Nutrition and GI mucosa problem during chemotherapy

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Mucositis

- Common complication of chemotherapy, radiotherapy and targeted agent

- Affects compliance
- Cause schedule delays
- Stop treatment
- Malnutrition and weight loss → Reliance on parenteral nutrition
- Hospitalization, and morbidity

Mucositis

- Pathogenesis ; multifactorial, damage effect to rapidly dividing normal cells of the GI tract
- Oral mucositis : upper aerodigestive tract
- Gastrointestinal mucositis : dominantly in the small intestine and rectum

Topics

- Clinical presentation and pathogenesis of mucositis
- Therapeutic and prevention strategies
  - Management according guidelines
- New data about treatment agent

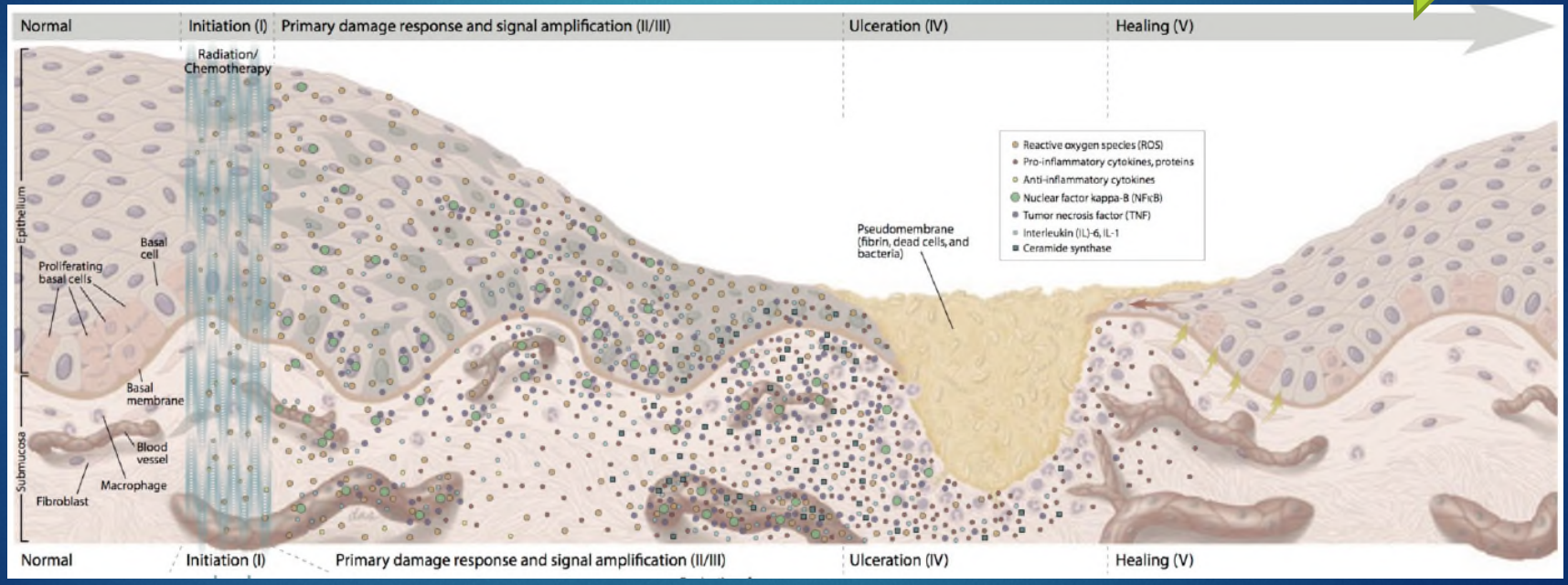
EPIDEMIOLOGY

- 15% of low-risk treatments
- up to 60–100% of patients treated with high-dose CT, radiotherapy and bone marrow transplantation
- About 40% in patients undergoing standard dose, cycled chemotherapy (CTx)
- 89% of FOLFIRI and 50% of patients treated with FOLFOX for colorectal cancer

Kwon, Y. et al OncoTargets Ther. 2016
Keefe, D Cancer Chemother. Pharmacol.2014, 74, 675–680,

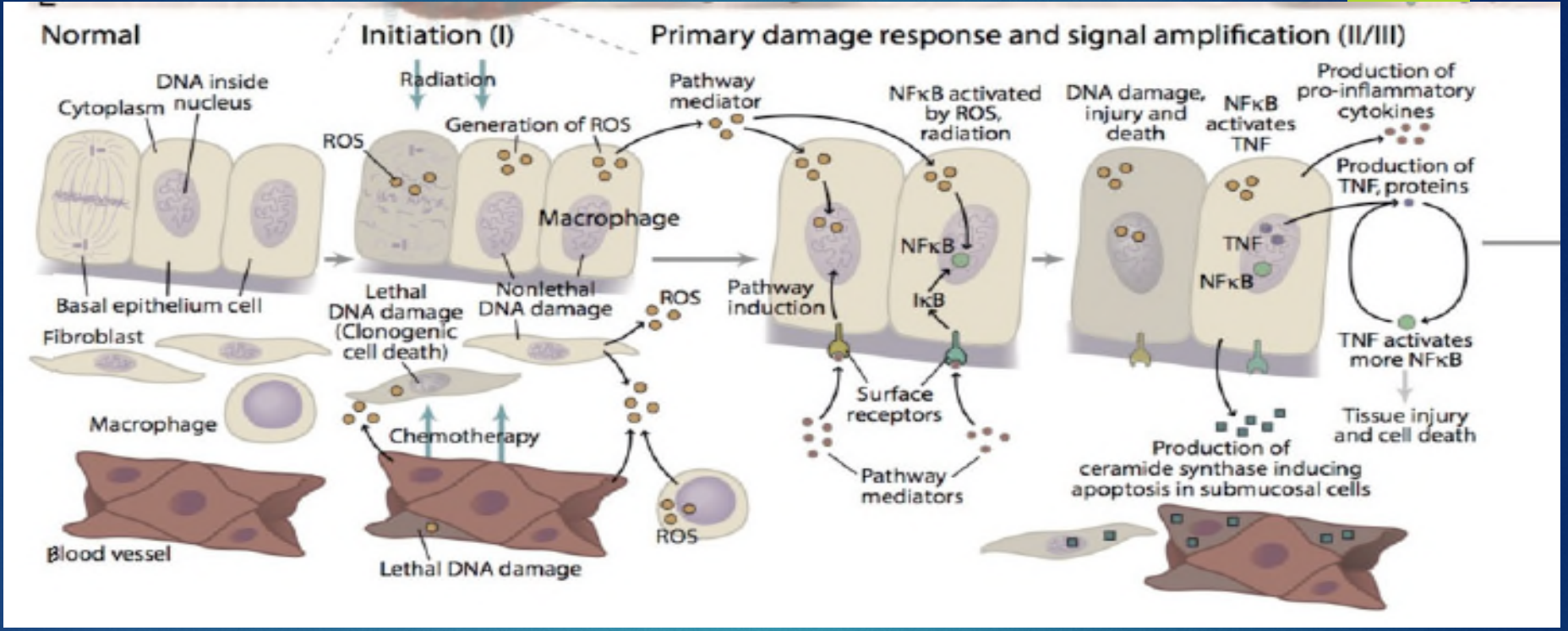
Pathobiology of mucositis : 5 phase

1. Initiation → 2. Primary damage response and 3.Signal amplification → 4. Ulceration → 5. Healing



Sonis, J. Support Oncol. 2007. 9 (Suppl 4), 3–11

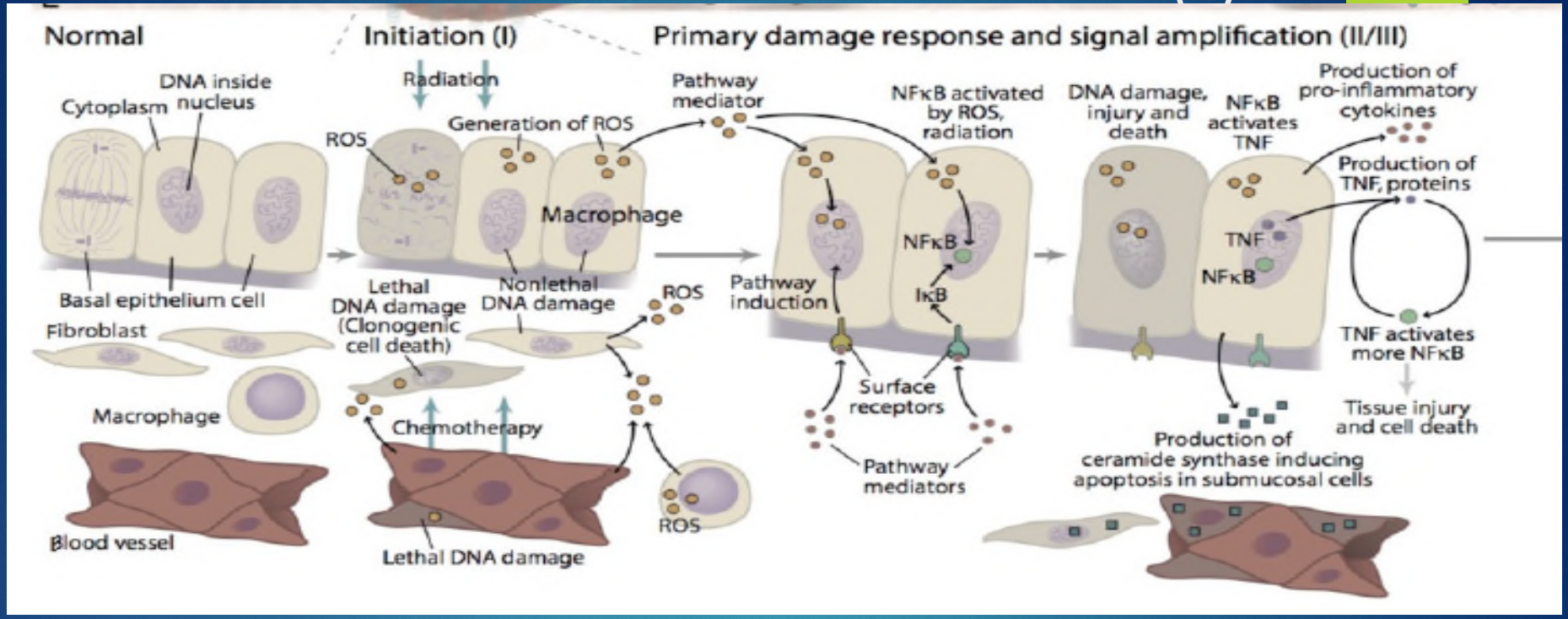
PATHOBIOLOGY OF MUCOSITIS



- Signaling from damaged endothelium, fibroblasts and infiltrating leukocyte cells contributes to apoptosis, loss of renewal, atrophy and ulceration
- Mucositis is triggered by oxidative stress and the generation of reactive oxygen species (ROS), direct DNA and non-DNA damage, and activation of the innate immune response.

Villa, ACurr. Opin. Oncol. 2015. 27, 159–164.

