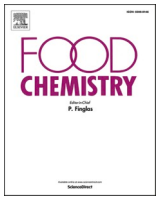
Food Chemistry 492 (2025) 145531

Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem



Review

Application of the INFOGEST 2.0 standardized method to study the behavior of phenolic compounds throughout gastrointestinal digestion

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ARTICLE INFO

Keywords:
Phenolic compounds
In vitro digestion
INFOGEST protocol
Bioaccessibility

ABSTRACT

The potential of phenolic compounds as molecules that exerted interesting biological activities has been exhaustively demonstrated. However, digestion may affect their stability, bioaccessibility and bioavailability. The INFOGEST 2.0 is a standardized methodology to *in vitro* simulate human gastrointestinal digestion. The main objective of this study was to systematically review the scientific literature related to INFOGEST 2.0 application to the study of food (poly)phenols, comprehensively and critically addressing how gastrointestinal digestion affects their stability, bioaccessibility and biological activity. From the 1658 articles obtained in the initial search, 121 were selected. Many works showed high bioaccessibilities for total phenolics (>100 %), although the ratios were very variable, particularly for individual species. Technological approaches (*e.g.*, encapsulation or microbial fermentation) could be applied to improved bioaccessibility. *In vitro* activities were also studied, with clear dominance of antioxidant assays, and the reviewed works suggested that, particularly when bioaccessibility is high, digestion might enhance bioactivity.

1. Introduction

Phenolic compounds are a wide class of bioactive molecules predominantly found in plant-based foods that have emerged as key contributors to human health due to their numerous biological properties. These compounds are renowned for their antioxidant, anti-inflammatory, antimicrobial effects and potential benefits against chronic disorders such as cardiovascular disease and diabetes (Armas Díaz et al., 2023; Esposito et al., 2021). Epidemiological evidence also suggests that diets rich in these phytochemicals can diminish the risk of pathological conditions, underscoring the importance of incorporating fruits and vegetables into healthy dietary patterns (Probst et al., 2017; Zhan et al., 2017).

The health-promoting effects of phenolic compounds depend not only on their dietary intake but also on their stability during digestion, release, metabolism and transformation into bioaccessible and bioavailable forms (Bohn, 2014). At this point, it is essential to clarify the differences between the terms bioaccessibility (BA) and bioavailability. BA refers to the fraction of an ingested compound that is biochemically and/or physically released from the food matrix and solubilized in the gastrointestinal fluids in an absorbable form. In contrast, bioavailability refers to the amount of a specific bioactive metabolite that is present in the bloodstream following ingestion (relative bioavailability), as well as the amount that reaches the target cells, tissues, or organs in the body (real bioavailability) (Grundy et al., 2025). Therefore, high bioavailability ratios are crucial for bioactive molecules to exert their biological effects in the organism. In this sense, during the digestive process, phenolic compounds are exposed to varying gastrointestinal conditions (*e.g.*, pH, osmolarity, motility, digestive enzymes, bile salts) which can lead to differences in solubility and chemical modifications such as hydrolysis, oxidation, and polymerization (Sęczyk et al., 2021; Tarko & Duda-Chodak, 2020). Polyphenols can also form complexes with other nutrients such as dietary fiber and proteins, affecting their release from the food matrix and bioaccesibility (Grundy et al., 2024; Jakobek, 2015). All these changes may result in degradation of the parent phenolic compound and/or the formation of derived metabolites with subsequent modified bioactivity in the human body. Moreover, it is important to highlight the crucial role of the gut microbiota in metabolizing and biotransforming (poly)phenols -often increasing their absorption and bioactivity-, which in turn modulates

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https://doi.org/10.1016/j.foodchem.2025.145531
Received 23 April 2025; Received in revised form 24 June 2025; Accepted 10 July 2025
Available online 12 July 2025

microbiota composition (Wojtunik-Kulesza et al., 2020).

Developed by an international consortium, the INFOGEST 2.0 protocol has become a worldwide recognized and standardized methodology for static *in vitro* simulation of gastrointestinal human digestion (Brodkorb et al., 2019). This protocol simulates the exposure of foods to sequential oral, gastric and intestinal digestion, and sets the key digestion parameters and conditions based on physiological data (electrolytes, enzymes, bile, dilution, pH, time of digestion). It uses constant ratios of meal to digestive fluids as well as constant pH values for each digestion step. This enhanced protocol overcomes the challenges of the previous method, such as the inclusion of the oral stage and the use of gastric lipase. Noteworthy, the harmonized nature of the INFOGEST 2.0 protocol enables reproducibility and meaningful comparison across studies, thereby facilitating an improved understanding of food compounds behavior during digestion and placing itself as an essential tool for researchers in food science and nutrition.

Therefore, this review aims to systematically analyze the existing literature on the application of the INFOGEST 2.0 protocol to food-derived (poly)phenols. By summarizing findings from current studies that have applied this method to diverse food categories, this article seeks to provide a comprehensive overview and critical update on how this standardized method impacts the stability, BA, and bioactivity of phenolic compounds.

2. Methods

A comprehensive literature search on the application of the INFOGEST 2.0 digestion protocol was conducted using the Web of Science Core Collection. The search included all references citing the study by Brodkorb et al. (2019), published in *Nature Protocols* (Brodkorb et al., 2019). This initial search retrieved a total of 1658 papers. The flow diagram of the bibliometric analysis was carried out according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Page et al., 2021) (Fig. 1). To refine the dataset, filters were applied to include only articles with the topic keyword (phenol*), written in English, and classified as research articles. This refinement and elimination of duplicates led to the identification of 289 papers for screening. From each article, bibliometric data such as author names, article title, abstract, journal name, volume, issue, page range, DOI, document type, publication date, and unique identifier (UT) were extracted and organized on a Microsoft Excel sheet.

The 289 studies were screened for inclusion by a process conducted independently by two investigators. Any discrepancies were resolved by a third investigator and a second-round revision. The analysis led to the exclusion of an additional 40 references, resulting in 249 reports selected for final analysis. The following inclusion criteria required that studies clearly employed INFOGEST 2.0 in their methodology as the digestion protocol of the investigation without any major modification. Papers that cited the protocol but introduced significant methodological adaptations, or that merely use its reference as conceptual support or contextual justification, were excluded. Additionally, studies outside the scope of polyphenol-related food research were removed. After applying these criteria, the bibliometric analysis resulted in a final selection of 121 studies included in the review. Studies in the sections below were organized in tables according to the food groups proposed by Food and Agriculture Organization of the United Nations (FAO/WHO GIFT, Global Individual Food consumption data Tool, https://www.fao.org/gift-individual-food-consumption/en/), thereby contributing to the global harmonization of dietary data.

3. Results and discussion

3.1. Impact of INFOGEST 2.0 protocol on the bioaccessibility (BA) values of Total phenolic compounds content (TPC) of food matrices and products

Gastrointestinal digestion clearly influences (poly)phenols BA through the oral, gastric and intestinal phases. The varying conditions (*e.g.*: digestive fluids, pH, enzymes, microbiota) are crucial factors. For instance: saliva can enhance phenolic solubility in certain food matrices, low pH in the stomach may lead to (poly)phenols degradation, small intestine enzymes can modify phenolic compounds increasing or decreasing their BA, and large intestine microorganisms metabolize non

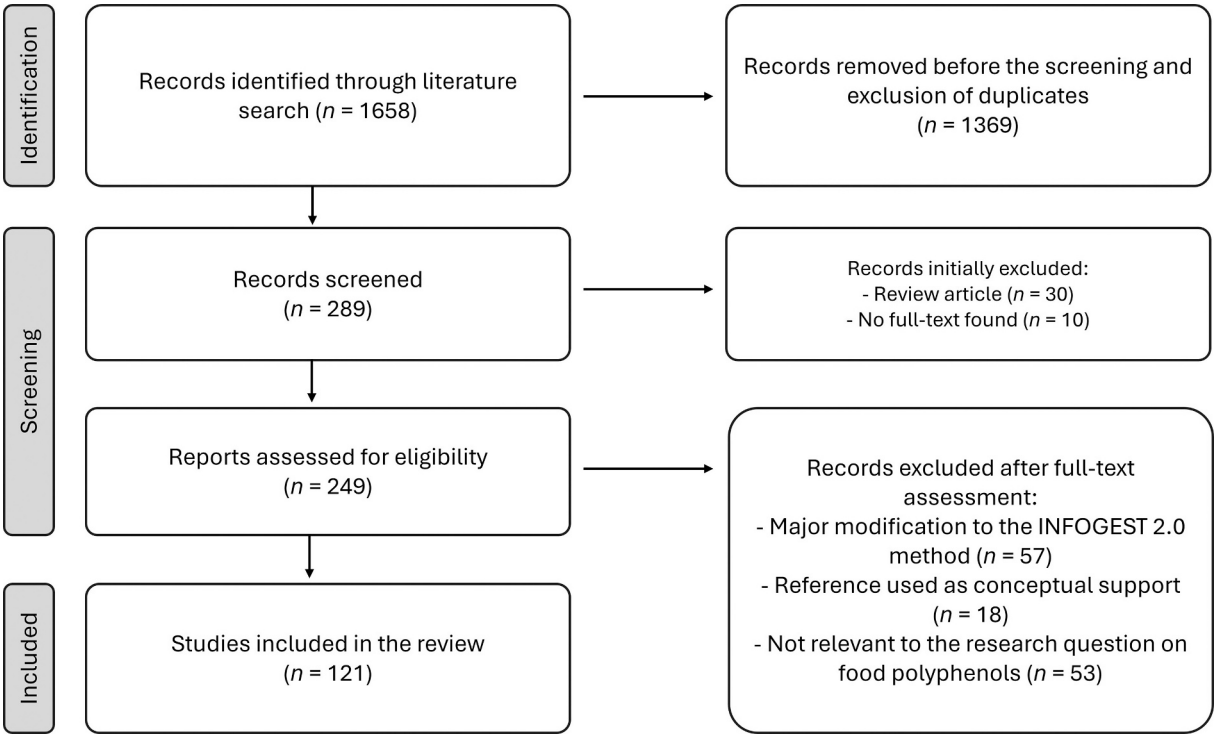

Fig. 1. Flow diagram of the bibliometric analysis.

previously absorbed phenolics generating simpler metabolites (Wojtunik-Kulesza et al., 2020).

