Dynamic Multistage Gastrointestinal Digestion Model Assessment of Microbial Fermentation Products of Collagen Hydrolysates

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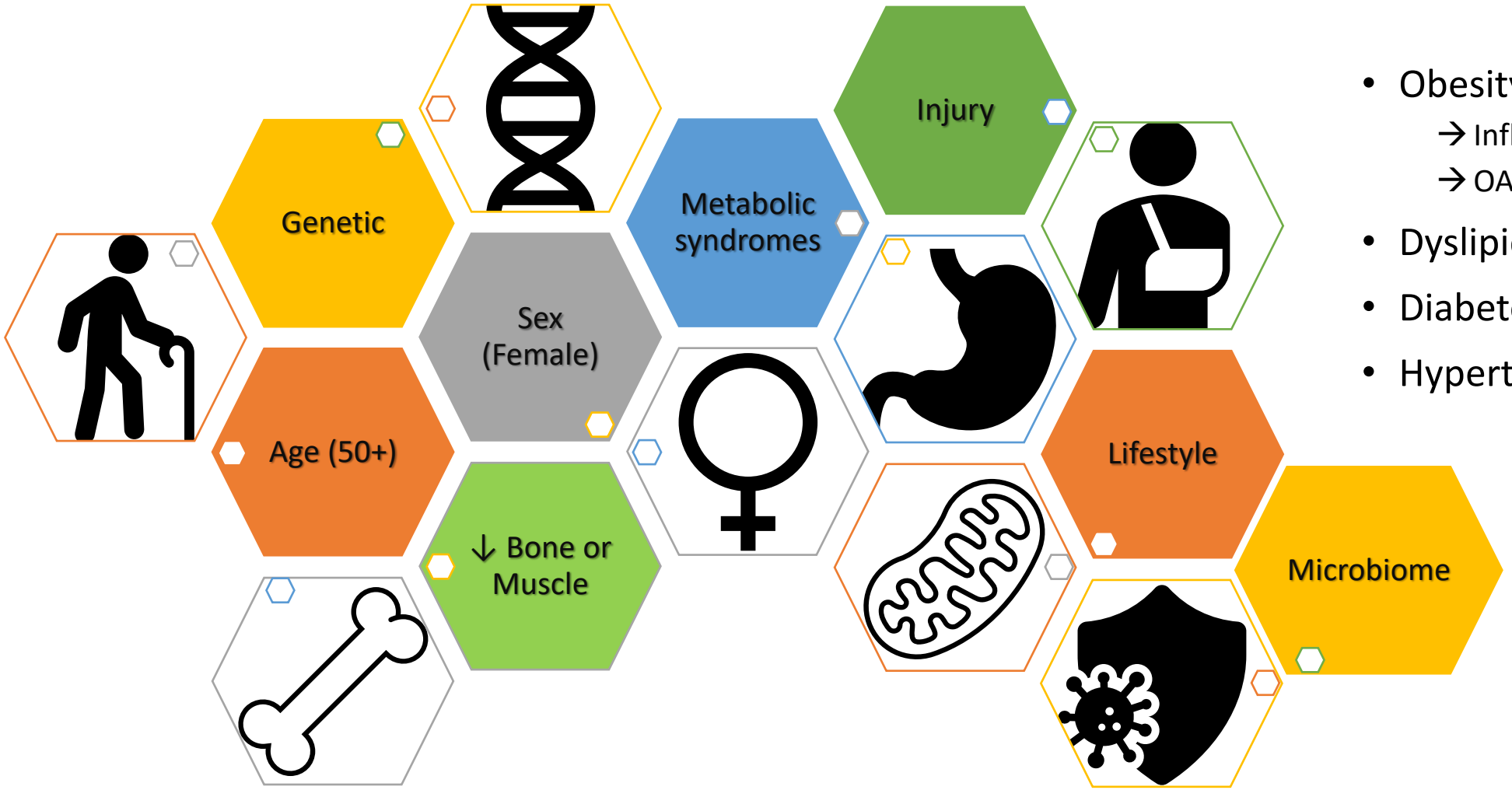
Nutritional and Microbiota Effects on Chronic Disease

Osteoarthritis (OA)

- Joint degeneration: ↓ cartilage content
- In any joint but mainly
  - Hands, knees, hips and spine
- Symptoms
  - Pain, stiffness, ↓ flexibility, swelling, bone spurs
- ↑ OA prevalence
  - 11th most debilitating disease globally
- Affects 50% of people over 75 years old

Lane (2017),
Bello et al., (2006)

Osteoarthritis Risk Factors



- Obesity
  - → Inflammation
  - → OA ↑ joint and body inflammation
- Dyslipidemia
- Diabetes
- Hypertension

Gut Microbiome – OA Connection

- Obesity → OA
  - Inflammatory process driven by obesity-related gut dysbiosis
- Treated using prebiotic fibers
  - Restored microbiome diversity
  - ↓ systemic inflammation
  - ↓ arthritic scores
- Restoring the gut microbiome = novel approach to address OA of obesity

Osteoarthritis Treatment Options

- Non-steroidal anti-inflammatory drugs (NSAIDs) for pain
- Physical therapy
- Synovial injections
- Surgery (last retort)

