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In Vivo Treatment of Humans with Quinic Acid Enhances DNA Repair and Reduces the Influence of lifestyle Factors on Risk to Disease.

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Abstract

Objectives: To test the hypothesis that in vivo oxidation of serum protein thiols can be used to estimate other clinical compromising events going on in the body such as the effectiveness of DNA repair and lifestyle-induced clinical responses

Design and Methods: (i) Serum protein thiols were quantified in 200 µl blood serum after treatment with saturated ammonium sulfate to give 80% of the saturated level and then further treatment with the colorimetric agent 5,5-dithio-bis-(2-nitrobenzoic acid (DTNB). (ii) A self-report clinical index score was created and administered to participants to simultaneously evaluate appetite, pain, fatigue, self-perceived health status, and energy for this purpose. (iii) A crossover trial design (i.e. before and after treatment) was used to further evaluate the clinical effectiveness of quinic acid ammonium chelate to enhance DNA repair.

Results: It was shown that enhanced repair of DNA using the surrogate estimate of serum thiols correlated by linear regression analyses to the degree and duration of the psychotropic-sensitive lifestyle clinical responses being evaluated($p < 0.02$).

Conclusions: A cheap and rapid biochemical method sensitive to estimating anti-aging effects of lifestyle criteria in clinical material and in blood serum is proposed.

Keywords: Quinic acid, clinical response, DNA repair, oxidative stress, serum protein thiol

Introduction

Quinmax™ is the 1.6: 1 molar ratio of the ammonium chelate of quinic acid. It is produced by treating quinic acid with aqueous ammonia to pH = 7.5. Quinic acid is also the major biochemical intermediate in the biosynthetic pathway (i.e. shikimate pathway) of most aromatic compounds that are found in plants and microorganisms, but it cannot be biosynthesized in animals including humans (1,2). Hence, quinic acid is ubiquitous as a plant constituent having detectable concentrations in fruit juices and bark such as from the cinchona plant. However, the highest concentrations of quinic acid exist naturally as quinic acid esters such as carboxy alkyl esters (8-20%) in Cat's claw (Uncaria tomentosa) and as chlorogenic acid such as in coffee, blueberries, grapes, apples, and cereals (3,4).

Pero and colleagues (4) while working at Lund University in Southern Sweden were the first to identify quinic acid analogs as the primary bioactive component of hot water extracts of Cat's Claw called C-Med-100. Cat's Claw is a plant well-known to have thousands of years of use as a historical traditional medicine, where it is indigenous to South America. The Ashinka Indians prepared a concoction from boiling the bark in water on an open fire overnight before decanting the mixture free from plant parts and sipping the resultant extract daily. Historical traditional use has involved mediating psychotropic responses (mental state) as well as treatment for infections and inflammation (4).

Oral administration of quinic acid (Quinmax^{TM}) in drinking water, was designed as a natural DNA protecting product after being isolated as the active ingredient (i.e. quinic acid) in Cat's Claw (4, 6). It mediates its health benefit by enhancing the natural enzymatic process of removing lesions in the DNA structure itself after oral supplementation. Thus, quinic acid has broad spectrum antioxidant properties which in turn can account for the traditional medical use of Cat's Claw extracts. The medical hypothesis being investigated in this study is that redox-sensitive enzymes and proteins involved in DNA repair and reflected by serum protein thiol analyses can also cause deleterious molecular changes in anti-aging functions. Some lifestyle events are also being regulated in parallel by psychotropic- or physiologic- sensitive oxidative stress phenomena.

Here we report on a clinical design to evaluate if a group of exceptionally healthy individuals, selected by Aqua Bimini Wordwide to represent their professions to the public (i.e. professional ambassadors), can be shown to have DNA repair levels assayed in serum proteins that increase their clinical responses when treated with the DNA repair enhancer, quinic acid (Quinmax^{TM}). A self-report clinical index score was created and used to simultaneously evaluate appetite, pain, fatigue, self-perceived health status, and energy for this purpose (Table 1).

