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Metadichol® and Vitamin C Increase *In Vivo*, an Open-Label Study

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Abstract

Vitamin C, also known as ascorbic acid, is a water-soluble antioxidant. Today we meet our requirements of vitamin C through consumption of fruits and vegetables or by supplementation. Homo sapiens cannot produce vitamin C like many other species that can convert glucose to vitamin C. The gene for enzyme production is dormant in humans. The gene, GULO, that we all carry converts glucose to Vitamin C. in other species but not in humans and primates. The open-label study showed Metadichol® raised levels of vitamin C by 3 fold, endogenously without supplementation of Vitamin C. Possible mechanisms for the increased Vitamin C levels through antioxidant pathways are presented. Metadichol® [1] is a nano-formulation of long chain alcohols derived from sugar cane. In addition to increased Vitamin C levels reduction in Potassium and uric acid, and decreased blood pressure and improvement in quality of life issues were also observed.

Keywords: Vitamin C; Dehydroascorbic acid; Gulo; Pseudogenes; Metadichol; Nano lipid; Long chain saturated alcohols; VDR; Inverse agonist; Protean agonist; VDR, Glutathione; Lipoic acid; Coq-10; Vitamin E; Vitamin C; NRF2; G6PD

Introduction

Vitamin C for treating scurvy was use was discovered by Christopher Columbus's sailors with fresh lime juice, during long sea voyages. The sailors, of course, did not know the chemical formula which Linus Pauling discovered in his laboratory. Pauling proclaimed to the world that ascorbic acid if consumed in massive doses, is the panacea for all human ills. Literature surveys suggest that ascorbate is essential for the immune system to work efficiently and strengthening the immune system and can help those with impaired immunity [2-5].

Homo sapiens, monkeys, and a few other species do not produce their own vitamin C. The rest of the animal kingdom synthesize their own vitamin C. For animals that synthesize vitamin C it is a hormone, not a dietary-acquired vitamin. Homo sapiens once made vitamin C in the liver by the production of four enzymes which converted circulating sugars into ascorbic acid (vitamin C). The first three of the four enzymes required to convert glucose (sugar) into ascorbic acid is present in humans today, but the fourth, not found in humans is the enzyme Gulo (gluconolactone oxidase) (Figure 1). A mutation at some same point deactivated the gene for the synthesis of vitamin C and the production of the fourth enzyme came to an end in humans [6]. Species that make their own vitamin C, live 8 to 10 times beyond their age of physical maturity. Species without this ability reach only 3 to 4 times their age of physical maturity. Researchers believe the reinstallation of the Gulo (gulonolactone oxidase) enzyme in humans would extend the lifespan to hundreds of years [6].

Can gluconolactone oxidase gene somehow be reinserted into the human genome? Guinea pigs, lacking gluconolactone oxidase, when given this enzyme by injection, can live on a diet deficient in vitamin C [7]. Scientists have taken the gluconolactone oxidase DNA from rat liver and successfully transplanted it into the tomato genome [8]. With advances in gene therapy, the feasibility of inserting the gluconolactone oxidase gene into the human genome has not been tried so far.

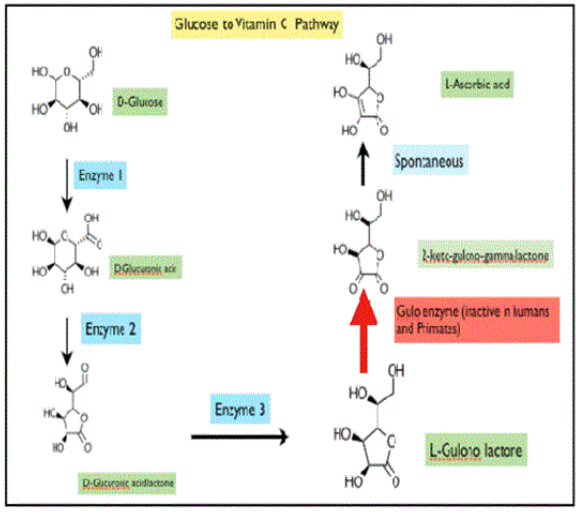


Figure 1: Glucose to Vitamin C pathway.

Supplementation of drinking water with vitamin C increased the average life span of mice by as much as 20 percent [9]. Pauling suggested humans supplement their diet continuously as a substitute to what the liver would make as if the gene for the gluconolactone oxidase enzyme were active [10]. Males who have higher blood serum levels of vitamin C had lower levels of mortality [10]. Men and women ages 40 and above a 50-milligram increase in vitamin C consumption reduced the death rate by 20 percent [11]. Vitamin C is an essential antioxidant in overcoming the effects of aging. Vitamin C slows down telomeres decline by 50 to 60 percent [12,13] (Table 1).