- **Many have adverse effects**
- **Limited efficacy**

→Common use of supplements/nutraceuticals

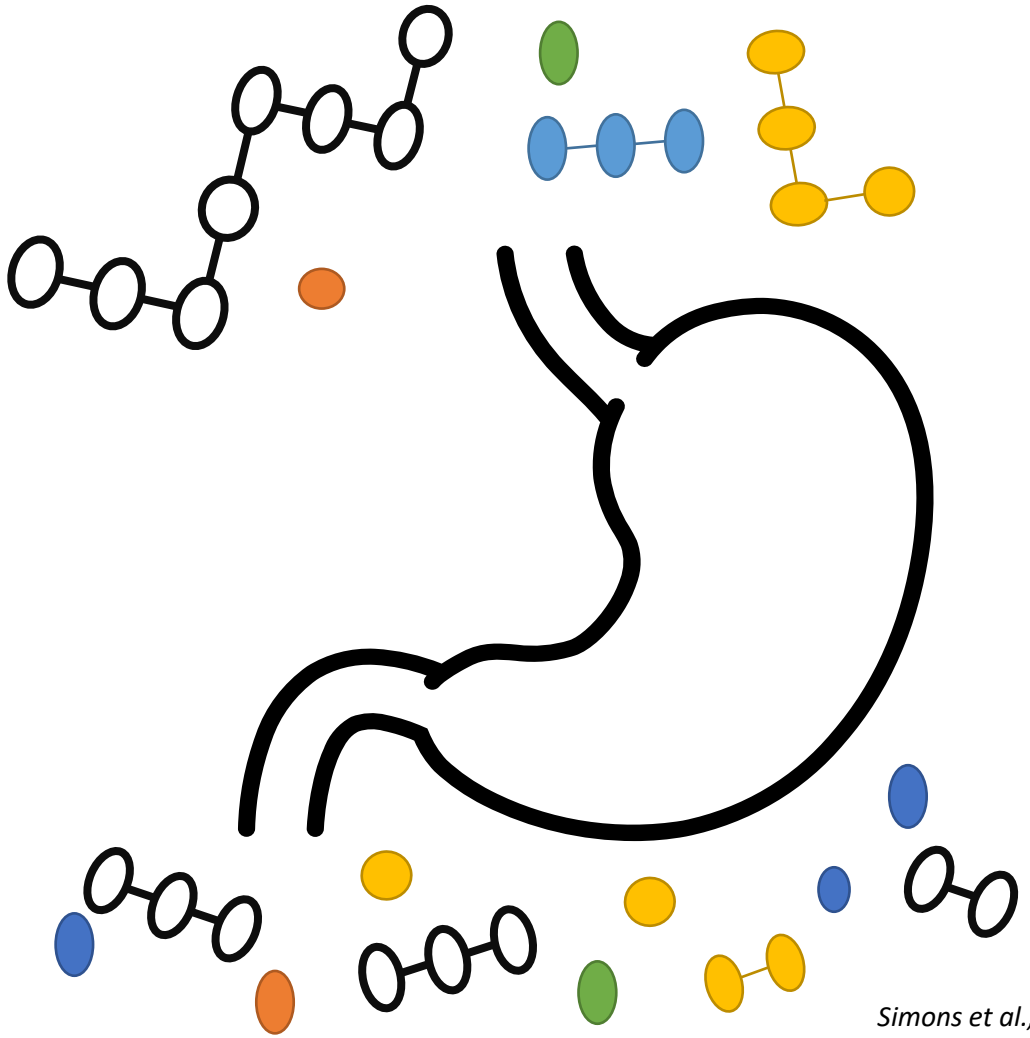
- Multiple clinical studies: oral use of collagen hydrolysates (CHs)
  - ↓ joint pain
  - ↑ mobility
  - ↑ cartilage synthesis

Bernado et al., (2012)
Bruyère et al., (2012)
Lugo et al., (2013)
Kumar et al., (2015)
Feliciano et al., (2017)

Collagen Hydrolysates (CHs)

- Industrially processed collagen
- Cocktail of peptides and amino acids
- Peptides further broken down during human digestion

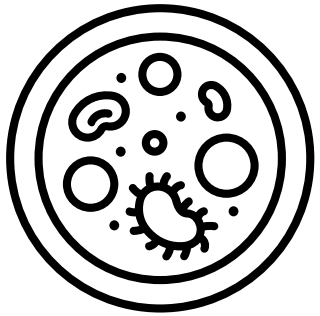
  → smaller peptides and amino acids



Simons et al., (2018)
Skov et al., (2019)

Prebiotics

- Dietary components (fiber, protein, amino acids)
- Beneficial Δ in gut microbiota
  - Activity, composition, growth
- Several health benefits
  - Regulate inflammation
  - Antioxidant activity
  - ↓ Symptoms associated with arthritis



Nyangale et al., (2012)
Ríos-Covián et al., (2016)

Major Short Chain Fatty Acids (SCFAs)

- Products of gut microbial fermentation
- Biomarkers of gut health/overall health
- Major SCFAs
  - Acetic acid
  - Propionic acid
  - Butyric acid

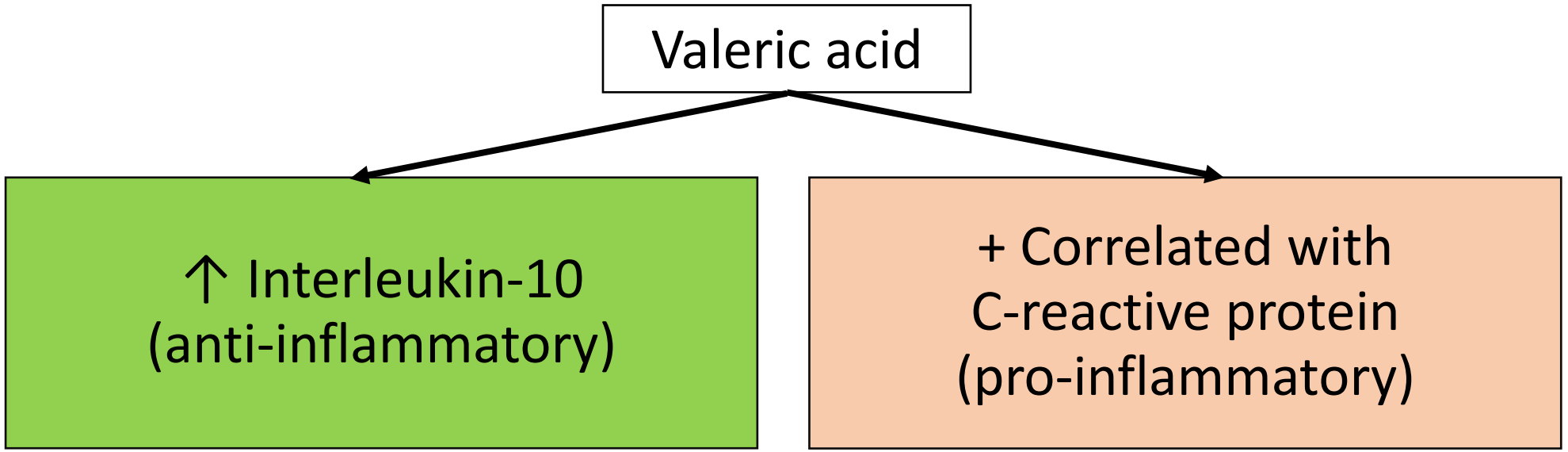
- Functions
  - ↓ Inflammation
  - Regulate appetite
  - Maintain liver mitochondrial function

