Nutrition Bulletin

EMERGING RESEARCH

DOI: 10.1111/nbu.12416

The FiberTAG project: Tagging dietary fibre intake by measuring biomarkers related to the gut microbiota and their interest for health

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Abstract

The scientific rationale for dietary fibre intake recommendations comes from the recognition of their benefits for health based on studies first published many years ago. It remains unclear which are the key physiological effects generated by dietary fibre in view of the diversity of the food components considered as dietary fibre, of the relevance of their classification (soluble and insoluble) and from the recent discoveries putting forward their interactions with the gut microbiota. The project *FiberTAG* (*Joint Programming Initiative 'A Healthy Diet for a Healthy Life'* 2017–2020 www.fibertag.eu/) aims to establish a set of biomarkers (markers of gut barrier function and bacterial co-metabolites including volatile compounds and lipid derivatives), measured in different biological compartments (faeces, blood or breath) linking dietary fibre intake and gut microbiota-related health effects. The *FiberTAG* consortium brings together academic and industrial partners from Belgium, France, Germany and Canada to share data and samples obtained from existing as well as new intervention studies in order to evaluate the relevance of such biomarkers. The *FiberTAG* consortium is currently working on five existing cohorts (prospective observational or nutritional interventions in healthy or obese patients), and a number of new intervention studies to analyse the effect of insoluble dietary fibre (wheat bran and chitin-glucan, provided by the industrial partners) in healthy individuals or in obese patients at high cardiometabolic risk.

Keywords: biomarkers, chitin-glucan, dietary fibre, exhaled volatile organic compounds, microbiota, wheat bran

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Introduction

Dietary fibre intake recommendations for adults range from 18 to 38 g per day; the World Health Organization/Food and Agriculture Organization (WHO/FAO)

and European Food Safety Authority (EFSA) recommend 25 g/day based on the amount needed for healthy laxation (EFSA 2010a; Jones 2014). The scientific rationale for dietary fibre recommendations derives from the recognition of their benefits for health based on studies first published many years ago. Dietary fibre is a broad category of non-digestible food ingredients that includes resistant starches, non-starch polysaccharides, oligosaccharides, lignin and analogous polysaccharides with associated health benefits (Stephen *et al.* 2017). Generally, dietary fibre is classified based on its solubility in water, microbial fermentation in the colon and viscosity (Stephen *et al.* 2017; Delzenne *et al.* 2019). The terms 'soluble' and 'insoluble' have been used in the literature to classify dietary fibres as viscous soluble in water (*e.g.* pectins), non-viscous soluble in water (*e.g.* inulin) or as water insoluble (*e.g.* cellulose) in an attempt to link different physical–chemical properties of fibre components to different physiological effects. However, the above classification is method-dependent, and water solubility does not always predict the physiological effects of dietary fibre (EFSA 2010b; Stephen *et al.* 2017). It remains unclear which are the key health physiological effects generated by insoluble dietary fibre, and whether they rely on the gut microbiota. The concept of prebiotics, initially elaborated with non-digestible oligosaccharides specifically fermented by gut bacteria (Gibson & Roberfroid 1995), was recently revisited by several partners of this project (Bindels *et al.* 2015a; Gibson *et al.* 2017). Prebiotics include fermentable dietary fibre which, through its interaction with the gut microbiota, modulates its composition and functions with beneficial effect for the host (Bindels *et al.* 2015a). On the basis of studies in animals and humans, it has been proposed that highly fermentable prebiotic dietary fibre might increase satiety, improve glucose tolerance and lipid metabolism and even control hypertension (EFSA 2010b; Delzenne *et al.* 2019). The mechanisms proposed to explain such effects often involve the bacterial metabolites or components capable of modification by prebiotic fibres. The identification of relevant biomarkers to assess these effects is thus a major objective.