Materials and Methods

Population: The subjects for this study were all non-smokers and recruited in South Africa by the water bottling company, Aqua Bimini Worldwide (Cederberg, Cape, South Africa). The motivation was to identify professionals who were well-recognized as celebrities having exceptional good health and daily concern about

good health practices. Drinking water everyday is an absolute necessity to survive, so identifying individuals willing to embrace the concept of functional water and be willing to share their experiences consuming it was considered invaluable. The strategy here was to identify a health conscious cohort already implementing and benefiting from many good health practices. Under these circumstances, if any benefit could be determined from the intervention, it would likely also benefit less healthy individuals. Seven females and 3 males were enrolled into the trial over a 2 month period, and they agreed to report on their experiences to the principle investigator as well as share them at a later date with the public. The case report questionnaires also included details of medical history, concomitant medications and demographic data (Table 2) filled out by each participant was clearly capable of demonstrating their overall good health.

Trial design: The clinical evaluation and blood sampling of the 10 participants were carried out in Capetown, South Africa under physician supervision, and the analyses of DNA repair, self-report questionnaire and statistical analyses at the Institute of Clinical Medical Science, Section of Immunology, Lund University during 2007. A cross over design was used where the same individual was evaluated before supplementation and then crossed over to treatment with supplement for evaluation of changes in clinical test parameters related to the supplement. Following this design each individual was controlled against his/her genetic, environmental, experimental or questionnaire bias. The 10 subjects were instructed to drink two 500 ml bottles of Quinic acid (Quinmax™) per day (1000 mg/day) for 60 days. The treated subjects were then instructed to slowly withdraw from quinic acid over the next 60-120 days (reduced treatment dryout, 500 mg/day every other day = early dryout). Accordingly at termination of the study all subjects had had no treatment for at least 120-180 days (i.e. 2 months no treatment = final dryout). This treatment schedule was used because we have previously determined that clinical efficacy remained even during dryout out periods up to 8 months after termination of quinic acid supplementation (6). Quinic acid (Quinmax^{TM}) was manufactured and supplied in 500 ml bottles by Aqua Bimini Worldwide (Cederberg Mineral Water PTY LtD, Vogelfonten Farm, Cederberg, Cape, South Africa, www.aquabimini.com). The quinic acid water called Aqua Bimini had the composition of: 1000 mg Quinmax^{TM} (quinic acid ammonium chelate), 4.7 mg Ca, 6.7 mg Mg, 25 mg Na, 9 mg K, 4.9 mg Cl, 28 mg SO_4, and < 0.1 mg F per 1000 ml in sterile water. The volunteers were instructed not to change their diet during the study.

Repeat blood samples were collected 30 days before quinic acid treatment and 180 day after treatment was stopped. Serum was prepared from the paired blood samples (i.e. before and after), and were analyzed for DNA repair capacity using the serum protein thiol surrogate assay (6). The average of the paired values was used to estimate the DNA repair capacity index during the clinical evaluation period for each individual in this study. The clinical evaluation was conducted according to the guidelines of the Declaration of Helsinki for humans. Moreover, informed consent was obtained from all participants that included individual permission to obtain blood samples only to be used in this study, and with institutional review approval.

Measurement of clinical response: The assessment of clinical responses to supplementation with quinic acid (Quinmax^{TM}) was accomplished by questionnaire and healthcare-assisted interviews involving each of the 10 individuals 30 days before treatment, +60 days after treatment, and +180 days after a treatment + dryout period. An example of the questionnaire is shown in Table 1, and it required participants to score graded answers to queries about the severity of symptoms for appetite, pain, fatigue, self-perceived health status, and energy (Table 1). These data could then be calculated numerically by adding them together to provide a general self-report clinical index score for evaluation of these endpoints in this study. Self-Report Clinical Index Score outlined in Table 1 = Appetite previous week bad (1), normal (2), good (3); skin quality poor (1,2,3)or good (4,5); pain previous month yes (1)moderate (2), no (3); fatigue previous month yes (1), moderate (2), no (3); self-perceived health poor (1,2,3,4), and good (5,6,7), energy previous month poor (1), moderate (2), and good (3).