PATHOBIOLOGY OF MUCOSITIS (II)

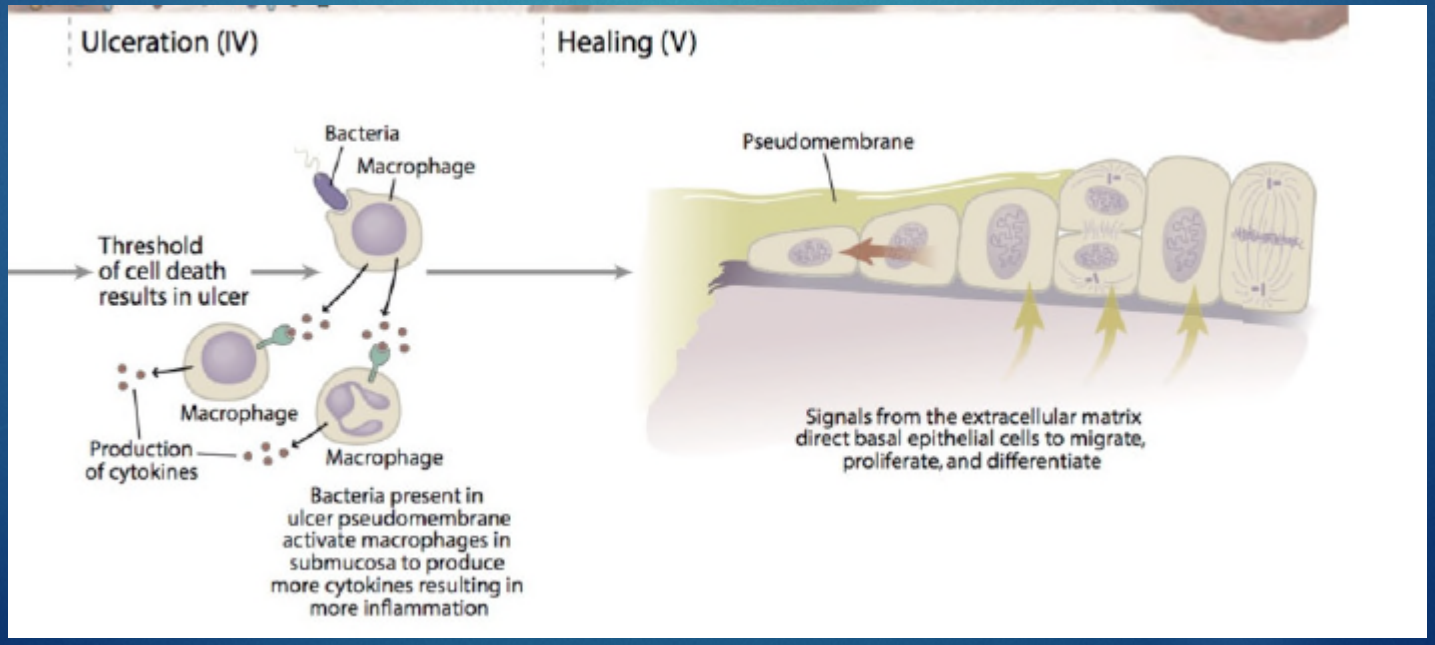


- Stimulate macrophages and activate several transcription factors of nuclear factor NF-*k*B
- → pro-inflammatory cytokines such as tumor necrosis factor-a (TNF-a), interleukin (IL)-6 and IL-1b and cyclooxygenase-2 (COX-2), expression of adhesion molecules and angiogenesis

Villa, A et al. Curr. Opin. Oncol. 2015. 27, 159–164.

PATHOBIOLOGY OF MUCOSITIS (III)

- apoptosis of epithelial stem cells and loss of renewal → atrophy and then ulceration
- time between initial basal cell injury and clinical notable mucosal changes (erythema and thinning) with ulceration → takes 4 days
- cellular damage in the intestinal villi → within 24–48 h of chemotherapy.



The Role of Microbiota

- Bacterial cell wall products ; easily penetrate disrupted mucosa → stimulate macrophages to produce pro-inflammatory cytokines

Stringer, A et al. J. Oral Pathol. Med. 2015. 44, 81–87.

- CTx ; decrease in Lactobacillus and other protective bacterial species and an increase in specific pathogenic species

Stringer, A. et al. 2013 Support. Care Cancer 21, 1843–1852.

- Probiotic : may activate cytoprotective pathways in epithelial cells, counteract ROS, displace pathogenic bacteria and interact with tight junctions to enhance mucosal integrity

Ciorba, M.et al. 2012.Clin. Gastroenterol.Hepatol. 10, 960–968

Chemotherapy-Induced Mucositis

- Characterized by decreased crypt length, blunting and fusion of villi, enterocytes hyperplasia and increased apoptosis
- small intestine is most often affected
- pro-inflammatory cytokines : TNF, IL-1b, and IL-6 levels elevated prior to tissue changes

Logan, R.et al.2008. Cancer Biol. Ther. 7, 1139–1145

- proteins associated with apoptosis (i.e.bcl-2)

Ribeiro, R. et al. Cancer Chemother. Pharmacol. 2016.78, 881–893

BACKGROUND

Chemotherapy Induced Mucositis

- Characteristics of chemotherapy induced mucositis
  - Nausea, vomiting, diarrhea, dehydration
  - Comorbidity with serious bacterial infection
  - Damage to the small intestinal epithelium
  - Apoptosis of enterocyte and regenerative stem cells
  - Decreased mucosal protein content
  - Blunted intestinal villi with crypt destruction

Br. J. Cancer 1998;77:1689–1695.
Eur. J. Cancer 2001;37:1994–2002

BACKGROUND

Chemotherapy Induced Mucositis

- Pathogenesis of chemotherapy induced mucositis
  - Production of reactive oxygen species
  - Increase of pro-inflammatory cytokines
    - Tumor necrotic factor- a (TNF- a)
    - Interleukin-1β (IL-1β)
    - Interleukin-6 (IL-6)
  - Damage to the mucosal components

Br. J. Cancer 1998;77:1689–1695.
Eur. J. Cancer 2001;37:1994–2002

- However, there are no definitely effective therapeutic agent for mucositis.

5-Fluorouracil (5-FU)

- thymidylate synthetase inhibitor, 5-FU
- interrupts DNA synthesis, leading to cell death by apoptosis
- 5-FU may reduce crypt and villus length through the apoptosis of enterocytes
- TNF-α and IL-1β is markedly increased in 5-FU-injected mice.
- NADPH oxidase (NOX)-dependent reactive oxygen species (ROS) generation in phagocytes.

Irinotecan

- Topoisomerase I inhibitor
- Tight junction disruption and matrix metalloproteinase-mediated connective tissue damage

Wardill, H. et al. 2014. Cancer Biol. Ther. 15, 236–244

- Mucositis is associated with the activation of caspases, p53 and downregulation of the PI3K/Akt pathway, activation of the MAPK and PKC pathways

Mayo, B. et al. 2017. Cancer Chemother. Pharmacol. 79, 233–249.

Irinotecan

- Reduction in goblet cells number and mucin hypersecretion → development of diarrhea
- Early-onset diarrhea ; activation of parasympathetic system leading to cholinergic syndrome
- Late-onset diarrhea ; cytokines and direct toxic inflammatory-mediated effects

Ribeiro, R.Cancer Chemother. Pharmacol. 2016. 78, 881–893.

RISK FACTORS FOR MUCOSITIS

- associated with the treatment regimen and/or the patient
- Antimetabolites CTx agent
  - 5-FU, methotrexate, irinotecan, alkylating agents like cyclophosphamide/cisplatin, anthracyclines and taxanes
- bolus infusion tends to be more toxic
- S-1 induced lower risk of mucositis compared to 5-FU.
- XELIRI (50%) higher rates of severe diarrhea than FOLFIRI

Villa, A et al. Curr. Opin. Oncol. 2015. 27, 159–164
Skof, E.,et al. 2009. BMC Cancer 9:120

Targeted Agents and mucositis

- FOLFIRI plus cetuximab showed higher frequency of grades 3 and 4 (CRYSTAL trial)
- FOLFOX and panitumumab or FOLFOX alone, showed similar results (PRIME trial)

Van Cutsem et al. 2009. N. Engl. J. Med. 360, 1408–1417
Douillard, J. Y., et al. 2014. J. Eur. Soc. Med. Oncol. 25, 1346–1355

- mTOR-inhibitors (i.e. everolimus) → highest risk of stomatotoxicity

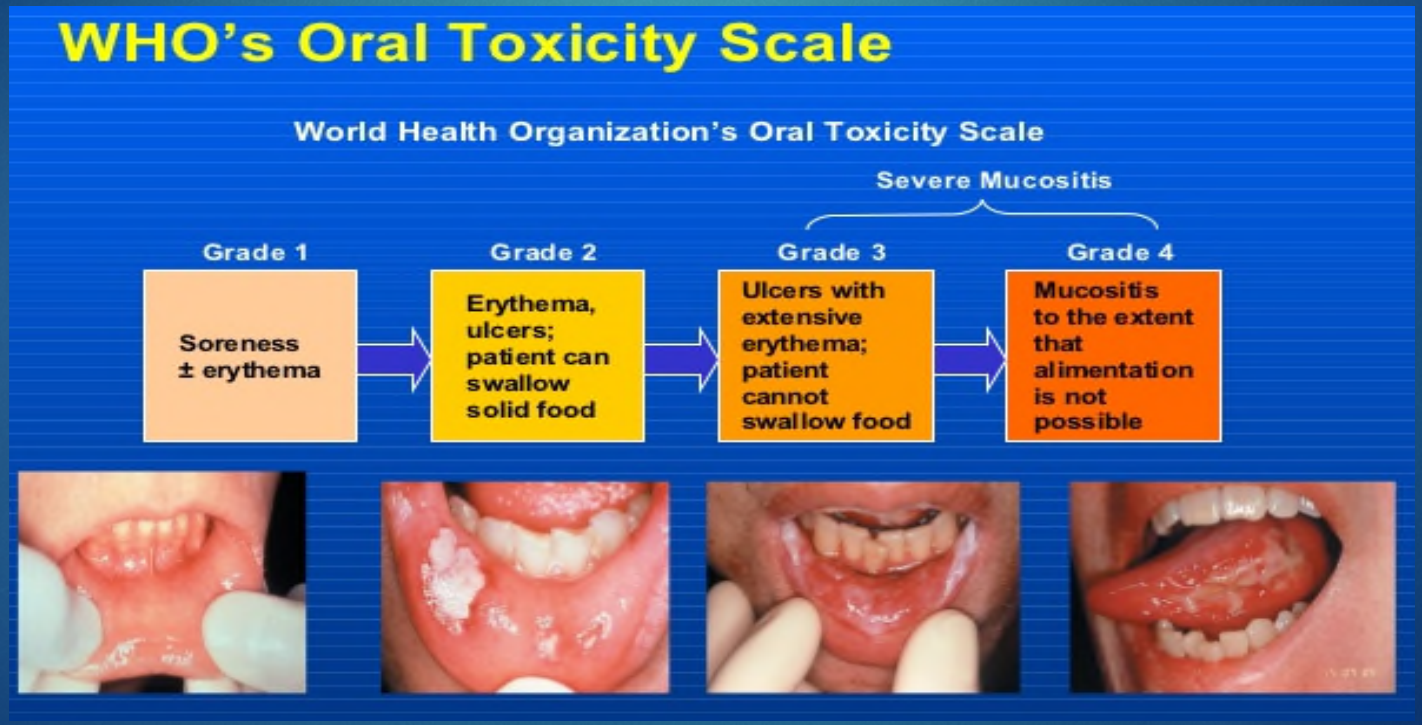
Shameem, R et al. 2015. Cancer Invest. 33, 70–77.