The BA of TPC has been widely studied for many and varied food matrices and derived fractions (Table 1). Generally, the TPC values were calculated in undigested samples through spectrophotometric methods following or adapting Folin-Ciocalteu's procedure (Lawag et al., 2023). Then, the samples were subjected to *in vitro* digestion by using INFOGEST 2.0 protocol, and phenolic content was subsequently and spectrophotometrically determined in the digestates. In some cases, individual phenolic molecules were quantified by using chromatography and mass spectrometry and the TPC values were determined by adding up all the individual data. However, these works were excluded from Table 1, since some minor phenolics might be present in very low concentrations even below the quantification limits, being discarded and non-included in the final TPC value.

At this point, some discrepancies in the utilized methodology after gastrointestinal digestion must be mentioned. In most cases, the resultant fraction was only filtered or centrifuged and the obtained filtrates or supernatants were considered the 'bioaccessible fractions'. However, other works utilized dialysis membranes to differentiate 'in' and 'out' fractions and exclusively the 'in' fractions that were recovered from the inside of the membranes were assumed as accessible to be absorbed in the small intestine. These dissimilarities between assays may affect the results. For instance, Perak Junakovic et al. (2023) encapsulated a propolis extract and studied phenolics BA using centrifugation and dialysis models. Since higher values were recorded applying the centrifugation model, the authors considered it as a more suitable protocol for these purposes (Perak Junaković et al., 2023). However, other researchers exclusively applied the dialysis model, focused on the molecules that were available for enterocytic absorption, mimicking the intestinal epithelium barrier with the membranes (Managa et al., 2021; Mashitoa, Akinola, et al., 2021).

BA values are often calculated based on the TPC in the bioaccessible fractions referred to the TPC in the undigested samples and expressed as percentage ((TPC in BA fraction / TPC in undigested sample) x 100). High BAs for TPC, frequently above 100 %, were reported in many works. Some examples are fermented ancient wheat and sourdough (Dapčević-Hadnađev et al., 2022), oat yoghurts with vegetal proteins (Demir et al., 2023), and biscuits prepared with chickpea (Delgado-Andrade et al., 2024) or pseudocereals flours (Paucar-Menacho, Simpalo-López, et al., 2022a). Several reasons have been discussed for the elevated TPC BA values: many phenolic compounds can be released from food matrices during gastric or intestinal digestion; some high-molecular weight (poly)phenols may suffer depolymerization reactions, increasing TPC counts; and bonds and linkages between phenols and macromolecules such as proteins or fibers might be broken, obtaining free bioaccessible molecules. One of the critical points must be the quantification of TPC in undigested samples, as the solubility and accessibility of (poly)phenols from unprocessed food matrices and mixtures might be limited due to the mentioned association with high-molecular-weight macromolecules. Since spectrophotometric determination requires the solubilization of (poly)phenols, particularly when Folin Ciocalteu's reagent is utilized, the accuracy of the quantification may be compromised. Therefore, optimizing sample pretreatment and processing, as well as adapting protocols to enable the measurement of molecules with different polarity, is essential to minimize interference and estimation errors. Moreover, the limitations of spectrophotometric methods such as Folin Ciocalteu's (*e.g.*: non-specific reactions, inteferences from reducing non-phenolic compounds) must be considered (Apak et al., 2016; Huang et al., 2005; Pérez et al., 2023).

In contrast, lower BAs could be also found in the related literature. For instance, Majumder et al. (2024) registered BA percentages $\leq$10 % in several fermented Nepali beverages (Majumder et al., 2024); berries pekmez (a molasses-like syrup from Oriental Mediterranean cuisine) showed 6 % (Özkan et al., 2021); a encapsulated extract from cold brew spent coffee grounds ranged from <1 to 25 % (Chongsrimsirisakhol & Pirak, 2023); and a cinnamon bark extract, 43 % (De Giani et al., 2022). These values can be explained by different phaenomena: susceptibility of phenolic species to oxidative, acidic, and/or enzymatic degradation; polymerization into higher molecular weight (poly)phenols; precipitation into the non-bioaccessible fraction; transformation into non-quantifiable molecules; complexation with proteins, carbohydrates, ions, *etc.* For instance, (poly)phenols can suffer complexation reactions with digestive enzymes or soluble proteins from the food matrix or digestion ingredients, negatively affecting spectrophotometric quantification due to the unavailability of phenolics, and, therefore, decreasing BA values (Kamiloglu et al., 2022).

Together with the common reactions and conditions mentioned that can increase or reduce TPC BAs, specific factors directly affected them. Logically, food processing is capable of provoking modifications in phenolic compounds and their potential BA. For instance, Ozkan et al. (2022) evaluated the impact of different drying methods in black grapes ('Isabel' variety). The published results indicated that 33 % BA was obtained for fresh grapes but, when the grapes were vacuum-dried, this value was increased up to 51 %, confirming that drying-related events such as microstructures formation and cell disruption intensified the release and the subsequent BA of phenolics (Ozkan et al., 2022). However, some culinary treatments exerted a reduction effect. In this sense, elaboration of mousses of hydrolyzed wheat bran reduced TPC BA from >100 % in the hydrolysate to 76-81 % in the different mousse recipes (Tomé-Sánchez et al., 2023). In addition, high temperatures and extreme pH values are able to degrade phenolic compounds, as in spent coffee grounds extracts (encapsulated), that showed BAs significantly low when subjected to thermal processes but particularly to pH = 3.0 (Chongsrimsirisakhol & Pirak, 2023).

Sometimes, other factors were responsible of BA oscillations. For instance, different varieties of grapes led to dissimilar BAs (Rodríguez et al., 2022), as well as different collection dates in bee pollen samples (during the same harvest season) (Akpinar Bayizit et al., 2023). Furthermore, the particle size of the matrix is also important. This fact was evidenced by Vilas-Boas et al. (2022) in carob (*Ceratonia siliqua*) fruit flour. When the particle size of the flour was extremely low (<100 μm) or high (>250 μm), the BA indexes were lower (25 and 40 %, approx., respectively) than in flour with intermediate particle size (100-250 μm), reaching >100 %. Differences in flour particle size led to dissimilar phenolic profiles, which affected BA values. Moreover, larger particle size fractions are expected to contain higher levels of insoluble fibers, which can form bonds with (poly)phenols and hinder their release and subsequent intestinal absorption (Vilas-Boas et al., 2022).

Moreover, food fermentation using specific microbial strains can be applied to improve BA of TPC. For example, pasteurised papaya puree that was fermented with lactic acid bacterial strain *Leuconostoc pseudomesenteroides 56*, reached >100 % BA, significantly higher than non-fermented puree (45 %) (Mashitoa, Akinola, et al., 2021). Pretreatments such as enzymatic hydrolysis before microbial fermentation can also improve BA, as in phenolic-rich spelt seeds, among other food products. The enzymatic action hydrolyses polymeric molecules, triggering the breakdown and enhancing the solubility of complex structures -in this case, from spelt cell walls- to improve the access of fermenting microorganisms. This study noticed increased BA values of *p*-coumaric and *trans*-ferulic acid when enzymatic pretreatment and microbial fermentation were combined (Mencin et al., 2022).

Another strategy towards increasing BA targeted protective and controlled delivery systems, such as encapsulation. Specific encapsulating materials are capable of preserving TPC integrity and stability from aggressive gastrointestinal conditions (pH, enzymes, oxidation, *etc.*). Small and simple phenolic compounds are directly absorbed in the small intestine, while complex phenolic structures reach the colon and require gut microbiota action to break them down into absorbable metabolites that might exert interesting bioactivities. Therefore, both the absorbed and colonic fractions are important -consistent with the concept 'expanded bioaccessibility'- (de Paulo Farias et al., 2025;

Table 1
Total phenolic compounds (TPC) bioaccessibility values calculated in different food samples, matrices and fractions.