Table 1: Example of the *clinical assessment* carried out by a self-reporting questionnaire on each participant in this study before and after receiving 2000 mg/day quinic acid (*Quinmax*™). QA = quinic acid

Patient Name: *Birth date:* *Treatment:*

Self-reported clinical observations	Baseline QA (before)< 30 Days	After QA 60 Days	After 90 days QA 180 Days
appetite previous week (bad(1), normal (2), good (3)			
Skin quality Poor # (1,2,3) or good # (4,5)			
Pain previous month Yes(1),mod(2),No(3)			
Fatigue previous month: Yes(1), mod(2), No(3)			
Self perceived health poor (1,2,3,4) and good (5,6,7)			
Energy previous month: poor (1), mod.(2) good (3)			

Compliance with clinical trial administered quinic acid (Quinmax™): Compliance was evaluated by questionnaire and example of which is presented in Table 2. It was >90% for all participants during the 60 day daily intervention period. It was not evaluated during the reduced dosage or dry-out periods.

Table 2: Example of the *case report form* collected for all participants in this study by self report questionnaire receiving 2000 mg/day quinic acid (Quinmax™).

Case Report Form

Subjects Initial: ⌊_⌋⌊_⌋ (first- and last name)		**Subjects birth of date:** ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ (yr/month/day)	
Demographic data	**Sex:**	Female:	Male:
	Ethnicity:	Caucasian:	
		Other, please specify:	

Relevant Diseases in history or present:				**Present**	
Yes	No	Disease	If Yes, describe disease	Yes	No
		Allergy (including drug allergy)			
		Eye, Ear Nose and Throat disease			
		Thyroid disease			
		Diabetes			
		Cardiac disease			
		Hypertension			
		Vascular disease			
		Neurol. disorder			
		Renal disorder			
		Liver disorder			
		Malignancy			
		GI- disease			
		Muscle/skeleton disease			
		Genitourinary disease			
		Psychiatric disorder			
		Skin disorder			
		Endocrinopathy (other than thyroid and diabetes)			

Weight:	kg	**Height:**	Cm		
Concomitant Medication:					
Brand name			Dose/day	Intake	
				Daily	Per need
Clinical Trial Medication			Number of 0.5 LITERS bottles	Date	Signature
Estimated by patient days taken			á		
Duration taken in days			-		
Compliance (days missed during trial persiod):			=		

Serum sampling procedures: Peripheral blood samples of 10-20 ml were collected by venal puncture using vacutainers (red top, 10 ml) usually after 4 hours of fasting. The blood samples were collected from the same individual 30 days before and 180 days after quinic acid intervention. Serum was separated from the blood clot after setting 2 hr on the lab bench top before centrifugation for 10 min at 1500 x g, and sent by air courier transport frozen on dry ice to Lund University, Lund, Sweden. After arrival from South Africa, the sera were stored at + 4 C until biochemical analysis usually within 30 days of collection and further transport to Lund University.

Estimate of individual DNA repair in blood serum: The in vivo level of serum protein thiols have been repeated used successfully as a surrogate estimate of DNA repair capacity (6-8, 10-12) In our last study[6] we presented how to standardize and improve reproducibility that would also allow for direct comparisons between various laboratories. The published protocol outline (6) was divided into the following sections for all of the biochemical details to estimate DNA repair by in vivo redox status of the serum samples as: (i) L-Cysteine standard curve calculation for serum thiol and (ii) Measuring serum protein thiols. When blood samples were collected and the serum isolated, then the level of serum protein thiols are a direct estimate of the concentration of reduced thiols compared to oxidized disulfides existing in protein structures. This estimate in turn is a measure of the existing oxidant environment an individual has been exposed to in vivo at the time of sampling. Thus, serum protein thiol analyses relate to the in vivo level of antioxidant activity of an individual, which in turn is correlated to up and down regulation of DNA repair.

