Curcumin and Astaxanthin for Lowering Triglyceride Readings and Inflammation
Protocol # 001, Version 2, 05/12/2025

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Summary

High serum triglyceride (TG) readings and low grade inflammation have been considered contributors to multiple health problems. However, a number of years ago, concern about TG readings fell off in some health care and research circles. Now, new research and reconsideration of old research has brought back interest in TG readings as a risk factor in various health problems. Inflammation concerns have remained constant. For people with just moderately elevated TG values and non-disease/non-injury inflammation, non-drug approaches to minimization seem justified. A project is proposed to test how much supplementation with a certain curcumin preparation or astaxanthin lowers TG levels and two inflammation related indicators. As a side note, each supplement will also be checked for possibly modestly raising values for HDL cholesterol (the so called good cholesterol). The subjects will be adult men and women with moderately high TG values.

Background

Moderately high readings for serum TG have been thought to place many people at risk for cardiovascular disease (CVD) and other problems. However, for a few years, doubts were expressed about high TG as an independent risk factor for CVD and maybe other problems in most people. This is discussed in a Medscape article (https://www.medscape.com/viewarticle/990126?form=fpf). More recently, the tide has begun to turn back due to new studies and new attention to old studies. Now, TG readings are again being thought to affect vulnerability to CVD, fatty liver, high blood sugar, and other problems including general inflammation (1-6). Some of these studies have shown evidence that TG effects can be independent of LDL or total cholesterol readings. Also, one of these studies suggest that even dropping TG readings from the top of the normal range to lower values can produce benefits (1).

People with TG readings between the top of the normal range to moderately high are not taking drugs to lower TG values. Therefore, a need exists for cost effective, low side effect alternatives to help maintain normal TG readings. Nutritional supplements could fit in here. The Dietary Supplement and Education Act (DSHEA) allows for structure function claims of helping maintain blood lipids in the normal range.

Low level general inflammation, which falls below what's seen with inflammatory diseases or injury, can also raise the risk for many health problems (7). Drugs are not generally employed to

minimize this type of inflammation. So, as with moderately high TG readings, relatively safe and inexpensive non-drug alternatives can be sought (including nutritional supplements).

This researcher has found that under certain conditions, two natural ingredients each lower TG readings. One of these two ingredients was a high absorption form of curcumin extract from the spice turmeric (8). The form is called Longvida Optimized Curcumin®. A dose of 400 mg per day (80 mg curcumin) lowered TG levels in healthy middle aged women.

In addition, another group has found that a third ingredient, astaxanthin can produce a substantial drop in TG values (9). A dose of 12 mg/day was more effective than 6 mg but the same as 18 mg. Also of note, readings for HDL cholesterol, the so called good cholesterol, rose a little. Another astaxanthin study found a drop in TG values in people with type 2 diabetes (10). A TG lowering effect of astaxanthin can also be seen in various types of animal studies (ie 11,12).

It's doubtful that any of these three ingredients could produce the really large TG drops needed by people with really high values. Even so, for people in the borderline to moderately high range, these ingredients, especially in combination, could work well enough to get and maintain normal range values.

Eventually, a combination product could be made of astaxanthin plus Longvida Optimized Curcumin® plus the third ingredient. However, there is work to be done before that can be considered. One lacking is that three ingredients have never been tried in combination. But, even before trying that, another issue must be addressed. For all three ingredients, the human research cited above have all been done in subjects whose TG readings were good to begin with. Therefore, it is not known how these ingredients, combined or individually, will affect TG readings in people with higher starting values.

On the inflammation side, both curcumin and astaxanthin are considered anti-inflammatory though a lot of disjointed data exists. A meta analysis exists for supplementation of curcumin (13) and supplementation of astaxanthin (14) in relation to c-reactive protein (CRP), a general marker of inflammation. Each analysis concluded that overall, CRP was decreased. However, some inconsistency existed in terms of results, types of subjects examined, doses, exact nature of the extracts, and co-treatments. The latter hold particular importance for curcumin, which was sometimes given with piperine, which can conceivably have its own effects (good and bad). Thus, a need exists to study the type of curcumin and astaxanthin of this project at reasonable doses in a population that is fairly broad.