Type of sample	Sample description	TPC Bioaccessibility (%)	Additional information	Reference
Cereals (and pseudocereals)	Wheat, pseudocereals and cushuro pasta	>100	Calculation was made based on soluble phenolic compounds	(Paucar-Menacho et al., 2023)
	Spelt-enhanced wheat breads	43 - 61	Discrimination was made between extractable and bound phenolics	(Mencin et al., 2023)
	Fermented ancient wheat varieties and sordough	>100	–	(Dapčević-Hadnađev et al., 2022)
	Formulations of sprouted quinoa flour and cañihua flour in corn grits-based extrudates	>100	Calculation was made based on soluble phenolic compounds	(Paucar-Menacho, Schmiele, et al., 2022)
	Bioprocessed spelt seeds	45 - 100	Discrimination was made between extractable and bound phenolics	(Mencin et al., 2022)
	Rice–tartary buckwheat composite	>100	–	(Li et al., 2022)
	Ternary blends of sprouted kiwicha, cañihua and wheat flours	>100	Calculation was made based on soluble phenolic compounds	(Paucar-Menacho, Simpalo-López, et al., 2022b)
	Sprouted wheat and wheat bran hydrolysate (spray-dried and microencapsulated)	90 (spray-dried) / >100 (microencapsulated)	Calculation was made based on soluble phenolic compounds	(Tomé-Sánchez et al., 2021)
Pulses, seeds and nuts and their products	Fermented dried lentils (and quinoa)	>100	–	(Sánchez-García et al., 2023)
	Oat yogurt with plant proteins	>100	–	(Demir et al., 2023)
	Black mustard grains	>100	–	(Boscariol Rasera et al., 2023)
Milk and milk products	Dairy-blackberry blends	45 - 70	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(van de Langerijt et al., 2023)
	Coffee-fortified yogurt, plain yogurt and fermented coffee	80 (approx.; fermented coffee) - >100 (plain and coffee-fortified yogurt)	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(Helal et al., 2022)
Meat and meat products	Mortadella with blueberry flour	>100	–	(Biasi, Huber, de Melo, et al., 2023)
	Mortadella with goldenberry flour	>100	–	(Biasi, Huber, Goldoni, et al., 2023)
	Pork liver pâtés with persimmon coproducts	89 - >100	Discrimination was made between free and bound phenolics	(Lucas-González et al., 2021)
Vegetables and their products	Piquillo peppers	>100	–	(Del Burgo-Gutiérrez et al., 2024)
	Butternut squash	>100	–	(Kamiloglu et al., 2024)
	Red bell pepper	63 (ultrasound-treated) - 92 (non treated)	–	(Reche et al., 2023)
	Tiger nut products (flour, oil, and milk with and without added sucrose)	>100	–	(Hernández-Olivas et al., 2022)
	False turkey tail mycelial substrate mixed with ginseng extracts	>100	–	(Yang et al., 2022)
Fruits and their products	Carob fruit flour	25-40 (approx.; lowest and highest particle size) - >100 (intermediate particle size)	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(Vilas-Boas et al., 2022)
	Red fruits and edible flowers extracts (spherifications/bubbles)	>100	–	(Bortolini et al., 2024)
	Goji fruits polysaccharide-rich extracts	>100	–	(Zeng et al., 2023)
	Seedless table grapes	13 - 46	–	
	Black Isabel grape	33 (fresh) - 51 (vacuum-dried)	–	(Ozkan et al., 2022)
	Fermented mango puree	33 (non-fermented) - >100 (fermented)	Digested fractions were subjected to dialysis procedures	(Mashitoa, Manhivi, et al., 2021)
	Pasteurised papaya puree (fermented and non-fermented)	45 (non-fermented) - >100 (fermented)	Digested fractions were subjected to dialysis procedures	(Mashitoa, Akinola, et al., 2021)
	Japanese apricot fruits (raw and processed)	1 (dry salt-cured) / 8 (non treated) / 11 (dried at low temperature)	–	(You et al., 2021)
	Syrian juniper berries pekmez	6	Digested fractions were subjected to dialysis procedures	(Özkan et al., 2021)
Fats and oils	Galician extra-virgin olive oil	8 (approx.)	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(Reboredo-Rodríguez et al., 2021)
Sweets and sugars	Chickpea flour biscuits	>100	–	(Delgado-Andrade et al., 2024)
	Cocoa chocolate	50 (approx.)	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(Becerra et al., 2024)
	Nutritive raw bars	31-69	–	(Dordai et al., 2023)
	Ternary blends of sprouted kiwicha, cañihua and quinoa flours in biscuits	>100	Calculation was made based on soluble phenolic compounds	(Paucar-Menacho, Simpalo-López, et al., 2022a)
Spices and condiments	White mugwort	>100	–	(Udomwasinakun et al., 2023)
	Cinnamon bark extract	43	–	(De Giani et al., 2022)

(*continued on next page*)

Table 1 (*continued*)

Type of sample	Sample description	TPC Bioaccessibility (%)	Additional information	Reference
Beverages	Fermented nepali beverages	2 - 10	–	(Majumder et al., 2024)
	Fermented coffee beans	>100	–	(Wu et al., 2023)
	Fermented *aloe vera* juices	>100	–	(Cuvas-Limon et al., 2022)
	Mistletoe (leaves, stems, whole plant) infusions from leaves, stems, and whole plant samples	<10	Folin-Ciocalteu's method results were described as 'total reducing capacity'	(Gutiérrez-Grijalva et al., 2022)
	Powdered fruit and vegetable drinks fortified with lentil proteins and stabilized with flax seed gums	>100	–	(Bochnak-Niedźwiecka et al., 2022)
	Terebinth coffee formulations	12 - 71	–	(Kamiloglu et al., 2022)
	Smoothies of pineapple and chayote leaves (fermented and non-fermented)	52 - 77	Digested fractions were subjected to dialysis procedures	(Managa et al., 2021)
	Fruit juices (pomegranate, orange, grapefruit) and commercial juices (cherry, black grapes, *aloe vera*, blackberry, chokeberry, raspberry)	13 - 26	–	(Mihaylova et al., 2021)
Food supplements	Microalgae	>100	–	(Uzlasir et al., 2023)
	Propolis extract (encapsulated)	54 - >100	Digested fractions were subjected to dialysis procedures (comparing this model with centrifugation without dyalisis)	(Perak Junaković et al., 2023)
	Phycocyanin-honey hydrogels	85	–	(Sahin et al., 2023)
	Bee polen	18 - 72	–	(Akpinar Bayizit et al., 2023)
	Probiotics in chocolate	>100	–	(Zoldan et al., 2023)
	Nano-phytosomes with phycocyanin	55 - 65	–	(Sahin et al., 2022)
	Ethanolic extract of organic propolis	11	–	(Martelli Chaib Saliba et al., 2023)
	Chlorella vulgaris (microalgae)	22 - 73	–	(Canelli et al., 2022)
Savory snacks	Freeze-dried carrot–orange–ginger snacks with powdered apple and blackcurrant pomace	>100	–	(Karwacka et al., 2022)
Plant-based by-product	Grape marc extract (whey-pectin microcapsules)	54 (non-encapsulated) - 83 (encapsulated)	–	(Cruz-Molina et al., 2023)
	Grape pomace	>100	–	(Ferreira-Santos et al., 2024)
	Grape pomace extract (encapsulated)	21 (non-encapsulated) / 47–96 (encapsulated)	–	(Martinović et al., 2023a)
	Coffee pulp (flour, extract)	>100	Discrimination was made between free and bound phenolics	(Cañas, Rebollo-Hernanz, Martín-Trueba, et al., 2023)
	Cocoa shell	44 - 66	Discrimination was made between free and bound phenolics. Bioaccesibility range for total phenolic compounds is shown in this table	(Benítez et al., 2023)
	Cocoa shell (flour, extract)	>100	Discrimination was made between free and bound phenolics	(Cañas, Rebollo-Hernanz, Bermúdez-Gómez, et al., 2023)
	Hydrolyzed wheat bran and mousse	76/81 (mousses) - >100 (hydrolyzed wheat bran)	Calculation was made based on soluble phenolic compounds	(Tomé-Sánchez et al., 2023)
	Cold brew spent coffee grounds extract (encapsulated)	<1 - 25	–	(Chongsrimsirisakhol & Pirak, 2023)
	Lentil hulls	72	–	(Guo et al., 2023)
	Olive mill waste waters extract	33 (approx.) – 100 (approx.)	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(Mercatante et al., 2023)
	Passion fruit peel extracts	20 (approx.)	Digested fractions were subjected to dialysis procedures and bioaccessibility values are approximated estimations since they were calculated based on published figures	(Tang et al., 2023)
	Coffee pulp flour and extract	44 (approx.) - >100	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(Cañas et al., 2022)
	Date fruit pomace (fermented and non-fermented)	4 (approx.) – 15 (approx.)	Bioaccessibility values are approximated estimations since they were calculated based on published figures	(Ayyash et al., 2022)
	Apple pomace (fresh and freeze-dried)	42 (freeze-dried) - 48 (fresh)	–	(Pollini et al., 2022)
	Passion fruit peel extracts	<20	–	(Cao et al., 2021)
	Pine bark extracts (encapsulated and non-encapsulated)	40 (non-encapsulated) - 54 (encapsulated)	–	(Ferreira-Santos et al., 2021)
	Olive pomace extract	>100	–	(Čepo et al., 2020)
	Açaí seed extract	70	–	(Melo et al., 2020)

Zieliński et al., 2021) and for both cases, the structure of phenolics should be protected enough to preserve their biological activities. With this aim, Tomé-Sánchez et al. (2021) encapsulated a wheat bran hydrolysate using spray-drying and microencapsulation with pea protein, showing 90 % and > 100 % BAs, respectively (Tomé-Sánchez et al., 2021). Accordingly, Cruz-Molina et al. (2023) prepared whey-pectin microcapsules loading a grape marc extract, improving from 54 % BA in the non-encapsulated extract to 83 % BA in the microcapsules (Cruz-Molina et al., 2023). Spherification procedures are also related to controlled delivery systems: Bortolini et al. (2024) designed edible calcium alginate bubbles loading fruits extracts, obtaining >100 % BAs for açaí (*Euterpe oleracea*) and jabuticaba (*Plinia cauliflora*) with strawberry extracts (Bortolini et al., 2024).

