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5Protocatechuic acid-metal-nicotine complexation study for chelation of smoking-related poisoning

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23 May 2020 Keywords: Chelation Antioxidant Nicotine Heavy metals Poisoning abstract Nephropathy in tobacco smoker is postulated to be caused by nicotine (Nic) and catalyzed by various heavy metals (M(II) = Ni(II), Pb(II), and Cd(II)) contained in commercial cigarettes. Once absorbed through the lungs, these compounds will eventually be ended in the kidney, and thus, trigger various diseases. Metal chela- tion therapy is

2known as one of the efficient treatments to reduce

the level of toxic metal in intoxicated patients. Here the interaction tendency of Nic and heavy metals to form complexes was investigated at a physiological condition (310.15 K and

100.15 mol·dm-3 NaCl). The stability constant of the

metal-Nic complex obtained in this study shows the possible binding between these two compounds. For the simultaneous removal of heavy metals and Nic, protocatechuic acid (PCA) was used since this antioxidant is also known to be deposited in the kidney. Thus, the interaction between PCA, Nic, and heavy metals is possible. In this work, stability constant of NiPCANic, NiPCA2Nic, PbPCANic, CdPCANic, and CdPCA2Nic were determined. Species distribution diagram of the ternary system showed that MPCANic complexes could be dominantly formed in pH 7.4 system when an ex- cess amount of antioxidant was added. This result suggests the possible usage of antioxidants for the simulta- neous removal of Nic and heavy metals via the metal chelation principle. © 2020

9Elsevier B.V. All rights reserved. 1. Introduction

People with tobacco smoking habits are prone to experience kidney disorders known as nephropathy. Formerly nicotine (Nic) in tobacco was thought to be the sole cause of nephropathy, but this only became a contemporary theory. Many studies have proven that, during smoking, not only Nic but also heavy metals enter the body and then be deposited in kidneys — thus aggravating nephropathy and triggering vascular endothelium damage or other health problems. Nic is an active compound that affects the nervous systems and causes addiction in many cases of tobacco addicts [1,2]. For many tobacco addicts, a sudden cessation of Nic supply (during Nic withdrawal attempt) can cause nau- sea, sore throat, headache, restlessness, insomnia, constipation, and tin-gling, thus known as Nic withdrawal syndrome. The peak of these symptoms is perceived between two to three days after withdrawal, which is a critical phase where addicts often gave up [3,4]. In the end, * Corresponding author. E-mail address: artikelisa@mail.ntust.edu.tw (A.E. Angkawijaya). 1These authors contribute equally, the accumulation of Nic and heavy metals in the kidneys is still an issue for tobacco addicts. The content of heavy metals in one cigarette varies from 0.5–1.5 µg for Cd, around 1.2 µg for Pb, and 0.078–5 µg for Ni [5–8]. Many studies show that heavy metal from tobacco smoke accumulated in some cru- cial organs such as kidneys, lungs, brain, and blood cells [4,7-9]. Nic, through its chelating action, is reportedly able to bind to some heavy metals, thus reduce the toxicity of heavy metals [10]. However, along with the consumption of Nic from tobacco smoking, heavy metals will also enter the body and create an endless detox-retoxification cycle. As a breakthrough to this endless cycle, we proposed the usage of an an-tioxidant, namely protocatechuic acid (PCA: 3,4-dihydroxybenzoic acid), for heavy metals and Nic intoxication. PCA is an antioxidant commonly found in fruits, nuts, vegetables, and various herbal medicines. A study by Ma et al. shows that PCA can be readily absorbed into humans' and animals' body through metabo- lism and tends to accumulate in the kidneys after administration [11]. Various studies reported the massive usage and benefit of PCA as a po- tent antioxidant, antimicrobial, anti-inflammatory agent, as well as pro- tectant against heavy metal toxicity [12-15]. Nevertheless, PCA is known for its potential therapeutic activity against numerous diseases.