Health impact & functions not completely understood

Matt et al., (2018), Li et al ., (2018)
Mollica et al.,(2017), Lau et al., (2019)

Minor SCFAs

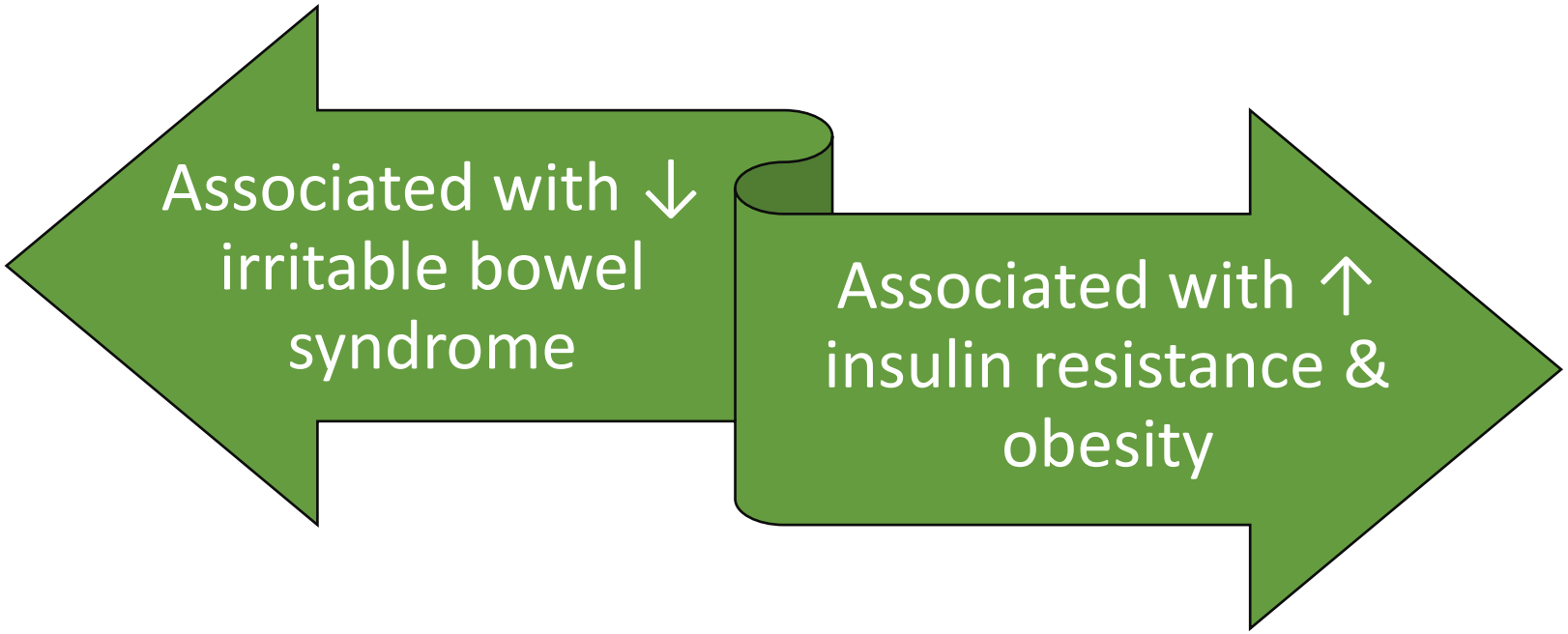
- Valeric, caproic and heptanoic acids
- Biofunctional roles not fully established
- Controversial effects on human health



Luu et al.,(2019),
Yamashiro et al., (2017),
Berenbaum et al., (2013)

Branched Chain Fatty Acids (BCFAs)

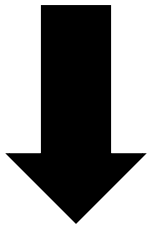
- Isobutyric, isopropionic, isovaleric, isocaproic acids
- Health impact of BCFAs unclear



Sheflin et al.,(2015)
Saresella et al., (2020)
Utzschneider et al., (2016)

CHs as Prebiotics?