One possible anti-inflammatory mechanism of both astaxanthin and curcumin is elevation of body glutathione. This molecule can inhibit inflammation (ie 15). Whole blood glutathione will be examined in this project.

One body area where inflammation protection may be especially useful is the liver. Many adults stress the liver through fat accumulation or other situations. Both curcumin and astaxanthin have shown protection against chemically induced liver injury in experimental animals (rev in 16,17). In addition, turmeric, the source of curcumin, has been used in Indian traditional medicine for treating liver problems. However, low information is available on curcumin and astaxanthin for

effects on liver in people without substantial current liver problems. In one exception, this researcher found that in generic middle aged women, Longvida lowered readings for alanine amino transferase or ALT (8). ALT is not a direct indicator of inflammation. However, liver inflammation can cause liver cell damage which leaks ALT into serum to elevate readings. The results obtained by this investigator need to be extended into both genders. Also needed is testing in people with higher TG readings than the previous study. As noted above, serum TG may reflect risk of fatty liver. In addition, the ALT measures can be used as a safety evaluation of early liver irritation (though as just noted, liver protection is more likely than liver irritation).

Hypothesis

This proposed project tests the hypothesis that astaxanthin or Longvida supplementation will lower TG readings in people with moderately high starting values. A secondary hypothesis is that the supplementation will raise HDL cholesterol readings and depress values for two markers of inflammation. Positive results in the current project can serve the following two purposes:

1. Data can be used to submit an NIH Small Business Innovation Research grant proposal. This researcher submitted one in the past for the three ingredient combination. Despite good comments, the grant was not funded. Such a resubmission requires more data on the individual ingredients in people with moderately high TG readings.
2. A finding of two anti-inflammatory effects for astaxanthin and Longvida can be used to expand research for more detailed studies on inflammation.

Methods

The trial will be conducted in compliance with the protocol, GCP and the regulations.

Subjects will be recruited locally using low cost advertising mechanisms and nationally using national message boards like Craig's list. The applicant has used these approaches previously.

Subjects will be adult males and females aged 21-59 that lack unstable health problems that can affect TG or systemic inflammation readings. Examples include:
Uncontrolled diabetes
Hypothyroidism or other hormonal problems that have not stabilized
Any liver diseases being actively treated
Cancer
Renal dialysis use
Rheumatoid arthritis and related issues like lupus
Inflammatory bowel disease

Other exclusion criteria are:
Smoking
Low blood pressure
Having more than 5 alcoholic drinks per week
Extreme obesity (BMI over 37)
Pregnancy or lactation

Taking weight loss drugs or statins
Allergies to algae or the drugs finasteride (Propecia, Proscar) or dutasteride (Avodart, Jalyn).

Subjects will be asked about health conditions and eligibility related criteria in an eligibility questionnaire. However, medical records will not be accessed.

Subjects in this project will have starting TG reading of 140-250 mg/dL. Initially, this eligibility will be based on eligibility questionnaire. However, if the initial blood draw finds TG readings outside the range, subjects will be excluded and replaced. Other discontinuations will be for a subject's decision or a change in health or medication disclosed by the subject to Medinutra. For these discontinuations, subjects will not be replaced. In the applicant's experience, no dropouts, or at most one, would be expected for this type of study.

For 6 weeks, subjects will take one of the following orally as one capsule per day (up to16 people/group):
Placebo*
Astaxanthin at 12 mg/day-furnished by BGG, one of the study sponsors (https://bggworld.com/)
Longvida Optimized Curcumin® at 400 mg per day (80 mg curcumin)-furnished by Verdure Sciences, one of the study sponsors (https://vs-corp.com/)
Longvida Optimized Curcumin® at 200 mg per day (40 mg curcumin)-furnished by Verdure Sciences, one of the study sponsors (https://vs-corp.com/)

