OULU 2019
D 1520

ACTA UNIVERSITATIS OULUENSIS

Ghulam Shere Raza

THE ROLE OF DIETARY FIBERS IN METABOLIC DISEASES

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
BIOCENTER OULU

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GHULAM SHERE RAZA

THE ROLE OF DIETARY FIBERS IN METABOLIC DISEASES

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium F202 of the Faculty of Medicine (Aapistie 5 B), on 23 August 2019, at 12 noon

UNIVERSITY OF OULU, OULU 2019

Acta Univ. Oul. D 1520, 2019

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ISBN 978-952-62-2302-5 (Paperback)
ISBN 978-952-62-2303-2 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

JUVENES PRINT
TAMPERE 2019

Raza, Ghulam Shere, The role of dietary fibers in metabolic diseases.
University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Biocenter Oulu
Acta Univ. Oul. D 1520, 2019
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Obesity and dyslipidemia are major risk factors for type 2 diabetes, cardiovascular diseases (CVD), cancer, and musculoskeletal disorders. In prevention, the major goal is to limit calorie consumption and to reduce LDL-C and triglyceride. Dietary fiber (DF) intake is inversely related to body weight gain, insulin resistance, dyslipidemia, and CVD. This thesis investigated the effects of the DFs polydextrose (PDX) and lignin-rich insoluble residue (INS) from brewer's spent grain (BSG) on lipid metabolism and obesity in diet-induced obese mice.

In study 1, PDX was investigated on lipid metabolism in Western-diet-fed mice. We found that PDX reduced fasting plasma cholesterol and triglyceride, food intake, and increased bacteria such as *Allobaculum*, *Bifidobacterium* and *Coriobacteriaceae* in the gut. These changes in the gut microbiota with PDX were associated with downregulation of the genes *Fiaf*, *Dgat1* and *Cd36*, and upregulation of *Fxr* in the intestine. We suggest that the hypolipidemic effect of PDX is exerted via diet-induced modification of gut microbiota and gene expression.

In study II, INS from BSG was studied for its degradation products in mice fed with a fiber-deficient diet. We found that INS was partially degraded by gut microbiota and contributed to the phenolic pool. The major metabolite in mouse urine was 4-methylcatechol, a degradation product of lignin.

In study III, the effects of INS from BSG were studied on lipid metabolism and obesity in high-fat diet-fed mice. INS showed hypocholesterolemic effects, reduced body weight and hepatic steatosis, and increased bacterial diversity, *Clostridium leptum*, and *Bacteroide*s. INS increased bile acid excretion in the feces and upregulated the genes *Srebp2*, *Hmgcr*, *Ldlr*, *Cyp7a1*, *Pparα*, *Fxr* and *Pxr* in the liver. The present results suggest that INS from BSG induced beneficial systemic changes via bile acid and gut microbiota.

In study IV, PDX was investigated for food intake and appetite-related parameters in healthy and overweight females in an acute study. A midmorning preload of 12.5 g PDX reduced hunger by 31.4% during satiation period while there was no significant change in energy intake compared to placebo. In addition, PDX intake with breakfast lowered plasma insulin significantly, by 15.7%, and increased GLP-1 by 39.9%. PDX may reduce appetite, but a larger trial would be needed.

Keywords: bile acids, cardiovascular disease, dietary fiber, gene expression, gut microbiota, obesity, plasma cholesterol, plasma triglyceride, type 2 diabetes

Raza, Ghulam Shere, Ravintokuitujen rooli aineenvaihduntasairauksissa.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Biocenter Oulu
Acta Univ. Oul. D 1520, 2019
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Liikalihavuus ja rasvatasapainon häiriöt ovat riskitekijöitä sydän- ja verisuonisairauksien, tyypin 2 diabeteksen, syövän sekä luuston ja lihaksiston sairauksien kehittymiseen. Näiden sairauksien ehkäisyssä pääasiallisena tavoitteena on vähentää energiansaantia, LDL-kolesterolia ja triglyseridejä. Ruoan ravintokuitujen saannin on osoitettu olevan yhteydessä painon ja plasman rasvatasojen laskuun sekä sydän- ja verisuonisairauksien vähenemiseen. Tässä tutkimuksessa selvitettiin ravintokuitu polydekstroosin (PDX) ja viljanjyvien prosessoinnista ylijäävän (BSG, brewer's spent grain) ligniinipitoisen liukenemattoman sivutuotteen (INS) merkitystä rasva-aineenvaihduntaan ja aineenvaihduntasairauksiin liikalihavilla hiirillä.

Tutkimuksessa I tarkasteltiin ravintokuitu PDX:n vaikutusta rasvojen aineenvaihduntaan länsimaisella ruokavaliolla ruokituilla hiirillä. Tutkimus osoitti, että ruokavalioon lisätty PDX alensi plasman kolesteroli- ja triglyseriditasoja paastossa sekä hillitsi ravinnonottoa ja lisäsi *Allobaculum*-, *Bifidobacterium*- ja *Coriobacteriaceae*-suolistobaktereja. Nämä suolistomikrobiston muutokset ovat yhteydessä *Fiaf*, *Dgat1* ja *Cd36* -geenien ilmentymistasojen laskuun ja *Fxr* -geenin ilmentymistason nousuun PDX-lisäruokittujen hiirien suolistossa. PDX:n hypolipideeminen vaikutus näyttäisi välittyvän ruokavaliosta johtuvan suoliston geenien ilmentymisen ja suolistomikrobiston muuttumisen kautta.

Tutkimuksessa II tarkasteltiin runsaasti ligniiniä sisältävän INS:n hajoamistuotteiden vaikutusta aineenvaihduntaan hiirillä, joiden ruokavaliossa on vähemmän kuitua. Tutkimuksessa havaittiin, että suolistomikrobit hajottivat ravintokuitu INS:n osittain fenoliyhdisteiksi verenkiertoon. INS lisäsi virtsassa 4-metyylikatekolin määrää, joka on ligniinin hajoamistuote.

Tutkimuksessa III tarkasteltiin INS-lisäyksen vaikutusta rasva-aineenvaihduntaan ja liikalihavuuteen korkearasvapitoisella ruokavaliolla ruokituilla hiirillä. Tulokset osoittivat, että INS-lisäys ruokavalioon alensi kolesterolia ja eläimen painoa, vähensi maksan rasvoittumista ja lisäsi vallitsevien bakteerien monimuotoisuutta, *Clostridium leptum*- ja *Bacteroides* -bakteereja. INS lisäsi sappihappojen erittymistä ulosteeseen ja *Srebp2*, *Hmgcr*, *Ldlr*, *Cyp7a1*, *Pparα*, *Fxr* ja *Pxr* -geenien ilmentymistä maksassa. Tuloksemme osoittivat, että BSG-ylijäämätuotteesta saatu ligniinipitoinenINS sai aikaan hyödyllisiä systeemisiä vaikutuksia suoliston mikrobiston ja sappihappojen muutosten kautta.

Tutkimuksessa IV tarkasteltiin PDX:n vaikutusta ravinnonottoon ja ruokahaluun vaikuttaviin muuttujiin normaalipainoisilla ja liikalihavilla naisilla akuutissa tutkimuksessa. Tulosten mukaan ravintokuitu PDX:n nauttiminen aamupäivällä vähensi näläntunnetta (31,4 %) seuraavalla aterioinnilla, kun taas plasebolla ei ollut vaikutusta. Lisäksi PDX aamiaisella alensi merkitsevästi insuliinitasoa (15,7 %) ja nosti GLP-1-tasoa (39,9 %). PDX vaikuttaisi vähentävän ruokahalua, mutta lisätutkimuksia tarvitaan.

Asiasanat: geenien ilmentyminen, liikalihavuus, plasman kolesteroli, plasman triglyseridi, ravintokuitu, sappihappo, suoliston mikrobiomi, sydän- ja verisuonisairaudet, tyypin 2 diabetes

To my lovely family

Acknowledgements

The work presented in the thesis was carried out at the University of Oulu, Faculty of Medicine, Research Unit of Biomedicine and Biocenter Oulu, Oulu, Finland, during the years 2012–2018. I sincerely thank all the colleagues, and especially DuPont and VTT who have participated in this work.

I am deeply grateful and express my sincere gratitude to my supervisor, Professor Karl-Heinz Herzig MD, PhD, for giving me the opportunity to work in his research group and for providing exceptional opportunities for research. His positive attitude, guidance and support have had a huge impact during this journey. His door has always been open for numerous discussions about science, social and many other things. He always supported new scientific ideas. I strongly appreciate all the support and guidance received during my PhD tenure.

I thank the pre-examiners, Professor Rikard Landberg, PhD, and Adjunct Professor Kati Hanhineva, PhD, for evaluation of my thesis manuscript and for all the constructive and valuable comments.

I personally thank all the co-authors from DuPont and VTT Technical Research Center of Finland for the scientific contributions that made this thesis possible. I express my gratitude to Heli Putaala, Ashley Hibberd and Johanna Maukonen from DuPont and VTT for the analysis of gut microbiota. I am very thankful to Professor Markus Mäkinen, MD, PhD, for liver histology imaging and analysis. I thank Prof. Jaroslaw Walkowiak, Prof. Kaisa Poutanen. Prof. Johanna Buchert, Dr. Kirsti Tiihonen, Dr. Alvin Ibarra, Dr. Kari Mäkelä, Laura Niiranen, Dr. Kaisa Olli, Prof. Esa Alhoniemi, Dr. Piritta Niemi, Dr. Anna-Marja Aura, Dr. Inga Mattila, for their scientific output and contributions.

I wish to thank my follow-up group members, Professor Thomas Kietzmann, MD, PhD, Dr. Olavi Vakkuri, PhD, and especially the chair of the follow-up group, Professor emeritus Esa Hohtola, PhD, for all the help and advice.

I owe my sincere thanks to my previous Institution Professor's Mallikarjuna Rao C and Gopalan Kutty from Manipal College of Pharmaceutical Sciences Manipal, India. Dr. Rosalind Marita A, Dr. Raghib Husain, Dr. Jessy Anthony, and Dr. Aditee Ghate from Piramal Life Sciences Ltd., India, who gave me an excellent opportunity to build my scientific career.

I wish to thank Prof. Jukka Hakkola, MD, PhD, for providing an excellent research environment and facilities at the Research Unit of Biomedicine. I owe my warmest thanks to all the members of the Research Unit of Biomedicine for creating such a pleasant working atmosphere. I would like to offer my special thanks to Kari

Mäkelä, PhD, Shivaprakash J. Mutt, MSc, Laura Niiranen, MSc, and Toni Karhu, PhD, for friendship, kind help and support inside and outside the lab. I sincerely thank technicians Tuula Taskinen and Meri Kroger for assistance in the lab and Anneli Rautio for cell culture help. I also want to thank my current and former colleagues, Remi Kamakura, MSc, Ville Stenbäck, MSc, Toni Karhu, PhD, Miia Kovalainen, PhD, Erja Metsämarttila, MSc, Dominique Gagnon, PhD, Marianne Haapea, PhD, and Anne Huotari, MSc – you all made these years enjoyable. I wish to thank Eero Kouvalainen for technical assistance with computers and lab equipment. I wish to extend my sincere thanks to Professor emeritus Juhani Leppäluoto, MD, PhD, for kind help and support, in addition to reviewing my thesis.

I thank my friends and family outside the lab. Thank you Avinash Bhakar and Suresh Kodukula for everything, all my friends in Oulu and India. I wish to express my deepest gratitude to my parents Atibur Rahim and Shakerun Nisha for their unconditional love and support during my whole life; thank you Abbu and Ammi for everything. I am very grateful to my brother Dr. Seraj Ahmed who has always supported me and stood beside me like a solid rock; thank you Bhai, I am really honored to have a brother like you. I owe thanks to my in-laws Jamil Ahmed and Shafikun Nisha, Jamal Ahmed and Sakeel Ahmed for their help and support during these years, thank you very much, without your support, it would have been very difficult. I am deeply grateful to my mother-in-law who helped and supported us during our emergency. I am also thankful to my younger brothers Sarfraj and Irshad, my sisters Taiba and Rehana and my cousins Vajhul, Ahmad Raza, Shaqqul and Swaleh and other relatives.

Finally, I am very thankful to my beloved Sarvari Khatoon and our children Aisha, Aakib, Maira and Ehan for all the joy and lovely moments in my everyday life. Sarvari, thank you for understanding, and especially for your support during the last two years when I was writing the publications and completing my thesis. You encouraged and supported me to go abroad for higher studies; without your support, it would not have been possible.

Jalmari ja Rauha Ahokkaan Säätiö is gratefully acknowledged for funding this project. Oulun Yliopiston Tukisäätiö provided some additional support, and UniOGS and Scandinavian Physiological Society (SPS) provided travel funding which enabled me to present the results at scientific meetings.

Oulu, August 2019 Ghulam Shere Raza

Abbreviations

Acat1	Acetyl-Coenzyme A acetyltransferase 1
Acsl3	Acyl-CoA synthetase long-chain family member 3
Acsl5	Acyl-CoA synthetase long-chain family member 5
Acot2	Acyl-CoA thioesterase 2
Acot3	Acyl-CoA thioesterase 3
Acot6	Acyl-CoA thioesterase 6
AMPK	Adenosine monophosphate-activated protein Kinase
Ato	Atopobium
ATP III	Adult treatment panel III
AUC	Area under curve
AX	Arabinoxylan
BA	Bile acid
Bfra	Bacteroides
Bif	Bifidobacteria
BMI	Body Mass Index
BSG	Brewer's spent grain
BSH	Bile salt hydrolase
CA	Chenocholic acid
CCK	cholecystokinin
CD36	Cluster of differentiation 36
CDCA	Chenodeoxycholic acid
CEL	Cellulose
Clept	Clostridium leptum
CD	Control diet
CHD	Coronary Heart Disease
CO2	Carbon dioxide
Cyp7a1	Cytochrome P450 family 7, subfamily a, member 1
CVD	Cardiovascular disease
Dgat1	Diacylglycerol O-acyltransferase 1
DCA	Deoxycholic acid
DP	Degree of polymerization
DRV	Daily reference value
EDTA	Ethylenediamine tetraacetic acid
ED	Enterodiol
EFSA	European Food Safety Authority

EL	Enterolactone
Erec	Eubacterium rectale
F/B	Firmicutes/Bacteroidetes
Fabp2	Fatty acid binding protein 2
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
Fgf15	Fibroblast growth factor 15
Fiaf	Fasting-induced adipose factor
Fxr	farnesoid X receptor
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GLP-1	Glucagon like peptide-1
GIT	Gastrointestinal tract
GPR91	G protein-coupled receptor 91
GTT	Glucose tolerance test
H2	Hydrogen
HFD	High-fat Diet
HDL-C	High-density lipoprotein cholesterol
Hmgcr	3-hydroxy-3-methylglutaryl CoA reductase
Hmgcs	3-hydroxy-3-methylglutaryl CoA synthase
HSL	Hormone-sensitive lipase
INS	Insoluble residue of BSG
ITT	Insulin tolerance test
IOM	Institute of Medicine
Lac	Lactobacillus
LDL-C	Low-density lipoprotein cholesterol
Ldlr	Low-density lipoproteins receptors
Lpl	Lipoprotein lipase
4-MC	4-methylcatechol
β-MCA	β-muricholic acid
NCEP	National Cholesterol Education Program
Npc1	Niemann-Pick type C1
Npcl1	Niemann-Pick C1 like 1
NSP	Nonstarch polysaccharide
PCR	Polymerase chain reaction
PDX	Polydextrose
PKA	Protein kinase A
PL	Pancreatic lipase

Pparα	Peroxisome proliferator activated receptor alpha
Pgc1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
Prkaα	Protein kinase AMP-activated catalytic subunit alpha
Prkacα	Protein kinase cAMP-dependent catalytic subunit alpha
Pxr	Pregnane X receptor
PYY	Polypeptide Y
Rplp0	Ribosomal protein, large, P0
SCFA	Short-chain fatty acid
Slc10a2	Solute carrier family 10, member 2
Slc27a2	Solute carrier family 27 (fatty acid transporter), member 2
Srebp2	Sterol regulatory element binding protein 2
Srebp1c	Sterol regulatory element-binding protein1c
TGR5	Takeda G protein-coupled receptor 5
TMAO	Trimethylamine N-oxide
Univ	Universal
VFA	Visceral Fat Area
WD	Western-diet
WHO	World health organization

Original publications

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals:

I Raza, G. S*., Putaala, H*., Hibberd, A. A., Alhoniemi, E., Tiihonen, K., Makela, K. A., Herzig, K. H. (2017). Polydextrose changes the gut microbiome and attenuates fasting triglyceride and cholesterol levels in Western-diet fed mice. *Scientific Reports, 7*(1), 5294-017-05259-3. doi:10.1038/s41598-017-05259-3

II Maukonen, J., Aura, A. M., Niemi, P., Raza, G. S., Niemela, K., Walkowiak, J., Mattila, I., Poutanen, K., Buchert, J., Herzig, K. H. (2017). Interactions of insoluble residue from enzymatic hydrolysis of brewer's spent grain with intestinal microbiota in mice. *Journal of Agricultural and Food Chemistry*, 65(18), 3748-3756. doi:10.1021/acs.jafc.6b05552

III Raza, G. S., Maukonen, J., Makinen, M., Niemi, P., Niiranen, L., Hibberd, A. A., Poutanen, K., Buchert, J., Herzig, K. H. (2019). Hypocholesterolemic effect of the lignin-rich insoluble residue of brewer's spent grain in mice fed a high-fat diet. *Journal of Agricultural and Food Chemistry*, 67(4), 1104-1114. doi:10.1021/acs.jafc.8b05770

IV Ibarra, A., Olli, K., Pasman, W., Hendriks, H., Alhoniemi, E., Raza, G. S., Herzig, K. H., Tiihonen, K. (2017). Effects of polydextrose with breakfast or with a midmorning preload on food intake and other appetite-related parameters in healthy normal-weight and overweight females: An acute, randomized, double-blind, placebo-controlled, and crossover study. *Appetite*, 110, 15-24. doi:S0195-6663(16)30882-0

Contributions:

I did animal feeding, blood and tissue collection and all the biochemical measurements (I-III). I performed much of the molecular work in (I) & (III), including designing primers, RNA isolation and real-time PCR. I measured gastric emptying in human (IV). I was involved in planning and wrote first draft of the manuscript (I-III).

*equal contribution

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1 Introduction

Obesity and dyslipidemia are the major risk factors for metabolic and cardiovascular diseases. Since 1980, the prevalence of obesity has increased dramatically worldwide. According to the World Health Organization, 39% of adults aged 18 years and above (38% of men and 40% of women, approximately 1.9 billion) were overweight. Overall, about 13% of the world's adult population (11% of men and 15% of women, 650 million adults) were obese in 2016 (WHO 2017). Obesity leads to cardiovascular disease (CVD), type 2 diabetes (T2D), certain types of cancer, musculoskeletal disorders, inflammatory diseases, Alzheimer's disease and dementia (Li, Bowerman, & Heber, 2005). Dyslipidemia is another major risk factor for CVDs and a leading cause of death worldwide, affecting almost 50% of the population (Saydah, Fradkin, & Cowie, 2004). Dyslipidemia is characterized by high plasma triglyceride, low high-density lipoprotein cholesterol (HDL-C) and increased low-density lipoprotein cholesterol (LDL-C) (Mooradian, 2009). The key contributing factor for CVD includes high intake of saturated and *trans* fats (Lloyd-Jones, 2010). One mmol/L total cholesterol reduction is associated with a 33% reduction in ischemic heart disease mortality in subjects aged 50–69 years and a 17% reduction in those aged 70–89 years (Prospective Studies Collaboration et al., 2007). Western diets high in saturated fat, processed meat, and refined carbohydrates are strongly implicated in the increasing prevalence of obesity, T2D and CVD (Pereira et al., 2009). People in Western countries consume more high-fat, low-fiber diets (Western diet), which are accompanied by a growing prevalence of obesity, insulin resistance and CVD (Galisteo, Duarte, & Zarzuelo, 2008).

The fundamental cause of obesity is long-term energy imbalance between energy intake and expenditure (Burton-Freeman, 2000). Hence, limiting calorie intake is the ultimate goal during weight loss programs. The major goal in the prevention of CVD is to reduce LDL-C and triglycerides by various means such as pharmacological and dietary interventions and exercise (Dunn-Emke, Weidner, & Ornish, 2001). Dietary interventions are highly recommended, as most patients prefer non-drug treatment because of the adverse effects of drugs. There is clear evidence that dietary fiber (DF) intake is inversely related to body weight gain, insulin resistance, dyslipidemia, and CVD (Dall'Alba et al., 2013). DFs prevent CVD by lowering LDL-C and total cholesterol (Anderson et al., 2009), lower body weight gain and plasma lipids, and therefore reduce cardiovascular and metabolic diseases.

