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Probiotik, *Gut Microbiota* dan Diabetes

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Disampaikan pada acara
Webinar Kedokteran Keluarga
Sabtu, 11 Desember 2021

PUIPT Probiotik
Pusat Studi Pangan dan Gizi UGM

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1 Pendahuluan

2 Makanan, *gut microbiota* dan kesehatan tubuh

3 Peran Probiotik dalam menangani T2D

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Status Diabetes di Indonesia

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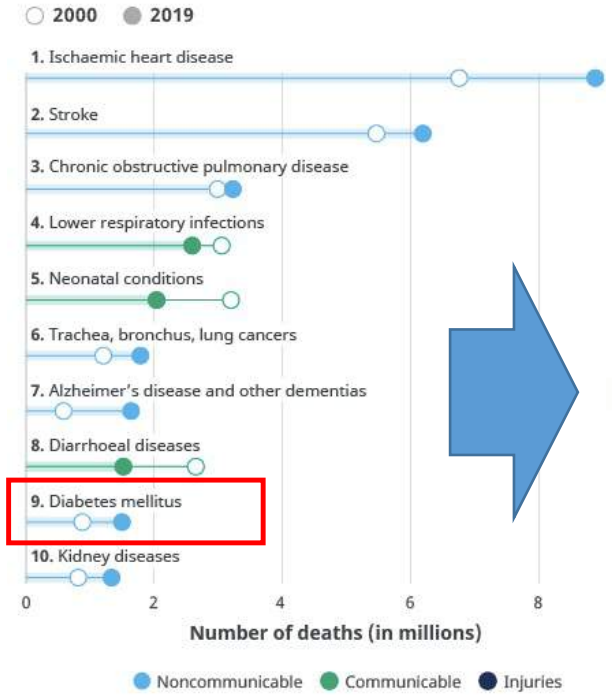
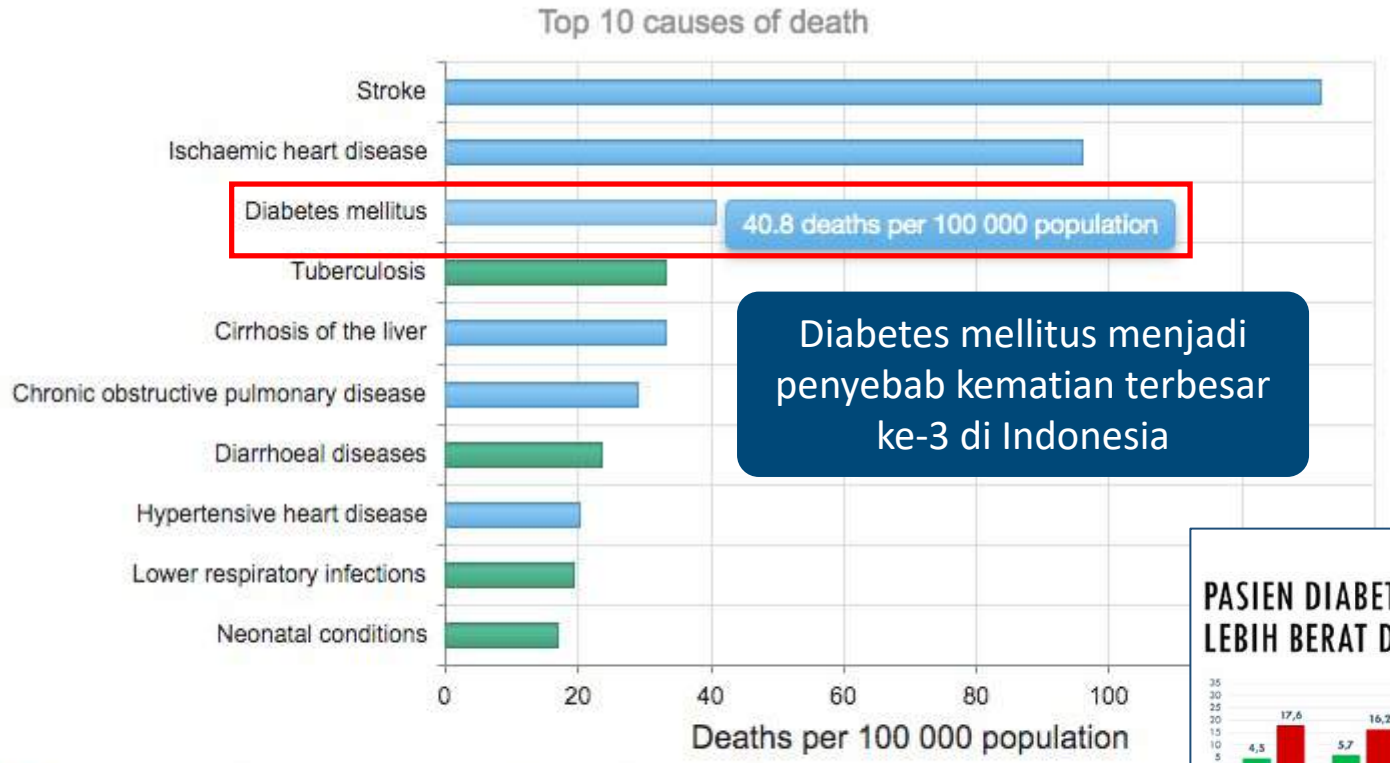
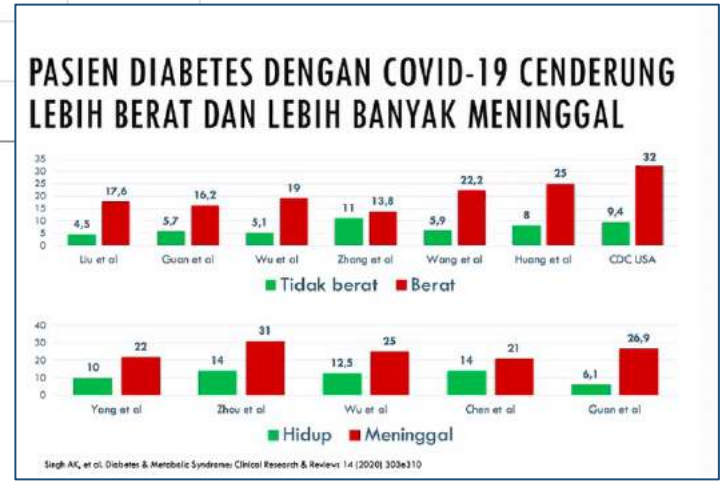




Diabetes mellitus menjadi penyebab kematian terbesar ke-3 di Indonesia

Sumber:
WHO Global Estimates

Diabetes mellitus menjadi penyebab kematian terbesar ke-9 di dunia



Di masa pandemi, pasien COVID-19 yang menderita Diabetes memiliki gejala yang lebih berat dan lebih banyak yang meninggal

Status Diabetes di Indonesia

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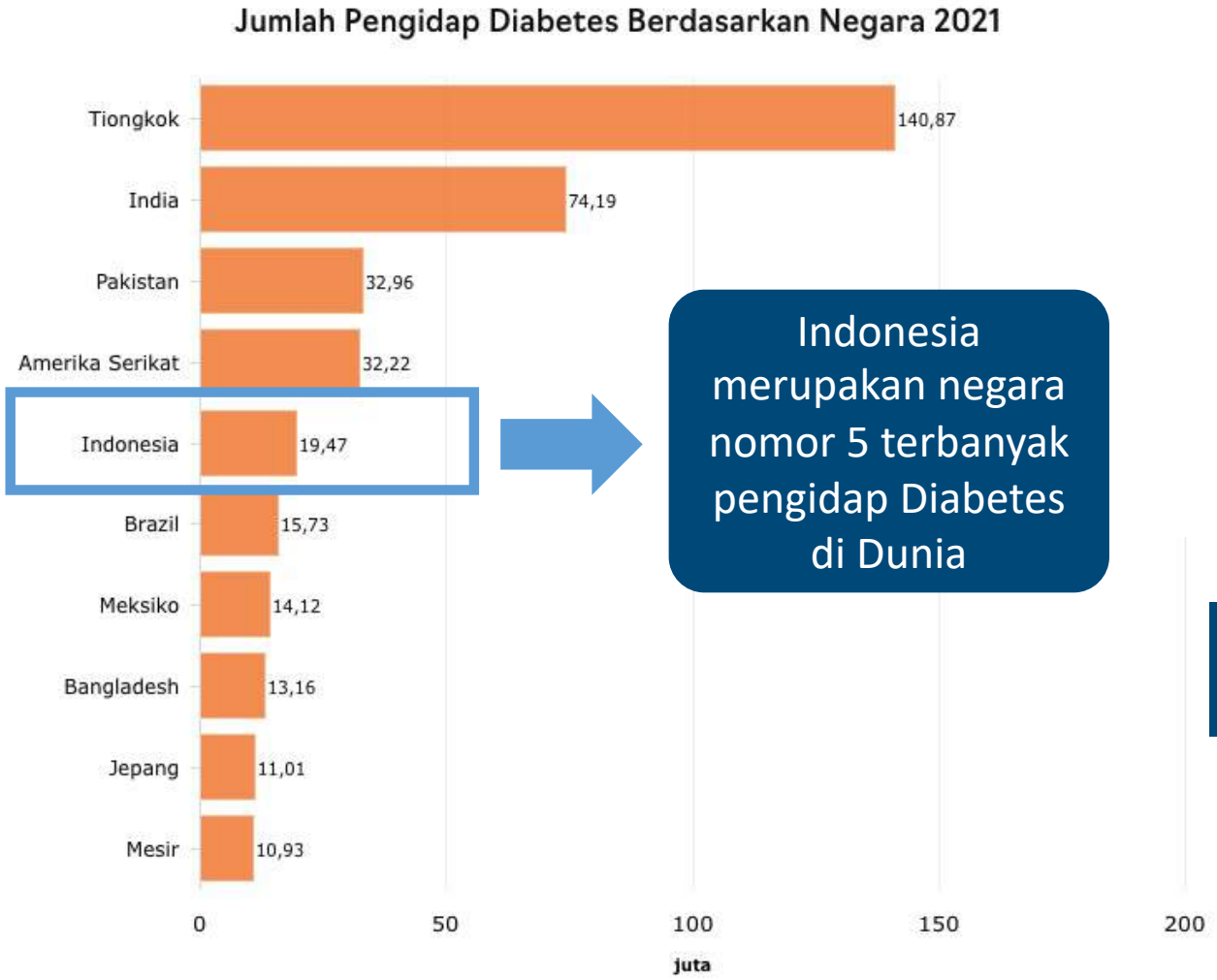
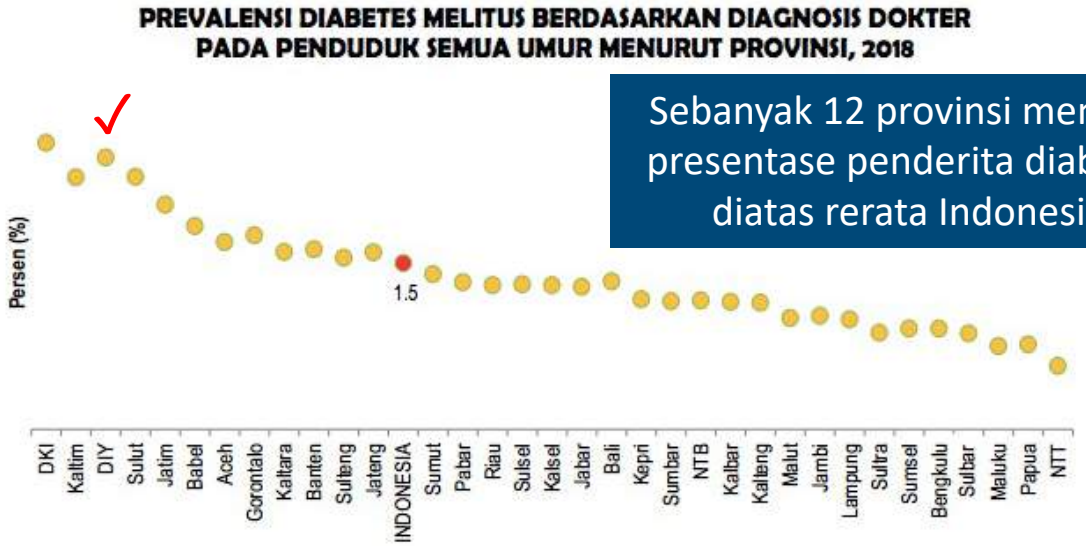
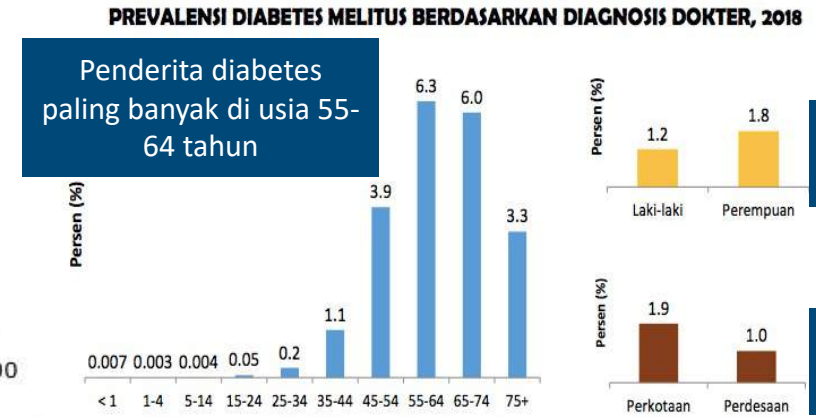