*Cellulose: https://www.amazon.com/Magic-Bullet-Placebo-Pills-Potential/dp/B089CXVH38/ref=sr_1_5?crid=18HXBJWI1T8RO&dib=eyJ2IjoiMSJ9.bY4P68cf7RUDayeax4XUI5h6RjJ8OPaImi8Ji8eh-GckllzkRVjJgHLqJfVFBJ3AnghpGigfe4F9O27V8cgI1XkH243qICdqwJtGn3O8iYvKYHSiwoYWIeNEgs25u1QTQGP4Vp88Q7FXZ3m6D2blsL--rMVbuiWb0mu_Kl5WJCRtsiMGlx5Ov9kvkf97XjWqQqJQWGHc5yOAtifzbp9RmL9zW8GkvjWtTPTKFfr87Gpykxd8dAhpPQD21m74pSqx44bRd67WK72kEtPNs0b4p_lcxBGjv_YxLD5oSPrgG2k.KO4W5ezQvdBeswhujFH_xF7nO2eHwm7W6dGBONeYzpU&dib_tag=se&keywords=placebo+capsules&qid=1729741059&sprefix=placebo+capsules%2Caps%2C122&sr=8-5

Subjects will be instructed to keep their current diet, activities, supplement use. They will also be told to report to Medinutra any changes in health or medication.

The 80 mg curcumin dose is a standard amount for this product. It is what was used in this researcher's study on TG lowering (8) and lower than what has been used in some studies. The present study's examination of 40 mg is being tried as a step to determining the lowest dose that can produce benefits. The astaxanthin amount is based on a dose response study for TG effects (9). A dose of 12 mg worked better than 6 mg, but as well as 18 mg.

The intervention time is longer than what was used in reference 8 (4 weeks), but shorter than that of reference 9 (12 weeks). Studies that involve nutritional supplements commonly use 8 weeks. Thus, 12 weeks is likely more than needed to see an effect. The use of 6 weeks falls halfway between the common 8 weeks and the 4 weeks that were sufficient in reference 8.

The subjects will be about equal between genders for total number as well as for each group. Each participant will be given a subject number. Treatment assignment will be random using a computer scrambling method for the subject numbers.

Blood will be drawn before and after the intervention by a Labcorp facility near the subjects' residence. Labcorp will measure a lipid panel, serum c-reactive protein, whole blood glutathione, and serum ALT activity. The lipid panel will include triglycerides and various cholesterol related measures. It not expected that most of the cholesterol measures will change except possibly a small increase in HDL.

Neither Labcorp nor the study subjects will not know the assigned capsule identity. Thus, this will be double blinded and randomized in terms of the participants and analyzers. Supplement and placebo capsules will be provided to the subjects in generic sterile plastic containers. These will be mailed to the subjects, or for some local participants, delivered to home or work. The delivery person will be paid by Medinutra, but won't know the product identity. They may or may not actually see the person receiving the delivery.

Subjects will be asked to email Medinutra at week 2, week 4, and at the end of participation stating how many capsules were taken in the previous 2 weeks. Anyone missing more than 3 days will have data excluded (though the person will still be paid). Since compliance is very easy for this study, it is not anticipated that anyone will have to be excluded.

LabCorp will be aware of the data gathered for each person. This will be emailed to the principal investigator Robert DiSilvestro. He will keep a record on 2 secure computers by name + subject number. He will also have access to the subject capsule assignment. As soon as the study concludes, names will be removed from the records.

For each measure, for each of the treatment groups, pre- and post-treatment values will be compared by paired t-test. In addition, the changes in values for each supplement group will be compared to placebo by unpaired t-test. For non-normal distribution, nonparametric tests can be used. Also, each group will be compared to the others by ANOVA followed by Tukey analysis when applicable. Significance is set at $p < 0.05$ for all tests.

Subject numbers and power calculation. This project is intended to see if further research is justified on certain wellness parameters in response to each of two supplements. Further research would be on the individual ingredients as well as the combination of both ingredients as well as these two ingredient + another ingredient. Justification for more work will only occur if substantial changes occur consistently. Therefore, a relatively small subject number should be sufficient to see such patterns. A power calculation was done for changes in serum TG levels for Longvida vs placebo. The previous study from this researcher (8) got a 15% drop in people with low starting values. The percent change may be bigger in people with higher starting values, but the power calculation was done with 15%. Placebo was set at 2%. An upper end of SD for the changes is hypothesized at 8.5%. Using a power value of 0.95 and $p = 0.01$, 15 subjects are needed per group. Recruitment will shoot for 16 subjects to allow for 1 drop out per group. Dropouts should not occur much if at all. That's because participation is not demanding and subjects can't tell if a treatment is not "working."

