BULETINUL INSTITUTULUI POLITEHNIC DIN IAȘI
Publicat de
Universitatea Tehnică „Gheorghe Asachi” din Iași
Volumul 64 (68), Numărul 3, 2018
Secția
CHIMIE şi INGINERIE CHIMICĂ

A SUITABLE METHOD FOR POLYPHENOLS COMPLEXES WITH COPPER

BY

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Received: June 26, 2018
Accepted for publication: July 30, 2018

Abstract. Polyphenols represent a class of natural compounds with significant bioactive attributes. One of the important property of polyphenols is the complexing of ion metals. Following this process, some complexes with impressive antioxidant properties could be obtained. The literature lists several methods considering different polyphenols, ion metals and reaction solution as well as experimental conditions including concentration, pH and temperature. This great variety of possibilities requires an analysis to establish the suitable reaction solution and the main parameters as well as their range of variation. Withal, some polyphenols model molecules have to be proposed.

Keywords: polyphenols; metal ions; complex combination; reaction solution and parameters.

1. Introduction

Polyphenols represent a large family of natural compounds structurally characterized by the presence of several phenolic groups (Maru *et al.*, 2014). These compounds are secondary metabolites synthesized by plants (Lin *et al.*,

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2016), which are essential for growth, development, pigmentation and pest control of biological systems.

Considering their chemical structure, polyphenols can be classified into two major groups: nonflavonoids and flavonoids each including more class. The nonflavonoids group cover simple phenols (C1), hydroxybenzoic acids (C6-C1), acetophenones (C6-C2), hydroxycinnamic acids (C6-C3), naphthoquinones (C6-C4), xanthones (C6-C1-C6), stilbenes (C6-C2-C6), lignans, neolignans $(C6\text{-}C3)_2$, hydrolysable tannins(C6-C1)n and lignin (C6-C3)n.

The flavonoids, defined by a more unitary structure (C6-C3-C6) enclose flavones, flavonols, flavanols, flavanones, isoflavones and anthocyanins.

Despite the great variety of classes, polyphenols exhibit some properties of great interest among the main studied being the strong antioxidant nature (Lin *et al*., 2016; Volf, 2011) that prevent the appearance of free radicals by combating cellular oxidation (Khalafalla *et al*., 2010; Mayo *et al*., 2012). Consequently, this process induces the preservation of essential biomolecules such as proteins, DNA, lipoproteins and lipids (Yazdanparast and Ardestani, 2007), causing numerous benefits in biological systems.

A specific feature of polyphenolic compounds is the capacity of complexing ion metals. Following this process some complexes with impressive antioxidant properties (Procházková *et al*., 2011) were obtained. The complex metal-flavonoid combinations amplify the therapeutic properties of polyphenols, being frequently more active compared to free ligands (Samsonowicz *et al*., 2017). As well, these complexes manifest other biological properties and thus received more interest in different fields such chemistry, biology, phytotherapy, environmental science and not only (Dasgupta *et al*., 2015).

The goal of this study was to review the complexation methods reported in literature in order to establish a suitable reaction environment and the main reaction parameters as well as their range of variation. Withal, some polyphenols model molecules have to be proposed.

2. The Polyphenols Complexation Reaction

Since the polyphenols are molecules characterized by numerous hydroxyl groups, the formation of metal-ligand bonding occurs through the ability to scavenge radicals by electron transfer processes. Polyphenols have a high affinity for transition metals in complex compounds formation, due to their ability to easily form covalent bonds.

Considering the flavonoids(+)-Catechin and (-)-Epicatechin, that are two stereoisomers, the reaction mechanism implies substitution bonds at the 3’, 4’ positions of the dihydroxyl groups in B ring (Brown *et al*., 1998; Samsonowicz *et al*., 2017) (Fig. 1).

Structurally, flavonols consist of two aromatic rings (A and B rings) linked by a 3-carbon chain that forms an oxygenated heterocyclic ring (C ring) and hydroxyl group substituted in 3 position (Samsonowicz *et al*., 2017).

