PALM TOCOTRIENOL: A POTENTIAL THERAPY FOR PEPTIC ULCER DISEASE

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INTRODUCTION
PEPTIC ULCER DISEASE (PUD)

- Ulcerated lesion in the mucosa of the stomach or first part of the small intestine.
General Peptic Ulcer Symptoms

- Epigastric tenderness
  - Gastric: epigastrium; left of midline
  - Duodenal: mid to right of epigastrium
- Sharp, burning, aching, gnawing pain
- Dyspepsia (indigestion)
- Nausea/vomiting
- Belching
**PATHOPHYSIOLOGY**

**NORMAL**
- **Damage forces:**
  - Gastric acidity
  - Peptic enzymes

**INJURY**
- **Defensive forces:**
  - Surface mucus secretion
  - Bicarbonate secretion into mucus
  - Mucosal blood flow
  - Apical surface membrane transport
  - Epithelial regenerative capacity
  - Elaboration of prostaglandins

**PEPTIC ULCERATION**
- **Increased damage or impaired defenses:**
  - Necrotic debris (N)
  - Nonspecific acute inflammation (l)
  - Granulation tissue (G)
  - Fibrosis (S)

- **Factors:**
  - H. pylori infection
  - NSAID
  - Aspirin
  - Cigarettes
  - Alcohol
  - Gastric hyperacidity
  - Duodenal-gastric reflux

- **Ischemia
  - Shock
  - Delayed gastric emptying
  - Host factors**
Complications of Peptic Ulcers

- Hemorrhage
  - Blood vessels damaged as ulcer erodes into the muscles of stomach or duodenal wall
  - Coffee ground vomitus or occult blood in tarry stools

- Perforation
  - An ulcer can erode through the entire wall
  - Bacteria and partially digested food spill into peritoneum = peritonitis

- Narrowing and obstruction (pyloric)
  - Swelling and scarring can cause obstruction of food leaving stomach = repeated vomiting
NSAIDS (Aspirin, ibuprofen, indomethacin, naproxen etc) induced gastric ulcers

Ethanol induced gastric ulcers

Stress induced gastric ulcers

Acetic acid induced gastric ulcers

Helicobacter pylori induced gastric ulcers
NSAIDs-induced ulcers

Boyacioglu et al. 2015
Ethanol-induced ulcers

Alvarez-Suarez et al. 2011
In rats, stress can be simply and reliably produced by the RESTRAINT model (Konturek et al. 2012).

Effect of such model include the development of gastric lesions/ulcers.

Restraint stress
Stress-induced Gastric lesions
Stress-induced Gastric lesions

Cold-restraint stress

Water-immersion restraint stress
Mechanism of stress-induced gastric lesion

Multifactorial:
- reduction of gastric blood flow (Konturek et al., 2012)
- oxidative stress (Megala dan Geetha 2012)
- suppression of endogenous prostaglandins (Brzozowski et al., 2008)
- alteration of gastric motility (Ibrahim et al., 2011)
- increased gastric acidity (Dalia et al., 2011)
- reduced gastric mucus (Pramod et al., 2012)
- inflammatory changes (Wang et al., 2011)
Why TOCOTRIENOL?

- Studies has shown that agents with antioxidant property reduces gastric lesions caused by various noxious stimuli.
- Tocotrienol possess a higher antioxidant capability compared to tocopherol (Bardhan et al. 2011)
- Palm tocotrienol - anti-inflammatory effect (Khan et al. 2011)
- Few studies had been done to elucidate the effect of tocotrienol on gastric ulcers.
Gastric ulcers

Gastric tissue of a rat exposed to 3.5 h WIRS with omeprazole (OMZ) supplementation

Gastric tissue of a rat exposed to 3.5 h WIRS with Tocotrienol (TT) supplementation
Gastric ulcers (2)

Gastric tissue of a rat exposed to 3.5 h WIRS

Gastric tissue of a rat exposed to 3.5 h WIRS with Tocotrienol supplementation

Gastric tissue of normal rat
GASTRIC LESIONS SCORING

*/* Significant compared to NS (p<0.05)
#//* significant compared to S (p<0.05)

Source: Nur Azlina et al. 2015 PLoS one; Ibrahim et al. 2012 Archives of Medical Science
Malondialdehyde Content

*/*a Significant compared to NS (p<0.05)
#/#b significant compared to S (p<0.05)

Superoxide dismutase Activity

* Significant compared to NS (p<0.05)
# significant compared to S (p<0.05)

