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4TH CLINICAL STUDY

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TEN

- SUPPORTS PRODUCTION OF MITOCHONDRIA & HEALTHY MITOCHONDRIA FUNCTION*
- PROMOTES CELLULAR ENERGY*
- PROVIDES ANTIOXIDANT CELLULAR PROTECTION AGAINST OXIDATIVE STRESS*

ultra-premium wellness supplement
CONTAINS 30 - VEGETARIAN CAPSULES

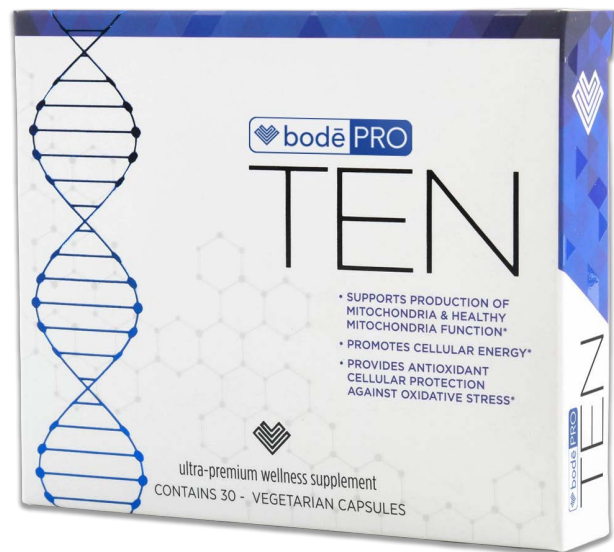## MITOCHONDRIA MARKERS
AND INHIBITION OF FREE RADICIAL STRESS.

In-Vitro and Human Clinical
Study Synopsis

EXECUTIVE SUMMARY

Bod•ē Pro has previously conducted three pilot clinical studies, including a small human clinical study on its TEN mitochondria support formula in order to test its effects on human mitochondria at the cellular level. The findings from these three studies indicated that TEN:

1. Induced a significant increase of 20% in mitochondrial mass in human white blood cells after 2 hours and an impressive 32% after 4 weeks;*

2. Created a significant increase of 14% in the functional capacity/ energetics of mitochondria within 2 hours of consumption;* and

3. Showed robust antioxidant capacity capable of penetrating into cells and protecting them from free radical stress from the inside of the cells.*

Bod•ē Pro has continued testing its TEN product with a 4th pilot in vitro study. When human cells are stressed by free radicals and by inflammatory conditions, mitochondria suffer. In this newest clinical study, it applied several types of stressors to human cells to evaluate the protection offered by TEN. The findings from this new study indicated that TEN showed multiple levels of support of mitochondria from the following 4 selected bioassays:

• TEN displayed strong anti-inflammatory protection by reducing from 50% to 60% the formation of free radicals under oxidative stress culture conditions.*

• TEN significantly protected cellular glutathione from oxidation under oxidative stress culture conditions.* Glutathione is one of the most important antioxidants that can prevent free radical damage to the mitochondria and is also a major detoxification system in the body.*

• TEN supported healthy mitochondrial membrane potential.* Mitochondria must maintain an electrical potential across their membranes in order to produce energy. Importantly, this protection was seen under normal culture conditions, oxidative stress, and inflamed culture conditions.* This is one of the critical processes for energy creation.

Although the TEN clinical studies were small in scale and no conclusive findings can be inferred from them, their results are extremely promising. Bod•ē Pro is planning to use the data gathered from these initial studies to conduct a larger human clinical study to further confirm these preliminary findings.

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REPORT 147-003. IN VITRO TESTING OF MITOCHONDRIAL MARKERS AND INHIBITION OF FREE RADICAL STRESS.

1. PURPOSE

The purpose of this project was to test the effects of TEN on cellular reduced glutathione levels and mitochondrial membrane potential under both normal and oxidative stress culture conditions, and to test TEN's effect on inhibiting free radical stress in human inflammatory cells.

This project is a direct continuation of previous testing.

The effects of the blend of mitochondria-targeted ingredients were documented, both under normal conditions, and under conditions of specific types of stress, reflecting situations simulating exercise-induced stress, as well as inflammation.

2. WORK PERFORMED

2.1 TESTS PERFORMED
This pilot project applied multiple tests to the increased understanding of TEN:

- Effect of product on intracellular levels of reduced glutathione under oxidative stress;

- Effect of product on mitochondrial membrane potential under normal and stressed culture conditions;

- Effect of product on free radical formation by human inflammatory cells under conditions of oxidative stress.

2.2 PRODUCT HANDLING
The energy formula TEN contains a blend of water-soluble and water-insoluble/poorly soluble compounds. Therefore, this pilot testing compared the cellular effects of three different methods of handling the product for introduction into cell culture.

Table 1. Description of product handling.

Extraction/handling	Solvent for making stock	Serial dilutions	Proportion
TEN Aqueous handling	Physiological saline	Physiological saline	
TEN Ethanol handling	Ethanol 95%	Physiological saline	
TEN Aqueous/ethanol blend	(blend)	Physiological saline	50:50 blend
Ethanol control	Ethanol 95%	Physiological saline	

3. DATA PRESENTATION

Data is presented in the Results section for each of the 4 bioassays following this system:

- An initial bar graph shows the most important data set for a particular bioassay, displayed as the percent change from control cultures;

- This is followed by a set of line graphs where all 4 doses of all 4 products are compared on single graphs, displayed as percent change from control data;

- Raw data is shown as bar graphs with any statistical significance indicated with asterisks. Each product is plotted separately with its appropriate control;

- For the reduced glutathione and mitochondrial membrane potential assays, several cell types were analyzed, and data is presented sequentially for individual cell populations (lymphocytes and monocytes for reduced glutathione; lymphocytes, monocytes and PMN cells for mitochondrial membrane potential).

4. RESULTS

4.1 INTRACELLULAR GLUTATHIONE LEVELS IN HUMAN CELLS

Glutathione (GSH) is an important antioxidant in plants, animals, fungi, and some bacteria. Glutathione is capable of preventing damage to important cellular components caused by damaging free radicals. Glutathione exists in two states: reduced (GSH) and oxidized (as the molecule glutathione disulfide, GSSG). In the reduced state, the thiol group of cysteine is able to donate a reducing equivalent to other molecules, such as reactive oxygen species, to neutralize the free radicals. We used an established protocoliv for flow cytometric evaluation of cellular protection by TEN, where product was applied to human peripheral blood mononuclear cells in the absence versus presence of free radical stress. ThiolTracker™ Violet is a bright intracellular thiol probe for reproducible detection of intracellular levels of reduced glutathione.v Since reduced glutathione represents the majority of intracellular free thiols in the cell, ThiolTracker™ Violet can be used to estimate the cellular level of reduced glutathione by flow cytometry.

Human peripheral blood mononuclear cells were treated with test products for 30 minutes, after which test products were removed. One set of cell cultures was handled using normal culture conditions (no stressors) while the other set of cell cultures was exposed to 1 mM H2O2 for 1 hour (oxidative stress culture conditions). Cells were then stained with ThiolTracker™ Violet and acquired by flow cytometry using an Attune® acoustic focusing cytometer. Data were analyzed for changes in fluorescence intensity, which reflects the reduced glutathione levels in the cells.

Cell types: During flow cytometric analysis, separate analysis was performed on the following two cell types in the blood sample:

- Lymphocytes (Ly): Fairly inactive in the types of cell cultures used here; Monocytes (Mono): Moderately active cells, highly reactive to stressors.
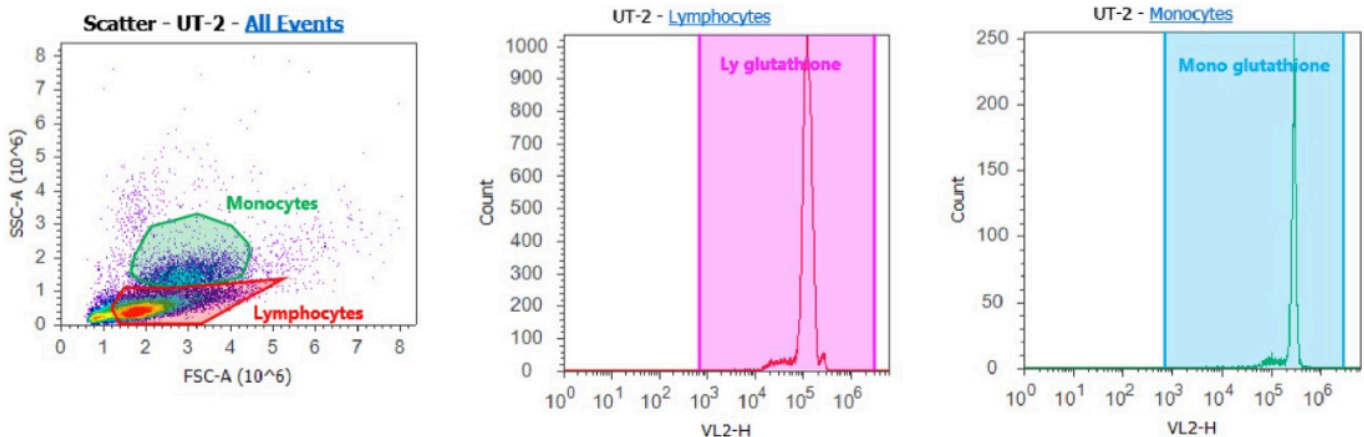

Figure 1. Flow cytometry analysis of cellular reduced glutathione levels. Electronic gates are set to define lymphocytes (Ly) and monocytes (Mono) based on their forward scatter (size) and side scatter (granularity) properties. The fluorescence intensity of the ThiolTracker™ Violet dye was measured for each cell type.

SYNOPSIS:

Note: When reviewing this set of data, an increase in fluorescence intensity is a positive finding, and shows protection of reduced glutathione.

- Normal culture conditions

  o Treatment of cells with products led to some slight reduction in cellular reduced glutathione levels;

  o Monocytes were more sensitive to this effect, particularly at the 2 g/L dose of TEN Aqueous.