Therefore, considering all these factors, it has been demonstrated that gastrointestinal digestion can lead to higher or lower TPC counts and, regardless of the TPC values in the digestate, it is crucial to validate the biological activities of the phenolic species after digestion (see section 3.3. and Table 3). Moreover, BA percentages provide a theoretical approach to the potential fraction that could be absorbed in the small intestine; however, bioavailability studies must be carried out to verify if phenolic compounds will reach their targets and effectively exert their bioactivities.

3.2. Identification of individual phenolic compounds and bioaccessibility (BA) calculation in food digestates obtained by applying INFOGEST 2.0 protocol

Apart from the quantification of total phenolic compounds through spectrophotometric procedures such as Folin Ciocalteu's method, specific phenolics were identified and quantified in undigested and digested samples by liquid chromatography coupled to different detectors or spectrometry mass equipment (Čepo et al., 2020; Kamiloglu et al., 2024; Mihaylova et al., 2021a). In most cases, BA values of these molecules were calculated or calculable, except for those works that did not determine the levels of individual phenolics in undigested matrices, perhaps because of the difficulty associated with reaching detection and quantification limits for minor compounds in highly complex samples before digestion (Table 2).

Attending to the type of main phenolic compounds that were commonly identified in food matrices and monitored during the *in vitro* gastrointestinal digestion, phenolic acids and flavonoids must be pointed as the most frequently found groups in already published works, such as ferulic and caffeic acids in different cereals, pulses and seeds (Boscariol Rasera et al., 2023; Sánchez-García et al., 2023; Tomé-Sánchez et al., 2021) or catechin, epicatechin and quercetin in vegetables, fruits and derived products and by-products, among other materials (Bortolini et al., 2024; Cattivelli et al., 2023). The number of identified compounds ranged from a unique molecule or just a few of them (Ciuffarin et al., 2023; Gomes Sá et al., 2023) to great amounts up to 178 metabolites (Cao et al., 2021). This diversity was linked to the complexity of the matrices but also to the instrumental methods applied for identification and quantification.

Furthermore, the BA indexes significantly varied depending on the phenolic species, the food source and, logically, the specific conditions that were used to treat or process the samples before the *in vitro* digestion. In this sense, it can be observed that BA values below 100 % are more frequent for individual than for total phenolic compounds. Digestive fluids and digestion characteristics can partially or totally degrade some phenolic compounds or transformed them into other phenolic or non-phenolic molecules. Regarding this, as an example, phenolic compounds that can be found in olive oil, such as oleacein and oleocanthal, that were found in high concentrations in the oral step of digestion, were reduced to non-detectable levels after the intestinal step, suggesting hydrolysis or degradation reactions (Reboredo-Rodríguez et al., 2021). These null or low BA ratios were observed for oleacein and oleocanthal but also tyrosol in extracts from olive mill wastewaters (Mercatante et al., 2023). In contrast, other compounds showed BA values above 100 %, suggesting that they were released from plant components or as result of hydrolysis, depolymerization or degradation phenomena. For instance, Thumann et al. (2020) prepared an herbal extract mixture (combining extracts from 9 medicinal plants) and applied the INFOGEST 2.0 protocol to simulate gastrointestinal digestion of the mix, subsequently analyzing the modifications in the metabolic profile by ultrahigh performance liquid chromatography-high resolution mass spectrometry (UHPLC-HRMS) based techniques. Compounds such as caffeic acid and liquiritigenin increased their levels after digestion of this herbal matrix since progenitor compounds seemed to be degraded during the process. These variations (to greater levels, in this case, but also to reduced concentrations for other phenolics) were explained by the authors as a result of isomerization, hydrolysis, and reactions of binding or releasing from proteins. Moreover, this work also highlighted that some phenolic compounds can noticed a significant reduction under digestive conditions because of their low water solubility (Thumann et al., 2020). In addition, Ferreira-Santos et al. (2024) demonstrated that digestion promoted the biotransformation of the phenolic compounds present in grape pomace extracts. While some flavonoids contents were drastically reduced during gastrointestinal digestion even to undetectable levels such as catechin, most of phenolic acids, *e.g.* ellagic acid, increased its level leading to BA indexes above 100 %. These outcomes suggest that higher-molecular weight compounds (for instance, flavonoids and stilbenes) were converted into smaller and simpler molecules as phenolic acids (Ferreira-Santos et al., 2024). It can be logically concluded that the specific structure of (poly) phenols influences their behavior under digestive conditions. For instance, factors such as molecular weight, the number and position of substitutions, glycosylation, *etc.* affect their stability and solubility during digestion, as more complex or highly substituted (poly)phenols may be less stable or less soluble. In contrast, smaller or simpler phenolics tend to exhibit higher BA, although less sterically hindered molecules often form stronger complexes with other macromolecules, such as polysaccharides or proteins (Eran Nagar et al., 2020; Wan et al., 2021; Wojtunik-Kulesza et al., 2020).

Because of the promising potential of dietary phenolic compounds as biologically active compounds for health purposes, many studies pursued the protection or controlled release of these molecules, aiming at BA ratios as highest as possible. Interestingly related works were compilated in Table 1 and Table 2. For instance, van de Langerijt et al. (2023) tested how adding milk (full-fat, semi-skimmed, skimmed or high-protein milk) to freeze-dried blackberry puree could influence BA and bioavailability of blackberry (poly)phenols. When the blends were prepared, protein aggregates were formed partially protecting anthocyanins during digestion. However, while milk fat seemed to increase anthocyanins BA, their permeability through Caco-2 cells -used as model of the intestinal barrier- was reduced, indicating that intestinal absorption and bioavailability was negatively affected (van de Langerijt et al., 2023). Technological approaches such as encapsulations, emulsions, *etc.* are widely used to protect (poly)phenols during digestion, control their delivery and increase their BA. In this context, Parralejo-Sanz et al. (2023) achieved BA increases of phenolic acids and flavonoids in extracts from the fruits of *Opuntia stricta* var. *dillenii* cactus by preparing oil-based double emulsions of the extracts, leading to formulations by using Tween 20 or sodium caseinate. The BA index of piscidic acid (phenolic acid) and isorhamnetin glucoxyl-rhamnosyl-pentoside (flavonoid) was enhanced in the double emulsions (compared to the free extract as control) from 64 to 253 % and 24 to 91 %, respectively (Parralejo-Sanz et al., 2023). As mentioned in the previous section, Bortolini et al. (2024) designed edible bubbles through calcium alginate spherification to load fruits extracts with improved BA of phenolic compounds. This controlled release system was successful for major flavonoids such as catechin and epicatechin but did not reach high BA ratios in other molecules, particularly those with higher molecular weight such as procyanidin B2 (Bortolini et al., 2024).

Table 2
Specific phenolic compounds (or groups) bioaccessibility values calculated in different food samples, matrices and fractions.