- 81% of patients treated with sunitinib and 90% of those treated with sorafenib (TKI)

Boers-Doets, C. B., et al. 2012. Oncologist 17, 135–144.

ASSESSMENT SCALES

- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, most recent version 4.03)
- The World Health Organization (WHO) scale



Peterson, D. E et al. 2015. Ann. Oncol. 26(Suppl. 5), v139–v151

The National Cancer Institute (NCI) of the National Institutes of Health (NIH)

Mucositis (diarrhea) grade	description
Grade 1	increase of less than four stools per day over baseline and mild increase in ostomy output compared with baseline
Grade 2	Increase of four to six stools per day over baseline and moderate increase in ostomy output compared with baseline
Grade 3	increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, and limitations on self-care activities during daily living
Grade 4	life-threatening consequences with urgent intervention indicated
Grade 5,	death

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Topics

- Clinical presentation and pathogenesis of mucositis
- Therapeutic and prevention strategies
  - Management according guidelines
- New data about treatment agent

MANAGEMENT OF GASTROINTESTINAL MUCOSITIS: CURRENT AND INVESTIGATIONAL APPROACHES

- Basic Oral Hygiene
- Antioxidant Agents
  - Amifostine, Glutamine, Oral Zinc, Vitamin E, N-Acetyl-Cysteine (NAC), Superoxide Dismutase Mimetics
- Inflammation and Cytokines Production-Inhibitors
  - Benzydamine, Pentoxifylline, Salicylates, Interleukin Inhibitors
- Cytoprotective Agents
  - Prostaglandin Analogs, Sucralfate
- Growth Factors
  - Palifermin, GM-CSF, G-CSF
- Antiapoptotic Agents

MANAGEMENT OF GASTROINTESTINAL MUCOSITIS: CURRENT AND INVESTIGATIONAL APPROACHES

- Physical Strategies
  - Oral Cryotherapy
  - Laser Therapy (Photobiomodulation)
- Pain Management
- Probiotics and Antimicrobial Agents
- Dexamethasone Mouthwash
- Glucagon-Like Peptide-2 (GLP-2) analogs
- Natural Remedies
  - Vitamin A, ascorbic acid, manuka honey, aloe vera, chamomile, curcumin

Prevention and treatment strategies for oral mucositis.

Intervention	Aim	Clinical setting	Authors' comment	Guidelines (grade of evidence)
Oral care protocols	Prevention	All cancer patients	General agreement on the value of oral care protocols	MASCC/ESMO (III) NCCN
Oral cryotherapy	Prevention	Bolus 5-FU chemotherapy	Safe, low cost, with some positive results	MASCC/ESMO (II) NCCN
		High-dose melphalan +/− TB-RT for HSCT	As above	MASCC/ESMO (III) NCCN
Palifermin	Prevention	High-dose CT and TB-RT for HSCT	Only approved agent for OM mitigation in a narrow patient population	MASCC/ESMO (II) NCCN ASCO
Low-laser therapy	Prevention	High-dose CT +/− TB-RT for HSCT	Data suggesting possible benefit	MASCC/ESMO (II)
		HN cancer patients receiving RT alone	Data suggests possible benefit, but potential tumor impact unresolved	MASCC/ESMO (III)
Benzydamine mouthwash	Prevention	HN cancer patients receiving moderate dose RT alone	Anti-inflammatory rinse with some data supporting its use in patients receiving radiation only	MASCC/ESMO (I)
0.2% morphine mouthwash	Pain treatment	HN cancer patients receiving CT-RT	Data suggests effective adjunct for topical pain control	MASCC/ESMO (III)
Doxepin mouthwash	Pain treatment	All cancer patients	Data suggests effective adjunct for topical pain control	MASCC/ESMO (IV)

CT, chemotherapy; RT, radiotherapy; TB-RT, total-body radiotherapy, HN, head and neck; HSCT, hematopoietic stem cell transplantation; MASCC, Multinational Association of Supportive Care in Cancer; ESMO, European Society for Medical Oncology.

Lalla, R. V., et al. 2014. Cancer 120, 1453–1461
Peterson, D. E et al. 2015. Ann. Oncol. 26(Suppl. 5), v139–v151

Prevention and treatment strategies for gastrointestinal mucositis.

Intervention	Aim	Clinical setting	Guidelines (grade of evidence)
Intravenous amifostine	Prevention of RT-induced proctitis	Patients receiving RT	MASCC/ESMO (II)
	Prevention of CT-RT-induced esophagitis	NSCLC patients	MASCC/ESMO (II) ASCO with reserve
Octreotide	Treatment of diarrhea	Standard or high-dose CT for HSCT	MASCC/ESMO (II)
Sucralfate enemas	Treatment of chronic RT-induced proctitis	Patients receiving RT with rectal bleeding	MASCC/ESMO (III)
Oral sulfasalazine	Prevention of RT-induced enteropathy	Patients receiving RT to the pelvis	MASCC/ESMO (II)
Lactobacillus probiotics	Prevention of diarrhea	Patients receiving CT +/– RT to the pelvis	MASCC/ESMO (III)
Hyperbaric oxygen	Treatment of RT-induced proctitis	Patients receiving RT for solid tumors	MASCC/ESMO (III)

CT, chemotherapy; RT, radiotherapy; NSCLC, Non-small cell lung cancer; HSCT, hematopoietic stem cell transplantation; ASA, acetylsalicylic acid; MASCC, Multinational Association of Supportive Care in Cancer; ESMO, European Society for Medical Oncology.

Topics

- Clinical presentation and pathogenesis of mucositis
- Therapeutic and prevention strategies
  - Management according guidelines
- Our research data

BACKGROUND

Aloe

- The gels of Aloe species contain immunomodulatory polysaccharides.
- Acetmannan: a mixture of polymer chains of β-(1,4)-linked acetylated galactomannan with different lengths

Arch. Pharm. Res. **2010**,*33*, 451–456
Clin. Cancer Res. **2006**, *12*, 3092–3098.
J. Biol. Sci. **2011**,*14*, 742–746
Int. J. Mol. Sci. **2014**, *15*

Aloe

- antitumor and antiviral activities of acetmannan are immune-mediated
  - primarily by activation of professional antigen presenting cells (APC) such as macrophages and dendritic cells.
  - activated macrophages to produce inflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-a (TNF-a), nitric oxide
  - induced phenotypic and functional maturation of immature dendritic cells

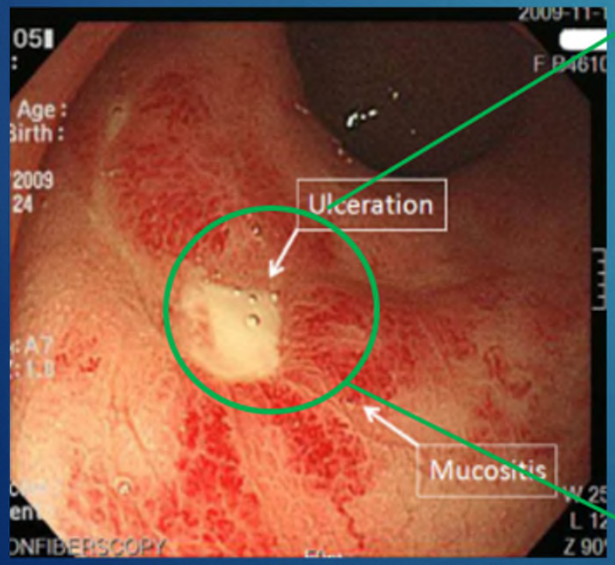
Arch. Pharm. Res. 2010,*33*, 451−456
Clin. Cancer Res. 2006, *12*, 3092–3098.
J. Biol. Sci. 2011,*14*, 742–746
Int. J. Mol. Sci. 2014, *15*

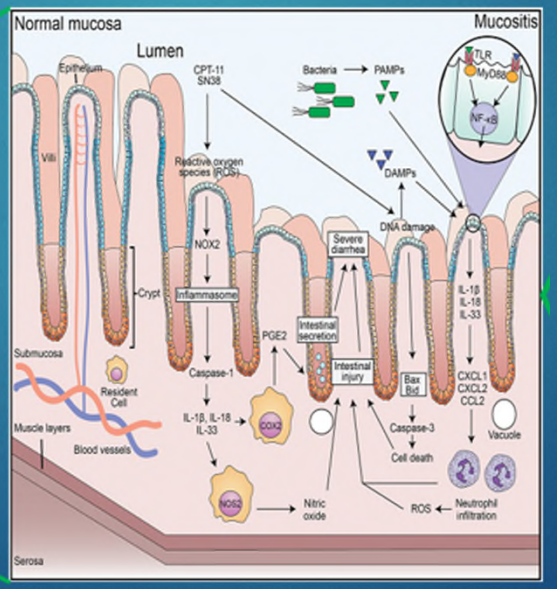
AIM

Study AIM

Investigate the mucosa protective effect of the Aloe for cancer chemotherapy-induced mucositis

