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Dietary Quinic Acid Supplied as the Nutritional Supplement AIO + AC-11® leads to Induction of Micromolar Levels of Nicotinamide and Tryptophan in the Urine

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Hippuric acid is synthesized and produced primarily by the gastrointestinal (GI) microflora. However, there is no known health benefit for hippuric acid except its catabolic conjugation of benzene-type compounds via glycine and subsequent excretion in the urine. For years the GI tract microflora were known to metabolize quinic acid to hippuric acid. Recently it was also proposed that DNA repair was strongly enhanced by quinic acid. In order to explain these quinic acid effects, Pero and colleagues have examined whether tryptophan and nicotinamide were also enhanced by quinic acid levels in urine. They were indeed, and so another study was designed using a natural supplement source of quinic acid called AIO + AC-11®, and then the effects of intervention were measured after only 21 days. It was possible to show profound increases in quinic acid that were again paralleled by increases in tryptophan and nicotinamide urinary levels. Because the high pressure liquid chromatography (HPLC) methods differed greatly between the two studies, differences in chemical analyses probably did not contribute to the data base.

Keywords: quinic acid; tryptophan; nicotinamide; urine levels; HPLC; gastrointestinal microflora.

INTRODUCTION

Beginning in the early 1900s it was commonly believed that hippuric acid was mainly metabolized in the kidney or liver where it could be synthesized easily via conjugation between benzoic acid with glycine (Quick, 1993; Dickens and Pearson, 1950). Quinic acid in fruit has been recognized as a dietary source for the catabolic synthesis of hippuric acid, and exposure to benzene-type compounds was another important source (reviewed in Pero and Lund, 2010). For example, historically it was known that man could produce as much as 10 g quinic acid after eating 450 g of prunes, and 4.7 g after eating 305 g of cranberries (Blatherwick and Long, 1923). Likewise, it was also believed in the early literature that benzoic acid and other benzene-type compounds were also primarily metabolized by the liver (Beer *et al.*, 1951; Borsook and Dubnoff, 1940; and as cited in Pero, 2010). With this scientific background a reluctant acceptance of the importance of the gastrointestinal tract in the primary metabolism of quinic acid to hippuric acid has developed slowly.

The real pivotal breakthrough in the pathway of hippuric acid synthesis was put forward when it was unequivocally established by a series of pioneer scientific reports that (i) quinic acid must be given orally, and not by subcutaneous (s.c.) or intraperitoneal (i.p.) injection, in order to produce hippuric acid (Adamson *et al.*, 1970), (ii) co-administration of antibiotics seriously depleted the production of hippuric acid from quinic acid (Adamson *et al.*, 1970; Asatoor, 1965; Cotrin *et al.*, 1960) and (iii) these effects were totally dependent on metabolically functional GI tract microflora (Herrmann, 1995; Herrmann and Weaver, 1993).

Hippuric acid synthesis is a well known catabolic metabolism with no known health function except to excrete potential toxic substances such as benzene-type substances. For over 70 years it was scientifically ignored that the shikimate pathway was also a plant metabolic route that could also synthesize other important ingredients such as essential amino acids and nicotinamide.

Connecting hippuric acid levels not only to quinic acid synthesis, but also to the parallel inductive synthesis of tryptophan and nicotinamide also metabolized within the same shikimate pathway was finally realized by reports by Pero (Pero, 2010; Pero *et al.*, 2009). These studies suggest that quinic acid is not only a good surrogate indicator of urinary tract hippuric acid concentration, but also it predicts the inducible health benefit level of the key nutritional ingredients, tryptophan and nicotinamide. Hence, it establishes quinic acid as having profound health benefits and opens up a novel approach to dietary supplementation benefits. The work presented here verifies our earlier studies and extends the analytical methods that can be used successfully to quantify these metabolites.

MATERIALS AND METHODS

Dietary supplement product being evaluated. The ingredients of AIO + AC-11® nutritional dietary

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supplement are listed in Table 1 and quantified based on a dosage of 4 fluid ounces per day as an overall enhancer of cellular health.