- Prebiotics → fermented proteins, peptides and amino acids
- CHs: rich in peptides and amino acids
- Knowledge gap on whether CHs can act as prebiotics

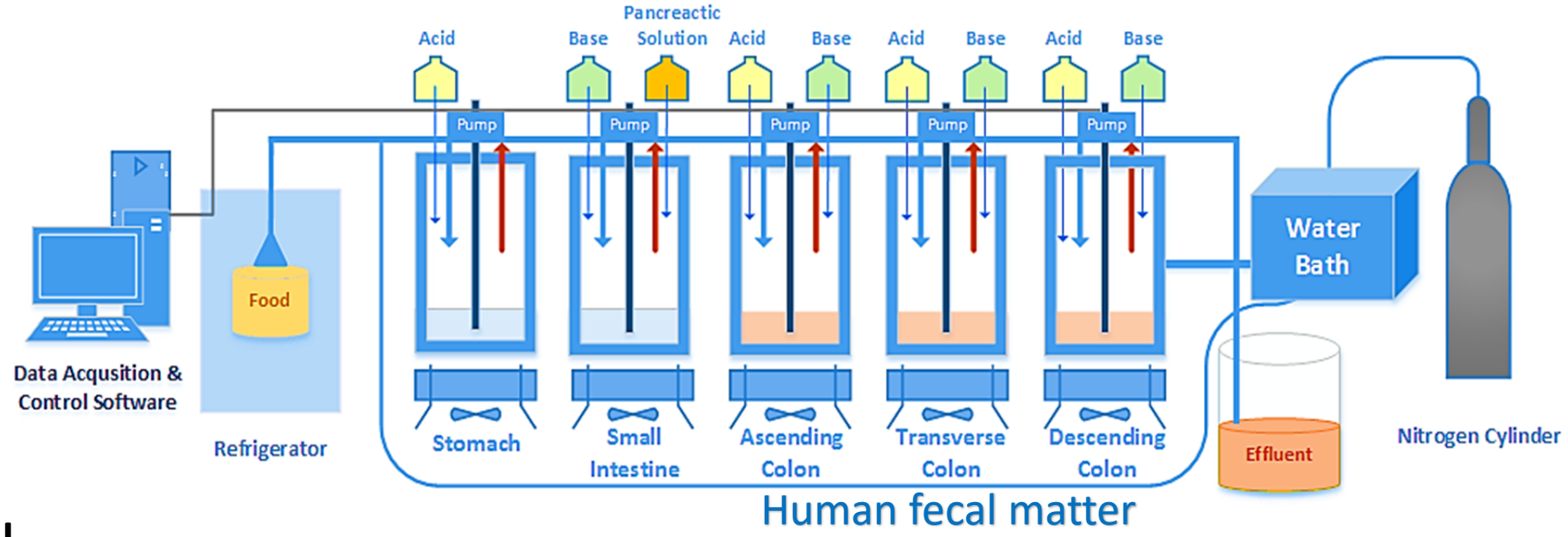


Need to investigate colonic fermentation of CHs

Computer Controlled Dynamic Multistage Gut Digestion Model

Gut models - generate peptide profiles matching human gastric/duodenal aspirates after protein supplementation

Thuenemann et al., (2015)



Kubow et al., (2017)
Habib et al., (2020) submitted
Gaisawat et al., (in preparation)

Computer Controlled Dynamic Multistage Gut Digestion Model

2 Weeks

- Stabilization of colonic fecal matter
- Injection of GI food every 8h

Time 0h

- Sample collection (**control)**
- Injection of GI food (every 8 h)
- Injection of CH