Selection of relevant biomarkers of gut microbiota involved in metabolic disorders

The beneficial effect of the interactions between dietary fibre and the microbiota can result from the modulation of the production of bioactive metabolites, and/or from changes in the composition and functions of the gut microbiota that are supposed to mediate the fibre-derived health benefits. Several key intestinal functions can be influenced by gut microbiota and related metabolites, and therefore potentially influenced by dietary fibre, including gut barrier function, the gut endocrine function (production of incretins and gut hormones controlling appetite or energy metabolism), the gut immune system or even the digestive processes.

Gut barrier function has been identified as central in the control of host energy metabolism and the low-tone, metabolic inflammation (endotoxemia) that characterises a wide range of nutritional disorders (Delzenne *et al.* 2011a; Delzenne *et al.* 2011b; Geurts *et al.* 2013; Bischoff *et al.* 2014; Leclercq *et al.* 2014).

Gut permeability can be assessed *in vivo* by the ingestion of inert marker molecules (^{53}Cr-EDTA, different sugars) (Bischoff *et al.* 2014; Wang *et al.* 2015). However, these tests are relatively complex and not always well accepted by patients. Moreover, they can be performed only in prospective trials. Therefore, other markers which can be measured in blood, urine or faeces are being tested in the *FiberTAG* project and are listed below:

- Lipopolysaccharide-binding protein (LBP) is a soluble acute-phase protein reflecting bacterial translocation (Bischoff *et al.* 2014; Wang *et al.* 2015).
- Albumin is the most abundant protein in blood and an increase of this protein in stool indicates a disturbed gut barrier (Bischoff *et al.* 2014; Wang *et al.* 2015). As albumin is sensitive to proteases, it is particularly adapted to assess the colon barrier function, where the gut microbiota is most abundant.
- Enterocytes of the intestinal mucosal layer, involved in the uptake of fatty acids, produce the intestinal fatty acid binding protein (I-FABP) (Bischoff *et al.* 2014; Wang *et al.* 2015). This protein is specific for intestinal cells, and its measurement in the blood has been shown to be a marker of intestinal tissue injury.
- Calprotectin is a protein released by neutrophils and has been shown to be a marker of gut inflammation when measured in faeces (Bischoff *et al.* 2014; Wang *et al.* 2015).
- Zonulin is expressed in both liver and intestinal cells and has been shown to regulate the tight junctions. In the gut, it can be modulated by the microbiota (Bischoff *et al.* 2014; Wang *et al.* 2015). It can be measured in faeces, where a high concentration correlates with increased permeability.

These different markers are taken into consideration and analysed in existing cohorts, in order to (i) to test their relevance as gut barrier biomarkers versus gold-

standard (but more elaborate) methodologies and (ii) to evaluate their relationship with nutritional and biological outcomes of dietary fibre administration, including those linked directly to the gut microbiota.

We, and others, have evaluated the mechanisms of interactions between the gut microbiota and host gut physiology using animal pre-clinical models (Haub *et al.* 2010; Spruss *et al.* 2012; Ritze *et al.* 2014; Delzenne *et al.* 2015; Bindels *et al.* 2015b; Volynets *et al.* 2016). When fermented, dietary fibre can induce production of gases (*e.g.* CO_2, H_2, CH_4) and short-chain fatty acid (SCFA, *e.g.* acetate, propionate, butyrate) synthesis (Nakamura *et al.* 2010; Bischoff *et al.* 2014; Salazar Garzo *et al.* 2015; Heinritz *et al.* 2016). SCFAs can be absorbed and used as metabolic substrates or regulators in many organs through binding to specific G-coupled receptors. SCFA profile appears as an important signature of fibre fermentation, and the use of ^{13}C-labelled substrates is needed to evaluate the relative contribution of specific fibre fermentation to SCFA production. Recent data suggest that other bioactive molecules, such as bile acids, conjugated polyunsaturated fatty acids (cPUFA) and volatile organic compounds (VOC) including indoles, phenols, nitrogen and sulphur metabolites, are involved in intestinal and metabolic integrity (Bischoff *et al.* 2014; Druart *et al.* 2014; Leclercq *et al.* 2014; Druart *et al.* 2015; Del *et al.* 2016; Wahlstrom *et al.* 2016).

