3	$Co(L^{12}\text{-}H)_2I$	16.0	≥100	≥100	≥100	≥100
13.1	$Cu(L^{13})Br_2$	65.6	≤0.01	1.3	0.39	1.23
13.2	$Cu(L^{13})(NO_3)_2$	25.1	0.040	0.14	0.3	1.3
13.3	$Cu(L^{13})Cl_2$	65.5	≤0.01	0.2	0.5	1.4
14.1	$Cu(L^{14}\text{-}H)Cl$	≥100	1.5	1.2	1.1	0.0
14.2	$Co(L^{14}\text{-}H)_2Cl$	≥100	7.1	≥100	12.5	≥100
15.1	$Cu(L^{15})Br_2$	≥100	8.5	1.4	16.6	2.39
15.2	$Ni(L^{15})_2Br_2$	88.7	32.2	≥100	≥100	≥100
15.3	$Fe(L^{15}\text{-}H)_2NO_3$	≥100	3.1	2.0	5.5	1.1
15.4	$Co(L^{15}\text{-}H)_2Br$	-	10.7	12.4	22.9	24.6
16.1	$Ni(L^{16}\text{-}H)_2$	48.8	88.8	≥100	16.7	≥100
16.2	$Co(L^{16}\text{-}H)_2NO_3$	≥100	21.9	≥100	≥100	≥100

Average results of three experiments, SEM < ±3%.

The diversity of biological activity in these compounds arises from the interplay of metal ion characteristics, proligand architecture, and the biochemical milieu in which they operate. Each transition metal's distinct coordination chemistry—including coordination numbers and spatial geometries—profoundly shapes ligand-target affinities, dictating their bioefficacy. For example, the structural motifs in Cu(II) complexes optimize engagement with biomolecular sites. Furthermore, the redox states and reactivity profiles of metals such as copper and nickel can trigger signaling cascades that amplify antiproliferative outcomes .

Proligand design critically modulates potency. Thiosemicarbazone functional moieties enhance the stability and responsiveness of metal complexes, directly elevating their antiproliferative impact. Electron-delocalizing ligands stabilize reactive intermediates or target cancer cell hotspots, synergistically bolstering both antioxidant and growth-inhibitory effects. These metal assemblies selectively disrupt key cellular enzymes and signaling receptors; copper derivatives, in particular, excel at triggering apoptosis in malignant cells. In terms of antioxidant performance, 3*d* metal complexes promote radical quenching. Ions like chromium and manganese drive redox cycling that elevates ligand antioxidative capacity, fortifying defenses against oxidative insult. Variations in metabolic routing and biodistribution further refine their therapeutic utility.

The established hierarchy of antiproliferative and antioxidative traits reveals intricate synergies among metal cores, ligand scaffolds, and physiological processes. Cu(II) and Ni(II) assemblies achieve peak performance through ideal physicochemical attributes and target interactions, whereas alternative metals face inherent limitations. Ongoing studies promise refined strategies for engineering potent anticancer therapeutics.

Comparative evaluation of 3*d* metal isothiosemicarbazone complexes illuminates the multifaceted roles of diverse metal centers in modulating APA and AOA. Data reveal that metal coordination typically augments antiproliferative prowess while often attenuating antioxidative strength. Strikingly, numerous such entities outperform benchmark chemotherapeutics like doxorubicin and cisplatin in growth suppression.

The antioxidant capacity of honey bee products

The biological material (honey, beeswax, royal jelly, bee uterus, propolis, and pollen) was collected in late May. The samples were collected and registered at the apiary of the Republic of Moldova.

Honey dissolved in a water-alcohol solution (1:1); beeswax, royal jelly, bee uterus, propolis, and pollen dissolved in 96% ethanol were incubated in a thermostat at 25°C for 2 days. The biological material is examined at least 3 times at different concentrations ranging from 0.01 to 100.00 μM. In this study, the two most frequently used methods for assessing free radical scavenging ability, $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ assays, were performed, and Trolox was used as a reference.