Times 8, 16, 24h

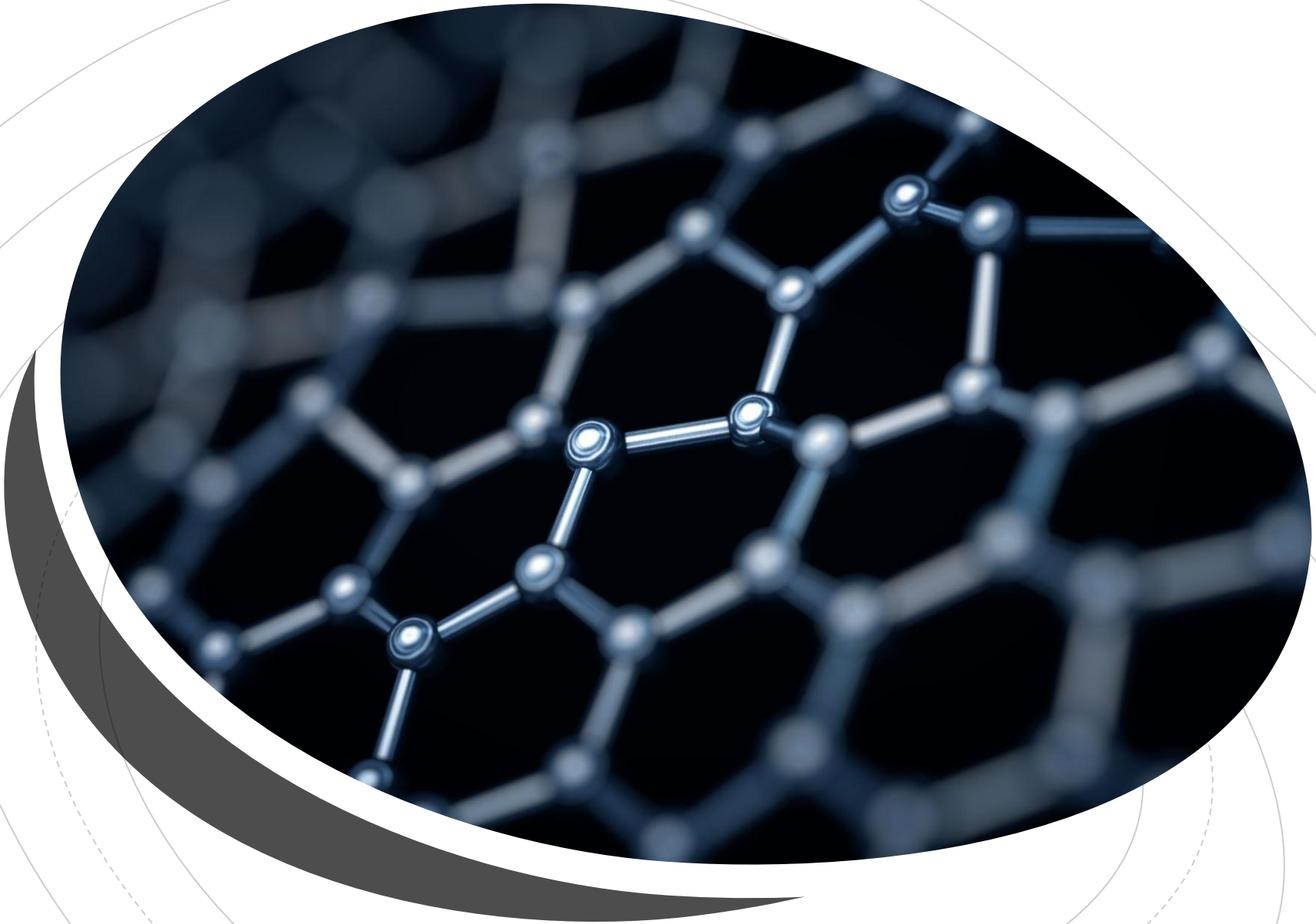
- Sample collection

3 days

- Washout period/stabilization before next treatment

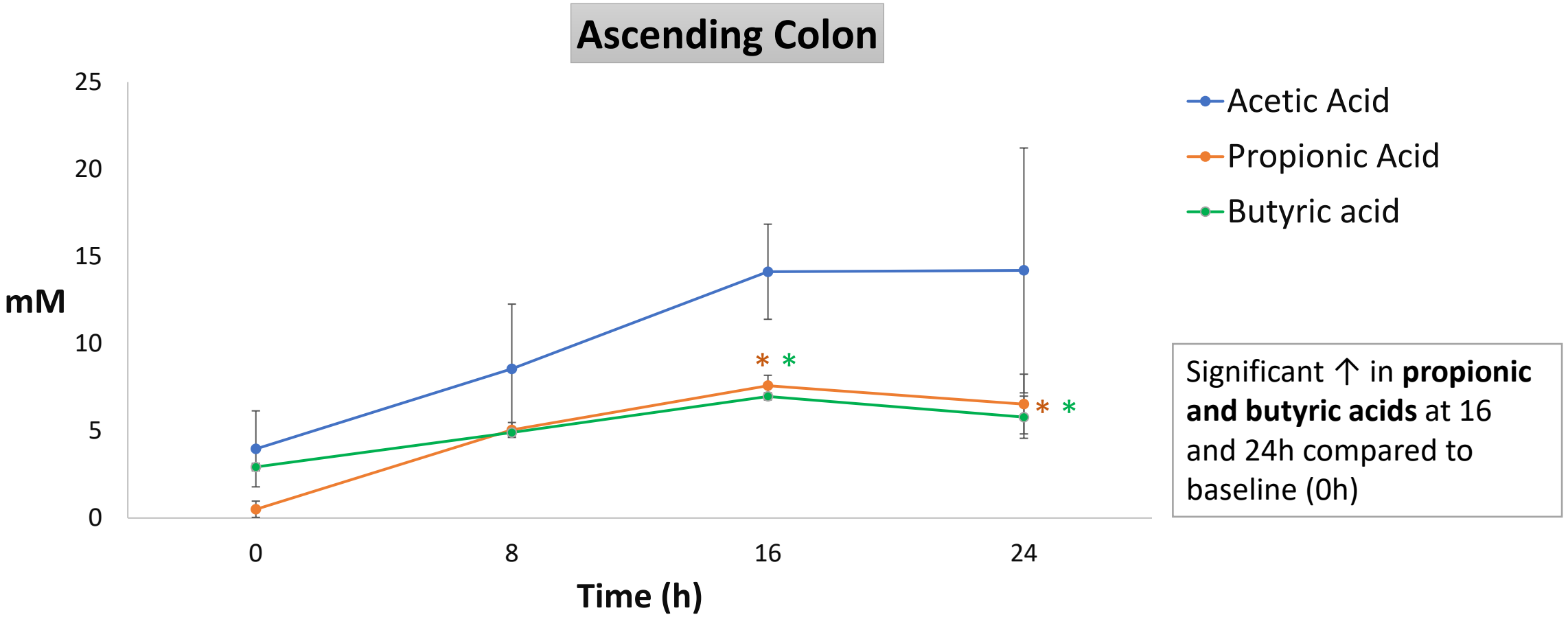
- Two bovine sourced CHs: CH-GL and CH-OPT (n=2/CH)
- Dose based on clinical studies (1200 mg)
- SCFAs and BCFAs: gas chromatograph with flame ionization detector

Kubow et al., (2017)
Ekbatan et al.,(2016)
Habib et al., (2020) submitted
Gaisawat et al., (in preparation)