Type of sample	Sample description	Instrumental method	Identified compounds		Bioaccesibility (%) of main compounds	Reference
			Total	Main compound/s		
Cereals (and pseudocereals)	Hulless barley	HPLC	5	Ferulic acid	–	(Drawbridge et al., 2023)
	Spelt-enhanced wheat bread	HPLC-MS	8	*Trans*-ferulic acid *Cis*-ferulic acid	1 - 3 4 - 9	(Mencin et al., 2023)
	Bioprocessed spelt seeds	HPLC-MS	9	*Trans*-ferulic acid *Cis*-ferulic acid *p*-Coumaric acid	<1 - 6 1 - 29 2 - 13	(Mencin et al., 2022)
	Rice–tartary buckwheat composite	UPLC-Triple-TOF/MS	8	Forsythobiflavone A Quercetin-3-O-rutinoside-7-O-glucoside Rutin	–	(Li et al., 2022)
	Sprouted wheat and wheat bran hydrolysate (spray-dried and microencapsulated)	HPLC-ESI-QTOF-MS	27	*Trans*-ferulic acid	77 - >100	(Tomé-Sánchez et al., 2021)
Pulses, seeds and nuts and their products	Fermented dried lentils and quinoa	HPLC	16	Caffeic acid Vanillic acid Ferulic acid	–	(Sánchez-García et al., 2023)
	Black mustard grains	LC-MS/MS	11	Caffeic acid *p*-Coumaric acid Sinapic acid Rutin	–	(Boscariol Rasera et al., 2023)
Milk and milk products	Dairy-blackberry blends	HPLC-Q-TOF / UPLC-MS/MS	14	Cyanindin-3-*O*-glucoside Ellagic acid Gallic acid	–	(van de Langerijt et al., 2023)
	Coffee-fortified yogurt, plain yogurt and coffee-water exrtacts	HPLC-ESI-IT-MS	18	Caffeoylquinic acids Feruloylquinic acids	15 74 - >100	(Helal et al., 2022)
Meat and meat products	Pork liver pâtés with persimmon coproducts	HPLC	16	Gallic acid Flavanone glucoside Gallocatechin gallate glucoside	92 - >100 >100 26 - 45	(Lucas-González et al., 2021)
Vegetables and their products	Piquillo peppers	HPLC-MS/MS	58	3-(3′-hydroxyphenyl) propanoic acid 4-hydroxy-3-methoxyphenylacetic acid Benzene-1,2-diol	–	(Del Burgo-Gutiérrez et al., 2024)
	Butternut squash	UPLC-MS/MS	10	Epicatechin Syringic acid	71 - >100 81 - >100	(Kamiloglu et al., 2024)
	Red-skinned onion	UHPLC-MS	44	Quercetin Quercetin-4'-*O*-β-glucoside Quercetin-3,4'-di-*O*-β-glucoside-4'-*O*-glucoside	24 - >100 12–87 16 - 92	(Cattivelli et al., 2023)
	Red radish, red cabbage, broccoli, and white mustard sprouts	HPLC-DAD-ESI/MSn	11	Kaempferol—7-glucoside-3-sinapoyl diglucoside Sinapoyl-glucose Trisinapoyl-gentibioside	0 - 9 9 - 79 0 - 31	(Abellán et al., 2021)
Fruits and their products	Red fruits and their extracts (spherifications/bubbles)	HPLC-DAD	12	Catechin Epicatechin Procyanidin B2	10 - >100 15 - >100 0 - 8	(Bortolini et al., 2024)
	Opuntia cactus fruits (extracts and emulsions)	HPLC-DAD-MS/QTOF and ESI/MS	9	Piscidic acid Isorhamnetin glucoxyl-rhamnosyl-pentoside	64 - >100 24 - 91	(Parralejo-Sanz et al., 2023)
	Elderberry	HPLC-DAD-ESI-MS	16	Cyanidin glucoside Rutin Feruloyquinic acid	52 69 0	(Haş et al., 2023)
	Prickly pear fruit (extract)	HPLC-DAD-ES-MS	14	Piscidic acid 4-hydroxybenzoic acid glycoside Rutin	77 - 94 70 - 99 30 - 95	(Fernández-Repetto et al., 2023)
	Seedless table grapes	HPLC-DAD	26	Catechin Peonidin-3-glucoside Malvidin-3-glucoside Quercetin-3-glucuronide	–	(Rodríguez et al., 2022)
	Black Isabel grape	HPLC-DAD	20	Chlorogenic acid Protocatechuic acid Catechin Malvidin-3-*O*-glucoside	3 - >100 1 - 82 1 - >100 –	(Ozkan et al., 2022)
	Prickly pear pulps and peels	HPLC-DAD, LC-ESI-QTOF-MS/MS	7	Piscidic acid	38 - >100	(Gómez-Maqueo et al., 2021)
	Prickly pear pulps and peels	HPLC-DAD-ESI/MS, HPLC-DAD-MS/QTOF	17	Piscidic acid	29 - 80	(Gómez-Maqueo et al., 2020)

(*continued on next page*)

Table 2 (*continued*)

Type of sample	Sample description	Instrumental method	Identified compounds		Bioaccesibility (%) of main compounds	Reference
			Total	Main compound/s		
	Pasteurised papaya puree (fermented and non-fermented)	HPLC-DAD	12	Gallocatechin gallate Quercetin	6 - 14 33 - 49	(Mashitoa, Akinola, et al., 2021)
	Cactus berry	HPLC-DAD-ESI/MS, HPLC-DAD-ESI-QTOF	12	Isorhamnetin rhamnosyl-rutinoside Quercetin-3-*O*- rhamnosyl-rhamnosyl- rhamnosyl-glucoside	21 15	(Montiel-Sánchez et al., 2021)
	Syrian juniper berries and pekmez	HPLC-DAD	8	Protocatechuic acid Chrysin Catechin	9 36 96	(Özkan et al., 2021)
	Apple and apple extract	UHPLC-ESI-QTOF MS/MS	45	Protocatechuic acid-4-*O*-glucoside 4-hydroxybenzoic acid-4-*O*-glucoside Chlorogenic acid	66 - >100 38–73 0 - >100	(Lopez-Rodulfo et al., 2024)
Fats and oils	Olive oil (oleogel)	UHPLC	2	Tyrosol Hydroxytyrosol	1 - 17 22 - 52	(Ciuffarin et al., 2023)
	Galician extra-virgin olive oil	LC-DAD/FLD/MS	21	Oleacein Oleocanthal Ligstroside aglycone	0 0 0	(Reboredo-Rodríguez et al., 2021)
Sweets and sugars	Chickpea flour biscuits	UPLC-MS/MS	6	*p*-Coumaric acid Ferulic acid	– 	(Delgado-Andrade et al., 2024)
	Cocoa chocolate	LQ-MS-QTOF	17	Catechin Epicatechin	22 - 50 10 - 40 (approx..)	(Becerra et al., 2024)
Spices and condiments	White mugwort	HPLC-DAD/MS	9	3,5-dicaffeoylquinic acid 3-caffeoylquinic acid 5-caffeoylquinic acid	0 - 16 0 - 58 0 - >100	(Udomwasinakun et al., 2023)
	Multi-ingredient herbal formulation	UPLC-HRMS	53	Caffeic acid Liquiritigenin acid Glycyrrhizic acid Luteolin	>100 >100 98 - >100 100 - >100	(Thumann et al., 2020)
	Purple coneflower extracts	HPLC-UV-MS/MS	7	Chicoric acid Caftaric acid	4 - 10 10 - 39	(Ávila-Gálvez et al., 2024)
	Mulberry leaves	LC-MS/MS	8	Ferulic acid *p*-Coumaric acid 5-Hydroxyferulic acid	–	(Zhao et al., 2024)
Beverages	Functional beverage (guave, mamey, stevia)	UHPLC-UV	9	Gallic acid Gallocatechin gallate *p*-Coumaric acid	0 0 Non quantifiable	(Belmonte-Herrera et al., 2024)
	Fermented coffee beans	HPLC-PDA	13	Chlorogenic acid Caffeic acid	59 - >100 15 - >100	(Wu et al., 2023)
	Chrysanthemum-coix seed beverage	UPLC-QTOF-MS	15	Chlorogenic acid Acacetin-7-*O*-glucoside Apigenin-7-*O*-glucoside	20 (approx..) - >100 70 (approx..) - >100 50 (approx..) - >100	(Rao et al., 2023)
	Fermented *aloe vera* juices	UPLC-DAD	14	Epicatechin Hesperidin Aloin	50–55 49 - >100 25–29	(Cuvas-Limon et al., 2022)
	Mistletoe (leaves, stems, whole plant) infusions from leaves, stems, and whole plant samples	UPLC-qToF-MS/MS	15	Ferulic acid Quinic acid Gallic acid	7 - 14 8 - 23 2 - 16	(Gutiérrez-Grijalva et al., 2022)
	Terebinth coffee formulations	HPLC-PDA	10	Catechin Gallic acid	82 - >100 52 - >100	(Kamiloglu et al., 2022)
	Fruit juices (pomegranate, orange, grapefruit) and commercial juices (cherry, black grapes, *aloe vera*, blackberry, chokeberry, raspberry)	HPLC-DAD	6	Chlorogenic acid Caffeic acid *p*-Coumaric acid Sinapic acid	9 - >100 7 - 78 21 - >100 30 - >100	(Mihaylova et al., 2021)
Food supplements	Propolis extracts and loaded liposomes	LC-MS/MS	15	Pinocembrin Pinobanksin Trans-ferulic acid Caffeic acid phenyl ester	2 - >100 2 - >100 3 - >100 <1 - 67	(Saroglu & Karadag, 2024)
	Propolis extracts (microencapsulated)	HPLC-MS	58	Prenyl caffeate isomers	1 - 23	(Cea-Pavez et al., 2024)
	Microalgae	HPLC-DAD-ESI-MS/MS	34	Dimethoxyflavone Quercetin derivative	–	(Uzlasir et al., 2023)
	Red propolis and brewer's spent yeasts	HPLC-ESI-QTOF-MS	21	Liquiritigenin Vestitol	– 	(Saliba et al., 2023)
	Bee polen	UHPLC-MS/MS	30	Isoquercitrin Luteolin Chrysin	7 - 12 4 - 12 4 - 8	(Akpinar Bayizit et al., 2023)

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Table 2 (*continued*)