- Aloe vera gel, Aloesin (aloe chromone), Aloe full leaves

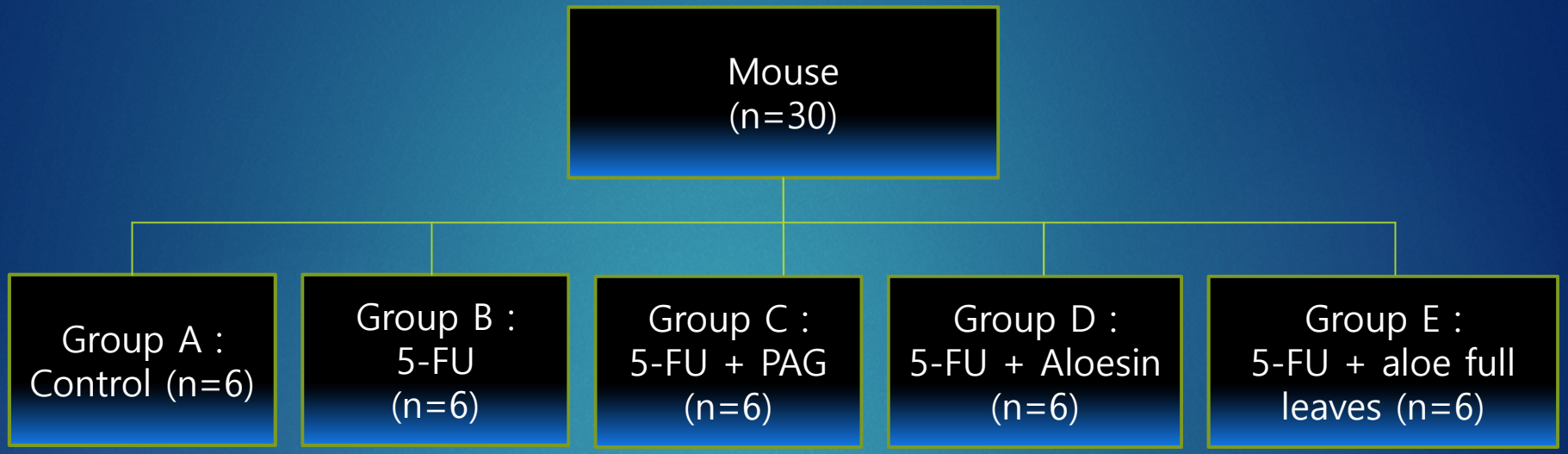




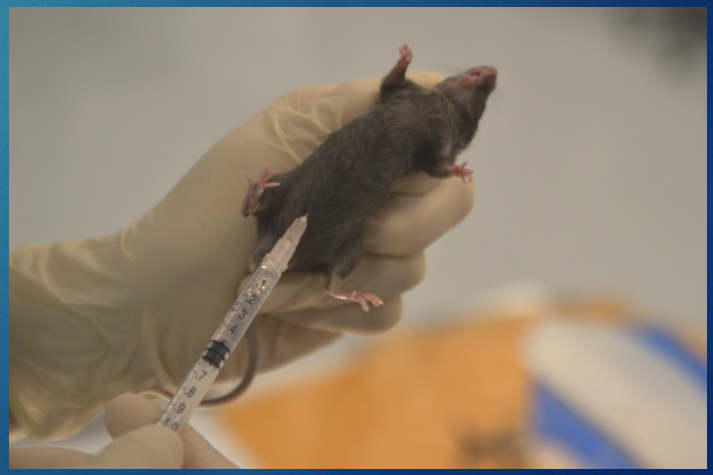
Methods

- Six-week-old BALB/c male mice
- After 1 week of acclimatisation, the mice were randomly classified into 5 experimental groups
- Weight and diarrhea scores were measured daily in all mice starting from the day of 5-. FU administration

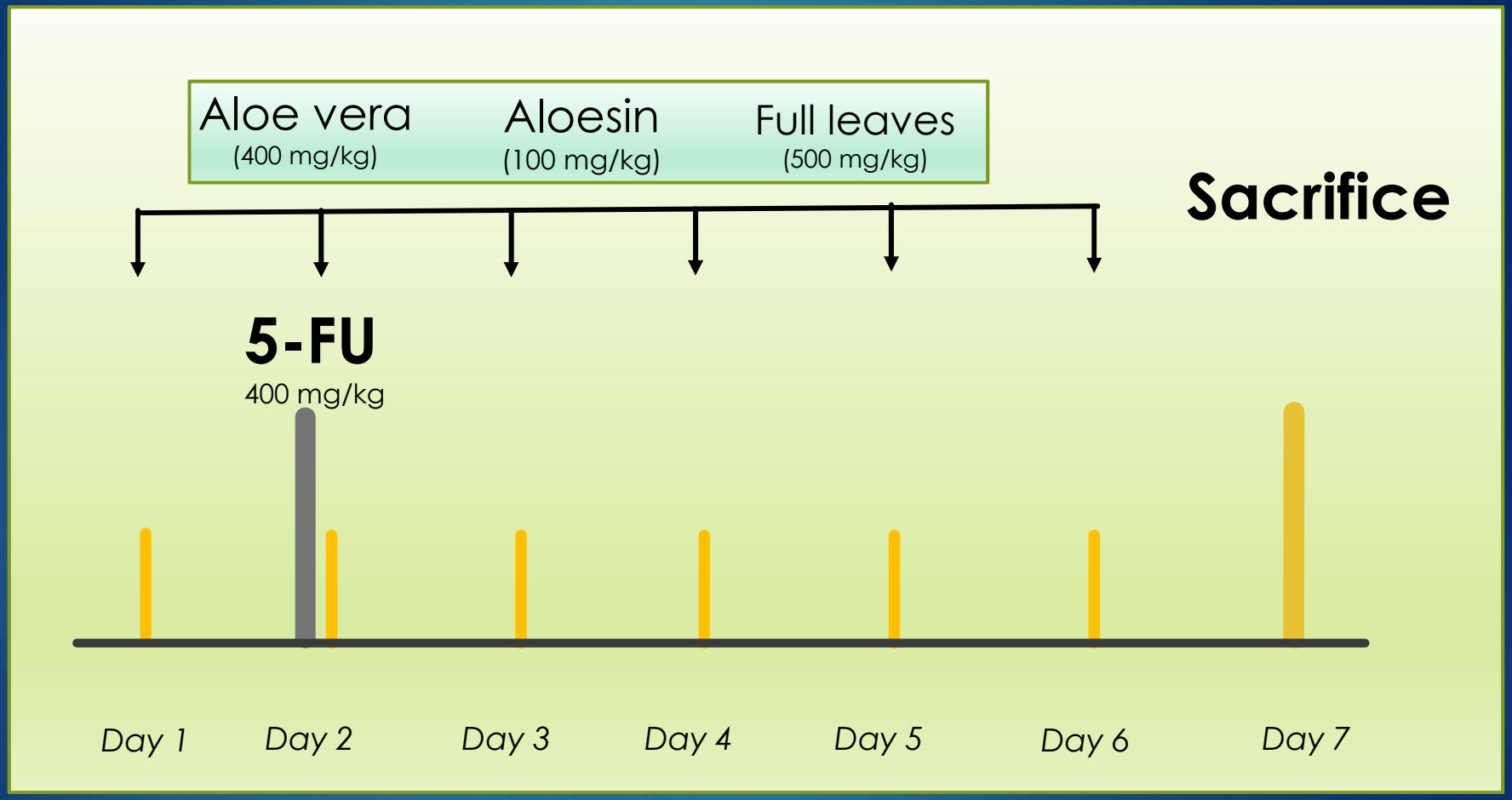
Methods



- Chemotherapy-induced mucositis was induced with 5-FU intraperitoneal injection.
- A single dose of 5-FU was administered on day 2 (400 mg/kg; 5-FU, JW Pharm, Seoul, Korea).

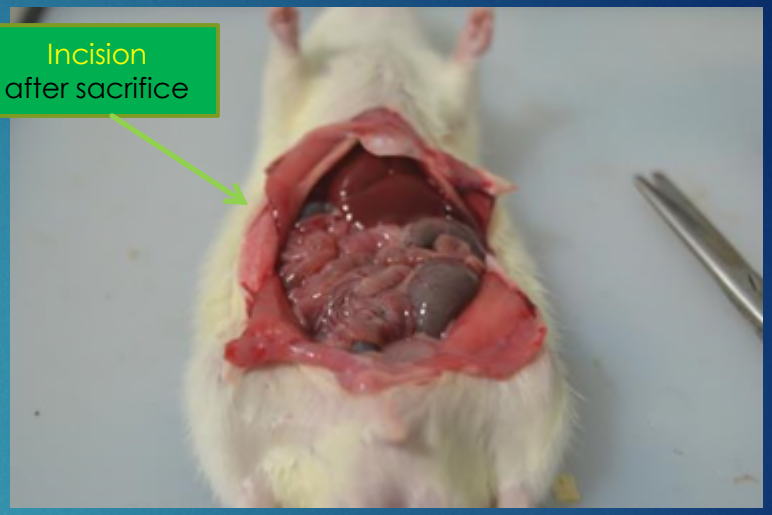


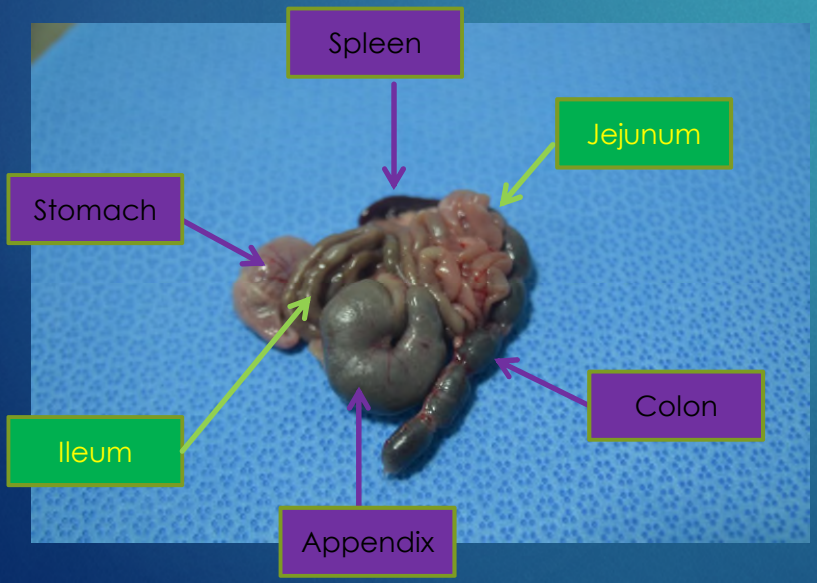
METHOD

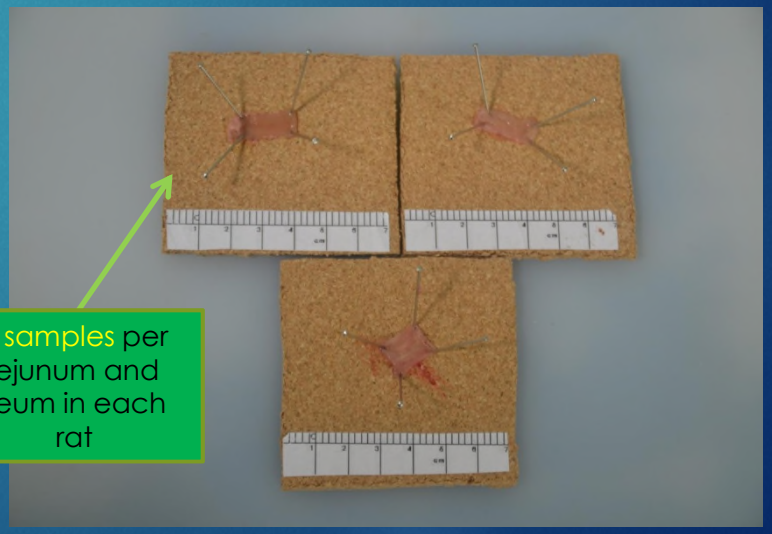

Aloe vera
(400 mg/kg)
Aloesin
(100 mg/kg)
Full leaves
(500 mg/kg)
Sacrifice
5-FU
400 mg/kg
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7

