

# Spectroscopic, thermogravimetric and biological studies of Na(I), Ni(II) and Zn(II) complexes of quercetin

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**Abstract** The Na(I), Zn(II) and Ni(II) complexes with quercetin have been synthesized. The composition of these compounds was established by means of elemental and thermogravimetric analyses. To study the molecular structure of synthesized compounds, many miscellaneous analytical methods, which complement one another, were used: infrared (FT-IR), Raman (FT-Raman) and electronic absorption UV/VIS spectroscopy. For studying the cytotoxic and genotoxic activity of synthesized compounds, bioreporter strain of *Escherichia coli* K-12 *recA::gfpmut2* has been used.

**Keywords** Quercetin · Metal complexes · Thermogravimetry · Cytotoxic study · FT-IR · UV/VIS

## Introduction

Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) is a major flavonoid in human diet such as fruits, vegetables, spices, red wine and tea [1]. Estimated mean intake of total flavonoids in Europe was  $428 \pm 49$  mg/day, and

$136 \pm 14$  mg/day of the total values was monomeric compounds [2]. In Japan, the average quercetin intakes were 16.2 mg/day [3]. The antibacterial [4], antiviral [5], antiallergic [6], anticarcinogenic [7, 8] and antioxidant [9, 10] properties of quercetin were widely studied and described. Moreover, quercetin can effectively chelate metal ions. Recently, the quercetin–metal complexes arouse much interest because of their higher antioxidant and anticancer properties than quercetin alone. Tan et al. [11] revealed that quercetin–nickel (II) complex successfully promotes the cleavage of plasmid DNA, producing single and double DNA strand breaks. In other study, the same authors showed that quercetin–copper(II) complex promoted the cleavage of plasmid DNA, producing single and double DNA strand breaks, and intercalated into the stacked base pairs of DNA. Moreover, the complex showed pro-oxidative properties and induced oxidative DNA damage involving generation of reactive oxygen species such ( $H_2O_2$  and  $CuOOH$ ) [12]. Other study of Tan et al. showed that antitumor activity of quercetin zinc(II) complex might be related to its intercalation into DNA [13].

Metal chelators can affect the bioavailability, speciation and toxicity of different metals. For example, the toxicity of aluminum was linked to many neurological and bone illness [14], and the complexation of quercetin with Al(III) can reduce the concentration of aluminum in diet [15]. Certain water-insoluble nickel compounds exhibit potent carcinogenic activity possibly by mutagenesis, chromosome damage, formation of Z-DNA, inhibition of DNA excision repair or epigenetic mechanisms [16, 17]. The formation of quercetin–nickel, quercetin–chromium or quercetin–copper complexes could as well decrease the toxic effect of these metals. The chelating properties of quercetin are determined by its chemical structure, i.e., the presence of two aromatic rings (benzoyl A ring and