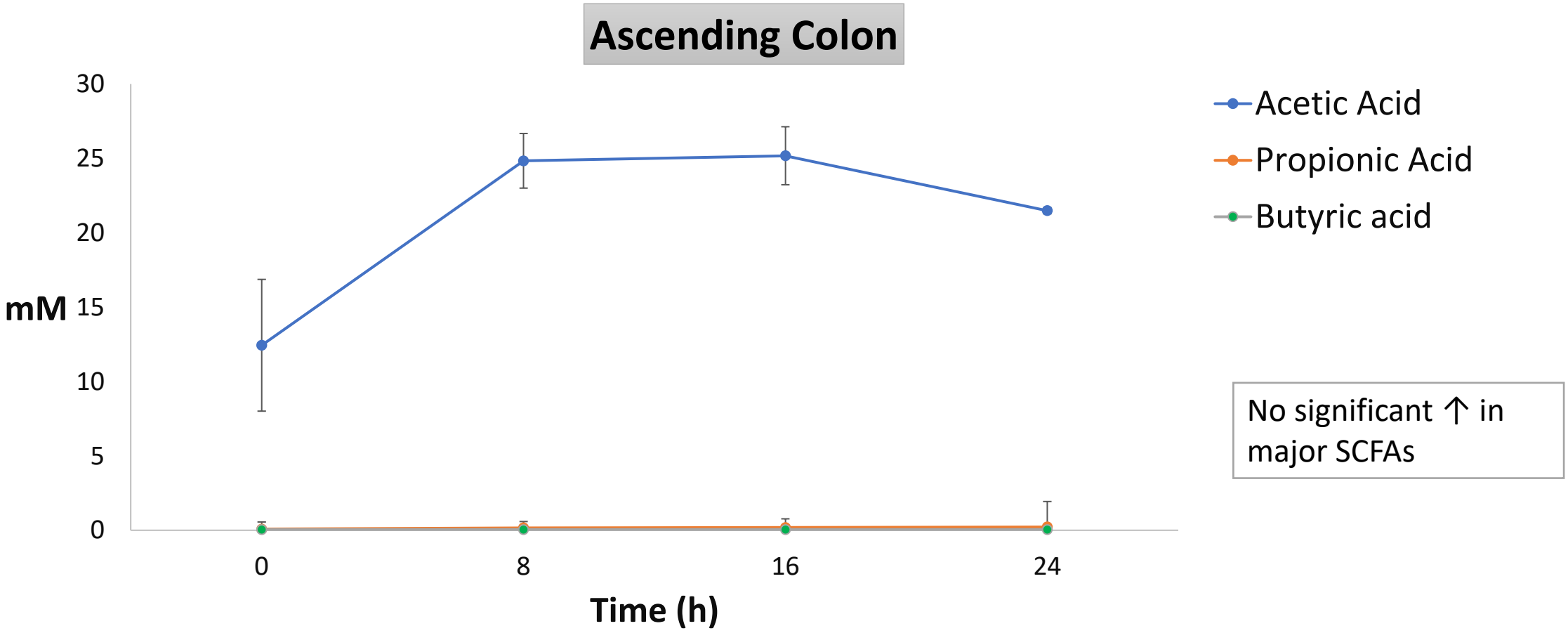
Results

↑ Propionic and Butyric Acids After Simulated Digestion and Microbial Fermentation of CH-OPT

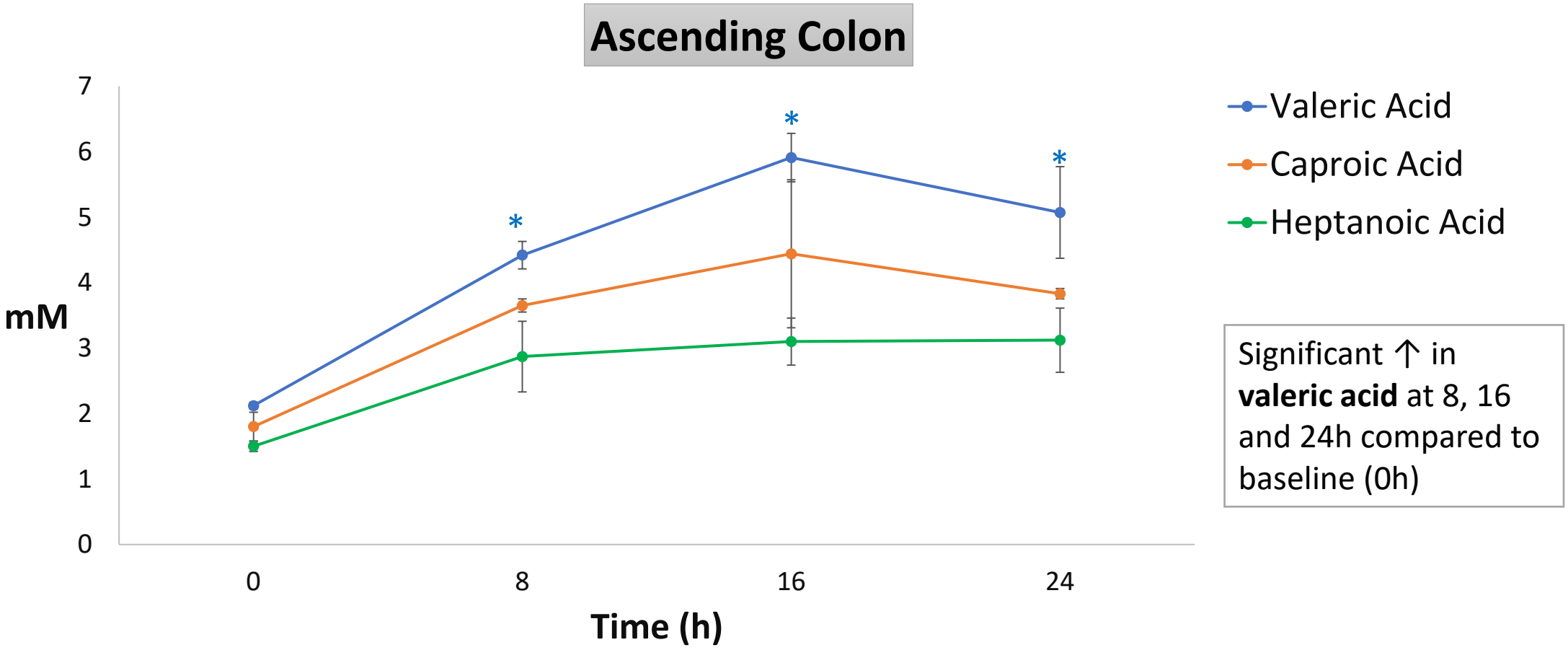


Significant ↑ in **propionic and butyric acids** at 16 and 24h compared to baseline (0h)