Volunteers used in the study. Volunteers for this study were recruited from the general population living in Southern Vermont near Arlington, Vermont 05250. There were four females and one male. Subject EP was 16 years old, 140 lbs and 5 feet 6 inches; MC was 64 years, 192 lbs and 5 feet and 9 inches; MO was 69 years, 198 lbs and 6 feet; LP was 61 years, 170 lbs and 5 feet 7 inches; and BW was 69 years 135 lbs and 5 feet 7 inches (range = 16–69 years, mean = 55.8 years). The volunteers were instructed not to change any of their lifestyle factors including concomitant dietary supplements and medications normally being taken during the baseline urine sampling collection period (i.e. 1 week prior to the start of treatment), and again 1 week after the intervention period (i.e. defined as a week of follow-up with no treatment for urine sample collection only). Besides agreeing not to alter any lifestyle factors during the clinical trial, none were obese, vegetarians, smokers, drug addicts or having untreated disease symptoms. All participants filled out a before and after self-report clinical evaluation. An example is in Table 2.

Table 1. Ingredients of A10 + AC-11® based on 4 fluid ounces daily

Calories	76
Saturated fat	0
Trans fat	0
Total dietary fiber	0.64 g
Total carbohydrates	16 g
Proteins	1.80 g
Sugars	2.20 g
AIO + AC-11® daily health	
Vitamin A	9000 IU
Vitamin B1	1800 mcg
Vitamin B2	204 mcg
Vitamin B6	24 mg
Vitamin B12	7.2 mcg
Vitamin C	496 mg
Vitamin D3	3000 IU
Vitamin E	36 IU
Biotin	360 mcg
Folic acid	480 mcg
Pantothenic acid	16 mg
Potassium	400 mg
Selenium	120 mcg
Inositol	12 mg
Lycopene	20 mg
Lutein	20 mg
Manganese	8 mg
Zinc	12 mg
Calcium	41.2 mg
Chromium	560 mcg
AIO + AC-11® premium cellular and DNA health	
Reservatrol	300 mg
AC-11®	400 mg
Carnosine	200 mg
Niacin	120 mg
Green tea	80 mg
AIO + AC-11® premium antioxidant blend	
53000 mg whole fruit per daily serving	
Amto puree	
Pomegranate puree	
Blueberry puree	
Mango puree	
Camu Camu puree	
Acerola puree	
Acai puree	
Dark cherry concentrate	
Other ingredients	
USP 32 purified water, Nisin	

Trial design. The AIO + AC-11® trial was carried out in the Arlington, Vermont area (Principle Investigator Ronald W. Pero, 1651 Rupert Road, Sandgate, Vermont 05250, USA) whereas the biochemistry and statistical analyses were undertaken at the University of Lund, Institute of Clinical Medical Sciences, Section of Immunology, BMC D:14, 221 84 Lund, Sweden. The composition of urine is well known to be strongly influenced by dietary factors, so that random a.m. sample collections of urine could vary considerably from day to day and from individual to individual. Hence, it was reasoned that when quantifying contents of urine there is likely to be less variation in the urine sample analyses, if individual urine samples are collected before (baseline, no treatment) and after 21 days AIO + AC-11® post intervention for comparison and statistical evaluation.

The primary specific aim of this study was to design a clinical evaluation in which a small sample size could be utilized to produce significant data to verify previously shown clinical facts: (i) quinic acid oral administration increases hippuric acid in urine (Adamson *et al.*, 1970; Asatoor, 1965; Cotrin *et al.*, 1960; Indahl and Scheline, 1973; Pero, 2010); (ii) quinic acid subcutaneous or intraperitoneal injections have no effect on urinary production of hippuric acid (Adamson *et al.*, 1970). On the other hand, oral administration of quinic acid yields high amounts of hippuric acid which in turn was suppressed by co-administration of antibiotics, clearly implicating the GI tract microflora (Adamson *et al.*, 1970; Asatoor, 1965; Cotrin *et al.*, 1960); (iii) hence, the GI tract microflora are the main metabolizers of quinic acid to biosynthetic products not synthesized inside animal bodies (Adamson *et al.*, 1970; Asatoor, 1965; Cotrin *et al.*, 1960; Pero, 2010); (iv) since quinic acid is a substrate for GI tract microflora, its metabolic conversion to hippuric acid, nicotinamide and tryptophan must be primarily via the shikimate pathway found only in the GI tract of animals, and this pathway is a well known metabolic source for microorganisms or plants (Herrmann, 1995; Herrmann and Weaver, 1993).

