Synbiotics: the State of the Science

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Outline

1. State of the science: synbiotics
2. State of the science: microbiota, prebiotics & probiotics
3. Gaps & next steps

Synbiotics

Synbiotic – *a **mixture** comprising **live microorganisms** and **substrate(s)** selectively utilized by host microorganisms that confers a **health benefit** on the host.*

Swanson, K. S., et al. (2020). The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nature Reviews Gastroenterology & Hepatology*.

Synbiotics

Synbiotic

Complementary Synbiotic

Prebiotic + probiotic that work *independently* to provide at least one health benefits.

Prebiotic: a substrate that is selectively utilized by host microorganisms conferring a health benefit.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.

Demonstrated health benefit in target host
Study does *not* need to show prebiotic is selectively utilized by microbiota.

Synergistic Synbiotic

Substrate enhances health benefit of co-administered live microorganisms

Components *work together*

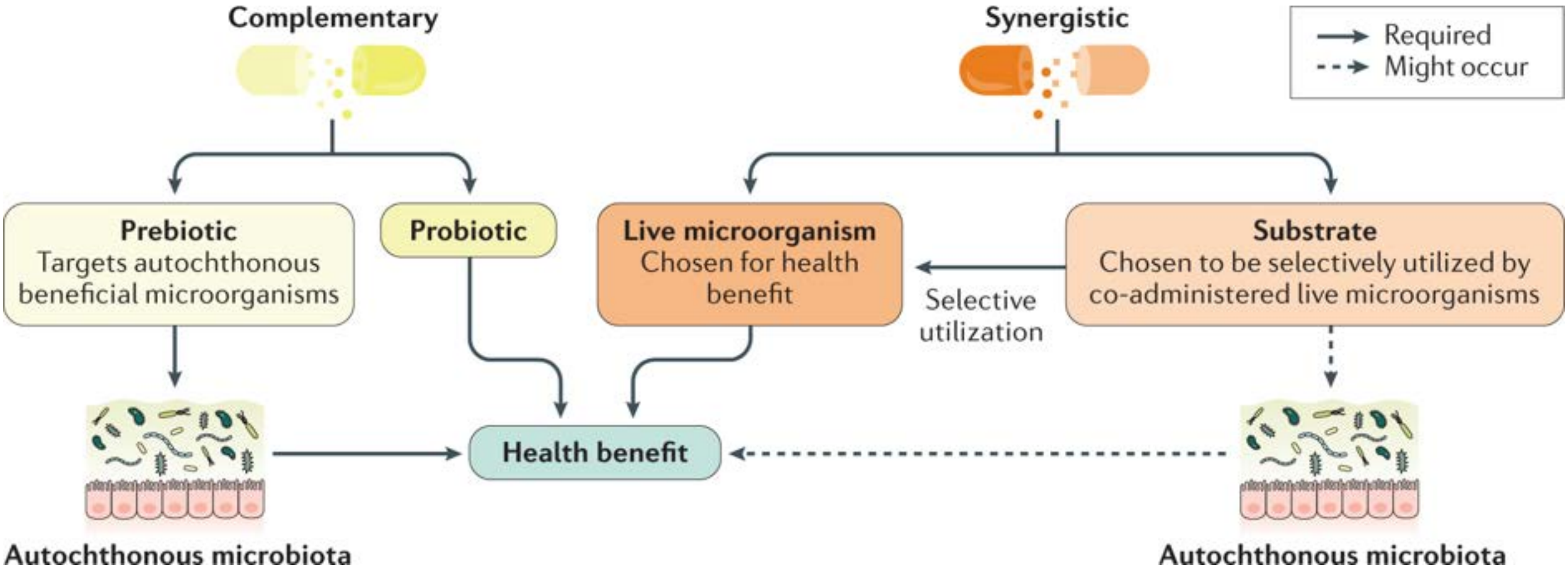
Live microorganisms do *not* need to be probiotics

Substrate does *not* need to be a prebiotic

Demonstrated health benefit in target host
Demonstrate *both* selective utilization and health benefit.

Swanson, K. S., et al. (2020). *Nature Reviews Gastroenterology & Hepatology*.

Synbiotics



Swanson, K. S., et al. (2020). *Nature Reviews Gastroenterology & Hepatology*.

Synbiotics

	Composition	Dose*	Microbiota	Study design	Health Benefit
Complementary	Prebiotic	Sufficient for selective utilization by microbiota	No additional evidence needed beyond prebiotic	2-arm trial: • synbiotic • control	Superior to control
	Probiotic	Sufficient for health benefit	No impact required		
Synergistic	Substance + live microorganism	Sufficient for selective utilization by microorganism	Substrate selectively utilized by co-administered live microorganism	4-arm: • microorganism • substrate • mixture • control	Superior to individual component
	Live microorganism + substance	Sufficient to selectively utilize substrate and result in health benefit			

Swanson, K. S., et al. (2020). *Nature Reviews Gastroenterology & Hepatology*.

Synbiotic Health Effects: Meta-Analyses

- Reduced respiratory tract infections (16 studies)[1]
- ***Reduced systolic blood pressure*** in adults (11 studies)[2]
  - No effect on diastolic blood pressure
- ***Decreased body weight*** and ***waist circumference*** *in adults with overweight and obesity (23 studies)*[3]
  - No *effect on body mass index (BMI) or body fat*

1. Chan CKY, et al. (2020) *Advances in Nutrition*
2. Hadi A, et al. (2022) *Crit Rev Food Sci and Nutrition*
3. Hadi A, et al. (2020) *Crit Rev Food Sci and Nutrition*

Synbiotic Health Effects: Meta-Analyses

- ***Glycemic control*** is unclear due to combined probiotic/synbiotic analyses (18 studies)[1,2]
- ***Oxidative stress*** is unclear due to combined probiotic/synbiotic analyses (9 studies)[3]

- Lack of randomized controlled trials on ***perinatal mental health***[4]
- Limited evidence in ***chronic kidney disease*** (5 studies)[5]

1. Paul P, et al. (2022) *Pharmacological Research*
2. Xu D, et al. (2022) *Crit Rev Food Sci and Nutrition*
3. Pourrajab B, et al. (2020) *Crit Rev Food Sci and Nutrition*
4. Desai V, et al. (2021) *Frontiers in Psychiatry*
5. McFarlane C, et al. (2019) *Renal Nutrition*

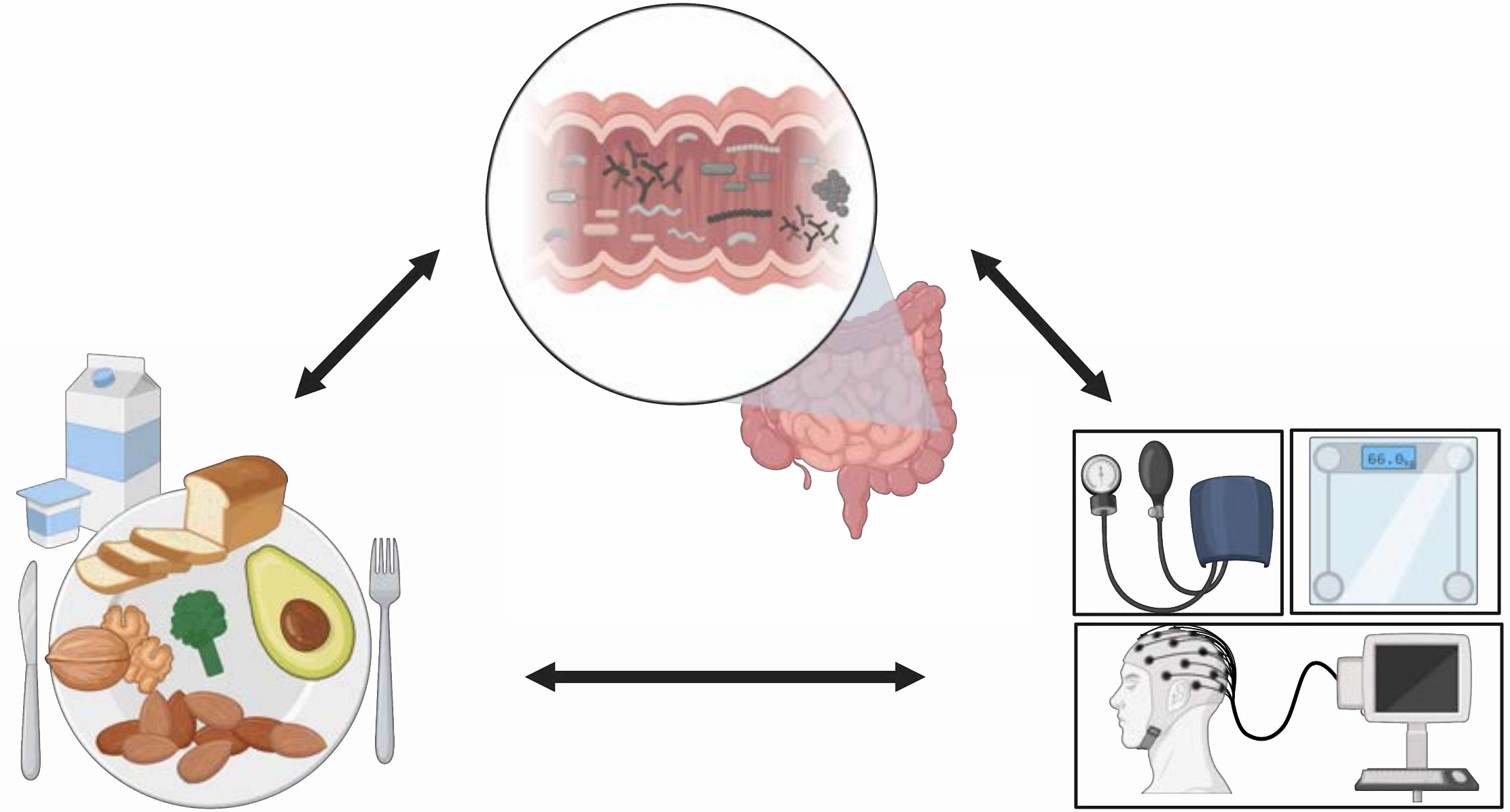
Limited Evidence on Synbiotic Health Benefits