No Δ in SCFAs After Simulated Digestion and Microbial Fermentation of CH-GL



↑ Valeric Acid After Simulated Digestion and Microbial Fermentation of CH-OPT



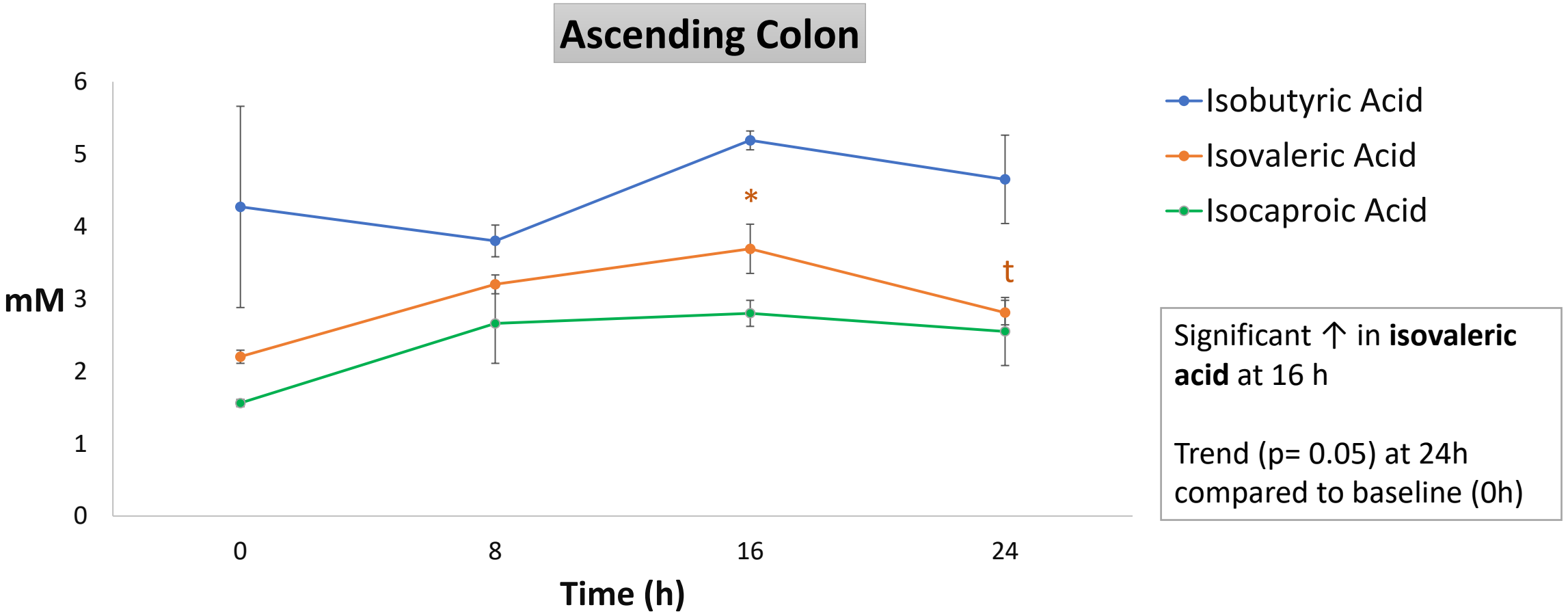
Significant ↑ in **valeric acid** at 8, 16 and 24h compared to baseline (0h)

No Δ in Minor SCFAs After Simulated Digestion and Microbial Fermentation of CH-GL

Ascending Colon			
Time (h)	Valeric aid (mM)	Caproic acid (mM)	Heptanoic acid (mM)
0	0.00±0.00	0.00±0.00	0.00±0.00
8	0.00±0.00	0.00±0.00	0.00±0.00
16	0.00±0.00	0.00±0.00	0.00±0.00
24	0.00±0.00	0.01±0.01	0.00±0.00

No significant content or Δ in minor SCFAs after CH-GL digestion

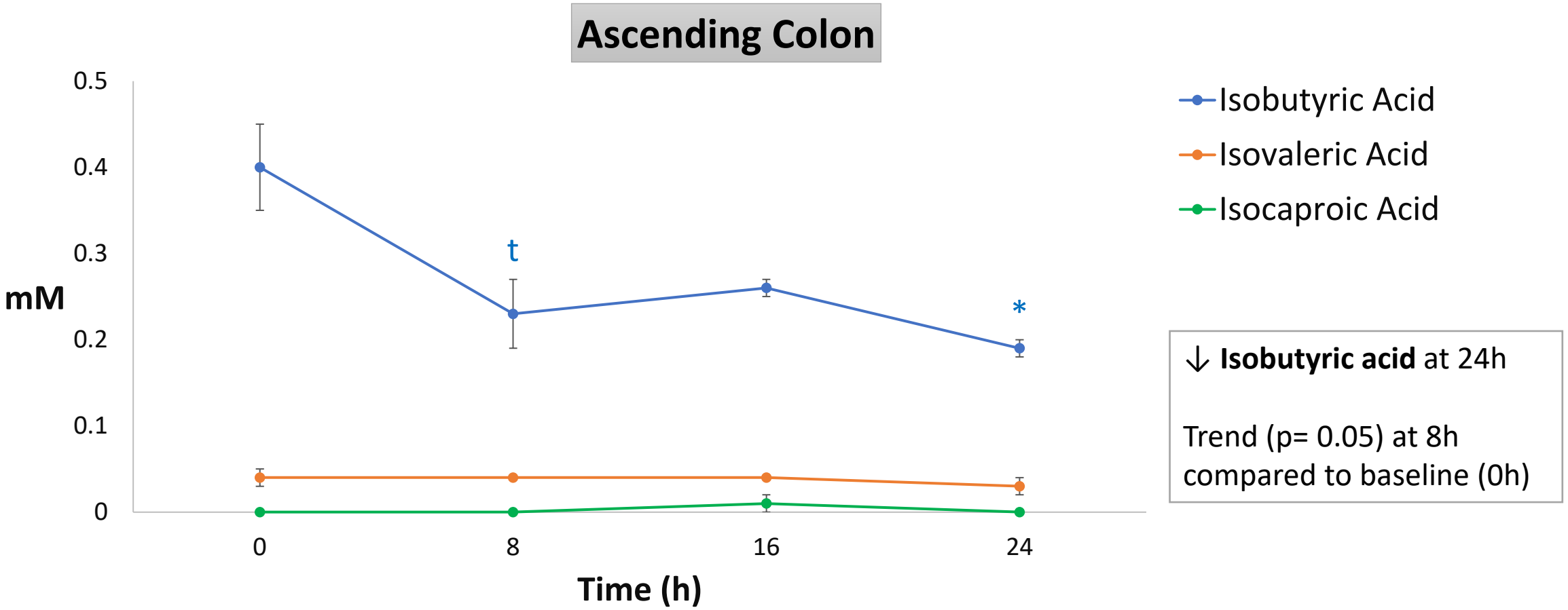
↑ BCFA Isovaleric Acid After Simulated Digestion and Microbial Fermentation of CH-OPT