- Oxidative stress culture conditions

  o Pretreatment of cultures with TEN Aqueous and TEN Ethanol prior to exposure to 1 mM H_2O_2 led to protection from loss of reduced glutathione*;

- For lymphocytes, protection was seen with the 3 highest doses of TEN Aqueous and the 0.4 and 0.08 g/L doses of TEN Ethanol*;

- Monocytes showed a reduction in cellular reduced glutathione when exposed to the 2 g/L dose of TEN Aqueous but were protected from loss of reduced glutathione by the 0.4 g/L dose of both TEN Aqueous and TEN Ethanol.*

o Immediately below is shown graphs for the protective results for 0.4 g/L TEN, specifically for the oxidative stress conditions.

o On subsequent pages the complete dose curves are shown, followed by raw data graphs.
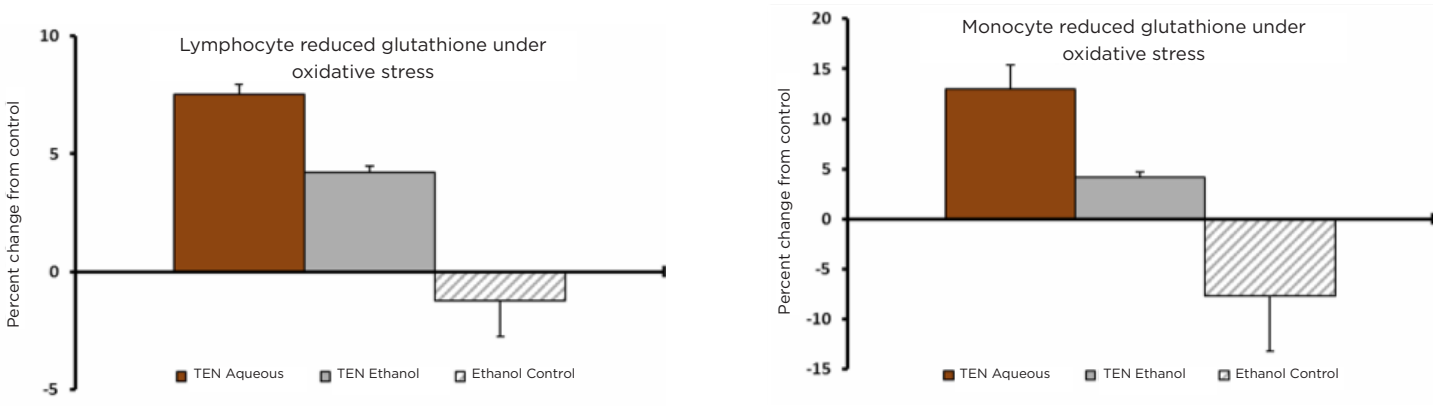
Figure 2. Effects of products on reduced glutathione levels in lymphocytes (left) and monocytes (right), shown as the percent change from control cultures. Oxidative stress culture conditions where cultures exposed to products prior to treatment with 1 mM H_2O_2 are shown as the percent change from cultures treated with H_2O_2 alone. The data shown here are for the 0.4 g/L dose of the aqueous and ethanol fractions of TEN, and also shows the corresponding ethanol control.
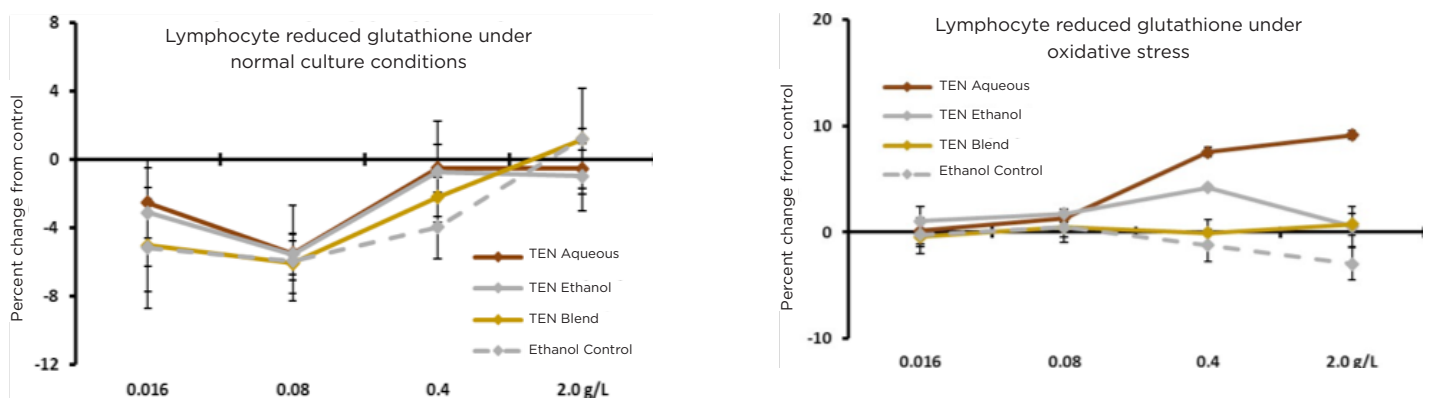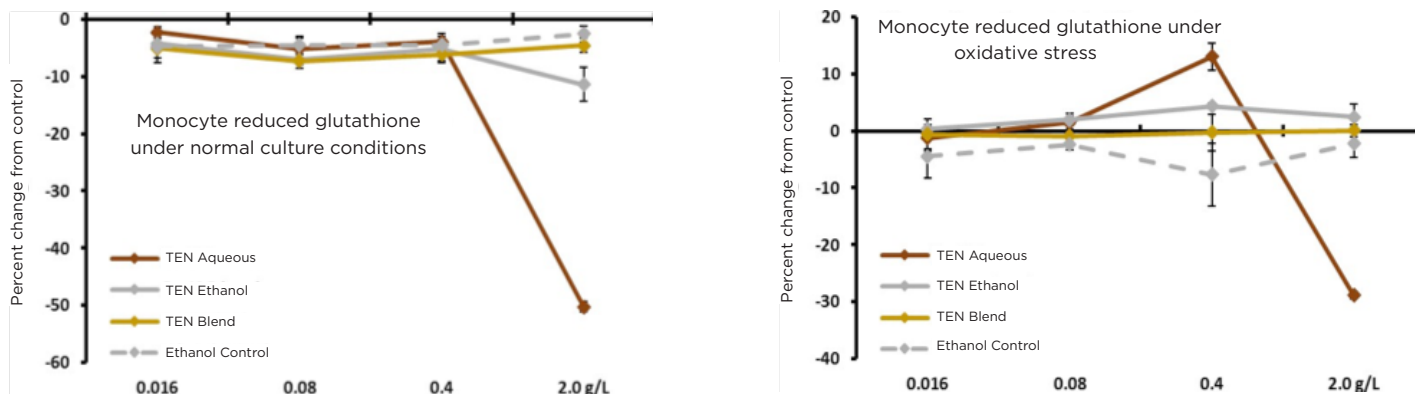

Figure 3. Effects of products on reduced glutathione levels in lymphocytes (percent change from control). Left: Normal cultures conditions where cellular glutathione levels in cultures exposed to products are shown as the percent change from untreated control cultures. Right: Oxidative stress culture conditions where cultures exposed to products prior to treatment with 1 mM H_2O_2 are shown as the percent change from cultures treated with H_2O_2 alone.

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Figure 4. Effects of products on reduced glutathione levels in monocytes (percent change from control). Left: Normal cultures conditions where cellular glutathione levels in cultures exposed to products are shown as the percent change from untreated control cultures. Right: Oxidative stress culture conditions where cultures exposed to products prior to treatment with 1 mM H_2O_2 are shown as the percent change from cultures treated with H_2O_2 alone.

6.1.1 RAW DATA - NORMAL CULTURE CONDITIONS

6.1.1.1   LYMPHOCYTES

• An initial bar graph shows the most important data set for a particular bioassay, displayed as the percent change from control cultures;

• This is followed by a set of line graphs where all 4 doses of all 4 products are compared on single graphs, displayed as percent change from control data;

• Raw data is shown as bar graphs with any statistical significance indicated with asterisks. Each product is plotted separately with its appropriate control;