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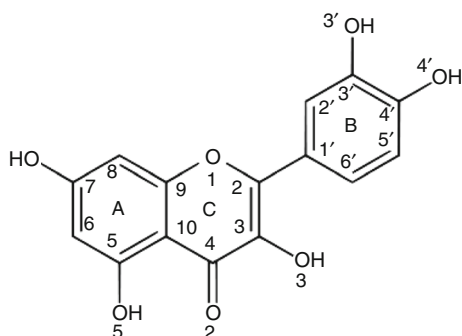
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cinnamoyl B ring) substituted by hydroxyl groups and linked together by O-heterocycle. The possible chelating sites are as follows: 3-hydroxychromone, 5-hydroxychromone and 3',4'-dihydroxyl groups (Fig. 1). Many studies are devoted to explain the chelating site between quercetin and different metals. For example, it was found that Al(III) could form two complexes of stoichiometry of Al(III)/quercetin 1:2 or 2:1 and the first site involved in the metal chelation was the 3-hydroxychromone and the second one was the 3',4'-dihydroxyl group [18]. The study of Bukhari et al. [19, 20] showed that Cu(II), Co(II) formed complexes with quercetin where the metal/ligand ratio was 2:1; the 3-hydroxychromone and the 3',4'-dihydroxyl groups were engaged in chelation. According to Torreggiani et al. [21] quercetin chelates Cu(II) ions through the 3',4'-dihydroxyl groups (metal/ligand ratio 0.5:1), in the excess of metal ions, the C=O group was also involved in metal chelation and the stoichiometry of Cu(II)/quercetin was 2:1. The complexes of Fe(II), Ni(II), Co(II) and Zn(II) with quercetin possessed metal/ligand stoichiometries 2:1, and the 5-hydroxychromone moieties were involved in metal coordination [22]. Moreover, the composition of Cd(II) [23], Ni(II), Co(II), Pd(II) [24], Cu(II) [25], Ca(II) and Mg(II) [26] complexes with quercetin was established as 1:1 in different pH from 5 to 11. In the case of Ca(II) and Mg(II) complexes, the metals were coordinated through a bidentate ligand (through the catechol moiety on the B ring) [26]. Due to the discrepancy in chelation of metal ions by quercetin, it is important to carry out studies that may confirm the exact chelating sites in quercetin molecule.

In this work, the quercetin sodium (I), zinc (II) and nickel (II) compounds were synthesized. Their composition was established on the basis of elemental and thermogravimetric analyses. The molecular structure of quercetin and obtained compounds was studied by IR, Raman and UV/VIS spectra. The studies relying on the synthesis of new derivatives of biologically important phenolic compounds are very important, because as a result the new compounds with the enhanced desirable biological



**Fig. 1** Atom numbering in the structure of quercetin

properties, i.e., antimicrobial, antioxidant and anticancer [27, 28], might be obtained. Many studies revealed that complexation with copper (II) or chromium (III) improves antioxidant properties of metal complexes comparing with the free ligand [19, 29] or complexation with rare earth metals (III) increases the antitumor activity of ligand [30].

## Experiment

### Sample preparation

Zn(II) and Ni(II) complexes with quercetin were synthesized by the following method. To the 0.01 mol of quercetin dissolved in CH<sub>3</sub>OH (20 mL), the 0.02 mol of ZnCl<sub>2</sub> or NiCl<sub>2</sub> was added. By adding NaOH, the pH of the mixture was about 10. After 1.5 h of stirring, the dark yellow precipitates were filtered, washed with the mixture methanol–water 3:1 and dried in room temperature for 3 days. In order to synthesize sodium salt, 0.01 mol of quercetin was dissolved in CH<sub>3</sub>OH (20 mL), and then, the 0.01 mol of NaOH was added. The obtained solution was stirred at room temperature for 1.5 h. After stirring, the reaction mixture was filtered and the filtrate was evaporated slowly at room temperature. The resulting dark yellow product was washed with t-butanol and dried in a desiccator.

### Measurement

The FT-IR spectra were recorded with an Alfa (Bruker) spectrometer within the range of 400–4000 cm<sup>-1</sup>. Samples in the solid state were measured in KBr matrix pellets. FT-Raman spectra of solid samples were recorded in the range of 100–4000 cm<sup>-1</sup> with a MultiRam (Bruker) spectrometer. The resolution of the spectrometer was 1 cm<sup>-1</sup>. Elemental analysis for the mass percentages of carbon and hydrogen was done with Perkin–Elmer 240 equipment. The UV/VIS spectra were registered in the range of 200–800 nm using Agilent Cary UV/VIS spectrophotometer. The thermal stability and decomposition of quercetin complexes were examined using a Setsys 16/18 (Setaram) thermal analyzer recording the TG/DSC/DTG curves. The samples (8–9 mg) were heated in a ceramic crucible in the range 30–1000 °C in flowing air atmosphere with a heating rate of 5 °C/min. The products of dehydration and decomposition processes were established on the basis of the TG curves.