Gender	Female Age (Years)	Male Age(Years)
N	17	14
Percentage	54.85	45.15
Minimum	31	32
Maximum	65	76
Mean	52	55.4
Std Deviation	10.58	11.78
Height (cm)		
Minimum	142	150
Maximum	171	177
Mean	155.76	166
Std Deviation	7.24	7.57
Weight (Kg)		
Minimum	52.8	59.7
Maximum	87	116.1
Mean	70.68	75.86
Std Deviation	10.16	15.03
BMI		
Minimum	22.6	22.9
Maximum	35.3	37.1
Mean	29.1	27.37
Std Deviation	4.12	3.46

Table 1: Gender showing standard deviation results.

Humans who consume 300 milligrams of daily vitamin C appear to reduce the risk of cataracts [13]. A 500-milligram daily dose of vitamin C is seen to reduce blood pressure among hypertensive patients who previously used prescription drugs [14].

A mouse and a 160-pound goat make about 275 and 13000 mg of milligrams of vitamin C per day respectively. This correlates in humans to 2,000-20,000 milligrams per day. The recommended dose today is only about 90 milligrams of vitamin C a day for adults, but that' dose is the minimum amount to prevent scurvy and promote general health, but does not achieve optimal health and longevity [15].

To reach Plasma vitamin C concentration of 0.6-1 mg/dl one needs a minimum of 1000 mg per day of Vitamin C. Less than 5% of US population have plasma vitamin C level above the 0.6 mg/dl [16].

A study conducted by NIH investigators states that doses of supplemental vitamin C above 200 milligrams daily are "nearly completely excreted in urine." Furthermore, the concentration of vitamin C in blood plasma never exceeds much more than 0.6-1.3 mg/dl regardless of the of vitamin C consumed [17].

Two thousand milligrams of oral vitamin C produced 1.3 mg/dl in plasma levels [18]. All the work reported so far deal with oral consumption of Vitamin C, but increasing levels endogenously without supplementation of vitamin C is rare. A recent study [19] showed that using hydroxytyrosol, the main phenolic component of olive oil at 45 mg per day, allowed the endogenous levels to increase two-fold. The impetus for this study was that policosanol, the main ingredient in Metadichol, is present in olive oil [20]. We reasoned that Metadichol should show similar effects. We now report that Metadichol raised Vitamin C levels by 3 to 4 folds without any diet restrictions as was the case in the hydroxytyrosol study.

Study

Primary objective

Non-randomized, open, single group, study to evaluate the safety and efficacy of Metadichol in subjects with various medical conditions to improve vitamin C levels from Day 0 to Day 90.

Secondary objective

To evaluate the safety of Metadichol.

This was a 90-day prospective, non-randomized, open, single-group study. Subjects aged 18 yrs. of age with had on an average three co-morbidities received Metadichol. Subject visits were scheduled at baseline/day O (visit 1), day 30 (visit 2), day 60 (visit 3), and day 90 (visit 4). End of the study. All visits occurred within follow-up visit day within plus /minus six days.

The study population consisted of male or non-pregnant female patients aged 18 and over with diagnosed various diagnosed medical conditions. All patients were provided written informed consent to participate in the study before screening. Twenty enrolled and 27 completed as per protocol (Table 2).

Patient information	Number
Enrolled	31
Completed	27
Per Protocol	27
Safety Population	31

Table 2: Patients list before screening test.

The patient information sheet contained procedures involved in the study (aims, methodology. potential risks, anticipated benefits) and was explained these to each patient. Signed the consent form to from each patient was obtained to indicate that the information had been disclosed and understood. The patient was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the investigator's central records.

Criteria for exclusion from the study included pregnant or lactating females any serious and uncontrolled medical conditions interfering with the study or placing the patient at unacceptable risk. Only patients who fulfilled all the inclusion criteria and did not meet any of the exclusion criteria were enrolled into the study. Each patient had on an average three co-morbidities.

The primary efficacy endpoint

Improvement (change) in vitamin C levels at the end of day 90 as compared to baseline safety evaluation.

Safety evaluation analysis of the following parameters: The type of AE(s), the number of AE (s), the frequency of AE(s) and proportion of patients with AE(s).

Physical examination.

Assessment of vital signs.