Polydextrose (PDX) is a synthetic DF, which is soluble and non-viscous in nature and only partially fermented by the gut microbiota. It is widely used as a fat and sugar replacement in various food and beverages and approved as DF in over 60 nations (FAO/WHO, 2009). PDX possesses various physiological effects such as improving intestinal functions, regulating lipid metabolism, increasing satiety and contributing to weight control. PDX increases the production of short-chain fatty acids (SCFAs) and promotes the growth of *Bifidobacteria* and *lactobacilli* while preventing the growth of harmful bacteria. PDX has been demonstrated to reduce plasma cholesterol and triglyceride in animals and humans; however, the results are mixed and the mechanism of the lipid-lowering effect of PDX is still unclear. BSG is rich in DF (70%) and protein (30%), which makes this material very interesting for the food industry and biotechnological applications. The insoluble residue of brewer-spent grain (BSG) is abundant in lignin, β-glucan and arabinoxylan (AX), well-known DF constituents. BSG has several health benefits, such as anti-inflammatory and immunomodulatory effects due to its high fiber and phenolic acid content. The insoluble residue (INS) of BSG produces SCFAs and is fermented in the gastrointestinal tract (GIT), but the health benefits of INS have not been investigated in detail.

The purpose of this thesis was to investigate

- the effects of the dietary fiber PDX and lignin-rich insoluble residue (INS) of BSG on lipid metabolism and obesity in diet-induced obese mice.
- the mechanism of cholesterol and triglyceride reduction with these fibers with special attention to gut microbiota, bile acids and gene expression.
- using a translational approach, the effect of PDX on food intake and appetite-related parameters in healthy and overweight females in an acute, randomized, double-blind, placebo-controlled, four-arm crossover study.

2 Review of literature

2.1 Dietary fibers (DFs)

DFs are defined as “edible parts of plants or analogous carbohydrates resistant to digestion in the small intestine and fermented in part in the large bowl by gut microbiota”. In 2009, the Codex Alimentarius Commission defined DFs as “carbohydrate polymers with ten or more monomeric units, which are neither digested nor absorbed in the human small intestine”. Basically, DFs are carbohydrates, which are resistant to digestion by mammalian enzymes. In May 2016, the FDA defined DFs as “carbohydrates possessing a physiological effect that benefits human health”. DFs include a number of nonstarch polysaccharides (NSP) such as cellulose, hemicellulose, β-glucans, pectins, mucilages and gums, oligosaccharides and non-polysaccharide lignin. The health benefits of fibrous food have long been appreciated: in 430 BC, Hippocrates described the laxative effects of coarse wheat compared to refined wheat, and in 1920, Kellogg published findings that bran increases stool weight, promotes laxation and prevents chronic diseases (Dreher, 2001). Hipsley used the term DFs in scientific literature in 1953, referred DFs to celluloses, hemicelluloses and lignin (HIPSLEY, 1953). Burkitt *et al*. re-popularized DF research and demonstrated that DFs affect the bacteriological and chemical processes in the gut (Burkitt, Walker, & Painter, 1972).

Cereals, vegetables, fruits, and nuts are a rich source of DF. Non-starch foods contain about 20–35 g, starch food about 10 g, and vegetables and fruit about 1.5–2.5 g fiber per 100 g dry weight of material (Selvendran & Robertson, 1994). The content of fiber in cereal grains is about 10–30% (Knudsen, 1997). Cereal is the major source of DF in Western countries, contributing about 50%, while vegetables contribute 30–40%, fruits about 16%, and other minor sources 3% (Lambo, Öste, & Nyman, 2005). The components of DF and their sources are presented in Table 1.

Table 1. DF constituents and their sources (Tungland & Meyer, 2002).

Fiber components	Principal groupings	Fiber sources
Non starch polysaccharides (NSP) and oligosaccharides	Cellulose	Cellulose plants (vegetable, sugar beet, brans)
	Hemicellulose	Arabinogalactans, β-glucans, arabinoxylans glucuronoxylans, xyloglucans, galactomannans and pectic substances
	Polyfructoses	Inulin, oligofructans
	Gums and mucilages	Seed extracts (galactomannans– guar and locust bean gum),Tree exudates (gum acacia, gum karaya, gum tragacanth), Algal polysaccharides (alginates, agar carrageenan), psyllium
Substances associated with NSP	Waxes, cutin, suberin	Plant fibers
Carbohydrate analogues	Pectin	Fruits, vegetables, legumes, potato, sugar beets
	Resistant starch and maltodextrin	Various plants such as maize, pea, potato
	Chemical synthesis	Polydextrose, lactulose, cellulose derivatives
	Enzymatic synthesis	Neosugar or short chain, guar hydrolyzate fructooligosaccharides, levan, xanthan gum, transgalactooligosaccharides, oligofructose, xylooligosaccharide
Lignin	Lignin	Woody plants
Animal origin fibers	Chitin, chitosan, Collagen, Chondroitin	Fungi, yeasts, invertebrates

The most widely accepted classification of DFs is based on their solubility in buffer at a defined pH and/or their fermentability in an *in vitro* system using an aqueous enzyme solution. Soluble fibers dissolve in water, form a viscous gel, and are easily fermented by gut microbiota. In contrast, insoluble fibers do not dissolve in water and their fermentation is severely limited. Soluble fibers include inulin, pectin

gums, and some hemicelluloses, while insoluble fiber mainly consists of cellulose, lignin, and some hemicelluloses. DFs, their physical properties and key health effects are summarized in Figure 1.

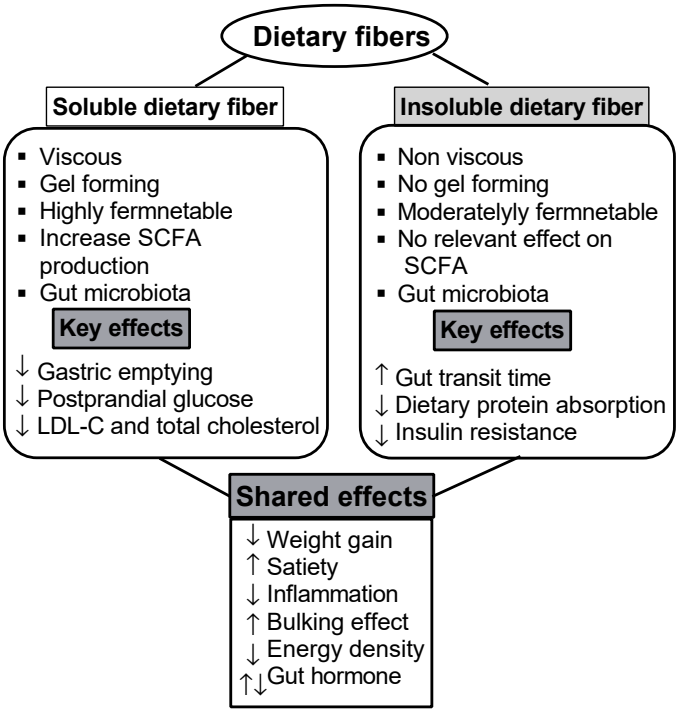

Fig. 1. Properties and health effects of soluble and insoluble DFs.

2.1.1 Daily intake and recommendations of dietary fibers

In the United States, the daily reference value (DRV) for dietary fibers on nutritional fact labels for packaged food and beverages was increased from 25 to 28 g by the FDA in May 2016 (FDA 2016). Dietary Guidelines for American 2015-2020 (8th edition) recommends a minimum intake of DF 14 g/1,000 Kcal (25–38 g) for all age groups (US Department of Health and Human Services, 2017). The Institute of Medicine (IOM) recommends a total DF intake of 38 and 25 g/day for men (age 14–50 years) and women (age 19–50 years), respectively (IOM 2002). Most recommendations suggest a total DF intake of 25–38 g, with 6–8 g soluble

fibers per day. Like other nutrients (proteins and carbohydrates), fibers are a source of metabolic energy for the human body, providing on average 2 kcal per gram (FDA 2016). According to EU Regulation No. 1924/2006 (EC 2006), nutrition claims are permitted for fiber and the amount of energy needs to be accounted when calculating the total energy content of foods (Zicari, Carraro, & Bonetta, 2007). However, most people do not meet the recommendation and eat only approximately half of the recommended fiber intake (NIH 2002/2005). Despite nutrition labeling and education, the gap between fiber intake and recommendation is still considerable, and an alternative strategy of using functional fibers in food products was suggested.

Functional fibers are exogenous fibers, which are synthesized or extracted from animal or plant material to be added to food products (Institute of Medicine (US) Panel on the Definition of Dietary Fiber and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 2001). The Adult Treatment Panel-III (ATP-III) of the National Cholesterol Education Program (NCEP) has issued guidelines on cholesterol management encouraging the use of soluble fibers (oats, guar, pectin, and psyllium) as therapeutic dietary options for lowering LDL cholesterol and coronary heart disease (CHD) (NCEP, 2002). The report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) identified LDL-C as the primary target for cholesterol-lowering therapy (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002). Based on ATP-III, LDL-C goals are defined as < 160 mg/dL (4.14 mmol) for individuals with 0–1 risk factor, < 130 mg/dL (3.36 mmol) for those with ≥ 2 risk factors, and < 100 mg/dL (2.59 mmol) for those with CHD or CHD risk equivalents, with an optional goal of < 70 mg/dL (1.81 mmol) for those with both CHD and additional risk factors (Grundy et al., 2004).

2.1.2 Polydextrose (PDX)

Polydextrose (PDX) is a polysaccharide produced by the irregular polymerization of glucose in the presence of sorbitol and acid catalyst as depicted in Figure 2 (Craig, Holden, Troup, Auerbach, & Frier, 1998).

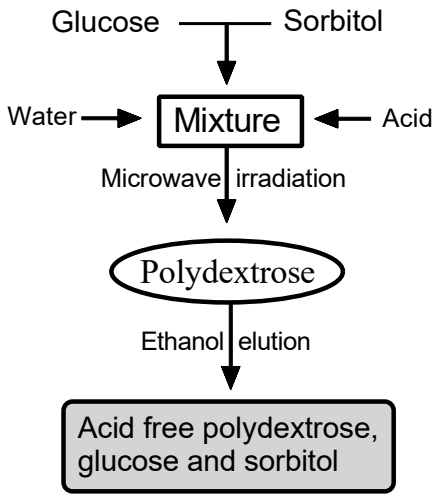

Fig. 2. PDX synthesis.

PDX is a mixture of glucose oligomers, with an average degree of polymerization (DP) ~12, but ranging from a residual monomer to DP >100. It is a highly branched molecule containing different combinations of α- and β-linked 1-2, 1-3, 1-4 and 1-6 glycosidic linkages. The 1-6 linkage is the predominant one which makes PDX resistant to digestion by mammalian enzymes. PDX is soluble, non-viscous and only partially digested in the small intestine, but largely fermented throughout the large intestine (Raninen, Lappi, Mykkanen, & Poutanen, 2011). Due to its low caloric content of about 1 kcal/g, (Achour et al., 1994) it is widely used as a fat and sugar replacement in various food and beverages. As a food additive, it offers the texture of sucrose with reduced energy and is used in baked products, dairy items, confectionery, and beverages (Auerbach, Craig, Howlett, & Hayes, 2007). PDX has been approved for use in various food products in over 60 nations (Alimentarius, 2010). It has been suggested to possess anti-inflammatory actions in dogs, increase immunoglobulin A amount in the rat cecum (Peuranen et al., 2004), and reduce intestinal lesions in rat colitis model (Witaicenis, Fruet, Salem, & Di Stasi, 2010).

2.1.3 Lignin-rich INS form brewer's spent grain (BSG)

Brewer's spent grain (BSG) is an insoluble residue after wort production and the main by-product from the brewing industry, which corresponds to approximately

85% of total byproduct, with 35 million tons generated annually worldwide (Mussatto, Dragone, & Roberto, 2006). BSG is produced from malted barley or other cereal grains and is considered a lignocellulosic material abundant in fiber (70%) and protein (20%) (Meneses, Martins, Teixeira, & Mussatto, 2013). Pires *et al*. have recently shown that BSG has about 20% cellulose, 25% hemicellulose, lignin 28% and protein 25% (Pires, Ruiz, Teixeira, & Vicente, 2012). BSG fiber is rich in AX (28%), attached to cellulosic microfibrils by hydrogen bonds. BSG has received little attention in industry and is used in animal feed (Xiros, Topakas, Katapodis, & Christakopoulos, 2008). This underutilization is due to its complex composition and high moisture (70%) content, leading to microbial degradation with a shelf life of 7 to 10 days in warm climates (Robertson et al., 2010). The lower cellulose content allows its use as raw material for the production of valuable compounds like phenolic compounds, activated charcoal, dispersants, chelating agents, fertilizers, polymers and adhesives (Mussatto, Fernandes, & Roberto, 2007). BSG is used as a raw material for lactic acid and xylitol production (Mussatto, Fernandes, Dragone, Mancilha, & Roberto, 2007). In addition, it has higher hemicellulose and protein content (30% of total protein content consists of essential amino acids and 70% of nonessential amino acids) (Waters, Jacob, Titze, Arendt, & Zannini, 2012). BSG is also a rich source of minerals, with silicon, phosphorus, calcium, and magnesium among the most abundant, and vitamins like biotin, choline, folic acid and niacin (Meneses et al., 2013).

The DF and protein in BSG make this material interesting for the food industry and biotechnological applications. BSG proteins and its hydrolysates are immunomodulatory and might help to prevent inflammatory bowel diseases (McCarthy et al., 2013). AX, β-glucan, and lignin are the main constituents of DF present in BSG, which is why we isolated the lignin-rich insoluble residue (INS) from BSG by enzymatic treatments with carbohydrases and proteases as shown in Figure 3.

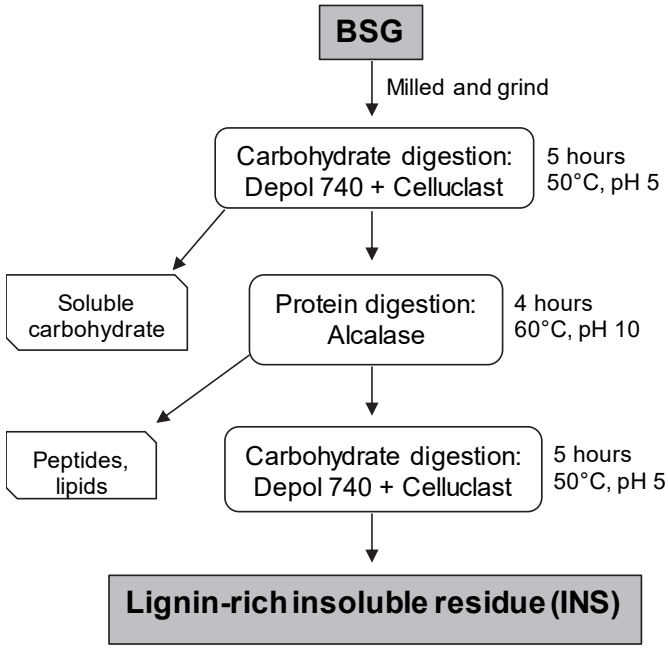

Fig. 3. Preparation of lignin-rich INS from BSG.

INS is insoluble and mainly consists of DF constituents like lignin (40%), AX (24%) and β-glucan (11%), as shown in Table 2 (Aura, Niemi et al., 2013). Lignin-rich INS has been investigated in regard to its degradation and SCFAs production. *In vitro* fermentation studies have demonstrated that lignin-rich INS is degraded by human microbiota and produces SCFAs (Niemi et al., 2013). Recently, an *in vivo* study found that lignin-rich INS is metabolized and 4-methyl-catechol (4-MC) is the major metabolite in mouse urine (Maukonen et al., 2017).

Table 2. Composition of lignin-rich INS from BSG.

Components	Brewer's Spent grain (BSG)	Lignin-rich insoluble residue (INS) of BSG
Carbohydrates	42.2%	39.2%
Arabinoxylan	22.2%	25.7%
Glucan	17.1%	11.2%
Lignin	19.4%	40.3%
Protein	22.8%	6.6%
Lipids	11%	3.1%
Ash	4.7%	8.7%

Lignin

After cellulose, lignin is the most abundant biopolymer on earth (Lewis & Yamamoto, 1990), constituting 20–30% of woody plant cell walls, providing rigidity, cohesion and forming a physicochemical barrier against microbial degradation. It has a molecular weight of 600–1,500 kD and a three-dimensional structure formed by three monomers: p-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol linked together. The most common linkage between the monomer units is β-aryl ether (β-O-4). Lignin is synthesized by the enzymes peroxidase and laccase, which polymerize the three monomeric p-coumaryl, coniferyl and sinapyl alcohols (Zhao et al., 2013). The concentration and heterogeneity of lignin depend on the proportion of these alcohols and the degree of polymerization. Softwood lignin contains about 800 g/kg coniferyl, 140 g/kg p-coumaryl and 60 g/kg sinapyl, whereas hardwood lignin contains 560 g/kg coniferyl, 40 g/kg p-coumaryl and 400 g/kg sinapyl alcohol (Jung & Fahey, 1983). Lignin can be sulfur or non-sulfur bearing, and it is the sulfur lignin, which is commercialized: lignosulfonates and Kraft lignin. Alkaline hydrolysis or enzymatic hydrolysis is used to isolate lignin from lignocellulosic materials (Mussatto, Fernandes, & Roberto, 2007). In human food, like cereal brans, beans, and some vegetables, and especially in various types of animal feed, lignin is present in up to 20 to 25% of the dry weight of the food (DeVries, 2003). Lignin is a common component of insoluble DF and found in different food by-products: sugarcane bagasse, bean dregs, sweet potato residue, bamboo shoots, sunflower seeds, and aged shells (Li, Sun, Xu, & Sun, 2012). Natural lignin is biodegradable, non-toxic, possesses antioxidant potential and stimulates activity of pancreatic α-amylase, an enzyme for dietary starch digestion (Zhang, Cui, Yin, Sun, & Li, 2013). The effect of lignin on pancreatic lipase (PL) depends on the reaction system; in a homogenous system, it stimulates PL activity

while inhibiting it in a heterogeneous system (Zhang, Xiao, Yang, Wang, & Li, 2014). PL is major lipolytic enzyme and hydrolyzes 50–70% of the dietary fat to monoglycerides and fatty acid (Birari & Bhutani, 2007). Inhibition of PL activity by natural products is one of the mechanisms for weight reduction.

Lignin is generally considered as inert in the human GIT. *In vitro* studies have demonstrated that DFs with high lignin content are fermented less compared to lower lignin-containing fibers. Lignin is covalently linked with carbohydrates and causes stearic hindrance for carbohydrate-degrading enzymes and could reduce the fermentation of lignin-rich DF. However, some insects including termites, white rot fungi and soil bacteria are known to degrade lignin. Lignin degradation has also been reported in cow, goats, and dogs as well as in some human studies, which challenges the general concept of the inertness of lignin (Holloway, Tasman-Jones, & Lee, 1978; Kelsay, Goering, Behall, & Prather, 1981; Silanikove & Brosh, 1989). Begum *et al*. demonstrated that lignin is metabolized to mammalian lignan: enterolactone (EL) and enterodiol (ED) in rats, confirming degradation of lignin in non-ruminants (Begum et al., 2004). Lignans are phytoestrogens found in flaxseed, fruits, vegetables, nuts and whole grain, and they have been shown to lower the risk of cancers and CVDs (De Silva & Alcorn, 2019; Parikh, Netticadan, & Pierce, 2018). Recently, *in vitro* and *in vivo* studies demonstrated that lignin-rich INS is degraded (Maukonen et al., 2017; Niemi et al., 2013).

Naturally occurring polyphenols have received more research attention as they exhibit several health benefits in humans. Polyphenols inhibit oxidation of low-density lipoprotein, thereby decreasing the risk of CVD; in addition, they have anti-inflammatory and anti-carcinogenic properties (Nakamura, Watanabe, Miyake, Kohno, & Osawa, 2003). The phenolic fragments of Kraft lignin, obtained as a by-product during cellulose extraction in the paper manufacturing process, are potential antioxidants, comparable to vitamin E in humans (Faustino, Gil, Baptista, & Duarte, 2010). Lignin and other polyphenolics of INS also possess antioxidant potential and radical scavenging properties due to the phenolic hydroxyl groups (Dizhbite, Telysheva, Jurkjane, & Viesturs, 2004). *In vitro* condition simulating the small intestinal environment has demonstrated that lignin is able to adsorb carcinogenic compounds, i.e. N-nitrosamines (Funk et al., 2006). Ferulates from lignin form π-π interaction with aromatic amines and diferulates crosslink polysaccharides and increase the hydrophobicity of aromatic amines, which enhances the adsorption of N-nitrosamines (Funk et al., 2006; Harris, Triggs, Roberton, Watson, & Ferguson, 1996). The antimicrobial efficacy of lignin against intestinal pathogens like *Escherichia coli*, *staphylococcus aureus* and *pseudomonas*

has been demonstrated dose-dependently in *in vitro* studies (Nelson, Alexander, Gianotti, Chalk, & Pyles, 1994; Phillip, Idziak, & Kubow, 2000). Antibacterial activity against *Escherichia coli* and *pseudomonas* was reported in mice infected with these pathogens (Oh-Hara et al., 1990). Furthermore, it has been reported that lignin inhibited the growth of aerobic bacteria in the cecum and reduced the translocation of pathogenic bacteria in lymph nodes and the liver following burn injury in mice (Nelson et al., 1994). The mechanism for the antibacterial activity of lignin is still not clear, and it has been suggested that lignin damages bacterial cell membrane (Jung & Fahey, 1983). Lignin that remains in polymeric form contributes to bulking effect and improves gut health (Raninen et al., 2011). Ferulic acid is one of the major phenolic metabolites possessing all these activities (Ou & Kwok, 2004); other phenolic metabolites, such as 4-methyl-catechol and 3,4-dihydroxyphenylacetic acid, have shown antioxidant potential (Glasser, Graefe, Struck, Veit, & Gebhardt, 2002).