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. As mentioned, several studies have shown that the kidney is one of the organs where Nic, PCA, and heavy metals built up [1,2,9,11]. Thus, it is expected that these accumulated substances will interact with each other. In this work, the interaction of metal-ligand complex formation be- tween PCA and Nic as organic ligands and heavy metals was studied. Here we reported that complex formation between PCA, divalent heavy metals (M(II) = Ni(II), Pb(II), and Cd(II)) and Nic are possible due to the presence of active binding sites. Specifically, Nic possesses ni- trogen active metal-binding sites in its pyridine and pyrrolidine ring, while PCA possesses three oxygen binding sites in the form of carboxyl and hydroxyl groups. The complex formation constants of binary sys- tem of M(II)-PCA or M(II)-Nic, and ternary system of PCA-M(II)-Nic were investigated in this work, with the aim to prove the chelating abil- ity between the investigated substances which can lead to heavy metal and Nic detoxification. The knowledge of the interaction of these compounds

9in binary and ternary systems will be the foundation for the

study of their complex interaction with other coexisting compounds in human blood plasma. software. For each solution mixture, at least three repetitions of pH- potentiometry titration were done. 2.3. Data analysis Hyperquad2008 program was used to process the obtained titration curves. This program uses a non-linear least-square algorithm to fit the proposed composition of complex species with the titration curve from pHpotentiometric titration and signified the best-fitted model by its sigma value [17]. For each fitting refinement, at least 100 points were used. From here, the protonation constants of the ligand (L), and stabil- ity constant of the metal-ligand in both binary and ternary system can be determined and expressed as the overall formation constant (log β). The higher value of log β indicated more excellent stability of the metal-ligand complex formed [18]. Once obtained, log β values of vari- ous metal-complex species were introduced to the HySS2009 program to simulate and illustrate the distribution of every possible species in the system at different pH [19]. 2. Materials and methods 2.1.

1Materials and solutions All chemicals used were of analytical grade and were used without

any pretreatment. The

2solutions were prepared daily in distilled deion-ized water with 18

.3 MΩ·cm. PCA (C7H6O4, Alfa Aesar, Heysham, En- gland); Nic (Alfa Aesar, Heysham, England), nickel chloride (NiCl2·6H2O, Alfa Aesar, Heysham, England), lead nitrate (Pb(NO3)2, Sigma, St. Louis, MO), cadmium nitrate tetrahydrate (Cd(NO3)2·4H2O, Alfa Aesar, Heysham, England), sodium chloride (NaCl, Showa, Tokyo, Japan), hydrochloric acid (HCl, Fisher Scientific, Hampton, NH), sodium hydroxide (NaOH, Fisher Scientific, Loughborough, UK), and oxalic acid (C2H2O4, Kukusan, Tokyo, Japan). 2.2. pH-potentiometric titration The pH-potentiometric titration was done according to the method described by Chandra et al. [16]. The solutions were prepared in a 50 mL volumetric flask with composition as listed in Table 1. Prior to ti- tration, each mixture was kept in 100 mL double-walled equilibrium cell at maintained temperature 310.15 K for at least 15 min to reach an equilibrium temperature. Afterward, each solution was titrated against ~0.1 mol·dm-3 standardized carbonate-free NaOH. The com- plexation studies were done



NaCl to mimic the human body fluid. The titrations were performed on 888-Titrando autotitrator equipped with

2an Ecotrode Plus pH glass electrode

, 805 Dosimat, 802 stirring rod, and 804 Ti stand. For the setting of titration parameter and data acquisition, the autotitrator

2was connected to a computer equipped with Tiamo 2.3

1Table 1 Metal (M) and ligand (L) concentrations used to determine the overall formation con- stants of the complexes at 310.15 K and 0.15 mol·dm-3 NaCl. Systems [M]: [M] Purpose [L] (mol·dm-3

) ratio L -

LNic 1:2:2 1.10-3 Determination of protonation constant Determination of metal-ligand complexes in the

2binary system Determination of metal-ligand complexes

in the ternary system 3. Result and discussion The titration curve of the system containing Ni(II) is presented in Fig. 1. Here, the representative curve includes titration curves of PCA, Nic, PCA/Nic + Ni(II)

7at the metal-ligand ratio of 1:1

, and PCA + Nic + Ni(II) at ratio 1:1:1. In both of the PCA + Ni(II) and Nic + Ni(II) systems, the curves shifted to lower pH compared to the re- spective PCA and Nic only.

2This shifting indicates that the formation of $M({\ensuremath{\mathsf{II}}})\-\ensuremath{\mathsf{Iigand}}$ complex occurred when the ligand

released its proton; thus, the buffer region was shifted to lower pH values. 3.1. Protonation constant The protonation constant of the ligands of Nic and PCA are presented as stepwise dissociation constant (pKa) in Table 2. The sequence of pro- tonation of Nic is shown in Fig. 2. The first acid dissociation (pKa1) of Nic is 3.01, which occurs at the ammine site of its pyridine ring. The second dissociation (pKa2) has a value of 7.85, which accounts for amine in the pyrrolidine ring. The obtained pKa is comparable to the previously reported data. However, slight differences can be observed due to the var- iance in the experimental condition

used (temperature and electrolyte) [20–22]. Re-determination the pKa value from PCA, in this study, yields an ex- cellent agreement with our previous study [16]. The pKa values for PCA are presented in Table 2, where these values sequentially refer to disso- ciation at the carboxylic site and the two hydroxyl sites of benzenediol ring. Fig. 1. Potentiometric titration curve represented by Ni(II) for the metal. V. Bundjaja et al. / Journal of Molecular Liquids 312 (2020) 113428