METHOD

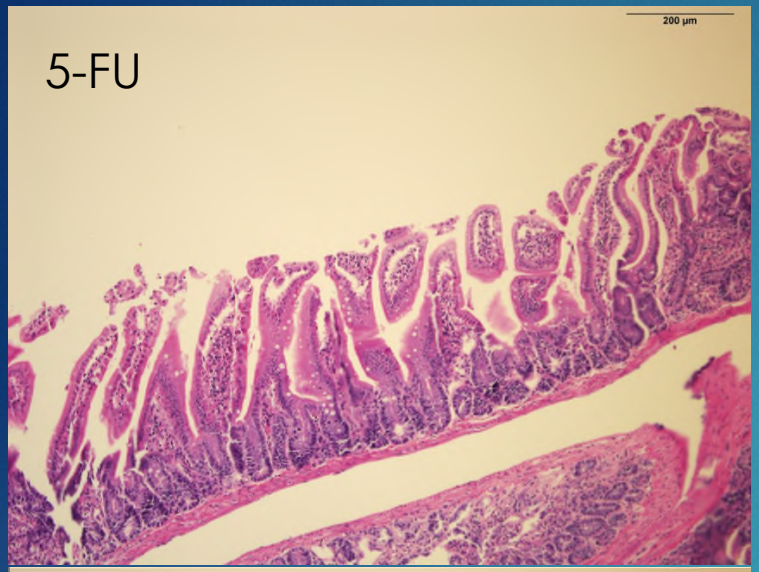

Inspection for the diarrhea

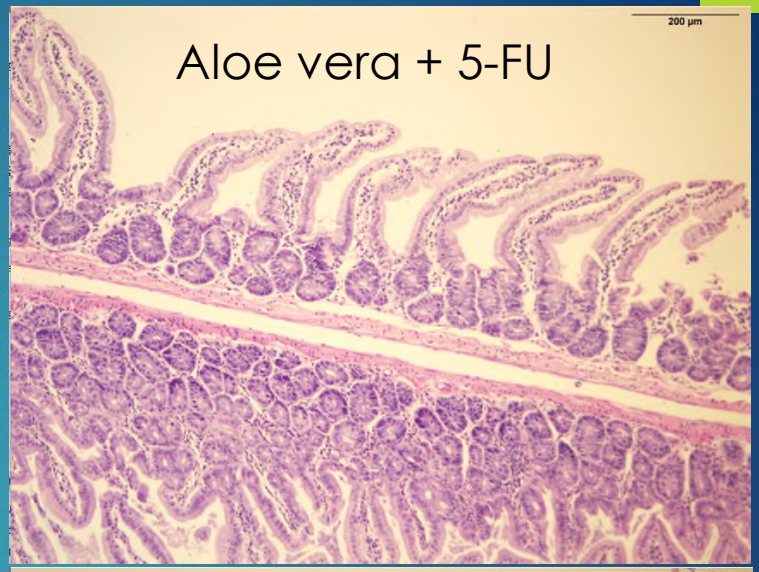

Incision after sacrifice

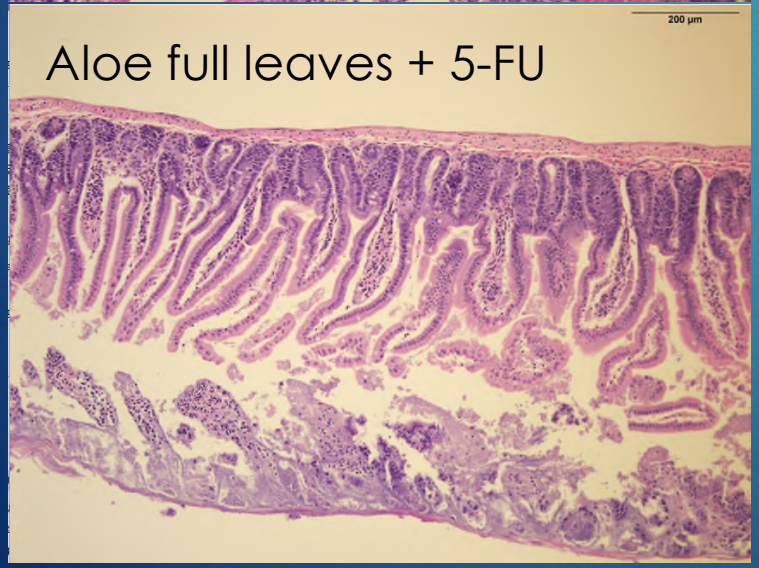

Spleen
Jejunum
Stomach
Colon
Ileum
Appendix

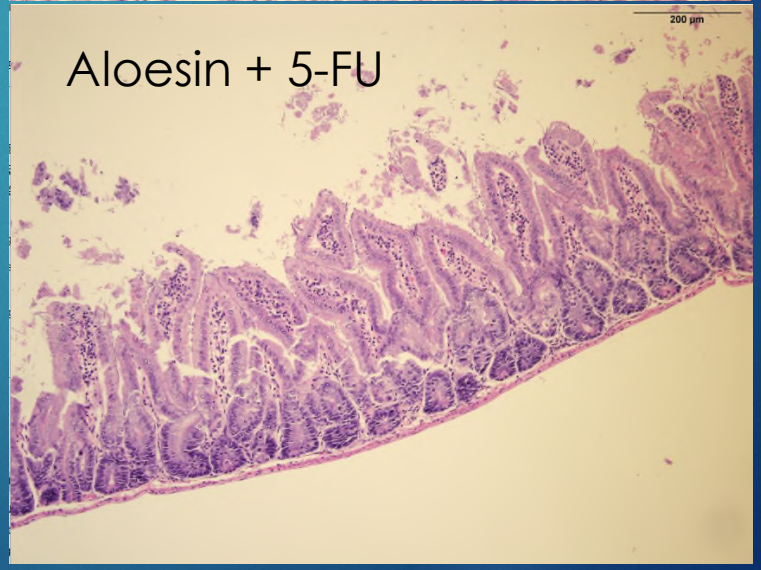

3 samples per jejunum and ileum in each rat

Histologic change



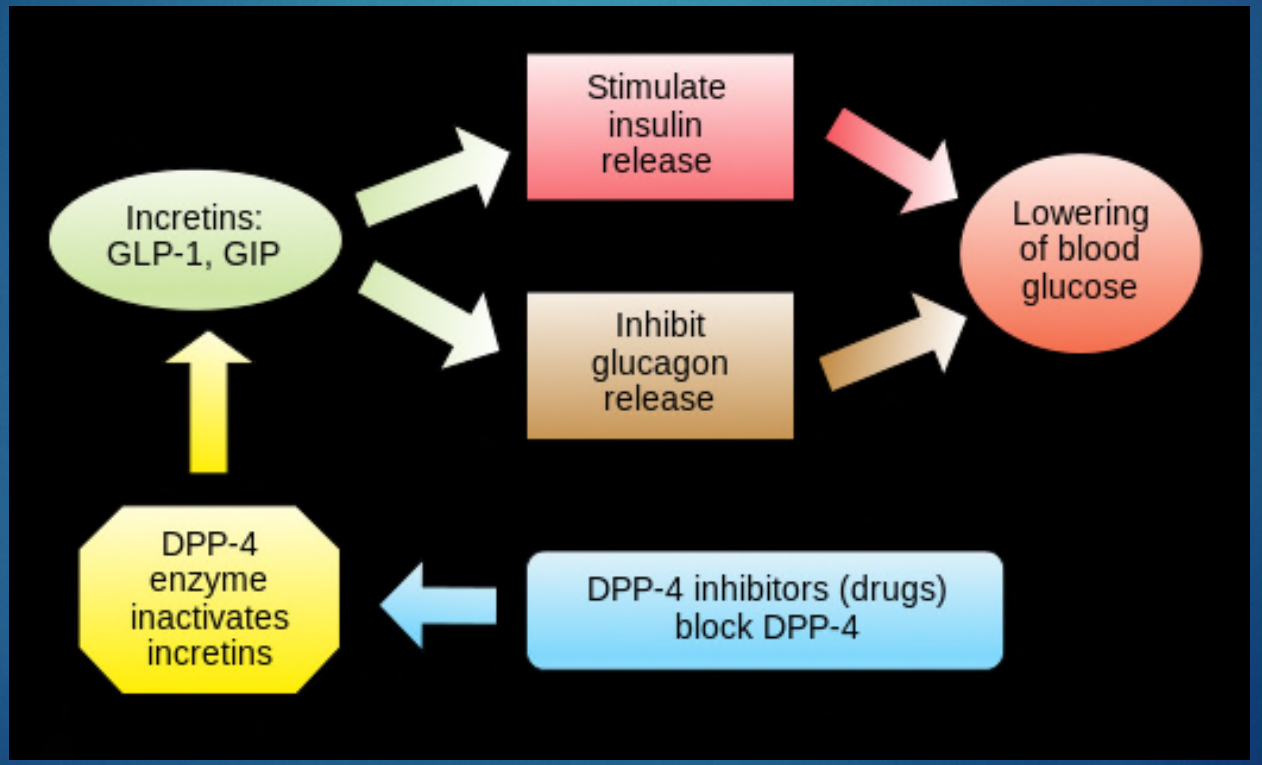






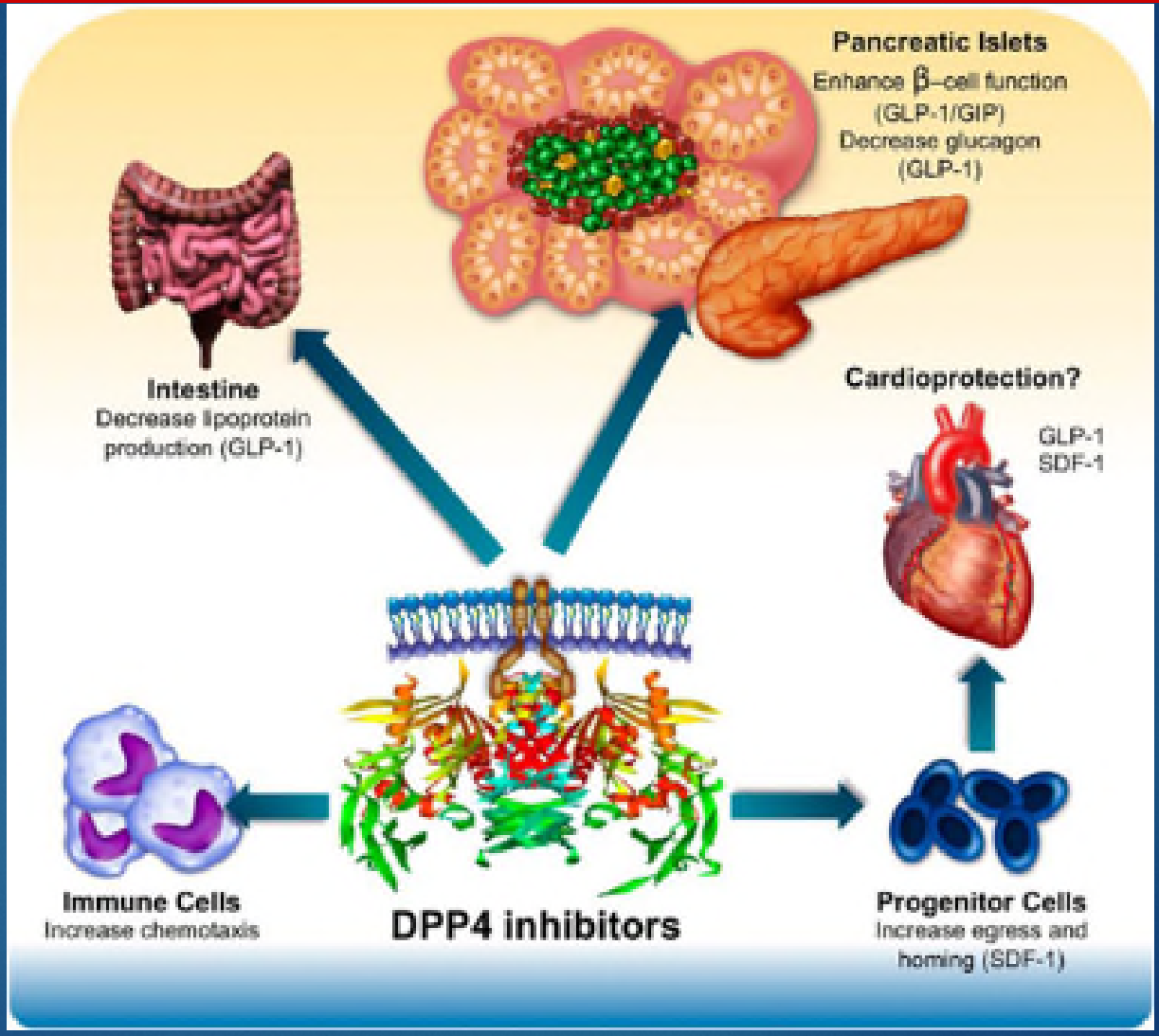
Backgrounds

- Dipeptidyl peptidase-4 (DPP4) inhibitor