Arabinoxylan (AX)

AX is a hemicellulose with a xylose backbone linked by glycosidic linkage and arabinose side chains (Izydorczyk & Biliaderis, 1995). The ferulic or coumaric acid residue is linked to an arabinose side chain via an ester linkage. AX is a major component of DF in many cereal grains such as wheat, rye, barley, oat, rice, and sorghum, comprising 50–80 g/kg of whole grain. Apart from cereal grains, psyllium husk, pangola grass, bamboo shoots, corn hulls, and banana peels also contain a substantial amount of AX. Wheat bran contains about 64–69% AX and endosperm about 88% (Mares & Stone, 1973). AX is present as both water extractable (minor) and unextractable (major) fractions due to diferulate crosslinks. In wheat bran AX is acidic and mostly insoluble, while in endosperm AX is neutral and soluble (Ring & Selvendran, 1980). In the GI tract, AX acts much like a soluble fiber and is degraded by colonic bacteria possessing enzymes like xylanases and arabinofuranosidases (Vardakou et al., 2008). The health benefits of AX consumption include prevention of T2D and CVD and the improvement of GI functions.

β-glucan

β-glucan are heterogeneous polysaccharides present in the cell wall of certain microorganisms (yeast, algae, and protists), mushrooms and grains. They are found

in both soluble and insoluble form. Insoluble β-glucan contains β-(1-3/1-4)-D-linked glucose units; whereas soluble glucan contains (1-3/1-6)-D-linked glucose (Barsanti, Passarelli, Evangelista, Frassanito, & Gualtieri, 2011). β-glucan NSPs are present in various grains like oats, rye and barley, as well as mushrooms, yeast and some grasses. In cereal grain, D-glucose monomers are linear chain linked with glycosidic-linkage, while in yeast, fungi and certain bacteria, they are linked with branched chains. β-glucan constitutes about 2–6% of the dry weight of food material, and in cereal grains like barley and oats β-glucan makes up about 2–14% of dry weight. β-glucan is the most widely studied natural fiber in functional foods and possesses several health benefits against hypercholesterolemia, obesity, T2D, and CVD.

2.2 Dietary fibers and plasma lipids

DFs (soluble & insoluble) have been shown to decrease cholesterol and triglyceride and to improve glucose control in diabetic subjects (Abutair, Naser, & Hamed, 2018; Dhingra, Michael, Rajput, & Patil, 2012). At the Ninth Vahouny Fiber Symposium, experts in the field identified nine physiological health benefit attributed to DF intake (Howlett et al., 2010): (1) Reduced LDL-C and total cholesterol, (2) attenuated postprandial glucose and insulin, (3) reduced blood pressure, (4) increased fecal bulk and laxation, (5) decreased transit time, (6) increased colonic fermentation and SCFA production, (7) positive modulation of colonic microflora, (8) weight loss, weight maintenance and reduction in adiposity, and (9) increased satiety.

2.2.1 Polydextrose and plasma lipids

PDX modulates blood lipids in animals and humans, depending on the type of diet. There were no significant changes in plasma lipids of rats fed 3–6% PDX in the normal diet for a period of 2–6 weeks (Choi, Cho, Kim, & Lee, 1998). However, when 5% PDX was supplemented with a lipid load representing a moderate or high-fat diet, plasma triglyceride was reduced and HDL-C was increased in rats (Choe, Kim, & Ju, 1992). A 6% PDX supplementation for 4 weeks to gerbils on high-cholesterol and high-fat diet reduced plasma and liver total cholesterol via increased clearance of the cholesterol pool (Pronczuk & Hayes, 2006). In addition, reduced plasma triglyceride was observed in an acute study in which 28% PDX solution was administered orally in combination with 26% lactitol to rats along a

high-fat diet (Shimomura et al., 2005). The effect of PDX on lipid metabolism in clinical interventions has been studied in healthy, hypercholesterolemic and impaired glucose tolerance subjects. In healthy humans, PDX supplementation at a dose of 4–15 g/day did not affect plasma LDL-C or total cholesterol or triglyceride over a 1- or 2-month feeding period (Jie et al., 2000). In hypercholesterolemic individuals, PDX 15–30 g/day over a 4-week feeding period reduced LDL-C and showed a decreasing trend in total cholesterol; however, the study included only 12 subjects and when outliers were included there was no significant change (Pronczuk & Hayes, 2006). In subjects with T2D or impaired glucose metabolism, PDX supplementation lowered plasma LDL-C, increased HDL-C, and produced no changes in triglycerides over a 12-week feeding period (Rivellese et al., 1980).

Earlier studies showed that the postprandial triglyceride response was reduced with PDX plus lactitol supplementation in rats and humans. PDX + lactitol reduced the increase in plasma triglyceride concentrations after the ingestion of chocolate in humans (Shimomura et al., 2005). It has recently been demonstrated in humans that 12.5 g PDX alone decreased postprandial triglyceride response when supplemented with a high-fat meal (Tiihonen et al., 2015). The decreased postprandial triglyceride response was more pronounced in normolipidemic subjects compared to hyperlipidemic and obese subjects. In a human colon simulator model of fermentation, PDX induced expression of genes such as peroxisome proliferator-activated receptor alpha (*Pparα*) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*Pgc1α*) involved in energy metabolism and regulation of triglyceride response (Putaala, Makivuokko, Tiihonen, & Rautonen, 2011). Recently, an increase in glucagon-like peptide-1 (GLP-1) secretion was observed in obese subjects with PDX (Olli, Salli, Alhoniemi, Saarinen, Ibarra, Vasankari, Rautonen, & Tiihonen, 2015). Studies in animals and humans showed that GLP-1 reduced postprandial triglyceride secretion (Hsieh et al., 2010; Meier et al., 2006). Clinical trials with GLP-1 receptor agonists found a consistent reduction in the level of triglyceride by 0.2–0.3 mmol (Nauck, Meier, Cavender, Abd El Aziz, & Drucker, 2017). PDX is a secretagogue of GLP-1. The mechanism of PDX in postprandial triglyceride reduction is still unclear.

2.2.2 Lignin-rich INS from BSG and plasma lipids

Little is known about the effect of lignin on plasma lipids and the results in the literature are controversial. A daily dose of 12 g lignin for 4 weeks did not change

the plasma lipids, and pectin and cellulose did not alter plasma lipids in healthy subjects (Hillman, Peters, Fisher, & Pomare, 1985). This effect could be due to normal diet and healthy subjects. However, plasma cholesterol was reduced in hypercholesterolemic subjects with 1.2 g lignin and methylcellulose (99.5: 0.5 w/w) intake for 2–3 months (Thiffault, Belanger, & Pouliot, 1970), indicating that lignin reduces hypercholesterolemia. The hypocholesterolemic activity of β-glucan has been demonstrated in animal and human studies (Braaten et al., 1994). β-glucan from Aureobasidium pullulans decreased atherosclerosis, hyperlipidemia, and liver damage in hamsters fed a high-fat diet (Lim, Ku, Choi, & Kim, 2015). The hepatoprotective effect has been suggested to be due to the antioxidative and radical scavenging activity of β-glucan (Krizkova et al., 2003). Furthermore, β-glucan 50 mg/kg daily by oral gavage for 10 days protected against sepsis-induced oxidative injury in rats by decreasing plasma tumor necrosis factor alpha (Sener, Toklu, Ercan, & Erkanli, 2005). β-glucan from oat and barley showed similar hypolipidemic and antiatherogenic activity in hamsters fed with hypercholesterolemic diet (Delaney et al., 2003), by increasing total fecal neutral sterol. Tong *et al*. demonstrated that β-glucan decreased LDL-C by inhibiting cholesterol synthesis through reduced expression of 3-hydroxy-3-methylglutaryl CoA reductase *(Hmgcr*) and increased its degradation to bile acid by increasing cytochrome P450 family 7, subfamily a, member 1 (*Cyp7a1*) expression in hamster liver (Tong et al., 2015).

It has recently been observed in hypocholesterolemic subjects that β-glucan administration did not change cholesterol synthesis or absorption but increased bile acid synthesis by increasing *Cyp7a1* activity (Wang et al., 2017). Several studies in humans have shown that β-glucan reduces LDL-C in hypercholesterolemic and hypertriglyceridemic subjects (Rondanelli et al., 2011). Previous meta-analyses showed that barley β-glucan (5–7 g/day) slightly reduced LDL-C levels (AbuMweis, Jew, & Ames, 2010). Ho *et al*. recently showed in a meta-analysis that barley β-glucan intake (6.5-6.9 g/day) decreased LDL-C, but had no effect on HDL-C (Ho et al., 2016). According to FDA, at least 0.75 g of oat β-glucan is required for these health benefits (US Food and Drug Administration). The FDA recommends using barley food, providing 0.75g of soluble fiber per serving, in order to reduce the risk of coronary heart diseases (Arndt, 2006). In 2006, the FDA stated that 3 g/day of barley or oats β-glucan is sufficient to reduce serum LDL-C, total cholesterol and hence CVD (Arndt, 2006), which was also accepted by the European Food Safety Authority (EFSA) (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011). The effect of β-glucan on plasma cholesterol and post-prandial glucose concentration is mainly due to its viscosity and molecular

weight. High molecular weight β-glucan (≥ 1,000 kDa) found in native forms of oat and barley is more effective as compared to processed forms (Wang & Ellis, 2014).

The effects of AX on reducing plasma lipid are controversial, with some studies reporting a decrease in plasma lipids while others have found no effect (Chen et al., 2018). The effect on plasma lipids mainly depends on the source of AX and its nature and degree of feruloylation. Soluble AX from corn bran lowered cholesterol levels in rats fed with a cholesterol-rich diet by reducing uptake by increasing *Hmgcr* expression in liver (Lopez et al., 1999). Corn bran AX increased lipid catabolism by downregulating bile acid binding protein and upregulating farnesoid x receptor (*Fxr*) in the ileum and *Pparα*, *Pparγ*, lipoprotein lipase (*Lpl*) and *Cyp7a1* in the liver (Hu, Wang, & Xu, 2008). Wheat bran AX 5 g/kg of the diet alleviated LDL-C and total cholesterol in hypercholesterolemic hamsters during a 30-day feeding period (Tong et al., 2014). The authors observed that AX increased the excretion of lipids, cholesterol and bile acids in feces. In addition, AX decreased cholesterol synthesis by inhibiting *Hmgcr* and increased its degradation by increasing *Cyp7a1* expression in the liver (Tong et al., 2014). In pigs, 8% soluble AX from wheat reduced postprandial triglyceride levels during a 4-week feeding period by inhibiting triglyceride digestion and absorption (Gunness et al., 2016).

2.3 Dietary fibers, body weight and obesity

The effect of intake of DF in weight management is well documented. Epidemiologic studies show that DF intake is associated with reduced risk of obesity; however, mixed results are found in intervention studies (Birketvedt, Aaseth, Florholmen, & Ryttig, 2000; Howarth et al., 2003). An observational study of 89,432 European men and women for 6.5 years showed that a daily intake of 10 g total DF reduced body weight by 39 g/year and waist circumference by 0.08 cm/year, while daily intake of 10 g whole grain fiber reduced weight gain by 77 g/year and waist circumference 0.10 cm/year (Du et al., 2010). Longitudinal studies showed that consumption of DF 10 g/1,000 Kcal per day reduced body weight by 1.2–3.6 kg in a follow-up of 8–12 years (Koh-Banerjee et al., 2004). A cross-sectional study demonstrated that waist circumference was reduced in individuals consuming 11.3 g DF/1,000 kcal compared to 6.6 g/1,000 Kcal (Newby et al., 2007). A longitudinal study in overweight young subjects showed that an increased intake of 3 g/1,000 kcal total DF or insoluble fiber from year 1 to year 2 decreased visceral adipose tissue (-4% vs. +21%) (Davis, Alexander, Ventura, Toledo-Corral, & Goran,

2009). Similarly, an inverse relationship between cereal fiber intake and trunk fat mass was observed in older adults (McKeown et al., 2009). Recently, a meta-analysis of 8 randomized controlled trials including 1,026 subjects (adults & children) showed that a diet rich in fruit and vegetables (consuming 50–456 g) reduced body weight by 0.54 kg over a 4- to 52-week-period (Mytton, Nnoaham, Eyles, Scarborough, & Ni Mhurchu, 2014). A, meta-analysis of 12 randomized controlled trials demonstrated that intake of soluble fiber (3–34 g/day) reduced BMI by about 0.84 kg/m2, body weight by 2.52 kg, and body fat by 0.41% in overweight and obese adults in feeding trials of 2–17 weeks (Thompson, Hannon, An, & Holscher, 2017).

An intervention with fiber 4 g/day along with a low-calorie diet (1,200 Kcal/day) significantly reduced body weight by 8 kg as compared to 5.8 kg on placebo in overweight females over a 24-week period (Birketvedt et al., 2000). An intervention study with 34 individuals found that *ad libitum* high-carbohydrate diet without energy restriction or change in energy intake reduced body weight and body fat in older subjects (Hays et al., 2004). Fiber intake from fruits and vegetables plays a role in weight management by decreasing energy density and energy intake and by promoting satiety (Rolls, Ello-Martin, & Tohill, 2004). Tucker *et al*. reported that every 1 g/day increase in DF intake reduced body weight by 0.25 kg and fat by 0.25% over a 20-month monitoring period in women (Tucker & Thomas, 2009). Howarth *et al*. analyzed 50 intervention studies and found that an increase in daily fiber intake of 14 g was associated with a 10% decrease in energy intake and a 2 kg weight loss over a 4-month period (Howarth, Saltzman, & Roberts, 2001). A high fiber diet typically lowers the fat content and energy density of food, both of which are helpful in the maintenance of body weight. Soluble DFs prolong gastric emptying by forming a viscous gel in the intestine, attenuating macronutrient absorption, and inducing satiety (Wanders, Mars, Borgonjen-van den Berg, de Graaf, & Feskens, 2014). However, PDX is non-viscous in nature and has been demonstrated to shorten colonic transit time in constipated patients consuming 3.5 g PDX over 2 weeks (Magro et al., 2014). Hengst *et al*. reported that PDX 8 g/day for 3 weeks shortened oro-fecal transit time in healthy volunteers and improved constipation (Hengst, Ptok, Roessler, Fechner, & Jahreis, 2009). The effect of PDX on body weight is still unclear, and in an acute study, replacing 30% carbohydrates with PDX reduced postprandial glucose and insulin response and increased fatty acid oxidation in overweight subjects; however, the effect was not due to fiber but to lower energy content (King, Craig, Pepper, & Blundell, 2005).

Studies in animals and humans have demonstrated that β-glucan efficiently lowers body weight (Mosikanon, Arthan, Kettawan, Tungtrongchitr, & Prangthip, 2017; Xu et al., 2017). Yeast β-glucan (477-954 mg/day) reduced waist circumference in overweight and obese subjects over a 6-week supplementation (Mosikanon et al., 2017). It has been shown that a β-glucan rich extract prevented body weight gain dose-dependently by increasing lipolysis in diet-induced obese mice (Kanagasabapathy et al., 2013). A 7 g/day β-glucan intake for 12 weeks reduced LDL-C, total cholesterol, visceral fat, BMI and waist circumference in hypercholesterolemic Japanese men (Shimizu et al., 2008). Recently, 4.4 g barley β-glucan intake for 12 weeks reduced body weight, BMI, and waist circumference in obese individuals, and visceral fat area (VFA) was reduced only in the individuals having VFA > 100 cm^2 (Aoe et al., 2017). The authors suggested that reduced VFA might be due to the ability of β-glucan to form a highly viscous solution in the gut, preventing fat absorption (El Khoury, Cuda, Luhovyy, & Anderson, 2012). Previously, the same authors demonstrated in diet-induced obese mice that barley reduced sterol regulatory element-binding protein-1c (*Srebp1c*) expression and adipocyte size in epidermal fat (Aoe, Watanabe, & Yamanaka, 2010). The reduction in VFA might be due to reduced lipogenesis and increased GLP-1 secretion with barley (Nilsson, Johansson-Boll, & Björck, 2015). These studies clearly demonstrate that weight reduction with DF intake is more pronounced in obese compared to lean individuals.

2.4 Dietary fibers, satiety and energy intake

DFs are well known for inducing satiety and reducing energy intake (Ho, Matia-Merino, & Huffman, 2015; Rebello, O'Neil, & Greenway, 2016). On the contrary, others have concluded that fibers do not affect satiety (Clark & Slavin, 2013; Wanders et al., 2011). The satiety effect of fiber is due to its physicochemical characteristics such as solubility, fermentability and viscosity. Fermentable DFs produce SCFA and induce satiety by increasing GLP-1 secretion and inhibiting food intake (Zhou et al., 2008). Lin *et al*. demonstrated that SCFAs protect against diet-induced obesity in mice and that butyrate and propionate regulate body weight, at least partially, by inhibiting food intake and stimulating the secretion of anorexigenic gut hormones (GLP-1 and PYY) (Lin et al., 2012). In mice, acetate reduced appetite directly via the central nervous system (Frost et al., 2014).

2.4.1 Polydextrose, satiety and energy intake

Several studies have indicated that PDX supplementation could be beneficial in body weight control and glucose homeostasis as it reduces energy intake. Increased satiety and reduced energy intake with PDX has been reported in many human studies. PDX supplementation 1–1.5 hour before lunch reduced energy intake during the subsequent meal (Astbury, Taylor, & Macdonald, 2013); however, no satiety effects were observed when PDX was administered during breakfast (Monsivais, Carter, Christiansen, Perrigue, & Drewnowski, 2011). Increased satiety was also observed when 30% of the carbohydrates in a meal were replaced with PDX equivalent to 50 g PDX/day (Konings, Schoffelen, Stegen, & Blaak, 2014). A lower concentration of PDX did not produce a consistent satiety response (King et al., 2005). In lean subjects, PDX increased satiation, GLP-1 and peptide YY (PYY) and lowered ghrelin levels (Astbury, Taylor, French, & Macdonald, 2014). Recently, Olli *et al*. reported increased postprandial plasma GLP-1 and satiety in obese subjects with 15 g PDX along with a high-fat meal (Olli, Salli, Alhoniemi, Saarinen, Ibarra, Vasankari, Rautonen, & Tiihonen, 2015). In addition, the GLP-1 response 120 min after PDX supplementation correlated with the PDX fermentation rate measured by breath hydrogen (Kondo & Nakae, 1996).

One way in which GLP-1 promotes satiety is by decreasing the gastric emptying rate in addition to central effects (Gallwitz, 2012). A meta-analysis also demonstrated reduced energy intake with PDX administered 60 to 90 min prior to *ad libitum* lunch (Ibarra, Astbury, Olli, Alhoniemi, & Tiihonen, 2015). A reduction in energy intake by 12.5% was seen in both genders at the subsequent meal at lunchtime. The reduced energy intake was dose-dependent; 5% lower energy intake with a preload of 6.25 g PDX and 17% less energy intake with 25 g PDX. In addition, no change in energy intake during the rest of the day or at dinner was observed, in agreement with a previous investigation showing that reduced energy intake at lunch by PDX was not compensated during the rest of the day (Hull, Re, Tiihonen, Viscione, & Wickham, 2012). A recent meta-analysis found that PDX reduces the desire to eat during the satiation period (Ibarra, Astbury, Olli, Alhoniemi, & Tiihonen, 2016). PDX induced SCFAs to stimulate the secretion of GLP-1 and PYY (Carlson, Turpin, Wiebke, Hunt, & Adams, 2009), which might affect appetite by prolonging the satiation period.

2.4.2 Lignin-rich INS from BSG, satiety and energy intake

β-glucan (3%) at breakfast has been reported to reduce energy intake by 19% at the subsequent lunch in healthy subjects eating an isocaloric breakfast by suppressing hunger and increasing satiety (Vitaglione, Lumaga, Stanzione, Scalfi, & Fogliano, 2009). Furthermore, the authors showed that the effects of β-glucan on satiety were mediated by decreased plasma ghrelin and increased PYY secretion (Vitaglione et al., 2009). An intake of 2.9 g of barley β-glucan at breakfast significantly reduced hunger as shown on a visual analog scale (VAS) score, as well as energy intake at lunch in healthy Japanese women (Aoe et al., 2014). The authors also reported that cumulative energy intake at dinner was significantly inhibited by ingestion of β-glucan at breakfast (Aoe et al., 2014). Barley-kernel consumption increased gut hormone secretion of GLP-1 and PYY and improved insulin sensitivity in middle-aged individuals during a 3-day trial period (Nilsson, Johansson-Boll, & Bjorck, 2015). Furthermore, it has been observed that oat β-glucan increases satiety in overweight subjects by stimulating cholecystokinin (CCK) secretion (Beck, Tosh, Batterham, Tapsell, & Huang, 2009).