13 Table 2 Protonation constants of

protocatechuic acid (PCA) and nicotine (Nic) in the

1water at 310.15 K and 0.15 mol·dm-3 NaCl. Ligand

pKa1 ± SD pKa2 ± SD pKa3 ± SD Nic 3.01 ± 0.05 (3.22a, 2.84/2.74b) 7.85 ± 0.02 (7.72a, 7.83/7.57b) – PCA 4.49 ± 0.09 (4.42c) 8.64 ± 0.09 (8.62c) 12.72 ± 0.09 (12.75c) a Ref [22], T = 40 °C; no supporting electrolyte. b Ref [21], T = 30/40 °C; no supporting electrolyte.

2c Ref [16], T = 37 °C; I = 0.15 mol dm-3

NaCl. 3.2.

10Stability of the binary and ternary system From the

Hyperguad2008 program, the stability constants of M(II)- PCA and M(II)-Nic binary complexes along with ternary complex PCA- M(II)-Nic were obtained as overall formation constant (logß) and is pre- sented in Table 3. Overall, the system containing Ni and Pb have compa- rable stability constant value disregards of the binding ligands, while the one containing Cd showed the lowest stability constant. For the bi- nary complexes of Nic, 1 to 1 metal-ligand complex can be observed with $\log\beta$ 3.83, 3.82, and 3.40 for NiNic, PbNic, and CdNic, respectively. So far, there have been no studies reported the stability constant of Nic with Pb(II) or Cd(II) ions; only Fazary et al. has reported the stability constant of Ni(II) with monoprotonated nicotine NicH (logBNiNicH 2.64) [20]. The NiNic stability constant obtained in our work is signifi- cantly higher than the previously reported NiNicH. This is due to the high electronegativity of Nic, which is fully deprotonated so that it can attract and bind the metal cations more strongly. Compared to the sta- bility of Ni(II) and pyridine binding, it seems that the binding mecha- nism of M(II)-Nic may not be the sole contribution of amine site in pyridine ring because the stability of Ni(II)-pyridine complex is consid- erably smaller ($\log\beta$ Ni-pyridine 1.88) than the one obtained in this work [23]. Thus, it suggests that both amines in pyridine and pyrrolidine ac- count for the formation of NiNic complex. The stability constants of M(II)-PCA and PCA-M(II)-Nic have the same trend Ni N Pb N Cd. The sequence of complex stability can be eval- uated from the effect of the ionic radius. As suggests by Irving-Williams, a larger ionic radius of metal demotes the stability of the complexes. Among the investigated divalent metals, Ni(II) has a smaller ionic radius of 83 pm. Meanwhile, Cd(II) and Pb(II) have a larger ionic radius of 95 and 119 pm, respectively [24]. Following this theory, the interaction of the ligand with Ni(II) produces complexes with the highest stability. Ac- cording to Pearson hard-soft acid-base (HSAB) principles, metal, as well as the ligand, can be categorized based on their criteria (ionic radius, po- larizability, electronegativity, affinity, etc.). PCA with R-O- and R-COOgroups, is a hard base, while Nic with the N-based binding groups is a borderline base [25]. The divalent metal Pb(II) and Ni(II) are borderline acids, and Cd(II) is a soft acid. Ligand tends to form a stable complex with metals that have similar criteria. The results obtained in this study are in a good accordance with this

HSAB principle, where border- line acid Ni(II) and Pb(II) form a more stable complex with the ligands compared to soft acid Cd(II).