• For the reduced glutathione and mitochondrial membrane potential assays, several cell types were analyzed, and data is presented sequentially for individual cell populations (lymphocytes and monocytes for reduced glutathione; lymphocytes, monocytes and PMN cells for mitochondrial membrane potential).
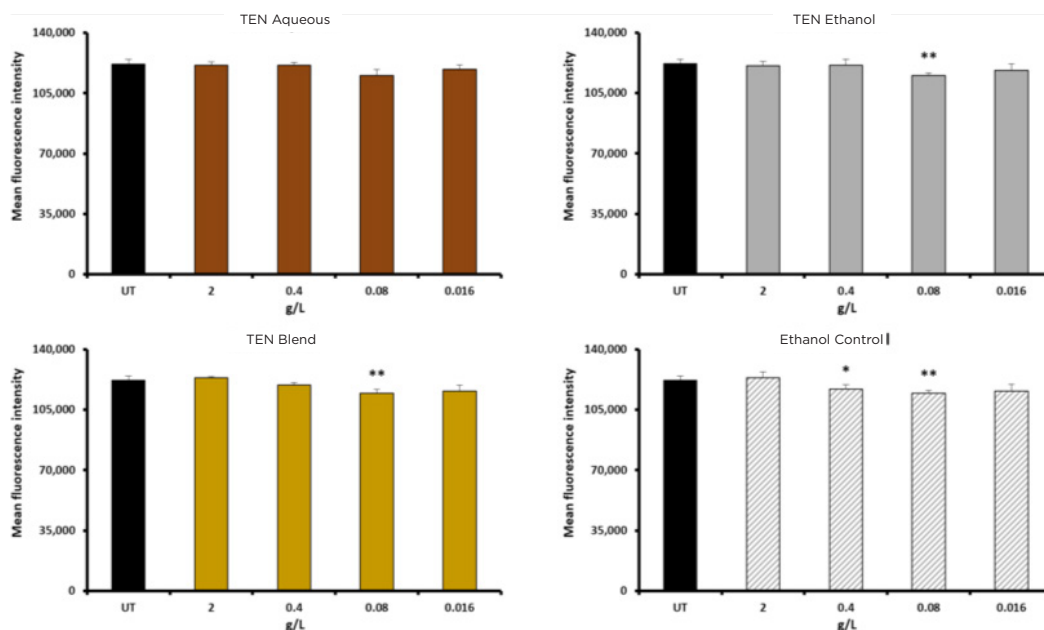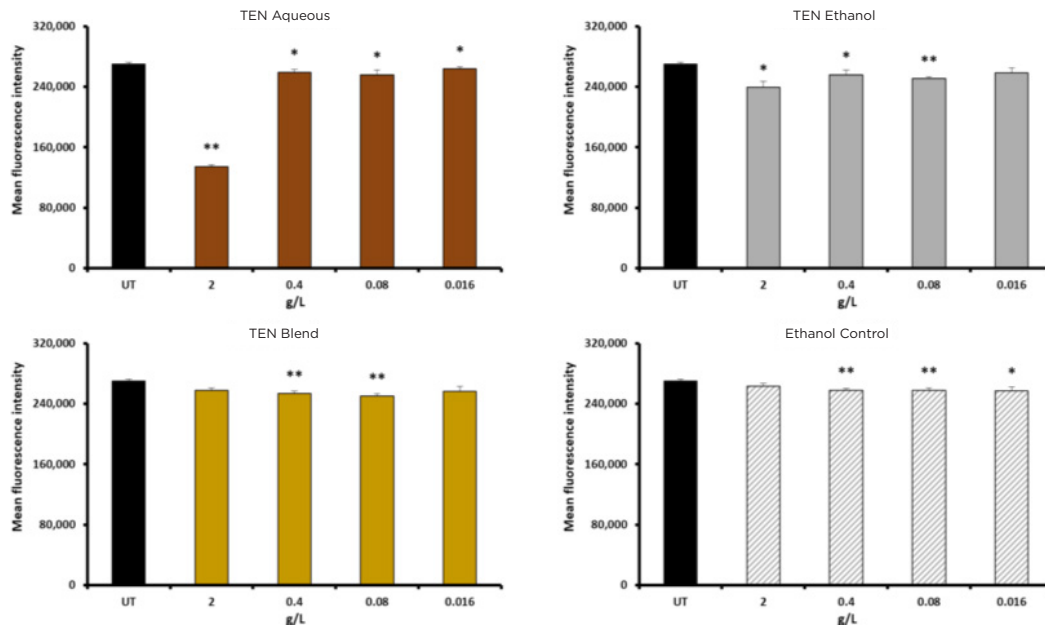

Figure 5. Effects of products on reduced glutathione levels in lymphocytes cultured under normal culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.

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6.1.1.2 MONOCYTES

*Figure 6. Effects of products on reduced glutathione levels in monocytes cultured under normal culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * $p<0.05$ and ** $p<0.01$.*

6.1.2 RAW DATA - OXIDATIVE STRESS CULTURE CONDITIONS
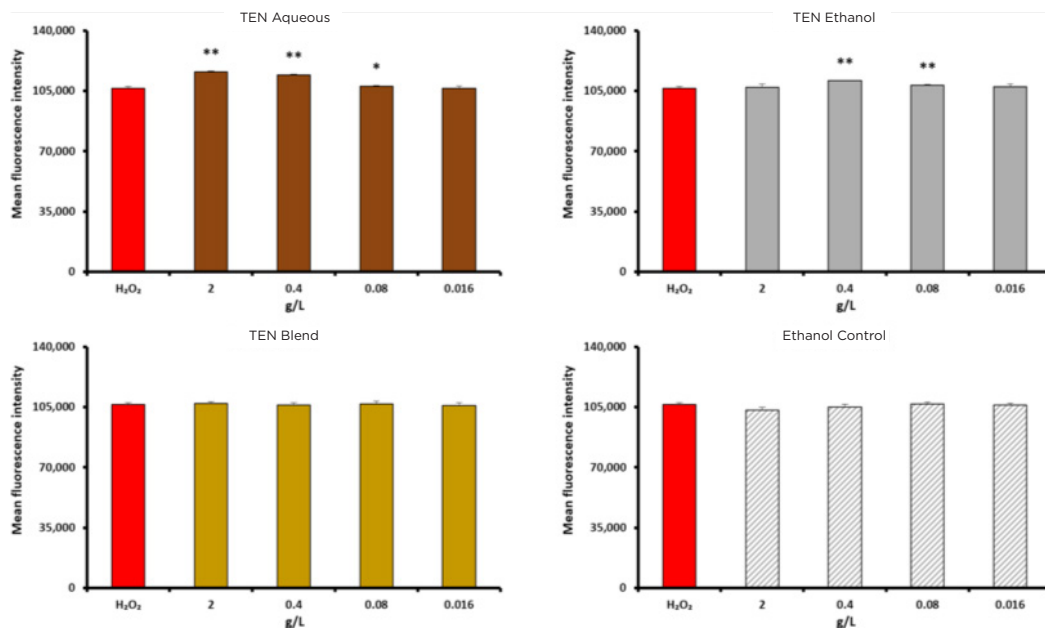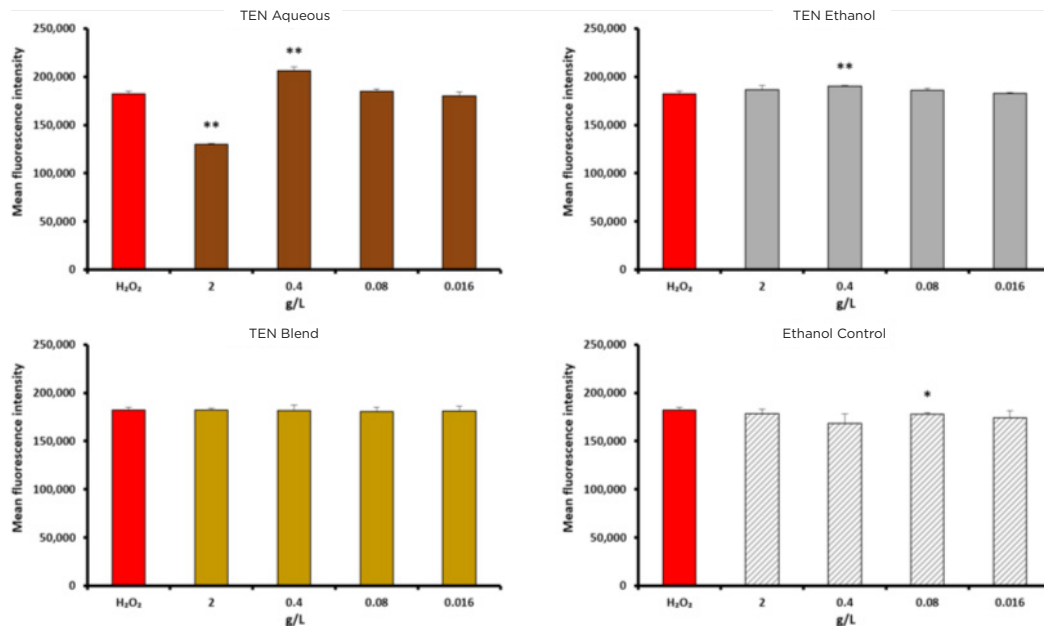
6.1.2.1 LYMPHOCYTES

*Figure 7. Effects of products on reduced glutathione levels in lymphocytes exposed to oxidative stress. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to cultures treated with H_2O_2 alone is indicated by * $p<0.05$ and ** $p<0.01$.*

*Figure 8. Effects of products on reduced glutathione levels in monocytes exposed to oxidative stress. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to cultures treated with H_2O_2 alone is indicated by * $p<0.05$ and ** $p<0.01$.*

6.2 MITOCHONDRIAL METABOLIC MEMBRANE POTENTIAL WHEN EXPOSED TO VARIOUS STRESSORS

JC-1 is a cationic carbocyanine dye that accumulates in mitochondria. The dye exists as a monomer at low concentrations and yields green fluorescence, similar to fluorescein. At higher concentrations, the dye forms J-aggregates that exhibit a broad excitation spectrum and an emission maximum at ~590 nm. These characteristics make JC-1 a sensitive marker for mitochondrial membrane potential. Healthy mitochondria will fluoresce in the orange spectrum, whereas stressed mitochondrial will fluoresce in the green spectrum.

The testing was performed on freshly purified white blood cells from a healthy human blood donor. Serial dilutions of the test product (using all 3 handling methods in parallel) were added to cell cultures, where the cultures were tested for mitochondrial membrane potential after 2 hours incubation (to mimic timing proposed for clinical study). Untreated control samples were processed in parallel.

One set of cell cultures was handled using normal culture conditions (no stressors). Two additional sets of cell cultures were made in parallel, where:

• Oxidative stress was induced by adding H2O2;

• Inflammation was induced by adding LPS (a highly inflammatory bacterial endotoxin).

Flow cytometric analysis for the mean fluorescence intensity in both the green and red spectrum were evaluated and the ratio between red (healthy membrane potential) and green (compromised membrane potential) fluorescence was used as a measure of relative mitochondrial membrane potential.