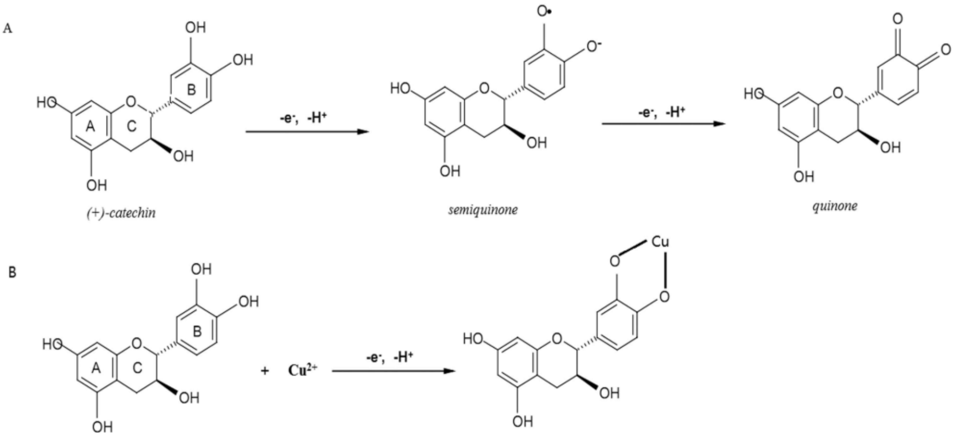

Fig. 1 – Oxidation reaction of (+)-Catechin (A) and complexation reaction between (+)-Catechin and Cu^{2+} (B) (after Li *et al.*, 2015).

Another compound commonly used is gallic acid, GA, correspond to class of phenolic acids. Gallic acid presents also a great affinity to transition metals, especially iron and forms complexes of high stability. Iron is attached to gallic acid through two adjacent hydroxyl groups presented on aromatic ring (Mamdouh *et al*., 2012) (Fig. 2).

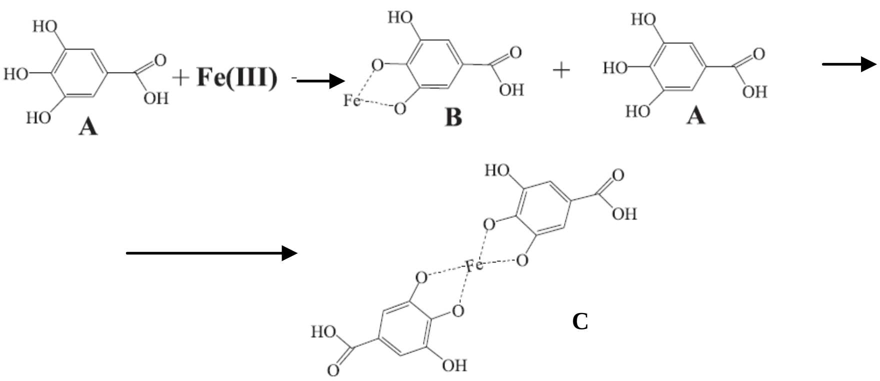

Fig. 2 – Possible reaction mechanism for Fe(III) and GA, (after Dong *et al*., 2016).

The metal ion is coordinated to two adjacent hydroxyl groups of the gallic acid (the third hydroxyl group remains protonated), forming the complex B.

The excess of gallic acid would compete with semiquinone for Fe(III) increase the formation of complex C (Dong *et al*., 2016).

3. Methods for Obtaining Polyphenols Complexes with Ion Metals

A large number of experimental studies on the chemical structure and mechanism of polyphenols coordination have been published.

Referring to the latest research reported, the Table 1 presents certain aspects related to some polyphenols and metal ions subjected for complexation, to concentration and metal-ligand ratio as well as experimental conditions as pH, temperature and reaction environment used to obtain stable complex combinations.

Table 1
Methods for Obtaining Complex Combinations, Referring to the Latest Research Reported in Literature

Polyphenols (L)	Solution	Metal ion (M)	Experimental conditions	M:L M:L:L\` ratio	References
(+)-CatH	$KC_4H_5O_6$	Cu(II)	C_L=4 mM C_M=0-40 mgL^{-1} pH=3.7 T=20-40°C	1:1	Es-Safi *et al.*, 2003
Gallic acid (-)-EGCG	MeOH	Cu(II)	C_M=2 mM pH=1-13 T=20°C, -196.15°C, -113.15°C	1:0 to 1:10	Pirker *et al.*, 2012
(-)-ECG	$C_2H_3O_2Na$	Cu(II)	C_L=0.057 mM C_M=0.58 mM pH=5 T=21-42°C	2:1	Ghosh *et al.*, 2006 Ghosh *et al.*, 2008
(-)-EGCG			C_L=0.17 mM C_M=0.58 mM pH=5 T=21-42°C		
(+)-CatH Quercitin Rutin	$C_2H_3O_2Na$ +EtOH (8%) MeOH	Zn(II) Cu(II)	C_L=0.58 µM C_M=0.60-1.45 µM pH=4	1:1 2:1	Esparza *et al.*, 2005
Condensed tannins	DDW	Fe(III)	pH=7-8	–	Çakar *et al.*, 2016