Indonesia merupakan negara nomor 5 terbanyak pengidap Diabetes di Dunia



Sebanyak 12 provinsi memiliki presentase penderita diabetes diatas rerata Indonesia

Riskesdas, 2018



Penderita diabetes paling banyak di usia 55-64 tahun

Diabetes lebih banyak terjadi pada wanita

Diabetes lebih banyak terjadi pada penduduk perkotaan

https://databoks.katadata.co.id/datapublish/2021/11/22/jumlah-penderita-diabetes-indonesia-terbesar-kelima-di-dunia

- *You are what you eat* (pepatah kuno Inggris)
- Gut dihuni oleh triliyunan mikroorganisme – *gut microbiota (gut microbiome)*
- *Superorganism* – individu bersama (*gut*) mikrobiotanya – terjadi interaksi antara sel manusia dan *gut microbiota* – bersymbiosis saling menguntungkan – normobiosis
- *Dysbiosis* – *gut microbiota* tidak seimbang – gangguan kesehatan
- Perkembangan *gut microbiota* – pola makan (yang paling utama), pola hidup, dll
- Apakah probiotik dapat membantu mengatasi dysbiosis?

"All disease begins in the gut"

Hippocrates (460-370BC)
Museum Rumah Atsiri

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2

Makanan, *gut microbiota* dan kesehatan tubuh

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Gut Microbiota – Superorganism:
Interaksi sel manusia dan *gut microbiota* – symbiosis saling menguntungkan – kondisi normobiosis – menguntungkan bagi kesehatan tubuh

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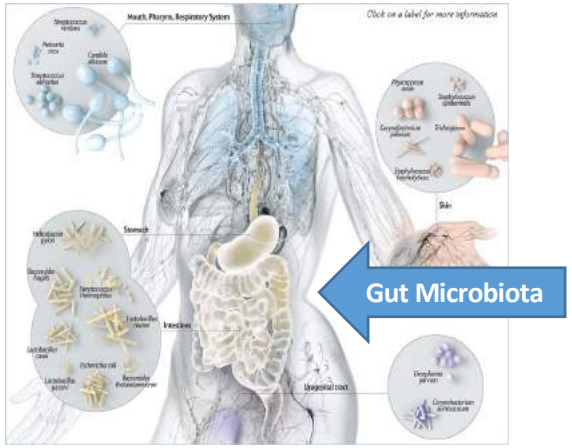
- ***Gut Microbiota***
- Komunitas yang kompleks dan dinamis
- Spesifik untuk masing-masing individu (lingkungan, pola makan, pola hidup dan faktor genetik)
- Jumlah > 1000 spesies (3000 – 4000)
- Jumlah 10 kali dari sel manusia (10^{14} sel)
- 10^{12} mikroorg/g content, total 10^{15}
- Gen mikroorganisme 10 – 100 kali gen manusia
- Beratnya mencapai 1,5 kg
- 60% berat feses adalah mikroorganisme



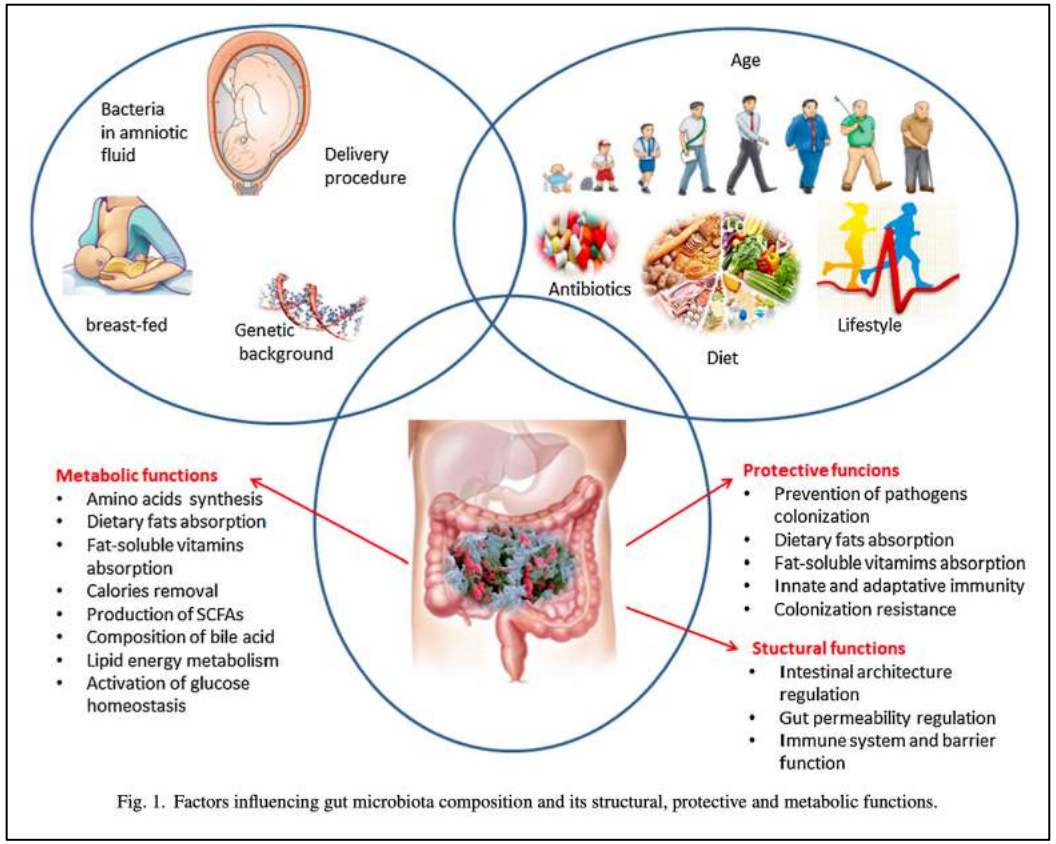


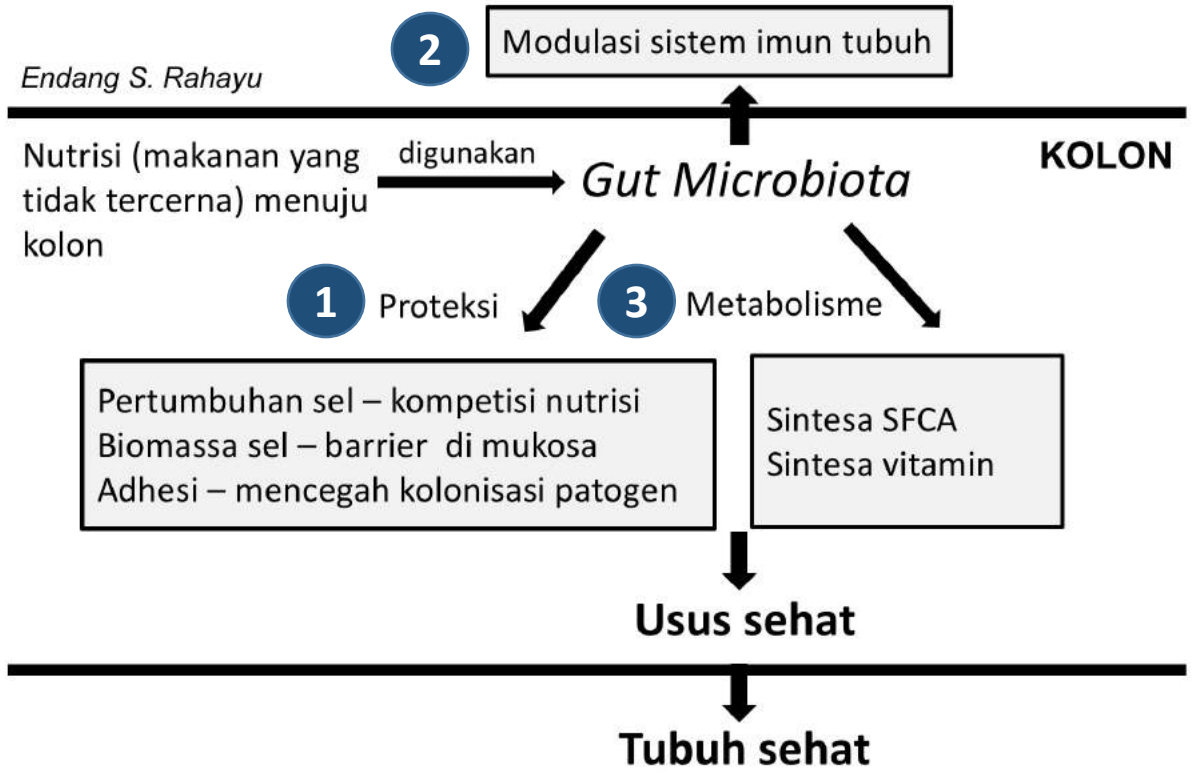
Fig. 1. Factors influencing gut microbiota composition and its structural, protective and metabolic functions.