Cell types: Different cell types have different mitochondrial activity levels, both under normal and under stressed conditions. During flow cytometric analysis, separate analysis was performed on the following three cell types in the blood sample:

• Lymphocytes (Ly): Fairly inactive in the types of cell cultures used here;

• Monocytes (Mo): Moderately active cells, highly reactive to stressors;

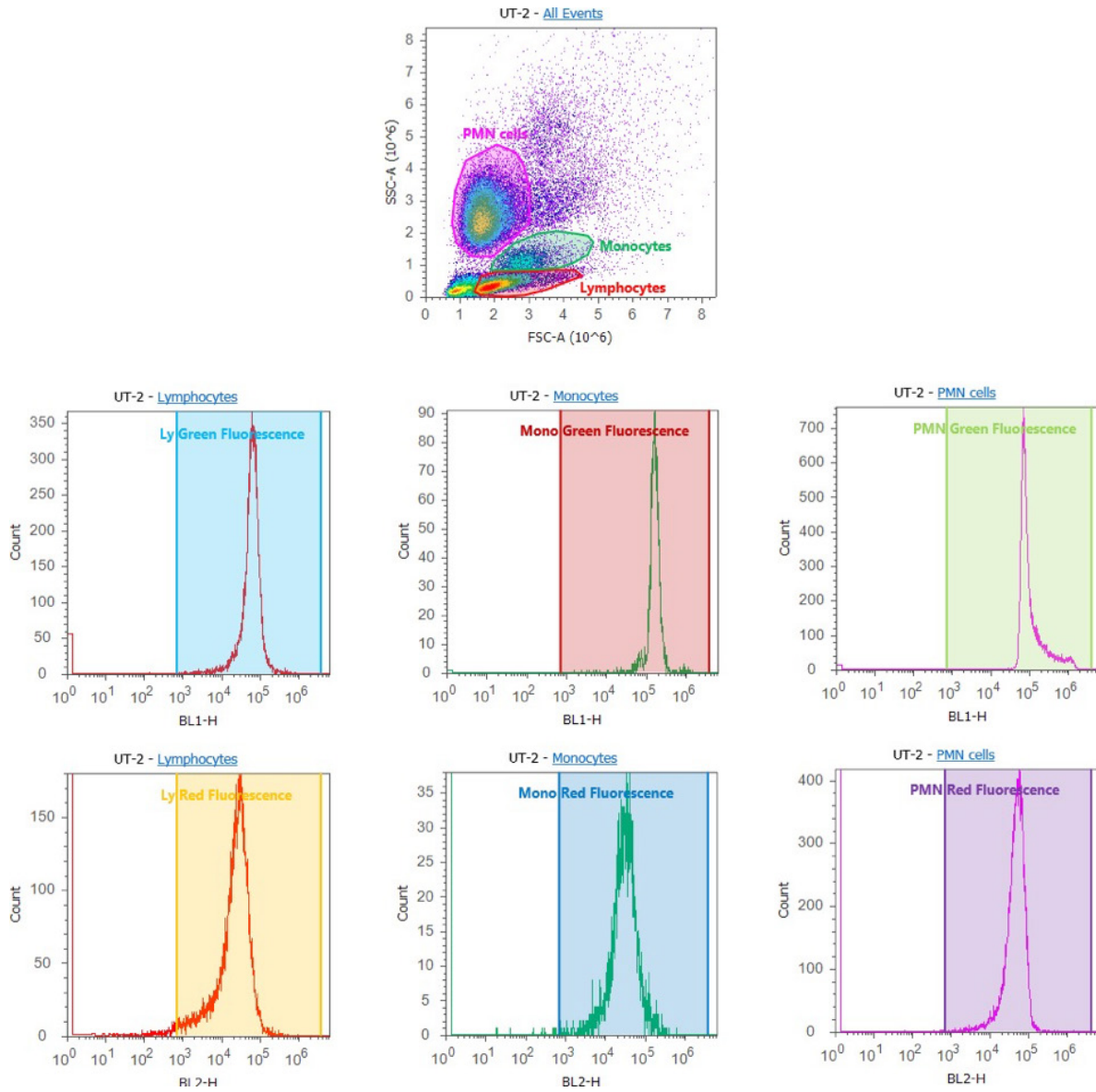Polymorphonuclear cells (PMN): Highly active cells, extremely reactive to stressors.

Figure 9. Flow cytometry analysis of mitochondrial membrane potential. Electronic gates are set to define lymphocytes (Ly), monocytes (Mono), and polymorphonuclear (PMN) cells based on their forward scatter (size) and side scatter (granularity) properties. Both green and red fluorescence intensity was measured for each cell type.

SYNOPSIS:

Note: When reviewing this set of data, <u>an increase in fluorescence intensity</u> is a positive finding, and shows <u>protection of the mitochondrial membrane potential</u>.

• Normal culture conditions

   o Treatment of cells with products led to increases in mitochondrial membrane potential*;

     - Treatment with TEN Aqueous led to consistent increases in both lymphocyte and monocyte mitochondrial membrane potential.*

     - The effects of the TEN Ethanol is inconclusive because higher increases were seen in cultures exposed to ethanol alone (Ethanol control)*;

     - For PMN cells, the highest increases in mitochondrial membrane potential were seen in cultures treated with TEN Ethanol and TEN Blend.* The increases were seen with all 4 doses and they were higher than those seen with the Ethanol control.

• Oxidative stress culture conditions

   o Treatment of lymphocytes with all 4 doses of TEN Aqueous, TEN Ethanol and TEN Blend led to significant increases in mitochondrial membrane potential*;

   o Treatment of monocytes with TEN Blend and ethanol alone (Ethanol control) led to higher increases in mitochondrial membrane potential than treatment with either TEN Aqueous or TEN Ethanol*;

   o Treatment of PMN cells with TEN Aqueous led to decreased mitochondrial membrane potential at the two highest doses while the two lowest doses and all 4 doses of TEN Blend led to increases in mitochondrial membrane potential.*

• Inflammatory culture conditions

   o Treatment of lymphocytes with the two highest doses of TEN Aqueous led to significant increases in mitochondrial membrane potential*;

   o Treatment of monocytes with products did not lead to increased mitochondrial membrane potential;

   o Treatment of PMN cells with the two highest doses of TEN Aqueous and the highest dose of Ethanol control led to decreases in mitochondrial membrane potential while treatment with the two highest doses of TEN Blend and the three lowest doses of Ethanol control led to slight increases.*

Immediately below is shown graphs for the protective results for 0.4 g/L TEN, specifically for the oxidative stress conditions.

On subsequent pages the complete dose curves are shown, followed by raw data graphs.
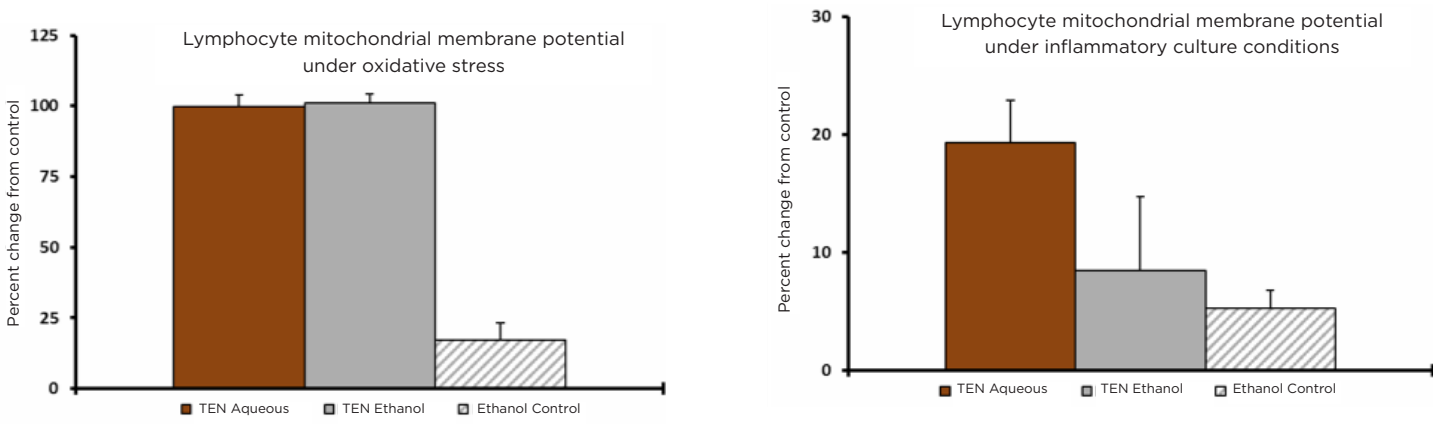