The cytotoxic studies of quercetin and its complexes with Na(I), Ni(II) and Zn(II) were conducted with use of *Escherichia coli* K-12 strain. The dynamic of the growth of bacteria strain within 3-h treatment with quercetin (Q), quercetin sodium salt (Q-Na), quercetin with Zn (II) and

quercetin with Ni (II) was monitored by the use of standard spectrophotometer analysis of optical density (OD) (GloMax<sup>®</sup>, Multi Detection System, Promega) values at the wavelength of 600 nm. The detailed methodology was described in [31].

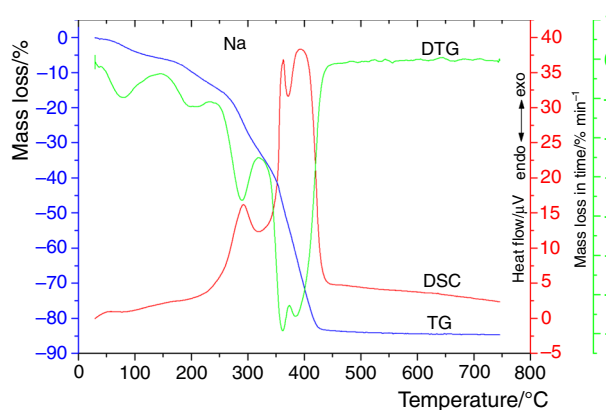
## Results and discussion

### Thermogravimetric and elemental analyses

The results of elemental and thermogravimetric analyses (Tables 1 and 2) allowed us to study the thermal stability as well as the thermal decomposition of Na(I), Zn(II) and Ni(II) complexes of quercetin. The results showed that studied complexes of quercetin were hydrated. Thermo-analytical curves of quercetin metal compounds (Figs. 2, 3, 4) indicated the stages of dehydration process and degradation of organic ligand. The results of thermal analysis data showed that the number of water molecules is in quite good agreement with that defined by elemental analysis [ $\text{Na}(\text{C}_{15}\text{H}_9\text{O}_7) \cdot 1\text{H}_2\text{O}$ ;  $\text{Ni}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 2.5\text{H}_2\text{O}$ ;  $\text{Zn}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 4\text{H}_2\text{O}$ ]. The metal percentages calculated from the metal oxide residues were also in good agreement with the results of elemental analysis (Table 1). The  $\text{Na}(\text{C}_{15}\text{H}_9\text{O}_7) \cdot 1\text{H}_2\text{O}$  salt heated in the temperature range of 30–135 °C dehydrated and formed an anhydrous compound (Fig. 2). The relative mass loss calculated from TG curve being equal to 5.77 % corresponded to the loss of one water molecule (calculated value was 5.26 %). In the temperature range of 145–460 °C, the anhydrous sodium salt of quercetin was finally decomposed to  $\text{Na}_2\text{CO}_3$ . The two and half hydrated nickel(II) complex of quercetin heated in air was stable up to 30 °C. Above this temperature, nickel compound was dehydrated (Fig. 3). The observed mass loss for total

**Table 2** The elemental analysis data of sodium and selected transition metal complexes with quercetin

Complex	C/%		H/%		Metal/%	
	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.
$\text{Na}(\text{C}_{15}\text{H}_9\text{O}_7) \cdot 1\text{H}_2\text{O}$	51.46	52.59	3.07	3.21	6.78	6.72
$\text{Ni}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 2.5\text{H}_2\text{O}$	42.81	44.56	3.03	3.22	15.12	14.49
$\text{Zn}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 4\text{H}_2\text{O}$	39.92	41.13	3.66	3.66	14.58	14.91



**Fig. 2** The TG and DSC curves of sodium salt of quercetin

dehydration process was equal to 11.17 % (calc. 11.11 %). The loss of all water molecules led to creation of anhydrous compound, which gradually decomposes to NiO with formation of intermediate, unstable compounds (195–560 °C). The  $\text{Zn}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 4\text{H}_2\text{O}$  complex dehydrated at 190 °C and forms an anhydrous quercetin complex (Fig. 4). The relative mass loss calculated from TG curve was equal to 16.44 % (calculated value was 16.42 %). In the