The IC_{50} values of the bee products in control exhibiting the concentration that caused 50% scavenging of free radicals $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ are presented in Table 4. These two free radical scavenging activities revealed that the IC_{50} values of the tested samples ranged from 0.13 -543.00 mg/mL for the $DPPH^{\bullet}$ assay and from 0.08 -159.40 mg/mL for the $ABTS^{\bullet+}$ assay. The Table 4 data indicate that all honey bee products display a significant antioxidant capacity. The $ABTS^{\bullet+}$radical scavenging ability of the tested samples can be ranked in the following order: Propolis ≥ Bee Bread ≥ Royal Jelly ≥ Beeswax ≥ Bee Uterus ≥ Honey.

Of honey bee products, propolis seems to be the most powerful antioxidant as it contains the highest levels of phenols and flavonoids, followed by pollen and royal jelly, according to literature data [18]. Our AOC studies on bee products in the control group showed a level of activity consistent with data from literary sources. Propolis has demonstrated the highest radical scavenging activity, IC_{50} making 0.08 mg/mL for $ABTS^{\bullet+}$ and 0.13 mg/mL for $DPPH^{\bullet}$.

Propolis (bee glue) is not a food, unlike honey and pollen. Bees utilize it as both a building material and a protective substance. They use it to repair combs and strengthen thin honeycomb edges. Propolis is also employed for its biological activity as an insulating material to prevent microorganisms (fungi and bacteria) from penetrating the hive and to build the most sterile environment known in nature [19]. It is also active against human pathogens. Generally, naturally-occurring propolis is composed of 50% resin and vegetable balsam (including phenolic compounds), 30–40% wax and fatty acids, 5–10% essential and aromatic oils, 5% pollen, and approximately 5% other substances, including micronutrients, amino acids, and vitamins (pyridoxine, thiamin, vitamins C and E and riboflavin).

Bee bread showed radical scavenging activity with IC_{50} values of 2.43 mg/mL for $ABTS^{\bullet+}$ assay and 1.45 mg/mL for $DPPH^{\bullet}$ assay. Bee bread is a part of the pollen stored by bees in their combs, sealed with a thin honey and beeswax layer, and matured in a beehive. It is used by worker bees as food for larvae, and the production of royal jelly by young bees. Bee bread is processed by bees for storage by adding various enzymes and honey, leading to fermentation renders. The end product is enriched with new nutrients and becomes more digestible due to this type of lactic acid fermentation, as cell walls are partly destroyed during this process. Bee bread is more nutritious than pollen because of its higher free amino acid content and easily assimilated sugars. Its almost unlimited storage capacity as compared with dried or frozen pollen in which nutritional values rapidly vanish is one of the bee bread advantages [20].

The royal jelly manifested high AOC, with IC_{50} values of 6.65 mg/mL and 15.14 mg/mL for $ABTS^{\bullet+}$ and $DPPH^{\bullet}$ radicals, respectively. Royal jelly is a compound that is secreted by the hypopharyngeal and mandibular glands of worker honeybees. It is a yellowish, creamy, acidic substance with a slightly acrid scent and taste constituted on a wet weight basis including water (60–70%), proteins (9–18%), sugars (7–18%) (mainly fructose, glucose, and sucrose), lipids (3–8%), minerals (0.8–3.0%), ash (0.8–3%), and traces of polyphenols and vitamins [21]. All bee larvae in the early stages of life and the queen bee until she dies are fed with royal jelly. It plays a decisive role in determining the class of honeybees because larvae fed with greater amounts of

royal jelly for longer periods grow into large, fertile, long-living queens rather than smaller, infertile, short-living workers. Ramadan and Al-Ghamdi reported in their review that royal jelly possesses a large number of functional properties such as disinfectant action, antibacterial, vasodilative, hypotensive, anti-inflammatory, antihypercholesterolemic, antioxidant, and antitumor activity [5].