Significant ↑ in **isovaleric acid** at 16 h

Trend (p= 0.05) at 24h compared to baseline (0h)

↓ BCFA Isobutyric Acid After Simulated Digestion and Microbial Fermentation of CH-GL

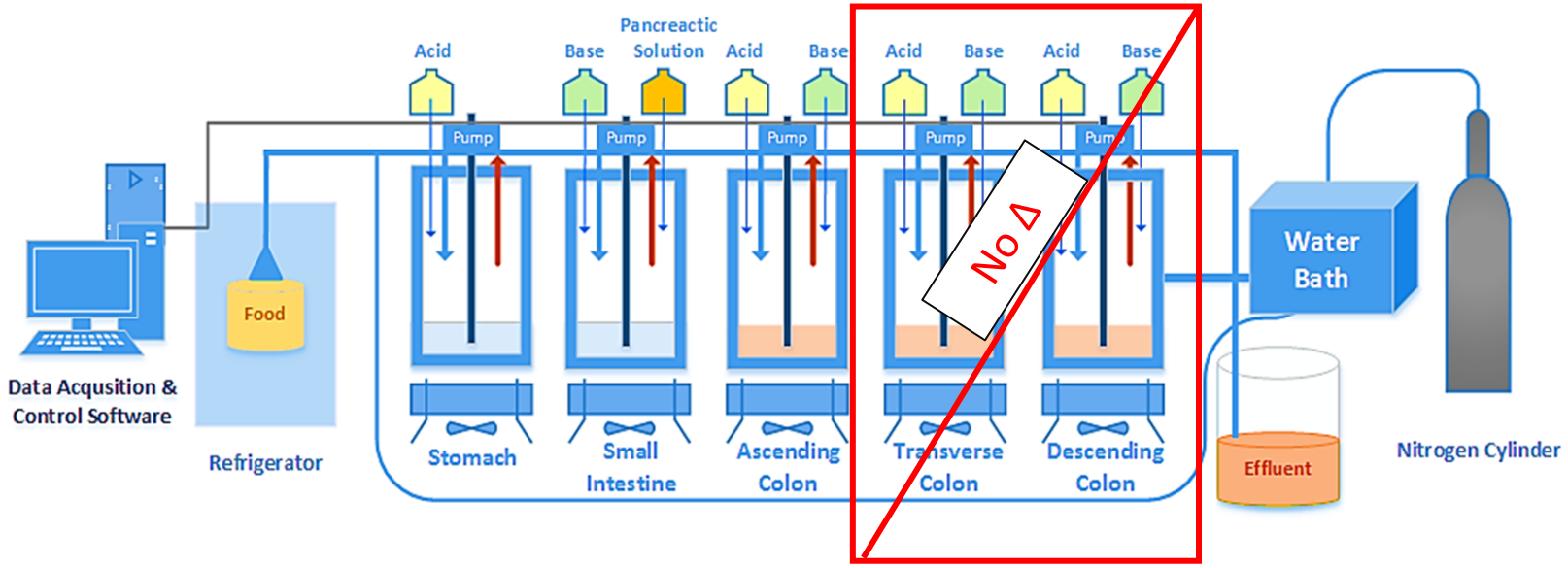


↓ **Isobutyric acid** at 24h

Trend (p= 0.05) at 8h compared to baseline (0h)

No Δ in SCFAs and BCFAs in Transverse and Descending Colon

- No Δ for CH-GL or CH-OPT
- Insufficient peptides survived to support microbial fermentation?



Implications of CH Fermentation on Human Health

- CH-OPT: Health benefits result from ↑ propionic and butyric acids
  - *But* ↑ fecal propionate = ↑ risk of type 2 diabetes
- Controversial health impact of valeric acid

- CH-OPT: Benefits of ↑ SCFAs offset by corresponding ↑ in BCFA?
  - ↑ gut exposure to BCFAs = ↑ risk for diabetes and obesity (two risk factors for OA)

No ↑ in SCFAs or BCFAs after CH-GL
= neither prebiotic or dysbiotic properties

Luu et al.,(2019)
Lau et al., (2019)
Utzschneider et al., (2016)
Yamashiro et al., (2017)
Berenbaum et al., (2013)

Final Remarks

- Limited published data on effects of food-derived peptides on the gut microbiome and microbial fermentation products

- 1st evidence that CHs lead to ↑ SCFAs and BCFAs
  - Microbial metabolic activity depends on CH product
    - *Are differences due to altered peptide and amino acid profiles resulting from different CH processing/purification processes?*

Thank you

Acknowledgements

Thanks to Mohd Baasir Gaisawat (PhD Candidate) for support in operating the dynamic gut model