Among the health effects attributed to dietary fibre, the interaction with dietary lipid compounds (steroids and fatty acids) is considered to be part of their physiological effects related to the control of blood lipids and energy metabolism. We showed that the profile of conjugated and *trans* fatty acid metabolites that result from the bacterial transformation of unsaturated fatty acids relates to the gut microbiota composition, since only specific bacteria (*Roseburia* spp. and lactobacilli), which can be increased by several dietary fibres, possess the enzymes needed to metabolise unsaturated fatty acids (Druart *et al.* 2014). In addition, bile acids participate in the metabolic relationship between the gut microbiota and host tissues (Kuipers *et al.* 2014). The gut microbiota is involved in bile acid profiling, namely through its reductase and hydrolase activity bile acids (Wahlstrom *et al.* 2016; Chavez-Talavera *et al.* 2017). Faecal bile acids are mainly non-conjugated due to their active deconjugation by the bacteria within the intestinal lumen. Bile acids are signalling molecules that regulate host metabolism and inflammation via the nuclear farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5). These receptors activate transcriptional networks and signalling cascades controlling the expression and activity of genes involved in bile acid, lipid and carbohydrate metabolism, energy expenditure, and inflammation by acting predominantly in enterohepatic tissues, but also in peripheral organs (Chavez-Talavera *et al.* 2017).

A large panel of volatile compounds released in the breath is co-metabolites issued from gut microbiota and are therefore interesting biomarkers, potentially linking health to microbial breakdown of nutrients or endogenous substrates (Ajibola *et al.* 2013; Raninen *et al.* 2016). Selected ion flow tube-mass spectrometry (SIFT-MS) has been developed by members of our team as a powerful and sensitive analytical technique to rapidly quantify low levels of volatile metabolites, including SCFAs, which could explain the biological effect of fermentable dietary fibre.

Fermentable dietary fibre and prebiotics also induce specific compositional shifts to the gut microbiota (Deehan *et al.* 2017). According to the prebiotic concept, such specific stimulations are implicated in the health effects. However, strong associations between dietary fibre-induced microbiome shifts and relevant health markers or disease manifestations have not been established. *FiberTAG* will investigate links between dietary fibre-induced microbial signatures and relevant biomarkers to determine their potential value in predicting the physiological effects of dietary fibre. This will be performed using an ecological approach that considers the characteristics of gut microbiomes (high inter-individual variation, stability, resistance and resilience to perturbations) and the complex syntrophic interactions within the communities to evaluate how reliably the gut microbiota is associated with key gut biological functions (resulting in the development of appropriate bioinformatic tools).

Objectives of the FiberTAG Project

We are developing innovative approaches to reconsider the nutritional advice and concepts concerning the health effects of prebiotic dietary fibre, namely by examining whether insoluble dietary fibre also functions as a prebiotic dietary fibre. In the context of the *FiberTAG* project, we are finalising a dedicated database detailing the soluble and insoluble dietary fibre and prebiotic (oligo)saccharide (ITF, FOS and GOS) content of food products consumed in Europe. In addition, we are building a food frequency questionnaire which focuses on all types of dietary fibre intake for use in intervention, retrospective or prospective studies.

Moreover, there is a crucial need to develop and validate new biomarkers associated with the various health effects of dietary fibre, which take into account their interaction with the gut microbiota. The *FiberTAG* project is developing experimental approaches in humans to cover those gaps using two approaches.

- First, the consortium is using existing cohorts to investigate the link between dietary fibre intake, gut microbial signature (the bacterial composition and the profile of key metabolites) and key gut biological functions such as gut barrier function.
- The second objective is to develop innovative approaches to evaluate in intervention studies the physiological effects of two different insoluble dietary fibres – one novel fibre specifically developed to interfere with gut microbiota (chitin-glucan) and one very frequently consumed in human diets (wheat bran) and capable of interacting with the gut microbiota.

Approach and tools to evaluate the link between dietary fibre intake and microbial and metabolic signatures

The overall organisation of the project is based on seven work packages (WPs), taking place over a period of 3 years (Figure 1).