Blandino G, et al. Impact of gut microbiota on diabetes mellitus. Diabetes Metab (2016), http://dx.doi.org/10.1016/j.diabet.2016.04.004

1. Fungsi protektif – pencegahan pertumbuhan patogen	2. Fungsi sistem imun	3. Fungsi enzimatis dan metabolit
• Kolonisasi probiotik • Kompetisi nutrisi • Kompetisi lokasi adhesi (penempelan pada sel epitel) • Memproduksi zat antimikrobia oleh probiotik (asam organik, hidrogen peroksida, bakteriosin) yang dapat menghambat patogen • Kemampuan menurunkan pH (produksi asam lemak rantai pendek/SCFA dan asam laktat) – menghambat patogen • Menstimulasi produksi musin epitel • Meningkatkan fungsi *barrier* (pertahanan) intestin	• Menstimulasi sistem imun • Menginduksi sekresi IgA • Meningkatkan aktivitas makrofag (fagositosis) • Memodulasi sitokin • Menginduksi *hiporesponsivenes* terhadap antigen makanan	• Memfermentasi sisa-sisa makanan (khususnya karbohidrat) yang tidak tercerna termasuk laktosa untuk yang *lactose intolerance* • Memproduksi SCFA (asam asetat, butirat, propionat) • Mensintesa vitamin (asam folat) • Menginaktivasi (mengikat) toksin • Memetabolisme kolesterol • Mengontrol penyerapan ion • Membersihkan radikal super oksida

Endand S Rahayu dan Tyas Utami 2019

Mekanisme probiotik dalam kesehatan tubuh



Gut Microbiota – Indonesian/Asian

- Diversity in gut bacterial community of **school-age** children in Asia https://www.nature.com/articles/srep08397
- Gut microbiota profile in **healthy Indonesians** https://pubmed.ncbi.nlm.nih.gov/30948911/
- Indonesian children fecal microbiome from **birth until weaning** was different from microbiomes of their mothers https://www.tandfonline.com/doi/full/10.1080/19490976.2020.1761240
- The Species-Level Composition of the Fecal ***Bifidobacterium* and *Lactobacillus*** Genera in Indonesian Children Differs from That of Their Mothers. https://www.mdpi.com/2076-2607/9/9/1995
- Gut Microbiota and Short-Chain Fatty Acid Profile between Normal and Moderate **Malnutrition Children** in Yogyakarta, Indonesia https://www.mdpi.com/2076-2607/9/1/127
- Gut Microbiome of Indonesian Adults Associated with **Obesity and Type 2** Diabetes: A Cross-Sectional Study in an Asian City, Yogyakarta https://www.mdpi.com/2076-2607/9/5/897
- Effect of probiotic *Lactobacillus plantarum* Dad-13 powder consumption on the gut microbiota and intestinal health of **overweight adults** https://www.wjgnet.com/1007-9327/full/v27/i1/107.htm?s=qc
- (AMP, Asian Microbiome Projects and ESR & team)

- *Gut microbiota* bayi ASI didominasi oleh *Bifidobacterium* dan *Lactobacillus* (berbeda dengan *gut microbiota* ibu)
- Setelah disapih dan mulai makan MPASI, gut microbiota bayi seperti ibu
- Enterotype untuk orang Indonesia mulai dari anak-anak s/d usia lanjut adalah Prevotella enterotype (karbohidrat nabati)
- Pada lanjut usia Bifidobacteriaceae menurun dan Enterobacteriaceae meningkat – perlu mendapat perhatian.
- Gut microbiota pada individu *overweight* dan diabetes tipe 2 berbeda dengan individu normal – perlu mendapat perhatian

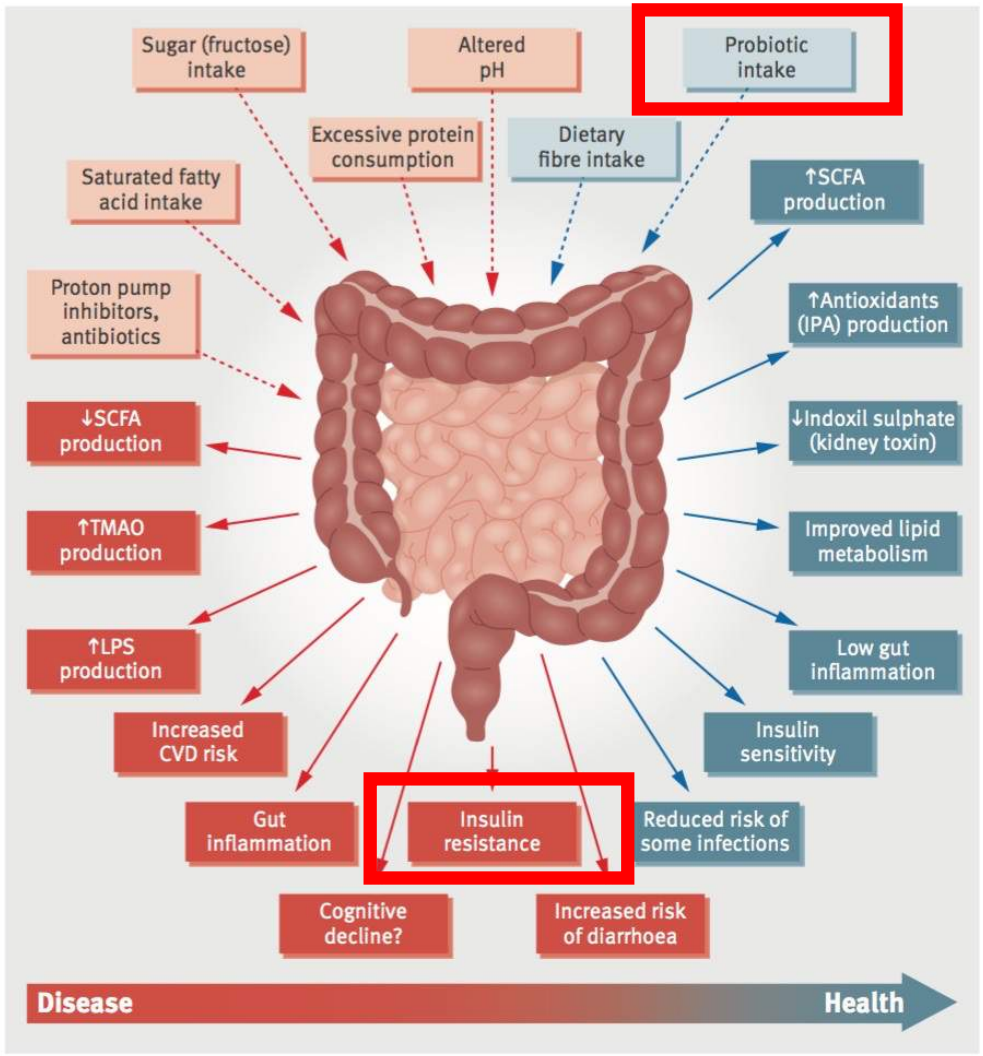


Fig 1 | Schematic representation of the role of the gut microbiota in health and disease giving some examples of inputs and outputs. CVD=cardiovascular disease; IPA=indolepropionic acid; LPS=lipopolysaccharide; SCFA=short chain fatty acids; TMAO=trimethylamine N-oxide

BMJ 361:Suppl | the bmj

SCIENCE AND POLITICS OF NUTRITION

Role of the gut microbiota in nutrition and health

Ana M Valdes and colleagues discuss strategies for modulating the gut microbiota through diet and probiotics

KEY MESSAGES

- Gut microbiota influences many areas of human health from innate immunity to appetite and energy metabolism
- Targeting the gut microbiome, with probiotics or dietary fibre, benefits human health and could potentially reduce obesity
- Drugs, food ingredients, antibiotics, and pesticides could all have adverse effects on the gut microbiota
- Microbiota should be considered a key aspect in nutrition; the medical community should adapt their education and public health messages
- Fibre consumption is associated with beneficial effects in several contexts

- Faktor yang berpengaruh pada DYSBIOSIS (merah), al: konsumsi protein yang berlebihan, lemak jenuh, kenaikan pH lambung, dll Dampaknya, al: produksi SCFA menurun, terjadi inflamasi dll.
- Konsumsi PROBIOTIK dan SERAT dapat menuju ke KESEIMBANGAN *GUT MICROBIOTA* dan mendukung tubuh yang sehat (warna biru-hijau muda)
- Paper ini juga menekankan peran *gut microbiota* untuk mendukung kesehatan tubuh dan perlu disosialisasikan juga ke masyarakat

Dysbiosis

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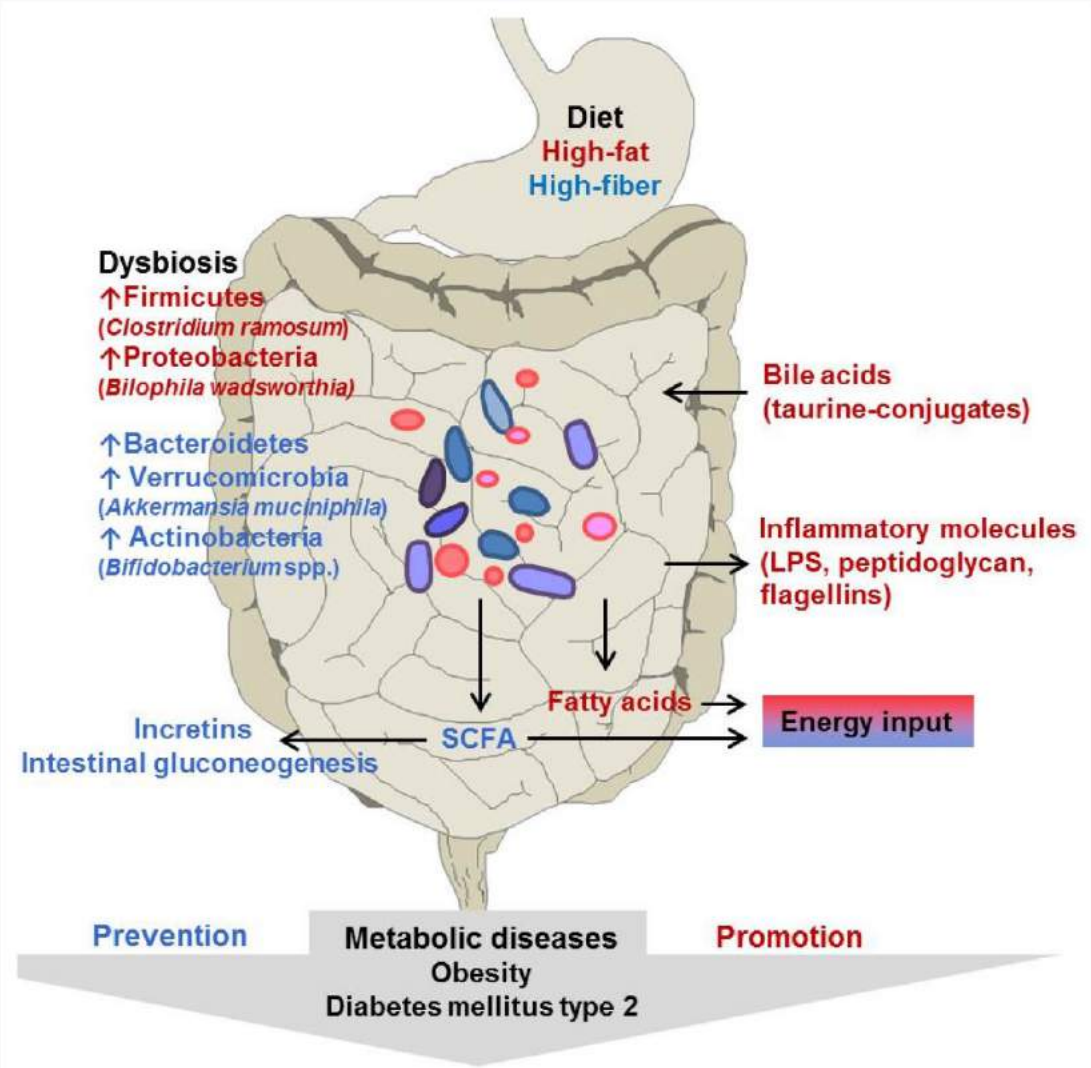
Figure 1. Hypothetical interplay between diet, gut microbiota and host in prevention and promotion of metabolic diseases. Consequences of high-fat diets and fiber-rich diets are indicated in red and in blue, respectively.