Source: Nur Azlina et al. 2015 PLoS one
GASTRIC ACID CONCENTRATION

* Significant compared to NS (p<0.05)
# significant compared to S (p<0.05)

Source: Nur Azlina et al. 2013; Evidence-Based Complementary and Alternative Medicine
* Significant compared to NS (p<0.05)
# significant compared to S (p<0.05)

Source: Nur Azlina et al. 2013, Evidence-Based Complementary and Alternative Medicine; Ibrahim et al. 2008, Indian Jr of Pharmacology
**GASTRIC COX-1 mRNA expression**

* Significant compared to NS (p<0.05)  
+ Significant compared to OMZ (p<0.05)  
# significant compared to OMZ (p<0.05)

Source: Nur Azlina et al. 2013; Evidence-Based Complementary and Alternative Medicine
**GASTRIC COX-2 mRNA expression**

* Significant compared to NS (p<0.05)
# significant compared to S (p<0.05)

Source: Nur Azlina et al. 2013; Evidence-Based Complementary and Alternative Medicine
iNOS expression & Nitric Oxide Content

* Significant compared to NS (p<0.05)
# significant compared to S (p<0.05)

Source: Nur Azlina et al. 2015, PLoS one
Pro-inflammatory Cytokines

* Significant compared to NS (p<0.05)
# significant compared to S (p<0.05)

Source: Nur Azlina et al. 2015, PLoS one
## Effects of different forms of vitamin E on gastric parameters in different stress models

<table>
<thead>
<tr>
<th>Vitamin E</th>
<th>Model</th>
<th>Gastric Parameters</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Tocopherol</td>
<td>Restraint alone</td>
<td>+</td>
<td>Nur Azlina et al. [2009, 2005]</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>Cold-restraint stress /WIRS</td>
<td>+</td>
<td>Al Moutairy et al. [2003], Ibrahim et al. 2011</td>
</tr>
<tr>
<td>Tocotrienol-rich fraction</td>
<td>WIRS</td>
<td>+</td>
<td>Ibrahim et al. [2008]; Ibrahim et al. [2011]; Kamisah et al. [2011]</td>
</tr>
<tr>
<td>Tocotrienol mixture</td>
<td>WIRS</td>
<td>+</td>
<td>Nur Azlina et al. [2013]</td>
</tr>
<tr>
<td>Tocotrienol (90%δ+10%γ)</td>
<td>WIRS</td>
<td>+</td>
<td>Rodzian et al. [2013]</td>
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</tbody>
</table>

+, positive effect; ±, no effect; ND, not determined.
## Effects of different forms of vitamin E on gastric parameters in various gastric lesion models

<table>
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<tr>
<td></td>
<td></td>
<td><strong>MDA</strong></td>
<td><strong>GSH</strong></td>
</tr>
<tr>
<td>Tocotrienol-rich fraction</td>
<td>Aspirin</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>α-Tocopherol + Tocotrienol</td>
<td>Indomethacin</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>Indomethacin</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>Aspirin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>Ethanol</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>C48/80</td>
<td>+</td>
<td>ND</td>
</tr>
</tbody>
</table>

+, positive effect; ±, no effect; ND, not determined.
CONCLUSION

- Tocotrienol provides a gastroprotective effect which are mediated through 1) free radical scavenging activity, 2) the increase in gastric mucosal antioxidant enzyme activity, 3) normalisation of gastric mucosal NO through reduction of iNOS expression, and 4) attenuation of inflammatory cytokines.

- It has the potential as a prophylactic agent against gastric ulcers disease.
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Enteral Supplementation of Palm Vitamin E and Alpha-Tocopherol: Preclinical Aspects

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Abstract

The occurrence of acute gastrointestinal bleeding had been described in 6% to 10% in critically ill patients. The morbidity and mortality of patients with critical illnesses are positively correlated with the degree of oxidative stress. Therefore, the administration of antioxidants such as vitamin E seems to be a reasonable therapeutic approach. However, there is conflicting evidence about antioxidant supplementation. This chapter will reveal the scientific evidence of enteral supplementation of vitamin E in the forms of tocopherol, tocotrienol-rich fraction, and α-tocopherol in animal models of stress. These models mimic the stress endured by critically ill patients in a clinical setting. The positive outcomes of enteral feeding with vitamin E in reducing the occurrence of stress-induced ulcers are discussed in this chapter. Evidences showing vitamin E's effects are not just related to its ability to reduce gastric aggressive factors and to maintain gastric protective factors but also on its effects on stress hormones and cateholamines.