L-Cysteine standard curve calculation for serum thiol analysis: Prepare a stock solution of the colorimetric agent 5,5-dithio-bis-(2-nitrobenzoic acid (DTNB), using: 9.5 mg/ml solid DTNB, 0.1 M K_2HPO_4, and 17.5 mM EDTA. Adjust pH to 7.5 and then dilute to desired volume. Prepare working DTNB solution by diluting DTNB stock solution 1:50 with saline. Prepare solutions of L-cysteine for the standard curve. The standard curve should be in the 0-100 µM range. However, make up the solutions

5 times more concentrated to begin with (they will be diluted 5 fold later). Make up a stock solution of 50 mM L-cysteine in saline. Dilute it 100 fold to get 500 µM. Make up 5-10 solutions of varying concentration from this solution. Use a transparent 96-well flat-bottom microtiter plate for the absorbance spectrophotometer evaluation. Put 50 µl L-cysteine solution with 200 µl working DTNB solution per well. Two to three replicates per concentration is sufficient. Make a working DTNB blank (50 µl saline + 200 µl working DTNB). Put the plate on a plate rotator for 15 minutes. Read absorbance at 412 nm with a microtiter plate scanner spectrophotometer. Calculate the average of every concentration. Subtract the DTNB blank from every value. 0 µM cysteine should therefore have an absorbance of 0.

Measuring serum protein thiols: Briefly, precipitate 200 µl serum with saturated ammonium sulfate to give 80% of the saturated level. The pellet is re-dissolved in a final volume of 600 µl saline. Replicate assays are carried out in microtitier plates prepared as: (i) A 50 µl aliquot of serum with 200 µl working DTNB in one well, and (ii) A serum background by putting a 50 µl aliquot with 200 µl saline in another well. Make a DTNB blank (50 µl working DTNB + 200 µl saline) and a saline blank (250 µl saline). Read absorbance in a microtiter plate scanner set at 412 nm and also as compared to a L-cysteine standard as described above. Hence, serum thiols are estimated as nmoles L-cysteine present in 80% ammonium sulphate precipitated serum proteins / 0.72 ml serum.

Statistical Analyses: The overall design for statisitical analysis of the influence of quinic acid supplementation on DNA repair capacity was that 10 healthy individuals were baselined as to their general health status by self-administered questionnaire retrieval data and their serum thiol status before being crossed over to daily quinic acid supplementation for 60 days at 1000 mg/day, then reduced to 500 mg/every other day for another 60-120 days and then no treatment dryout upto 180 days. Each individual was finally sampled at 180 days to determine the after intervention values for serum protein thiol levels (i.e. DNA repair index) and self-report clinical index values, which were then compared by two-way t-test to the before baseline no treatment values (-30 days) of the same individual. In addition, the individual DNA repair index values were also compared directly with the individual clinical index scores for the same individual by linear regression analysis. The data are presented in Table 4.

Results

Analysis of demographic factors including medical history and concomitant medications in relation to DNA repair capacity: Serum protein thiols as a surrogate indicator of DNA repair were used to evaluate the in vivo antioxidant status of individuals by orally administering quinic acid (Quinmax^{TM}) at a dose of 1000 mg/day for 60 days and up to another 120 days of 500 mg/every other day quinic acid plus dry-out to equal 180 days from start of trial. Both DNA repair and oxidative stress are potent regulators of aging phenomena having influence from both genetic (30%) and

environmental (70%) factors, so although a useful marker of aging it varies from individual to individual and must be controlled experimentally.[7] Age, sex, weight, smoking, medical history and medications are known strong variables correlated to aging effects, and thus in order to assess DNA repair capacity in relation to clinical response, they must be controlled as having no influence on the results (9). These data have been collected, arranged and analyzed in relation to DNA repair capacity in Table 3. The individuals selected for this study were supposed to have unusually good health in order to test the hypothesis that even good health could be improved on by DNA repair. The individual DNA repair values were arranged in Table 3 in descending order to create 2 groups; i.e. one with higher DNA repair values n = 5, Mean = 207 and one with lower values n = 5, Mean = 160. When comparing these 2 groups for age and body mass index they had almost identical values, which, in turn, not only reflected their good health status, but also limited these strong age-related parameters had no influence on the individual DNA repair data being anlayyzed for this study. Likewise, distribution of sex, medical history and concomitant medications between the 2 groups was not significant. Hence, it was concluded that none of these lifestyle or demographic factors had influenced the level of DNA repair in this study.