The first objective focuses on five existing cohorts (see Table 1 for details of cohorts), for which some data (dietary questionnaires, anthropometric data and clinical biology) were already available. These cohorts, well-characterised and representative of different populations/phenotypes are being characterised for soluble/insoluble dietary fibre and prebiotic intake and used for the measurement of specific metabolites selected as biomarkers of fermentation in available samples (stool, urine and serum) and gut-related function and for faecal microbiota composition (using next-generation sequencing). Correlation studies

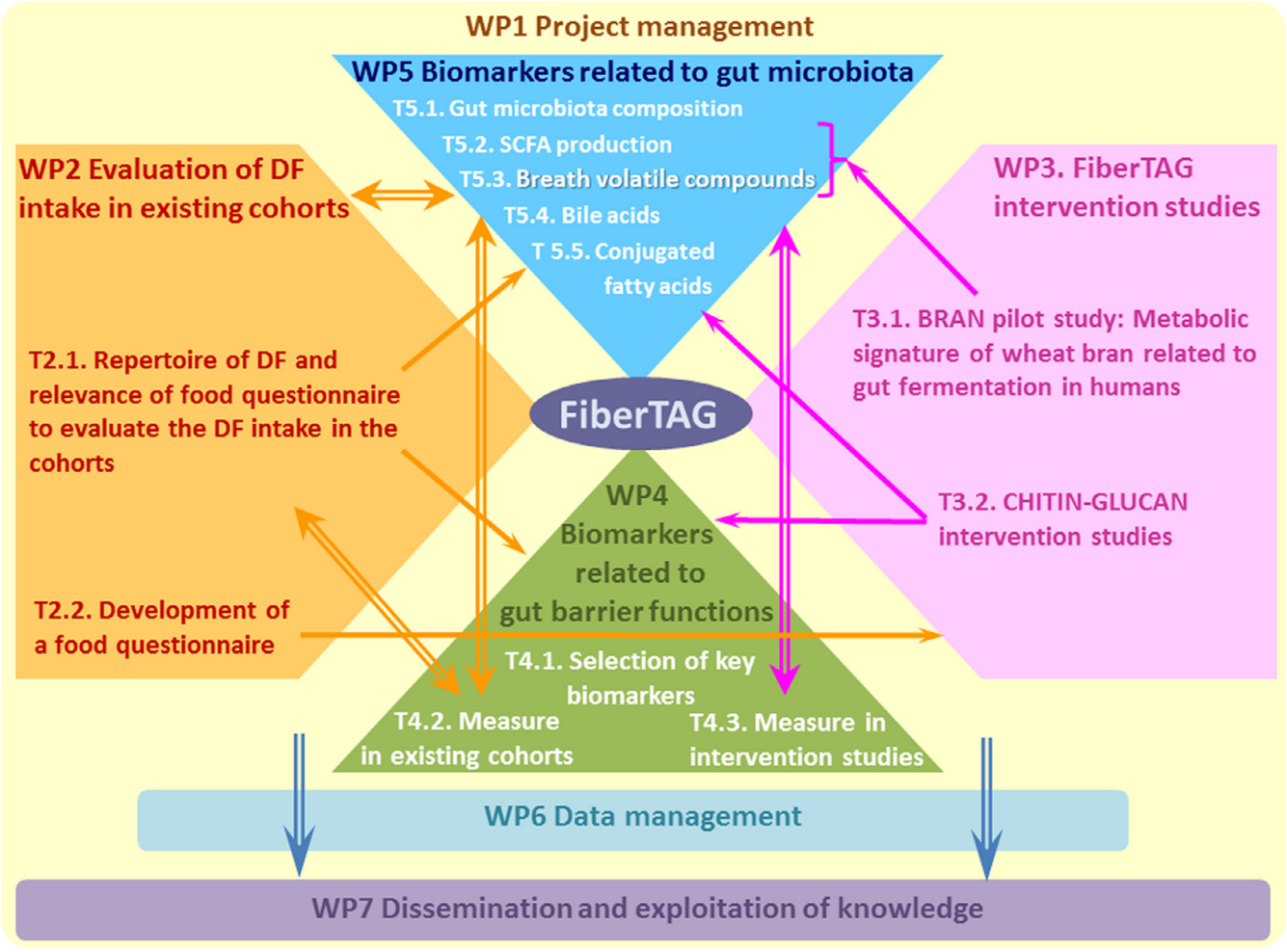

Figure 1 Work package (WP) components, flows and interactions between tasks (T) of the FiberTAG project. DF, dietary fibre; SCFA, short-chain fatty acid. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Descriptive characteristics of the five cohorts examined in the FiberTAG project

Cohort	Country	Size (for FiberTAG)	Target population	Intervention/groups
ALCOHOL	Belgium	60 (30)	Subjects with a diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	Observational prospective study; 2 groups: subjects clinically evaluated by a psychiatrist and admitted to the gastroenterology ward for a 3-week detoxification and rehabilitation program (control group: 15 subjects age-, sex- and BMI-matched controls who socially consumed less than 20 g of alcohol per day). Duration: 3 weeks
FOOD4GUT	Belgium	150 (50)	Obese subjects BMI >30 kg/m^2; aged 18–65 years; with at least one of the following criteria: hypertension, (pre-) diabetes, dyslipidemia, liver steatosis	Simple blind parallel randomised placebo-controlled trial; 2 groups: 16 g/day of inulin with dietary advice to promote the consumption of vegetables rich in ITF or 16 g/day maltodextrin (control) with dietary advice provided to promote the consumption of vegetables poor in ITF. Duration: 3 months
FYBER	Canada	220 (31)	Overweight to moderately obese subjects	Simple blind parallel randomised placebo-controlled trial; 2 groups: either corn arabinoxylan or microcrystalline cellulose (control); 35 g/day for males and 25 g/day for females. Duration: 6 weeks