The hypothesis being tested by this trial design is the elevation of quinic acid concentrations in urine after AIO +AC-11® (4 fluid ounces daily) that contains significant levels of quinic acid which, in turn, can also metabolically induce high concentrations of nicotinamide, tryptophan and hippuric acid in urine.

Urine sample collection and transport. Each individual participating in the study donated seven 15 mL purple-cap VWR test tubes nearly full of urine (13–15 mL), and always collected on separate days during the study. More specifically three test tubes were collected 1 week before initiation of the study, or during the baseline period. Another four test tubes were collected 21 days

Table 2. Physician-assisted self-report clinical examination. Example of summary data sheet for all physician-assisted and self-reported clinical examinations used for final analysis

Patient name ..... Birth date ..... Treatment .....

Observation	Baseline (before trial initiation)	+21 days treated (after trial initiation)	Comments
Body weight (kg)			
Height			
BMI			
Work attendance Previous month (%)			
Flu incidence previous month			
Sore throats previous month (*n*)			
Headaches previous month (*n*)			
Diarrhea/constipation previous month?			
Appetite previous week bad (1), normal (2), good (3)			
Rash previous month (yes, no)			
Pain previous month yes (1), some (2), no (3)			
Fatigue previous month: yes (1), some (2), no (3)			
Concentration previous month poor (1), mod. (2) good (3)			
Self-perceived health: poor (1, 2, 3, 4) and good (5, 6, 7)			
Energy previous month poor (1), mod. (2) good (3)			
Doctor signed			

after the start of intervention with AIO + AC-11® or 1 week after the intervention period was stopped, and the post intervention urine sampling period began. In such a manner, each individual provided three urine specimens for before (baseline) evaluation to be directly compared with four urine specimens after the intervention. All urine specimens ($n = 34$) were stored at +4°C until being shipped to Lund, Sweden on 27 May 2010, also as refrigerated samples (+4°C), and arriving within 12 h of the time shipped. After arrival in Lund the samples were centrifuged at 18000 × **g** for 5 min and then further stored at –20°C until used experimentally. The average induction ratios for nicotinamide and tryptophan were used for direct comparison with quinic acid in urine. Informed consent was obtained from all participants that included individual permission to obtain urine samples for use only in this study, and with institutional review approval.

HPLC analytical methods. The urine samples were injected routinely onto the HPLC system without any further clean-up steps. Analytical separations were done on a Genesis® AQ reversed phase column. This is a column that is especially suited for 100% aqueous mobile phases, and maintains stable retention times in them. The particle size was 4 μm, length, 50 mm, internal diameter 4 mm. The mobile phase was delivered with a HP 1050 series pumping system with an online ERC-3415 degasser. The flow rate was 1.0 mL/min. Samples were injected with a HP 1100 Series thermostatted autosampler.

Depending on the compounds being analysed, the mobile phase composition, injection volume and detection method differed. For simultaneous detection of quinic acid and nicotinamide, the mobile phase was 100% 25 mM ammonium acetate (pH 7), the injection volume 10.0 μL. Compounds were detected with a HP 1100 series diode array detector at 215 nm. Quinic acid eluted at 0.75–0.77 min and nicotinamide at 6.70–7.00 min.

Standard curves were produced for quinic acid and nicotinamide and were linear in the ranges examined. Standards of quinic acid (5–260 mM) were produced in water, whereas nicotinamide (0–410 μM) was produced from spiked urine samples. The nicotinamide peak suffered from bad resolution and high background, therefore, spiked urine samples gave a more reliable standard curve, produced in the matrix from which it was analysed.