Table 1
Continuation

Polyphenols (L)	Solution	Metal ion (M)	Experimental conditions	M:L M:L:L` ratio	References
(-)-EC (-)-EGC (-)-ECG (-)-EGCG	HCl	Cu(II) Fe(II) Fe(III)	C_L=0.5– 2 mMpH=7-8 T=25°C	1:1	Yasuda *et al.*, 2012
Gallic acid	$C_2H_3O_2Na$	Fe(III) Fe(II)	C_L=0.1 mM C_M=0.18 mM pH=5-6.3	–	Knockaert *et al.*, 2014
Gallic acid	$C_4H_6O_6$, HNO_3 + $NaNO_3$	Cu(II); Ni(II) Co(II)Zn(II)	pH=3-8.2 T=25°C	1:1 1:2 1:1:1	Radalla, 2015
FSE MYC Quercitin KMP Galangin	DMSO $C_{26}H_{20}N_2$	Cu(I) Cu(II)	C_L=100 µM C_M=100 µM pH=7.5	–	Arif *et al.*, 2018
(-)-EGCG (+)-CatH	DMSO	Zn(II)	C_L=100 µM pH=7.4-11 T=25°C	1:1	Clergeaud *et al.*, 2016
(+)-CatH	H_2O_{di}	Mg(II)	C_L=0.5mM C_M=0.5mM T=26°C	1:1	Zhenhua *et al.*, 2015
Leucocia-nidin	DMSO H_2O_d $C_4H_6O_3$	Cu(II) Fe(II)	pH=1.7-5.8 T=18-100°C	–	Nien-Chih *et al.*, 2017
(+)-CatH	$C_2H_3O_2Na$ MeOH	Zn(II)	pH=4	1:1 1:2	Yasarawan *et al.*, 2013
Quercitin Rutin Hyperin	PO_4^{3-} $C_2H_3O_2Na$	Cu(II)	C_L=1 mM C_M=5 mM pH=4-7 T=20°C	–	Zhang *et al.*, 2018
Naringin	MeOH	Cu(II)	C_L=2.5x10^{-4}mol C_M=1.25x10^{-4}mol T=242°C	–	Mello *et al.*, 2007
Quercitin	MeOH	Cu(II)	C_L=4x10^{-4} M C_M=4x10^{-4} M T=20°C	1:9 to 9:1	Bukhari *et al.*, 2009
Rutin	MeOH	Zn(II)	T=37-40°C	–	Ikeda *et al.*, 2015

Table 1
Continuation

Polyphenols (L)	Solution	Metal ion (M)	Experimental conditions	M:L M:L:L` ratio	References
Chrysin	MeOH	Cu(II)	pH=8 T=20°C	1:2	Samsonowicz *et al.*, 2017
Polyphenols (tea extract)	EDTA	Fe(II)	C_M=30 mmol/L pH=7 T=20°C	–	McGee *et al.*, 2018
(-)-EGCG	$C_2H_3O_2Na$	Cu(II)	C_L=0.25 mM C_M=1 mM pH=5	1:2	Zhang *et al.*, 2017
KMP Luteolin	PO_4^{3-}	Cu(II)	C_L=1 mM C_M=1 x 10^{-6} M to1 x 10^{-11}M pH=7.5	–	Oztekin *et al.*, 2011
Gallic acid	H_2O_d	Fe(III)	C_L=100 mM C_M=100 mM pH=8.5	1:1	Barcelo *et al.*, 2014
Luteolin	$C_2H_3O_2Na$ BCS	Cu(II)	C_L=0.25 mM C_M=100 mM pH=4.5-5.5	–	Riha *et al.*, 2014
Gallic acid	H_2O_{mi}	Cu(II)	C_L=5 mM C_M=0.1–7.5 mM pH=11	1:0 1:1 1:2 1:5 1:10	Severino *et al.*, 2011
Henna 8-OQ	MeOH	Cu(II)	C_L=287 mmol C_M=2.87 mmol	1:1 1:2 1:3 1:1:1 1:2:1	Shebl *et al.*, 2017
Condensed tannin	H_2O_{di}	Fe(II) Cu(II)	T=25°C, 100°C	–	Hsiao *et al.*, 2017
Quercitin (+)-CatH Rutin	MeOH:H_2O (80%:20%)	Fe(III) Cu(II) Zn(II)	C_L=2-5x10^{-5} M C_M=5-8x10^{-2}M pH=7.4 T=25±2°C	–	Cherrak *et al.*, 2016

*Abbreviations: (+)-CatH=(+)-catechin; GA→gallic acid; (-)-EGCG→(-)-epigallocatechin gallate; (-)-ECG → (-)-epicatechin gallate; Q → quercitin; RUT → rutin; (-)-EC → epicatechin; (-)-EGC → epigallocatechin; FSE → fisetin; MYC → myricetin; KMP → kaempferol; 8-OQ →

8- hydroxyquinoline; Henna → 3-formylchromone; MeOH → methanol; EtOH→ ethanol; H_2O_d → distilled water; H_2O_{di} → deionized water;H_2O_{mi}→millipore water; Lutl→ luteolin, C_L→ ligand concentration; C_M→ metal ion concentration T→ temperature; M:L and M:L:L` → stoichiometric metal-ligand ratio.