Few studies meet criteria outlined in synbiotic definition

- Complementary synbiotics
  - Prebiotics
  - Probiotics
- Synergistic synbiotics
  - Substrates
  - Live microorganisms

State of the Science: Microbiota, Prebiotics, & Probiotics

Diet, Gut Microbiome, & Physiology



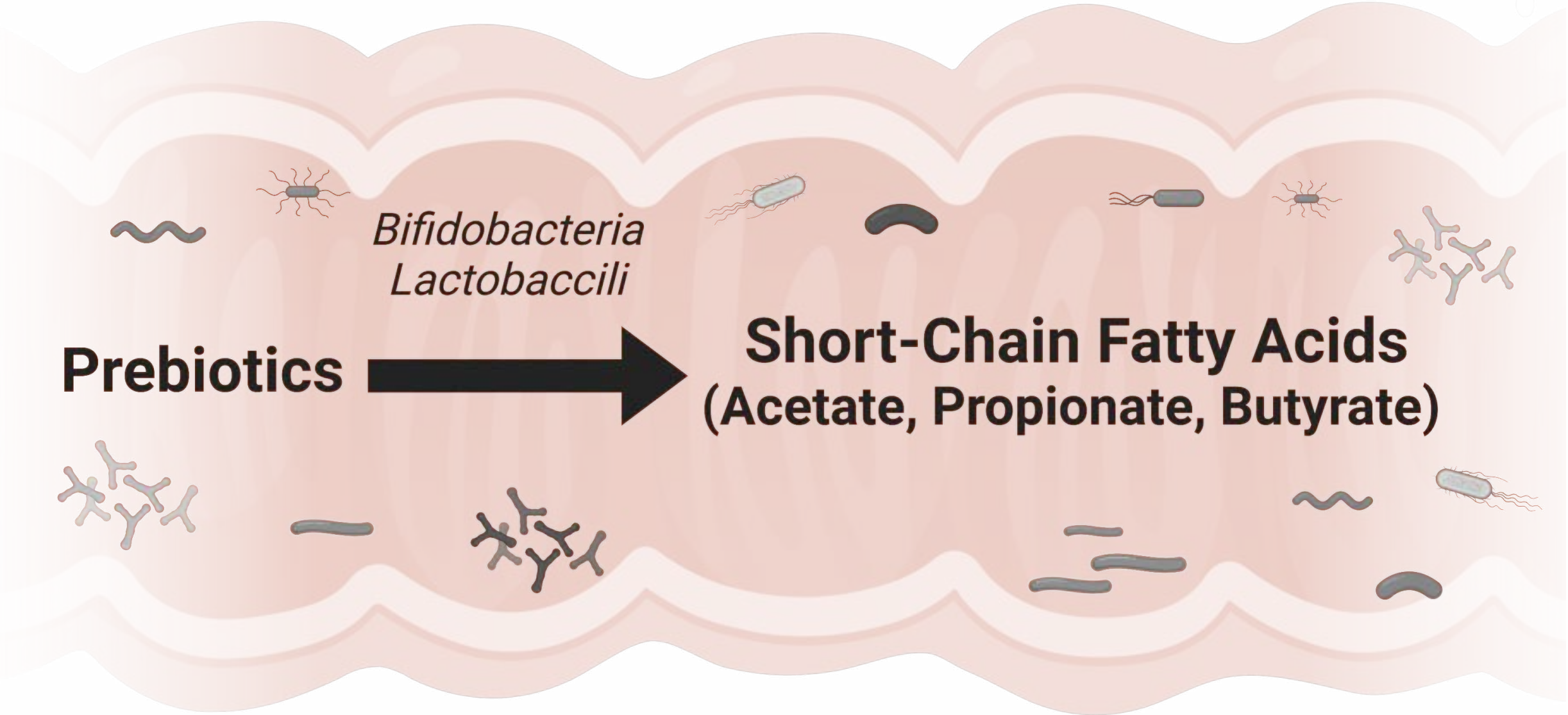
Prebiotics

Prebiotic – *a substrate that is **selectively** utilized by host microorganisms **conferring a health benefit**.*

- Galactooligosaccharides (GOS)
- Fructooligosaccharides (FOS)
- Inulin

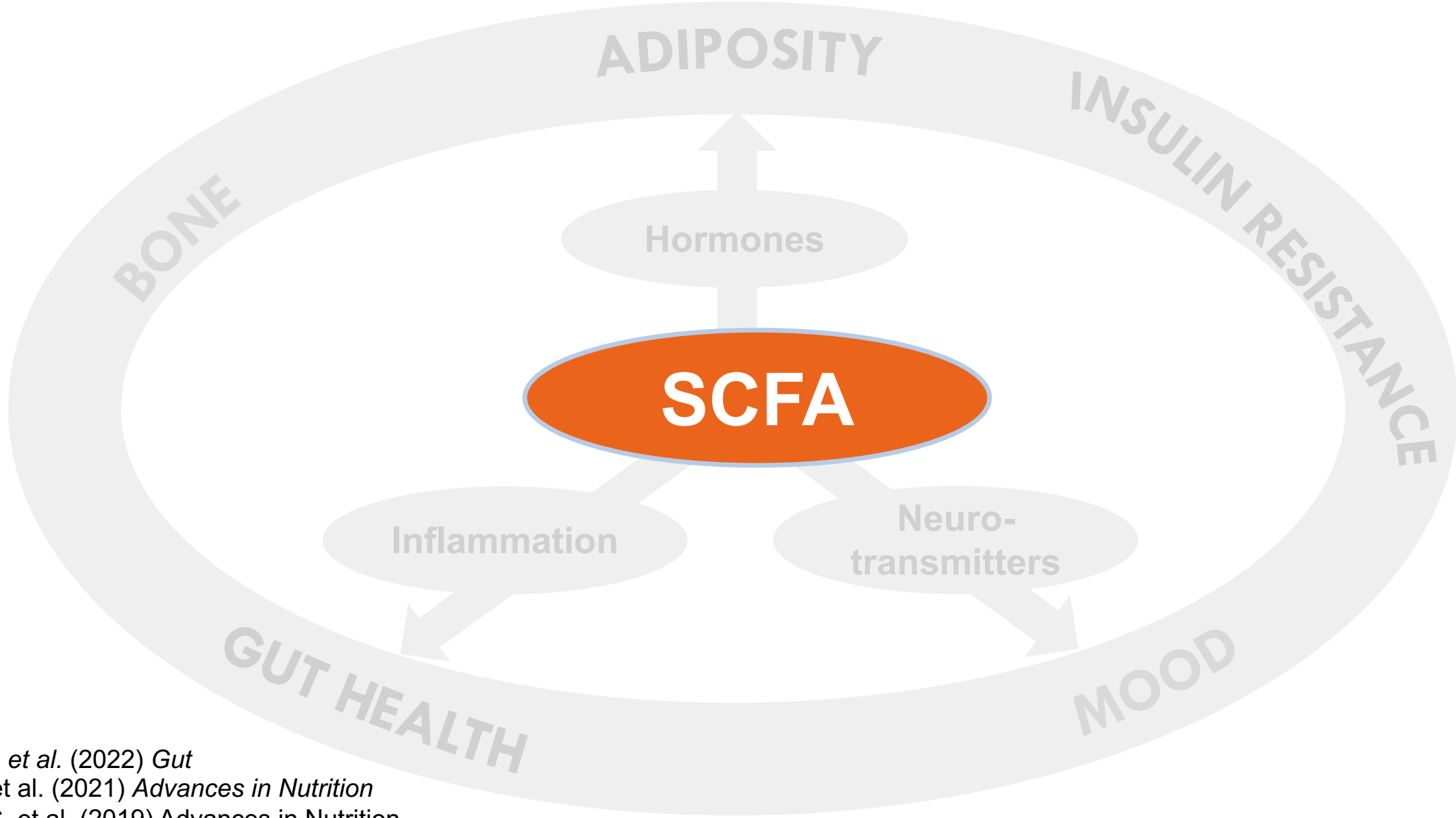
Gibson, G. R., et al. (2017). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology.*