Type of sample	Sample description	Instrumental method	Identified compounds		Bioaccesibility (%) of main compounds	Reference
			Total	Main compound/s		
				p-Coumaric	39 - 58	
				Caffeic acid	12 - 65	
	Red propolis extract (encapsulated)	HPLC	1	Formononetin	<1 - 2	(Gomes Sá et al., 2023)
	Ethanolic extract of organic propolis	HPLC-ESI-QTOF-MS	17	Secoisolariciresinol	–	(Martelli Chaib Saliba et al., 2023)
				Pinoresinol		
				Matairesinol		
				Caffeic acid		
Plant-based by-product	Olive leaf extract (encapsulated)	HPLC-MS	13	Oleuropein	40 - 60 (approx..)	(Duque-Soto et al., 2024)
	Grape pomace	HPLC	17	Ellagic acid	>100	(Ferreira-Santos et al., 2024)
				Naringenin	78	
				Apigenin	>100	
	Grape pomace extract (encapsulated)	UHPLC	27	Oenin (chloride)	0 - 33	(Martinović et al., 2023b)
				Epicatechin	0 - >100	
				Catechin	0	
	Coffee pulp (flour, extract)	HPLC-PDA-ESI/MSn	16	Protocatechuic acid	92	(Cañas, Rebollo-Hernanz, Martín-Trueba, et al., 2023)
				4-caffeoylquinic acid (*trans*)	79	
	Coffee pulp (flour, extract)	HPLC-DAD-ESI/MSn	16	Gallic acid	32 - 33	(Cañas et al., 2022)
				Protocetechuic acid	71–92	
				Cryptochlorogenic acid (*trans)*	45 - 79	
	Cocoa shell (flour, extract)	HPLC-PDA-ESI/MSn		Gallic acid	74 - 90	(Cañas, Rebollo-Hernanz, Bermúdez-Gómez, et al., 2023)
				Catechin	>100	
				Protocatechuic acid	89 - >100	
	Hydrolyzed wheat bran and mousse	HPLC-DAD	2	Ferulic acid (*trans*)	85 - >100	(Tomé-Sánchez et al., 2023)
				Ferulic acid (*cis*)	96 - >100	
	Lentil hulls	HPLC	4	Catechin glucoside	36	(Guo et al., 2023)
				Procyanidin dimer	46	
				Dihydroxybenzoic acid-O-dipentoside	25	
				Kaempferol tetraglucoside	37	
	Lentil hull extract	HPLC-DAD-ESI-MS	5	Protocatechuic acid glycoside derivative	–	(Peng et al., 2022)
	Olive mill waste waters extract	HPLC	5	Hydroxytyrosol	44 - >100	(Mercatante et al., 2023)
				Tyrosol	0 - >100	
				Oleacein	0 - 12	
				Oleocanthal	0 - 20	
				Verbascoside	0 - 71	
	Passion fruit peel extracts	LC-MS	13	Salicylic acid	80	(Tang et al., 2023)
				2,3-dihydroxybenzoic acid	80	
				Gentistic acid	78	
	Passion fruit peel extracts	HPLC-MS/MS	178	Xanthohumol	>100	(Cao et al., 2021)
				Cyanidin-3-*O*-glucoside	66	
	Apple pomace varieties (fresh and freeze-dried)	LC-Q-TOF-MS	3	Chlorogenic acid	44 - 46	(Pollini et al., 2022)
				Phlorizdin	17 - 18	
				Gallic acid	6 - 9	
	Olive pomace extract	HPLC-UV	2	Hydroxytyrosol	>100	(Morgana et al., 2022)
				Luteolin	75	
	Bilberry, lingonberry and blueberry leaves (microencapsulated powder and aqueous extracts)	HPLC-DAD-ESI-MS	20	Chlorogenic acid	2 - 11	(Ștefănescu et al., 2022)
				Quercetin-glucoside	0 - 19	
	Green pea hull	UHPLC-LTQ-Orbitrap-MS/MS	12	Kaempferol trihexoside	–	(Guo et al., 2022)
	Olive leaf extract	HPLC-microTOF-QII-MS	34	Oleuropein	>100	(Duque-Soto et al., 2022)
	African pumpkins leaves	UPLC-Q-TOF/MS	13	4-feruloylquinic acid (*cis*)	41 - 60	(Mashiane et al., 2021)
				4-feruloylquinic acid (*trans*)	36 - >100	
				Nicotiflorin	16 - 33	
	Olive pomace (pâté)	HPLC-DAD	8	Hydroxytyrosol	9 - 12	(Bellumori et al., 2021)
				Verbascoside	3	
	Pine bark extracts (encapsulated and non-encapsulated)	UHPLC-DAD	18	Taxifolin	7 - 15	(Ferreira-Santos et al., 2021)
				Catechin	58 - 72	
				Gallocatechin	0 - 18	
	Olive pomace extract	HPLC-FLD	2	Hydroxytyrosol	55 - >100	(Čepo et al., 2020)
				Tyrosol	67 - >100	
	Açaí seed extract	HPLC-DAD	4	Catechin	47	(Melo et al., 2020)
				Epicatechin	55	
				Procyanidin B1	72	
				Procyanidin B2	87	
	Olive pomace extract	HPLC-FLD	2	Hydroxytyrosol	74 - >100	(Radić, Dukovski and Čepo, 2020)
				Tyrosol	>100	

As previously described, microbial activity significantly affects the BA of (poly)phenols. Consequently, another technological process identified as a BA-enhancer was food fermentation using specific microorganisms, as described by Cuvas-Limon et al. (2022), who fermented *Aloe vera* juices with *Enterococcum faecium* and *Lactococcus lactis*. The juices were digested and fermented samples showed increased BA of phenolic compounds such as hesperidin, aloin, kampferol, ellagic acid, resveratrol, and ferulic acid. Not all the main phenolics displayed greater BA ratio in the fermented samples: for instance, epicatechin BA was reduced from 55 to 50 % comparing non-fermented and fermented juice (Cuvas-Limon et al., 2022).

Occasionally, the chosen food matrix proved to be crucial for the BA of specific compounds. It was previously mentioned that some phenols derived from olive and their products and by-products showed low BA. To assess this matrix effect, Čepo et al. (2020) digested an olive pomace extract together with different foods. None of the products significantly improved the BA of tyrosol or hydroxytyrosol. However, some high-protein foods decreased the BA of these individual phenolics, such as soy flakes, Bolognese sauce, breakfast cereals, and whole-grain bread, although this reduction effect was less pronounced than for total phenolic compounds. Therefore, the interaction between phenolic molecules and proteins might detrimentally affect their BA (Čepo et al., 2020).

Besides, processing and culinary methods had an evident impact on phenolic species. Ozkan et al. (2022) dehydrated black Isabel grapes by hot-air, vacuum-, ultrasound-assisted vacuum- and freeze-drying. Drying methods demonstrated their effectiveness improving the BA of major grape phenolics, particularly when vacuum was applied. Thus, vacuum-drying increased BA indexes of protocatechuic acid and catechin from 1 to 82 % and from 1 to >100 %, respectively. Moreover, ultrasound-vacuum-drying was the most adequate method for improving chlorogenic acid BA (from 3 to >100 %). However, other main compounds from black Isabel grapes such as malvidin-3-*O*-glucoside were not found in the intestinal phase neither for fresh nor dehydrated fruits (Ozkan et al., 2022). Regarding cooking impact, Cattivelli et al. (2023) confirmed that air-frying was more recommendable than deep-frying to prepare red-skinned onions in terms of the BA of total identified phenolics, since both techniques enhanced the index for raw onions (39 %), being higher in air-fried (90 %) than for deep-fried onions (61 %). However, when main compounds such as quercetin and related molecules were targeted, this tendency was not so clear: deep-frying improved BA of quercetin (182 % *vs.* 24 and 101 % in raw and air-fried onions, respectively); quercetin-4'-*O*-β-glucoside BA was higher in raw samples (87 %) than in air-fried (72 %) or deep-fried onions (12 %); and quercetin-3,4'-di-*O*-β-glucoside highest BA was observed for air-fried onions (92 %), followed by raw (68 %) and deep-fried ones (16 %) (Cattivelli et al., 2023).

3.3. *In vitro* activity of phenolic-rich digestates obtained applying INFOGEST 2.0 protocol

Standardization of simulated *in vitro* gastrointestinal digestion through the INFOGEST 2.0 protocol has allowed improvements in the understanding of the BA, bioavailability and bioactivity of several bioactive compounds including (poly)phenols. Despite the multifunctional bioactivity of these phytochemical compounds is well-known, their mechanistic effects are not completely understood, but stand out for their antioxidant capabilities, as well as include the regulation of inflammatory mediators, nuclear transcription factors, and fat and carbohydrate metabolism (Fraga et al., 2019).

Several food groups contain valuable amounts of different classes of (poly)phenolic compounds that can contribute to human health (Tables 1 and 2). However, assessing the fate of these compounds during gastrointestinal digestion is crucial to ascertain their real health benefits. (Poly)phenols bioavailability is influenced by some factors such as the food matrix, processing methods, and interactions with other nutrients during digestion (Tarko & Duda-Chodak, 2020). Digestion of (poly)phenols reveals a complex interplay between food components and physiological responses, which can either enhance or hinder their intestinal absorption, as previously mentioned in section 3.1., highlighting factors throughout the different digestion stages (fluids, pH, enzymes, gut microbiota) that affect their BA, and, therefore, their bioavailability and functionality (Wojtunik-Kulesza et al., 2020).

From the literature search previously specified (Fig. 1), including a total of 121 selected references, we could identify 76 studies (62.8 %) that performed different bioactivity assessments of digested samples. These studies are summarized in Table 3. Most studies (72/76, 94.7 %) performed antioxidant assays with these digested samples, consistent with the well-known antioxidant activity of (poly)phenols, while only 4 studies (5.3 %) did not evaluate this effect. Considering the 72 references that evaluated the antioxidant effect of digested (poly)phenols, most of them (87.5 %) aimed to characterize the antioxidant potential through different biochemical assays, while 9 out of those 72 studies (12.5 %) made use of cell culture experiments (5 studies in conjunction with biochemical assays, and 4 studies exclusively used cell lines).

