IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 13, Issue 1 Ver. VI (Jan. – Feb. 2018), PP 44-47
www.iosrjournals.org

Aurintricarboxylic Acid-Derived Polysalicylates as Platforms for Drug Development: A Mini-Review

Timothy J. Smith, RPh, PhD
Department of Physiology and PharmacologyThomas J Long School of Pharmacy and Health Sciences
University of the PacificStockton, California 95211 USA
Corresponding Author:Timothy J. Smith, RPh, PhD

Abstract: *Aurintricarboxylic acid, a dye developed for the colorimetric assay of aluminum ion, has diverse effects on many biological systems. Many of these effects are due to the complex chemical composition of the commercial grade material used in these studies. These components include small molecular weight species as well as progressively larger complexes derived from salicylate residues. Since certain pharmacological properties have been linked to structural subsets of the complex commercial mixture, the aurintricarboxylic acid-derived polysalicylates offer a unique opportunity for drug development.*

Keywords: *aurintricarboxylic acid, polysalicylates, polymers, drug development*

Date of Submission: 15-02-2018 Date of acceptance: 03-02-2018

I. Introduction

Chemistry of Aurintricarboxylic Acid-Derived Polysalicylates

Aurintricarboxylic acid (ATA) was originally synthesized for the assay of aluminum ion. While variations exist in the preparation of ATA, it is derived from the reaction of salicylic acid with sodium nitrite and sulfuric acid[1]. It is more commonly available as an ammonium salt, although free acid and sodium salts have been commercially available. While commercial preparations of ATAcontain the triphenylmethane dye (Figure no 1), the preparations used by most investigators for testing ATA for biochemical activity over several decades contain other components; including polymeric forms that may be generally described as polysalicylates, due to the covalent aggregation of salicylate moieties. An example of one of these polysalicylates is shown in Figure no 2[2]. These aggregates may form during synthesis and freely in various aqueous systems[2].

II. Selected Activities of ATA

In Vitro and In Vivo

In retrospect, the complex composition of commercial ATA contributed to the wide array of biochemical activities found through *in vitro* studies (Table no 1)[2,4-13]. These biochemical activities include, but are not limited to inhibition of nuclease and protein synthesis as well as anti-apoptotic effects[4,8,10]. These may play a role in the *in vitro* actions seen with ATA, which include antiviral[2,5,6,7], antiparasitic[9], antitumor[13] and antimicrobial activities[11,12]. While many investigators note that the commercial preparations of ATA they use are complex mixtures, it is clear that isolation of the active agent responsible for the activity they observe may be more formidable than characterization of ATA's observed effects. In addition to the *in vitro* activities, the ability of commercial ATA to produce effects *in vivo* is promising (Table no 2)[9,14-19]. These include protection of neuronal ischemia[14], endotoxin shock[15] and beryllium poisoning[16]. Antiplatelet[17,18,19] and anti-Cryptosporidium activities[9] have been characterized *in-vivo*. Attempts to isolate components responsible for a few of these activities have been restricted to a much smaller group of laboratories, and rarely to homogeneity[2,3,19].

Figure no 1: Aurintricarboxylic Acid.

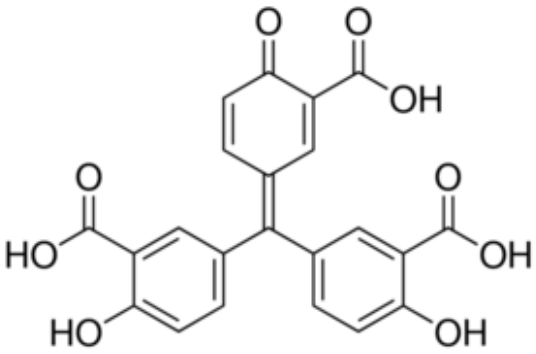

Figure no 2: An aurintricarboxylic acid polysalicylate (adapted from Cushman, et al.,[2])