Table 4. AOC of the bee products

Control	ABTS$^{\bullet+}$					DPPH$^{\bullet}$			
	C (mg/mL)	Abs 734nm	Inh (%)	SD (%)	IC_{50} (mg/mL)	Abs 517nm	inh (%)	SD (%)	IC_{50} (mg/mL)
HONEY	100.00	0.506	39.76	0.51	159.40±8.91	0.561	33.15	0.08	543.00±38.18
	10.00	0.782	6.85	0.59		0.708	15.71	0.17	
	1.00	0.813	3.15	0.42		0.722	13.99	0.08	
	0.10	0.825	1.79	0.67		0.759	9.64	1.18	
BEE BREAD	50.00	0.054	93.57	0.34	2.43±0.01	0.026	96.85	0.08	1.45±0.04
	5.00	0.369	56.07	0.34		0.126	85.00	0.17	
	0.50	0.591	29.58	0.42		0.685	18.39	0.93	
	0.05	0.775	7.68	0.42		0.802	4.52	1.85	
BEESWAX	50.00	0.063	92.44	0.42	9.26±0.07	0.019	97.74	0.01	9.04±0.04
	5.00	0.597	28.93	0.67		0.644	23.33	0.51	
	0.50	0.770	8.33	0.17		0.753	10.30	1.26	
	0.05	0.838	0.24	0.17		0.800	4.70	0.25	
PROPOLIS	5.00	0.060	92.86	1.52	0.08±0.01	0.092	88.99	0.42	0.13±0.01
	0.50	0.291	65.30	0.08		0.145	82.74	1.52	
	0.05	0.404	51.90	0.17		0.633	24.64	0.51	
	0.01	0.735	12.44	0.25		0.772	8.04	1.43	
ROYAL JELLY	50.00	0.045	94.58	0.93	6.65±0.05	0.050	93.99	0.08	15.14±1.51
	5.00	0.512	39.05	0.34		0.755	10.12	0.84	
	0.50	0.732	12.86	0.34		0.761	9.35	0.59	
	0.05	0.827	1.55	0.17		0.796	5.24	1.01	
BEE UTERUS	50.00	0.060	92.86	1.68	9.11±0.24	0.061	92.74	2.69	12.54±0.89
	5.00	0.594	29.23	0.25		0.709	15.54	0.42	
	0.50	0.748	10.89	0.25		0.738	12.08	0.93	
	0.05	0.836	0.42	0.25		0.833	0.77	0.42	

The antioxidant performance of royal jelly is attributed to its free amino acids, including essential ones; polyphenolic and flavonoid compounds; small peptides, such as di-peptides (Lys-Tyr, Arg-Tyr, and Tyr-Tyr) yielded from protease hydrolyzed royal jelly proteins; vitamins; fatty acids (the main being 10-hydroxydecanoic acid); and peptides and proteins [5]. The major flavonoids that occur in royal jelly include flavonols (e.g., kaempferol, quercetin, fisetin, and

galangin), flavanones (e.g., pinocembrin, naringin, and hesperidin), and flavones (e.g., acacetin, apigenin, luteolin, and chrysin). A family of proteins secreted by honey bees comprises major royal jelly proteins (MRJPs). The family includes nine proteins, of which MRJP1 (also called royalactin), MRJP2, MRJP3, MRJP4, and MRJP5 are present in the royal jelly secreted by worker bees. MRJP1 is the amplest and largest in volume. The five proteins make 82–90% of the total proteins in royal jelly [5]. DPPH radical-scavenging assay carried out by Park et al. confirmed the antioxidant capacity of MRJPs 1–7 of *Apis mellifera* at levels varying between approximately 30 and 80% of the residual radical.