Gastric emptying

Gastric emptying is one of the mechanisms for inducing satiety with DF intake. DF increases gastric distention, which induces satiety via the vagal nerves and by inhibiting the secretion of ghrelin (hunger stimulating hormone) (Mion et al., 2005; Wijlens et al., 2012). In addition, DF influences gastric emptying via secretion of gut hormones such as GLP-1 and PYY (Brownlee, 2011). Ghrelin accelerates gastric emptying while CCK, GLP-1 and PYY delay it (Steinert et al., 2017). Delayed gastric emptying with DF intake has been observed in several human studies (Georg Jensen, Kristensen, Belza, Knudsen, & Astrup, 2012; Sanaka, Yamamoto, Anjiki, Nagasawa, & Kuyama, 2007). Various factors such as size, water holding capacity, viscosity, solubility and fermentability determine the effect of fiber on gastric emptying (Juvonen et al., 2009; Tan, Wei, Zhao, Xu, & Peng, 2017). Several studies have reported that viscous fibers delay gastric emptying and induce satiety although some studies have failed to find such effects (Odunsi et al., 2010; Wanders et al., 2013). Recently, a meta-analysis of 11 intervention studies with different soluble fibers concluded that not all soluble fibers delayed gastric emptying (Salleh, Fairus, Zahary, Bhaskar Raj, & Mhd Jalil, 2019). PDX is a soluble non-viscous fiber, which has been shown to delay gastric emptying in

human studies. Twelve grams of PDX in low-protein/high-protein soya bean curd showed delayed gastric emptying and reduced energy intake in healthy individuals (Soong et al., 2016). The authors indicated that delayed gastric emptying is partly responsible for the reduced energy intake with PDX. In healthy and T2D subjects, 7.5 g of soluble oat β-glucan delayed gastric emptying (Yu, Ke, Li, Zhang, & Fang, 2014). The authors suggested that delayed gastric emptying is responsible for the improved glucose control with DF intake in T2D.

2.5 Dietary fibers and gut microbiota

DFs modulate the gastrointestinal microbiota (Makki, Deehan, Walter, & Backhed, 2018). Gut microbiota consists of bacteria, archaea, protozoa and viruses present in the GIT, with bacteria account for the major proportion (99.1%) (Bruzzese, Volpicelli, Squaglia, Tartaglione, & Guarino, 2006). Bacterial density in the human colon has been estimated at about 10^{11}–10^{12} cells/g (Backhed, Ley, Sonnenburg, Peterson, & Gordon, 2005; Otte, Kiehne, & Herzig, 2003). There are more than 1,000 bacterial species inside the gut; about 160 species are shared among individuals (Qin et al., 2010). The gut microbiota plays a major role in the metabolism of indigestible DF, differentiation, and development of host intestinal epithelium and immune homeostasis (Smith, McCoy, & Macpherson, 2007). The gut microbiome is also considered as an endocrine organ as it secretes gut hormones and produces vitamins and SCFAs (Mishra, Dubey, & Ghosh, 2016). The gut microbiota is essential for human health as it modulates villus architecture, angiogenesis, and aids in digesting food and protects against pathogenic bacteria (Sommer & Backhed, 2013). It affects the early nutritional status, energy balance, growth, and individual susceptibility to infections and immune disorders throughout the lifespan (Agostoni & Kim, 2015). Manipulations of the gut microbiome have demonstrated that it could have beneficial effects in various diseases such as obesity, T2D, nonalcoholic fatty liver disease (NAFLD), inflammatory bowel diseases (IBD), colon cancer, and CVD (Emoto et al., 2017; Tilg, Adolph, Gerner, & Moschen, 2018).

Environmental factors such as diet, lifestyle, hygiene and use of antibiotics affect the gut microbiome. Diet is a major contributing factor for the microbial composition of the gut. The microbiome changes after the first year of life, resembling the adult gut microbiome after approximately 36 months (Koenig et al., 2011). A major change in diet – switching from meat to plant-based foods or vice versa – changes the gut microbiome very rapidly, within 2-3 days, in humans and

animals (David et al., 2014; Walker et al., 2011). This is not at all surprising considering that the microbial population doubles within an hour and the microbial community is purged every 24–48 hours. In addition, it has been shown that a Western diet significantly alters the gut microbial composition in various strains of mice. These findings suggest that diet is the major factor for gut microbial composition over host genetics (Carmody et al., 2015). The dietary patterns influence the host metabolism favorably, and targeting the gut microbiome might be a useful approach for the management of obesity and other metabolic diseases (Mikkelsen, Knop, Frost, Hallas, & Pottegard, 2015). In healthy humans and animals, the majority of gut microbes fall into two predominant (> 90%) phyla: Firmicutes and Bacteroidetes, while lower numbers of Actinobacteria, Proteobacteria and Verrucomicrobia are also present (Marchesi et al., 2016).

Phylum Bacteroidetes

The phylum Bacteroidetes (gram-negative) genera include *Bacteroides*, *Prevotella*, *Porphyromonas*, and others such as *Alistipes* and *Parabacteroides*. The members of this phylum are efficient degraders of DFs. *Bacteroides*, *Prevotella*, and *Porphyromonas* utilize polysaccharides and possess relatively high amounts of carbohydrate-active enzymes (hydrolases and lyases), which enable the digestion of both dietary and host mucosal glycan (Backhed et al., 2005). Bacteroidetes mainly respond to energy load with a reduced abundance in obese mice (Turnbaugh et al., 2006). Bacteroidetes were decreased by about 20% in overfed lean subjects and Finnish monozygotic twins with excess energy availability (Jumpertz et al., 2011). Interestingly, gastric bypass surgery increased *Bacteroides* (Furet et al., 2010). These observations suggest that Bacteroidetes are mainly dependent on nutrient status. However, malnourishment depleted Bacteroidetes in Bangladeshi children, with *Prevotella* more abundant in healthy and *parabacteroides* in malnourished children (Monira et al., 2011). Monira *et al*. suggested that a reduction in Bacteroidetes decreases glycan fermentability, contributing to malnourishment through decreased SCFAs production. In rats, time-restricted feeding increased *Bacteroides* and *Prevotella* while the overall Bacteroidetes abundance was reduced (Queipo-Ortuno et al., 2013). Barley kernel bread increased *Prevotella* and improved glucose metabolism in humans (Kovatcheva-Datchary et al., 2015). *Prevotella* increases hepatic glycogen storage in mice, indicating that *Prevotella* improves glucose metabolism by promoting glycogen

storage (Kovatcheva-Datchary et al., 2015). Therefore, Bacteroidetes might be a valuable target for therapeutic interventions.

In T2D subjects, the genera *Bacteroides*, *Alistipes*, and *Parabacteroides* were increased in Chinese individuals, whereas in Swedish women, a decrease in *Bacteroides* with high hemoglobin A1c was observed (Karlsson et al., 2013). These studies highlight the complexity of the interactions within this phylum. Short-term feeding in humans demonstrated that *Bacteroides* were negatively associated with DF intake and positively associated with a diet rich in protein and animal fat (Wu et al., 2011). In contrast, long-term feeding showed that *Bacteroides* correlated positively with DF intake, as demonstrated in Finnish monozygotic twins receiving similar amounts of calories (Simoes et al., 2013).

Phylum Firmicutes

The phylum Firmicutes (gram-positive) includes the genera *Clostridium*, *Lactobacillus*, *Ruminococcus*, *Eubacterium*, *Faecalibacterium*, and *Roseburia*. Firmicutes account for about 70% of species diversity within human gut microbiota but have received considerably less research attention compared to Bacteroidetes (Eckburg et al., 2005). The genome size of Firmicutes is smaller in comparison to Bacteroidetes because they carry fewer genes related to polysaccharide degradation (Kaoutari, Armougom, Gordon, Raoult, & Henrissat, 2013). Members of this phylum stabilize the gut microbiome and prevent lactate accumulation and acidity by converting lactate to butyrate or propionate (Belenguer et al., 2007). *Faecalibacterium* and *Eubacterium* are dominant members of this phylum, which produces butyrate (Louis, Young, Holtrop, & Flint, 2010). Mutant obese (*ob/ob*) and diabetic (*db/db*) mice had a higher abundance of *Ruminococcaceae* and *Rikenellaceae* compared to lean ones, and high-fat diet consumption led to an increase of these genera (Kim, Gu, Lee, Joh, & Kim, 2012).

Reduced dietary intake of carbohydrates decreased butyrate-producing Firmicutes in obese human subjects (Duncan et al., 2007). A rapid decreased in abundance of Firmicutes and an increase in Bacteroidetes was reported under extreme diet change, such as switching from a plant-based to an animal (David et al., 2014). Daniel *et al*. showed in mice that high-fat diet decreased *Ruminococcaceae,* which utilize plant polysaccharides (Daniel et al., 2014). High-fat diet also suppressed the relative abundance of *Ruminococcaceae* in rats while quercetin supplementation increased *Ruminococcaceae* with a decrease in weight and inflammation (Zhao et al., 2017). Insoluble starch and wheat bran are mainly

fermented by Firmicutes; especially *Ruminococcus* were enriched in subjects consuming starch (Leitch, Walker, Duncan, Holtrop, & Flint, 2007). *Ruminococcus bromii* plays a major role in the degradation of resistant starch, and individuals lacking this species are unable to degrade resistant starch (Ze, Duncan, Louis, & Flint, 2012).

Other bacterial phyla

Bifidobacterium is a major genus within Actinobacteria, Proteobacteria include *Escherichia* and *Desulfovibrio*, whereas Verrucomicrobia include only *Akkermansia*. *Bifidobacteria* are gram-positive bacteria that account for 3–6% of the total bacterial population in adult intestine, whereas in breastfed infants they constitute more than 80% of the gut microbiota (Lewis et al., 2015). *Bifidobacteria* are saccharolytic and play an important role in the fermentation of carbohydrates and other complex carbon sources like gastric mucin, oligosaccharides and pectin. They differ from other gut bacteria as they metabolize carbohydrates via the bifid shunt. The bifid shunt, also known as fructose-6-phosphate shunt, converts monosaccharides to intermediates of the hexose fermentation pathway, and finally to SCFAs and other organic acids (de Vries & Stouthamer, 1967). In human interventions, supplementation with prebiotics such as inulin, fructo-oligosaccharides, and galacto-oligosaccharides has been demonstrated to stimulate *lactobacilli* and *Bifidobacteria* (Macfarlane, Steed, & Macfarlane, 2008). High-fat diet increased endotoxemia in mice by decreasing *Bifidobacteria* whereas prebiotics supplementation reduced endotoxemia by restoring *Bifidobacteria* (Cani et al., 2007). *Lactobacillus* and *Bifidobacteria* express bile-salt hydrolases, which, through deconjugation, can potentially modify bile-salt profiles in the gut lumen (Martoni, Labbe, Ganopolsky, Prakash, & Jones, 2015).

The phylum Verrucomicrobia mainly includes mucus-degrading bacteria, representing 1–4% of the bacterial population in the colon. The genera *Akkermansia* correlates inversely with body weight gain in rodents and humans (Everard et al., 2013), but it has also been reported to be increased in T2D (Qin et al., 2012). Feeding a high-fat diet decreased *Akkermansia* while fish oil consumption increased *Akkermansia* in mice (Caesar, Tremaroli, Kovatcheva-Datchary, Cani, & Backhed, 2015), indicating that saturated and unsaturated fatty acids affect the gut microbiome differently. Lard, rich in saturated fatty acids, increased the abundance of *Bilophila* in mice while fish oil, rich in unsaturated fatty acids, decreased their abundance (Caesar et al., 2015). An increase in *bilophila* was

also observed in humans consuming diets rich in saturated fats (David et al., 2014). *Bilophila wadsworthia* are sulfide-producing microbes and belong to the phylum Proteobacteria. Milk, high-fat diet, and bile acids stimulated the growth of *Bilophila* in mice (Devkota et al., 2012). *Bilophila wadsworthia* increased gut inflammation in interlukin-10 deficient mice, and an increased abundance was detected in colorectal cancer patients (Yazici et al., 2015).

2.5.1 Gut microbiota and obesity

The change in microbial composition is considered an important causal factor in the development of obesity and metabolic diseases. The microbial diversity is reduced in obese humans, but whether the reduced diversity is the cause or the consequence of obesity is still inconclusive (Turnbaugh et al., 2009). Qin *et al*. demonstrated in Chinese individuals that the gut microbiota was altered in T2D (Qin et al., 2012). The link between metabolism and gut microbiota was also demonstrated in germ-free mice. Reduced adiposity and weight gain in germ-free mice compared to conventionally raised mice were caused in part by the reduced energy extraction capability from diet (Backhed et al., 2004). In addition, germ-free mice were resistant to diet-induced obesity when fed with high-fat or/and Western diet (Backhed, Manchester, Semenkovich, & Gordon, 2007). Backhed *et al.* suggest that the increased fatty acid oxidation in skeletal muscle is caused by an upregulation of fasting-induced adipose factor (*Fiaf)* in the intestine (Backhed et al., 2007). These observations demonstrate that the gut microbiome is altered in obesity and various other metabolic diseases. Animal studies have demonstrated a significant increase in Firmicutes and a decrease in Bacteroidetes in *ob/ob* mice compared to wild-type mice despite similar energy intake and level of activity (Ley et al., 2005). Surprisingly (because of different food and life style), similar observations were made in human studies, with increased Firmicutes and decreased Bacteroidetes in obese and T2D patients (Karlsson et al., 2013). Furthermore, a greater Firmicutes/Bacteroidetes (F/B) ratio was observed in obese animals or humans (Everard & Cani, 2013; Sweeney & Morton, 2013).

However, some conflicting results were observed in human studies: an increase in Bacteroidetes in obese or overweight subjects and no significant difference in F/B ratio in obese compared to lean subjects (Million et al., 2013). Still, most of the studies in humans indicate that an increase in Firmicutes and a decrease in Bacteroidetes is associated with obesity. The inconsistencies in human results are due to various factors like diet, physical activity, socio-economic conditions, and

environment (Dugas, Fuller, Gilbert, & Layden, 2016). Furthermore, it has been reported that genes encoding carbohydrate-metabolizing enzymes were enriched in obese mice compared to non-obese mice, enabling them to extract more energy from diet (Turnbaugh et al., 2006). Long-term high-fat diet feeding decreased *Enterobacteriaceae*, *Bacteroides*, *Proteobacteria* and *Bifidobacterium* (Murphy et al., 2010). High-fat diet increased the Firmicutes/Bacteroidetes ratio and decreased *Bifidobacterium* in mice (Gauffin Cano, Santacruz, Moya, & Sanz, 2012). DF has been shown to reduce obesity, insulin resistance, and other metabolic diseases induced by a high-fat diet by modulating gut microbiota. Prebiotics (inulin-type fructans) supplementation improved metabolic phenotypes in obese mice with an increase in Proteobacteria (Everard et al., 2011). DF from bamboo shoot prevented body weight gain and insulin resistance induced by a high-fat diet by increasing Bacteroidetes and decreasing Firmicutes in mice (Li, Guo, Ji, & Zhang, 2016).

2.5.2 Gut microbiota and lipids

Various studies have reported a close association between the gut microbiota and dyslipidemia. Germ-free mice first supported the role for gut microbes in both affecting host energy metabolism and modulating lipid levels (Velagapudi et al., 2010). In hyperlipidemic patients, gram-negative *bacilli* were increased and SCFA-producing bacteria decreased (Wang et al., 2016). Furthermore, a 20% increase in Bacteroidetes and 24% decrease in Firmicutes was observed in non-obese NAFLD patients (Wang et al., 2016). A significant correlation was observed between Bacteroidetes, Firmicutes and their ratio with total plasma cholesterol and triglyceride in obese rats (Dong et al., 2016). Fu *et al*. analyzed blood lipids and gut microbiota in 893 subjects, and showed that 34 bacterial taxa significantly correlated with blood lipids, accounting for 6% of the change in cholesterol and 4% in HDL-C (Fu et al., 2015). Rhizoma coptidis, an alkaloid showing a lipid-lowering effect in mice fed a high-fat and high-cholesterol diet, was observed to have lipid-lowering activity due to gut microbiota and bile acid (He et al., 2016). These findings indicate that the gut microbiota plays a critical role in dyslipidemia, but the mechanism is still unclear.

Production of SCFAs, secondary bile acids, and trimethylamine N-oxide (TMAO) by gut microbiota could be the mechanism for the reduction in plasma lipids. Studies in humans and animals demonstrated that TMAO levels are increased in atherosclerosis (Wang et al., 2011). TMAO is produced by hepatic oxidation of trimethylamine, which is a microbial intermediate derived from

dietary choline and L-carnitine (Bennett et al., 2013). TMAO exerts an anti-atherogenic effect by modulating reverse cholesterol transport, cholesterol, sterol metabolism, and bile acids (Warrier et al., 2015). Interestingly, host DNA appears to play a negligible role in the TMAO regulation, particularly in humans, which suggests that dietary factors and gut microbiome are more important determinants than the host genome (Hartiala et al., 2014).

2.5.3 Polydextrose and gut microbiota

The prebiotic potential of PDX has been shown in *in vitro* and human interventions. PDX positively modifies the gut microbial composition and its activity (Canfora & Blaak, 2015; Holscher et al., 2015). In contrast to other prebiotics, PDX is slowly and partially fermented and produces a minor amount of gas (Roytio & Ouwehand, 2014). PDX supplementation in healthy men increased Bacteroidetes abundance by 12% and concomitantly suppressed Firmicutes by 12% (Holscher et al., 2015). Similarly, Hooda *et al*. showed an increase in *Clostridiaceae* (5%) and *Faecalibacterium* (5%), and lower numbers of *Eubacteriaceae* (4%) with PDX in healthy men, concluding that PDX has positive impacts on gut microbiota and host health (Hooda et al., 2012). PDX supplementation of 8 g/day for 3 weeks in humans increased the abundance of *Ruminococcus intestinalis* (butyrate producing) and *clostridia* while decreasing *Lactobacillus* and *Enterococcus* (Costabile et al., 2012). In addition, a decreased genotoxic effect of fecal water in the colon was reported for PDX, indicating that PDX may aid in genotoxic events (Costabile et al., 2012). Forssten *et al*. demonstrated that PDX at a concentration of 2% and 4% v/v inhibited the growth of *Clostridium difficile* (pathogenic bacteria) in an *in vitro* colon model (Forssten, Roytio, Hibberd, & Ouwehand, 2015).

Metabolomics analysis of human feces from subjects consuming PDX demonstrated a wide range of metabolites related to oligosaccharides (Lamichhane et al., 2014). In an *in vitro* fermentation study, PDX significantly increased *Bifidobacteria*; however, contradicting results were obtained concerning *lactobacillus*. PDX-containing chocolate intake demonstrated an increase in *Bifidobacteria* and *lactobacilli* in human feces (Beards, Tuohy, & Gibson, 2010). An *in vitro* study demonstrated an increase in *Erysipelotrichaceae* in the feces of humans consuming PDX (Lamichhane et al., 2018). The family *Erysipelotrichaceae* is well known as a producer of SCFAs (Vital, Howe, & Tiedje, 2014).

2.5.4 Lignin-rich INS from BSG and gut microbiota

Lignin-rich INS increases intestinal *Bifidobacteria* in mice fed with fiber-deficient diet (Maukonen et al., 2017). An *in vitro* fermentation study demonstrated that lignin-rich INS favored the growth of *Bifidobacteria* (Niemi et al., 2013). Lignin-rich INS also increased the bacterial diversity of *Ruminococcaceae* and *Lachnospiraceae* in mice fed a fiber-deficient diet (Maukonen et al., 2017). β-glucan favored bacterial growth of *Lactobacilli* and *Bifidobacteria* as observed in various *in vitro* and *in vivo* studies (Kristek et al., 2019; Mitsou et al., 2009). The bifidogenic capability of β-glucan has also been shown in humans. Oat β-glucan increases *Bifidobacteria* and *Lactobacilli* more than barley β-glucan, and higher amounts of β-glucan are more effective than lower amounts (Hughes, Shewry, Gibson, McCleary, & Rastall, 2008). Oat β-glucan reduced lipid plaques and atherogenesis in the aortic wall by regulating gut microbiota *Akkermansia muciniphila* in apolipoprotein-E-deficient mice on high-fat/high-cholesterol diet (Ryan et al., 2017). *Akkermansia muciniphila* stimulates gut peptide secretion (Everard & Cani, 2013), improves insulin sensitivity, and is a potent mucin degrader (Derrien, Vaughan, Plugge, & de Vos, 2004). Oat β-glucan also attenuated *Desulfovibrio spp*., which catalyzes choline to atherogenic TMA (Craciun & Balskus, 2012).