**Table 1** Results of thermal decomposition of sodium salt and selected transition metal complexes with quercetin in air

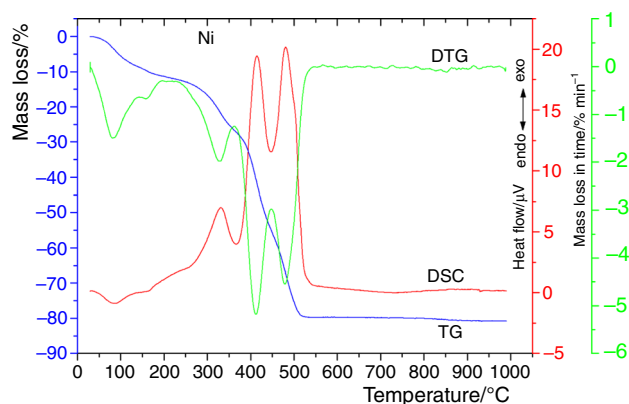
Complex	$T_1/^\circ\text{C}$	$T_{\text{endo}}$	Mass loss/%		Anhydrous form	$T_2/^\circ\text{C}$	$T_{\text{exo}}$	Residue/%		Residue
			Exp.	Calc.				Exp.	Calc.	
$\text{Na}(\text{C}_{15}\text{H}_9\text{O}_7) \cdot 1\text{H}_2\text{O}$	30–135	80	5.77	5.26	$\text{Na}(\text{C}_{15}\text{H}_9\text{O}_7)$	145–460	290	15.59	15.49	$\text{Na}_2\text{CO}_3$
$\text{Ni}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 2.5\text{H}_2\text{O}$	30–195	85	11.17	11.14	$\text{Ni}(\text{C}_{15}\text{H}_8\text{O}_7)$	195–560	330	19.24	18.49	NiO
							415			
							480			
$\text{Zn}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 4\text{H}_2\text{O}$	30–190	95	16.44	16.45	$\text{Zn}(\text{C}_{15}\text{H}_8\text{O}_7)$	190–480	420	18.15	18.60	ZnO

$T_1$  Temperature range of dehydration

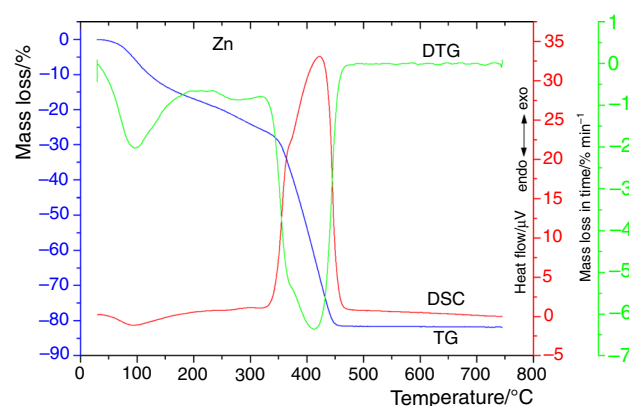
$T_2$  Temperature range of degradation of anhydrous complexes to suitable oxides or  $\text{Na}_2\text{CO}_3$