Figure 10. Effects of products on the mitochondrial membrane potential in lymphocytes under oxidative stress (left) and under inflammatory culture conditions (right), shown as the percent change from control cultures. The data shown here are for the 0.4 g/L dose of the aqueous and ethanol fractions of TEN, and also shows the corresponding ethanol control.
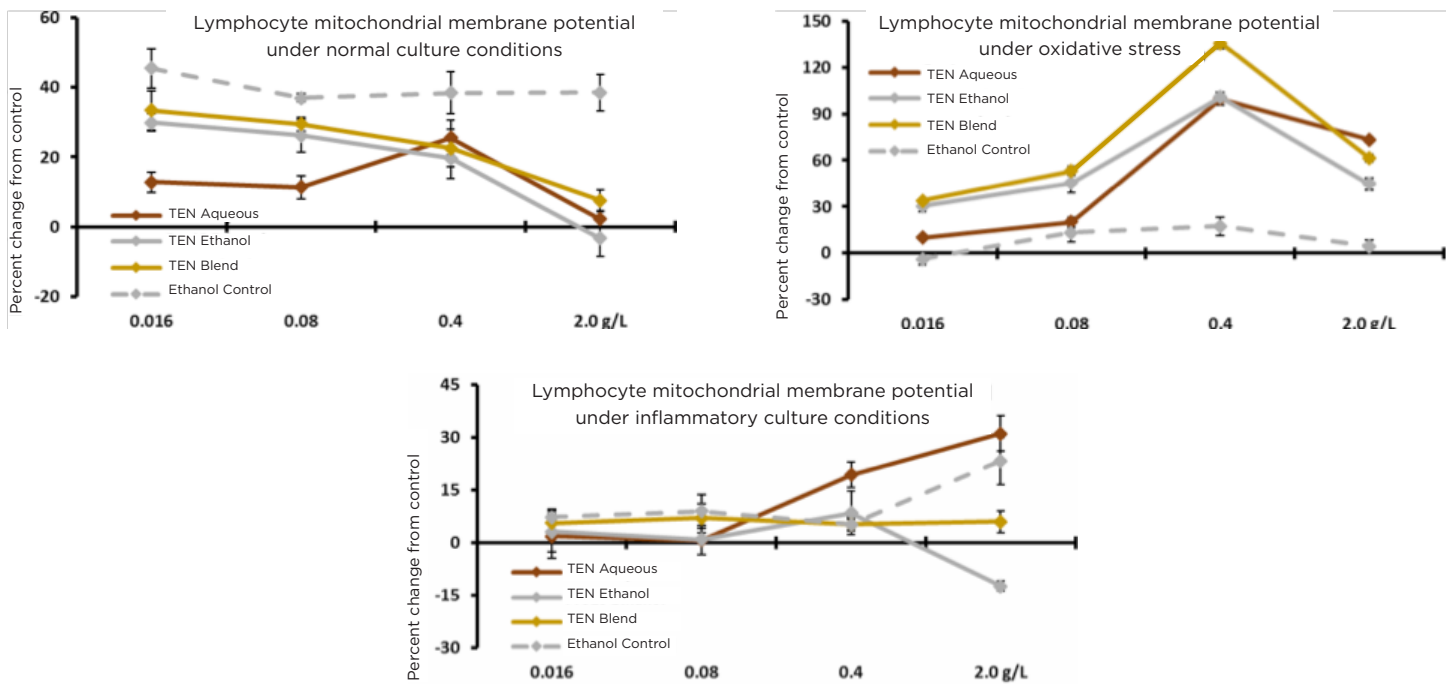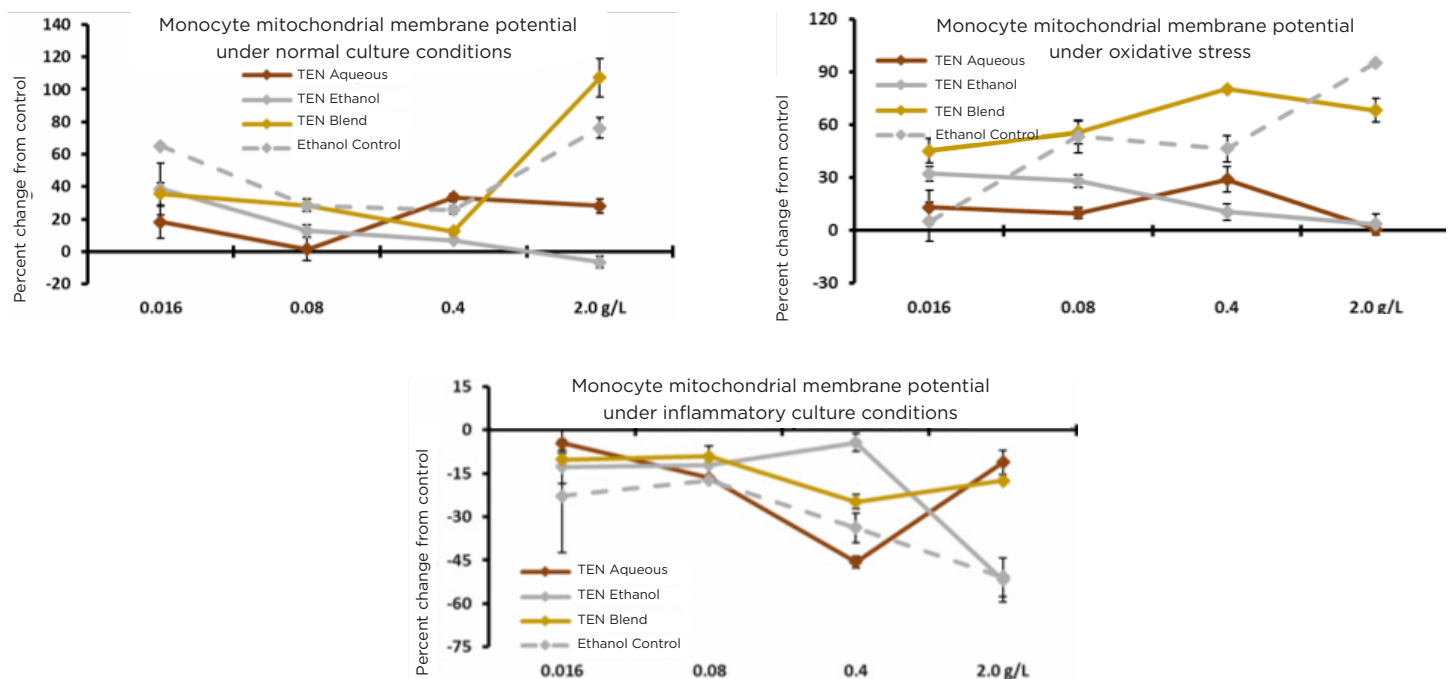
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Figure 11. Effects of products on mitochondrial membrane potential in lymphocytes (percent change from control). Top left: Normal cultures conditions where cultures exposed to products are shown as the percent change from untreated control cultures. Top right: Oxidative stress culture conditions where cultures exposed to products are shown as the percent change from cultures treated with H_2O_2 alone. Bottom: Inflammatory culture conditions where cultures exposed to products are shown as the percent change from cultures treated with LPS alone.
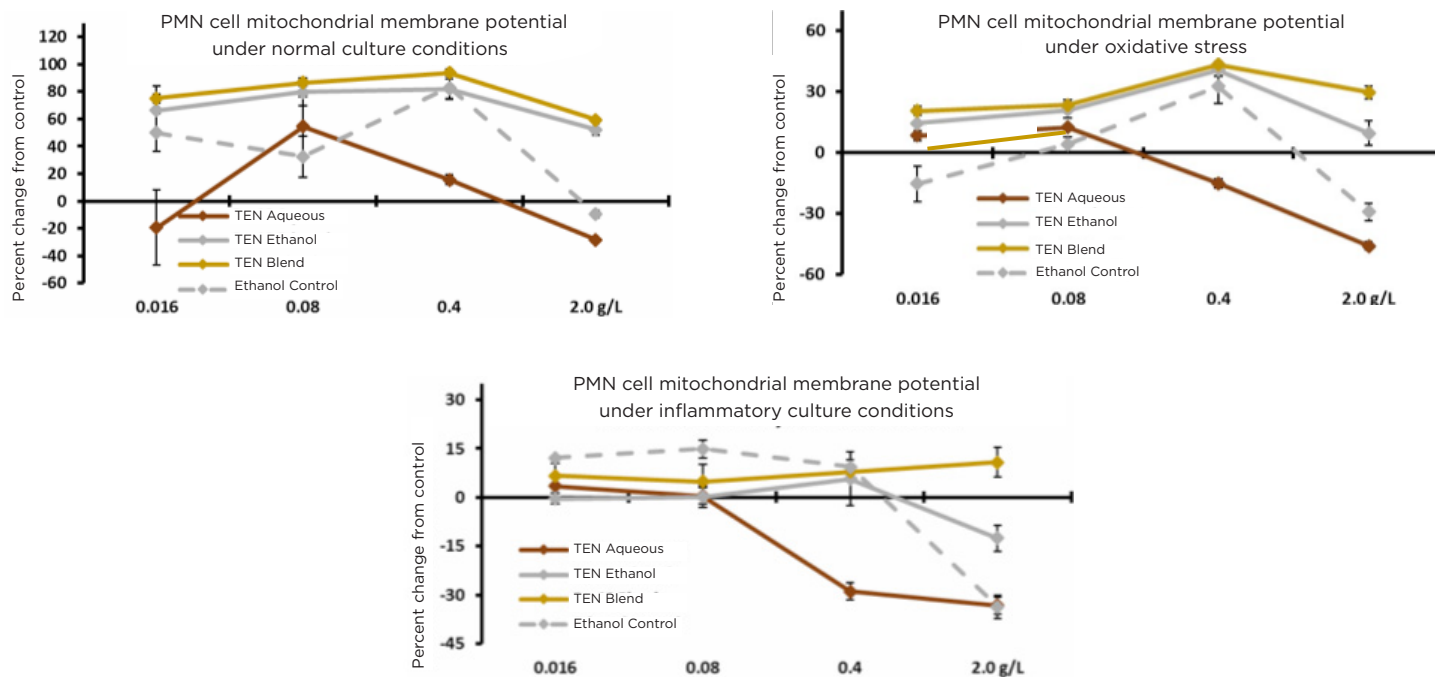

Figure 12. Effects of products on mitochondrial membrane potential in monocytes (percent change from control). Top left: Normal cultures conditions where cultures exposed to products are shown as the percent change from untreated control cultures. Top right: Oxidative stress culture conditions where cultures exposed to products are shown as the percent change from cultures treated with H_2O_2 alone. Bottom: Inflammatory culture conditions where cultures exposed to products are shown as the percent change from cultures treated with LPS alone.

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Figure 13. Effects of products on mitochondrial membrane potential in PMN cells (percent change from control). Top left: Normal cultures conditions where cultures exposed to products are shown as the percent change from untreated control cultures. Top right: Oxidative stress culture conditions where cultures exposed to products are shown as the percent change from cultures treated with H_2O_2 alone. Bottom: Inflammatory culture conditions where cultures exposed to products are shown as the percent change from cultures treated with LPS alone.