Detection of tryptophan was mobile phase 15 mM acetic acid (pH 4) + 1% acetonitrile, injection volume was 2.0 μL. Tryptophan was detected with an Agilent 1100 series fluorescence detector. The excitation wavelength was 286 nm, emission wavelength 366 nm. Tryptophan eluted at 9.30–9.70 min. The standard curve of tryptophan was linear in the examined range 1–50 μM.

Statistical analysis procedures. Three statistical approaches were utilized and compared for utility to determine whether quinic acid could significantly induce the levels of nicotinamide and tryptophan in urine. The unpaired *t*-test was applied to the total sample ($n = 34$), the paired *t*-test applied to the means of before and after samples of each individual ($n = 10$) and for each individual group of before and after samples the unpaired *t*-test was used ($n = 7$). In addition, the induction ratios of urinary metabolites for comparing after/before concentrations were calculated by dividing the concentrations of quinic acid, nicotinamide and tryptophan after/before intervention, and then comparing them by linear regression analysis.

RESULTS

The data supporting the hypothesis that quinic acid in urine is also the main metabolic source for the synthesis of nicotinamide and tryptophan in urine are reported in Table 3 and Fig. 1. It has been shown from a historical

Table 3. The influence and statistical analysis of the metabolism and uptake of quinic acid, nicotinamide and tryptophan in urine treated with 2 × 2 fluid ounces per day 1 h before breakfast and dinner for 21 consecutive days of the dietary supplement AIO + AC-11®

Patient		QA mM		Nicotinamide μM		Tryptophan μM	
EP	Before		mean		mean		after
	#1	9.6		12.4		30.5	
	#2	12.0		9.5		51.9	
	#3	12.1	**11.3**	4.8	**8.9**	55.3	**45.9**
	After						
	#4	31.5		8.9		74.7	
	#5	74.9		26.7		104.1	
	#6	86.4		38.9		127.5	
	#7	43.1	**59.0**	21.7	**24.1**	96.0	**100.6**
	Induction ratio (after/before)		**5.2**		**2.7**		**2.2**
	Unpaired *t*-test (before vs after) $n = 7$	**0.017**		**0.044**		**0.005**	
LP	Before		mean		mean		mean
	#1	20.9		28.9		45.4	
	#2	10.2		14.2		25.6	
	#3	39.5	**23.5**	19.8	**21.0**	49.7	**40.2**
	After						
	#4	18.5		7.8		16.0	
	#5	48.6		26.5		54.0	
	#6	72.3		47.3		67.6	
	#7	38.5	**44.5**	15.9	**24.4**	54.0	**47.9**
	Induction ratio (after/before)		**1.9**		**1.2**		**1.2**
	Unpaired *t*-test (before vs after) $n = 7$	**0.099**		0.369		0.295	
MC	Before		mean		mean		mean
	#1	14.6		29.2		22.8	
	#2[a]	0.0		105.1		77.5	
	#3	13.6	**14.1**	24.6	**26.9**	13.2	**18.0**
	After						
	#4	38.4		87.8		19.7	
	#5	33.5		83.1		17.3	
	#6	41.0		35.9		41.3	
	#7	40.2	**38.3**	32.6	**59.9**	34.6	**28.2**
	Induction ratio (after/before)		**2.7**		**2.2**		**1.6**
	unpaired *t*-test (before vs after) $n = 6$	**0.0002**		**0.056**		0.128	
BW	Before		mean		mean		mean
	#1	90.5		29.3		61.7	
	#2	70.6		14.3		77.2	
	#3	93.5	**84.9**	13.8	**19.1**	77.8	**72.2**
	After						
	#4	42.9		19.7		79.7	
	#5	48.8		14.8		85.5	
	#6	35.0		19.5		86.5	
	#7	55.7	**45.6**	10.6	**16.2**	76.3	**82.0**
	Induction ratio (after/before)		**0.5**		**0.8**		**1.1**
	Unpaired *t*-test (before vs after) $n = 7$	**0.007**		0.315		**0.098**	
MO	Before		mean		mean		mean
	#1	34.4		23.5		130.9	
	#2	70.3		45.5		153.2	
	#3	19.4	**41.4**	25.3	**31.4**	139.3	**141.1**
	After						
	#4	81.7		23.2		152.3	
	#5	52.6		42.8		161.2	
	#6	113.1		75.0		195.5	
	#7	85.8	**83.3**	56.8	**49.5**	144.2	**163.3**
	Induction ratio (after/before)		**2.0**		**1.6**		**1.2**
	Unpaired *t*-test (before vs after) $n = 7$	**0.047**		0.114		**0.077**	
Total sample mean ($n = 34$)	Before ($n = 14$)	**36.5**		**21.1**		**66.7**	
	After ($n = 20$)	**54.1**		**34.8**		**84.4**	
t-test	Unpaired *t*-test (before vs after) $n = 34$	**0.044**		**0.017**		0.146	
	Paired *t*-test (before vs after of means) $n = 10$		0.142		**0.050**		**0.039**