Analysis of clinical response compared to DNA repair capacity: For this purpose, again the DNA repair values were arranged into the same 2 groups of high and low values as was done in Table 3, but this time the groups were compared to clinical responses evaluated by a self-report clinical index score created and graded according to the summed-up variables for appetite, pain, fatigue, self-perceived health status, and energy. The summed clinical scores in relation to DNA repair are reported in Table 4, where the two groups were compared by t-test for significance. Whether analyzed as before, after, or arranged as ratios of after/before Aqua bimini treatment, the data demonstrated that the highest DNA repair values had greater significant clinical response levels than did the low DNA repair group. Thus, according to these analyses (Tables 3-4), there remained one dominant logical conclusion, and that was DNA repair capacity predicted an improved clinical response.

Linear regression analysis of clinical response: The data reported in Table 4 was also further analyzed in relation to DNA repair capacity by comparing before quinic acid treatment (-30 days), + 60 days after, and +60-120 days after quinic acid treatment, plus another 60 days complete dryout by linear regression: Both the ratios of clinical response (i.e. before/before groups (no effect controls), after +60 days/before -30 days groups, and after +120-180 days/before -30days groups), as well as the raw value clinical scores recorded in Table 4, were statistically significant. Figure 1 confirms that even if differences in the initial clinical response values were factored out of the analyses by creating the ratios of after/before groups, there still remained a significant influence on DNA repair values and in relation to duration of treatment displayed in Fig 1 (High DNA repair , $p < 0.01$ and low DNA repair, $p < 0.02$, respectively). The raw clinical response score data reported in Table 4 also gave similar significance when analyzed by linear regression. These analyses further support what already has been shown by t-test in Table 4.

Table 3: The *DNA repair index compared to demographic, medical history and concomitant medication endpoints* retrieved by self report questionnaire (Table 2) for subjects studied before and after treatment with quinic acid (Quinmax™) at 1000 mg/day.

Patient Identity	DNA Repair Index[a]	Age Years	Body Mass Index[b]	Sex	Medical History	Concomitant Medications
A.vdW.	250	35	18.8	female	diabetes	Normison,Elfertil,Liviton
T.F.	227	35	20.2	female	none	none
R.R.	193	33	26.9	male	none	Salmon oil, Vit.C and B
K.M.	182	45	19.4	female	none	none
M.K.	181	38	31.9	male	allergy, psoriasis	none
Mean ± SD	207 ± 31	37 ± 5	23 ± 6	3/5 F/M	3/5 ND/D	2/5 CM/NCM
T.M.	172	24	18.7	female	none	Myprodol
J.vdW.	167	36	26.7	male	torchims eyes	none
G.vdM.	164	47	22.0	female	none	none
L.S.	158	38	26.3	female	none	none
J.B.	141	43	21.7	female	none	None
Mean ± SD	160 ± 12	38 ± 9	23 ± 3	4/5 F/M	4/5 ND/D	1/5 CM/NCM
t-test	$p < 0.0137$	N.S.	N.S.	N.S.	N.S	N.S.
(two way)						

[a]DNA Repair Index = Average of 75% ammonia sulfate precipitated serum protein thiols before (< 30 days) and after (155-184 days) treatment with quinic acid expressed as nmoles cysteine / 0.72 ml serum

[b]Body Mass Index = weight in kg divided by height in m^2

[c]Abbreviations: QA = quinic acid, F/M = female/male, ND/D = no disease/disease, CM/NCM = concomitant medications/no concomitant medications, N.S. = not significant

Table 4: Comparison of the *DNA repair capacity to the clinical responses* self-reported by subjects before and after treatment with quinic acid (Quinmax™) at 1000 mg/day. Baseline QA is defined as the biological and medical conditions existing in the patient 30 days before starting QA treatment. The dryout period is defined here as 60-120 days reduced QA (500 mg/day every 2-3 days), and then followed by no supplementation from 120-180 days = total of 180 days post treatment. QA = quinic acid

