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Review

Extending *in vitro* digestion models to specific human populations: Perspectives, practical tools and bio-relevant information

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ABSTRACT

Background: *In vitro* digestion models show great promise in facilitating the rationale design of foods. This paper provides a look into the current state of the art and outlines possible future paths for developments of digestion models recreating the diverse physiological conditions of specific groups of the human population.

Scope and approach: Based on a collective effort of experts, this paper outlines considerations and parameters needed for development of new *in vitro* digestion models, e.g. gastric pH, enzymatic activities, gastric emptying rate and more. These and other parameters are detrimental to the adequate development of *in vitro* models that enable deeper insight into matters of food luminal breakdown as well as nutrient and nutraceutical bioaccessibility. Subsequently, we present an overview of some new and emerging *in vitro* digestion models mirroring the gastro-intestinal conditions of infants, the elderly and patients of cystic fibrosis or gastric bypass surgery.

Key findings and conclusions: This paper calls for synchronization, harmonization and validation of potential developments in *in vitro* digestion models that would greatly facilitate manufacturing of foods tailored or even personalized, to a certain extent, to various strata of the human population.

1. Introduction

1.1. *In vitro* models for food research

In vitro digestion (IVD) modelling is a vivid field of research that shows great promise in facilitating the development of foods and oral formulations based on better understanding of their digestive fate in the stomach and small intestine in as well as downstream

Abbreviations: CF, Cystic Fibrosis; EFFoST, European Federation of Food Science and Technology; GBP, Gastric Bypass; GI, Gastrointestinal; GIT, Gastrointestinal tract; IBD, inflammatory bowel disease; IVD, *In vitro* digestion; PTL, Pancreatic Triglyceride Lipase; SG, Sleeve Gastrectomy.

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ramifications to the gut microbiome (Bornhorst, Gouseti, Wickham, & Bakalis, 2016; Guerra et al., 2012; Hur, Lim, Decker, & McClements, 2011; Payne, Zihler, Chassard, & Lacroix, 2012). Although human or *in vivo* animal studies are still considered a "gold standard" for tackling issues of bioaccessibility, absorption, bioavailability, metabolism and excretion, IVD methods have the advantage of being more rapid, less labor intensive and having significantly less bioethical restrictions. In fact, various IVD models have been increasingly applied to assess the digestive fate and potential toxicity of ingested natural and engineered nano-materials (Lefebvre et al., 2015). This has led to great variability in scientific efforts, including some contradicting studies, and stimulated the recent effort of the INFOGEST network of scientists to develop a consensus harmonized static *in vitro* digestion model based on physiologically relevant conditions gathered from humans (Minekus et al., 2014). This harmonized protocol was validated in a wide inter-laboratory trial (Egger et al., 2016) and is currently pending on-going efforts to correlate findings of protein digestibility with an *in vivo* trial in pigs and biochemical assays with human aspirates (yet to be published). However, these and other numerous scientific publications focus on IVD systems designed for evaluating the digestive fate of foods and oral formulations in the adult alimentary canal.

During a dedicated workshop held by the European Federation of Food Science and Technology (EFFoST) in Athens on November 2015, we found that current physiological literature offers professionals additional opportunities to recreate the unique and specific gastro-intestinal (GI) functions of other human populations, such as infants, the elderly and more. Such intriguing possibilities would open new opportunities to study and develop foods and oral formulations better tailored to the needs of such specific populations. Based on the pooled and accumulated experience of the INFOGEST network, it was decided to help a systematic and responsible orchestration of relevant global efforts, maximize synergisms between researchers and harmonize efforts to develop new IVD models. Thus, this paper provides a look into the current state of the art and paves possible future paths for developments, all with the aim of ensuring adequate and fruitful endeavors and outputs to the food and health community.

1.2. Current status of adult in vitro digestion (IVD) models

In vitro digestion models were initially developed to serve as research tools to characterize and clarify the structural and biochemical changes of food components under physiological conditions, caused by alimentary enzymes (Romano et al., 2016), GI motility and by the colonic microbiota. In principle, IVD models of the upper GI need to overcome the shortcomings of *in vivo* trials (*i.e.* ethical constraints, low throughput, control over subjects and reproducibility) and account for the most bio-relevant anatomical and physiological considerations mirroring the mouth, stomach, small and large intestine lumen and gut lining. In fact and in spite of their limitations, IVD models are particularly suited for investigating the luminal physiochemical changes in food, matters of bioaccessibility and some aspects of bioavailability.