LIBRE	Germany	600 (200)	Female BRCA 1/2 mutation carriers, both with and without previous cancer diagnosis	Prospective, open, controlled intervention study; 2 groups: either intensive nutrition education with focus on Mediterranean diet, regular physical activity training or single nutrition information on healthy diet and physical activity (control). Duration: intervention: 3 months intensive (weekly intervention meetings), 9 months less intensive (monthly intervention meetings); follow-up: month 24 + 36, afterwards open-end follow-up
ObC	Germany	100 (60)	Adults aged 18-65 years, BMI >30 kg/m^2, (Optifast52® programme)	Prospective observational uncontrolled study. All participants: Multidisciplinary weight loss programme comprising initial VLCD, nutrition education, behavioural modification and physical exercise. Duration: 1-year intervention, 2-year follow-up

BMI, body mass index; BRCA 1/2, breast cancer 1/2; ITF, inulin-type fructan; VLCD, very-low calorie diet.

between biomarkers, gut microbiota and health outcomes with a special emphasis on gut barrier function, inflammation and cardiometabolic risk factors will allow the identification of those biomarkers that are the most relevant for evaluating the health effects of dietary fibre.

Exploring the metabolic signature of two selected insoluble fibres – wheat bran fraction and chitin-glucan – related to gut fermentation in humans

The second objective of the project is to evaluate in new intervention studies the potential relevance of two selected insoluble fibres (provided by the industrial partners) as modulators of host physiology through their interaction with the gut microbiota.

Chitin-glucan fermentation and related effects

The first intervention study consists of the evaluation of the fermentability of chitin-glucan in 15 healthy volunteers. Chitin-glucan, developed by KitoZyme (EFSA 2010c), has beneficial effects on the development of obesity and associated diabetes and hepatic steatosis in mice, through a mechanism related to the restoration of the composition and/or the activity of gut bacteria (Neyrinck *et al.* 2012). It modulates the human gut microbiota in the *in vitro* SHIME microbiota simulator (Marzorati & Possemiers 2017). This fibre is being tested in human volunteers in order to develop a non-invasive procedure for the measurement of volatile metabolites and gases in breath, reflecting the fermentation pattern of the dietary fibre.

