Alternatives for vitamin E

Theo van Kempen
Life; a balancing act between oxidizing and being (per)oxidized

- The essence of life
  - Converting the energy in food into growth and labor
    
    \[ \text{CH}_x + \text{O}_2 \rightarrow \text{ATP} \]
    
    \[ \text{H}_2\text{O} + \text{CO}_2 \]

- Nothing is perfect
  - Radicals are co-produced
    - Dangerous if not neutralized!

- Tissue damage
  - Lipids
  - Proteins
  - DNA

\[ \text{O}_2^-, \text{H}_2\text{O}_2, \text{OH}^- \]
Balance exposure/defense critical

- Increasing oxidative stress, either through increased exposure and/or weakened defenses, leads to disease.

Kothari, 2010

After Blumberg and Lekkesfeldt
Oxidative stress influences production performance
Oxidative stress influences fertility

Fertility in poultry: Radwan, 2008
Oxidative stress influences parturition

Parturition in cattle: Bernabucci, 2002
Oxidative stress influences stress susceptibility

Heat stress in poultry: Altan, 2003
Oxidative stress influences meat quality

Meat quality in lambs: Nieto, 2010
Multiple defense mechanisms in place

- Membranes
- Peroxisomes
- DNA
- Lysosomes
- Mitochondria

After Surai
Multiple defense mechanisms in place

- And 3, catabolism of damaged molecules

1. Enzymes
   - Catalase
   - GSH-Px (Se)

2. Antioxidants
   - Vitamin E
   - Lipoic acid
   - Cu,Zn-SOD
   - Mn-SOD
   - GSH-Px (Se)
   - Polyphenols
   - Vitamin C
   - Polyphenols
   - PH-GSH-Px
   - GSH, carotenoids, ubiquinols

After Surai
Vit. E: *polyphenol* we’ve come to depend on

- α-Tocopherol: ‘to carry a pregnancy’

![Chemical structure of α-Tocopherol]

Anti-oxidant  Lipophilic
Key player in antioxidant cascade

- 1000x more reactive to \( \text{H}_2\text{O}_2 \) than PUFA
- Vit E prevents formation of dangerous peroxidation products
- Part of reaction cascade also involving Vit. C and thiols

Rimbach, 2010
Role evolving from AO to gene regulator?

- Evolving role of Vit. E

![Diagram showing the evolution of Vitamin E from 1922 to 2000 with different activities such as antioxidant activity, disease preventing activity, transport and metabolism, modulation of signal transduction, and modulation of gene expression.](image)

Rimbach, 2010

Zingg, 2007
Basal vit. E requirements: sound basis?

- **Poultry, 1994 NRC**

  Tentative values have been expressed for all ages. The results of the few studies conducted are variable. The requirement for prevention of encephalomalacia may be higher than that for growth only (Singsen et al., 1955). In addition, the requirement for maximum immune response may be much higher than that for growth (Tengerdy and Nockels, 1973; Colnago et al., 1984).

  ![ACRBC Males - 2001 Feed](image1)

  ![Ross Males - 2001 Feed](image2)

- **Swine**
  - 2012 NRC refers to 1998 NRC
  - 1998 NRC refers to 1981 review by Ullrey and ARC
    - Focus is on 40-50 year old literature!
AO Requirement depends on health status

- Vit. E requirement affected by
  - Stress level
  - Growth rate
  - Meat quality
    - Example for poultry (modified):

Radicals are also a double-edged sword for fighting infections
Meta-analysis confirms limits

- Meta-analysis for swine meat quality
  - 90% of the improvement in TBARS occurs at a tissue level of 3.4 ug/g tocopherol, which is obtained with a dose of 90 mg/day
  - Optimum dose of Vit. E for meat quality is 30-35 ppm
Vit. E bio-availability: poor

- Pharmacokinetics trial with swine
  - Bio-efficacy oral 5.4%
  - Elimination half-life 2.6h
  - Plasma level ~3 µM

- Cause
  - Low-fat diet (6%)
  - Poor hydrolysis of acetate ester
  - Use of stereo-isomers
  - High dose vs. requirement
Vit. E one of many antioxidants in nature

- Plants contain an array of antioxidants besides Vit. E
  - Some plants have a very strong anti-oxidant protection

Apak, 2007
Polyphenols; a colorful tree
Potent AO alternatives to Vit. E

- Similar phenolic structure as Vit. E
  - Often more hydroxy groups than Vit. E
  - More anti-oxidant capacity per mole
  - But typically smaller molecules
  - Much more anti-oxidant capacity per gram

Tabart, 2009
Vit. P, again?