The molecular weight of β-glucan is important for its influence on the gut microbiome. Low molecular weight β-glucan was ineffective while high molecular weight β-glucan significantly altered the gut microbiota (Wang et al., 2016). An increased abundance of Bacteroidetes and a decreased abundance of Firmicutes and their respective taxa was observed in humans consuming 3 g/day high molecular weight as compared to low molecular weight β-glucan (Wang et al., 2016). β-glucan induced Bacteroidetes and the bacterial genera *Prevotella* and *Roseburia* as well as propionate production (Fehlbaum et al., 2018). In addition, *Bacteroides*, *Prevotella*, and *Dorea* correlated inversely with BMI, waist circumference, plasma triglyceride and blood pressure in humans (Wang et al., 2016). β-glucan consumption favored the growth of Firmicutes in HFD-fed mice (Drew et al., 2018). AX also showed prebiotic capability by stimulating the growth of *Bifidobacteria* in animals and humans. The effect of long-chain AX on *Bifidobacteria* and SCFA production has been investigated using *in vitro* gut models (Van den Abbeele, Venema, Van de Wiele, Verstraete, & Possemiers, 2013). AX supplementation increased *Bacteroides*, *Prevotella*, *Roseburia,* and *Bifidobacterium* after a high-fat diet in mice (Neyrinck et al., 2011). AX reduced *Clostridium* and Proteobacteria

(colitis and inflammatory bacteria) as well as *Desulfovibrionaceae* while increasing *Butyricicoccus* (gut barrier protection) bacteria (Suriano et al., 2017).

2.6 Dietary fibers and short-chain fatty acids (SCFAs)

SCFAs are major microbial metabolites and an end product of bacterial fermentation of DFs (den Besten et al., 2013). The principal site of fermentation is the proximal colon due to high substrate availability, and the primary fermenters are Bacteroidetes. During fermentation, non-digestible carbohydrates are hydrolyzed into oligosaccharides and monosaccharides by gut microbiota. The major pathway includes the Embden-Meyerhof-Parnas and pentose-phosphate pathways that convert monosaccharides into phosphoenolpyruvate, which is finally converted to acids and alcohols (Miller & Wolin, 1996). The fermentation also produces gases like carbon dioxide (CO2) and hydrogen (H2) along with SCFAs (Topping & Clifton, 2001). Acetate, propionate, and butyrate are the most abundant SCFAs (~100 mmol/kg colonic material), with a decreasing concentration from the cecum/proximal colon to the distal colon in humans and animals (Macfarlane, Gibson, & Cummings, 1992). Acetate, propionate, and butyrate are present in a molar ratio of 60:20:20 in human colon and stool (Cummings, Pomare, Branch, Naylor, & Macfarlane, 1987). SCFAs are rapidly absorbed (up to 95%) by the colonocytes; only a minor fraction is excreted in feces (Topping & Clifton, 2001). SCFA is then assimilated into the host lipid and carbohydrate metabolism providing approximately 10% of our daily energy requirements (Bergman, 1990). Acetate and butyrate act as a substrate for lipogenesis and cholesterol synthesis, while propionate is primarily a precursor for gluconeogenesis. Butyrate is more selective for free fatty acid receptor 3 (FFA3) while acetate is more selective for free fatty acid receptor 2 (FFA2), and propionate has equal affinity for both (Le Poul et al., 2003). FFA2 and FFA3 receptors are G-protein coupled receptors abundantly expressed in the colon, white adipose tissue, liver and skeletal muscle (Brown et al., 2003).

2.6.1 Role of short-chain fatty acids in metabolic diseases

SCFAs modulate host appetite and food intake by promoting the release of GLP-1 and PYY, which affects glucose homeostasis and lipid accumulation (Psichas et al., 2015; Tolhurst et al., 2012). SCFAs prevent insulin resistance and obesity by increasing energy expenditure and inducing mitochondrial functions. SCFAs

promote fatty acid oxidation and inhibit de novo synthesis and lipolysis, resulting in decreased plasma concentrations of fatty acids and reduced body weight (Kondo, Kishi, Fushimi, Ugajin, & Kaga, 2009). SCFAs stimulate adenosine monophosphate kinase (*AMPK*) activity in muscle and liver which triggers *Pgc1α* expression resulting in decreased fatty acid synthesis and increased fatty acid oxidation (Gao et al., 2009). *Pgc1α* plays an important role in fatty acid and glucose metabolism by regulating various transcription factors such as *Pparα-γ*, *Lxr*, and *Fxr*, stimulating fatty acid oxidation in muscle, liver and inhibiting *de novo* fatty acid synthesis in the liver. It also stimulates fatty acid oxidation and thermogenesis in brown adipose tissue by upregulating *Pgc1α* and uncoupling protein-1 (*UCP1*) expression (Gao et al., 2009). *AMPK* increases phosphorylation of *Pgc1α* both directly and indirectly by preventing its degradation by p38. *In vitro* studies have demonstrated that SCFAs increases the AMP/ATP ratio and *AMPK* activity in liver and muscle (Kondo, Kishi, Fushimi, & Kaga, 2009).

SCFAs reduced lipolysis in adipose tissue by activating FFA2 receptors as shown in isolated adipocytes (Ge et al., 2008). Intravenous acetate and propionate decreased plasma glycerol and free fatty acid in humans (Al-Lahham, Peppelenbosch, Roelofsen, Vonk, & Venema, 2010). The reduction in lipolysis is mediated via inactivation of hormone-sensitive lipase (*HSL*), which hydrolyzes triglycerides in adipose tissue (Carmen & Victor, 2006). SCFAs bind to FFA2 receptor in adipose tissue and decrease the production of cAMP, which in turn decreases protein kinase A activity (PKA). The decreases in PKA activity lead to inactivation of *HSL* in adipose tissue by dephosphorylation (Carmen & Victor, 2006). It has been demonstrated that resistant starch increases SCFAs in plasma and lowers *HSL* activity in adipose tissue (Robertson, Bickerton, Dennis, Vidal, & Frayn, 2005). The effects of SCFAs in various tissues are summarized in Figure 4.

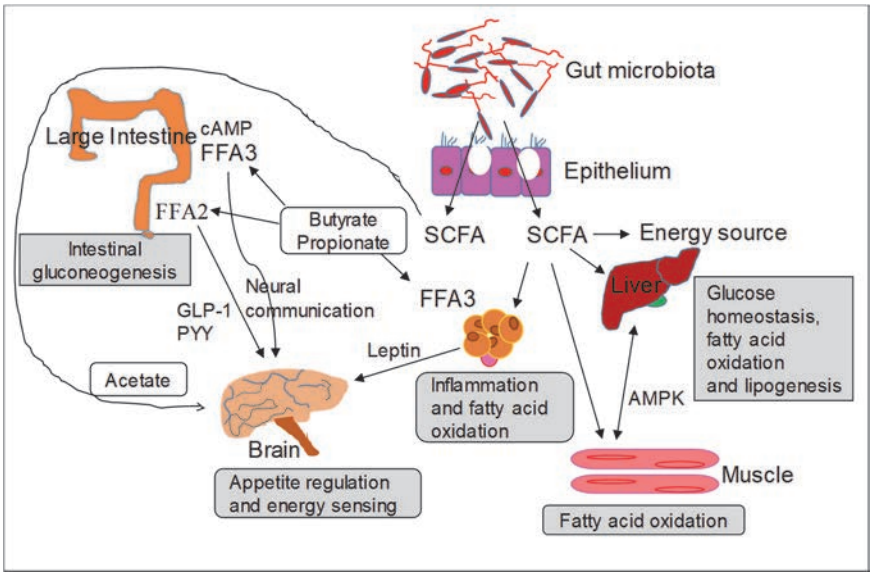

Fig. 4. SCFA and their role in various tissues (modified from Hobden, Guerin-Deremaux, Rowland, Gibson, & Kennedy, 2015).

The phylum Bacteroidetes mainly produces acetate and propionate, whereas Firmicutes produces butyrate (Macfarlane & Macfarlane, 2003). SCFAs reduce plasma cholesterol in humans and rodents: propionate reduces cholesterol synthesis by inhibiting *Hmgcs* and *Hmgcr*, while acetate inhibits *Hmgcs* and increases the metabolism of cholesterol to bile acid by *Cyp7a1* activity (Kondo, Kishi, Fushimi, Ugajin et al., 2009). Various studies have shown that butyrate prevents colon cancer by inhibiting histone deacetylase influencing apoptosis, cell proliferation, and differentiation (Donohoe et al., 2012). During fermentation, the gut microbiome produces succinate, which is a major intermediate in the tricarboxylic acid cycle. Succinate is an intermediary product in propionate synthesis during fermentation and hence it is detected in very low levels (1-3 mM) in human intestinal content and feces (Meijer-Severs & van Santen, 1987). DF feeding increased cecal succinate concentration in mice (De Vadder et al., 2016) and succinate production was increased when the fiber was supplemented with a high-fat diet. Succinate is the endogenous ligand of G-protein coupled receptor 91 (*GPR91*). Plasma concentrations of succinate ranged from 2 to 20µM in mice and humans suggesting that, under physiological conditions, activation of *GPR91* by succinate might only be relevant in the gut lumen (Sadagopan et al., 2007).

2.6.2 Polydextrose and short-chain fatty acids

The complex structure of PDX makes it a slowly fermentable fiber (Makelainen, Makivuokko, Salminen, Rautonen, & Ouwehand, 2007) and even undigested PDX is found in human feces (Costabile et al., 2012). The fermentation of PDX depends on glycosidic linkage and gut microbes prefer 1-6 pyranose linkage (Lahtinen et al., 2010). SCFAs are produced as major fermentation products along with gases (H2, CO2 & methane). An *in vitro* fermentation study demonstrated that compared to other galactooligosacchrides and fructans, PDX produced significantly less gas due to the smaller amounts of H2 (Hernot et al., 2009). PDX is well tolerated at higher doses in humans (up to 50 g bolus and daily consumption of up to 90 g) (Flood, Auerbach, & Craig, 2004). *In vitro* studies showed that PDX increased the concentration of all three SCFAs (Makelainen et al., 2007). Recently, an *in vitro* fermentation study using nuclear magnetic resonance (NMR) spectroscopy observed an increase in SCFAs (acetate, butyrate, and propionate), succinate and lactate in human fecal samples with PDX (Lamichhane et al., 2018). An increase in SCFAs, especially acetate and propionate, was found in gastrectomized rats with 7.5% PDX supplementation over 60 days (do Carmo et al., 2018). In healthy dogs, PDX (0.5–1.5% of diet) feeding increased fecal acetate, propionate and total SCFAs over 14 days (Beloshapka, Wolff, & Swanson, 2012). In contrast to the various *in vitro* and *in vivo* studies, SCFA production was reduced in the colon of PDX supplemented pigs (Fava et al., 2007), with increased acetate and lactate blood levels, indicating that the reduction was due to increased SCFAs absorption. The effects of PDX on SCFAs in humans are still unclear, with no change or decrease in fecal SCFA levels (Boler et al., 2011; Costabile et al., 2012; Hengst et al., 2009). It may be possible that serum levels of these SCFAs are increased in humans as in pigs.

2.6.3 Lignin-rich INS from BSG and short-chain fatty acids

Klason lignin and food containing lignin produced butyrate in the human colon by increasing the levels of *Bacteroides* and *Bifidobacterium* (Fernandez-Navarro et al., 2018). *In vitro* and animal studies demonstrated that β-glucan increased the production of SCFAs, mainly propionate and butyrate (Hughes et al., 2008; Mikkelsen, Jensen, & Nielsen, 2017; Teixeira, Prykhodko, Alminger, Fak Hallenius, & Nyman, 2018). An increase in fecal SCFAs was found in hypercholesterolemic individuals consuming 3 g/day high molecular weight β-glucan (Thandapilly, Ndou,

Wang, Nyachoti, & Ames, 2018). Barley β-glucan 6 g/day increased fecal propionate in patients with high risk of metabolic syndrome (Velikonja, Lipoglavsek, Zorec, Orel, & Avgustin, 2019). AX produced acetate, butyrate, and propionate in animal and human interventions (Hald et al., 2016; Le Gall, Serena, Jorgensen, Theil, & Bach Knudsen, 2009). Arabinoxylan oligosaccharides (AXOS) represent prebiotic potential similar to the well-known inulin-type fructans, and an *in vitro* fermentation study demonstrated an increase in acetate, propionate and butyrate (Van den Abbeele et al., 2018). AXOS increased mainly butyrate in healthy volunteers (Damen et al., 2012). *In vitro* studies using human fecal material demonstrated that lignin-rich INS was fermented to acetic acid, propionate, and butyrate (Niemi et al., 2013).

2.7 Dietary fibers and bile acid (BA)

Bile acids (BAs) are another group of gut microbiota-derived metabolites involved in various metabolic diseases (Parseus et al., 2017). BAs are synthesized from cholesterol in the liver as taurine or glycine conjugated bile acid, stored in the gallbladder, and secreted into the intestine, facilitating the absorption of dietary lipids and fat-soluble vitamins. Primary bile acids (mainly cholic acid (CA) and chenodeoxycholic acid (CDCA) in humans) (Kuipers, Bloks, & Groen, 2014), (CA and β-muricholic acid (β-MCA) in rodents (Kerr et al., 2002) are synthesized in the liver. About 95% of biliary secreted BAs are reabsorbed by the apical sodium-dependent bile acid transporter (ASBT) in the ileum, predominantly as conjugated BA and transported back to the liver for secretion; known as the enterohepatic circulation of BA.

The gut microbes with bile salt hydrolase (BSH) activity deconjugate primary bile acids and prevent their intestinal reuptake. The deconjugated BAs are poorly absorbed and thus excreted with the feces (Chiang, 2009). The BSH-possessing bacteria include *Lactobacillus*, *Bifidobacterium*, *Methanobrevibacter*, *Clostridium*, *Enterococcus*, and *Bacteroides* (Tremaroli & Backhed, 2012). The primary BAs that escape the reuptake reach the colon and are metabolized by gut microbiota into secondary bile acids such as deoxycholic acid and lithocholic acid (Ridlon, Kang, & Hylemon, 2006). The secondary bile acid-producing bacteria include *Clostridium*, *Eubacterium*, *Actinobacteria*, *Proteobacteria*, *Firmicutes*, and *Bacteroidetes* (Kisiela, Skarka, Ebert, & Maser, 2012; Ridlon, Kang, Hylemon, & Bajaj, 2014). The gut microbes that metabolize primary bile acids into secondary bile acids have also been demonstrated in germ-free or antibiotic treated animals.

The bile acid pool in these animals mainly consists of primary conjugated bile acid (Selwyn, Csanaky, Zhang, & Klaassen, 2015). These secondary BAs are excreted in feces and only a minor fraction is absorbed (Lepercq et al., 2004). These findings show a clear bidirectional relationship between gut microbiota and BA metabolism.

2.7.1 Factors affecting bile acid

The BA pool is affected by several factors including feeding: a significant increase in the BA pool has been shown in mice after feeding, and these diurnal changes seem to be regulated by the transcription of *Cyp7a1* by the clock gene *Rev-erbα* and by fibroblast growth factor 15 (*Fgf15*) (Le Martelot et al., 2009). The postprandial BA pool is larger compared to the fasting state (Haeusler et al., 2016). Obese subjects showed higher circulating levels of BAs after a mixed meal due to the reduced hepatic expression of BA transporter compared to lean subjects (Haeusler et al., 2016). Obese and diabetic mice had a higher serum BA pool due to increased *Cyp7a1* activity and expression (Li et al., 2012). Consistent with the results in mice, humans showed an elevated BAs pool after an oral glucose tolerance test (Shaham et al., 2008). Insulin given during a hyperinsulinemic clamp study acutely reduced BAs while the effect was diminished in obese subjects (Haeusler et al., 2016).

BA sequestrants are non-absorbable resins and well-known hypolipidemic agents (Hansen et al., 2017). Prior to the statins, bile acid sequestrants were the first line of treatment for reducing LDL-C plasma concentrations. Bile acid sequestrants bind BA in the intestinal lumen and increase their excretion in feces, interrupting their enterohepatic circulation. Since the BA pool is reduced under BA sequestrants, bile synthesis is increased, as demonstrated by an increase in *Cyp7a1* expression in the liver (Einarsson et al., 1991). The increased catabolism of cholesterol to bile acid enhances the demand for cholesterol in the liver by increasing cholesterol synthesis and uptake, with a reduction in plasma LDL-C and total cholesterol levels. DF supplementation increases *Hmgcr* and low-density lipoprotein receptor (*Ldlr*) expression and activity in the liver. Several studies have shown that cholesterol reduction with DF intake is due to increased bile acid excretion (Andersson et al., 2013; Togawa, Takahashi, Hirai, Fukushima, & Egashira, 2013). DFs such as oat bran, bagasse, pectin, psyllium and mixture of soluble and insoluble fibers bind to BAs, increase their excretion, and reduce cholesterol in animals and humans (Andersson et al., 2013; Togawa, Takahashi, Hirai, Fukushima, & Egashira, 2013). Previously, it has been demonstrated that β-glucan induced BA excretion by

forming a viscous gel in the intestine (Behall, Scholfield, & Hallfrisch, 2004). Furthermore, BA binding activity of lignin has been demonstrated in *in vitro* studies (Camire & Dougherty, 2003).

2.7.2 Bile acid receptors

Bile acids modulate host glucose, lipid metabolism, and energy expenditure and are linked to several diseases, such as dyslipidemia, fatty liver disease, obesity, T2D, atherosclerosis, cholestasis, gallstones, and various types of cancer (Li & Chiang, 2014). The major bile acid receptors include nuclear receptor *Fxr* and membrane-bound Takeda G protein-coupled receptor 5 (*Tgr5*). *Fxr* is ubiquitously expressed in various tissues such as liver, intestine, white adipose tissue and heart. Bile acid signaling in the gut and liver has been extensively studied (Schaap, Trauner, & Jansen, 2014). *Fxr* regulates glucose and lipid metabolism by affecting the gene transcription involved in primary BA synthesis (Wahlstrom, Sayin, Marschall, & Backhed, 2016). *Fxr* inhibits the hepatic and intestinal expression of *Cyp7a1* directly and indirectly, respectively, by induction *Fgf15* (human *Fgf19*) expression in animals (Potthoff, Kliewer, & Mangelsdorf, 2012). *Fxr*-deficient (*Fxr-/-*) mice show increased plasma bile acid, cholesterol, and triglyceride compared to wild-type mice due to increased *Cyp7a1* activity in mutant mice (Lambert et al., 2003). CA supplementation to these mice reduced their body weight and increased serum bile acid levels 23-fold, with a decreased total bile acid pool compared to wild-type mice. These results demonstrate that *Fxr* plays a major role in regulating BA synthesis, especially feedback control in BA overload. *Fxr-/-*mice on a cholesterol-rich diet had high plasma cholesterol and triglyceride levels and atherogenic profiles (Hanniman, Lambert, McCarthy, & Sinal, 2005).

Liver Fxr

Liver *Fxr* expression was reduced in streptozotocin-induced diabetic rats (Duran-Sandoval et al., 2004). They also observed in primary rat hepatocytes that insulin repressed whereas glucose increased *Fxr* expression (Duran-Sandoval et al., 2004). *Fxr-/-* mice display glucose intolerance and insulin resistance (Zhang et al., 2006). The *Fxr* agonist (GW4064) treatment or overexpression in the liver reduced blood glucose levels in both diabetic (*db/db)* and wild-type mice by suppressing gluconeogenic genes and activating glycogenesis in the liver (Zhang et al., 2006). However, Prawitt *et al*. demonstrated in obese mice (*ob/ob* and diet-induced) that

Fxr deficiency reduced weight gain and improved glucose homeostasis (Prawitt et al., 2011). Similar findings were reported in *ob/ob Fxr-/-* mice, and diet-induced *Fxr-/-* mice, indicating that loss of *Fxr* prevents genetic or diet-induced obesity (Zhang et al., 2012). *Fxr* activation had different outcomes in obese and lean mice: Obese *Fxr-/-* mice had lower body weight, improved glycemia and insulin sensitivity, while lean *Fxr-/-* mice were dyslipidemic, with impaired glucose and insulin resistance (Ryan et al., 2014). *Fxr* agonist (GW4064) supplementation to obese mice aggravated weight gain, dyslipidemia and glucose intolerance in long-term studies (Watanabe et al., 2011), indicating that in obesity, *Fxr* inhibition has a favorable effect.

Intestinal Fxr

Liver-specific *Fxr-/-* mice were not protected against diet-induced obesity and insulin resistance, indicating a role of nonhepatic *Fxr* (Prawitt et al., 2011). Intestinal *Fxr* inhibition improved glucose homeostasis and *Fxr-/-* mice were protected from obesity and glucose intolerance (Jiang et al., 2015). Several studies have reported that intestinal *Fxr* deficiency or antagonism improved insulin resistance, fatty liver and energy expenditure in obese and diabetic mice by reduction of ceramide levels (Jiang et al., 2015; Xie et al., 2017). Recently, it has been shown that low ceramide levels diminished hepatic gluconeogenesis by decreasing acetyl-CoA levels and pyruvate carboxylase activity (Xie et al., 2017). In contrast to improved metabolic outcome with reduced intestinal *Fxr*, treatment with intestinal *Fxr* agonist (fexaramine) led to reduced weight gain and insulin resistance in diet-induced obese mice (Fang et al., 2015). The authors, showed that fexaramine promoted thermogenesis and fatty acid oxidation; however, the same metabolic phenotype was not seen in mice lacking *Tgr5*, suggesting that fexaramine partially regulates *Tgr5* signaling in addition to *Fxr* (Fang et al., 2015). *Tgr5* is a G protein-coupled receptor expressed in various tissues like intestine, adipose tissue, skeletal muscle, brain, and pancreas. BA activation of *Tgr5* led to GLP-1 secretion through cAMP, which further activate glucose-stimulated insulin secretion (Katsuma, Hirasawa, & Tsujimoto, 2005). Interestingly, bariatric surgery disrupts the enterohepatic circulation and increases BA levels (Ahmad, Pfalzer, & Kaplan, 2013). Intestinal *Fxr* activation has a detrimental effect on obesity, glycemic response, and energy expenditure, indicating that inhibition of intestinal *Fxr* signaling has potential in treating metabolic abnormities associated with obesity and T2D.