[a] Unanalysable by current available techniques for this method because of high unknown HPLC background.

The statistical design was that each subject was base lined by providing three different daily urine samples 1 week before the AIO + AC-11® intervention was initiated for 21 days, and then another 4 days of different daily urine samples day 22–26 days after the 21 day intervention period. In such a way, each subject could be controlled against his/her own individual variation. Because individuals eat differently on a daily basis, and because the diet is reflected in the urinary composition, this protocol was believed to be appropriate and less variable.

Boldface print shows the means, or approaching statistical significance whether analysed by unpaired *t*-test, paired *t*-test, or patient by patient group analyses.

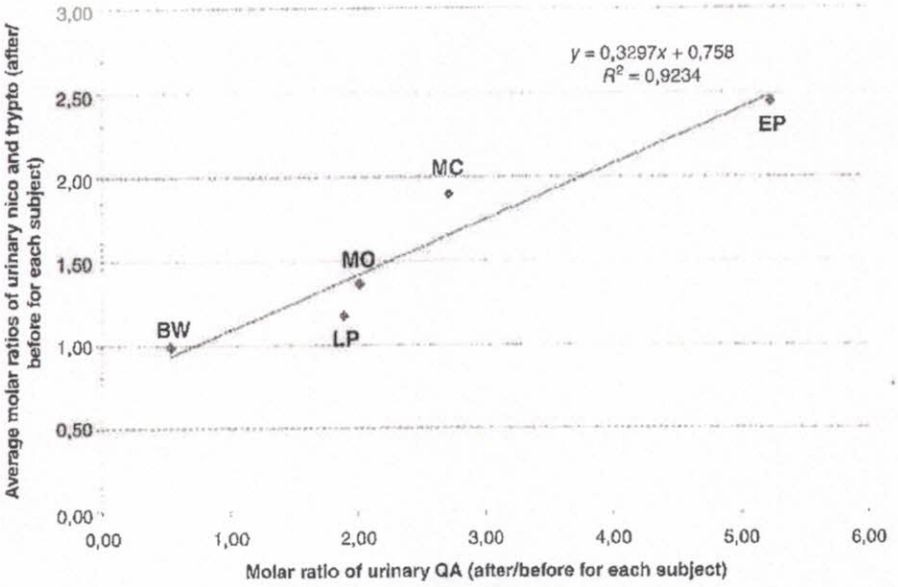

Figure 1. Interdependence of the μM urinary levels of nicotinamide (nico) and tryptophan (trypto) on the mM amounts of quinic acid (QA) in urine. Inductive urinary levels of nicotinamide and tryptophan calculated as their after/before ratio of concentrations in urine after treatment for 21 days with AIO + AC-11® containing about 4–5% quinic acid esters (QAEs). The data points for five individuals had a highly significant linear correlation coefficient ($r = 0.96$, $n = 5$, $p < 0.01$), thus providing strong statistical evidence that the levels of quinic acid in urine induced the synthesis of nicotinamide and tryptophan in a positive linear manner from quinic acid. The subject's initials appear next to the individual data points and are also independently presented in Table 3. These data were analysed by linear regression analysis as the induction ratios calculated as after/before urinary concentrations of QA, nicotinamide and tryptophan.