  - treatment for type 2 diabetes mellitus



Regulatory Peptides. 128 (2): 159–65.

Backgrounds



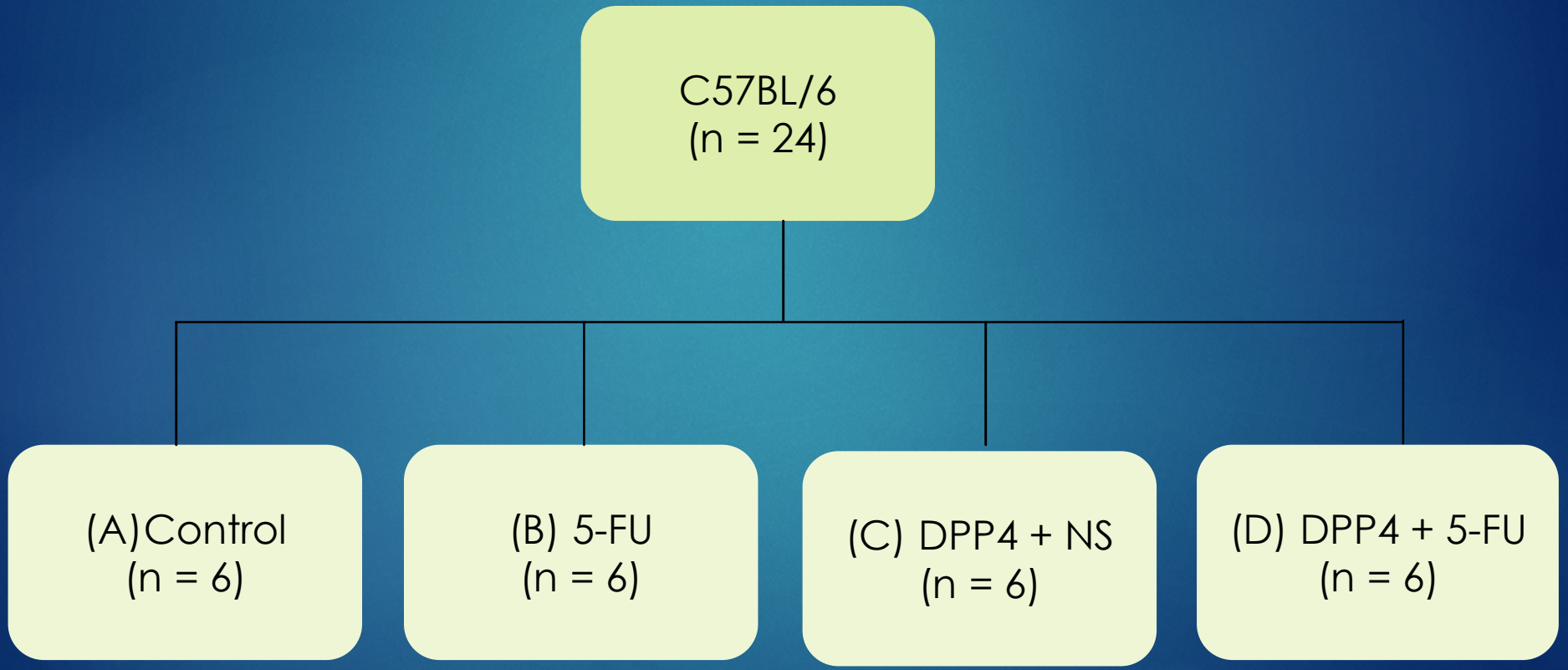
Endocr Rev. 2014 Dec;35(6):992-1019.

Aims

This study aimed to prove the anti-inflammatory effect of dipeptidyl peptidase-4 (DPP4) inhibitor in chemotherapy-induced mucositis mice model.

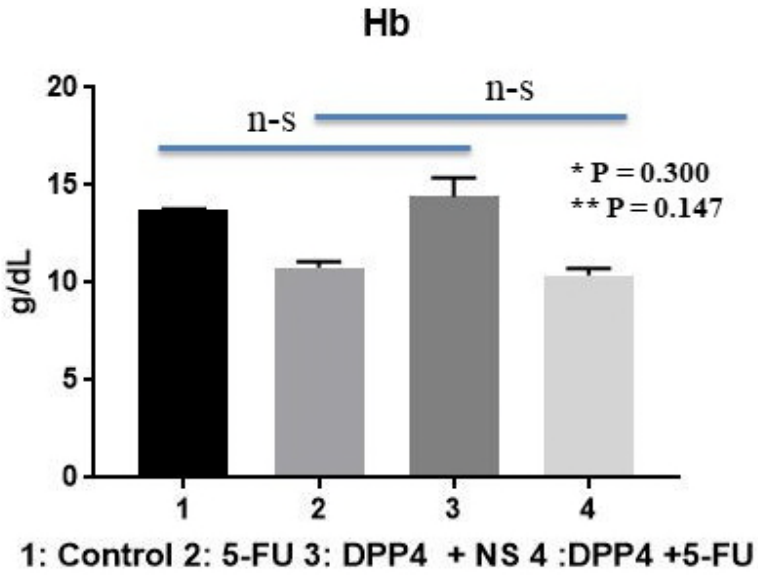
Methods

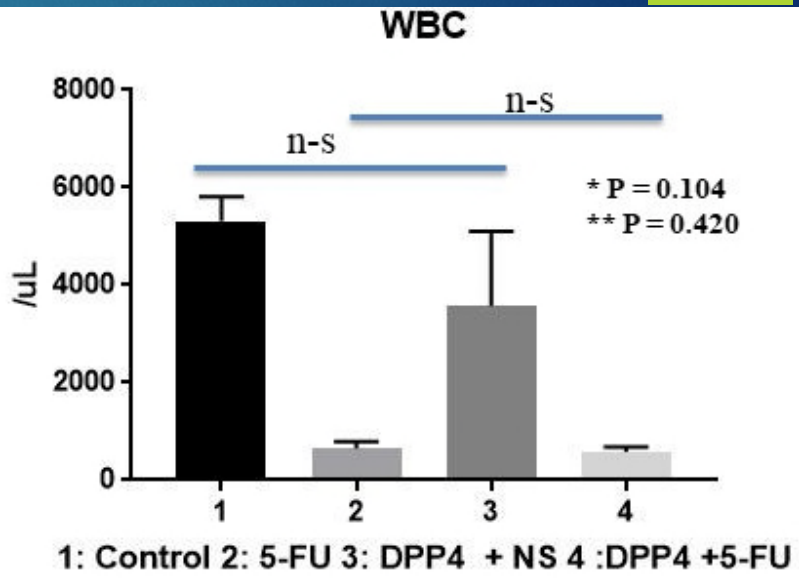
- Animals
  - Twenty-four 8-wk-old male C57BL/6 mice were randomized to 4 groups