Diet memiliki peran penting di dalam perkembangan *gut microbiota*
*Tinggi serat – mendukung *gut microbiota* yang seimbang (warna biru)
Bacteroidetes lebih tinggi (catatan: Indonesia *Prevotella enterotype* didukung oleh diet karbohidrat nabati)
Diversity in gut bacterial community of school-age children in Asia
https://www.nature.com/articles/srep08397
Gut microbiota profile in healthy Indonesians
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6441913/
Akkermansia muciniphila dan *Bifidobacterium* sebagai bakteri baik meningkat
SCFA meningkat – **inkretin** meningkat - usus sehat
Inkretin adalah hormone yang menjadi stimulator sekresi hormone insulin

*Tinggi lemak – *Firmicutes & Proteobacteria* meningkat;
molekul penyebab inflamasi (LPS, peptidoglikan, flegelin) meningkat

nutrients
2016

MDPI

Review

The Intestinal Microbiota in Metabolic Disease

Anni Woting * and Michael Blaut

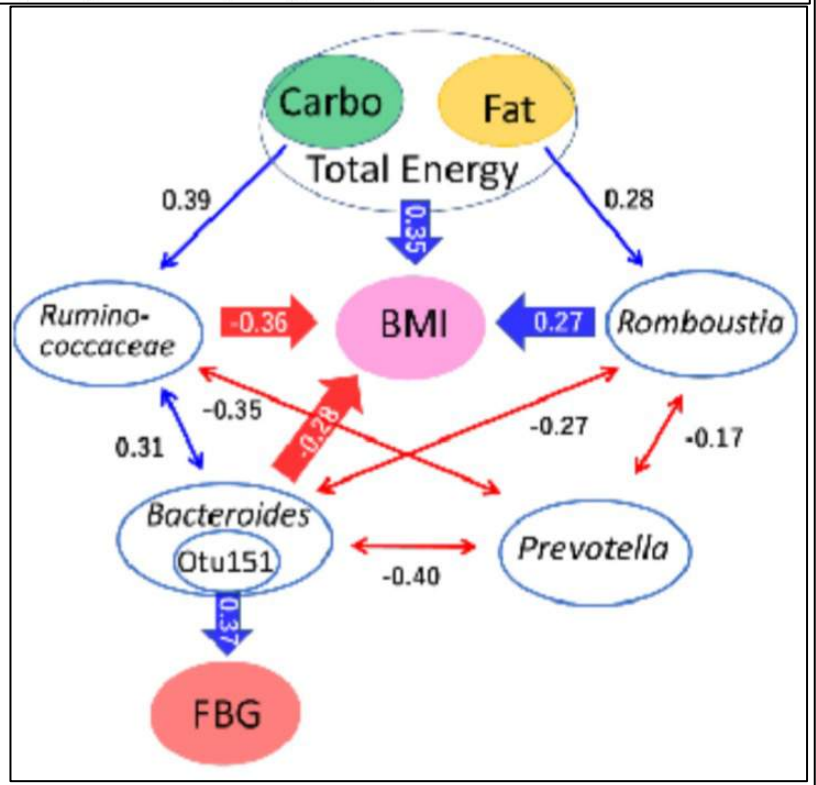
Gut Microbiota pada obesitas dan diabetes type-2: Terjadi DYSBIOSIS

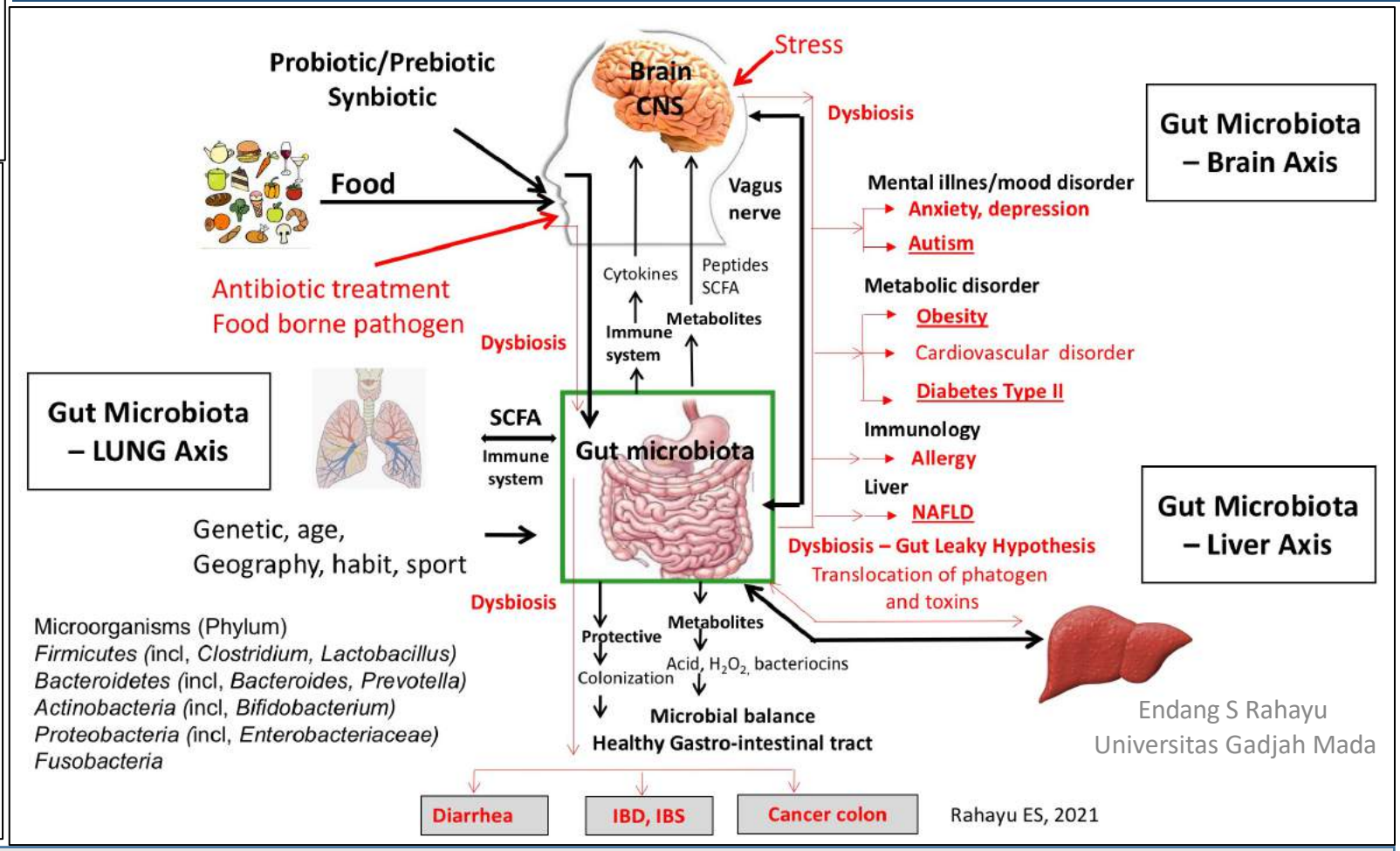
microorganisms MDPI

Article

Gut Microbiome of Indonesian Adults Associated with Obesity and Type 2 Diabetes: A Cross-Sectional Study in an Asian City, Yogyakarta

Phatthanaphong Therdtatha [1], Yayi Song [1], Masaru Tanaka [1], Mariyatun Mariyatun [2], Maisaroh Almunifah [2], Nancy Eka Putri Manurung [2], Siska Indriarsih [2], Yi Lu [3], Koji Nagata [3], Katsuya Fukami [4], Tetsuo Ikeda [5,6], Yuan-Kun Lee [7], Endang Sutriswati Rahayu [2] and Jiro Nakayama [1,*]





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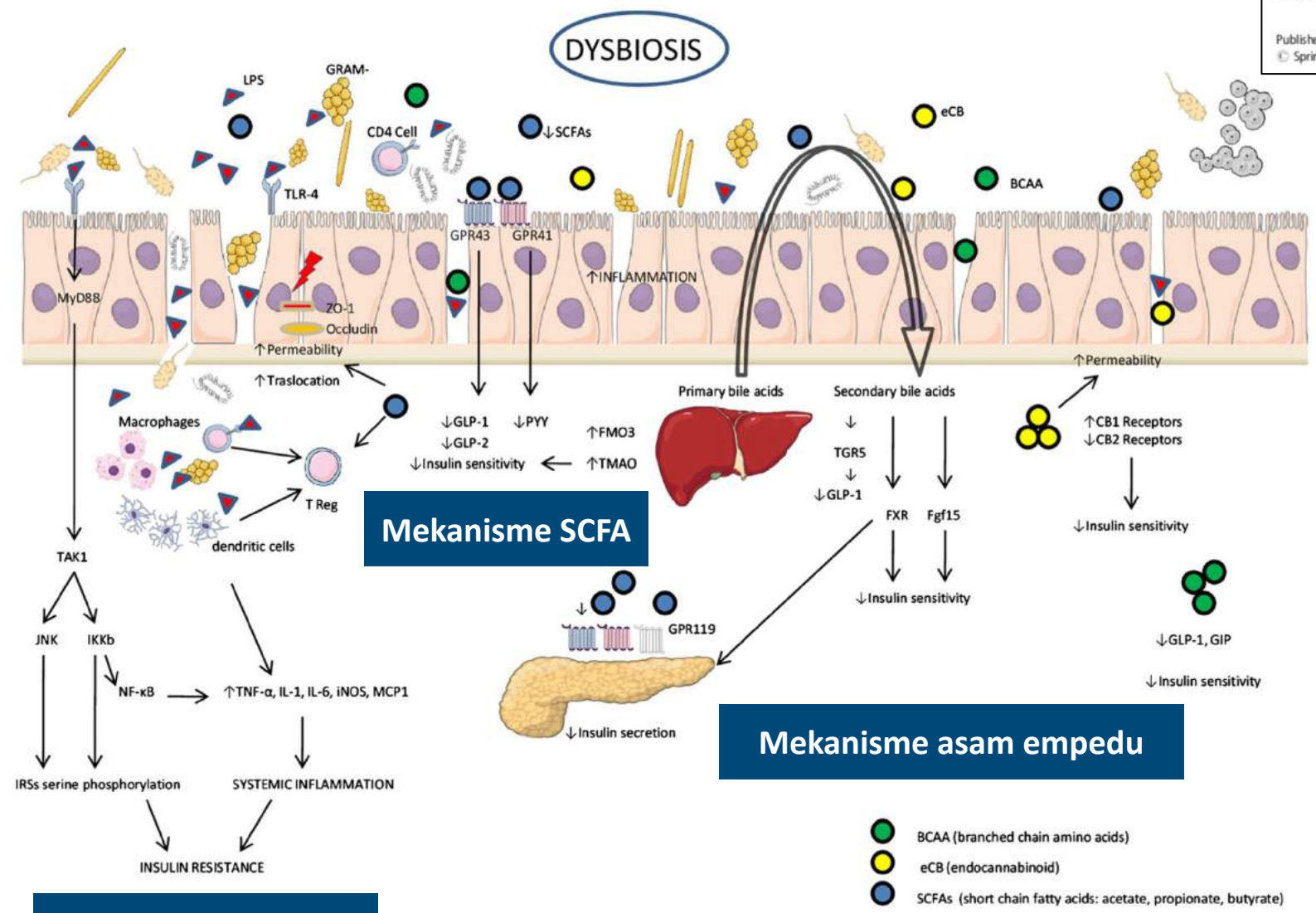
Diabetes Tipe 2, *Bacteroides* dan *Ruminococcaceae* secara bersamaan meningkat berkolerasi diet tinggi karbohidrat. Terjadi **DYSBIOSIS**

Mekanisme Gut Mikrobiota pada Resistensi Insulin



Altered Gut Microbiota in Type 2 Diabetes: Just a Coincidence?