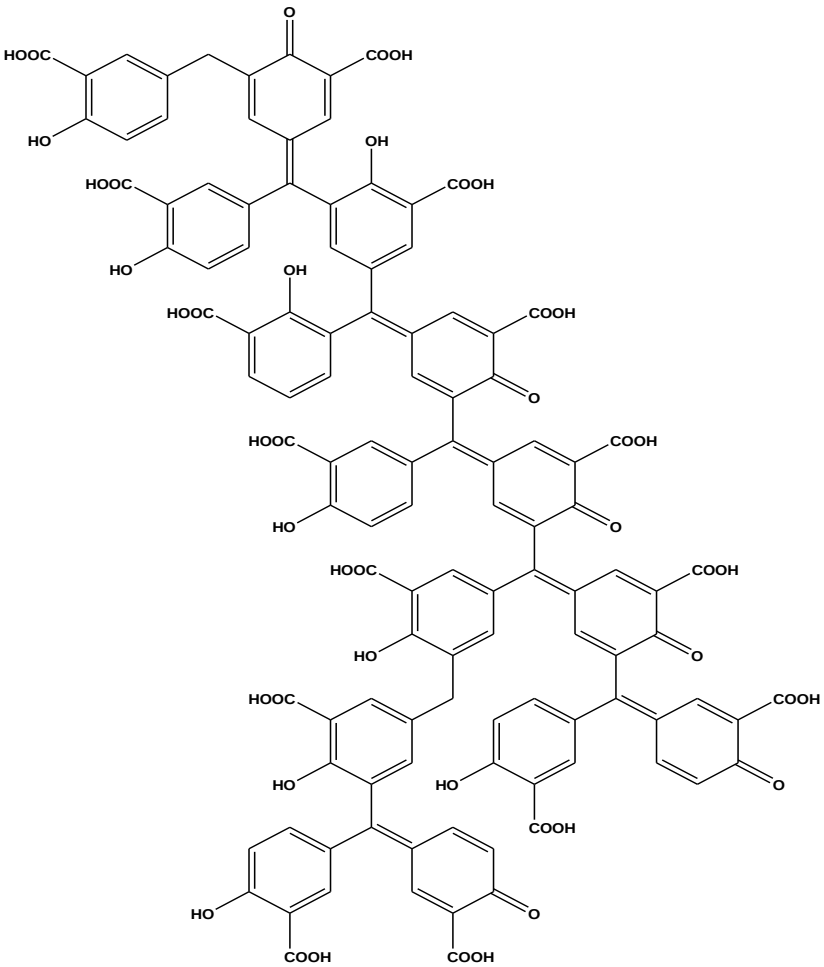

Table no 1: Examples of ATA activities *in vitro*

ACTIVITY	REFERENCE
Inhibition of Nuclease	4
Antiviral	
Influenza	5
Enterovirus	6
Vaccinia	7
HIV	2
Inhibition of Apoptosis	8
Anti-Cryptosporidium	9
Inhibition of Protein Synthesis	10
Reduction in Microbial Virulence	
Staphylococcus sp.	11
Yersinia pestis	12
Antitumor	13

Table no 2: Examples of ATA activities *in vivo*.

ACTIVITY	REFERENCE
Anti-Cryptosporidium	9
Protection from Neuronal Ischemia	14
Protection from Endotoxin Shock	15
Protection from Beryllium Poisoning	16
Anti-Platelet	17,18,19

III. Opportunities and Challenges

It is remarkable that a polymeric variation in salicylate moieties can result in such an extensive pharmacological profile. While the complex mixture of ATA is suitable for its application as a complexation reagent, this is problematic for drug development. Isolation and characterization of a single molecular structure associated with a pharmacological activity is often required for successful manufacturing, quality control, drug approval and clinical applications. In addition, the reactive nature of ATA in solution must be considered during drug development processes, even when a pure form of a component is isolated initially. The challenge associated with the diverse chemical composition of ATA in commercial preparations extends to potential drug delivery systems, when considering the activity and polyanionic nature of ATA[20,21,22]. Isolation of ATA components associated with the aforementioned activities, while daunting, offers an unusual opportunity to model the interaction of various ligands with molecular targets as templates for drug design. While the components of ATA may not be ideal as drug candidates, their derivatives and analogues identified through molecular modeling studies may be important alternatives. Clearly ATA components remain as valuable molecular probes in drug development.