1Table 3 Overall formation constant of metal ions (M

), protocatechuic acid (PCA), and nicotine (Nic) complexes in the

1water at 310.15 K and 0.15 mol·dm-3

NaCl. Speciation Stoichiometric coefficient $log\beta \pm SD \text{ Ref M}(II)$ PCA Nic H Nickel complexes NiPCA 1 NiPCA2 1 NiNic 1 NiPCANic 1 NiPCA2Nic 1 1 2 0 1 2 0 0 1 1 1 0 0 0 0 0 Lead complexes PbPCA 1 PbNic 1 PbPCANic 1 1 0 1 0 1 1 0 0 0 Cadmium complexes CdPCA 1 1 0 0 CdPCA2 1 2 0 0 CdNic 1 0 1 0 CdPCANic 1 1 1 0 CdPCA2Nic 1 2 1 0 7.99 12.59 3.82 11.19 15.66 $\pm \pm \pm \pm \pm 7.49$ 3.83 10.57 $\pm \pm \pm 6.62$ 11.08 3.40 9.73 14.13 $\pm \pm \pm \pm \pm 0.06$ 0.11 0.05 0.05 0.06 0.09 0.08 0.06 0.10 0.07 0.05 0.10 8.06a 12.65a a Ref [16], T = 37 °

2C; I = 0.15 mol dm-3 NaCl

. 3.3. Effect of PCA amount on detoxification performance at physiological pH Once obtained, the logβ of the complexes was introduced to the HySS2009 program, and the speciation diagram in the ternary system was generated and presented in Fig. 3A-C. In every system, free metal ions can be observed at acidic pH. The complexes of NiNic, PbNic, and CdNic started to form at pH ~3 and reach their respective peak at pH 5.78 (77.09%), 5.98 (82.18%), and 6.32 (79.09%). With further in- creasing pH, MPCA and MPCANic complexes started to form. In the Ni- containing system, ~10-11% of NiPCA and ~87-89% of NiPCANic oc- curred at pH higher than 6.5 and 7.5, respectively. Similarly, ~91–93% of PbPCANic and ~76–78% of CdPCANic can be obtained at neutral to basic pH (pH 8). As observed in Fig. 3, the metals tend to form com- N plexes with Nic at more acidic pH and form complexes with PCA in the binary and ternary form at neutral to basic pH. The speciation diagram also can be used to elucidate the composi- tion of the complexes in the system at a certain pH. Since the goal of this study is to utilize antioxidants such as PCA to reduce Nic and heavy metals poisoning, it is necessary to find out what complexes par- ticularly formed at biological pH. As a representative, the system con- taining Ni(II) was used. For the system with [M]:[LPCA]:[LNic] ratio 1:1:1, it can be observed that at pH 7.4, 0.26% of Ni occurred in its free form, while 11.58% in Ni-Nic, 7.37% in Ni-PCA, 0.96% in Ni-PCA2, 80.02% in NiPCANic, and 0.68% in NiPCA2Nic form. The UV-vis spectra of Ni2+/PCA/Nic are shown in Fig. 4. Prominent peak at 283 nm and small hump around 300-390 nm can be observed in Ni-Nic systems. While for the Ni-PCA system, broad spectra between 276 and 360 nm occurred from the UV–Vis reading. In the ternary sys- tem of NiPCANic system, the sharp peak hyperchromically pronounced Fig. 2. Protonation equilibria of nicotine. Fig. 3. The species distribution curves of divalent metal (M), protocatechuic acid (PCA), and Nicotine (Nic) with [M]:[LPCA]:[LNic] ratio 1:1:1 for (A) M = Ni2+, (B) M = Pb2+, and (C) M = Cd2+; and (D) [Ni]:[LPCA]:[LNic] ratio 1:5:1. at 284 nm and small hump can be observed around 353-393 nm, which suggests the binding of Ni and Nic in the ternary system. Besides the typical NiNic spectra, the Ni-PCA-Nic system showed a characteristic broad shoulder peak of Ni-PCA, which bathrochromically shifted to Fig. 4. UV-vis spectra of the binary and ternary system of Ni2+, protocatechuic acid (PCA), and nicotine (Nic). 300-352 nm. These UV-Vis spectra indicate the binding of Ni2+ to PCA and Nic in the ternary system. When the amount of PCA was increased, different composition of complexes can be found in the system. As pictured in Fig. 3D, 0.01% of Ni occurred in free form, 0.30% in NiNic, 6.00% in NiPCA, 2.38% in NiPCA2, 70.75% in NiPCANic, and 20.56% in NiPCA2Nic form. This result suggests that by increasing the PCA amount in the system, the free Ni and NiNic can be reduced from 11.84% to 0.31%. In this work, the species distribution diagram of the system con- taining all studied heavy metals along with