Microbes Ferment Prebiotics



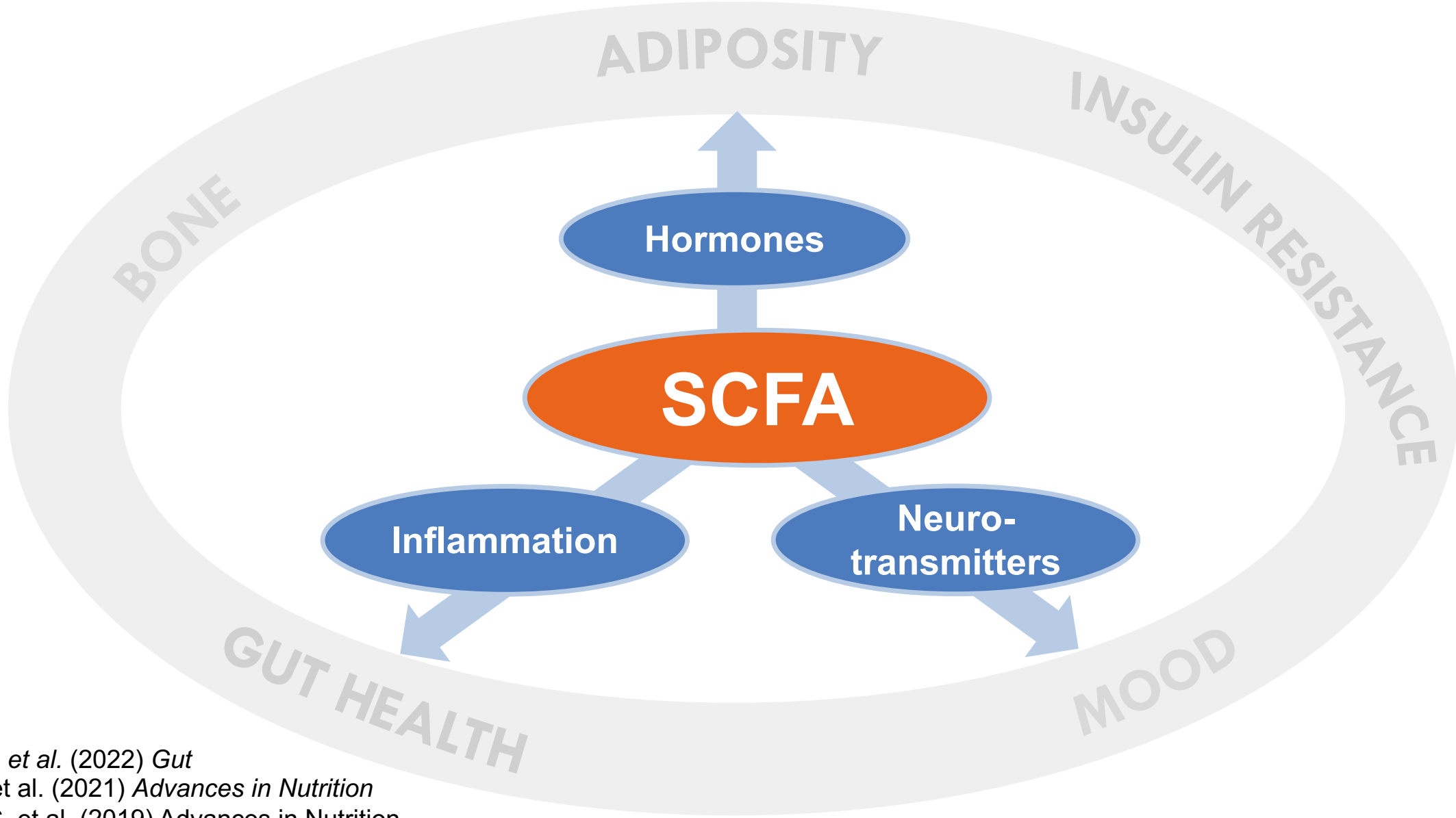
Holscher, H. D. (2017). Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes*, 8(2), 172-184.

Microbiota-Derived Signaling



de Vos WM, *et al.* (2022) *Gut*
Berding K, et al. (2021) *Advances in Nutrition*
Alexander C, et al. (2019) Advances in Nutrition

Microbiota-Derived Signaling



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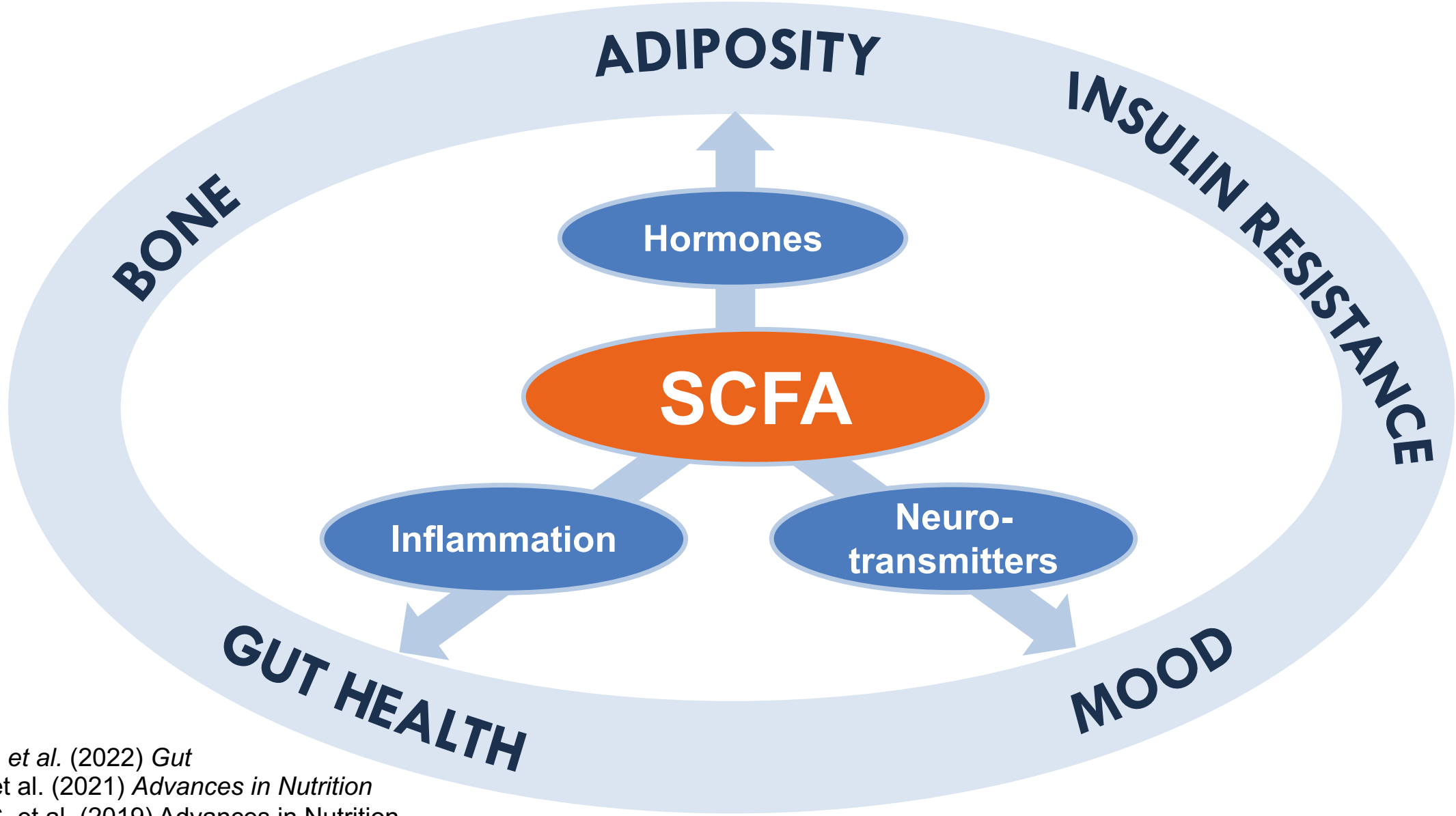
Microbiota-Derived Signaling