$T_{\text{endo}}$  Peak top of endothermic effect

$T_{\text{exo}}$  Peak tops of exothermic effect



**Fig. 3** The TG and DSC curves of nickel (II) complex of quercetin



**Fig. 4** The TG and DSC curves of zinc complex of quercetin

temperature range of 190–480 °C, the anhydrous zinc complex of quercetin was finally decomposed to ZnO. According to the literature data, other metal complexes of quercetin showed similar thermal behavior. The thermogravimetric analysis of the sodium(I) salt and Fe(II) complex of sulfonic derivative of quercetin revealed that these compounds underwent one step dehydration in the temperature range 20–150 °C for sodium salt (loss of four water molecules) and 20–160 °C for the iron complex (loss of 12 molecules of water) [32]. The increase of temperature in the range of 150–560 °C caused the decomposition of the anhydrous compounds. For the vanadyl complex of quercetin (i.e.,  $\text{VO}(\text{OH})\text{C}_{15}\text{H}_{10}\text{O}_7(\text{H}_2\text{O})_2$ ), one step of dehydration was established as well [33]. The loss of two water molecules occurred in the temperature range 50–150 °C. The next steps were associated with the oxidative degradation of organic ligand and oxidative degradation of the remained intermediate that led to the final product formation, i.e.,  $\text{V}_2\text{O}_5$ .

According to the results of thermal and elemental analyses, the proposed possible place of metal coordination was the 3',4'-dihydroxyl groups in the B ring with  $\eta^2$  chelating catechol group (Fig. 5) [34]. Although

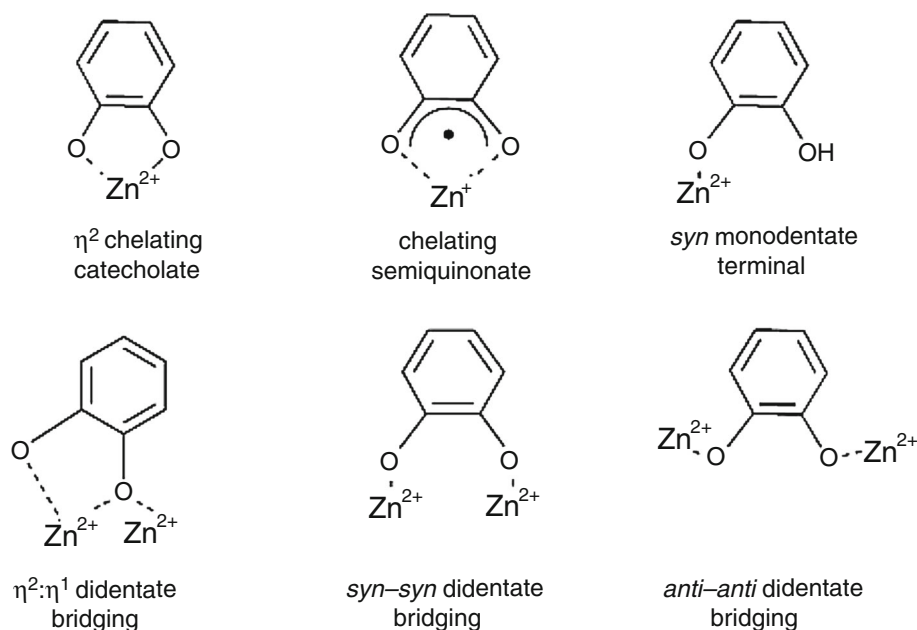
generally the chelating properties of flavonoids have been attributed to the presence of the 3- and 5-hydroxychromone moieties, there were studies revealing the catechol moiety as well [18, 26, 35]. For example, in the paper of Conrad and Merlin describing the Al(III) complex of quercetin, in the alkaline medium one of the complex form was Al(III)/quercetin 1:1 where the complexing site was catechol group [18]. In the acidic solution, the ortho-dihydroxyl group was not involved in Al(III) complexation. In the alkaline medium, the previous studies [18, 36] showed that the 3',4'-dihydroxyl group possessed strong chelating properties in comparison with the 3- and 5-hydroxychromone group.