Safety considerations. A safety review of astaxanthin says that natural versions are safe at doses equal or greater than the current project dose (18). This was based on 35 human studies.

The FDA classifies curcumin as Generally Regarded as Safe (GRAS): https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=686. The dose there is less than the higher dose in the current project, but only by 25%.

Despite this classification, and despite use of curcumin to treat liver problems, a few reports of curcumin-induced liver injury have been reported. To my knowledge, none have involved the form or dose of the current project. A survey was done on liver toxicity cases where a person was taking supplements of either curcumin or turmeric, the spice that contains curcumin (19 and discussed in https://www.medicalnewstoday.com/articles/turmeric-black-pepper-supplements-linked-liver-injury). In 12 years, only 10 cases were found. The authors of the survey concede that not all the cases of liver toxicity could be definitely attributed to curcumin or turmeric. In fact, as noted below, for at least two of the cases, there is evidence against turmeric or curcumin involvement.

The authors also note that for 7 of the cases, the people carried a gene that causes sensitivity to liver problems. The authors further state that for the other 3, no checking was done for the gene. So, possibly all 10 cases had this gene.

For at least 4 of the cases, the subjects took curcumin + piperine, a compound that by itself sometimes causes liver injury. A median of 86 days prior to onset of injury with laboratory abnormalities was seen (the current study uses a 42 day intervention).

One fatality was noted, but it's questionable that it had anything to do with the turmeric she had taken for 14 months. An NIH report gives some details about this person: https://www.ncbi.nlm.nih.gov/books/NBK548561/. This person seemed to have multiple medical problems. Also, this person only took 500 mg of Rite Aid turmeric. The amount of turmeric absorbed from that type preparation would likely run too low to have produced toxicity.

The NIH publication also gave details about two of the other cases. For the one they called Case 1, the person was taking multiple drugs and had a range of symptoms that are not known as common for curcumin. Thus, the role of curcumin here is unknown. In the other case reported (case 2), the subject took a black pepper absorption enhanced curcumin dose that runs 12 times higher than what will be used in the present study.

The published survey study article (19) prompted a letter to the editor (20). Although the author of the letter is not an accomplished researcher, most of the points of the letter are valid. The letter states the following: "For context, that is 0.83 TALI cases/year or ~3×10−9 cases/capita/year. Half were "mild" and did not involve hospitalization. The median body mass index was 26.7 kg/m^2 ("overweight"), with one body mass index of 39.5 kg/m^2 ("obese"). Overweight and obesity are associated with acute liver injury and failure… therefore, some of the observed effect may be attributable to confounding. Seventy percent also used alcohol."

Also of note, compared to liver toxicity, curcumin has far more reports for hepato-protective actions in humans and experimental animals. As noted earlier, these reports have included a study led by this researcher (8). In this work, in 19 generic middle aged women, mean plasma ALT activity, a marker of liver injury, went down after sustained intake of the higher dose and type of curcumin to be used in the current study. The decrease was statistically significant. Only 1 of 19 women showed a substantial rise in ALT readings (25 to 42). The final reading was still inside the 7-56 normal range used by Cleveland Clinic: https://my.clevelandclinic.org/health/diagnostics/22028-alanine-transaminase-alt. Furthermore, 2 placebo subjects had similar increases.

For astaxanthin, despite its proposed uses in liver protection, has been reported to raise ALT values (21). However, this report gives strange results. Both the starting and ending ALT values lie way below the normal range. Also, other indicators of liver injury did not change.

Since the current project intervention time does not run very long, even if liver issues were to develop, the progress would be very early. This will be detected by the ALT measures that are part of the project. In the very unlikely event of ALT readings rising, subjects will be informed and told to follow up with their physician.

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