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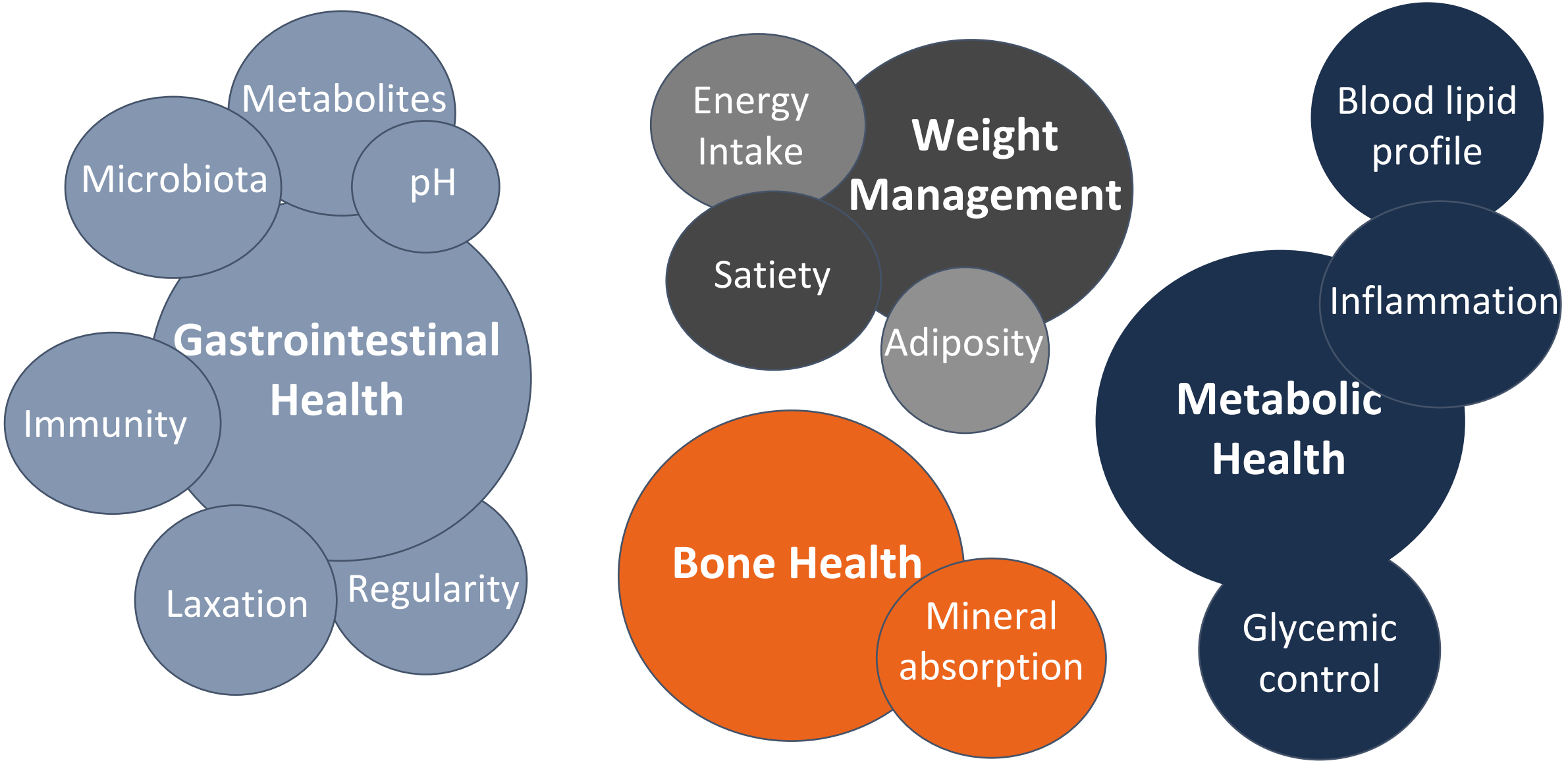
Berding K, et al. (2021) *Advances in Nutrition*
Alexander C, et al. (2019) Advances in Nutrition

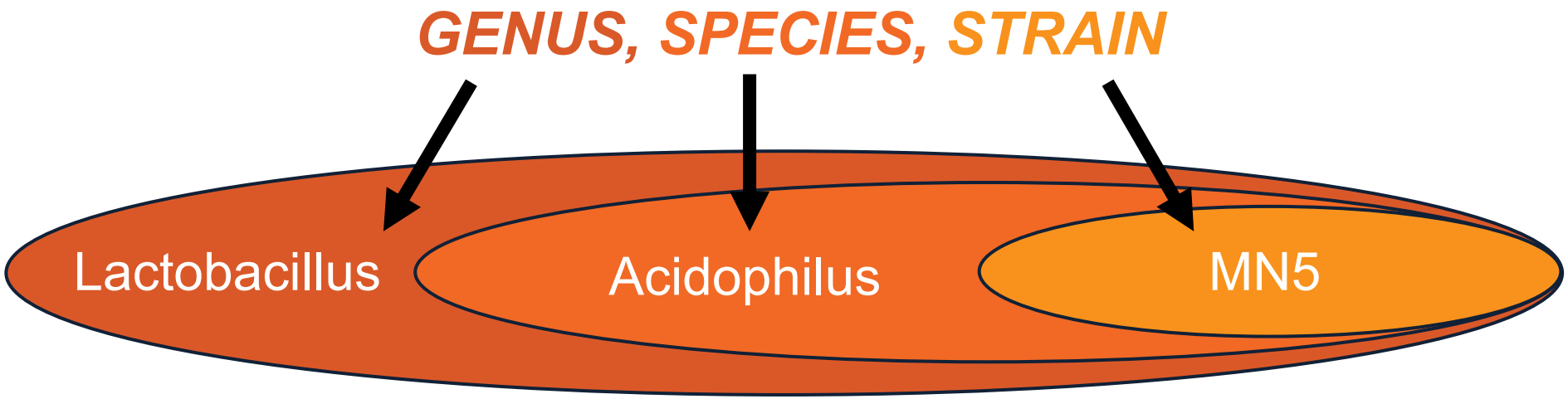
Prebiotics: Health Benefits



Hughes RL, et al. (2022) *Adv Nutr*; So D, et al. (2018) *AJCN*; Lohner S, et al. (2014) *Nutr Rev;* Beserra BT, et al. (2015) *Clin Nutr*; McLoughlin RF, et al. (2017) *AJCN*; Kellow NJ, et al. (2014) *Br J Nutr*.; Liu F, et al. (2017). *Eur J Clin Nutr*; Zhang, et al (2020) *J Clin Biochem Nutr*; Yurrita LC, et al. (2014) *Nutr Hosp*

Probiotics

Probiotics *are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.*[1]