3.3.1. *In vitro antioxidant activity determined by biochemical assays*

Biochemical antioxidant assays are characterized by the chemical mechanism involved in the total antioxidant determination (Sadeer et al., 2020). They can be categorized as single electron transfer assays based on a redox reaction with an oxidant, hydrogen atom transfer reaction-based assays, and the chelation of transition metals as Zn^{2+}, Fe^{2+}, and Cu^{2+} (Santos et al., 2017). In this review, from the 68 references using biochemical methods, most of them decided to use a combination of two or more methods to characterize the antioxidant potential of (poly)phenols'digestates (50/68, 73.5 %). Currently, there is not a gold-standard assay which can measure the total antioxidant capacity of a given sample; hence a combination of a few assays is recommended to obtain the most accurate assessment of the antioxidant capacity of bioactive molecules such as (poly)phenols (Sadeer et al., 2020). Contrarily, a notable number of studies from our review (18/68, 26.5 %) only applied one antioxidant methodology, and thus the findings for these digested samples are more limited. Moreover, out of the 68 studies using biochemical assays, we could identify that the antioxidant methodologies most applied were the assays: DPPH (64.7 %), ABTS (58.8 %), FRAP (50.0 %), and ORAC (17.6 %), followed by a variety of less representative radical scavenging and chelating power determinations.

The differential effect of the digestion process on the release, stability and modification of phenolic compounds in the gastrointestinal tract includes a variety of factors, hence, the bioactivity of digestion-derived compounds can be significantly modified in comparison to the original compounds analyzed in undigested samples (Martinez-Gonzalez et al., 2017). In this scenario, this review attempts to shed some light on this issue by compiling the bioactivity of (poly)phenol-containing samples before and after application of the INFOGEST 2.0 digestion protocol. From the references displayed in Table 3, we could perform this comparison in a total of 66 studies, whereas reported data from the remaining 10 studies did not allow this analysis. The main reason for this was the publication of data from different digestion phases/times/conditions, or comparison of data from different food preparations, but lacking the comparison between pre-digested and post-digested samples. Therefore, we critically reviewed the reported data and categorized the impact of the *in vitro* digestion process in the bioactivity of digested samples as "Increase, Decrease or Equal"; this is indicated in the column "Results" of Table 3 and described below.

From these 66 references, it was proven that there was an increased bioactivity in 25 studies (37.9 %). Interestingly, most of them were studies in which we could also identify a high BA of TPC (TPC >100 %, Table 1), suggesting the positive impact of digestive process that favors the release of TPC in some samples and their ultimate antioxidant effect after digestion. Hence, structural modifications occurring in phenolic

Table 3
In vitro activity evaluation of digested samples from different phenolic-containing food samples, matrices and fractions.

Sample		*In vitro* activity of digested samples			Reference
Food group	Description	*In vitro* properties	Antioxidant method	Results	
Cereals (and pseudocereals)	Wheat, pseudocereals and cushuro pasta	Antioxidant	ORAC	Increase	(Paucar-Menacho et al., 2023)
	Hulless barley	Antioxidant	DPPH	–	(Drawbridge et al., 2023)
	Spelt-enhanced wheat bread	Antioxidant	DPPH	Increase/ Decrease	(Mencin et al., 2023)
	Fermented ancient wheat varieties and sordough	Antioxidant	DPPH	Increase	(Dapčević-Hadnađev et al., 2022)
	Formulations of sprouted quinoa flour and cañihua flour in corn grits-based extrudates	Antioxidant	ORAC	Increase	(Paucar-Menacho, Schmiele, et al., 2022)
	Bioprocessed spelt seeds	Antioxidant	DPPH, ABTS	Equal/ Decrease	(Mencin et al., 2022)
	Rice–tartary buckwheat composite	Antioxidant	DPPH, ABTS, OH, O2-	Increase/ Decrease	(Li et al., 2022)
	Ternary blends of sprouted kiwicha, cañihua and wheat flours	Antioxidant	ORAC	Increase	(Paucar-Menacho, Simpalo-López, et al., 2022b)
	Sprouted wheat and wheat bran hydrolysate (spray-dried and microencapsulated)	Antioxidant, anti-inflammatory	DPPH, ABTS, ORAC, FRAP	Increase	(Tomé-Sánchez et al., 2021)
	Dry beans	Antioxidant, anti-inflammatory	Cellular model	–	(Guha & Majumder, 2024)
	Fermented dried lentils (and quinoa)	Antioxidant	DPPH, ABTS, FRAP	Increase/ Equal/ Decrease	(Sánchez-García et al., 2023)
Pulses, seeds and nuts and their products	Oat yogurt with plant proteins	Antioxidant, antihypertensive, hypoglycemic	DPPH, ABTS	Increase	(Demir et al., 2023)
	Black mustard grains	Antioxidant	DPPH, ABTS, FRAP	Increase/ Decrease	(Boscariol Rasera et al., 2023)
Milk and milk products	Coffee-fortified yogurt, plain yogurt and fermented coffee	Antioxidant	DPPH, ABTS, FRAP	Increase	(Helal et al., 2022)
	Mortadella with blueberry flour	Antioxidant	DPPH, ABTS, FRAP	Increase	(Biasi, Huber, de Melo, et al., 2023)
	Mortadella with goldenberry flour	Antioxidant	DPPH, ABTS, FRAP	Increase	(Biasi, Huber, Goldoni, et al., 2023)
Meat and meat products	Pork liver pâtés with persimmon coproducts	Antioxidant	Lipid oxidation (TBARs)	Increase	(Lucas-González et al., 2021)
	Red bell pepper	Antioxidant	ABTS, CUPRAC, FRAP	Decrease	(Hernández-Olivas et al., 2022)
Vegetables and their products	Tiger nut products (flour, oil, and milk with and without added sucrose)	Antioxidant	DPPH, ABTS, FRAP	Increase/ Decrease	(Yang et al., 2022)
	Carob fruit flour	Antioxidant	DPPH, ABTS, ORAC	Increase/ Equal/ Decrease	(Vilas-Boas et al., 2022)
	Iridoids from Gaultheria *spp.* berries	Antioxidant	Cellular model	Increase	(Lauer et al., 2024)
	Red fruits and edible flower extracts (spherifications/bubbles)	Antioxidant	DPPH	Increase	(Bortolini et al., 2024)
	Goji fruits polysaccharide-rich extracts	Antioxidant	ORAC, ABTS, FRAP	Increase	(Zeng et al., 2023)
	Seedless table grapes	Antioxidant	DPPH, FRAP	Decrease	(Rodríguez et al., 2022)
	Black Isabel grape	Antioxidant	DPPH, ABTS, FRAP, CUPRAC	Increase/ Equal/ Decrease	(Ozkan et al., 2022)
	Fermented mango puree	Antioxidant	FRAP	Increase	(Mashitoa, Manhivi, et al., 2021)
	Pasteurised papaya puree (fermented and non-fermented)	Antioxidant	FRAP	Increase/ Decrease	(Mashitoa, Akinola, et al., 2021)
Fruits and their products	Syrian juniper berries pekmez	Antioxidant	DPPH, ABTS, FRAP, CUPRAC	Decrease	(Özkan et al., 2021)
Fats and oils	Galician extra-virgin olive oil	Antioxidant, hypoglycemic	DPPH	Decrease	(Reboredo-Rodríguez et al., 2021)
	Chickpea flour biscuits	Antioxidant	ABTS, FRAP, Cellular model	Increase	(Delgado-Andrade et al., 2024)
	Cocoa chocolate	Antioxidant	DPPH, ABTS	Decrease	(Becerra et al., 2024)
	Nutritive raw bars	Antioxidant	Photochem (ACL kit)	Decrease	(Dordai et al., 2023)
Sweets and sugars	Ternary blends of sprouted kiwicha, cañihua and quinoa flours in biscuits	Antioxidant	ORAC	Increase	(Paucar-Menacho, Simpalo-López, et al., 2022a)
	White mugwort	Antioxidant	DPPH, FRAP	–	(Udomwasinakun et al., 2023)
	Cinnamon bark extract	Antiproliferative, antimicrobial, probiotic	–	Increase/ Decrease	(De Giani et al., 2022)
Spices and condiments	Purple cornflower extracts	Anti-inflammatory	–	Equal/ Decrease	(Ávila-Gálvez et al., 2024)
	Mulberry leaves	Hypoglycemic	–	–	(Zhao et al., 2024)

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Table 3 (*continued*)