perspective in 1970 (Adamson *et al.*, 1970) that quinic acid was metabolized primarily in the GI tract and not in the liver. However, the scientific documentation was based on the catabolic metabolism of quinic acid to hippuric acid, a well known excretory product. More recently it was also demonstrated (Pero *et al.*, 2009) that the synthetic pathway for conversion of quinic acid to other plant metabolites including nicotinamide and tryptophan was also shown in the GI tract via the shikimate pathway (Herrmann, 1995; Herrmann and Weaver, 1993). Hence these published data strongly support the logic that quinic acid is a previously unrecognized major dietary source for essential amino acid synthesis (tryptophan, tyrosine and phenylalanine) that could directly supply the human body with these nutrients, that could otherwise render the human diet nutritionally deficient. In addition, healthy dietary components such as brightly colored vegetables and fruits are also the richest sources of dietary quinic acid, and thus supportive of essential amino acid biosynthesis (Engelhardt and Maier, 1985; Van Gorsel *et al.*, 1992; Beveridge *et al.*, 1999; Jensen *et al.*, 2002).

Here it is shown that oral intervention of an antiaging supplement called AIO + AC-11® (containing 4–6% quinic acid esters as QAE = 16–24 mg/day quinic acid) can also elevate urinary nicotinamide and tryptophan, as do dietary sources of quinic acid (Table 3). Quite remarkably, when the inductive ratios of quinic acid were compared with those calculated for nicotinamide/tryptophan there was a strong correlation coefficient ($r = 0.96$). In other words, when subject BW had a QA induction ratio of <1 (i.e. 0.99) there were no significant increases in either nicotinamide or tryptophan molar concentrations in urine. However, induction ratios of >1 correlated well with the molar levels of increases between QA and those for nicotinamide and tryptophan (Table 3, Fig. 1).

Lifestyle factor analysis before and after intervention with AIO + AC-11® was implemented using a self-report clinical examination form. Summation of the results are recorded in Table 4. Because of the small sample size for this pilot clinical study, no statistical analysis could be employed. Nonetheless, there were some clear trends that should be validated by a larger population study. (i) The self-report questionnaire comparing each participant before and after intervention response values, yielded some valuable data as in the past (Pero and Lund, 2010). (ii) When evaluating each subject's overall self-report responses, the worse they felt at the start of the study (e.g. subject EP rated her condition 4 out a possible 7), the greater was the perceived benefit from the AIO + Ac-11® intervention. On the other hand, the four other subjects in the study were already quite highly self-evaluated for good health at the start, and hence it was impossible to show any improvement on such a small sample size. (iii) Subject EP had the greatest increases in induced urinary levels of quinic acid, nicotinamide and tryptophan (Table 3, Fig. 1), and in turn also had the greatest health benefit from the AIO + AC1-11 intervention (Table 4). This was taken as an encouraging association to further validate, i.e. if less healthy subjects were evaluated within a larger cohort a more clear clinical improvement in lifestyle responses would be established.

DISCUSSION

One point deserving further detailed discussion is the reliability of the HPLC methods used for quantifying quinic acid, nicotinamide and tryptophan in urine. First of all there are only two studies that have reported on the determination of quinic acid in urine. They were

Table 4. Analysis of the influence of lifestyle factors before and after supplementation with AIO + AC-11® evaluated from a physician assisted self-reported clinical examination questionnaire. Scoring system format presented in Table 2.