1. Hill, C et al. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology & Hepatology*.

Probiotics

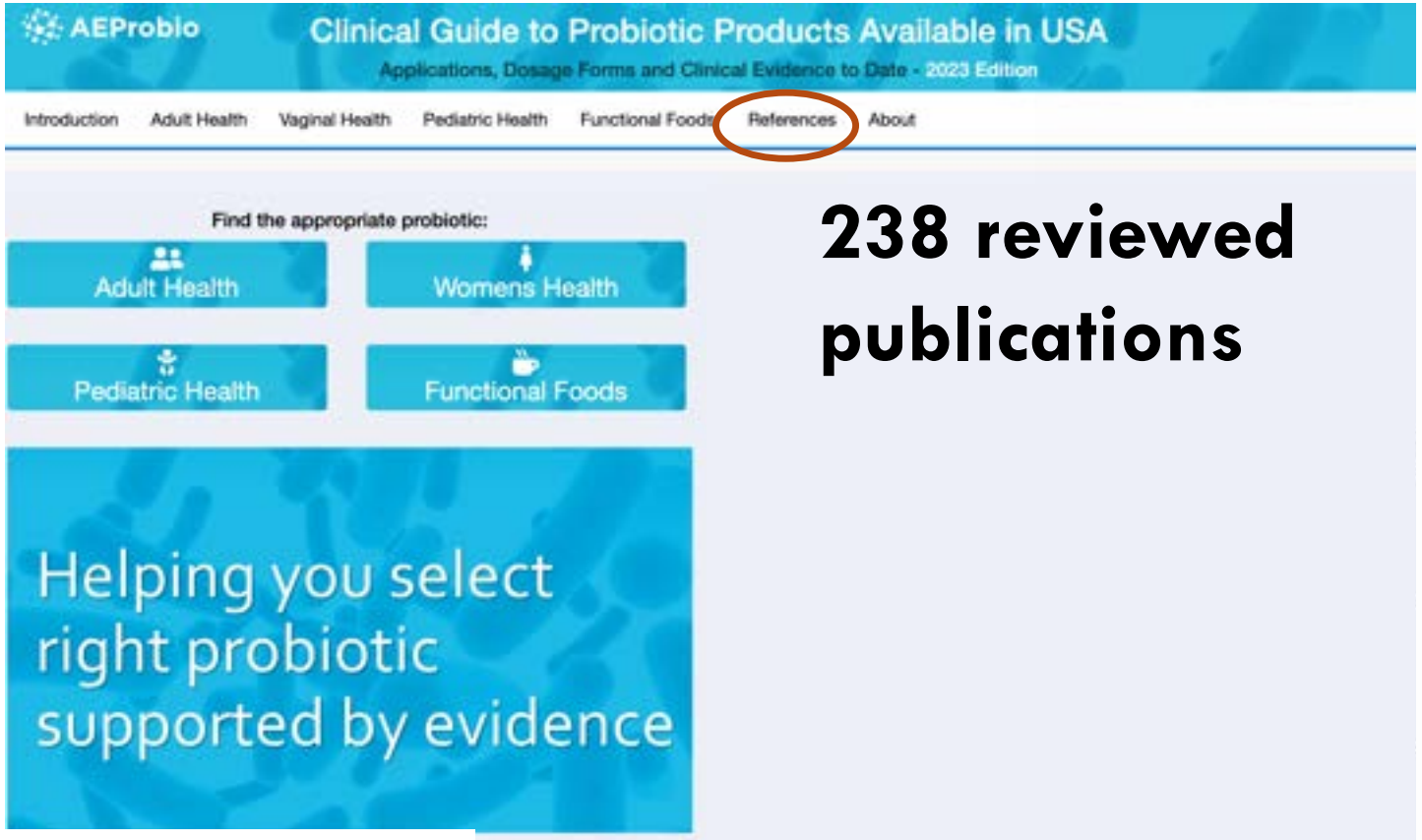
- ***Strains*** and ***dosages*** impact health outcomes
  - ***Strains***
    - taxonomically defined
    - genome sequence available
  - ***Doses***
    - Adequate
    - 100 millions to 450 billion CFUs

Most commonly studied

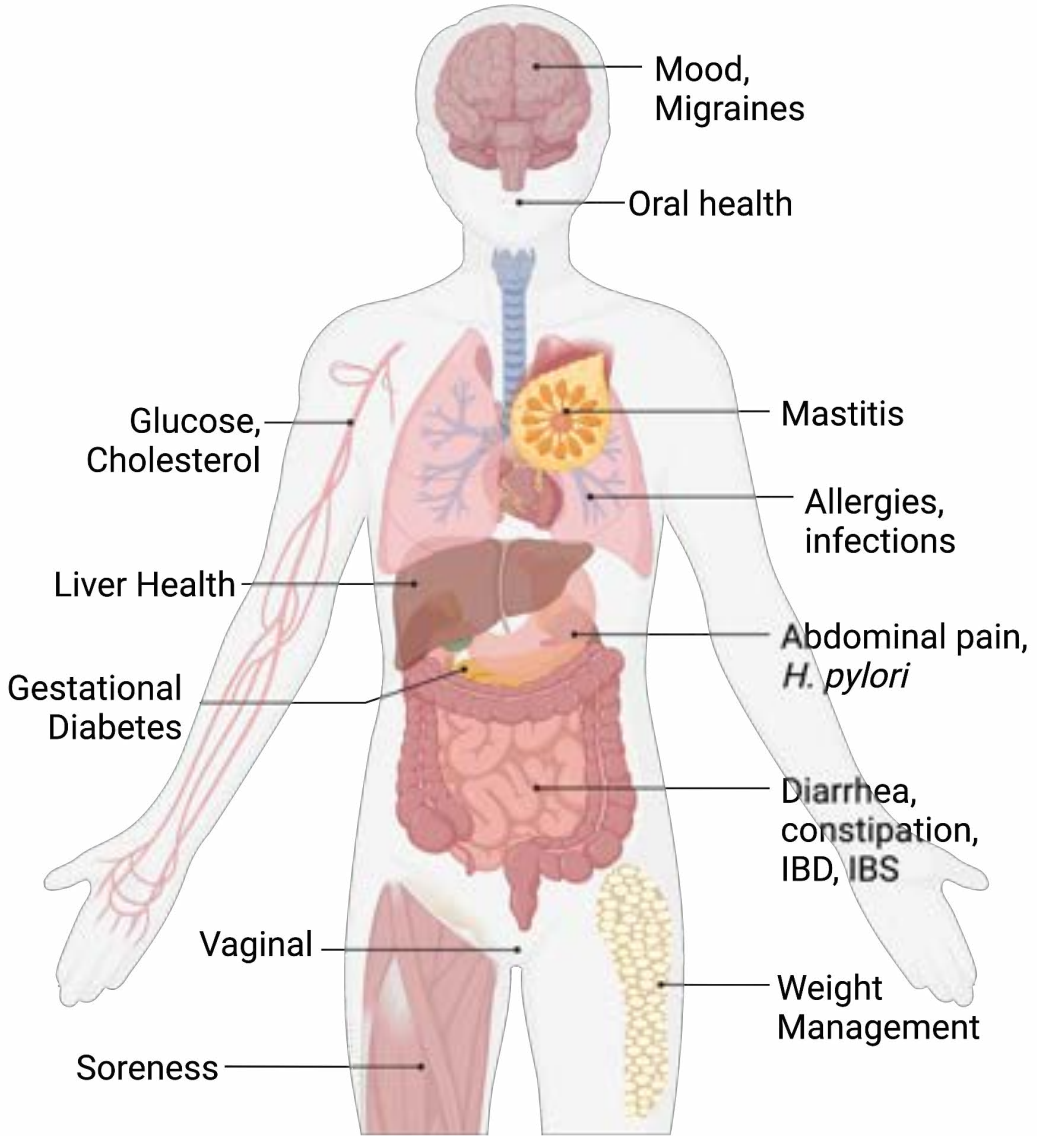
- *Bifidobacterium*
  - *B. lactis*
- *Lactobacilli*
  - *L. acidophilus*
  - *L. casei*
  - *L. plantarum*
  - *L. rhamnosus*
  - *L. reuteri*
- *Saccharomyces boulardii*

1. Hill, C et al. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology & Hepatology*.

Probiotics: Clinical Guide 2023



238 reviewed publications



Evidence Evaluation

Level I: At least 1 appropriately designed trial with power calculation for outcome

Level II: Well designed controlled trials w/o randomization, cohort or case-controlled