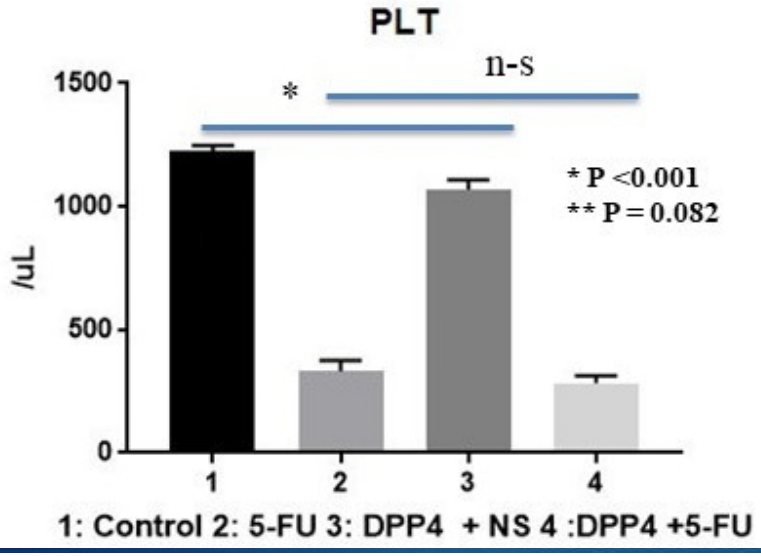


Result

Laboratory finding

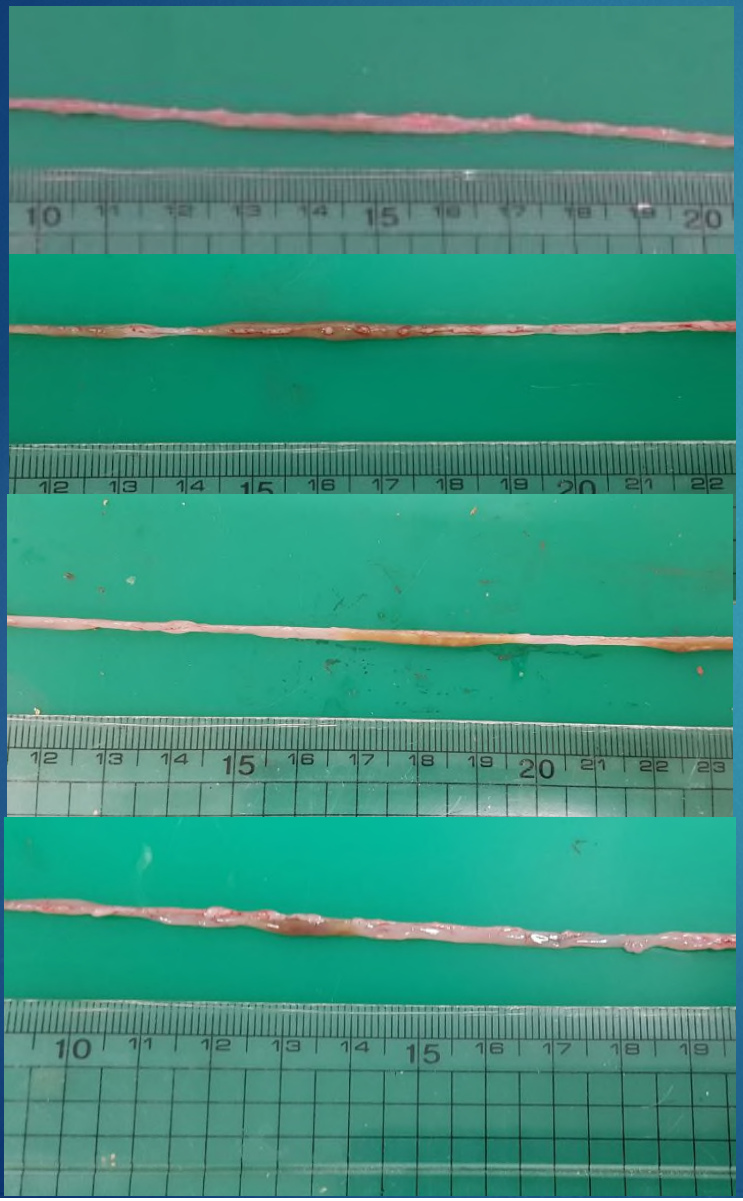






Result

Gross specimen



(A) Control

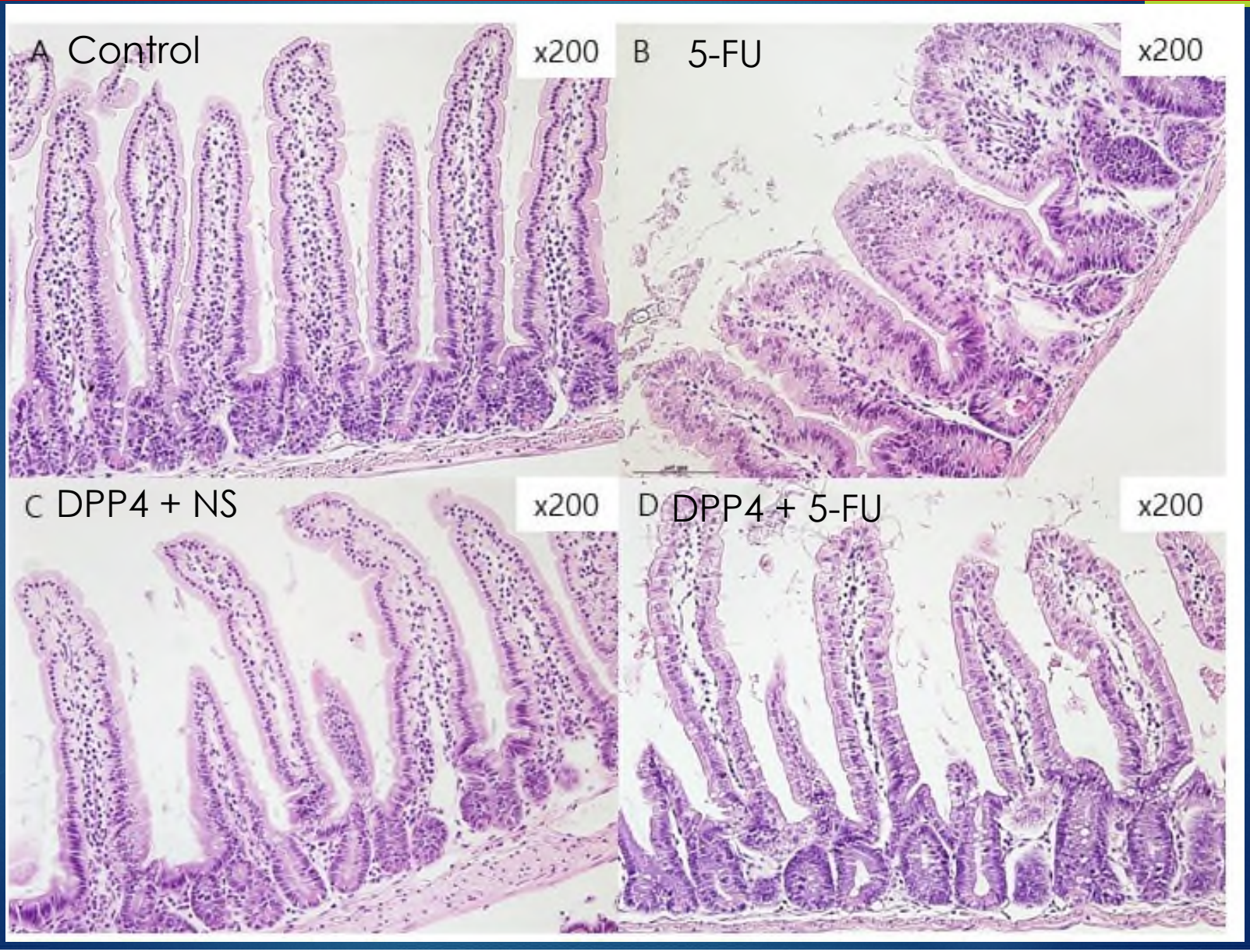
(B) 5-FU

(C) DPP4 + NS

(D) DPP4 + 5-FU

Result

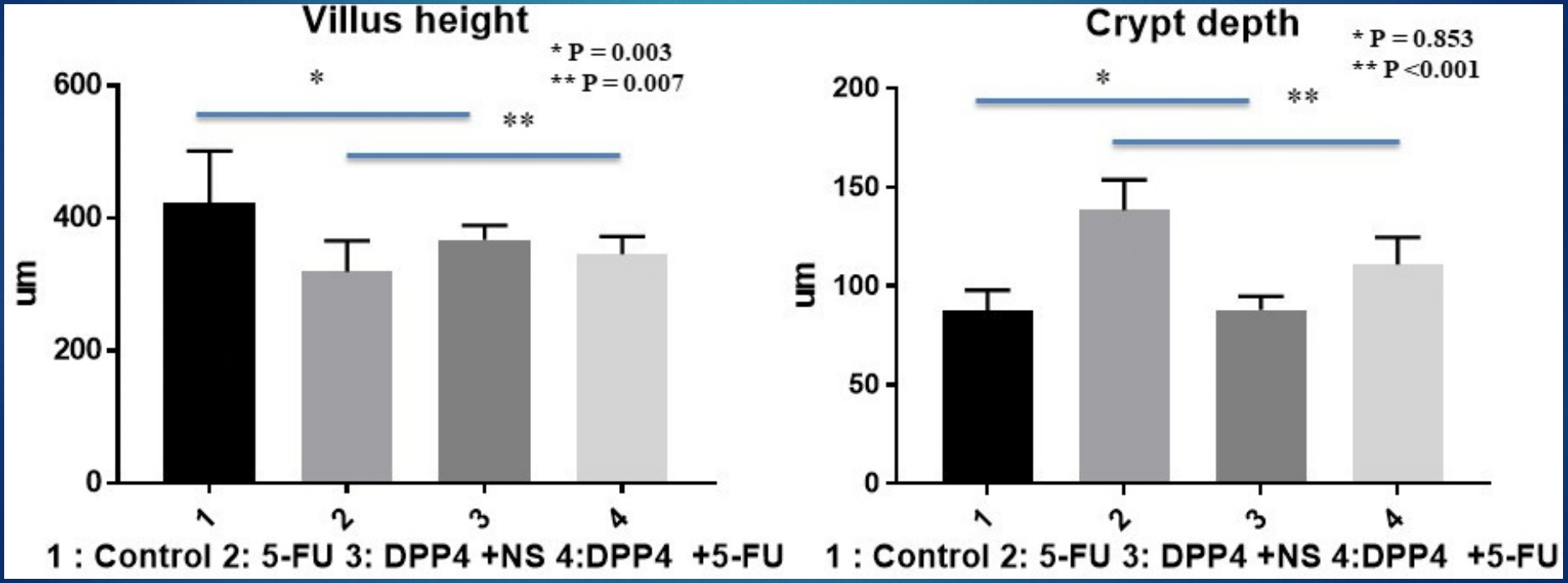
Histologic assessment - jejunum



Result

Cellular change of villus

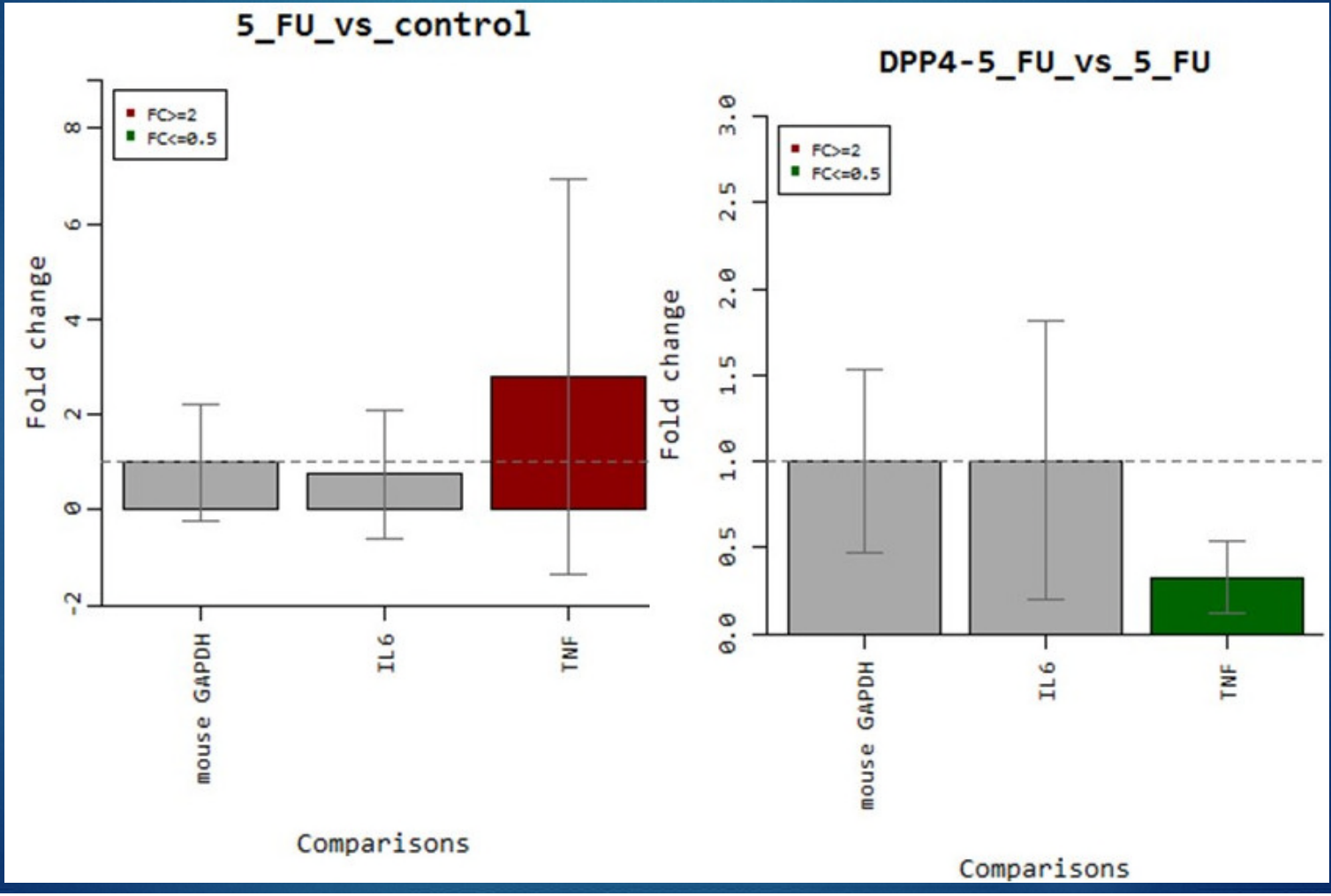
- mean villus height : DPP4 plus 5-FU, 352 μm; 5-FU, 319 μm
- villus/crypt ratio : DPP4 plus 5-FU, 3.28; 5-FU, 2.31
  - compared with 5-FU treated group, were significantly higher.