Beeswax and Bee Uterus demonstrated relatively similar strong AOC, with IC_{50} values of 9.26 mg/mL ($ABTS^{\bullet+}$) – 9.04 mg/mL ($DPPH^{\bullet}$) and 9.11 mg/mL ($ABTS^{\bullet+}$) – 12.54 mg/mL ($DPPH^{\bullet}$), respectively. Beeswax is secreted by Beeswax Worker bees through wax glands located in the abdomen. The peaks of this substance production fall generally during the colony growth phase in late spring. Beeswax is used to make combs. The synthesis of beeswax starts from honey sugars, and it has a crystalline structure suitable for hive construction. Chemical composition depends on bee species and geographical zones and includes free fatty acids, free fatty alcohols, and hydrocarbons, linear wax monoesters, hydroxymonoesters deriving from palmitic, 15-hydroxypalmitic and oleic acids, and complex wax esters containing 15-hydroxypalmitic acid and diols.

The studies on the beeswax AOC involve the by-products of wax recycling and the associated cost-benefit tradeoff. Honey, propolis, pollen, and royal jelly are considered commodities, while honeycomb is discarded as a by-product in bee product processing and production. Beeswax recycling can transform it into compounds previously considered industrial waste, though they could be of great value in biomedicine. This issue needs further exploration. It has been demonstrated by Zhao et al. and Giampieri et al. that byproducts from beeswax recycling present a rich source of proteins, minerals, and polyphenols, conferring strong total antioxidant capacity and low toxin levels.

Honey, a sweet naturally-occurring product appreciated for its nutritive value and beneficial health effects, is produced by honeybees *Apis mellifera* that directly select nectar from plants or the excretions of plant-sucking insects. Honey is known for its high antibacterial activity; thus, its use in modern medicine represents an attractive alternative treatment to deal with multidrug-resistant pathogens. Different factors, including hydrogen peroxide, a low pH, and high osmolarity contribute to honey's antibacterial activity. The presence, among its various components, of natural antioxidants is the most important therapeutic property of honey. It contains about 200 compounds, which are mainly sugars (fructose 25–45% and glucose 20–40%), water, and other substances, such as protein, amino acids, vitamins, enzymes, ash, organic acids, minerals, and phenolic and flavonoid compounds, which greatly contribute to its biological activity. The therapeutic capacity of honey is linked to the presence, variety, and amounts of bioactive compounds. In its turn, this depends on the type of flora, climatic conditions, geographical location of production, soil composition, seasonal factors, environmental conditions, botanical and entomological sources, as well as the production process. The enormous number of bioactive compounds in honey consists of molecules with phenolic structures, such as phenolic acids, flavonoids, anthocyanins, procyanidins, vitamin E, vitamin C (ascorbic acid), enzymes (e.g., catalase, peroxidase), carotenoids, Maillard reaction products, and trace elements. The principle composition of phenolic compounds in different honey varieties is relatively similar and includes phenolic acids, such as ellagic, caffeic, p-coumaric, and ferulic acids; flavonoids, including galangin, apigenin, chrysin, kaempferol, hesperetin, quercetin, and pinocembrin, and antioxidants, such as ascorbic acid, tocopherols, catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH) [5]. In our studies, the

Honey displayed AOC in the IC_{50} values (159.40 mg/mL for $ABTS^{\bullet+}$ and 543.00 mg/mL for $DPPH^{\bullet}$).

All bee products have a high AOC, which is correlated with the content of antioxidant compounds such as flavonoids, phenolic acids, organic acids, amino acids, vitamins, enzymes, minerals, etc. The AOC of bee products in most cases exceeds the activity of a water-soluble analog of vitamin E - Trolox, which is a common standard antioxidant employed in biochemical techniques conducted to reduce oxidative stress.