References

[1]. Scherrer JA and Smith WH. Preparation of ammonium aurintricarboxylate, Research Paper RP1118. J. Res. Natl. Bureau of Standards. 1938;21:113-115.
[2]. Cushman M, Wang P, Reymen D, Este J, Witvrouw M, Neyts J and De Clercq E.Anti-HIV and anti-HCMV activities of newaurintricarboxylic acid analogues. Antiviral Chemistry & Chemotherapy1995;6(3):179-186.
[3]. Gonzalez RG, Blackburn BJ and Schleich T. Fractionation and structural elucidation of the active componentsof aurintricarboxylic acid, a potent inhibitor of proteinnucleic acid interactions. Biochim.Biophys.Acta1979;562:534-545.
[4]. Hallick RB, Chelm BK, Gray PW and Orozco Jr. EM. Use of aurintricarboxylic acid as an inhibitor of nucleases during nucleic acid isolation. Nucleic Acids Research1977;4(9):3055–3064.
[5]. Hung HC, Tseng CP, Yang JM, Ju YW, Tseng SN, Chen YF, Chao YS, Hsieh HP, Shih SR and Hsu JT. Aurintricarboxylic acid inhibits influenza virus neuraminidase. Antiviral Res. 2009;81(2):123-31.
[6]. Hung HC, Chen TC, Fang MY, Yen KJ, Shih SR, Hsu JTA and Tseng CP. Inhibition of enterovirus 71 replication and the viral 3D polymerase by aurintricarboxylic acid. Journal of Antimicrobial Chemotherapy 2010;65(4):676–683.
[7]. Myskiw C, Deschambault Y, Jefferies K, He R and Cao J. Aurintricarboxylic acid inhibits the early stage of vaccinia virus replication by targeting both cellular and viral factors. J Virol. 2007;81(6):3027–3032.
[8]. Cho H,Lee DY, Shrestha S, Shim YS, Kim KC, Kim MK,Lee KH, Won J and Kang JS.Aurintricarboxylic acid translocates across the plasma membrane, inhibits protein tyrosine phosphatase and prevents apoptosis in PC12 cells.Mol Cells.2004;18(1):46-5.
[9]. Klein P, Cirioni O, Giacometti A and Scalise G. In vitro and in vivo activity of aurintricarboxylic acid preparations against Cryptosporidium parvum. Journal of Antimicrobial Chemotherapy 2008;62(5): 1101–1104.
[10]. Stewart, ML, Grollman AR and Huang MT. Aurintricarboxylic acid: inhibitor of initiation of protein synthesis. Proceedings of the National Academy of Sciences 1971;68(1):97-101.
[11]. Zheng W, Cai X, Xie M, Liang Y, Wang Tand Li Z. Structure-based identification of a potent inhibitor targeting Stp1-mediated virulence regulation in Staphylococcus aureus. Cell Chem Biol.2016;23(8):1002-13.
[12]. Liang F, Huang Z, Lee SY, Liang J, Ivanov MI, Alonso A, Bliska JB, Lawrence DS, Mustelin T and Zhang ZY. Aurintricarboxylic acid blocks in vitro and in vivo activity of YopH, an essential virulent factor of Yersinia pestis, the agent of plague. JBC 2003;278:41734-41741.

[13]. Roos A, Dhruv HD, Mathews IT, Inge LJ, Tuncali S, Hartman LK, Chow D, Millard N, Yin HH, Kloss J, Loftus JC, Winkles JA, Berens MEand Tran NL. Identification of aurintricarboxylic acid as a selective inhibitor of the TWEAK-Fn14 signaling pathway in glioblastoma cells. Oncotarget 2017;8:12234-12246.
[14]. Roberts-Lewis JM, Marcy VR, Zhao Y, Vaught JL, Siman R and Lewis ME. Aurintricarboxylic acid protects hippocampal neurons from NMDA-and ischemia-induced toxicity in vivo. Journal of Neurochemistry 1993;61:1471-4159.
[15]. Laufenberg L, Kazi AA and Lang CH. Salutary effect of aurintricarboxylic acid (ATA) on endotoxin- and sepsis-induced changes in muscle protein synthesis and inflammation. Shock 2014;41(5):420–428.
[16]. White MR and Schubert J. Studies on the mechanism of protection by aurintricarboxylic acid in beryllium poisoning. IV. Comparative effects of related compounds on survival of Be-poisoned animals and on distribution of Be. Arch Biochem Biophys. 1954;52(1):133-42.
[17]. Strony J, Phillips M, Brands D, Moake J and Adelman B. In vivo antiplatelet aurintricarboxylic acid in a canine model of coronary artery thrombosis. Circulation 1990;81:1106-1114.
[18]. Kawasaki T, Kaku S, Kohinata T, Sakai Y, Taniuchi Y, Kawamura K, Yano S, Takenaka T and Fujimura Y. Inhibition by aurintricarboxylic acid of von Willebrand factor binding to platelet GPlb, platelet retention, and thrombus formation in vivo. American Journal of Hematology 1994;47:6-15.
[19]. Weinstein M, Vosburgh E, Phillips M, Turner N, Chute-Rose Land Moake J.Isolation from commercial aurintricarboxylic acid of the most effectivepolymeric inhibitors of von Willebrand factor interaction with platelet glycoprotein Ib. Comparison with other polyanionic and polyaromatic polymers. Blood 1991;78(9):2291-2298.
[20]. Martien R, Loretz B and Schnürch AB. Oral gene delivery: design of polymeric carrier systems shielding toward intestinal enzymatic attack. Biopolymers 2006;83(4):327-36.
[21]. Smith TJ, Haddad L, Faizyar S, Valdez E, Gramer E. Derreja LS and Bowers SM. Novel suppository design for HIV chemoprophylaxis. Pharmaceutical Technology 2010;34(7):68-72.
[22]. Fong K and Smith TJ. Citrate-mediated release of aurintricarboxylic acid from a calcium alginate complex: implications for intravaginal HIV chemoprophylaxis and related applications. Pharmaceutical Development and Technology 2009;14(4):341-342.

IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) is UGC approved Journal with Sl. No. 5012, Journal no. 49063.

Timothy J. Smith, RPh, PhD, "Aurintricarboxylic Acid-Derived Polysalicylates as Platforms for Drug Development: A Mini-Review." IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 13.1 (2018): 44-47.