### Infrared and Raman analysis

The assignments of the wavenumbers of selected bands from the FT-IR and FT-Raman spectra of quercetin and its sodium salt and complexes with Zn(II) and Ni(II) are gathered in Table 3 and shown in Figs. 6 and 7 (additional spectra in the Electronic Supplementary Material). The assignment was done on the basis of the literature data [19–21]. In the spectral range of 3390–3250  $\text{cm}^{-1}$  bands assigned to the stretching vibrations of the -OH groups appeared. Strong band derived from the stretches of the C=O in quercetin molecule was present at 1672  $\text{cm}^{-1}$ . The stretching  $\nu(\text{OH})$ ,  $\nu(\text{C}=\text{O})$  and deforming  $\beta(\text{C}-\text{OH})$  vibrations were moved toward lower wavenumbers due to the breakdown of the hydrogen bonds in favor of the metal chelation. The formation of metal complexes affected as well the electronic charge distribution in the whole molecules what can be seen via the decrease in the wavenumbers of the aromatic ring vibrations, increase in the wavenumbers of  $\nu(\text{C}-\text{O}-\text{C})$  and occurrence in the spectra of complex bands assigned to the  $\nu(\text{C}-\text{O})$  of the catechol group engaged in metal coordination. The presence of the stretching metal-O vibrations proved the metal coordination.

### UV/VIS analysis

In Table 4, the maximum of bands from the UV/VIS spectra of quercetin and sodium(I), zinc(II) and nickel(II) compounds is shown. The bands were related to the  $\pi \rightarrow \pi^*$  transition within the aromatic rings of ligand. The band I (at about 256 nm) corresponded to A ring absorption, whereas band II (at  $\sim 370$  nm) was associated with the B ring absorption. The band I was shifted toward higher and lower wavelengths only in the case of spectra of Zn(II) complex registered in the methanolic and aqueous solution, respectively. The band II, however, was moved to higher wavelengths (bathochromic shift) for spectra registered for both Ni(II) and Zn(II) complexes in both methanolic and

**Fig. 5** Different types of metal ion coordination by the ortho-dihydroxyl group [34]**Table 3** The wavenumbers and intensity of selected bands from the FT-IR and FT-Raman spectra of studied compounds

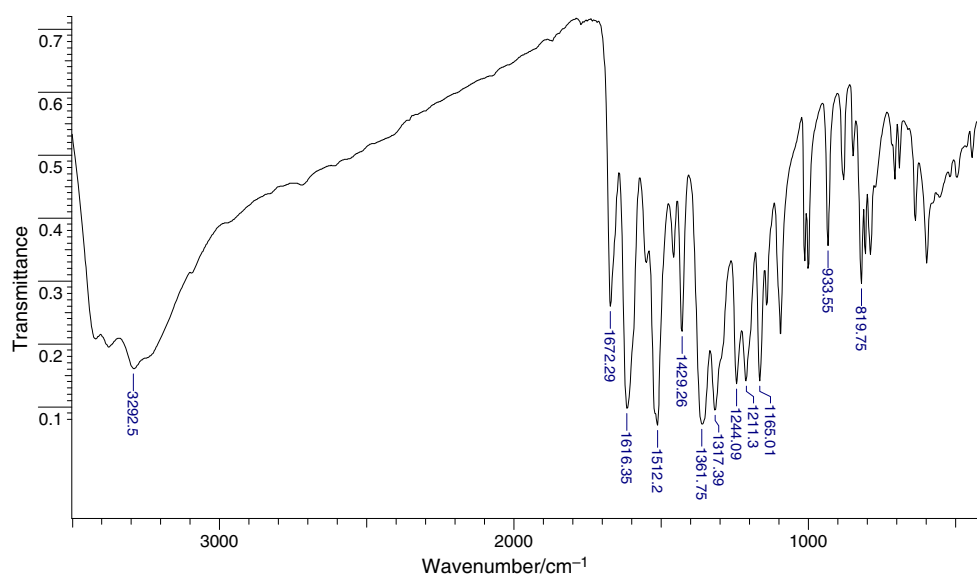
Bands	Quercetin				Na(I)-Q salt		Zn(II)-Q complex		Ni(II)-Q complex	
	IR	Int	Raman	Int	IR	Int	IR	Int	IR	Int
$\nu(\text{OH})^*$	3390–3250	s			3390–3250	s	3390–3250	s	3390–3250	s
$\nu(\text{C}=\text{O})$	1672	s			1652	s	1651	m	1651	s
$\nu$ ring	1616	vs	1615	s	1601	s	1614	vs	1601	vs
$\nu$ ring	1512	vs	1512	s	1508	s	1505	vs	1503	s
$\nu(\text{C}-\text{O})$ catechol group							1462	m		
$\nu$ ring	1429	s	1430	s					1444	s
$\nu(\text{C}-\text{O})$ catechol group							1402	s	1421	s
$\beta(\text{C}-\text{OH})$	1362	vs	1353	s	1362	m	1344	s	1346	s
$\beta(\text{CH})$	1317	s	1314	s			1319	s	1319	s
$\nu(\text{C}-\text{O}-\text{C})$	1244	vs	1243	s	1256	s	1250		1246	s
$\beta(\text{OH})$	1211	vs	1212	s	1209	s	1211	s	1210	s
$\nu(\text{C}-\text{CO}-\text{C}) + \beta(\text{C}-\text{CO}-\text{C})$	1165	vs	1162	s	1167	m	1169	s	1167	s
$\nu(\text{metal}-\text{O})$					463	m	453	vs	443	s