Safety Laboratory tests included complete blood count, liver function tests, urea, creatinine electrolytes, and urine analysis.

Safety results

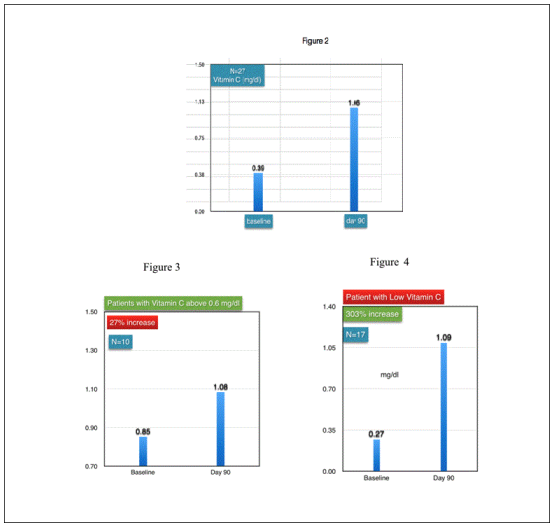
Metadichol was safe and tolerated, and this was confirmed by no incidences of adverse events and good compliance.

No deaths, and or any side effects were seen or reported by patients in this study.

Vital signs were found normal range during the study. There were no clinically significant abnormal findings at any of the visits. There were no abnormal clinical findings at any of the visits.

Results

The results of this study demonstrate that Metadichol has a better efficacy profile as evidenced in the changes (improvement) in the levels of vitamin C (Figure 2). Lymphocyte, ESR, ACE (absolute Eosinophil counts), potassium, and other biomarkers (Table 3). Metadichol, at the end of day 90+6 days, is safe and well tolerated. Analysis of Variance one way was carried out using JMP software from SAS.



Figures 2-4: 2) Vitamin C; 3) Patients with Vitamin C; 4) Patient with Low Vitamin C.

The increase in vitamin C levels was remarkable and statistically significant with values <0.00001 as shown in Table 4. Vitamin C levels below 0.6 mg/dl are considered deficient. Comparing patients with vitamin C below 0.6 mg/dl (17 patients) and those above (10 patients) the increase was remarkable as shown in Figures 3 and 4. Both sets of patients reached similar levels 1.06-1.09 mg/dl. All patients were interviewed at the end of their study, and every patient reported a quality of life improvement and improvement in medical issues of concern to them. Patient feedback and observations from the doctors are summarized in Table 5.

Biomarkers	Baseline	Day 90
Vitamin C (mg/dl)	0.39	1.06
Potassium (mmol/L)	4.38	3.88
Uric acid (mg/dl)	6.23	4.71
ESR (mm/hr)	22.29	18.14
TSH (µIU/ml)	3.58	3.02
Systolic BP (mm Hg)	129.33	123.3
Diastolic BP (mm Hg)	82.27	79.57
Body Fat (%)	37.4	36.03
Bone Mass (%)	2.59	2.69
Muscle Mass (%)	42.71	44.4
Total Body fat (%)	43.77	41.88
Sodium (mEq/L)	135.6	140.1
HbA1C (%)	6.74	6.4
Mean plasma glucose (mg/dl)	146.6	136.88

Absolute Eisnophil Count (cmm)	390.9	349.9
WBC (thou/µL)	7.25	6.98
Hemoglobin (g/dl)	13.52	13.5
RBC (mil/µlL)	4.9	4.86
Mean plasma glucoe	146.6	136.88
SGPT (U/L)	34	30
SGOT (U/L)	20.45	21.07

Table 3: Biomarkers Baseline.

	Baseline	Day 90	Total
N	27	27	54
∑X	13.11	29.38	42.49
Mean	0.4856	1.0881	0.7869
∑X2	9.3313	36.7028	46.0341
Std.Dev.	0.3377	0.4267	0.4876
Result Details			
Source	SS	df	MS
Between-treatments	4.9021	1	4.9021
Within-Treatments	706987	52	0.1481
Total	12.6008	53	P<0.00001

Table 4: Baseline results.