		Degree of change	
Subject identity	Lifestyle parameter improved	Before	After
EP	Self perceived health (1–7)	4	6
	Work attendance	70%	90%
	# Sore throats	1	0
	# Headaches	10	5
	# diarrhea	3	1
	Appetite (1–3)	1	2
	Fatigue previous month (1–3)	1	2
	Concentration previous month (1–3)	2	3
	Energy	2	3
MC	Self perceived health (no change)	6	6
MO	Self perceived health (no change)	5	5
	Pain previous month (1–3)	1	2
	Fatigue previous month (1–3)	1	2
	Energy previous month (1–3)	2	3
LP	Self perceived health	6	7
	Energy previous month	2	3
BW	Self perceived health (1–7)	6	7
	# headaches	daily	less
	Energy previous month (1–3)	2	3

There were no adverse events recorded, and no parameters being scored by a graded number response decreased when comparing the before and after responses. This was interpreted as either there were no adverse events induced, or there was no effect yet induced by the intervention. Positive changes for each subject are shown.

carried out and developed by the same laboratory. Hence, they deserve in turn to be summarized and further discussed below. Although both studies had similar trial designs, and the chemical endpoint analyses for quinic acid, nicotinamide and tryptophan using before/after interventions with AIO + AC-11® or Quinmax™ (i.e. quinic acid ammonium chelate), they also differed greatly in regard to collection time of the urine samples during follow-up being 9 months for Pero *et al.* (2009) and 1 week for the post intervention collection period. In addition, the daily doses of quinic acid were also quite different being ≥1500 mg/day (Pero *et al.*, 2009) and ≥20 mg/day (i.e. estimated from 400 mg dose of AC-11®, this study), respectively. Furthermore, the HPLC analytical procedures varied greatly between the two studies with regard to the columns and mobile phases used (i.e. (i) Pero *et al.*, 2009: C18 150 × 4.6 mm, urine clean-up 1 ml urine: 2 ml ethanol: 4 ethyl acetate (1:2:4 v/v) and the mobile phase was 0.2% trifluoroacetic (TFA): methanol: acetonitrile (70:30): water in a ratio 8:8:84 (v/v/v), (ii) this study: Genesis® AQ 50 mm × 4 mm, no clean-up urine, and a mobile phase of 15 mM ammonium acetate. Despite the dramatic differences between these analytical procedures, both of them quantified quinic acid, nicotinamide and tryptophan within approximately the same molar ranges as presented below in the comparative summary studies outline.

Taken together it would appear to be obvious the following conclusions can safely be drawn. 1. The urine analysis of quinic acid, nicotinamide or tryptophan were not influenced by the analytical procedures used, and hence reflect the true molar concentrations in urine. 2. The after/before urine sample collection design allows for appropriate quantitative estimation of the induction ratios representing the induced molar concentrations of quinic acid, nicotinamide and tryptophan in urine. 3. Substantial variation in the collection time of the urine samples during follow-up from 9 months (Pero *et al.*, 2009) to 1 week (this study) when there was no intervention treatment going on, did not seriously alter the measured the concentrations of these parameters established after 3–4 weeks of daily intervention. 4. The composition of AIO + AC-11® was consistent with providing a natural blend of quinic acid by the fact that comparable stimulation of quinic acid synthesis was observed (see Table 5). This point was supported by the fact that similar increases in stimulation of quinic acid, tryptophan and nicotinamide levels were observed for ≥20 mg AIO + AC-11® dose compared with ≥1500 mg pure quinic acid (i.e. quinic acid ammonium chelate).

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Conflict of Interest

The authors have declared that there is no conflict of interest.

Table 5. Summary of published studies comparing urinary quinic acid (QA) to urinary nicotinamide (nico) and tryptophan (trypto)

Trial data	QA-containing agent being tested in clinic	Evaluation period	Samples analysed during follow-up (value ranges)		
			QA mM	Nico μM	Trypt μM
Pero *et al.*, 2009 $n = 36$, urine samples analysed	Quinmax (QA-NH_4^+) = ≥1500 mg/day	4 week treatment + 9 month follow-up	58–184	21–453	13–30
This study $n = 34$, urine samples analysed	AIO + AC-11® (AC-11® 400 mg = >20 mg QA)	3 week treatment + 1 week follow-up	38–83	16–60	28–163

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