

PICO Worksheet and Search Strategy Protocol

1. Defining PICO question by identifying: Patient/Problem (P), Intervention (I), Comparison (C), and Outcome (O):
 - ☒ Patient/Problem: **Human colorectal cancer cells**
 - ☒ Intervention: **Tocotrienols (α , β , γ , & δ)**
 - ☒ Comparison: **Untreated colorectal cancer cells (*if any*)**
 - ☒ Outcome: **Modulated genes and proteins**
2. Type of PICO question:
 - ☒ **Therapy**
 - ☒ **Prevention**
 - ☐ Diagnosis
 - ☐ Etiology
 - ☐ Prognosis
3. The main topics and alternate terms that can be used for the search:
 - ☒ **Tocotrienols**
 - ☒ **Genes**
 - ☒ **Proteins**
 - ☒ **Colorectal cancer**
 - ☒ **Colon cancer**
- ∴ PICO question: What genes and proteins that tocotrienols modulate in colorectal cancer cells to induce anti-cancer effects?
4. Type of studies to include in the search:
 - ☒ **Research studies or articles**
 - ☐ Meta-analysis
 - ☐ Systematic review
 - ☐ Clinical practice guidelines
 - ☐ Randomized controlled trial
 - ☐ Case report or series
 - ☐ Research report or other grey literature
5. Additional limits that may apply to the search:
 - ☒ **Year(s) of publication: 2010-2021 (Present)**
 - ☒ **Language(s): English**
 - ☐ Gender: N/A
 - ☐ Age: N/A

6. The databases for the search:

- ☑ **Ovid MEDLINE**
- ☑ **PubMed**
- ☑ **Scopus**
- ☑ **Embase**

7. PICO search strategy:

- Tocotrienol* [Truncated – Stemming]
- **AND** Gene* [Truncated – Stemming] **OR** Protein* [Truncated – Stemming]
- **AND** Colorectal **OR** Colon
- **AND** Cancer

∴ **Table S1.** Inclusion and exclusion criteria for screening and full-text review.

Category	Included	Excluded
Problem type	Human colon cancer cells	Animal colon cancer cells
Intervention type	Tocotrienols (α , β , γ , & δ)	Tocopherols (α , β , γ , & δ)
Outcome type	Modulated genes/proteins	Synergistic effects
Study type	Research studies only	All other types of studies and reviews
Study design	<i>In vitro</i> studies only	<i>In vivo</i> studies and others
Publication Language	English only	Any other languages
Publication period	Published between 2010-2021	Published before 2010