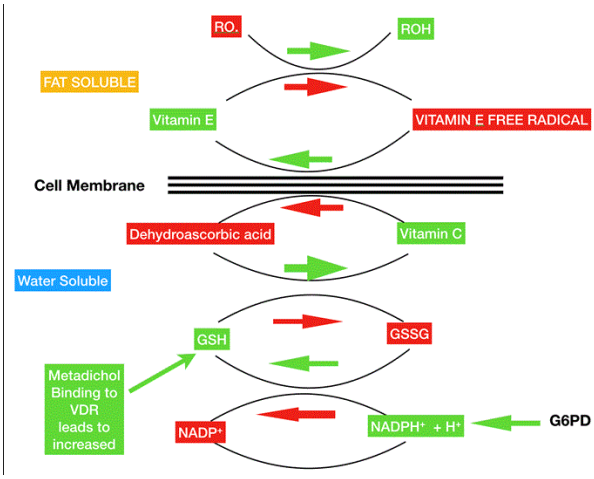


Figure 5: Metadichol and Cellular Homeostasis.

Discussion

Antioxidant pathways in humans work synergistically to protect body systems from free radical damage (Figure 5). Antioxidants operate in biological systems in a lipophilic phase (example, membranes or lipoproteins such as vitamin E and ubiquinols) or aqueous phases such as ascorbate, glutathione, and thioredoxin [21].

The human body has several mechanisms to counteract oxidative stress by producing antioxidants and recycling them. As part of an antioxidant defense system. Vitamin E, vitamin C and glutathione play a significant role in antioxidant metabolism (Figure 5). Oxidized glutathione and vitamin E and vitamin C have to be converted to their antioxidant state, for the completion of the antioxidant cycle to prevent the build of free radicals [22].

Vitamin C, for example, forms the transient ascorbyl radical which is either quickly recycled to vitamin C, or when oxidative stress is high, oxidized to form dehydroascorbic acid. Dehydroascorbic acid is rapidly transported into cells (example: erythrocytes, leukocytes, Dehydroascorbic acid) and is recycled by conversion back to vitamin C by many enzyme systems. The recycling of Vitamin C includes glutathione-dependent systems or reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent systems [23] (Figure 5).

Antioxidant regeneration pathway is limited by the availability of glutathione, and vitamin C. We have previously shown that Metadichol increases glutathione in Zucker diabetic rats [1]. Our explanation for the observed increase in Vitamin C levels is that Metadichol by binding with VDR increases glutathione levels and thus increases / maintains required Vitamin C levels (Figure 5). This is not surprising given that the natural ligand of VDR, 1,25(OH)2D is also known to participate in the regulation of gamma-glutamyl transpeptidase, an enzyme which up-regulates the glutathione (GSH) pool [24]. This effect was associated with the activation of the redox-sensitive transcription factor NRF2 and decreased activation of NF-kB [25,26]. Metadichol inhibits NF-KB. The glucose-6-phosphate dehydrogenase (G6PD or G6PDH) pathway supplies reducing energy to cells by maintaining steady levels of NADPH, which maintains the level of glutathione to protect cells against oxidative damage from compounds like hydrogen peroxide [27].

Based on the results, we are now exploring the possibility that Metadichol® perhaps may be activating the Gulo gene in the last step for formation of Vitamin C (Figure 1). The implications of such a development would lead that it could in principle to the eradication of diabetes, blood vessel disease, cataracts, gallstones. The breakdown of collagen with advancing age will be slowed. Ono can only imagine the social, political and medical ramifications if humans could extend their lifespan by a decade or decades. We have shown that in this study,

Metadichol® is well tolerated and improves the quality of life of patients with existing multiple medical conditions.

S.No	Feedback and Observations
1	Weakness and tiredness disappeared, Patients felt physically active, and this was expresses by all.
2	Mental Happiness; Interest in their work, concentration at work. Cooking etc. Satisfaction was expressed by all people," I am happy". Enthusiastic.
3	Acidity, Gastritis; Enhanced interest in food intake increased, and food digestion was complete, and absorption, assimilation, and expulsion was complete.
4	Arthritis; People could walk with ease and briskly with reduced pain.
5	Asthma; some patients cut completely or reduced to great extent their inhaler use.
6	Back pain; some patients had much-reduced back pain.
7	Dry skin; Cleared in some patents.
8	Tan; Complexion enhancement has been seen in and reported by all patients.
9	Dysuria; urination enhanced, frequent micturition stopped.
10	Headaches reduced.
11	Diabetes Millitus, Glucose and HbA1C levels reduced.
12	Hypertension; Reduction in blood pressure observed.
13	Sweating reduced.
14	Skin allergy; Good results were seen in Atopic Dermatitis, Skin rashes subsided, Submucosal infection also subsided, Vaginal itching reduction was also reported.
15	Voice clarity was observed and reported by one patient.
16	Loose motions; total relief reported by a few patients.
17	Constipation issues were resolved.

Table 5: Feedback and Observations.

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