Several polyphenols were considered for possible complexation reactions. The most used was gallic acid, the simplest phenolic acid molecule also wide spread in plants. From flavonoids, rutin, quercitin and kaempferol are also propose for complexation studies. Quercetin and rutin were mostly examined hydroxyflavonols. Even if quercetin present a poor bioavailability in *vivo* due to its poor solubility, its complexes with transition metals show increasing bioavailability (Samsonowicz *et al*., 2017). These molecules, occurring especially in fruits and vegetables, are extensively studied due to their pharmacological effects, including anti-inflammatory, antiproliferative, and protective properties against oxidative stress (Angeloni *et al.*, 2012).

Other flavonoids such as (+)-Catechinor its derivatives as (-)-Epicatechin(-)-Epigallocatechin gallate and (-)-Epicatechin gallate are intensely studied due to potential therapeutic activities such as antibacterial, antioxidant, anticancer activities or prevention of atherosclerosis. Catechins have low bioavailability and stability in slightly alkaline or neutral solutions and are incapable of crossing cell membranes. However, the catechin derivatives exhibit greater improvements in biological and chemical activity (Kumar *et al*., 2015).

Recently, even condensed tannins or crude polyphenols extracts were subjected to complexation reaction expressing the large interest in the topic.

Considering the metal ion, by far the most used are transition metals, especially iron, copper, zinc, nickel, cobalt or magnesium. It is well known these metals are part of enzymes and proteins (tyrosine, hemocyanin, ascorbate oxidase etc.) favoring metabolic and catalytic processes.

The complexation reactions were conducted in the presence of several solutions or reaction environment such as water, ethanol, methanol, water/alcohol, sodium acetate, potassium acid tartrate or DMSO solutions.

One of the important factors influencing the complexation reaction is the pH value. Depending on pH, the hydroxyl ion may lead to deprotonation and then to complexes.

According the state of the art, three model molecules, illustrative for polyphenols group, have to be considered: gallic acid (a hydroxybenzoic acid), and resveratrol (stilbens) from nonflavonoids polyphenols and (+)-Catechin and (-)-Epicatechin from flavonoids ones. Also, three different reaction solutions: sodium acetate, ethanol/water and potassium hydrogen tartrate could be evaluated.

The complex combinations could be carried out considering the following parameters range: the ligand concentration between 2 and 4 mM, copper ions concentration from 0.781 mM to 6.25 mM, aqueous potassium hydrogen tartrate 20 mM in ethanol 20%, v/v and sodium acetate 20 mM at pH between 3 and 5. A pH-meter and a UV-vis spectrometer have to be used to control the pH and reveal the complex combination formation indicated by the occurrence of a yellow to orange colour. The UV-vis spectra reveal the formation of complexes in B ring.

4. Conclusions

This review offers an overview of the main group of polyphenolic compounds, including the chemistry reaction with metal ions as well as a brief description of the main reaction parameters.

Precipitation of some metal ions such copper(II) and zinc(II) by low molecular weight phenols, such gallic acid or (+)-Catechin and (-)-Epicatechin or crude phenolic extracts have to be studied at pH 5. The metal ions precipitation depends on the initial concentration of both metal and phenolic compounds and on the control of acidification, which results from complexation. The copper/phenol ratio in the precipitate could be determined by elemental analysis. Stability of the precipitates obtained with copper(II) and various polyphenols in water, sodium acetate, ethanol/water have to be considered.

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METODE ADECVATE PENTRU OBȚINEREA DE COMPLECȘI POLIFENOLI-IONI METALICI

(Rezumat)

Polifenolii reprezintă o clasă de compuși chimici ce se găsesc larg distribuiți în regnul vegetal, având importante proprietăți biologic active. O caracteristică importantă a compușilor polifenolici este cea de a complexa cu ionii metalici. Literatura prezintă numeroase exemple de astfel de reacții de complexare însă condițiile de obținere sunt foarte diferite. În acest context este necesară o trecere în revistă a posibilităților raportate și o evaluare a condițiilor de lucru pentru obținerea facilă a unor complecși cât mai stabili.

Complexarea între compuși polifenolici cu moleculă mică precum acidul galic, sau catehina/epicatehina trebuie condusă la pH 5. Reacția depinde de concentrația inițială a ionului metalic și a compusului polifenolic, dar și de controlul pH-ului ce se poate modifica mult în timpul reacției de complexare.