- 1939: Polyphenols were considered as vitamins!
  - Cured some diseases linked to oxidative stress

- 2006: ‘Lifespan essential’ (Williamson)

**Nutrients and phytochemicals: beyond antioxidants**

*by Birgit Holst and Gary Williamson*

The effect of any dietary compound is influenced by the active bioavailable dose rather than the dose ingested. Depending on the individual predisposition, including genetics and the individual’s diet, a bioavailable dose may vary. The effects of nutrients may vary, and thus the requirements for nutrients vary. This suggests that besides ascorbic acid, flavonoids, phenolic acids and glucosinolates are essential for phytoneutrients (e.g., phytochemicals such as flavonoids, phenolic acids and glucosinolates). These are not essential for phytoneutrients.

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**RESEARCH FOR VITAMIN P.**

*BY SHIRO MORI*

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(Received for publication, December 25, 1938)

There is no doubt of the fact that crystallized ascorbic acid has curative effects on hemorrhagic diseases, but we have frequently heard that it is not always effective in the treatment of all hemorrhagies. Moreover, notwithstanding the fact that disposition to hemorrhage is often improved by the application of paprika or lemon, there are cases in which pure ascorbic acid alone has no effect. This suggests that besides ascorbic acid, lemon and paprika contain other substances which have effective results on hemorrhagic disposition.

Szent-Györgyi and co-workers identified of the these effective substances as belonging to the flavonoid group, and named it “Vitamin P,” which is probably so-called because it has an effect on capillary permeability.

Together with ascorbic acid, Vitamin P has great significance in the plasma oxidation system. It is especially important in the peroxidase system. Szent-Györgyi and co-workers extracted from 200 kilograms to 50 litres of citrus juice, 2 grams of crystallized flavon, which they named citrin. This substance is slightly yellow in color and is insoluble in water and alcohol, but dissolves in alkaline solvents. Analytically, it has the following composition.

\[ C_{24}H_{36}O_{17} \text{. Its melting point is } 205^\circ. \]
Like all-rac Vit. E, not all polyphenols equal

- Polyphenol bio-availability varies from 0 to >80%
  - But fermentation can yield digestible fragments
    - E.g., proanthocyanidins
      - Too large to be absorbed in small intestines
        - Digestibility = 0%
      - Can be fermented
        - Key product is hydroxyphenyl acetic acid
    - Mass recovery is only 0.8%
Polyphenol selection

- Ruminant: bypass or polyphenols which are fermented into potent anti-oxidants
- Monogastrics: digestible with high ORAC (dORAC)

Manach, 2005; tocopherol = Michiels, 2013
AO-mix: adapted to species

- Components selected for high bio-availability

Graph showing antioxidant capacity (ORAC in mol/kg) and bio-availability for different components: Vitamin E-50, Grape, Curcumin, Rosmarinic. Bio-availability is measured in %.
AO-mix prevents heat-stress complications: swine

- Both Vit. E and AO-mix prevented an increase in lipid peroxidation (measured as MDA) in heat-stressed piglets

![Graph showing Malondialdehyde (MDA) levels before and after stress for different treatments: Control, 11 ppm, Vit E, 80 PPM, 11E+69 AO mix. The graph illustrates a decrease in MDA levels post-stress for all treatments compared to pre-stress.]
AOmix prevents heat stress complications: poultry

- Both Vit. E and Selko AOmix prevented an increase in peroxidation (measured as MDA) in heat-stressed broilers
AOmix prevents heat stress complications: poultry

- AOmix resulted in a lower SOD (ns) in heat-stressed birds
  - MDA and SOD positively correlated
AO-mix prevents heat-stress complications: poultry

- Heat stressed broilers in Asia
  - AO-mix improved BW, FI, and cellular immunity, while reducing MDA
Field experience in South Africa confirms benefits

- 5 barns treated, 5 barns control
  - Interim results
    - Heavier carcasses & breasts
    - Less breasts with oxidation problems (day 28 data only)
AO-mix & Vit E: polyvalent defense

1. Enzymes
   - Catalase
   - GSH-Px (Se)
   - Mn-SOD
   - Cu,Zn-SOD

2. Antioxidants
   - Rosmarinic acid, vit. E.
   - GSH-Px (Se)
   - PH-GSH-Px
   - Polyphenols
   - Curcumin, vit. E.
AO-mix boosts antioxidant defenses

- **Conclusions**
  - Oxidative stress a challenge in health and even more so in disease or high metabolic activity
  - Vit. E potent antioxidants but with limits
  - AO-mix can boost AO defenses beyond Vit. E