		----------Self Report Clinical Score [b]----------				
Patient Identity	DNA Repair Index [a]	Baseline before QA -30 days	After AB +60 days	Ratio After/base	After QA 120 days + 60 days dryout	Ratio After/base
A.vdW.	250	13	14	1.07	17	1.3
T.F.	227	8	10	1.25	12	1.5
R.R.	193	10	17	1.70	18	1.8
K.M.	182	16	20	1.25	23	1.4
M.K.	181	16	16	1.00	16	1.0
Mean ± SD	207 ± 31**	13 ± 4	15 ± 4	1.3 ± 0.3	17 ± 4	1.4 ± 0.3
T.M.	172	17	20	1.18	21	1.2
J.vdW.	167	20	23	1.15	24	1.2
G.vdM.	164	23	23	1.00	23	1.0
L.S.	158	23	26	1.13	25	1.1
J.B.	141	23	26	1.13	25	1.1
Mean ± SD	160 ± 3	21 ± 3	24 ± 3	1.1 ± 0.1	24 ± 2	1.1 ± 0.1
t-test	0.013**	0.0026**	0.0035**	0.31	0.01**	0.038*
(1* or 2** tailed)						

[a]DNA Repair Index = Average of 80 % ammonia sulfate precipitated serum protein thiols before (-30 days) and after (60-180 days) treatment with quinic acid expressed as nmoles cysteine / 0.72 ml serum.

[b]Self-Report Clinical Index Score = Appetite previous week bad (1), normal (2), good (3); skin quality poor (1,2,3)or good (4,5); pain previous month yes (1)moderate (2), no (3); fatigue previous month yes (1), moderate (2), no (3); self-perceived health poor (1,2,3,4), and good (5,6,7), energy previous month poor (1), moderate (2), and good (3).

Figuire 1. Clinical response analyzed by a healthcare-assisted self reported questionnaire involving individuals orally administered quinic acid (Quinmax™) at 1000 mg/day. Before and after clinical index values were analyzed by linear regression as the ratio of after/before clinical index scores recorded in Table 4 (i.e. before ratio was calculated as before /before = 1 or no effect). Each individual clinical ratio value was then matched to their corresponding DNA repair index values by linear regression also reported in Table 4. Significant linear regression lines were determined: High DNA values, $Y = 0.002X + 1.85$, $n = 5$, $p<0.01$ and Low DNA repair values, $Y = 0.001(X) + 1.04$, $n = 5$, $p< 0.02$. Moreover, the raw clinical index scores reported in Table 4 for before (i.e -30 days), +60 days after and +120-180 days after treatment were also significant by linear regression analyses ($p < 0.05$). However, the non-ratio data reported in Table 4 did not account for any differences in the starting levels of clinical responses. The self-report clinical index score evaluated the clinical response to appetite, pain, fatigue, self-perceived health status, and energy.

Discussion

The data presented in this study on oral administration of quinic acid (Quinmax™) confirm earlier reports (6-22) that quinic acid or quinic acid-containing water extracts possess DNA repair, immune and anti-inflammatory enhancing properties when evaluated using serum thiol analyses as a surrogate DNA repair estimate. Despite the overwhelming evidence of a link between DNA repair and clinical outcome, it has never been established directly in humans until the results of this study were presented in Table 4 and Figure 1. The level of clinical responses to appetite, skin quality, pain, fatigue, self perceived health status and energy were predicted by their DNA repair in serum, even when the starting level of clinical responses (before treatment) were eliminated from the analyses after treatment with 1000 mg/day Aqua Bimini for 60 days by calculating the ratio after/before groups.

Recently the mode of action of oral supplementation of quinic acid (Quinmax™) have been further characterized[6]. In this report, it was demonstrated that quinic acid given orally was metabolized by gastrointestinal tract microflora to tryptophan and nicotinamide, and resulted in elevation of these essential nutrients 5-10 times in urine. Tryptophan and nicotinamide are well-documented and powerful antioxidants known to protect individuals on a daily basis, thus providing a potent anti-aging protection quantifiable by increased levels of serum protein thiols, a surrogate estimate of DNA repair.

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