Level III: Expert opinions

Clinical Guide to Probiotic Products 2023 (http://usprobioticguide.com/)

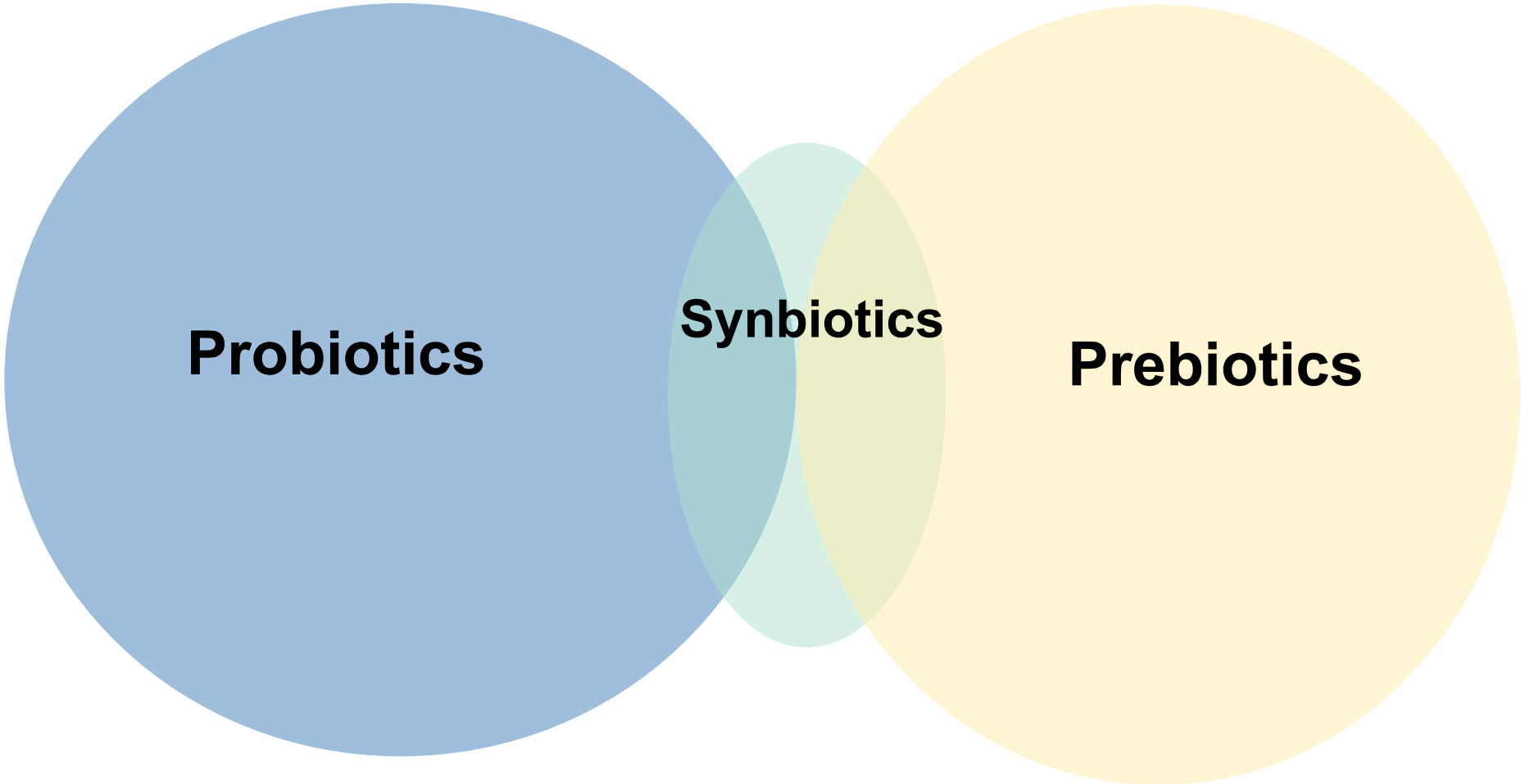
Prebiotics and Probiotics Confer Health Benefits

Build upon existing research to design synbiotics

- Complementary synbiotics
  - Strategic selection of probiotic(s) and prebiotic(s)
  - Use of next generation probiotics and prebiotics

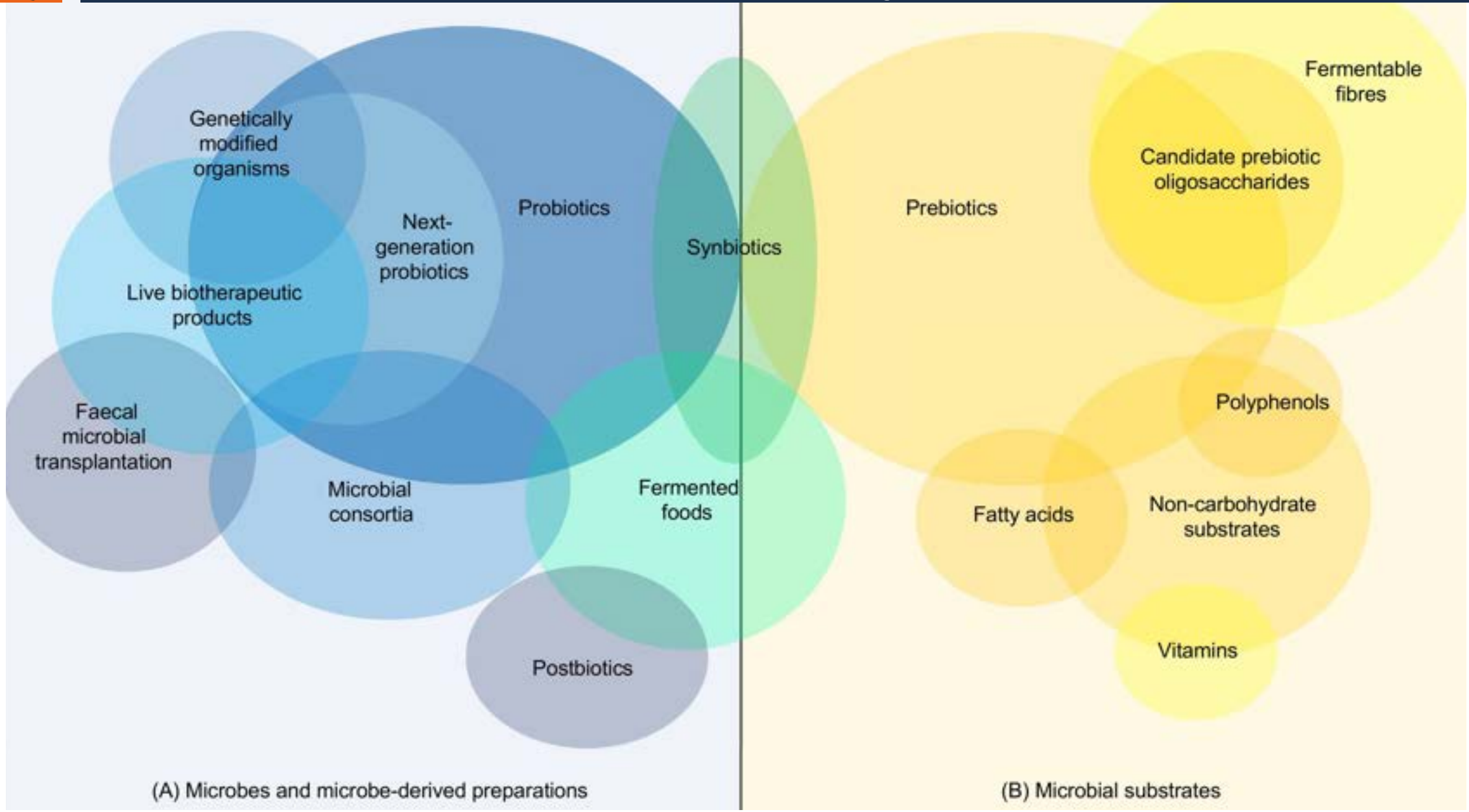
- Synergistic synbiotics
  - Strategic selection of substrate(s) and live microorganism(s)
  - Innovative pre-clinical screening and testing

State of the Science



Cunningham et al. (2021). Shaping the future of probiotics and prebiotics. *Trends in Microbiology*.