Conclusions

Thiosemicarbazone-based compounds have garnered significant interest in recent years due to their remarkable potential as inhibitors of cancer cell proliferation. These compounds not only exhibit powerful antiproliferative effects but also possess antioxidant properties, which are crucial in combating oxidative stress associated with cancer progression. This article discusses their antioxidant and antiproliferative activities, as well as how the antitumor activity is related to the antioxidant properties of isothiosemicarbazones, and their coordination complexes with transition metals such as zinc(II), copper(II), nickel(II), cobalt(III), and iron(III).

Research indicates that coordinating thiosemicarbazones with copper(II) enhances their antiproliferative properties; however, these compounds often lack optimal selectivity, though their selectivity indexes compare favorably with those of doxorubicin and cisplatin used in medical practice. Notably, copper coordination compounds derived from *N*4-allylthiosemicarbazide have shown significant inhibitory effects against various cancer cell lines, often surpassing established chemotherapeutic agents. Coordination compounds involving nickel(II), iron(III), and cobalt(III) may exhibit lower overall activity against cancer cells but demonstrate improved selectivity, targeting cancer cells more effectively than normal cells.

Furthermore, enhancing the anticancer properties and selectivity of copper(II) coordination compounds can be achieved by introducing specific *N*-heteroaromatic bases. The search for new anticancer agents should extend beyond copper(II) to include promising candidates from nickel(II), zinc(II), cobalt(III), and iron(III) coordination compounds, which possess noteworthy selectivity.

This study underscores the importance of the antioxidant activity of isothiosemicarbazones, considering the role of oxidative stress in cancer progression. This work presents data on the ability of these compounds to neutralize free radicals, which is critical for protecting cellular components from oxidative damage. The results indicate that certain coordination compounds, especially those containing nickel, zinc, and iron, demonstrate superior antioxidant activity compared to their copper and cobalt counterparts. It was observed that many coordination compounds generally exhibit lower antioxidant activity than their corresponding free ligands.

Electrophoretic separation techniques revealed that interactions between the tested compounds and DNA resulted in fragmentation, highlighting the initiation of apoptosis in these cells. This apoptosis was characterized by significant morphological changes and was further corroborated through a microscopic cell analysis and flow cytometry.

Furthermore, an X-ray diffraction analysis revealed the electron density distribution within one of the most promising molecules, 4-allylthiosemicarbazone 2-formylpyridine, which exhibits high antiproliferative activity. The data indicate that a high electron density on the nitrogen atom of the pyridine ring plays a crucial role in facilitating the formation of hydrogen bonds with DNA. This interaction underscores the compound's capacity to interfere with DNA functions.

Nuclear magnetic resonance (NMR) studies supported these findings, confirming that the interactions between the molecular proliferation inhibitors and DNA indeed lead to the establishment of hydrogen bonds. Such interactions are pivotal for apoptotic signaling pathways,

emphasizing that enhanced binding to genomic DNA is a significant mechanism underlying the anticancer activity of these compounds.

Our correlation analysis of the overall data block conducted as part of our study indicates a potential correlation between AOA and APA. This suggests that some compounds with high antioxidant activity may also have enhanced anticancer properties.

The observation that some compounds may operate through similar or complementary mechanisms highlights the need for further exploration of the relationships between AOA and APA. Investigating how antioxidant properties can enhance the anticancer efficacy of specific compounds is crucial for developing more potent therapeutic strategies.

This research illustrates that, despite extensive previous studies on thiosemicarbazones, many unknowns remain. Their coordination with 3*d* metal ions and modifications of their inner sphere can lead to the development of new compounds with promising biological activity and selective action. Therefore, these substances may have potential applications in drug development, targeted therapies, and combination treatments.

Bee products provide complementary natural antioxidants. Propolis proved most potent (IC_{50} ABTS = 0.08 mg/mL; DPPH = 0.13 mg/mL), ~2000× superior to honey (543 mg/mL), followed by bee bread (1.45 mg/mL), royal jelly (6.65 mg/mL), beeswax/queen bee (9 mg/mL).

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