Antonio Sircana[1] · Luciana Framarin[2] · Nicola Leone[2] · Mara Berrutti[2] · Francesca Castellino[2] · Renato Parente[2] · Franco De Michieli[3] · Elena Paschetta[2] · Giovanni Musso[2]

Published online: 13 September 2018

Mekanisme – dampak disbysis terhadap sekresi insulin

1. Terjadi inflamasi sistemik sel epitel yang berakibat pada resistensi insulen
2. Sintesa SCFA menurun berakibat pada penurunan sensitivitas insulin
3. Jalur metabolism bile acid – bile acid yang tidak terserap ke hati, digunakan oleh mo usus menjadi BA primer dan sekunder yang mempengaruhi sekresi insulin
4. BA sekunder dapat menstimulasi sekresi GLP-1 melalui TGR5 memodulasi ekspresei FXR dan pertumbuhan figroblast factor (fgfl5) yang mengatur metabolism glukosa dan sensitivitas insulin.
5. BCAA yang tinggi berasosiasi dengan peningkatan risiko T2D

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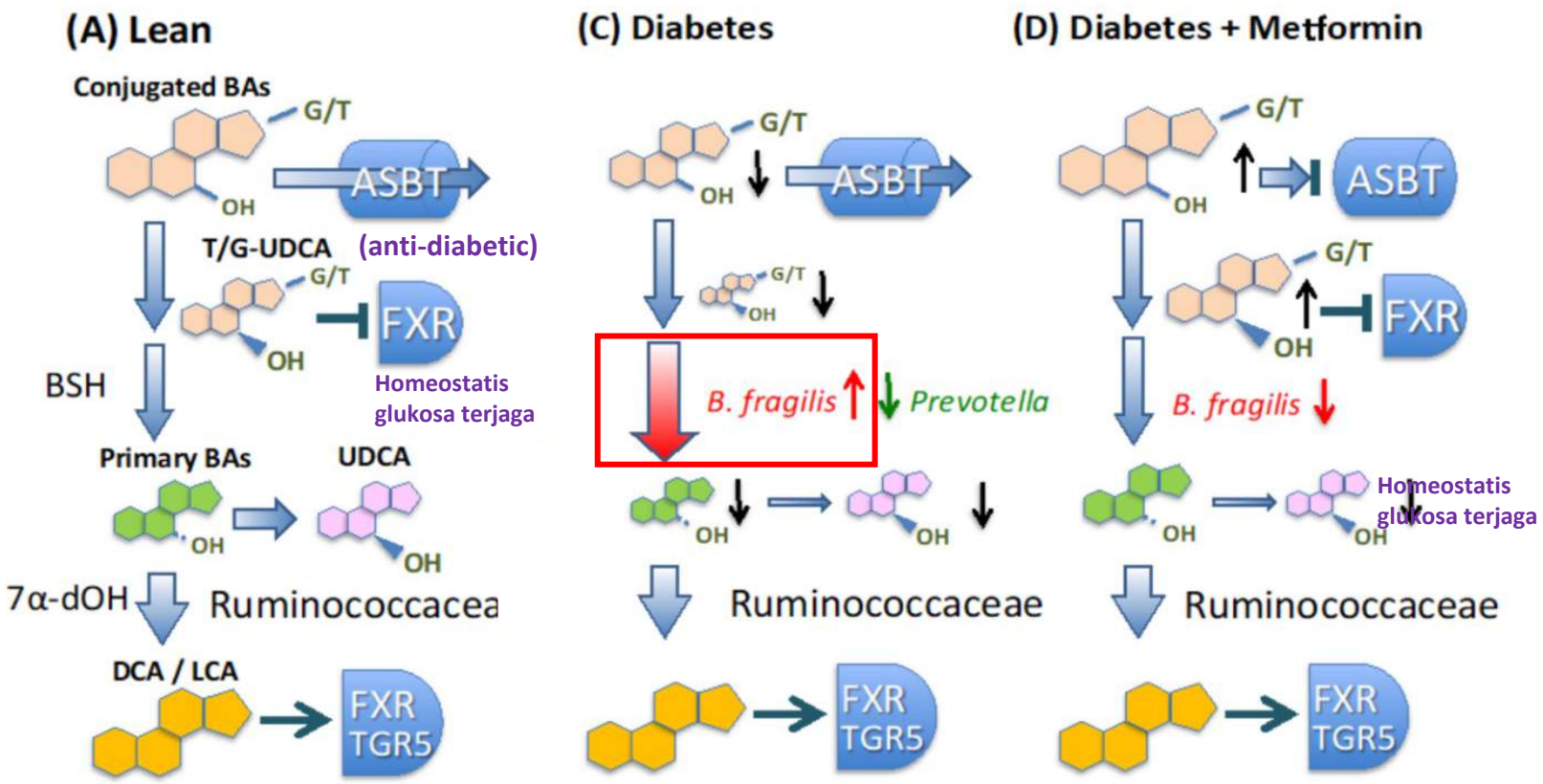
Article

Gut Microbiome of Indonesian Adults Associated with Obesity and Type 2 Diabetes: A Cross-Sectional Study in an Asian City, Yogyakarta



Indonesia memiliki enterotype *Prevotella*, namun pada pasien T2D *Bacteroides (fragilis)* meningkat. Level *Bacteroides* yang tinggi dapat meningkatkan level LPS pada darah – menyebabkan sensitivtas insulin menurun

BA terkonjugasi yang disekresikan dalam usus bagian atas diserap kembali ke dalam hati melalui ASBT (Apical Sodium Bile Salt Transporter)
Yang tidak terserap T/G-UDCA berkontribusi pada homeostatis glukosa melalui penghambatan antagonis signal FXR (berfungsi sebagai anti-diabetik)
BA yang tidak terserap di-dekonjugasi oleh bakteri hidroksilase.
Pada pasien diabet – terjadi dysbiosis, *Bacteroides fragilis* meningkat disertainya dengan turunnya T/G-UDCA sehingga homeostatis glukosa terganggu

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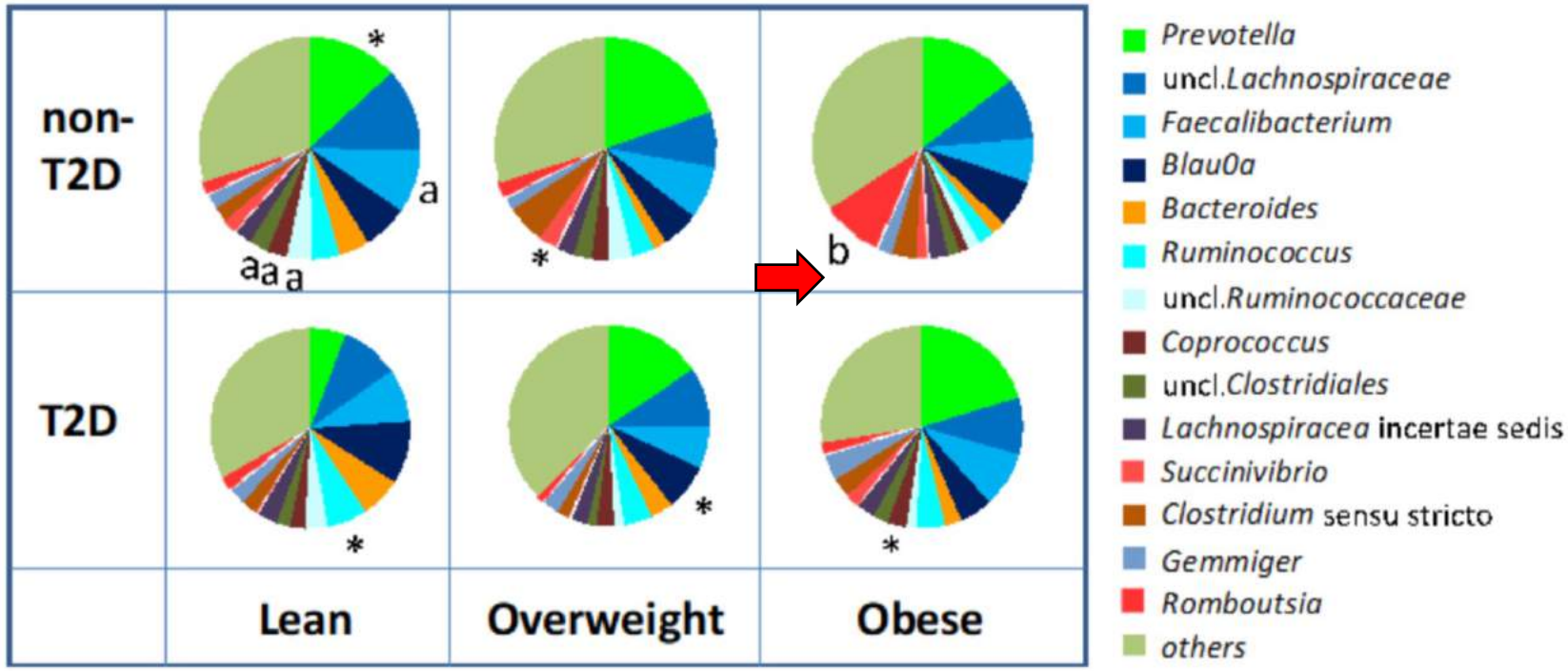
microorganisms

MDPI

Article

Gut Microbiome of Indonesian Adults Associated with Obesity and Type 2 Diabetes: A Cross-Sectional Study in an Asian City, Yogyakarta

Phatthanaphong Therdtatha [1], Yayi Song [1], Masaru Tanaka [1], Mariyatun Mariyatun [2], Maisaroh Almunifah [2], Nancy Eka Putri Manurung [2], Siska Indriarsih [2], Yi Lu [3], Koji Nagata [3], Katsuya Fukami [4], Tetsuo Ikeda [5,6], Yuan-Kun Lee [7], Endang Sutriswati Rahayu [2] and Jiro Nakayama [1,*]



Microorganisms **2021**, *9*, 897. https://doi.org/10.3390/microorganisms9050897

Terdapat perbedaan komposisi (Keragaman) *gut microbiota*, pada Individu NORMAL dengan

Berat normal + diabet type 2
Over weight
Overweight + diabet type 2
Obese – muncul *Romboutsia*
Obese + diabet type 2

Diperkirakan terjadi *Dysbiosis*

Modulasi *Gut Microbiota* dengan PROBIOTIK? – menuju proporsi normal *gut microbiota*

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Peran Probiotik dalam menangani T2D