We are evaluating the gastrointestinal tolerance (by visual analogue scale) and the kinetics of exhaled gases and VOC (through SIFT-MS technology) over 12 hours as markers of fermentation following the ingestion of 4.5 g chitin-glucan compared with the ingestion of 4.5 g of maltodextrin (placebo). In a second intervention study, the effect of the chronic intake of chitin-glucan on gut microbiota composition and function is being assessed in the same healthy volunteers over 3 weeks. Daily chitin-glucan supplementation (4.5 g per day) versus maltodextrin will be given for 21 days with assessment of food intake and gastrointestinal tolerance, as well as faecal sampling for gut microbiota analysis. At day 0 (before intervention) and day 21 (after the intervention), the metabolites related to gut fermentation (exhaled gases and VOC after a test meal, bile acids, cPUFA, SCFAs in faeces) will be measured. This protocol evaluates the tolerance towards chitin-glucan in humans, its fermentability and its potential interaction with the gut microbiota composition and function. This study is a prerequisite to the third intervention, a randomised, controlled cross-over trial which aims to test the efficacy of the chitin-glucan intervention in the control of metabolism in metabolic risk individuals. For that purpose, 15 subjects (aged 30–65 years) male and female at cardiometabolic risk (abdominally obese, waist circumference >102 cm for men and >88 cm for women) will be selected.

Wheat bran fermentation

A wheat bran fraction has been provided and characterised by the industrial partner Mondelez, as an interesting source of fermentable insoluble dietary fibre (arabinoxylans). Indeed, wheat is one of the major cereal-based foods in occidental countries and increased knowledge about wheat bran fermentability will provide valuable information to promote its consumption in the general population. An enriched ^{13}C-wheat bran has been produced to enable the fate of the ^{13}C-labelled gut-derived metabolites in biological samples to be followed in a pilot study in healthy volunteers (Nazare *et al.* 2010; Vinoy *et al.* 2013). An *in vivo* pilot study is evaluating the extent and metabolic signature of the insoluble dietary fibre bran fermentation in six human healthy volunteers using ^{13}C-wheat bran (biscuit prototype). For that purpose, we are analysing the kinetics of key exhaled gases in breath (H_2, CO_2, CH_4) and of ^{13}C-metabolites and ^{13}C-SCFAs released in the blood and faecal material after ^{13}C-wheat bran ingestion. This innovative process will provide evidence on the relevance of fibre fermentation by observing the profile of ^{13}C-metabolite production in blood and exhaled gases.

Conclusions

The *FiberTAG* project is in the last phase of development and will end in 2021. Some preliminary data have recently been communicated in several key meetings. We hope, as a consortium, that the huge amount of data obtained from existing and new cohorts will bring new insights in the way we envisage the contribution of insoluble fibre to the modulation of the gut microbiota, and in the identification of adequate biomarkers linking dietary fibre intake, gut microbiota modulation (including co-metabolite production) and health outcomes.

Acknowledgement

The *FiberTAG* project consortium also includes Julie-Anne Nazare, Maud Alligier and Anne-Ester Breyton from the Centre de Recherche en Nutrition Humaine Rhône-Alpes (Univ-Lyon, France), Zhengxiao Zhang from the Department of Medecine (University of Alberta, Canada), Benjamin Seethaler from Institute of Nutritional Medicine (University of Hohenheim, Germany), Alexandra Meynier from Mondelez Int. R&D (France).

Conflict of interest

The authors declare that they have no competing interests.

Funding

FiberTAG project was initiated from a European Joint Programming Initiative 'A Healthy Diet for a Healthy Life' (JPI HDHL). Funding for this article is provided by the Service Public de Wallonie (SPW-DGO6, convention 1610365, Belgium), the Agence Nationale de la Recherche (ANR, France), the Canadian Institutes of Health Research (CIHR, Canada) and German Federal Ministry for Education and Research (BMBF, Germany).

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