3 Aims of the study

The purpose of the thesis was to investigate the effects of the dietary fiber PDX and the lignin-rich insoluble residue (INS) of BSG on obesity and lipid metabolism in diet-induced obese mice and to elucidate the mechanisms by which these fibers reduce cholesterol and triglycerides.

Our hypotheses were as follows:

1. PDX improves lipid metabolism by modulating gastrointestinal microbiota in mice fed Western diet D12079B.
2. Lignin-rich insoluble residue (INS) from brewer's spent grain (BSG) is not inert but degraded in the mouse colon by the gut microbiome.
3. Lignin-rich insoluble residue (INS) from brewer's spent grain (BSG) may improve obesity and dyslipidemia induced by high-fat diet in mice.
4. PDX intake as part of breakfast or a midmorning preload may reduce energy intake and appetite-related parameters in healthy and overweight females

4 Materials and methods

4.1 Materials

Polydextrose was obtained from DuPont Kantvik, Finland. BSG was obtained from Sinebrychoff brewery, Kerava, Finland. Lignin-rich INS from BSG was obtained from VTT Technical Research Center of Finland, Espoo, Finland. CEL came from James River Corporation, Berlin, NH, USA. Enzymes were obtained as follows: Depol 740 L from Biocatalysts Ltd., Cefn Coed, Wales, UK, celluclast 1.5 from Novozymes, Bagsvaerd, Denmark, and alcalase 2.4 from Novozymes Bagsvaerd, Denmark. Human Insulin Actrapid came from Novo Nordisk, Kuesnacht, Switzerland. Cholesterol FS, Triglyceride FS, HDL-C and LDL-C kits were obtained from DiaSys (Diagnostic Systems GmbH, Holzheim, Germany). Glucose was purchased from Roche Diagnostics GmbH, Germany, Insulin from Roche Diagnostics GmbH, Germany, CCK from Euro Diagnostic AB, Malmö, SE, and Ghrelin, GLP-1 and PYY from EMD Millipore, MO, USA. Nonfat yogurt was obtained from Friesland Campina, Netherland, and ^{13}C-octanoate sodium salt from Campro Scientific GmbH, Germany. Breath bags were from Wagner, GmbH, Bremen, Germany. Total RNA NucleoSpin RNA kit from Macherey Nagel GmbH & Co. KG, Düren, Germany, and qScripts from Applied Biosystems, Foster City, CA, USA. Organic solvents: methanol, analytical grade, was obtained from Fisher Scientific, Loughborough UK and ethanol from VWR international, Leicestershire, UK. Whatman filter paper no.2, Sep-Pak column Plus C18 from Waters Corporation Milford, Massachusetts, USA. Other chemicals and reagents were purchased from Sigma-Aldrich, St Louis, MO, USA.

4.1.1 Preparation of lignin-rich INS from BSG (II-III)

The main components of BSG were lignin, AX, β-glucan, protein, lipids, and ash. Ferulic and p-coumaric acid contents were 3.0 and 1.1 mg/g BSG, respectively. An enzymatic hydrolysis of BSG was performed for carbohydrates and protein removal followed by an additional cellulose digestion step, rendering a lignin-rich insoluble residue (INS) as depicted in Figure 3. In detail, a BSG suspension (6%) was prepared and passed through a grinder (MKZA10-15J, Masuko Sangyo Co. Ltd., Japan MKGA10–80 grinding stones, speed of 1,500 rpm) several times. The suspension was centrifuged and water-decanted, and solid residues were stored

overnight at 4°C. Enzymatic hydrolysis was carried out in two steps in a 10-L reactor using a 10% (w/w) solids content. In the first hydrolysis step, 1,000g BSG preheated to 50°C was treated with enzymes Depol 740 L (5000 nkat of xylanase activity per gram of BSG) and celluclast 1.5 L (50 FPU per gram of BSG) for digestion of carbohydrates. The mixture was continuously stirred at 48 rpm at pH 5.4. After 5 h, the suspension was centrifuged in a precooled SorvallRC12BP centrifuge with an H12000 rotor (Sorvall Products L.P., Newton, CT, USA) at 4°C and 4,000 rpm for 30 min. The solid residue was collected and washed twice with water to remove solubilized components and traces of enzymes, and small aliquots were taken for composition analysis of the dry matter. The solid residue was used in the second step of the hydrolysis.

The second step was proteolytic hydrolysis with the enzyme alcalase 2.4 L (20 µL enzyme/g BSG) for 4 hours at 60°C and pH 10 in 100mM sodium carbonate buffer. The pH was kept constant at 10 during the hydrolysis by using 10M NaOH solution. Hydrolysis was terminated by centrifugation and washing with water. After proteolytic treatment, the carbohydrate digestion was repeated for removal of residual carbohydrates. After hydrolyzes, the insoluble residue was separated from the slurry with an Alfa-Laval separator BTPX 205SGD-34CDP-50 (Alfa Laval, Tumba, Sweden). The obtained solid fraction was washed with distilled water and centrifuged, the supernatant was removed, and the solid fraction was freeze-dried and designated as lignin-rich insoluble residue (INS).

4.1.2 Preparation of feed (II-III)

The animal feeds were prepared by Altromin Spezialfutter (GmbH & Co. KG, Lage, Germany). The feeds were based on 60% fiber-deficient diet C1013 (10% Kcal fat) and 40% of INS, 40% CEL or their mixtures 40% INS-CEL (3:2 ratio), respectively (II publication). In our other experiments, the high-fat diet (HFD) C1090-60 (60% Kcal fat, < 0.05% fiber) was mixed with 20% INS, CEL, or their combination (INS-CEL, 1:1) and pelleted (III publication). The HFD contained 21% protein, 33.2% carbohydrates and 35% lard fat. The control diet (CD) C1090-60 (10% Kcal fat, < 0.05% fiber) had a similar composition as HFD, with no additional fibers added.

4.2 Animal feeding experiment (I-III)

All animal experiments were approved by the National Animal Experiment Board of Finland. Animal experiments were conducted in accordance with the guidelines

set by the Finnish Act on Animal Experimentation, Statute of Animal Experimentation, the animal protection legislation (62/2006, 36/2006 and HE32/2005), European Union Directive 2010/63/EU, and European Union Commission recommendation 2007/526/EC.

In publication I, male C57BL/6NCRl mice were fed Western diet D12079B and oral gavage with 75 mg PDX in water (referred to as WD+PDX group) or water alone as control (referred to as WD group) twice daily at 8 am and 6 pm for 14 days. Body weight and food intake of all the animals were recorded on a daily basis. In publication II, male C57BL/6NCRl mice were fed fiber-deficient diet C1013 supplemented with 40% INS, 40% CEL and 40% INS-CEL (3:2 ratio) for 15 days. In publication III, male C57BL/6NCRl mice were fed a high-fat diet C1090-60 supplemented with 20% INS, 20% INS-CEL and 20% CEL for 14 weeks. Body weight was recorded weekly and food intake monitored for one week at the beginning and at the end of week 12.

4.2.1 Feces and urine collection (I-III)

In publication I, 24-hour fecal samples were collected from the mice for fat analysis before and at day 14 of the experiment. In publication II, urine and feces were collected in metabolic cages individually before and after 14 days of feeding. Samples were collected for 24 hours at two intervals: 8 hours and 24 hours. In publication III, 24-hour fecal samples from the mice were collected for bile acid analysis after 14 weeks of feeding.

Fecal fat analysis (I)

Fecal fat content was analyzed using an accredited gravimetric method (Korpi-Steiner, Ward, Kumar, & McConnell, 2009). Feces were hydrolyzed with 3 M hydrochloric acid (HCl) by boiling for 45 min, and extracted with organic solvents (Eurofins Scientific, Raisio, Finland) and analyzed.

Extraction and analysis of metabolites in urine (II)

Due to the small volume of urine, the two fractions (8- and 24-hour samples) were combined, and the 500-µL urine sample was hydrolyzed using β-glucuronidase (0.1 mg/mL) in 1.5 mL hydrolysis solution. 15 µL 2-hydroxycinnamic acid (123 ppm) was added as an internal standard and samples were incubated for 16 hours at 37°C.

After hydrolysis, samples were washed with water on preconditioned OASIS® HLB 1cc Extraction Cartridge (Waters Corp., Milford, MA, USA). Samples were extracted using 400 µL of methanol and after extraction, the methanol was evaporated under nitrogen flow. Comprehensive profiling of the urine metabolites was performed using two-dimensional gas chromatography coupled with time-of-flight mass detection (GCxGC-MSTOF; Leco Pegasus 4D, St. Joseph, MI, USA). The following compounds were used as standards: benzoic acid, 3-hydroxybenzoic acid, 3-(4′-hydroxyphenyl) propionic acid, 4-methylcatechol, and 3-(3′,4′-dihydroxyphenyl) propionic acid, 4-hydroxybenzoic acid, 2-(3′-hydroxyphenyl) acetic acid, 2-(3′,4′-dihydroxyphenyl) acetic acid, 4-hydroxycinnamic acid, and ferulic acid, 3-phenylpropionic acid, vanillic acid (3-methoxy-4-hydroxybenzoic acid), and 3,4-dihydroxybenzoic acid, 3-(3′-hydroxyphenyl) propionic acid and gallic acid.

N-Methyl-*N*-trimethylsilyl-trifluoracetamide (MSTFA) and methoxyamine hydrochloride (MOX) (2%) in pyridine were used in the derivatization of the metabolites. Urinary samples were silylated with MSTFA and MOX using GCxGC-TOFMS instrument as previously described (Aura et al., 2013). The 15-day urinary metabolite profile data sets were compared with the 0-day urinary data set and significant values (FDR) q value < 0.05) were selected using the Guineu software (Castillo, Mattila, Miettinen, Oresic, & Hyotylainen, 2011). The fold test was performed using Guineu showing a ratio of average responses (15d vs. 0d profile). Data were filtered and structurally relevant metabolites with higher folds than 3.7 were displayed in a heat map. Most of these compounds were identified based on model compounds, commercial library, and earlier studies (Aura, Niemi et al., 2013).

Fecal bile acid analysis (III)

The collected fecal samples were lyophilized using a vacuum concentrator (Savant Speed Vac Plus SC210A, Savant Vapornet VN100, Savant Refrigerated Vapor Trap RVT400, Savant Vacuum Pump VP190, GMI, MN, USA). One hundred mg from each sample was weighed and ground to a fine powder using a ball mill (MM400 Retsch GmbH, Haan Germany). One mL of freshly prepared 2 mg/mL sodium borohydride solution in ethanol was added to reduce 3-keto bile acid to 3-alpha bile acid, the mixture was vortexed, and incubated at room temperature for 1 hour. The samples were saponified by adding 50 µL 2 N HCl and 200 µL 10 N NaOH, sealed and incubated for 12 hour at 120°C in heated blocks to extract bile acid. The

samples were filtered through Whatman filter paper no. 2 and the filter was rinsed twice with 500 µL ethanol. The filtrate (2 mL) was dried under nitrogen at 70°C and re-suspended in 2 mL of distilled water. Chromatography was performed on the aqueous suspension using individual C18 Bond Elute columns (500 mg/6 mL). The columns were pre-washed with 2 mL 100% methanol followed by 2 mL distilled water; 2 mL samples were loaded onto the columns. The columns were then washed twice with 2 mL of 20% methanol. Bile acids were eluted with 2 mL methanol, dried at 60°C under nitrogen gas, and re-suspended in 2 mL methanol for storage at -20°C until further analysis. Fecal bile acids were measured by an enzymatic assay using a specialized mouse total bile acid assay kit (Cat: 80470, Crystal Chem Inc Elk Grove Village, IL USA) according to the manufacturer's protocol.

4.2.2 Insulin tolerance test (ITT) and glucose tolerance test (GTT) (III)

ITT was performed at week 12 and GTT at week 13 (III). For ITT, animals fasted for 4 hours (8:00–12:00) and basal blood glucose was recorded. Immediately after basal recording human insulin, 0.35 IU/kg body weight was injected intra-peritoneally. Blood glucose was measured at 15, 30 and 60 minutes after insulin injection. For GTT, animals were fasted for 12 hours (20:00–8:00) and blood glucose was measured at 0 minutes. Immediately after 0 minutes all animals were injected intra-peritoneally with glucose solution (20% in saline), 1.5 g/kg body weight. Blood glucose was measured at 15, 30, 60 and 120 minutes after glucose injection. Blood glucose was measured by One Touch Ultra glucometer using One Touch Ultra 2 glucose strips (LifeScan Johnson & Johnson, PA, USA). Food was provided to animals immediately after the test.

4.2.3 Blood and tissue collection (I-III)

Terminal blood samples were collected from 12-hour fasted mice via retro-orbital plexus under isoflurane anesthesia in EDTA tubes (I and III) and fed blood samples (II). EDTA blood was centrifuged at 8,000 rpm for 7 min at 4°C, plasma was separated for clinical chemistry, and stored at -70°C until further measurements. The animals were sacrificed immediately thereafter by cervical dislocation. Liver, epididymal fat pad, small intestine (duodenum, jejunum, and ileum), colon, and cecal contents were collected. The wet weight of the liver and epididymal fat pad was measured immediately after isolation and they were snap frozen in liquid

nitrogen and stored at -70°C until further analysis. Cecal contents were transferred into 1.5 mL pre-weighed Eppendorf tubes, wet weight was recorded, the contents were snap frozen in liquid nitrogen, and stored at -70°C until analysis.

4.2.4 Histology and image analysis (III)

Liver tissues were fixed overnight in 10% neutral buffered formalin, and subsequently dehydrated via graded alcohol series and xylene, and mounted in paraffin. For light microscopy, 4-µm thick sections were cut and stained with hematoxylin and eosin and periodic acid-Schiff (PAS) stains. For image analysis, Image J (National Institute of Health, MD, USA) was used. Representative samples from each liver specimen were photographed with a Nikon Eclipse E600 microscope (Nikon Inc. Tokyo, Japan) using a 20x apochromatic objective. Images were converted into grayscale. Subsequently, thresholds for binary images were manually adjusted. Intracellular fat accumulations that were overlapping were separated using the Watershed algorithm (separate attached cells). Sinusoid areas were manually deselected, and the number of fat particles was measured using the Measure algorithm and the corresponding area occupied by fat analyzed using the Analyze Particles algorithm (https://imagej.nih.gov/ij/). The results were exported in CSV format and evaluated in Excel and SPSS 23.

4.2.5 Barcoded 16S rRNA amplicon sequencing (I)

Microbial DNA was extracted from the cecal digesta using the QIAamp DNA stool Mini extraction kit (Qiagen, Hilden, Germany). Before extraction, the samples were dispersed using bead-beating. The microbial community composition was analyzed using high throughput amplicon sequencing as previously described (Caporaso, Kuczynski et al., 2010). Briefly, the V4 region of the 16S rRNA gene of Bacteria and Archaea was amplified in triplicates by polymerase chain reaction (PCR) using primers 515F (GTGCCAGCMGCCGCGGTAA) and 806R (GGACTACHVGGGTWTCTAAT) with the addition of appropriate Illumina sequencing adapters and a unique 12 bp Golay barcode in the reverse primer. PCR products were purified, normalized by DNA concentration, and pooled into one library for sequencing on the Illumina MiSeq platform.

4.2.6 Microbial analyses of fecal (II) and cecal material (II, III)

DNA was extracted from fecal (II) and cecal samples (II, III) of mice as previously described (Maukonen et al., 2006). Briefly, 200 mg of fecal or cecal material was used for DNA isolation using Fast DNA Spin kit for soil (MP Biomedicals, Santa Ana, CA, USA) as per manufacturer's instructions. Before using the DNA isolation kit, samples were broken with a Fast Prep instrument (Bio 101 Savant, Holbrook, NY) at 6.0 m/s for 60 s from one (reference strains) to three (some clostridial reference strains and mouse fecal samples) times. DNA was isolated, quantified by using NanoDrop 2000c (Thermo Fisher Scientific), and stored at -20°C until future analysis. The number of fecal and cecal bacteria was analyzed by performing quantitative-PCR (qPCR) for the predominant bacteria, which includes *all bacteria* (Univ), *Eubacterium rectale* (Erec), *Clostridium leptum* (Clept), *Bacteroides* (Bfra), *Atopobium* (Ato), *Bifidobacteria* (Bif), and *lactobacilli* (Lac) as previously described (Maukonen, Simoes, & Saarela, 2012; Simoes et al., 2013).

4.2.7 Gene expression analysis from liver and intestine (I)

Real-time PCR analysis was performed for the analysis of gene expression. Total RNA was isolated from the liver and small intestine (duodenum, jejunum, ileum, and colon) using Total RNA NucleoSpin® 96 RNA kit. RNA concentrations were measured by Qubit 3.0 Fluorometer (Thermo Fisher Scientific, MA, USA) and cDNA was synthesized using SuperScript III and random primers (Thermo Fisher Scientific, MA, USA) as per manufacturer's instructions. The concomitant relative gene transcript analyses were performed in triplicates (7500 FAST Real-Time PCR System, Thermo Fisher Scientific, MA, USA) using specific TaqMan Gene Expression Assays. A fatty acid metabolic gene array of the liver tissue was performed (PAMM-007Z#geneglobe Qiagen, Hilden Germany) and the most promising candidates from the array were selected for real-time PCR analysis (Putaala et al., 2011). The genes from intestinal tissues were *Acsl3*, *Acsl5*, *Cd36*, *Dgat1*, *Fabp2*, *Fgf15*, *Fiaf*, *Npcl*, *Npcl1*, *Fxr*, *Pparα*, and *Pgc1α*, and from liver tissues, *Prkacα*, *Prkaα*, *Hmgcr*, *Acat*, *Acot2*, *Cyp7a1*, *Ldlr*, *Slc27a2*, *Acot3*, *Acot6*, *Cd36*, *Pparα* and *Pgc1α* (Thermo Fisher Scientific, MA, USA) (I, Supplementary Table 1). Ribosomal protein, large, P0 (*Rplp0*) was used as a reference gene for both intestinal and liver tissues, which showed consistent expression.

4.2.8 Liver Gene expression analysis (III)

Total RNA was extracted from the liver tissue as described above. Genomic DNA was removed via G-DNA column. RNA concentration and quality were determined with NanoDrop ND-1000 UV-Vis Spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). One µg RNA was transcribed to cDNA using cDNA synthesis kit qScripts. The specific primers for mouse *Hmgcr*, *Ldlr*, *Pparα*, *Fxr*, and *Pxr* were used and samples normalized to *GAPDH* endogenous control. Primers for SYBR green were purchased from TAG Copenhagen A/S (TAG Copenhagen, Frederiksberg, Denmark); sequences are shown in III, Supporting Table S3. Real-time PCR reactions were performed with the ABI-PRISM 7700 sequence detection system (Applied Biosystems Thermofisher Scientific, MA, USA) in a total volume of 30 µL. All samples were subjected in duplicates to the following conditions: 2 min at 50°C and 10 min at 95°C, followed by 42 cycles of 15 s at 95°C and 1 min at 62°C. Each assay included a relative standard curve of three serial dilutions of cDNA from mice and no-template controls. The cycle threshold (Ct) values below 34 were considered positive and the others negative. The results were calculated according to the manufacturer's descriptions using ABI PRISM 7700 Sequence Detection System (Applied Biosystems Thermofisher Scientific, MA, USA).

4.3 Polydextrose and gastric emptying in humans (IV)

PDX was investigated in an acute, randomized, double-blind, placebo-controlled crossover study in healthy and overweight females (n=32). The subjects were to refrain from food, exercise and alcohol after 11:00 pm before the test day. On the test day, 12.5 g PDX was served at 8:30 am as part of breakfast (t=0 min) or a midmorning preload (t=150 min) before an *ad libitum* lunch meal (t=240 min). The volunteers consumed the same amount of calories, 800 KJ, at breakfast on all test days within 30 min and a nonfat yoghurt that provided an additional 800 KJ with 12.5 g PDX (PDX-B) or placebo (CON-B) with breakfast. For the midmorning preload, a nonfat yoghurt providing an additional 800 KJ with 12.5 g PDX (PDX-M) or placebo (CON-M) was consumed 150 min after breakfast. Thus all the volunteers consumed 1,600 KJ before an *ad libitum* lunch. All the volunteers were given a food diary to complete throughout the day. Energy intake and appetite were assessed in all the treatment groups. Plasma glucose, insulin and gut peptides (CCK, ghrelin, GLP-1 and PYY) were measured for treatments PDX-B and CON-B.

Gastric emptying was measured for treatments PDX-B and CON-B by ^{13}C-octanoid breath test, using IRIS®^{13}C-Breath Test System (IRIS®, nondispersive infrared spectroscopy; Wagner, GmbH, Bremen, Germany). ^{13}C-octanoate sodium salt was administered in the yogurt as shown in Table 3 and breath samples were collected in aluminum bags at predetermined time points as shown in (IV, Table S4). The results were expressed as t_{lag} denoting the time at which the gastric emptying was maximal and $t_{1/2}$ the time of half-gastric emptying (Ghoos et al., 1993).