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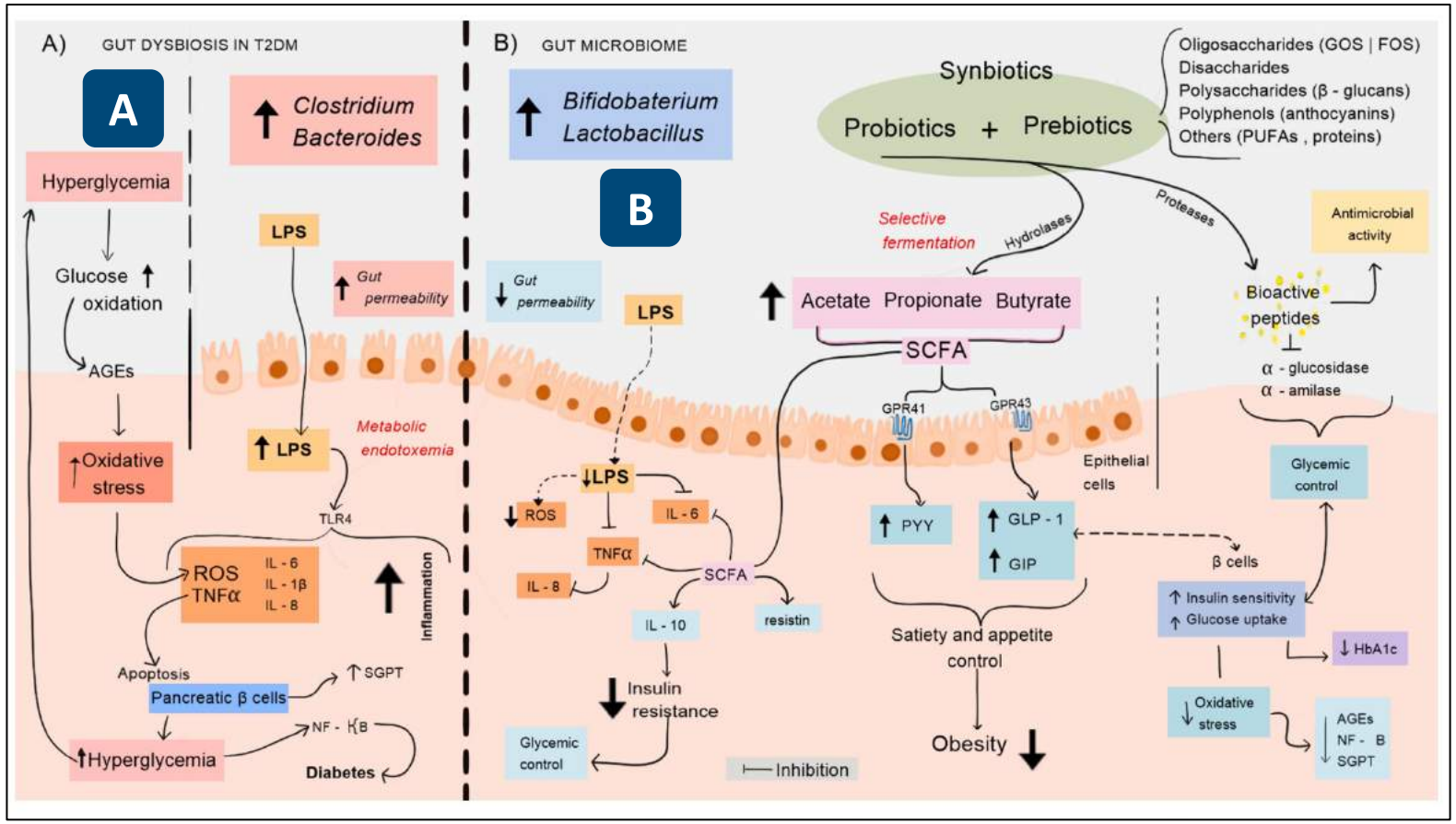
DISBIOSIS dan Peran Probiotik



Probiotics, prebiotics, and synbiotics added to dairy products: Uses and applications to manage type 2 diabetes

Andrea Zepeda-Hernández [a], Luis Eduardo Garcia-Amezquita [a], Teresa Requena [b], Tomás García-Cayuela [a,*]

[a] Tecnologico de Monterrey, Escuela de Ingeniería y Ciencias, Ave. General Ramón Corona 2514, 45138 Zapopan, Jalisco, Mexico
[b] Department of Food Biotechnology and Microbiology. Institute of Food Science Research, CIAL (CSIC), Madrid, Spain

A

DISBIOSIS -> *Clostridium* dan *Bacteroides* meningkat -> **permeabilitas usus meningkat** -> memicu **peningkatan jumlah LPS** -> menyebabkan respon *inflammatory,* kematian sel (apoptosis) dan **hiperglikemik** -> **DIABETES**

B **Peningkatan *Bifidobacterium* dan *Lactobacillus*** -> Memberikan Efek Positif (Pemberian PROBIOTIK)

- Mengurangi stress oksidatif
- Menghambat *pro-inflammatory* sitokin
- Meningkatkan produksi SCFA
- Kontrol glikemik

- Memodulasi permeabilitas saluran pencenaan
- Memproduksi peptide bioaktif -> memberikan efek antimikroorganisme, menghambat aktivitas amilase dan glucosidase – sensitivitas insulin naik

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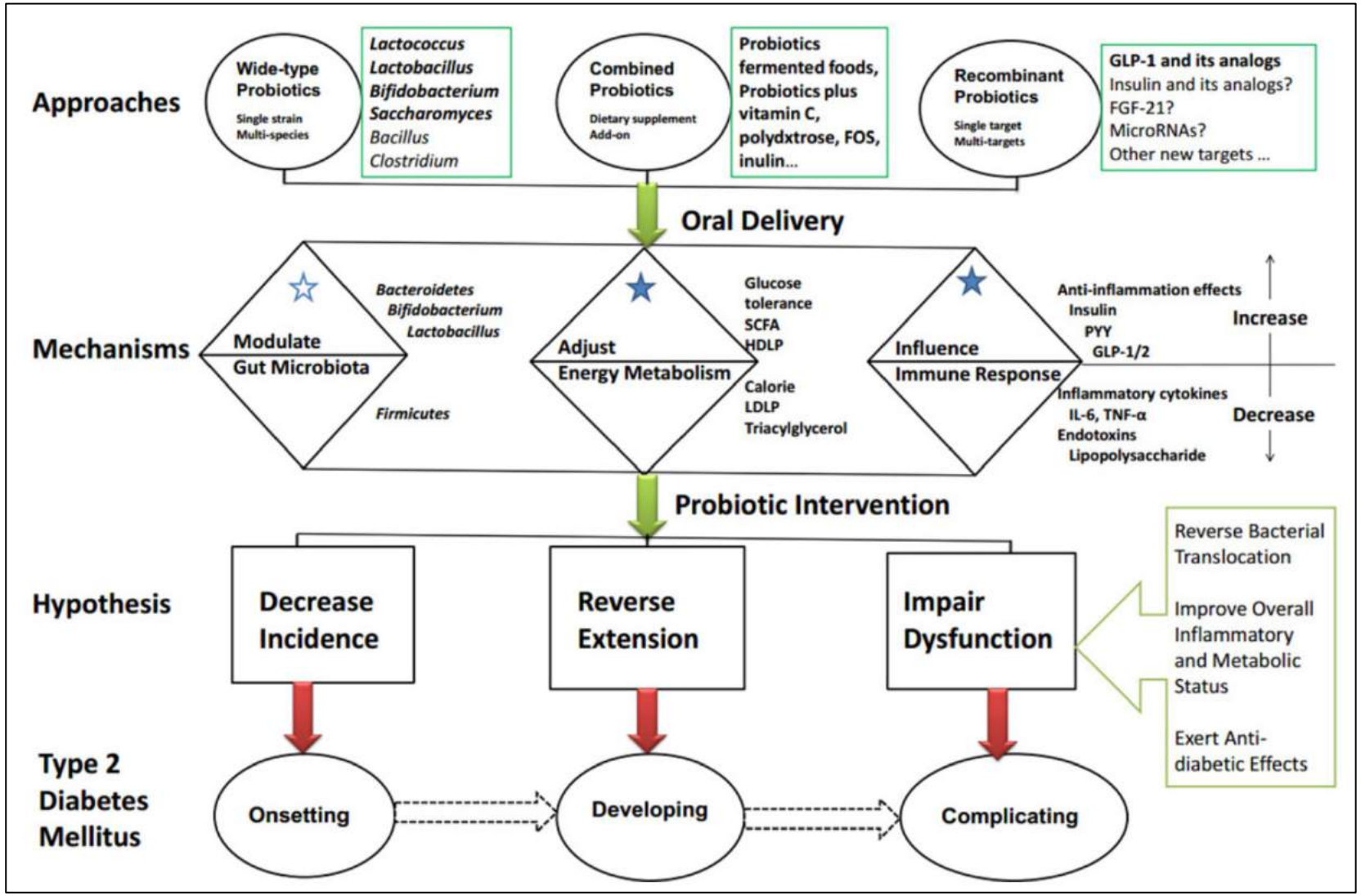
Diabetes - Intervensi menggunakan Probiotik



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Using probiotics for type 2 diabetes mellitus intervention: Advances, questions, and potential.

Zhongke Sun et al., Critical Reviews In Food Science And Nutrition
https://doi.org/10.1080/10408398.2018.1547268

- Probiotik yang ditambahkan bisa dalam bentuk *single strain, multiple strains* atau dikombinasikan dengan makanan. Umumnya : *Lactococcus, Lactobacillus* dan *Bifidobacterium.*
- Mekanisme: modulasi *gut microbiota* (meningkatkan bakteri baik); pengaturan metabolism energi (meningkatkan toleransi glukosa, SCFA, dll); serta melalui imun respon (anti inflammatory – meningkatkan insulin
- Hipotesis intervensi probiotik dapat menurunkan kasus, menunda dan menghambat/mencegah onset, pengembangan, dan komplikasi DMT2.