Areas of New Discovery

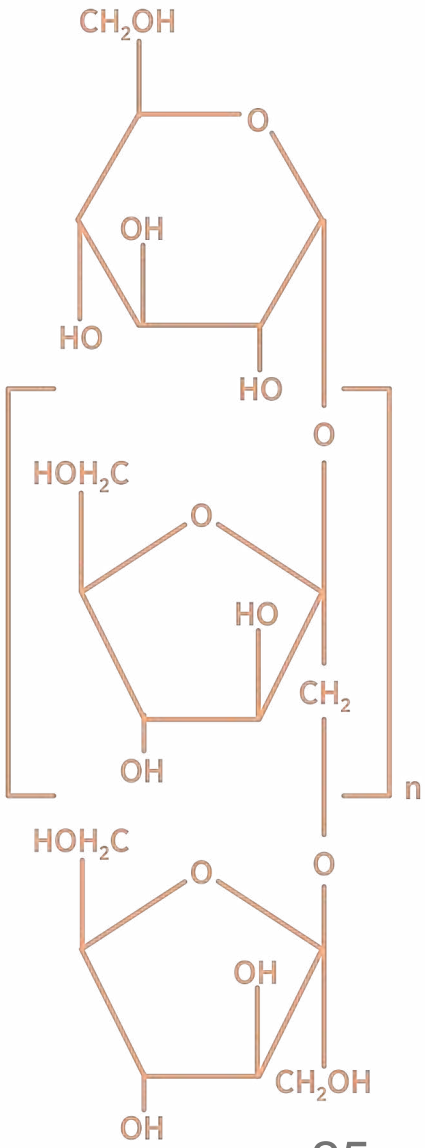


Cunningham et al. (2021). Shaping the future of probiotics and prebiotics. *Trends in Microbiology*.

Next Steps

Next Generation Prebiotics

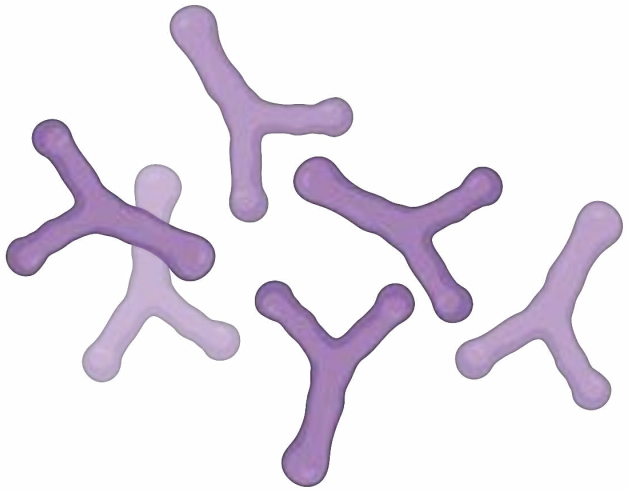
- ***Accepted Prebiotics***
  - Galactooligosaccharides (GOS)
  - Fructooligosaccharides (FOS)
  - Inulin
- ***Candidate Prebiotics***
  - Other oligosaccharides (*e.g.*, mannanoligosaccharide, xylooligosaccharide
  - Human milk oligosaccharides
  - Phenolics and phytochemical
  - Conjugated linoleic acid
  - Polyunsaturated fatty acid



Gibson, GR, et al. (2017) *Nature Reviews Gastroenterology & Hepatology*; Cunningham et al. (2021) *Trends in Microbiology*.

Next Generation Probiotics

- ***Commonly Studied***
  - Bifidobacterium
  - Lactobacilli
  - *Saccharomyces boulardii*
- ***Next Generation[1,2,3]***
  - *Faecaelebacterium prausnitzii*
  - *Akkermansia muciniphila*
  - *Bacteroides fragilis*
  - *Dysosmobacter welbionis*[4]



1. O'Toole PW, Marchesi J & Hill C (2017). *Nature Microbiology*
2. Kaźmierczak-Siedlecka K, et al. (2022) *Gut Microbes*
3. https://www.nccih.nih.gov/news/events/precision-probiotic-therapies-challenges-and-opportunities
4. Le Roy T, et al. (2022) *Gut*

Synbiotics: Blood Pressure

- Acetylated and butyrylated high-amylose maize starch (40g/d)[1] decreased systolic blood pressure 4.1 mmHg[1]

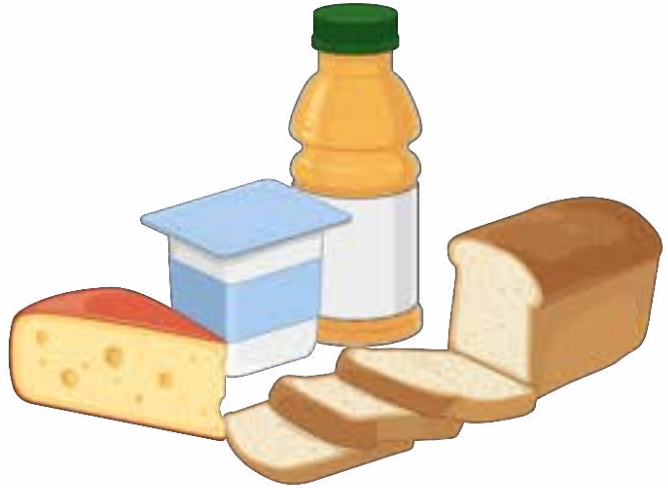
- ***Probiotics***[2]
  - *Lactobacillus helveticus* reduced blood pressure (7 studies)
    - Systolic: 2.3 to 15.8 mmHg reduction
    - Diastolic: 1.8 to 10.3 mmHg reduction

1. Jama HA, et al. (2023) *Nature Cardiovascular Research*
2. Zhao TX, et al. (2022) *Food Science Nutrition*

Synbiotics: Formulations

Food Sources

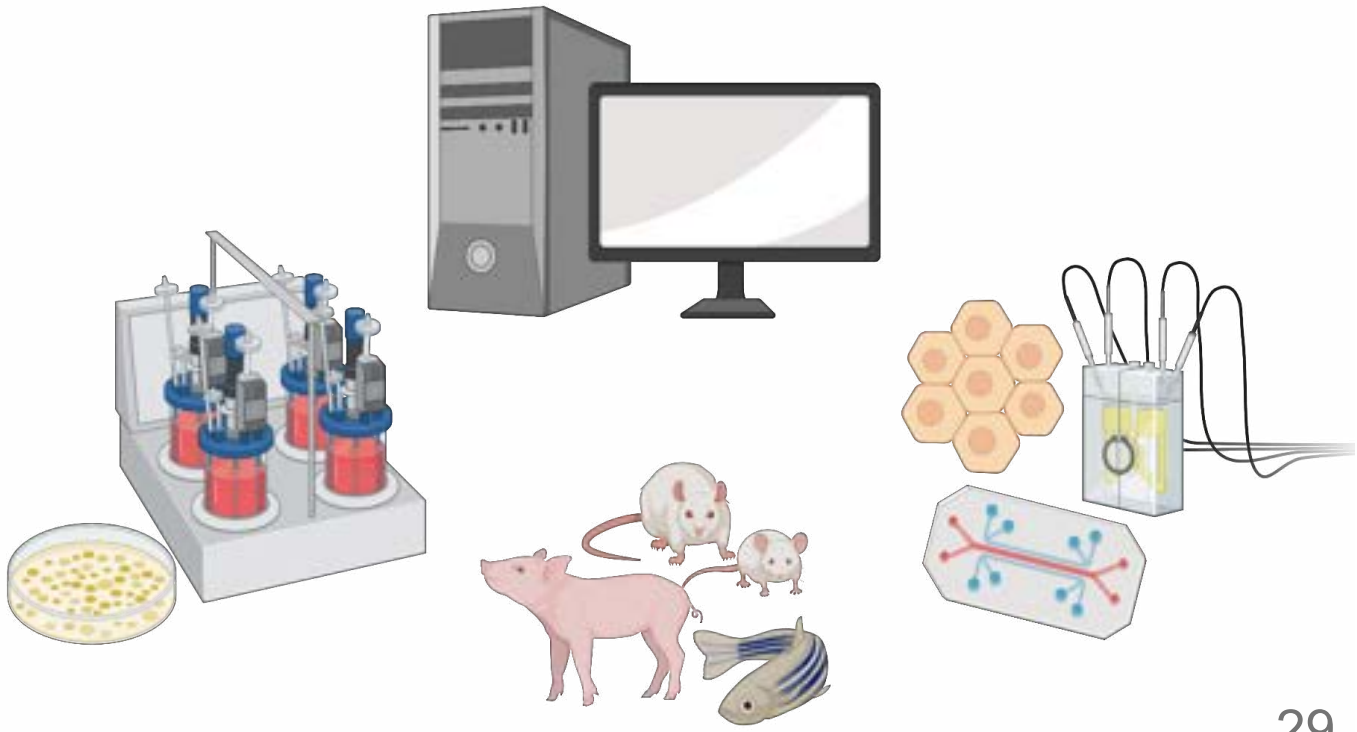
- Bakery products
- Beverages
- Breakfast cereals
- Cereal bars
- Dairy alternatives
- Dairy products
- Desserts
- Dry mixes
- Fillings
- Formula
- Fruit preparations
- Meat products
- Soups & sauces