Result

Real time RT-PCR

- mRNA expression of TNF-α was significantly lower in DPP4 plus 5-FU group compared with 5-FU group (P <0.05)



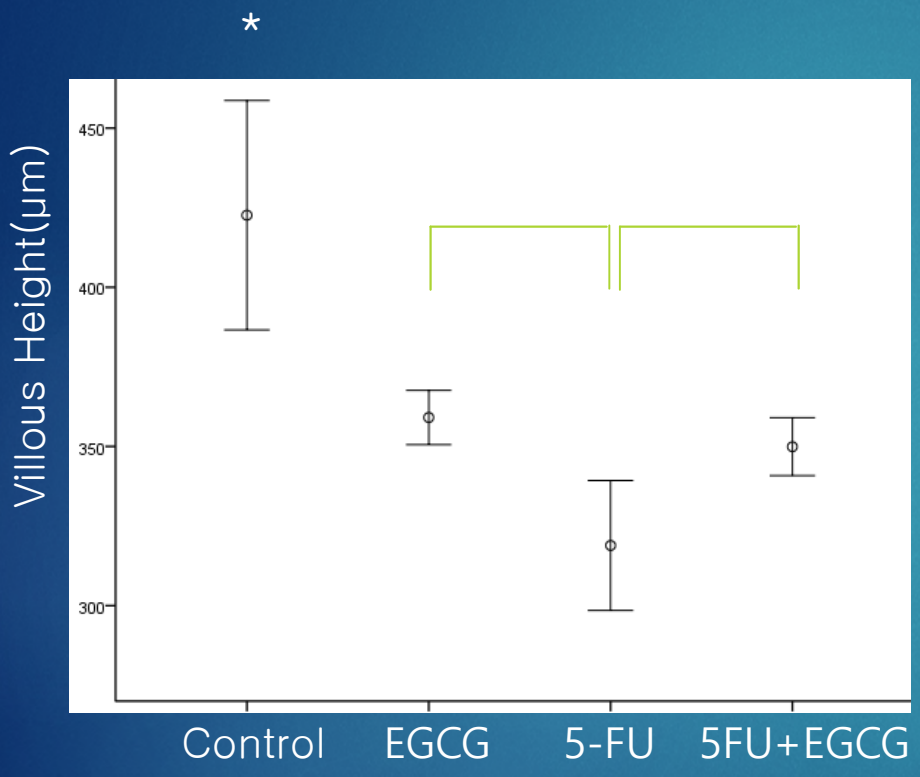
Tea Catechins

- Green tea catechins
  - (-)-epigatechin
  - (-)-epicatechin gallate
  - (-)-epigallocatechin
  - **(-)-epigallocatechin gallate : EGCG,most common**

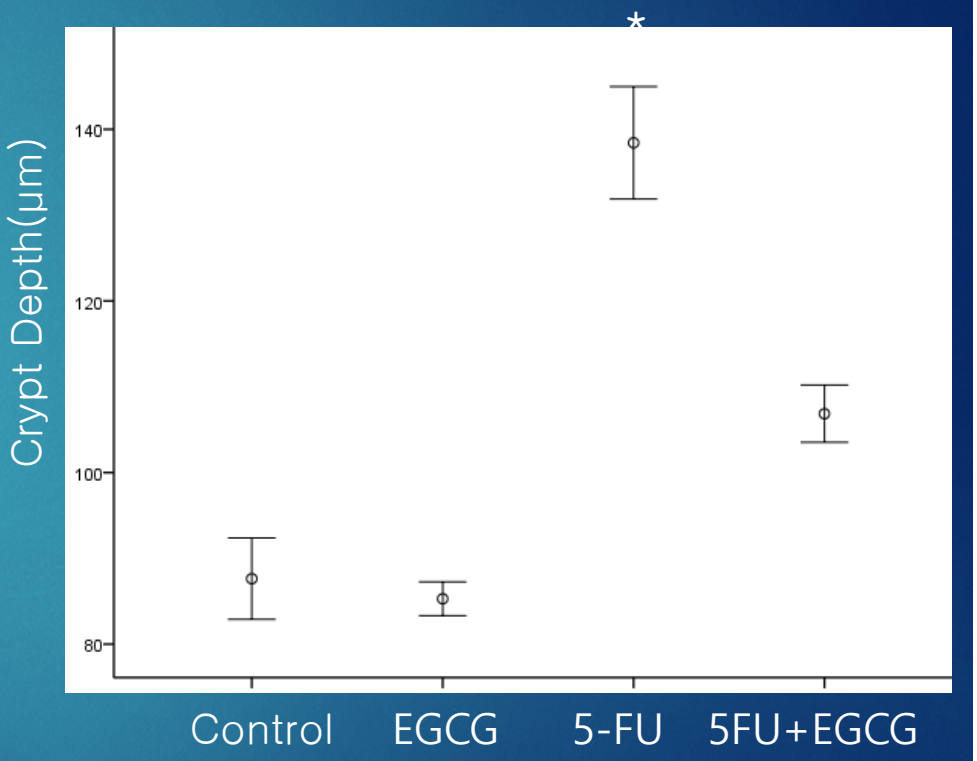
- Oxidized and dimerized in Black/Oolong
  - Theaflavin
  - Theaflavin-3-gallate
  - Theaflavin-3'-gallate
  - Theaflavin-3,3'-digallate

Villous height & Crypt Depth

A

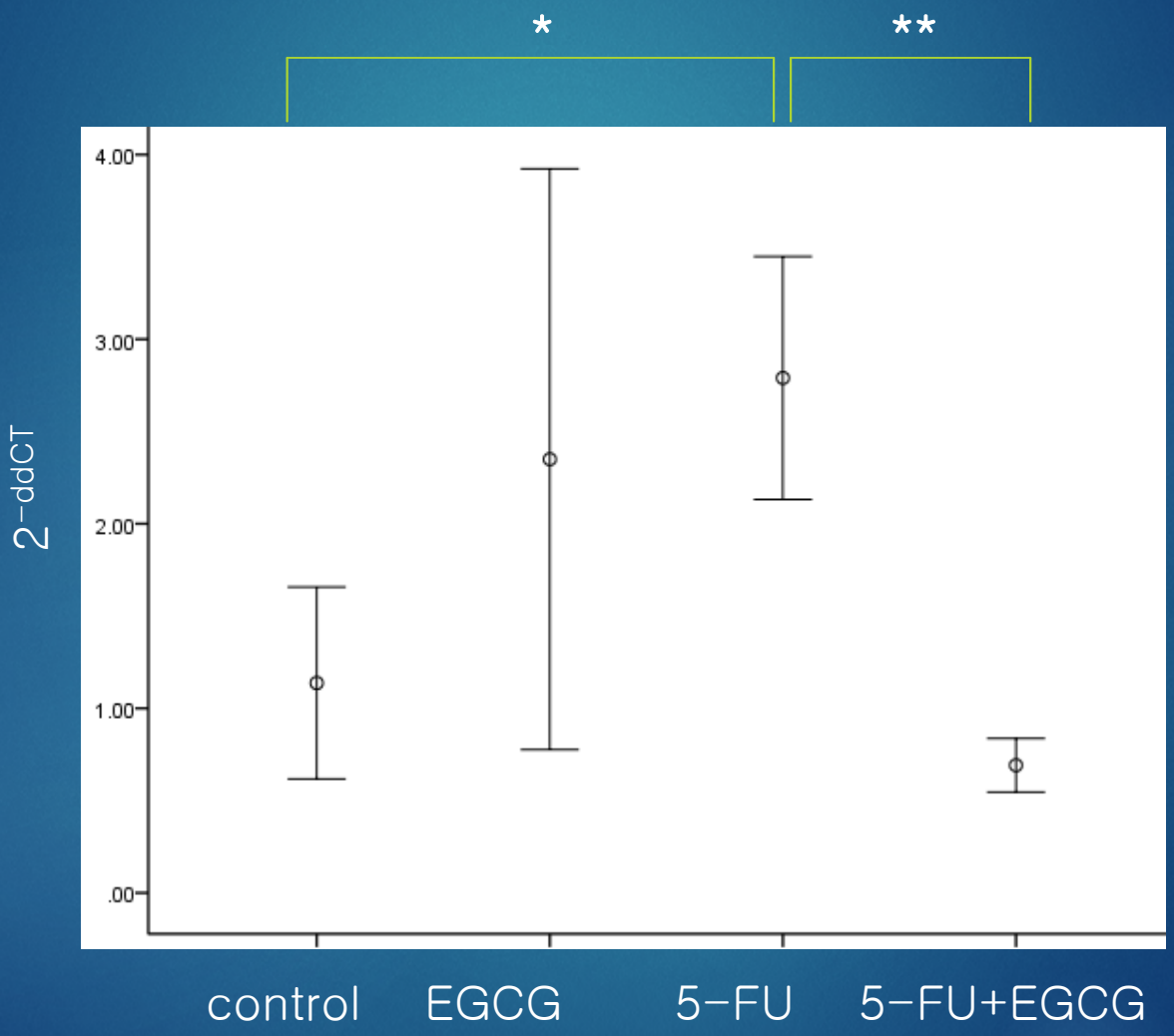


B



*,**, †; P < 0.05
; P = 0.056

TNF-a expression



*,** P<0.05

Summary

- Gastrointestinal mucositis : significant, common unmet clinical need in cancer patients.
- The treatment options for mucositis are disappointingly sparse.
- Although an increasing number of possible treatments have emerged, no standard treatment have been established.
- Unmet need : A future, biologically based strategy may consist in combining interventions acting on the different phases of mucositis' pathogenesis.

Thank You