6.2.1 RAW DATA - NORMAL CULTURE CONDITIONS
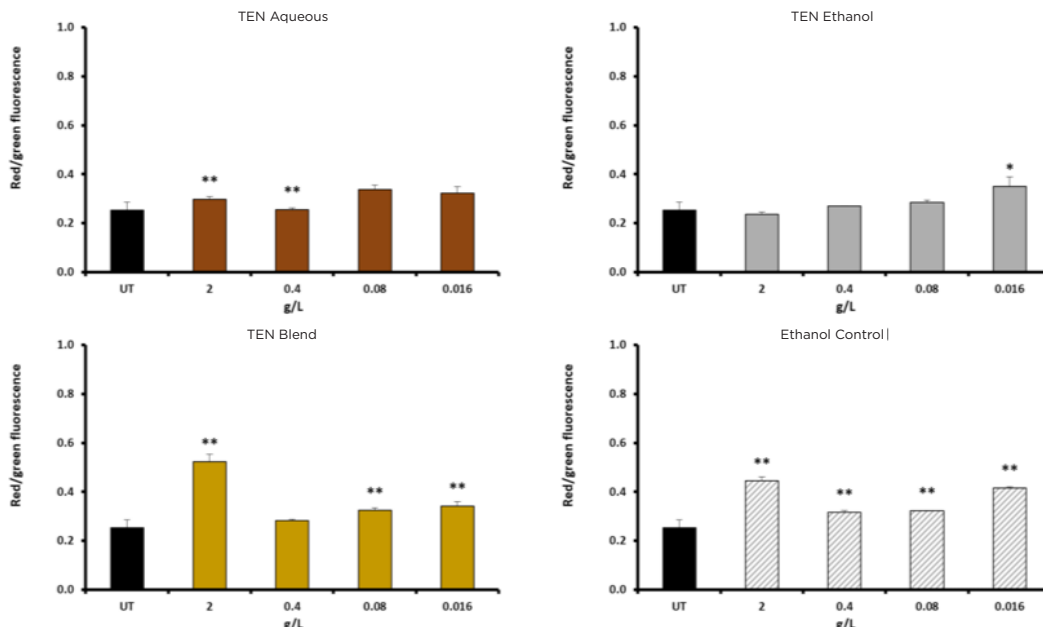
6.2.1.1 LYMPHOCYTES
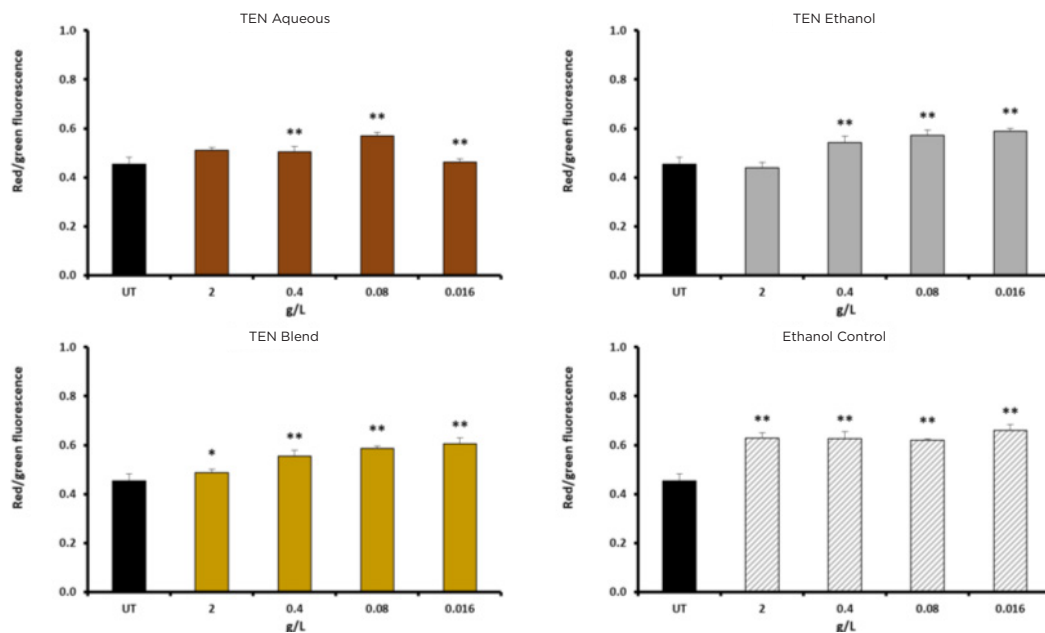
*Figure 14. Effects of products on mitochondrial membrane potential in lymphocytes cultured under normal culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.*

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6.2.1.2 MONOCYTES

Figure 15. Effects of products on mitochondrial membrane potential in monocytes cultured under normal culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.
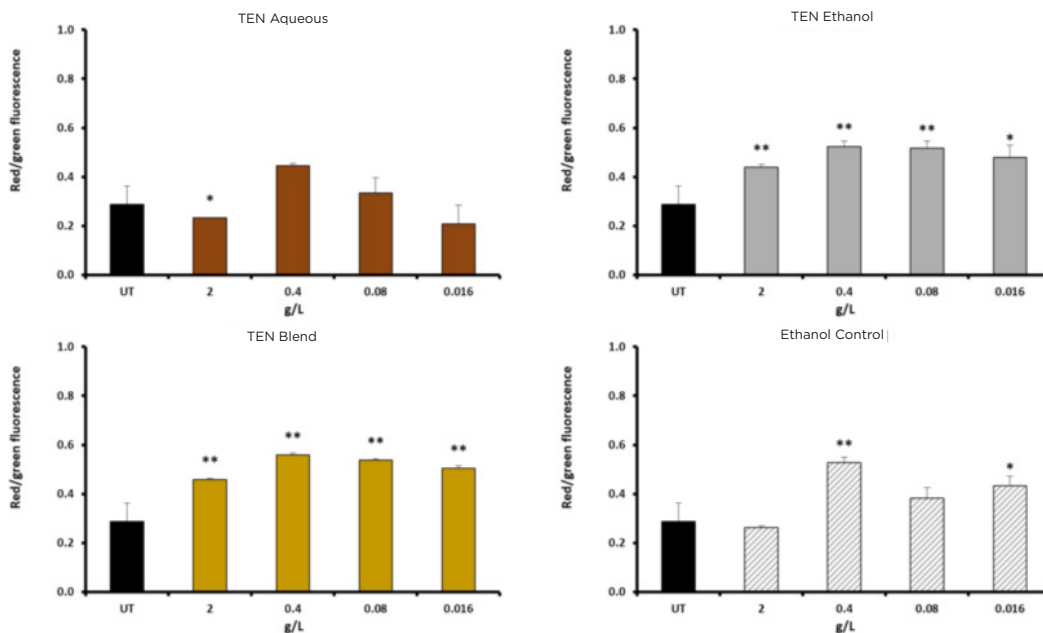
6.2.1.3 PMN CELLS

Figure 16. Effects of products on mitochondrial membrane potential in PMN cells cultured under normal culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.

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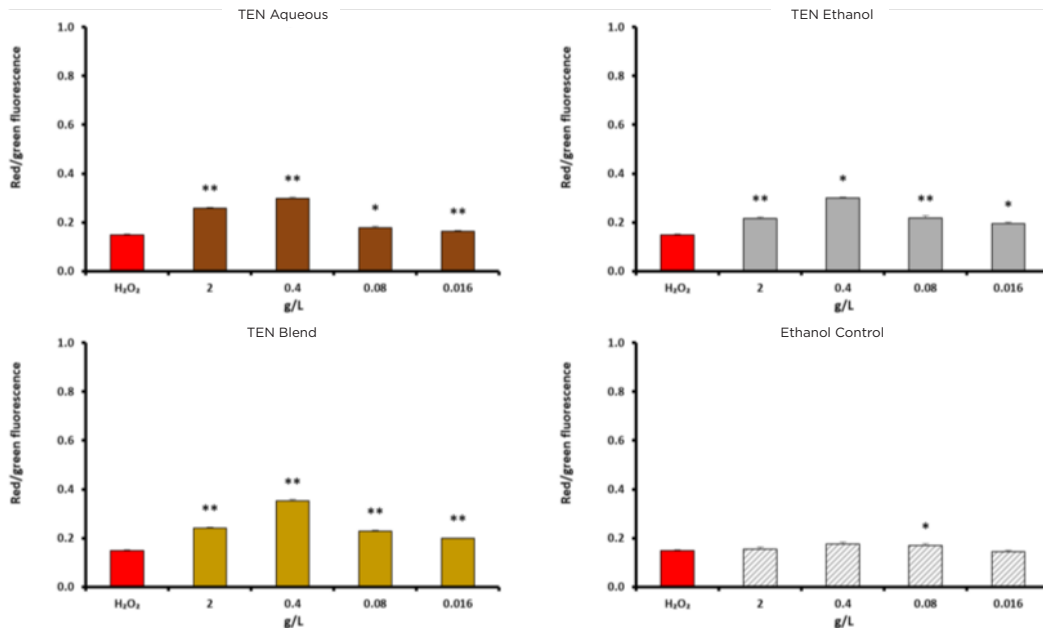# 6.2.2 RAW DATA - OXIDATIVE STRESS CULTURE CONDITIONS
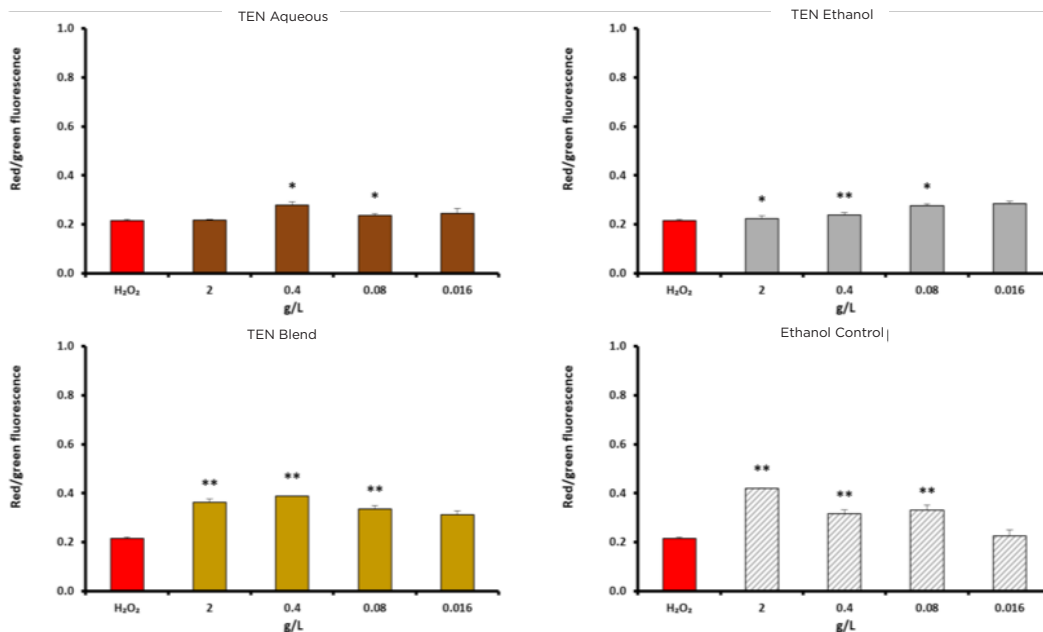
6.2.2.1 LYMPHOCYTES