Table 3. Formulation of experimental nonfat yogurt (400 g).

Ingredients	Verum (g)	Placebo (g)
Non-fat Friesland Campina yogurt	372.64	388.60
12.5 g PDX	17.86	0.00
Glucose syrup 42% Dextrose Equivalent	9.30	11.20
^{13}C-octanoate sodium salt	0.10	0.10
Flavor	0.10	0.10

4.4 Statistical analyses (I-IV)

Statistics were calculated either with GraphPad Prism version 7 or SPSS 21. Comparison of two groups was performed using unpaired "t" test (I) and multiple groups were analyzed by one-way ANOVA followed by Dunnett's multiple comparison (II, III). The data are expressed as the mean ± standard deviation (SD) and significances are two-sided. Differences were considered to be statistically significant when $P < 0.05$. The qPCR data were transformed to logarithmic scale before analyses by ANOVA. Steatosis was graded as follows: Grade 0 (0% to 5%) Grade 1 (> 5% to 33%), Grade 2, (> 33% to 66%) and Grade 3, (> 66%) (Brunt, 2007). Median steatosis grade and mean surface area percentage were used in the estimation of the severity of steatosis between different groups (III).

Microbiome Sequence Analysis and Statistics (I)

The sequencing data were processed and analyzed using the QIIME (v. 1.8) pipeline. Overlapping 2 x 250 bp reads were stitched together using fastq-join (Aronesty, E., 2011) allowing for 5% nucleotide difference in a minimum 200 bp overlap. Reads that were unpaired, contained ambiguous bases, or had a Phred quality score of less than 20 were discarded. Sequences were clustered into

operational taxonomic units (OTUs) at 97% sequence similarity using an open reference clustering scheme with uclust in QIIME (Edgar, 2010). OTUs that did not match a reference sequence in the Green genes database (13_8 version available from http://greengenes.lbl.gov/) were retained and clustered de novo (DeSantis et al., 2006). Representative sequences were aligned using PyNAST and a taxonomic tree was constructed using FastTree (Caporaso et al., 2010; Price, Dehal, & Arkin, 2010). The resulting OTU table was filtered to remove OTUs containing less than five sequences, and the relative abundance of the bacterial taxa is reported as a percentage of total sequences.

Alpha (within the sample) and beta (between-sample dissimilarity) diversity were analyzed in QIIME with an OTU table rarefied at a depth of 24,279 sequences per sample. Alpha diversity was assessed by the Observed OTUs and Phylogenetic Diversity Whole Tree metrics, and group comparisons were made using t-test with 1,000 Monte Carlo permutations (Faith, 1992). Beta diversity was measured with unweighted and weighted UniFrac metrics (Lozupone & Knight, 2005). The resulting distance matrix was visualized using a principal coordinate analysis (PCoA) plot with the top ten most abundant genera using the bi-plot function and EMPeror in QIIME (Vazquez-Baeza, Pirrung, Gonzalez, & Knight, 2013). The significance of sample clustering was assessed using permutational multivariate analysis of variation (PERMANOVA) with 1,000 permutations. Discriminate taxa between groups were determined using the Mann-Whitney U test in QIIME. Spearman correlation analysis was conducted for microbial genera, lipid parameters, and gene expression values that showed group differences using GraphPad Prism version 6. For all tests, p values were subjected to the Benjamini-Hochberg false discovery rate (FDR) correction and $p<0.05$ was considered a significant difference.

For intestinal tissue, data were analyzed using statistical software R (version 3.2.3; www.r-project.org). The statistical models were computed using R package nlme, and the contrasts with the corresponding p-values were obtained using R package multcomp. The data of each parameter (i.e. expression of each gene) was log-transformed and modeled using a linear model with terms for the intestine part, treatment, and their interaction. The model used was a mixed model with a subject-wise random intercept term or, if the mixed model could not be fitted to the data, a generalized least squares model. The comparisons were performed using model contrasts, and the p values were adjusted for multiple comparisons. The adjusted p values were computed from the joint normal or t distribution of the z statistics, which is the default method of the multcomp package (Hothorn, Bretz, & Westfall,

2008). Adjusted p-values < 0.05 were considered statistically significant. Spearman correlation analysis was conducted for microbial groups, lipid parameters, and gene expression values using R v. 3.4 Hmisc and gplots packages (R development core team 2008, http://www.R-project.org, http://CRAN.R-project.org/package=Hmisc & http://CRAN.R-project.org/package=gplots).

5 Results and Discussion

The most relevant findings from the original publications are presented as well as discussed here. The original publications are referred to with Roman numerals I-IV and the figures with the same numbers as in the original publications. The main findings from the animal feeding experiments with PDX and lignin-rich INS from BSG are summarized in Tables 4-6.

The phenotypic and biochemical parameters with PDX and lignin-rich INS in mice are shown in Table 4. PDX, a soluble fiber, significantly decreased fasting plasma triglyceride, cholesterol and food intake during the 2-week feeding trial. Lignin-rich INS, an insoluble fiber, reduced fasting plasma LDL-C and total cholesterol, but no significant change was seen in plasma triglyceride during the 15-week feeding period. An increased food intake was observed with lignin-rich INS during the monitoring period, but there was no change in energy intake. Body weight and hepatic steatosis were significantly reduced with lignin-rich INS, while a trend towards a reduced body weight was observed with PDX feeding. Lignin-rich INS increased the excretion of bile acid in feces and showed no effect on insulin sensitivity.

Table 4. Effect of PDX and lignin-rich INS on phenotypic parameters.

Phenotypic parameters	PDX in Western diet fed mice	Lignin-rich INS in high-fat diet fed mice
Duration of feeding	2 weeks	15 weeks
Body weight	Reducing trend	↓
Food intake	↓	↑
Energy intake	N/A	No change
Fasting plasma cholesterol	↓	↓
Fasting plasma triglyceride	↓	Reducing trend
Fasting LDL-C	N/A	↓
Fasting HDL-C	N/A	No change
Fecal bile acid	N/A	↑
Hepatic steatosis	N/A	↓
Insulin sensitivity	N/A	No effect

N/A= not measured

The effects of PDX and lignin-rich INS on intestinal microbiota in mice are presented in Table 5. The predominant bacterial diversity was decreased with PDX, while an increased diversity was observed with lignin-rich INS. PDX increased the bacterial genera *Allobaculum* and decreased *Clostridiales Ruminococcus* and

Oscillospira, while lignin-rich INS increased *Clostridium leptum* from the phylum Firmicutes. PDX increased the phylum Actinobacteria and its taxa *Bifidobacterium* and *coriobacteriaceae* and decreased the phyla proteobacteria (*Bilophila* decreased, *Suterella* increased) and Deferribacters (*Mucispirillum* decreased).

Table 5. Effect of PDX and lignin-rich INS on gut microbiota.

Gut microbiota	PDX in Wester diet fed mice	Lignin-rich INS in high-fat diet fed mice
Predominant bacteria	↓	↑
Bacteroidetes	↓	↑
Bacteroides	N/A	↑
Parabacteroides	↑	N/A
Firmicutes	No change	N/A
Clostridium leptum	N/A	↑
Allobaculum	↑	N/A
Clostridiales	↓	N/A
Ruminococcus	↓	N/A
Oscillospira	↓	N/A
Actinobacteria	↑	N/A
Bifidobacterium	↑	N/A
Coriobacteriaceae	↑	N/A
Proteobacteria	↓	N/A
Bilophila	↓	N/A
Sutterella	↑	N/A
Deferribacteres	↓	N/A
Mucispirillum	↓	N/A
Verrucomicrobia	Increasing trend	N/A
Akkermansia	Increasing trend	N/A

Gene expression profiles with PDX and lignin-rich INS aredepicted in Table 6. The expression of genes *Fiaf*, cluster of differentiation 36 (*CD36*), diacylglycerol O-acyltransferase 1 (*Dgat1*), Niemann-Pick type C1 (*Npc1*), Niemann-Pick C1 like 1 (*Npcl1*), fatty acid binding protein 2 (*Fabp2*), acyl-CoA synthetase long-chain family member 3 (*Acsl3*) and *Pparα* were reduced and *Fxr* expression was increased in the intestine (duodenum, jejunum, ileum, and colon) with PDX feeding. Lignin-rich INS showed an increased expression of genes such as *Hmgcr*, *Ldlr*, sterol regulatory element binding protein 2 (*Srebp2*), *Cyp7a1, Fxr* and pregnane x receptor (*Pxr*) in mice liver. In the liver, PDX did not show significant change in the gene expression, but an increasing trend in *Hmgcr* (p=0.07) and *Ldlr* (p=0.06) expression was observed.

Table 6. Effect of PDX and lignin-rich INS on gene expression.

Gene expression	PDX in Western diet fed mice	Lignin-rich INS in high-fat diet fed mice
Intestine	Yes	N/A
Fiaf, CD36, Dgat1, Npcl, Npcl1, Fabp2, Acsl3 and Pparα	↓	
Fxr	↑	
Liver	Yes	Yes
Hmgcr and Ldlr	Increasing trend	↑
Srebp2, Cyp7a1 and Pxr	N/A	↑

5.1 Polydextrose and lipid metabolism (I)

We investigated the effect of PDX on lipid metabolism in Western diet-fed mice. Our results demonstrate that PDX fed with Western diet decreased food intake, fasting plasma cholesterol, and triglyceride in C57BL/6 mice as shown in Table 4 (I, Fig. 1b-d). Satiety effect and reduced energy intake with PDX have been reported in humans (Ibarra et al., 2015; Soong et al., 2016). SCFAs and fermentable carbohydrates have been demonstrated to protect from diet-induced obesity and to inhibit food intake by increasing plasma GLP-1 and PYY in animals (Arora et al., 2012; Tolhurst et al., 2012). The GLP-1 secretion with PDX has been demonstrated in human intervention studies (Ibarra et al., 2017; Olli et al., 2015). The reduced food intake in our study might be due to an increase in GLP-1 secretion. The genes in our study with PDX are known to be regulated by either SCFAs or gut microbiota. Butyrate and propionate have been shown to stimulate *Fiaf* production, and butyrate to regulate *CD36* expression (Aguilar et al., 2014; Grootaert et al., 2011). The bacterial metabolites from *Bacteroides dorei* and *Eubacterium limosum* enhanced *Fxr* gene expression and alleviated weight gain in diet-induced obese mice (Zhang, Osaka, & Tsuneda, 2015). In addition, DF downregulated *Dgat1* expression and reduced hepatic triglyceride in mice (Caz et al., 2015). *Dgat1* enzyme synthesizes triacylglycerol from diacylglycerol and fatty acyl-CoA (DeVita & Pinto, 2013).

5.2 Polydextrose and gut microbiota (I)

PDX in the Western diet reduced microbial diversity as shown in Table 5 (I, Fig. 3). However, the inclusion of PDX as part of a snack bar did not affect the microbial

diversity in humans (Hooda et al., 2012). Reduced microbial diversity has been reported in some studies in relation to obesity and metabolic syndrome, but differences in host species, diet, age, genetics, and host environment have also been reported as confounding factors (Lim et al., 2017; Turnbaugh, Backhed, Fulton, & Gordon, 2008). We found that the most affected phyla with PDX supplementation were Deferribacteres, Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes. Actinobacteria were enriched in the WD+PDX mice, while Bacteroidetes, Proteobacteria, and Deferribacteres were enriched in WD mice, as shown in Table 5 (I, Fig. 5a). In rodents, an increased ratio of Firmicutes to Bacteroidetes has been proposed as a characteristic of gut bacteria in obesity, but subsequent studies have not been consistent (Duncan et al., 2008). The most prominent change at genus level between the groups was observed within the phylum Firmicutes. Within this phylum, *Allobaculum* spp. was significantly increased, while *Clostridiales*, *Ruminococcus*, and *Oscillospira* spp. were significantly decreased with PDX as shown in Table 5 (I, Fig. 5b). *Allobaculum* was often depleted in obese mice and correlated positively with plasma HDL-C (Ravussin et al., 2012). Interestingly, increased *Allobaculum* was observed in another study in which a soluble fermentable fiber, oligo-fructose, was fed with HFD, providing further evidence that a fermentable fiber increases the relative abundance of this genus (Everard et al., 2014).

Within Actinobacteria, the relative abundance of *Coriobacteriaceae* and *Bifidobacterium* was significantly increased with PDX as shown in Table 5 (I, Fig. 5b). Enrichment of *Bifidobacterium* in PDX-fed mice is interesting, as low abundance of *Bifidobacteriaceae* was found during high-fat diet feeding and associated with the development of obesity (Cani et al., 2007). Prebiotics selectively increase *Bifidobacterial* growth, improve gut barrier function and glucose metabolism, and decrease body fat (Cani et al., 2007). We observed a significant reduction in epididymal fat mass with PDX feeding (I, Supplementary Fig. S1). In humans, PDX has been shown to reduce body fat mass when administered together with *Bifidobacterium animalis* ssp. *lactis* 420 (Stenman et al., 2016). Our findings support the combination effect of PDX and *Bifidobacteria* in the regulation of body fat mass. In contrast, the abundance of genera associated with high-fat feedings, such as members of the families *Ruminococcaceae*, *Rikenellaceae*, *Desulfovibrionaceae* and *Deferribacteraceae* (Walker et al., 2014), decreased with PDX supplementation. *Bilophila* produced hydrogen sulfide and can cause gut barrier dysfunction, and increased intestinal permeability was decreased with PDX supplementation (Shen et al., 2014). Thus, the inclusion of

polydextrose exerts changes in the gut microbiome with significant influence on the host metabolism.

5.3 Polydextrose and gene expression in intestine (I)

PDX supplementation downregulated *Dgat1*, *Cd36,* and *Fiaf* genes and upregulated *Fxr* expression in the intestine as shown in Table 6 (I, Fig. 2). Triglycerides and total cholesterol as well as gene expression in the intestine were inversely correlated with microbial genera that were more abundant in WD+PDX mice (I, Fig. 6). Previous studies have indicated that PDX-derived microbial metabolites regulate gene expression (Putaala et al., 2011). PDX affects intestinal genes known to be connected to lipid metabolism. *Fiaf* is produced in adipose tissue, liver and intestine and inhibits *Lpl*, which catalyzes the uptake of circulating lipids into tissues and regulates fatty acid oxidation in both muscle and adipose tissue (Conterno, Fava, Viola, & Tuohy, 2011). The intestinal expression of *Fiaf* was upregulated in germ-free and conventional mice on either high-fat or Western diet without affecting circulation levels (Fleissner et al., 2010), indicating that intestinal *Fiaf* does not have a role in the gut microbiota-mediated effects on fat storage. Therefore, the reduction in systemic lipids with PDX is not mediated by intestinal *Fiaf* expression.

CD36 expression correlated positively with fatty acid absorption; it has been shown that fatty acid uptake was reduced in *CD36* null mouse (Drover et al., 2008), suggesting that *CD36* might act as a lipid sensor optimizing the formation of large chylomicrons in the small intestine (Tran et al., 2011). Furthermore, we found significant downregulation of *Dgat1* in the intestine after PDX supplementation. *Dgat1*-deficient (*Dgat1-/-*) mice were lean and resistant to diet-induced obesity, with decreased *Dgat* enzyme activity (Smith et al., 2000). The obesity resistance of *Dgat-/-* mice is due to the absence of intestinal *Dgat1* expression (Lee, Fast, Zhu, Cheng, & Buhman, 2010). In *Dgat1,* knockout mice *Pparalpha*, *gamma* and *delta* expression was decreased (Liu et al., 2011). With PDX supplementation, we found a reduction in intestinal *Pparα* expression. *Fxr,* another important regulator of triglyceride and cholesterol homeostasis, was upregulated in the ileum and colon with PDX. *Fxr* knockout mice had elevated plasma triglyceride and cholesterol levels, and the *Fxr* agonist (INT-747) reduced plasma triglyceride and cholesterol (Mencarelli, Renga, Distrutti, & Fiorucci, 2009). Furthermore, Zhang *et al*. showed that soluble metabolites of specific strains of bacteria enhanced *Fxr* gene

expression, alleviated weight gain in diet-induced obese mice, and decreased biochemical markers of liver injury and lipid metabolism (Zhang et al., 2015).

5.4 Metabolites of lignin-rich INS from BSG (II)

We investigated whether lignin-rich INS from BSG is inert or degraded in the mouse colon by the microbiome. We used a higher percentage (40%) of INS in the diet in order to detect changes in the gut microbiome and metabolites. The 40% INS in the diet was chosen from the literature (Cameron & Speakman, 2011). We could not get 100% pure lignin from INS and the lignin content of INS was just 40%: in the 40%, INS supplemented diet the actual content of lignin in the diet/gram feed eaten was 16%. We did not observe any adverse effects (behavior and food intake) in the animals during the 15-day feeding period. We were able to detect increased amounts of 4-MC as metabolite from lignin in 24-hour urinary excretion. Excretion of 4-MC was significantly higher in mice fed with the INS containing diet as compared to mice fed with CEL (II, Fig. 5). This finding correlates with previous results, which showed production of 4-MC from lignin-rich INS of BSG in the *in vitro* colon model (Aura, Niemi et al., 2013). The 4-MC excretion in urine before the administration of the dietary supplement (II, Fig. 5) might originate from other sources in the diet since also cereal grains contain small amounts of lignin. A metabolite of homoprotocatechuic acid, 4-MC has been shown to stimulate brain-derived neurotrophic factor (BDNF) synthesis in rats (Kourounakis, Bodor, & Simpkins, 1997). It stimulates sciatic nerve regeneration and improves diabetic or acrylamide-induced neuropathy in rats (Hanaoka et al., 1994; Sameni & Panahi, 2011). Intracerebroventricular injection of 4-MC ameliorated chronic pain and depression-like behavior in peripheral nerve injured rats by producing BDNF (Fukuhara et al., 2012).

Non-targeted metabolite profiling of urine showed increased metabolites (3.7- to 83.7-fold change) in INS fed mice compared to CEL; these may have been possible additional degradation products of lignin (II, Fig. 6). Microbial metabolism of a lignin-rich INS from BSG showed similar catechol, 4-MC, vanillyl, and dilignol metabolites in the human colon model (Aura, Niemi et al., 2013). There are only few animal studies on phenolic metabolites originating from lignin in the literature (Begum et al., 2004; Silanikove & Brosh, 1989). In addition to lignin, INS also contained other phenolic compounds such as ferulic acid, and this compound may have caused the phenolic acid excretion in our study (Aura, Niemi et al., 2013). Urinary excretion includes not only colonic metabolites but also other

metabolites from the liver such as glycinate components, e.g. hippuric acid. BSG has 5-fold more phenolic metabolites such as ferulic acid, p-coumaric acid and ferulic acid dehydrodimers than barley grains (Hernanz et al., 2001). In addition, Braune *et al*. showed that ferulic acid dimers are metabolized to dihydroferulic acid, 3-(3′, 4′-dihydroxyphenyl) propionic acid and 3-(3′-hydroxyphenyl) propionic by human fecal microbiota (Braune, Bunzel, Yonekura, & Blaut, 2009).

5.5 Hypocholesterolemic effect of lignin-rich INS from BSG (III)

In study III, the effect of administration of lignin-rich INS from BSG on lipid metabolism and obesity in mice fed a high-fat diet was studied. Fasting plasma LDL-C and total cholesterol were significantly decreased after INS and INS-CEL diet feeding as shown in Table 4 (III, Fig. 1B &1D). DFs have been shown to decrease cholesterol levels and insoluble fiber decreases nutrient utilization and absorption by increasing GI transit (Renteria-Flores, Johnston, Shurson, & Gallaher, 2008). Various DFs such as oat bran, bagasse, pectin, psyllium and a mixture of soluble and insoluble fiber increase bile acid excretion and thereby reduce cholesterol in animals and humans (Togawa et al., 2013). Our results exhibited a significant increase in fecal bile acid excretion with all fibers, of which INS showed the highest potency as shown in Table 4 (III, Fig. 3A). β-glucan increased bile acid excretion by forming a viscous gel in the intestine (Behall et al., 2004) and bile acid binding of lignin-rich INS has been demonstrated (Niemi et al., 2013). INS, which is rich in lignin and β-glucan, increased bile acid excretion and reduced plasma cholesterol in our study. In addition, the probiotic bacteria *Lactobacillus*, *Bifidobacterium*, *Clostridium*, and *Bacteroide*s possess bile salt hydrolase (BSH) activity and promote the deconjugation of bile acids. Deconjugated bile acids are poorly reabsorbed and are thus excreted with the feces (Li et al., 2012). As shown in Table 6 (III, Fig. 5), our results clearly demonstrate a significant increase in cecal *Clostridium leptum* with all fibers and in *Bacteroides* with INS feeding, which further increased bile acid excretion.