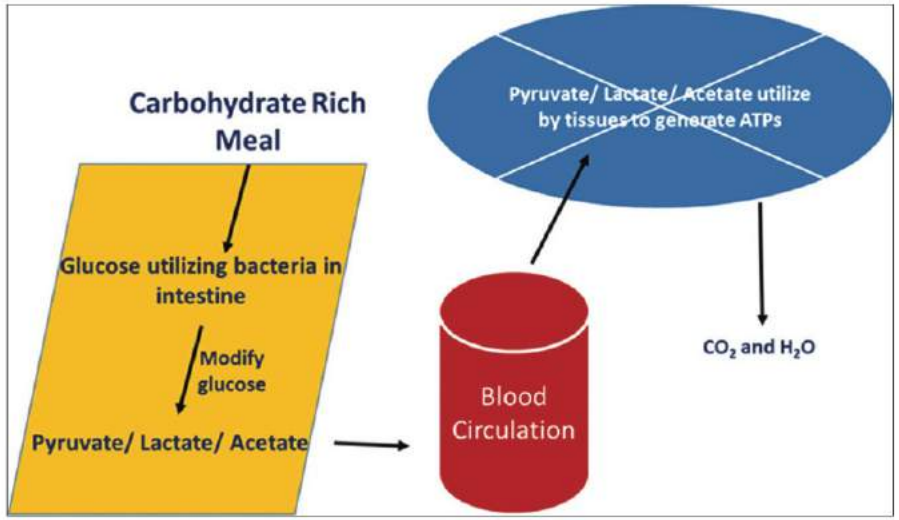

Figure 1: Effect of gut microbiota on carbohydrate digestion, absorption, and metabolism

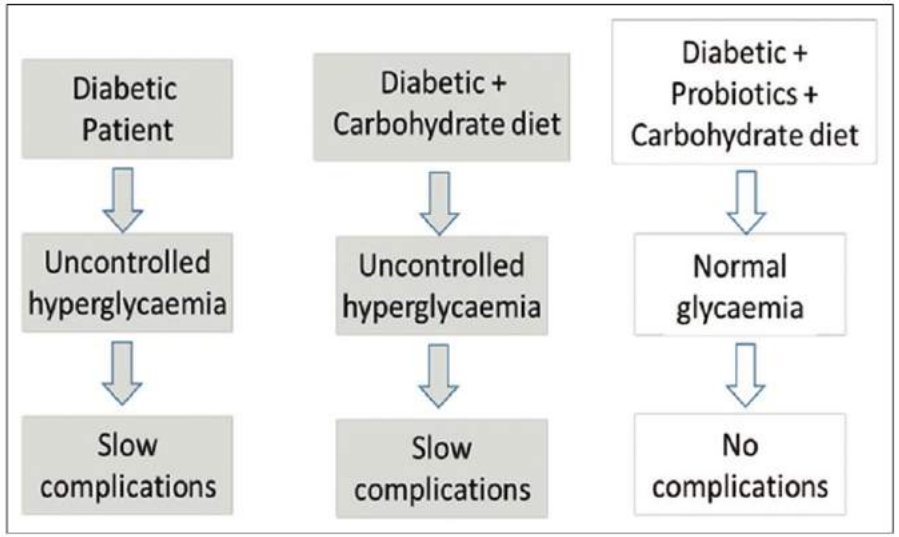

Figure 2: Model for management of hyperglycaemia in diabetes

Target : mengkontrol hiperglikemia dengan membatasi absorbsi glukosa dalam usus dengan menambahkan mikroorganisme pemecah KH (glukosa) secara anaerobic menghasilkan piruvat, asam laktat, asetat yang selanjutnya disirkulasikan oleh darah

Probiotics- A new diabetes management tool

Rajesh Prasad Jayaswal[1], Pranav Kumar Prabhakar[2]

[1]Department of Medical Laboratory Technology, Amity University, Gurgaon, Haryana, India, [2]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, Lovely Professional University, Phagwara, Punjab, India

Abstract

Diabetes mellitus is commonly known worldwide by the name of diabetes which occurs in all age groups. About >90% of diagnosed patient specially are Type-2 diabetes. The hallmark of Type 2 diabetes developments is increased insulin resistance, whereas Type 1 is related to less production of insulin which leads to uncontrolled hyperglycemia. Hyperglycemia slowly produces mild-to-very serious complications in patient mainly affecting vital organs such as blood vessels, eyes, neurons, nephrons, heart, and brain which increase the risk of heart attack, retinopathy, nephropathy, neuropathy, and stroke. Proper management of hyperglycemia is a key to prevent from diabetes and its complications. This concept has attracted many researchers to target various cells and tissue through special remedy so that hyperglycemia can be managed and complications can be reduced. The patient shows numerous side effects during therapy. There is craving demand for the proper cure of diabetes by sufferers. In this aspect, probiotics can be more helpful if proper research and formulation are done. Probiotics are good microorganism which can control hyperglycemia and its complications by utilizing and modifying glucose before absorption. Appropriate research is required to make strategy for searching and formulating good microorganism to be used as probiotics for the regulation of blood glucose and prevention from complexity.

Key words: Diabetes, hypeglycemia, nephropathy, neuropathy, probiotics, retinopathy

Current Diabetes Reports (2018) 18: 98
https://doi.org/10.1007/s11892-018-1057-6

PATHOGENESIS OF TYPE 2 DIABETES AND INSULIN RESISTANCE (M-E PATTI, SECTION EDITOR)

Altered Gut Microbiota in Type 2 Diabetes: Just a Coincidence?

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Penelitian intervensi powder probiotik dan makanan probiotik pada manusia, menggunakan strain spesifik (Tabel 1).
Beberapa hasil penting:
Pada umumnya memberikan efek positif dan tidak memberikan efek negatif
Ivey dkk., intervensi kapsul berisi *L. acidophilus* La5 dan *B. animalis* subsp. *lactis* Bb12, selama 6 minggu oleh subjek yang kelebihan berat badan – tidak berpengaruh pada parameter glikemik.
Intervensi *L. reuteri* SD5865, selama 4 minggu; terdapat peningkatan GLP-1 dan sekresi insulin, namun tanpa perubahan sensitivitas insulin.
Intervensi *Lactobacillus reuteri* DSM 17938 selama 12 minggu pada pasien dengan T2D pada terapi insulin: terjadi peningkatan sensitivitas insulin dalam subkelompok tetapi tidak mempengaruhi kontrol glikemik keseluruhan yang diukur dengan HbA1c.
Probiotik dapat memiliki efek menguntungkan pada kontrol glikemik pasien T2D, tetapi efek pada HbA1c, manfaat anti-inflamasi dan anti-oksidatif tidak konsisten.
Masih perlu dilakukan data yang lebih banyak

Table 1 Overview of randomized clinical trials performed to evaluate the effects of probiotic strains

Probiotic	Source	Patient	Duration of treatment (weeks)	Sample size (intervention/control)	Positive effects	Negative or no effects(≡)	References
Lactobacillus acidophilus NCFM	Capsules	T2D	4	21/24	Preserved insulin sensitivity	≡Inflammatory markers	Andreasen et al. [76]
L. acidophilus La5 and *Bifidumbacterium lactis* Bb12	Probiotic or conventional yogurt	T2D	6	30/30	↓FBG and HbA1c ↓ antioxidant status	≡Insulin concentration and erythrocyte catalase activity	Ejtahed et al. [77]
L. acidophilus, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, and *Streptococcus thermophilus*	Capsules	T2D	8	27/27	Prevented rise in FBG ↓hs-CRP ↑GSH	↑Serum insulin ↑HOMA IR (but lower than that in the placebo group)	Asemi et al. [78]
L. acidophilus, *L. bulgaricus*, *L. bifidum*, and *L. casei*	Capsules	T2D	6	16/18	↓MDA, IL-6 and HOMA IR (not statistically significant)	≡FBS ↑ hs-CRP (not statistically significant)	Mazloom et al. [79]
L. acidophilus La5, *B.animalis* subsp. *lactis* Bb12	Probiotic yogurt ± probiotic capsule; control milk ± probiotic capsule	Overweight subject	6	Yogurt 40/37 Milk 39/40		↑HOMA-IR ↑FBG ≡Fasting insulin and HbA1c	Ivey et al. [80]
L. casei, *L. acidophilus*, *B. lactis*	600 mL/day probiotic fermented milk (kefir) vs. conventionally fermented milk	T2D	8	30/30	↓FBG, HbA1c		Ostadrahimi et al. [81]
L. reuteri SD5865	Capsules	Glucose-tolerant humans	4	11/10	↑GLP-1, GLP-2 release ↑Insulin and C-peptide secretion	≡Peripheral and hepatic insulin sensitivity ≡Circulating cytokines	Simon et al. [82]
L. acidophilus, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum*, and *B. infantis*	Powder	T2D	12	68/68	↓HbA1c and fasting insulin ↓HOMA IR	≡hs-CRP	Firouzi et al. [83]
L. reuteri DSM 17938	Powder	T2D	12	29/15	↑ISI and DCA (in subgroup with higher microbial diversity at baseline)	≡HbA1c	Mobini et al. [84]
L. acidophilus La5 and *B. animalis* subsp. *lactis* BB-12	Probiotic fermented milk vs. conventional fermented milk	T2D	6	25/25	↓HbA1c and fructosamin levels ↓TNF-α and resistin	≡IL-10 ↑Acetic acid	Tonucci et al. [85]
Lactobacillus planetarum A7	Probiotic soy milk	T2D	8	20/20	↓LDL ↑HDL	≡FBG, adiponectin, TNF-α and hs-CRP	Feizollahzadeh et al [86]
Lactobacillus casei	Capsules	T2D	8	20/20	↓FBG, insulin, HOMA-IR ↑SIRT1; ↓fetuin-A ↓HbA1c (not significant)		Khalili et al. [87]
14 probiotic bacteria genera *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, *Propionibacterium*	Sachet formulation	T2D	8	31/22	↓HOMA-IR, HbA1c (only in probiotic responders) ↓TNF-α, IL-1β, IL-6	≡BFG, IL-8, γ-INF	Kobyliak et al. [88]

FBG fasting blood glucose, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostasis model of assessment-insulin resistance, *hs-CRP* high-sensitivity C-reactive protein, *MDA* malondialdehyde, *GSH* glutathione, *ISI* insulin sensitivity index, *DCA* secondary bile acid deoxycholic acid, *LDL* low-density cholesterol, *HDL* high-density cholesterol, *SIRT1* sirtuin 1

Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials

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Probiotics have been reported to have a positive impact on the metabolic control of patients with type 2 diabetes. We aimed to systematically evaluate the effects of probiotics on cardiometabolic parameters in type 2 diabetes based on randomized controlled studies. MEDLINE, Embase, and CENTRAL databases were reviewed to search for randomized controlled trials that examined the effects of probiotic supplementation on cardiometabolic parameters in patients with type 2 diabetes. 32 trials provided results suitable to be included in the analysis. The effects of probiotics were calculated for the following parameters: BMI, total cholesterol levels, LDL, triglycerides, HDL, CRP, HbA1c levels, fasting plasma glucose, fasting insulin levels, systolic and diastolic blood pressure values. Data analysis showed a significant effect of probiotics on reducing total cholesterol, triglyceride levels, CRP, HbA1c, fasting plasma glucose, fasting insulin levels, and both systolic and diastolic blood pressure values. Supplementation with probiotics increased HDL levels however did not have a significant effect on BMI or LDL levels. Our data clearly suggest that probiotics could be a supplementary therapeutic approach in type 2 diabetes mellitus patients to improve dyslipidemia and to promote better metabolic control. According to our analysis, probiotic supplementation is beneficial in type 2 diabetes mellitus.

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- Probiotik memiliki dampak positif pada kontrol metabolik pasien dengan diabetes tipe 2.
- Telah dilakukan evaluasi secara sistematis efek probiotik pada diabetes tipe 2 (32 RCT)
- Probiotik dapat digunakan sebagai terapi tambahan pada pasien diabetes mellitus tipe 2 untuk mengatasi dislipidemia dan untuk meningkatkan kontrol metabolik
- Suplementasi probiotik bermanfaat pada diabetes tipe 2.

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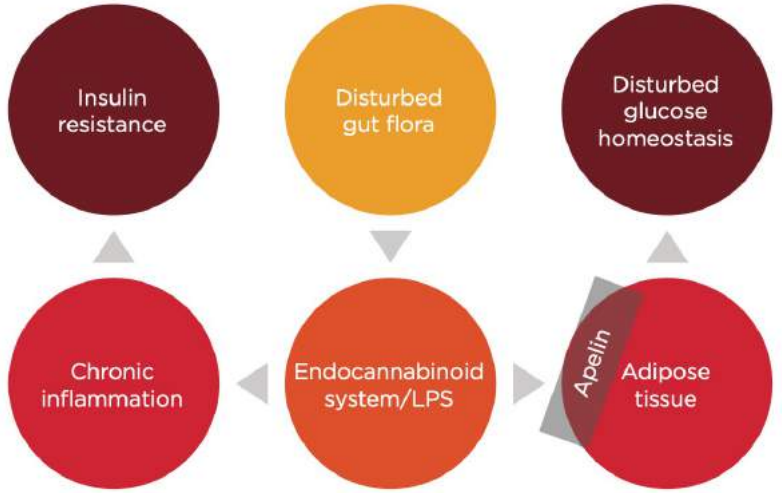
Diabetes - Probiotik untuk Manajemen Diabetes

ROLE OF PROBIOTICS IN DIABETES:
A REVIEW OF THEIR RATIONALE AND EFFICACY
Neel Jayesh Shah, Onkar C. Swami
Citation: EMJ Diabet. 2017;5[1]:104-110.