*Figure 17. Effects of products on mitochondrial membrane potential in lymphocytes exposed to oxidative stress. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.*

6.2.2.2 MONOCYTES

*Figure 18. Effects of products on mitochondrial membrane potential in monocytes exposed to oxidative stress. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.*
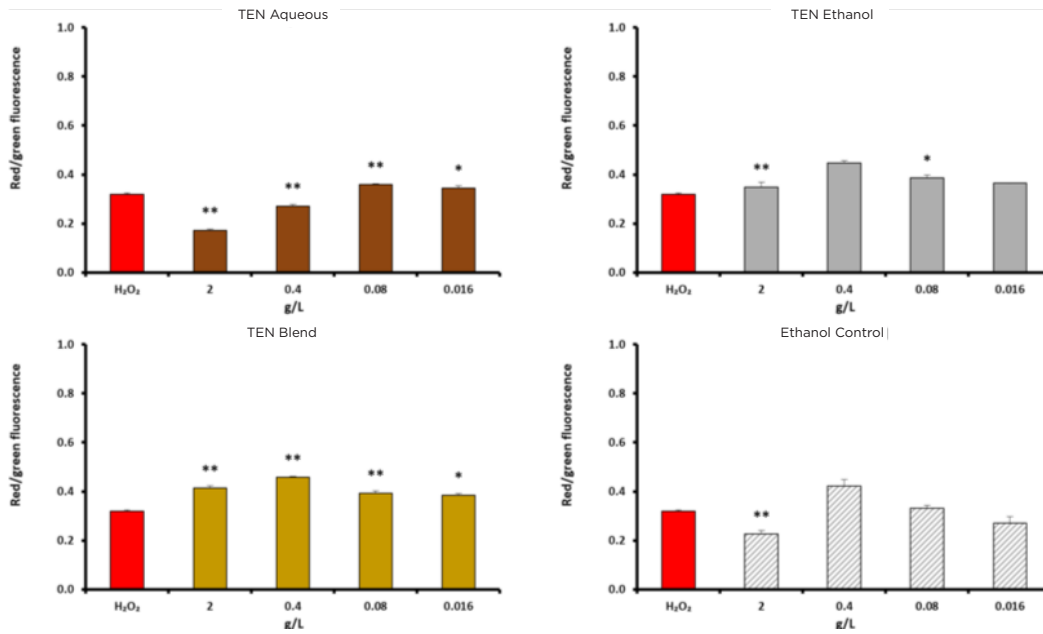
6.2.2.3 PMN CELLS

Figure 19. Effects of products on mitochondrial membrane potential in PMN cells exposed to oxidative stress. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.

6.2.3 RAW DATA - INFLAMMATORY CULTURE CONDITIONS
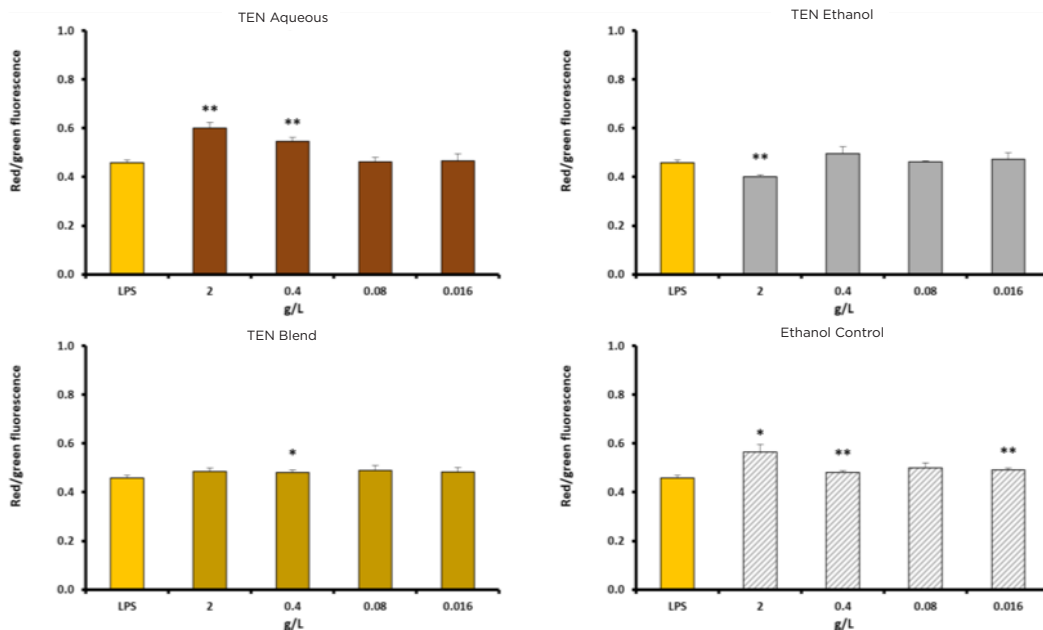
6.2.3.1 LYMPHOCYTES

Figure 20. Effects of products on mitochondrial membrane potential in lymphocytes cultured under inflammatory culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.
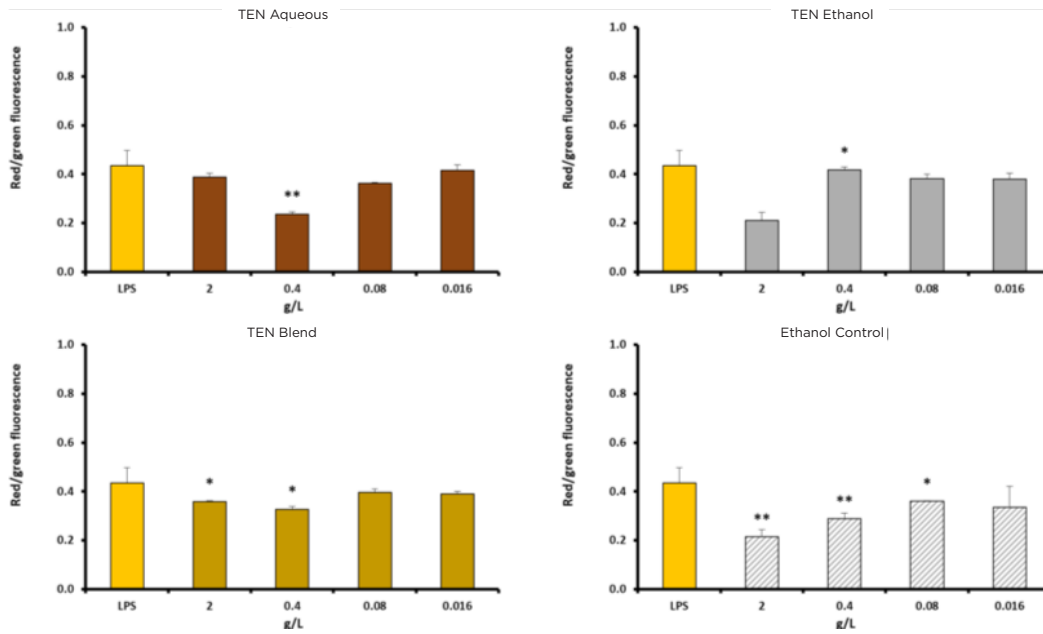
6.2.3.2 MONOCYTES

Figure 21. Effects of products on mitochondrial membrane potential in monocytes cultured under inflammatory culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.
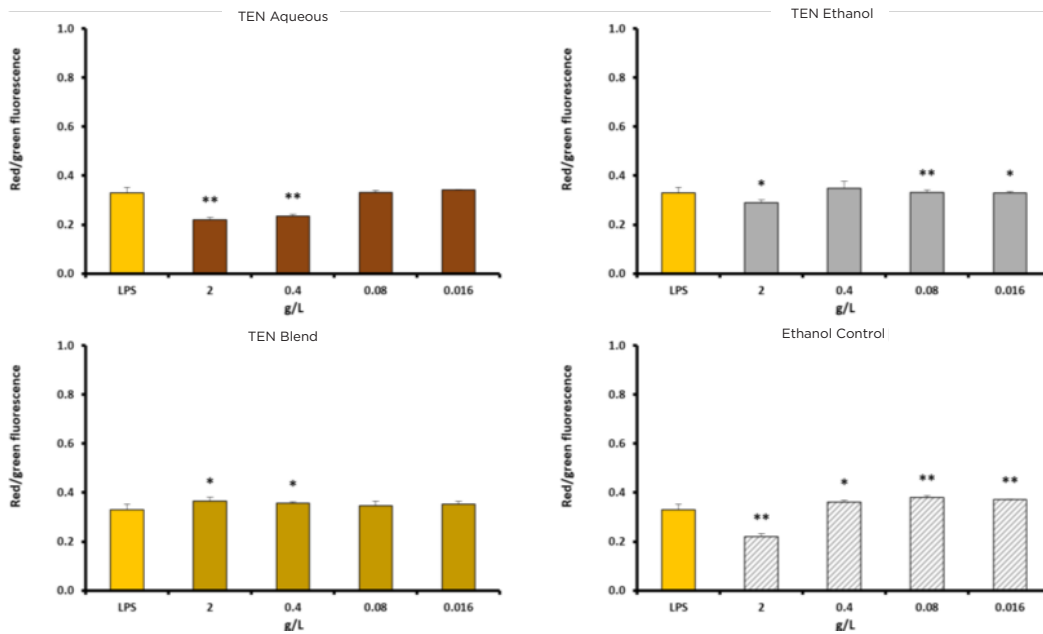
6.2.3.3 PMN CELLS

Figure 22. Effects of products on mitochondrial membrane potential in PMN cells cultured under inflammatory culture conditions. Results are shown as the average ± standard deviation for each triplicate data set. Statistical significance when compared to untreated cultures is indicated by * p<0.05 and ** p<0.01.