\* Symbols denote:  $\nu$  stretching vibrations,  $\beta$  deforming in-plane vibrations; *int* intensity, *m* medium, *s* strong, *vs* very strong

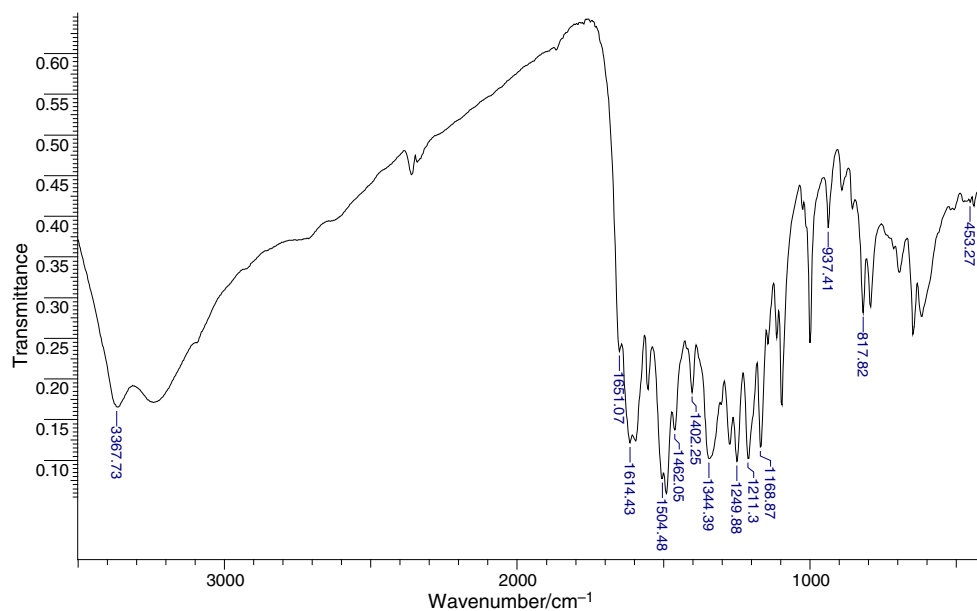
aqueous solutions. It can be explained by the extension of the conjugated system as a result of metal complexation. The very distinct bathochromic shift of band II might confirm the participation of the B ring in metal chelation. Moreover, there were evident differences between the value of the shift in the spectra of sodium salt and transition metal complexes, what could be explained by different type of metal-ligand bonding, i.e., ionic in the sodium compound and covalent in the Ni(II) and Zn(II) complexes of quercetin.