Next Steps: Pre-clinical Studies

- ***Computational approaches***
  - Pipelines for discovery and testing
  - Identifying novel substrates and microorganisms

- ***Model systems***
  - *In vitro*
  - *In vivo*
  - *Ex vivo*



Next Steps: Clinical Studies

- ***Need high quality clinical trials on synbiotics***
  - Health benefits from prebiotics and probiotics
  - Growing evidence for synbiotics
- ***Reporting and Reproducibility***
  - Preparation and storage methods/records
  - Detailed analysis of the synbiotic (as consumed)
  - Consumption and compliance measures
- ***Establish causal relationships: synbiotics & health***
  - Design
  - Population
  - Interventions & Comparators
  - Outcomes & Statistics

Key Takeaways

1

Synbiotics are ***complex.***

2

Build upon ***probiotic and prebiotic research***.

3

Causally link health to consumption of synbiotics.

Discussion

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References

- Swanson, K. S., et al. (2020). The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nature Reviews Gastroenterology & Hepatology*.
- Chan CKY, et al. (2020). Preventing Respiratory Tract Infections by Synbiotic Interventions: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Advances in Nutrition*
- Amir Hadi, Makan Pourmasoumi, Maryam Kazemi, Ameneh Najafgholizadeh & Wolfgang Marx (2022) Efficacy of synbiotic interventions on blood pressure: a systematic review and meta-analysis of clinical trials, Critical Reviews in Food Science and Nutrition, 62:20, 5582-5591, DOI: 10.1080/10408398.2021.1888278
- Amir Hadi, Kimia Alizadeh, Hossein Hajianfar, Hamed Mohammadi & Maryam Miraghajani (2020) Efficacy of synbiotic supplementation in obesity treatment: A systematic review and meta-analysis of clinical trials, Critical Reviews in Food Science and Nutrition, 60:4, 584-596, DOI: 10.1080/10408398.2018.1545218
- Paul P, et al. (2022). The effect of microbiome-modulating probiotics, prebiotics and synbiotics on glucose homeostasis in type 2 diabetes: A systematic review, meta-analysis, and meta-regression of clinical trials. *Pharmacological Research*
- Dengfeng Xu, Lingmeng Fu, Da Pan, YiFang Chu, Meiyuan Feng, Yifei Lu, Chao Yang, Yuanyuan Wang, Jiayue Xia & Guiju Sun (2022): Role of probiotics/ synbiotic supplementation in glycemic control: A critical umbrella review of meta-analyses of randomized controlled trials, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2022.2117783
- Behnaz Pourrajab, Somaye Fatahi, Mohammad Hassan Sohouli, Mihnea-Alexandru Găman & Farzad Shidfar (2022) The effects of probiotic/synbiotic supplementation compared to placebo on biomarkers of oxidative stress in adults: a systematic review and metaanalysis of randomized controlled trials, Critical Reviews in Food Science and Nutrition, 62:2,490-507, DOI:10.1080/10408398.2020.1821166
- Desai V, Kozyrskyj AL, Lau S, Sanni O, Dennett L, Walter J and Ospina MB (2021) Effectiveness of Probiotic, Prebiotic, and Synbiotic Supplementation to Improve Perinatal Mental Health in Mothers: A Systematic Review and Meta-Analysis. Front. Psychiatry 12:622181. doi: 10.3389/fpsyt.2021.622181
- McFarlane C, et al. (2019). Prebiotic, Probiotic, and Synbiotic Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-analysis. Renal Nutrition
- Gibson, G. R., et al. (2017). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology.*
- Holscher, H. D. (2017). Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes*, 8(2), 172-184.
- de Vos, W. M., Tilg, H., Van Hul, M., & Cani, P. D. (2022). Gut microbiome and health: mechanistic insights. Gut, 71(5), 1020-1032.
- Berding, K., Vlckova, K., Marx, W., Schellekens, H., Stanton, C., Clarke, G., Jacka, F., Dinan, T.G. and Cryan, J.F., 2021. Diet and the microbiota–gut–brain axis: sowing the seeds of good mental health. Advances in Nutrition, 12(4), pp.1239-1285.
- Alexander, C., Swanson, K. S., Fahey Jr, G. C., & Garleb, K. A. (2019). Perspective: physiologic importance of short-chain fatty acids from nondigestible carbohydrate fermentation. Advances in Nutrition, 10(4), 576-589.

References

- Hughes, R. L., Alvarado, D. A., Swanson, K. S., & Holscher, H. D. (2022). The prebiotic potential of inulin-type fructans: a systematic review. Advances in Nutrition, 13(2), 492-529.
- So D et al. (2018). Dietary fiber intervention of gut microbiota composition in healthy adults: a systematic review and meta-analysis. AJCN 107(6): 965-983
- Lohner S et al. (2014) Prebiotics in healthy infants and children for prevention of acute infectious diseases: a systematic review and meta-analysis. Nutr Rev. 72(8): 523-531
- Beserra BT, et al. (2015). A systematic review and meta-analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. Clinical Nutrition, 34(5), 845-858.
- RF McLoughlin, et al. Short-chain fatty acids, prebiotics, synbiotics, and systemic inflammation: a systematic review and meta-analysis. AJCN. 2017
- Kellow NJ. (2014) Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. Br J Nutr. 111:1147–61.
- Liu F (2017). Effect of inulin-type fructans on blood lipid profiles and glucose level: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr 71(1):9-20
- Zhang et al (2020). Efficacy of inulin supplementation in improving insulin control, HbA1c and HOMA-IR in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. J Clin Biochem Nutr.
- Yurrita, L. C., Martín, I. S. M., Calle-Purón, M. E., & Cabria, M. H. (2014). Effectiveness of inulin intake on indicators of chronic constipation; a meta-analysis of controlled randomized clinical trials. Nutricion hospitalaria, 30(2), 244-252.
- Hill, C et al. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology.
- Clinical Guide to Probiotic Products 2023 (http://usprobioticguide.com/)
- Cunningham, M., Azcarate-Peril, M. A., Barnard, A., Benoit, V., Grimaldi, R., Guyonnet, D., ... & Gibson, G. R. (2021). Shaping the future of probiotics and prebiotics. Trends in microbiology, 29(8), 667-685. O'Toole PW, Marchesi J & Hill C (2017). *Nature Microbiology*
- Kaźmierczak-Siedlecka, K., Skonieczna-Żydecka, K., Hupp, T., Duchnowska, R., Marek-Trzonkowska, N., & Połom, K. (2022). Next-generation probiotics–do they open new therapeutic strategies for cancer patients?. Gut Microbes, 14(1), 2035659
- https://www.nccih.nih.gov/news/events/precision-probiotic-therapies-challenges-and-opportunities
- Le Roy T, Moens de Hase E, Van Hul M, et al. Dysosmobacter welbionis is a newly isolated human commensal bacterium preventing diet-induced obesity and metabolic disorders in mice. Gut 2022;71:534–543.
- *Jama, H. A., Rhys-Jones, D., Nakai, M., Yao, C. K., Climie, R. E., Sata, Y., ... & Marques, F. Z. (2023). Prebiotic intervention with HAMSAB in untreated essential hypertensive patients assessed in a phase II randomized trial. Nature Cardiovascular Research, 1-9.*
- *Zhao TX, et al. (2022). Long-term use of probiotics for the management of office and ambulatory blood pressure: A systematic review and meta-analysis of randomized, controlled trials. Food Science & Nutrition*