6.3 EFFECT ON FREE RADICAL FORMATION BY INFLAMMATORY CELLS

Many natural products with antioxidant capacity also reduce the ROS formation in inflammatory cells.[vi][vii] However, other products may actually increase the ROS formation, despite antioxidant capacity, and this may indicate an interesting cooperation between support of antimicrobial defense mechanisms and antioxidant capacity.[viii]

Thus, natural products may affect PMN cell ROS formation by three different mechanisms (see figure below):

1. Neutralizing ROS by direct antioxidant affect;

2. Triggering an anti-inflammatory cellular signal, leading to reduced ROS formation;

3. Triggering an immune reaction, leading to enhanced ROS formation.

TEST PRODUCT

POLYMORPH NUCLEATED GRANULOCYTE
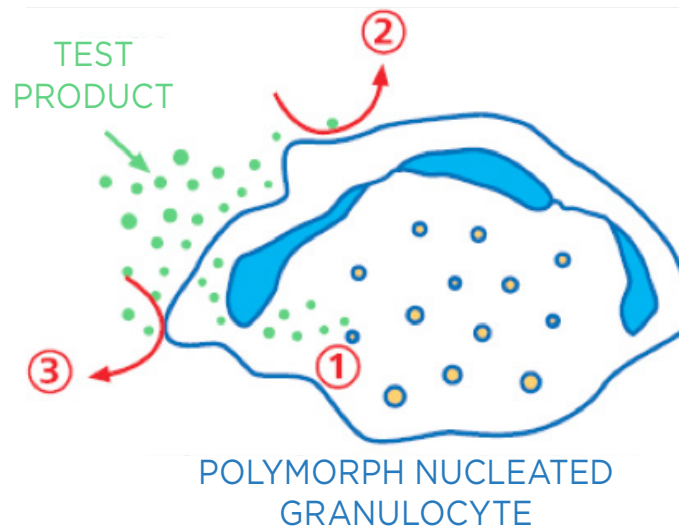
Human polymorphonuclear (PMN) cells are used for testing effects of a product on ROS formation. This cell type constitutes approximately 70% of the white blood cells in humans. PMN cells produce high amounts of ROS upon certain inflammatory stimuli.

Freshly purified human PMN cells were exposed to the test products. During the incubation with a test product, any antioxidant compounds able to cross the cell membrane can enter the interior of the PMN cells, and compounds that trigger a signaling event can do so. Then the cells were washed, loaded with the DCF-DA dye, which turns fluorescent upon exposure to ROS. Formation of ROS was triggered by addition of H_2O_2. The fluorescence intensity of the PMN cells was evaluated by flow cytometry. The low fluorescence intensity of untreated control cells served as a baseline and PMN cells treated with H_2O_2 alone served as a positive control.

If the fluorescence intensity of PMN cells exposed to an extract, and subsequently exposed to H_2O_2, is reduced compared to H_2O_2 alone, this indicates that a test product has anti- inflammatory effects.

In contrast, if the fluorescence intensity of PMN cells exposed to a test product is increased compared to H_2O_2 alone, this indicates that a test product has pro-inflammatory effects by enhancing this aspect of anti-microbial immune defense mechanisms.

The testing is a direct extension on the previously performed cellular antioxidant protection (CAP-e) assay and was performed in triplicate on cells from a healthy blood donor.

SYNOPSIS:

• Treatment of PMN cells with the two highest doses of TEN Aqueous (0.4 and 2.0 g/L) led to a strong reduction in the formation of damaging reactive oxygen species by human inflammatory cells (decreases of 50% and 60% respectively)*;

• Treatment of PMN cells with the highest dose of TEN Ethanol (2.0 g/L) also reduced formation of damaging reactive oxygen species by human inflammatory cells (50% reduction)*.
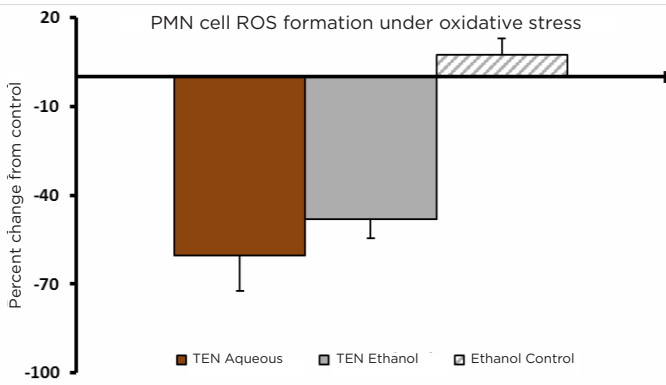
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Figure 23. Effects of products on the intracellular formation of Reactive Oxygen Species (ROS) in polymorphonuclear (PMN) cells under oxidative stress culture conditions (bottom), shown as the percent change from control cultures. The data shown here are for the 2.0 g/L dose of the aqueous and ethanol fractions of TEN, and also shows the corresponding ethanol control.
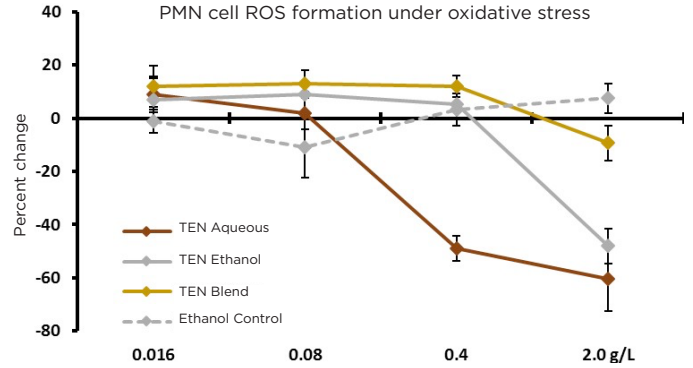

Figure 24. Cellular free radical formation in cultures where inflammation was induced by addition of H2O2. The percent change from the H2O2-treated control cultures is shown for each of the test products.
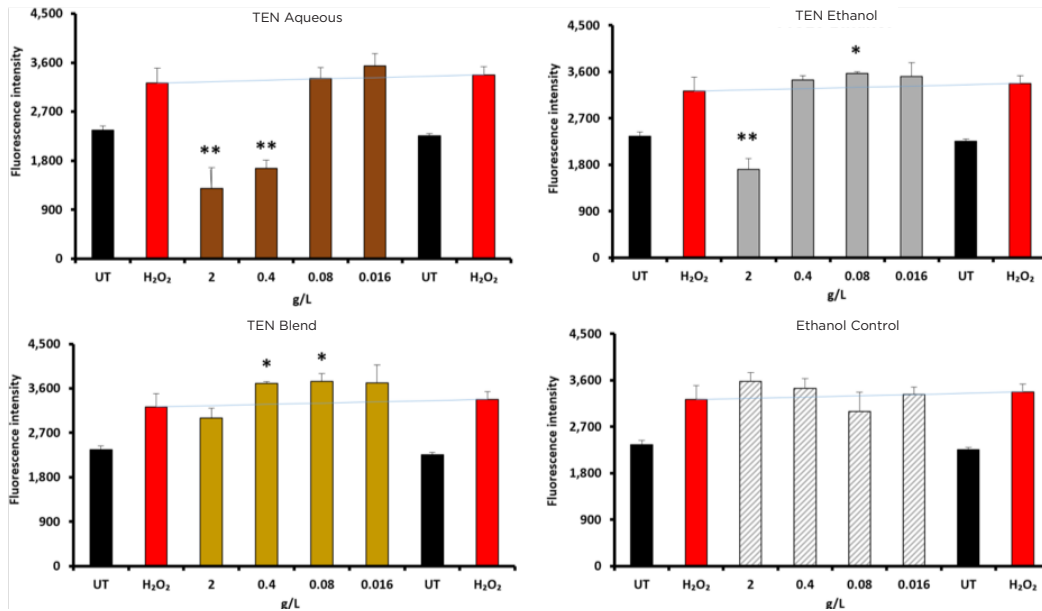

Figure 25. Intracellular free radical formation in cultures where inflammation was induced by addition of H2O2. Untreated (UT) negative control cultures and H2O2-treated positive control cultures were analyzed in hexaplicate at the beginning and at the end of the flow cytometry acquisition. The thin blue line connects the two set of H2O2-treated controls and show only a very minimal change in cellular function over the time of data acquisition. The cell cultures treated with test products before inducing inflammation by addition of H2O2 were performed in triplicate. For all data sets, the average + standard deviation is shown. Statistical significance between a test sample and H2O2-treated control cell cultures is indicated by * $p<0.05$ and ** $p<0.01$.

7 CONCLUSIONS

This project has generated additional results to support the effects of TEN at the cellular level, particularly under stressed culture conditions.

- TEN protected cells from oxidation of glutathione under oxidative stress culture conditions, for both lymphocytes and monocytes.*

- TEN supported mitochondrial membrane potential under normal, oxidative stress, and inflamed culture conditions.*

- TEN demonstrated anti-inflammatory effects on human inflammatory by decreasing formation of reactive oxygen species when exposed to oxidative stress.*

Although these Pro Ten studies were small in scale and no conclusive findings can be inferred from them, their results are extremely promising. Bod•ē Pro is planning to use the data gathered from these initial studies to conduct a larger human clinical study to further confirm these preliminary findings.
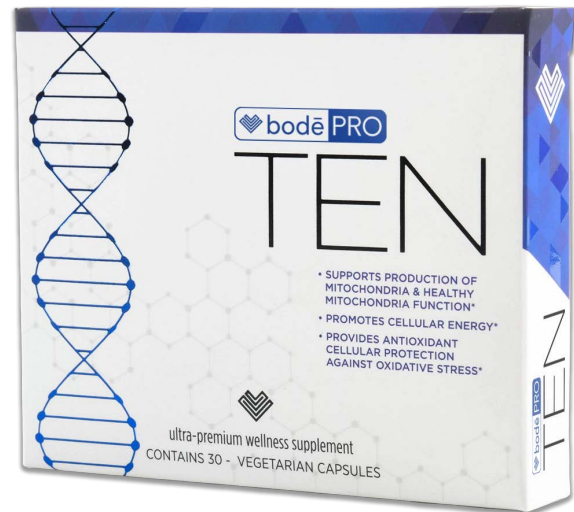
8 REFERENCES

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