Historically, efforts to develop IVD models began in the early 1990's with pioneering works to develop reliable, robust, reproducible and bio-relevant tools like the multi-compartmental GI model developed by TNO in the Netherlands (Minekus, Marteau, Havenaar, & Huisintveld, 1995) or the three stage continuous fermentation systems recreating the human colon (Macfarlane, Macfarlane, & Gibson, 1998; Molly, Woestyne, & Verstraete, 1993). Since, the field has boomed with numerous IVD models, ranging from simple static mono-compartmental models to computer-controlled multi-compartmental dynamic IVD models, as reviewed by others (Glahn, Wien, VanCampen, & Miller, 1996; Guerra et al., 2012; Hur et al., 2011; McClements & Li, 2010; Payne et al., 2012; Yoo & Chen, 2006). Recent studies even raised the possibility of using human GI aspirates in IVD models (Ulleberg et al., 2011) or coupling IVD models with human cell cultures of Caco-2 epithelial cells or Caco-2 co-cultures with HT-29 mucus producing cells (Deat et al., 2009; Vors et al., 2012). Yet, the low accessibility and stability of human aspirates and the complexity of coupling IVD research with cell cultures, challenge the wide spread use of highly bio-relevant alternatives over simple protocols currently used in IVD models. Further, *in vitro* cell culture systems have been coupled to some IVD models to enable investigating questions of cellular uptake and brush border enzymatic breakdown, which better elucidate the bioavailability of specific substances (Deat et al., 2009; Manione et al., 2015; Vors et al., 2012).

Concomitantly, various efforts reported to develop and apply sophisticated IVD models that are intended to be more realistic, encompassing various aspects of digestion dynamics (e.g. physiological acid secretion and gastric emptying), mass transport phenomena (*i.e.* absorption and diffusion) and rheological aspects (*i.e.* mixing) (Blanquet et al., 2004; Dekkers, Kolodziejczyk, Acquistapace, Engmann, & Wooster, 2016; Kong & Singh, 2010a; Levi & Lesmes, 2014; Mercuri, Lo Curto, Wickham, Craig, & Barker, 2008; Shani-Levi, Levi-Tal, & Lesmes, 2013; Tharakan, Norton, Fryer, & Bakalis, 2010; Yoo & Chen, 2006). To date, both advanced and simple IVD models have be used to investigate a variety of systems. Examples include investigations of simple high purity protein solutions, multi-component model systems like emulsions and even more real foods, like dairy gels and pasta. These and other investigations have significantly advanced our understanding of the interplay between food ingredients, food products and the alimentary canal of healthy adults. Such insights include not just understanding of food breakdown but also its impact on gastro-intestinal functions, e.g. gastric emptying and intestinal motility, as detailed by others (Grundy et al., 2016; Houghton, Hickson, & Read, 1987; Meyer, Elashoff, & Lake, 1999; Sarosiek et al., 2010).

1.2.1. Identified research needs

Despite the various hectic activity in the field of understanding food's digestion in adults, there is still much room for further advancements and breaching of current gaps in knowledge and capabilities. The various discussions held during the Athens workshop identified that amongst future advancements in the field, research should include efforts: [I] To improve the bio-relevance of luminal composition and dynamics (e.g. pH profiles and use of gastric lipases); [II] To validate and/or correlate IVD data with *in vivo* findings; [III] To recreate the 3D micro-architecture of the intestinal lining and mucosa through co-cultures (e.g. Caco-2 and HT29 cell lines, grown on various scaffolds); and [IV] To develop predictive *in silico* models. All of these topics were enthusiastically discussed in separate work groups during the workshop and are expected to bring up further scientific publications.

1.3. Rationale and approach for extending IVD models

Advancements in the field of food science and technology need to address numerous challenges that humanity is and will be facing in the 21st century (Floros et al., 2010). These challenges will include feeding the growing and ageing world population, better and sustainable use of natural resources as well as improving our ability to exploit foods' potential to prevent diseases and maintain health promote wellness. In this respect, personalized or tailored nutrition seem highly promising and challenging strategies (Joost