Table 2: Overview of important clinical studies demonstrating the effect of probiotics on metabolic profiles in patients with Type 2 diabetes mellitus.

Study	Probiotics used	Participant age in years (N)	Design	Duration	Outcome
Mazloom et al.[49]	*L. acidophilus, L. bulgaricus, L. bifidum, L.* casei	25–65 (34)	Single-blind, PC	6 weeks	Non-significant declining trend in the level of TG, MDA, and IL-6 and insulin resistance
Ejtahed et al.[43]	Yogurt containing *L. acidophilus La5, B. lactis Bb12*	30–60 (64)	Double-blind	6 weeks	Improved fasting blood glucose and antioxidant status
Moroti et al.[46]	*L. acidophilus, B. bifidum,* fructooligosaccharides	50–60 (20)	Double-blind, PC	30 days	Significant increase in HDL and a significant decrease of glycaemia
Andreasen et al.[36]	*L. acidophilus*	55-62 (45)	Double-blind, PC	4 weeks	Preserved insulin sensitivity, but did not affect the systemic inflammatory response
Asemi et al.[45]	*L. sporogenes* and inulin as prebiotic	35-70 (62)	Double-blind, PC	6 weeks	Significant effects on serum insulin, hs-CRP, uric acid, and plasma total GSH levels
Tonucci et al.[50]	*L. acidophilus La-5, B. animalis subsp lactis BB-12*	35-60 (50)	Double-blind, PC	6 weeks	Improved glycaemic control, decrease in inflammatory cytokines (TNF-α and resistin) and increase in acetic acid
Firouzi et al.[51]	*Lactobacillus and Bifidobacterium*	30–70 (136)	Double-blind, PC	12 weeks	Modest improvement in HbA1c and fasting insulin

B. species: *Bifidobacterium*; GSH: glutathione; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; *L.* species: *Lactobacillus*; MDA: malondialdehyde; PC: placebo controlled; TG: triglyceride; TNF: tumour necrosis factor.



Pasien Diabetes mellitus tipe 2 memiliki ***gut metagenome*** yang berbeda dengan orang yang memiliki control glukosa normal -> **metagenome dapat dijadikan faktor untuk memprediksi Diabetes Mellitus Tipe 2**

Apelin -> molekul yang berpotensi menyimpan sensitivitas insulin, memicu penurunan glukosa dengan meningkatkan *uptake* glukosa pada otot dan jaringan adiposa

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Probiotic reduces bacterial translocation in type 2 diabetes mellitus: A randomised controlled study

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Gut bacterial translocation to the blood may play an important role in the development of insulin resistance in type 2 diabetes. Here, we performed an interventional randomised control study to investigate whether probiotics could reduce bacterial translocation and cause changes in the gut microbiota. Seventy Japanese patients with type 2 diabetes were randomised to two groups: the probiotic group drank *Lactobacillus casei* strain Shirota-fermented milk, while the control group ingested no probiotics. The trial was conducted for 16 weeks. At baseline, 8 and 16 weeks, the gut microbiota composition in feces and blood, fecal organic acids, and other biochemical parameters were measured. At the end of the study, the fecal counts of the *Clostridium coccoides* group and *Clostridium leptum* subgroup in the probiotic group were significantly higher than in the control group. As expected, the fecal counts of total *Lactobacillus* were significantly higher in the probiotic group. Intriguingly, the total count of blood bacteria was significantly lower in the probiotic group. However, fecal organic acids were comparable between the two groups. Our results showed that probiotic administration reduced bacterial translocation and altered the gut microbiota in Japanese patients with type 2 diabetes mellitus.

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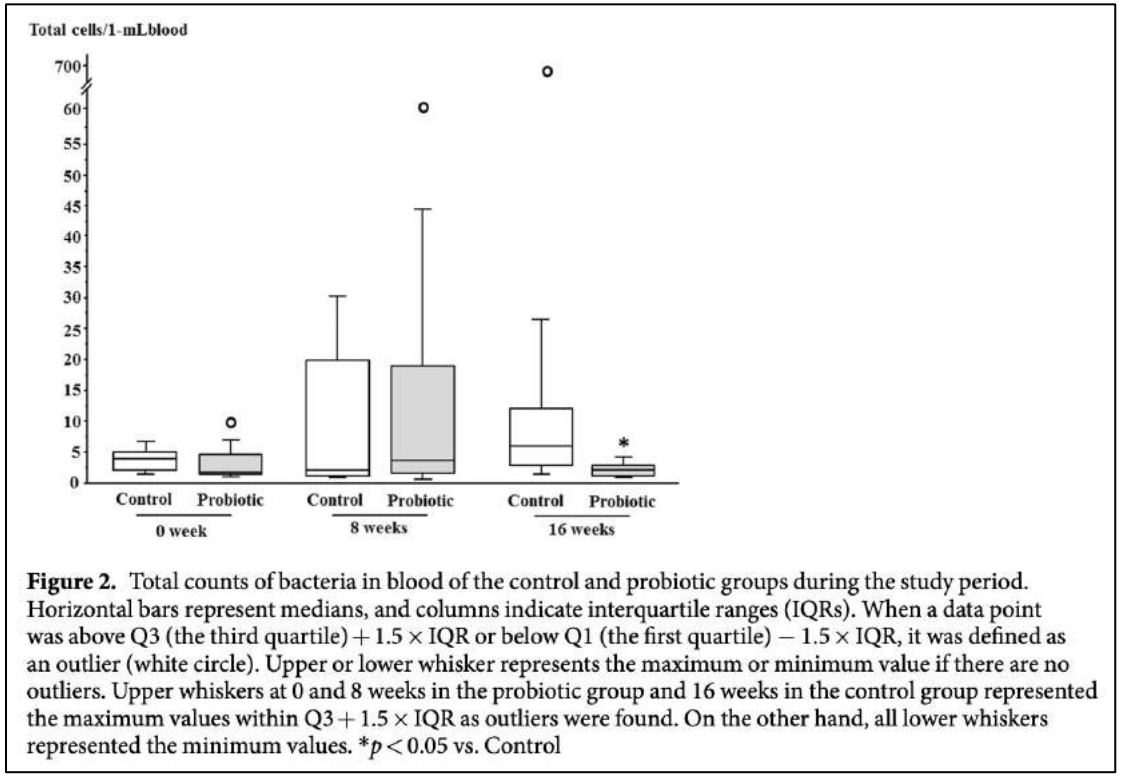

Figure 2. Total counts of bacteria in blood of the control and probiotic groups during the study period. Horizontal bars represent medians, and columns indicate interquartile ranges (IQRs). When a data point was above Q3 (the third quartile) + 1.5 × IQR or below Q1 (the first quartile) − 1.5 × IQR, it was defined as an outlier (white circle). Upper or lower whisker represents the maximum or minimum value if there are no outliers. Upper whiskers at 0 and 8 weeks in the probiotic group and 16 weeks in the control group represented the maximum values within Q3 + 1.5 × IQR as outliers were found. On the other hand, all lower whiskers represented the minimum values. $*p < 0.05$ vs. Control

Bakteri yang ditemukan dalam darah: *Clostridium cocoides* group, *C. leptum* subgroup, *Atopobium* cluster, *Bacteroides fragilis* group, *Prevotella, Streptococcus*.

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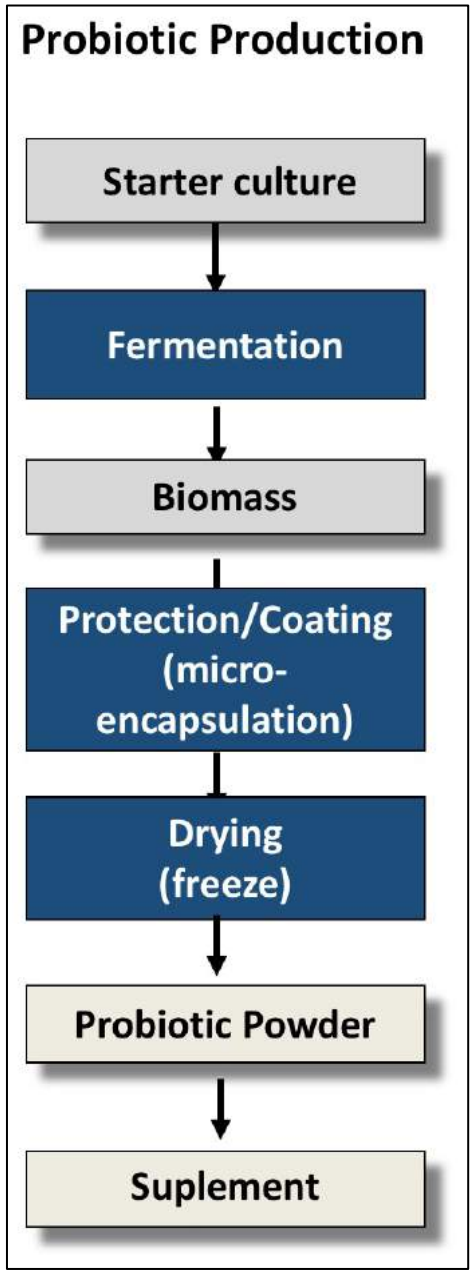
Probiotik Lokal Dad-13



- Probiotik local Dad-13 merupakan suplemen makanan, berisi powder probiotik indigenous ***Lactobacillus plantarum* Dad-13** (di koleksi di FNCC UGM)
- Berupa powder dalam saset, dengan jumlah sel hidup $10^{9\text{-}10}$ CFU
- Di produksi di Unit Produksi Probiotik dan Kultur Starter di Pusat Studi Pangan dan Gizi Universitas Gadjah Mada (PUI-PT Probiotik UGM)
- Sertifikat Halal LPPOM MUI – Unit Produksi Probiotik dan Kultur Starter PSPG UGM sebagai salah satu luaran penelitian Rispro-LPDP (nomor sertifikat: 1230005561019)

- Penelitian pengaruh intervensi Probiotik *Lactobacillus plantarum* Dad-13 oleh responden T2D telah dilakukan, RCT double blind, dengan jumlah responden terbatas (DIY), lama intervensi 3 bulan. Parameter yang dianalisa *gut microbiota*, parameter glikemik, SCFA, dll. – Ninik Rustanti, dkk

- Kedepan – akan dilakukan kembali penelitian intervensi probiotik *Lactobacillus plantarum* Dad-13 oleh responded T2D, dengan *design RCT multi sites. Parameter yang dianalisa gut microbiota*, parameter glikemik, SCFA, bile acid dan turunannya, dll

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Mifta Gatya, S.T.P.

Probiotik dapat membantu dalam penatalaksanaan Diabetes Tipe 2 (T2D), namun diet, olah raga, serta ceria tetap yang utama

Terima kasih

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