ligands Nic and PCA were simulated. The 1:1:1:1:1 and 1:1:1:5:1 ratio of [MNi]:[MPb]: [MCd]:[LPCA]:[LNic] were used to understand the tendencies of the complex formation in the system with excess amount of antioxidant. These speciation diagrams were generated based on Nic in the sys- tem (Fig. 5). At concentration 3:1:1 of [MNi+Pb+Cd]:[LPCA]:[LNic], 0.18% of Nic occurred in NicH2 and NicH form, 81.70% bind to Ni, Pb, or Cd ions, and 18.11% forming a ternary complex of M-PCA-Nic (Fig. 5A). When an excess amount of PCA added, as can be observed in Fig. 5B, the composition in the system is as follow: 0.41% NiH2 and NiH, 4.06% MNic, 87.93% MPCANic, and 7.60% MPCA2Nic. These V. Bundjaja et al. / Journal of Molecular Liquids 312 (2020) 113428 5 Fig. 5. The species distribution curves of combined metal ions (M = Ni2+, Pb2+, Cd2+), protocathecuic acid (PCA), and Nicotine (Nic) in Nicotine basis. (A) [MNi]:[MPb]:[MCd]: [LPCA]:[LNic] ratio 1:1:1:1:1. (B) [MNi]:[MPb]:[MCd]:[LPCA]:[LNic] ratio 1:1:1:5:1. suggest that the addition of an excess amount of antioxidant PCA can reduce N95% of the free Nic and MNic in the system. The addition of PCA also can reduce the formation of free Nic and MNic at a broader pH spectrum. At five times the molar ratio of PCA, MPCANic complexes started to form at pH higher than 6 and reach op- timum reduction at pH N 7.3, which depresses the occurrence of free Nic and MNic to b5%. While with the system containing one molar ratio of PCA, the earliest MPCANic formation occurred at pH 6.5 and reached its peaks at the same pH (pH N 7.31), with merely 18% of MPCANic formed. The increased availability of PCA might not be the sole reason for the formation of MPCANic and MPCA2Nic. Several studies postulated the molecular interaction of tertiary amines and various carboxylic acids [26-28]. The logβ values of MPCA, which lie between 6.62 and 7.99, sug- gest that PCA act as a bidentate ligand by chelating the divalent metal ions with the deprotonated catecholate sites to form five-membered ring complex. The logß values of MPCA also found to be greater than the stability constant of Ni2+ and carboxylate site (0.67), which confirm that the binding did not occur in the carboxylate site of PCA [29]. Thus, it is possible that the free carboxylic acid site of PCA may interact with one of the amine sites, either in pyridine or pyrrolidine ring, of Nic and later synergistically binds the heavy metals and promote the formation of MPCANic and MPCA2Nic complexes. The intake of non-nutrient antioxidants (or total phenolic com- pounds) consumed by elderly individuals was 2196 mg/person/day [30]. This normal daily intake is significantly greater than five times the dosage of PCA used in this study (which is 77 mg). The five times in- crease of PCA dosage is chosen with consideration to investigate the minimum dosage that needed to give enough therapeutic effect in the human body. Particularly for this work, the consideration is based on the simultaneous reduction of heavy metals and Nic. 4. Conclusion The complex formation constant of MPCA, MNic, MPCANic, and MPCA2Nic were determined in this work. Disregard of the ligand (PCA or Nic), Pb and Ni were able to form stronger complexes compared to Cd. Similarly, in the ternary system, NiPCANic had the largest stability constant value (log β 11.19) followed by PbPCANic and CdPCANic had the smallest stability constant (log β 9.73). Species distribution diagram of the ternary system showed that optimum NiNic, PbNic, and CdNic formation occurred between pH 5.78 to 6.32. In a system containing a combination of all metal ions, Nic, and PCA, administration of PCA at excess amount can reduce the content of free metals, free Nic, and MNic complexes up to 95%. This suggests the possible usage of antioxi- dant PCA for the simultaneous binding of Nic and heavy metals via ter- nary metal-ligand complex formation.

3CRediT authorship contribution statement Vania Bundjaja: Investigation, Formal analysis

. Shella Permatasari Santoso: Methodology, Writing - original draft, Writing - review & editing. Alchris Woo Go: Supervision, Resources. Ronald Wijaya: Visu- alization. Chi Thanh Truong: Writing - review & editing. Maria Yuliana: Validation, Writing - review & editing. Felycia Edi Soetaredjo: Supervi- sion, Writing - review & editing. Yi-Hsu Ju: Supervision, Writing - re- view & editing. Artik Elisa Angkawijaya: Conceptualization, Funding acquisition, Methodology, Formal analysis, Writing - original draft, 3Writing - review & editing. Declaration of competing interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influ- ence the work reported in this paper. Acknowledgement Financial support by the National Science Council of Taiwan

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8MOST 108-2218-E-011-033) and National Taiwan University of Science and Technology (101H451403) are much appreciated. References

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