The present study suggests that the reduction in plasma cholesterol is due to increased catabolism of cholesterol to bile acid and its excretion in feces as shown in Figure 5. Interestingly, we found that INS feeding in our study increased hepatic expression of *Srebp2* and its target genes, *Hmgcr* and *Ldlr,* as shown in Table 6 (III, Fig. 6A-C). *Srebp2* is an important transcription factor in cholesterol homeostasis, which regulates the expression of various genes like *Hmgcr*, *Hmgcs*, and *Ldlr* (Xiao & Song, 2013). *Hmgcr* is the rate-limiting enzyme for cholesterol biosynthesis, and

fiber supplementation increased *Hmgcr* expression in the liver (Chan & Heng, 2008). *Ldlr* binds and internalizes circulating lipoprotein particles that contain cholesterol. The increased expression of these genes indicates that hepatic cholesterol biosynthesis and uptake is increased with INS supplementation in mice.

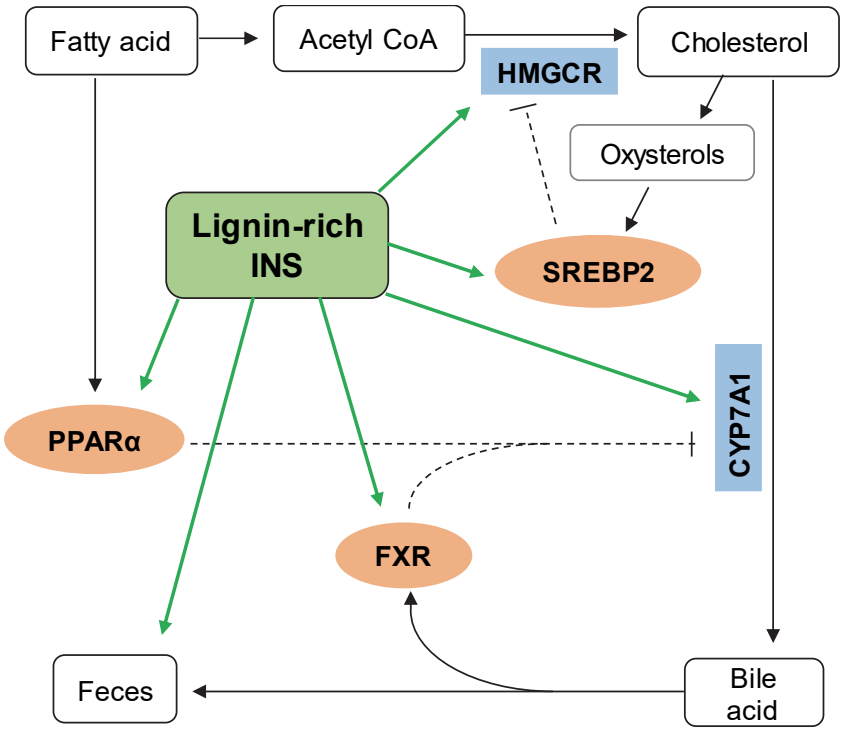

Fig. 5. Suggested pathway of cholesterol reduction with INS supplementation in high-fat diet-fed mice. The classical pathway of fatty acid and cholesterol metabolism to bile acid. Dotted lines show inhibition (black color). The green line shows the stimulation with INS. INS upregulates liver gene expression of *Hmgcr* and *Cyp7a1* (blue color) and *Srebp2*, *Pparα*, and *Fxr* (orange color).

Despite increased cholesterol biosynthesis, plasma cholesterol was decreased, indicating that cholesterol was converted to bile acids and excreted in feces. Surprisingly, we found an increased expression in the liver of *Cyp7a1*, the rate-limiting enzyme in bile acid synthesis from cholesterol, as shown in Table 6 (III, Fig. 6D). It has been demonstrated that decreased reabsorption of bile acid from the intestine induces *Cyp7a1* expression with increased production of bile acid from cholesterol (Pozzo et al., 2015). Probiotics increased *Cyp7a1* expression and excretion of fecal bile acid in mice (Degirolamo, Rainaldi, Bovenga, Murzilli, & Moschetta, 2014). Furthermore, *Pparα* stimulated *Cyp7a1* expression in the liver (Cao et al., 2012). We found an increased expression of liver *Pparα* and *Fxr* expression by INS feeding as shown in Table 6 (III, Fig. 6E & F). *Pparα* upregulation has been shown to improve lipid metabolism in various animal studies (Misawa et al., 2012). *Fxr* plays a major role in cholesterol and triglyceride homeostasis. Zhang *et al*. found that *Fxr*−/− mice showed increased plasma triglyceride and cholesterol levels (Zhang et al., 2006) and *Fxr* agonist (INT-747) reduced plasma triglyceride and cholesterol levels (Mencarelli et al., 2009). Moreover, it has been demonstrated that *Fxr* activation repressed hepatic *Srebp1c* and reduces plasma triglyceride (Watanabe et al., 2004). We did not measure *Srebp1c* expression in our study since there was reduction in plasma triglyceride.

5.6 Lignin-rich INS from BSG and body weight (III)

INS from BSG supplementation significantly reduced body weight gain in high-fat diet-fed mice as shown in Table 4 (III, Fig. 1A). In contrast, BSG feeding has been shown to increase body weight gain in cattle, poultry, pigs and fish (Kaur & Saxena, 2004). The increased body weight gain with BSG feeding was probably due to its lower lignin and higher protein and carbohydrate content. However, INS is an insoluble residue from BSG, which mainly contains lignin (40%). Studies in humans and animals have demonstrated that insoluble fiber decreases body weight gain (Isken, Klaus, Osterhoff, Pfeiffer, & Weickert, 2010). Our results are consistent with these previous findings of reduced weight gain with insoluble fibers (Cameron & Speakman, 2011). Insoluble fibers are well known as bulk-forming agents that decrease energy density and prevent body weight gain (Anderson, 1985). They are also partly fermented in the GIT and produce SCFAs (Ostman, Liljeberg Elmstahl, & Bjorck, 2002). INS has been shown to generate acetic acid and high concentrations of propionic and butyric acids (Niemi et al., 2013).

CEL was used as a positive control in our study as an insoluble fiber without lignin content. Previous studies have reported that in rats, CEL at concentrations of 15, 30, and 50% of the feed increased the amount of food intake by 3.5, 12.0, and 26.9%, respectively (DALTON, 1963). We observed a significant increase in food intake with the fiber diet compared to HFD, but no significant difference in energy intake as shown in Table 4 (III, Supplementary Fig. S1). Mammalian enzymes do not digest CEL, and a 57% increase in mean wet fecal weight was observed in healthy volunteers consuming CEL (Hillman, Peters, Fisher, & Pomare, 1983). We also found a significant increase in fecal weight with INS as with CEL, but CEL feeding showed the highest feces weight, which was significantly higher than in the INS- and INS-CEL-fed mice (III, Supplementary Fig. S2). Insoluble fiber consumption demonstrated an inverse correlation to the risk of T2D in humans (Montonen, Knekt, Jarvinen, Aromaa, & Reunanen, 2003). An epidemiological study of 42,000 men demonstrated that cereal fiber decreased the prevalence of T2D while DFs from fruit and vegetables had no effect (Salmeron et al., 1997). In our study, CEL supplementation, either alone or in combination with INS, improved insulin sensitivity in HFD-fed mice, but INS alone was ineffective (III, Fig. 2). Our results are consistent with a previous study on CEL, which reported a decrease in postprandial glucose and insulin in rodents (Schwartz & Levine, 1980).

5.7 Lignin-rich INS from BSG and hepatic steatosis (III)

All fiber diets significantly reduced the hepatic steatosis induced by HFD feeding in mice as shown in Table 4 (III, Fig. 4). HFD and cholesterol are the major contributors to the development of hepatic steatosis (Subramanian et al., 2011). DF intake reduced the risk of hepatic steatosis and NALFD (Choi et al., 2013). High-fiber diets have hypolipidemic activity, and insoluble fibers mainly reduce serum cholesterol and alleviate steatosis in humans and animals (Estruch et al., 2013). Insoluble fibers also have antioxidant activity due to their high polyphenol content (> 75%) (Zunft et al., 2003). Lignin, the major fraction in INS, is a polyphenolic molecule that might reduce hepatic steatosis via its antioxidant potential. A decrease in the abundance of Bacteroidetes and *Clostridium leptum* has also been observed in nonalcoholic hepatosteatosis patients (Mouzaki et al., 2016). INS increased the abundance of *Bacteroides* and *Clostridium leptum*, while CEL and INS-CEL increased only *Clostridium leptum* (III, Fig. 5) and reduced hepatic steatosis. The upregulation of *Cyp7a1* in the liver improved hepatic steatosis and obesity by repressing hepatic lipogenesis. In addition, mice overexpressing *Cyp7a1*

in the liver are resistant to hyperlipidemia (Li et al., 2010). The reduced hepatic steatosis with INS might be due to increased *Cyp7a1* expression in the liver.

5.8 Lignin-rich INS from BSG and gut microbiota (II-III)

The diet-induced changes in the gut microbiota were comparable to each other as all the mice showed similar numbers of bacteria at baseline day 0 (II, Fig. 1). Cecal bacterial numbers were lower than fecal bacterial numbers at the beginning of the study and after the dietary intervention (II, Fig. 1). Previously, it has been shown in mice that the relative abundance of *Bacteroides*, *Lactobacillus*, and Actinobacteria was lower in cecum compared to feces (Gu et al., 2013). Our results are consistent with these findings (Gu et al., 2013). *Bifidobacteria* were increased with INS and INS-CEL compared to CEL (II, Fig. 1), indicating that these bacteria were able to utilize nutrients from INS. Previously, it has been shown that *Bifidobacteria* were increased with INS from BSG in an *in vitro* fermentation model (Niemi et al., 2013). *Bifidobacteria* are considered beneficial for health, and fermentable DFs support *Bifidobacterial* growth. In our study, the predominant bacterial diversity was increased with INS and INS-CEL compared to CEL (II, Fig. 3 and III, Fig. 5). Moreover, the diversity of predominant cecal and fecal bacteria was higher after the intervention containing INS compared to baseline samples, whereas no change was seen with CEL. Reduced bacterial diversity in the GI tract has been linked to numerous diseases and disorders (Turnbaugh et al., 2009). Hydroxypropyl methylcellulose has also previously been shown to reduce the diversity of these bacterial groups in C57BL/6 mice (Cox et al., 2013). Our result with CEL feeding is in line with these findings.

Long-term HFD feeding significantly decreased *Enterobacteriaceae*, *Bacteroides*, and *Bifidobacterium* and increased Proteobacteria (Qiao, Sun, Ding, Le, & Shi, 2013). Our results are consistent with these findings: HFD feeding decreased predominant bacterial diversity and *Clostridium leptum* and *Bacteroides* members of Firmicutes and Bacteroidetes, respectively (David et al., 2014). INS, INS-CEL, and CEL supplementation increased the abundance of *Clostridium leptum* while *Bacteroides* only increased in INS-fed mice, as shown in Table 5 (III, Fig. 5). Soluble fiber intake led to an increase in *Bacteroides* and *Clostridium leptum* in humans (Simoes et al., 2013). Furthermore, HFD feeding in Wistar rats reduced *Clostridium leptum* and worsened weight gain, adiposity, hyperleptinemia and hypertriglyceridemia (Marques et al., 2015). A negative correlation of *Clostridium leptum* with fat mass, fasting glycemia, HOMA index

and BAs (CA and CDCA) has been observed in women (F S Teixeira et al., 2013). In addition, *Clostridium leptum* modifies primary bile acid by 7α-dehydroxylation to secondary bile acid (Midtvedt, 1974). Long-term high-fiber feeding favored an increase in Bacteroidetes and a decrease in Firmicutes in rats (Saha & Reimer, 2014). Bacteroidetes mainly respond to energy load, and reduced levels were observed in obese mice (Turnbaugh et al., 2006). The increased *Bacteroides* in our study might be due to reduced energy load with INS. The *Atopobium* belong to the *Coriobacteriaceae* family, phylum Actinobacteria. In humans, supplementation with inulin extracted from globe artichoke increased *Atopobium* (Costabile et al., 2010). In contrast, we found that CEL supplementation decreased the abundance of *Atopobium*. The decrease in *Atopobium* might be due to the non-fermentable characteristics of the CEL.

5.9 PDX and appetite (IV)

PDX was investigated in an acute, randomized, double blind, placebo-controlled, and crossover study for its effects on energy intake and appetite-related parameters in healthy and overweight females. Our results demonstrate that PDX intake in midmorning significantly reduced hunger by 31.4% during satiation period (IV, Table 3, Fig. 2). Appetite was assessed by measuring subjective feeling as previously described (Howarth, Saltzman, & Roberts, 2001). Intervention studies have found variable responses on satiety with the intake of dietary fiber (Clark & Slavin, 2013; Leidy, Gwin, Roenfeldt, Zino, & Shafer, 2016). Some studies have reported significant effects of PDX on satiety (King, Craig, Pepper, & Blundell, 2005) while others have not (Monsivais, Carter, Christiansen, Perrigue, & Drewnowski, 2011a; Willis, Eldridge, Beiseigel, Thomas, & Slavin, 2009). Our findings are consistent with a recent meta-analysis, which showed that PDX preloads reduce the desire to eat during the satiation period (Ibarra, Astbury, Olli, Alhoniemi, & Tiihonen, 2016). In our study, no significant change was observed in hunger or desire to eat during the satiety period with PDX due to high variability. There was no significant change in subjective feeling of appetite (IV, Fig S3.1 to S3.4). PDX demonstrated a less clear difference from placebo at breakfast compared to the midmorning preload. Our results on appetite are consistent with previous studies which demonstrated no significant differences in VAS scores with PDX intake at breakfast (Monsivais, Carter, Christiansen, Perrigue, & Drewnowski, 2011b; Timm, 2012).

We found that PDX supplementation at breakfast increased plasma GLP-1 in females (IV, Fig. 4). Our results are consistent with previous studies of PDX on GLP-1 in lean and obese subjects (Astbury, Taylor, French, & Macdonald, 2014; Olli et al., 2015). GLP-1 suppresses appetite and reduces energy intake in normal weight, overweight/obese and T2D patients (Bergmann et al., 2019; Flint, Raben, Astrup, & Holst, 1998; Flint, Kapitza, & Zdravkovic, 2013). The increased GLP-1 (markedly between 60 and 150 min) may partly explain the reduced energy intake in previous studies where PDX was administered within this time window (Astbury et al., 2013; Hull et al., 2012; Ranawana et al., 2013).

5.10 PDX and energy intake (IV)

We did not find any significant change in energy intake with PDX served as part of breakfast or a midmorning preload (IV, Table 2). Different energy intakes for individuals between sequences were obtained (IV, Fig S2.1to S2.3) due to variability in BMI. A meta-analysis of 120 individuals showed that PDX reduced energy intake at subsequent meal when served as part of a midmorning preload (Ibarra, Astbury, Olli, Alhoniemi, & Tiihonen, 2015). A previous intervention study with PDX reported a significant reduction in energy intake when consuming a meal above 4,000 kJ (Astbury, Taylor, & Macdonald, 2013; King et al., 2005; Ranawana, Muller, & Henry, 2013). The lack of difference in energy intake with PDX in our study could be due to the large variation in BMI (IV, Fig S1), the caloric density of the subsequent meal, and poor appetite suppression in overweight and obese subjects (Bryant, King, & Blundell, 2008). In our study, all volunteers consumed an isocaloric breakfast, independent of their BMI, which may also have increased the variability. In previous studies with PDX, the variability in energy intake was reduced by standardizing the caloric content of dinner before test day and breakfast on test day with the metabolic rate of each volunteer (Astbury et al., 2013; Hull, Re, Tiihonen, Viscione, & Wickham, 2012; King et al., 2005; Ranawana et al., 2013).

5.11 Polydextrose and gastric emptying (IV)

PDX intake during breakfast did not alter gastric emptying parameters in healthy and overweight females as shown in Table 7. PDX showed a decreasing trend in half gastric emptying time ($t_{1/2}$), which is a notable observation.

Table 7. Gastric emptying parameters with PDX-B and CON-B.

Parameters	PDX-B mean (SD)	CON-B mean (SD)	p value
t_{lag}	127 (25)	131 (32)	0.52
$t_{1/2}$	162 (39)	181 (52)	0.11

Our results on gastric emptying with PDX are in line with a previous observation on solid food (Hellmig et al., 2006). In contrast to our result, overweight and obese females show delayed gastric emptying and a prolonged lag phase (t_{lag}) compared to lean individuals (Jackson et al., 2004). Soluble fiber intake has been demonstrated to slow gastric emptying in human and animal studies (Hlebowicz et al., 2007; Rainbird, 1986). Delayed gastric emptying and reduced energy intake was found in healthy Chinese individuals with a preload of 12 g PDX in low protein/high protein soya bean curd (Soong et al., 2016). The authors suggested that the reduced energy intake with PDX was partly related to delayed gastric emptying. Recently, a meta-analysis of 11 intervention studies with different soluble fibers concluded that not all soluble fiber delayed gastric emptying (Salleh, Fairus, Zahary, Bhaskar Raj, & Mhd Jalil, 2019). The differences in gastric emptying with PDX might be due to the wide BMI (Fig. S1) range in our study.

6 Conclusion

In the present study, the effects of the dietary fibers polydextrose (PDX) and lignin-rich insoluble residue (INS) from brewer's spent grain (BSG) on lipid metabolism and obesity were investigated in Western diet/high-fat diet-fed mice. The effects of PDX on food intake and appetite-related parameters in healthy and overweight females were also investigated in an acute double-blind placebo-controlled study.

The main findings:

- Polydextrose decreased fasting plasma triglyceride and cholesterol levels in mice fed with a Western diet. In addition, we found a significant inhibition of food intake by polydextrose. Polydextrose increased, *Allobaculum*, *Bifidobacteria,* and *Coriobacteriaceae* and, and reduced bacteria associated with high-fat diet feeding, such as *Clostridiales* and members of the families *Ruminococcaceae*, *Rikenellaceae*, *Desulfovibrionaceae,* and *Deferribacteraceae.*
- The alterations in the gut microbiota with polydextrose were associated with reduced expression of genes such as *Fiaf*, *Dgat1*, and *Cd36* and increased *Fxr* in the intestine, which are known to be regulated by either dietary fibers or short-chain fatty acids. Our results also indicated that polydextrose could upregulate hepatic gene expression of *Hmgcr* and *Ldlr*.
- PDX intake at midmorning reduced hunger by 31.4% during satiation period while there was no significant change in energy intake and gastric emptying. PDX intake with breakfast increased plasma GLP-1 significantly, by 39.9%.
- Lignin-rich INS from BSG was degraded in mice and contributed to the phenolic pool circulating in the mammalian body before excretion. The major metabolite in urine was 4-methylcatechol, which is due to lignin degradation.
- Lignin-rich INS from BSG decreased plasma cholesterol levels and reduced body weight gain and hepatic steatosis in high-fat fed mice. The reduction in cholesterol plasma levels was caused by increased bile acid binding and excretion in feces.
- Interestingly, the bacterial diversity of predominant bacteria was increased with lignin-rich INS; this finding opens up very interesting perspectives for the future.
- Lignin-rich INS from BSG is slowly fermentable, modulates gut microbiota, upregulates genes of fatty acid and bile acid metabolism such as *Srebp2*, *Hmgcr*, *Ldlr*, *Pparα*, *Cyp7a1* and *Fxr,* and attenuates plasma cholesterol.

7 Implications and future peropective

Polydextrose is a well-known dietary fiber supplement used in several countries in various foods and beverages, whereas brewer's spent grain (BSG) is produced as a by-product of brewing industry and mainly used in animal feed. Lignin-rich insoluble residue (INS) from brewer's spent grain contains lignin, arabinoxylan and β-glucan, the constituents of dietary fibers. Dietary fibers possess several health benefits, including positive effects on diabetes, obesity and cardiovascular diseases. After proper fractionation, lignin-rich INS from BSG may be used for human nutrition as a supplement in bread and various other foods.

Polydextrose reduced food intake and body weight (trend) during a 14-day supplementation period in mice. Lignin-rich INS from BSG showed reduced weight gain and hepatic steatosis during a 14-week feeding trial. Longer feeding trials in animals are needed with different types of diets in order to investigate the effect of polydextrose in obesity, and especially its translational value, i.e. whether it is able to reduce weight gain in humans. The energy intake with PDX supplementation in different types of diets needs to be investigated in larger human (males and females) trials. Reduced hunger and an increased GLP-1 secretion with polydextrose might be feasible in obesity, type 2 diabetes and cardiovascular diseases.

Hypercholesterolemia is a major risk factor for CVD. Polydextrose reduced fasting plasma lipids and could be used as an adjunct to lipid-lowering drugs or as monotherapy for dyslipidemia and to lower the risk of CVD. The reduction in LDL-C and total cholesterol with lignin-rich INS may reduce the risk of CVDs. The hypocholesterolemic effect of lignin-rich INS of BSG needs to be further investigated in human interventions. Lignin-rich INS is high in lignin, which is a polyphenolic molecule and may be of benefit in metabolic and cardiovascular diseases. 4-methylcatechol, a metabolite of lignin-rich INS, stimulates nerve growth factor synthesis and could thus be beneficial in neurodegenerative diseases. Furthermore, the ability of lignin-rich INS to increase the diversity of gut microbiota opens up very interesting perspectives for the future and requires investigation in humans.

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ISBN 978-952-62-2302-5 (Paperback)
ISBN 978-952-62-2303-2 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)