### Cytotoxic study

The results of the cytotoxic study are shown in Fig. 8. Monitoring of the bacteria culture growth of *E. coli* K-12 strain after 3 h of incubation with chemicals indicated a significant decrease in the optical (OD) of bacteria culture incubated with quercetin and Ni(II) complex at the concentration of  $0.001 \text{ mg mL}^{-1}$  in comparison with the control sample. There were no statistical differences for OD values in the case of the other tested chemicals.



**Fig. 6** The FT-IR spectra of quercetin

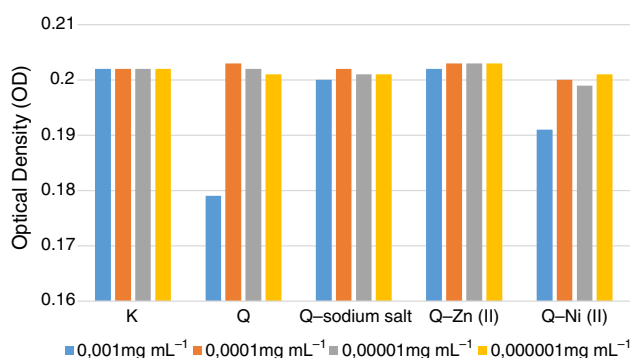


**Fig. 7** The FT-IR spectra of zinc(II) complex of quercetin

**Table 4** The maximum of absorption from the UV/VIS spectra of aqueous and methanolic solutions of quercetin and its metal compounds

Compound	Aqueous solution		Methanolic solution	
	Band I/nm	Band II/nm	Band I/nm	Band II/nm
Quercetin	256	370	256	374
Na(I)-Q salt	256	370	256	374
Zn(II)-Q complex	250	427	268	430
Ni(II)-Q complex	256	426	257	429





**Fig. 8** The comparison of optical density (OD) values for stationary phase *E. coli* K-12 treated 3 h with quercetin (Q), quercetin sodium salt, Zn(II) and Ni(II) complexes of quercetin in comparison with control sample (K) (bacteria strain in PBS buffer without treatment of any chemicals). Data points represent mean values  $\pm$  SD ( $n = 8$ )

The obtained results indicated the cytostatic ability of quercetin and its complex with Ni (II) in relation to *E. coli* living cells. The details of this study are presented in [31].

## Conclusions

The sodium(I) salt and zin(II) and nickel(II) complexes of quercetin were obtained in the solid state. The composition of these compounds was established by means of thermogravimetric and elemental analyses. The general formula of the obtained compounds were  $\text{Na}(\text{C}_{15}\text{H}_9\text{O}_7) \cdot \text{H}_2\text{O}$ ,  $\text{Ni}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 2.5\text{H}_2\text{O}$  and  $\text{Zn}(\text{C}_{15}\text{H}_8\text{O}_7) \cdot 4\text{H}_2\text{O}$ . The quercetin complexes dehydrated in the range of temperature about 30–195 °C (in the case of Zn(II) and Ni(II) compounds) and 30–135 °C (sodium salt of quercetin). These compounds totally decomposed in the temperature range 145–460 °C (Na salt), 195–560 °C (Ni complex) and 190–480 °C (Zn complex). In the alkaline medium, Zn(II) and Ni(II) ions were chelated by the 3',4'-dihydroxyl groups in the B ring of quercetin. The changes in the FT-IR and UV/VIS spectra of complexes comparing with the spectra of quercetin resulted from metal cation coordination and alternation in the electronic charge distribution in ligand. Mostly affected were bands assigned to the ring and C–OH vibrations. Metal ion coordination through the hydroxyl group caused an appearance of new bands assigned to  $\nu(\text{C}-\text{O})$  in the FT-IR spectra of complexes. The cytotoxic study showed that *E. coli* K-12 strain is sensitive to quercetin and Ni(II) complex of quercetin at the concentration of 0.001 mg mL<sup>-1</sup>.

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