Sample		*In vitro* activity of digested samples			Reference
Food group	Description	*In vitro* properties	Antioxidant method	Results	
Beverages	Fermented nepali beverages	Antioxidant, antimicrobial	DPPH, iodometric assay, lipid peroxidation inhibition	Decrease	(Majumder et al., 2024)
	Fermented coffee beans	Antioxidant, hypoglycemic	DPPH, FRAP	Increase	(Wu et al., 2023)
	Fermented *aloe vera* juices	Antioxidant	DPPH, ABTS, FRAP	Equal/ Increase	(Cuvas-Limon et al., 2022)
	Mistletoe (leaves, stems, whole plant) infusions from leaves, stems, and whole plant samples	Antioxidant, hypolipidemic	ABTS, ORAC	Decrease	(Gutiérrez-Grijalva et al., 2022)
	Powdered fruit and vegetable drinks fortified with lentil proteins and stabilized with flax seed gums	Antioxidant, antiproliferative	ABTS, reducing power, chelating power, hydroxyl radicals quenching ability	Increase	(Bochnak-Niedźwiecka et al., 2022)
	Terebinth coffee formulations	Antioxidant	CUPRAC, DPPH	Equal/ Increase	(Kamiloglu et al., 2022)
	Smoothies of pineapple and chayote leaves (fermented and non-fermented)	Antioxidant	FRAP	Increase	(Managa et al., 2021)
	Fruit juices (pomegranate, orange, grapefruit) and commercial juices (cherry, black grapes, *aloe vera*, blackberry, chokeberry, raspberry)	Antioxidant	DPPH, ABTS, FRAP, CUPRAC	Decrease	(Mihaylova et al., 2021)
Food supplements	Tetraselmis chuii (microalgae)	Antioxidant	DPPH, ABTS, CUPRAC	Increase/ Decrease	(Moon & Cho, 2023)
	Microalgae	Anti-inflammatory	–	Equal/ Increase	(Uzlasir et al., 2023)
	Baccharis beebread	Antioxidant, anti-inflammatory	Peroxyl radical, superoxide radical, hydrogen peroxide and hypochlorous acid scavenging assays	Increase/ Equal/ Decrease	(de Oliveira et al., 2024)
	Red propolis and brewer's spent yeasts	Antioxidant	DPPH, CUPRAC	Decrease	(Saliba et al., 2023)
	Bee polen	Antioxidant	DPPH, ABTS, FRAP	Increase	(Akpinar Bayizit et al., 2023)
	Probiotics and chocolate	Antioxidant	DPPH, ABTS	–	(Zoldan et al., 2023)
	Nano-phytosomes with phycocyanin	Antioxidant, anti-inflammatory, antimicrobial, antilarvae	Peroxyl radical, superoxide radical, hydrogen peroxide and hypochlorous acid scavenging assays	Increase/ Equal/ Decrease	(Sahin et al., 2022)
	Ethanolic extract of organic propolis	Antioxidant	DPPH, ABTS	Increase/ Decrease	(Martelli Chaib Saliba et al., 2023)
Savory snacks	Freeze-dried carrot–orange–ginger snacks with powdered apple and blackcurrant pomace	Antioxidant	DPPH, ABTS	Increase/ Decrease	(Karwacka et al., 2022)
Plant-based by-product	Olive pomace	Antioxidant, anti-inflammatory	Inhibition of $^{\bullet}$OH generation, GSH protection capacity, ORAC, cellular model	–	(Schmidt et al., 2023)
	Grape marc extract (whey-pectin microcapsules)	Antioxidant	DPPH, ABTS, FRAP	Decrease	(Cruz-Molina et al., 2023)
	Grape pomace	Antioxidant	DPPH, FRAP	Increase	(Ferreira-Santos et al., 2024)
	Coffee pulp (flour, extract)	Antioxidant	FRAP, scavenging, cellular model	Increase	(Cañas, Rebollo-Hernanz, Martín-Trueba, et al., 2023)
	Cocoa shell	Antioxidant	ABTS	Increase/ Decrease	(Benítez et al., 2023)
	Cocoa shell (flour, extract)	Antioxidant	FRAP, ABTS, scavenging, celular model	Increase/ Decrease	(Cañas, Rebollo-Hernanz, Bermúdez-Gómez, et al., 2023)
	Hydrolyzed wheat bran and mousse	Antioxidant, immunomodulatory, antiproliferative	ORAC, DPPH, ABTS, FRAP	Increase	(Tomé-Sánchez et al., 2023)
	Cold brew spent coffee grounds extract (encapsulated)	Antioxidant	DPPH	–	(Chongsrimsirisakhol & Pirak, 2023)
	Lentil hulls	Antioxidant	DPPH, ABTS, FRAP	Decrease	(Guo et al., 2023)
	Olive mill waste waters extract	Antioxidant	DPPH, ABTS, ORAC	Equal/ Decrease	(Mercatante et al., 2023)
	Coffee pulp flour and extract	Antioxidant	ABTS, FRAP	Increase/ Decrease	(Cañas et al., 2022)
	Date fruit pomace (fermented and non-fermented)	Antioxidant, antihypertensive, antimicrobial, antiproliferative	ABTS, DPPH	Decrease	(Ayyash et al., 2022)
	Olive pomace extract	Antioxidant	DPPH	Increase	(Morgana et al., 2022)
	Lentil hull extract	Antioxidant, anti-inflammatory	DPPH, ABTS, FRAP	–	(Peng et al., 2022)
	Green pea hull	Antioxidant, anti-inflammatory	FRAP	–	(Guo et al., 2022)

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Table 3 (*continued*)

Sample		*In vitro* activity of digested samples			Reference
Food group	Description	*In vitro* properties	Antioxidant method	Results	
	African pumpkins leaves	Antioxidant, hypoglycemic	DPPH, ABTS, FRAP	Increase/ Equal/ Decrease	(Mashiane et al., 2021)
	Olive pomace	Antioxidant	ABTS	Decrease	(Bellumori et al., 2021)
	Passion fruit peel extracts	Antioxidant, hypoglycemic	DPPH, ABTS, FRAP	Increase/ Decrease	(Cao et al., 2021)
	Pine bark extracts (encapsulated and non-encapsulated)	Antioxidant	DPPH, ABTS, FRAP, cellular model	Decrease	(Ferreira-Santos et al., 2021)
	Olive pomace extracts	Antioxidant, antiproliferative	Cellular model	Increase/ Equal/ Decrease	(Radić, Dukovski and Čepo, 2020; Radić, Vinković Vrček, et al., 2020)
	Açaí seed extract	Antioxidant, anti-inflammatory	Peroxyl radical, superoxide radical and hypochlorous acid scavenging assays	Increase/ Decrease	(Melo et al., 2020)

compounds during simulated digestion may improve their antioxidant activity (Platzer et al., 2021). For example, this was demonstrated in the study of Cañas, Rebollo-Hernanz, Bermúdez-Gómez, et al. (2023), which found liberation of phenolic acids and flavonoids from the non-digested insoluble fiber residue of cocoa shell flour during digestion. However, these authors also recognized that other non-phenolic compounds such as melanoidins, proteins/peptides, and their complexes with phenolic compounds present in the digested sample, might also interfere with the biochemical antioxidant assay (Cañas, Rebollo-Hernanz, Bermúdez-Gómez, et al., 2023), as recently described elsewhere (La Mantia et al., 2023). In our review, we found an enhanced bioactivity of digested samples from diverse food groups, although the most frequent were: cereals (and pseudocereals), and fruits and their products and plant-based by-products, with 5 and 4 studies each category, respectively. Moreover, it should be noted that the increased bioactivity was not only demonstrated by different antioxidant biochemical assays for the same sample, but also for different sample processing such as germination, hydrolysis, or fermentation (Tomé-Sánchez et al., 2021; Wu et al., 2023). Nonetheless, from these 25 studies, identification of phenolic compounds was only performed in 12 studies, which showed a high variability between sample sources, (poly)phenolic subgroups, and identification methods (Table 2), thereby hindering to clearly ascertain the individual phenolic compounds responsible for the enhanced antioxidant potential.

In addition, several references in Table 3 showed a mixed bioactivity profile (26/66, 39.4 %). Our critical approach could detect some reasons behind this phenomenon. Firstly, the employment of different biochemical assays stood out as the main factor determinant for the inconsistencies. As an example, three studies found an increased antioxidant effect measured by the ABTS assay, but diminished in case of application of FRAP and DPPH methods to the same digested sample (Cao et al., 2021; Karwacka et al., 2022; Sánchez-García et al., 2023). Therefore, this review reinforces the necessity of applying a combination of different chemical-based methodologies to better understand the complexity of the potential antioxidant effect of (poly)phenols (before and after gastrointestinal digestion) (Sadeer et al., 2020). Furthermore, some other reasons responsible for the variability between bioactivity results were recognized including food matrix (Hernández-Olivas et al., 2022), subtypes of bound and extractable (poly)phenols (Mencin et al., 2022), fermentation (Mashitoa, Akinola, et al., 2021), extrusion (Benítez et al., 2023), fractionation of samples and particle sizes (Vilas-Boas et al., 2022) or household cooking methods (Mashiane et al., 2021). However, in this case we could not identify a clear relationship between the mixed bioactivity profile and the reported % TPC (Table 1).

Lastly, 15 out of the 66 evaluated references (22.7 %) reported a lowering impact in bioactivity (Table 3). Indeed, the decreased bioactivity was confirmed by the application of different antioxidant methods to the same sample. Although it was found for varied food groups, the more predominant were plant-based by products and beverages (5 and 3 studies, respectively). In this sense, it has been proposed that pH changes during digestion alongside the partial deprotonation of the hydroxyl groups of aromatic rings from phenolic compounds, induces its reduction in antioxidant capacity (Cao et al., 2021). Interestingly, these 15 studies also showed a parallel decline in the BA of TPC (Table 1), which further reinforces the decreased bioactivity and the impact of gastrointestinal digestion. This decline was particularly marked in some samples as fermented Nepali beverages (Majumder et al., 2024), date fruit pomace (Ayyash et al., 2022), Galician extra-virgin olive oil (Reboredo-Rodríguez et al., 2021), Syrian juniper berries and pekmez (Özkan et al., 2021), and mistletoe infusions (Gutiérrez-Grijalva et al., 2022), which showed TPC BA values inferior to 10 % following the application of INFOGEST 2.0 methodology.

Altogether, it could be deduced the rather positive impact of gastrointestinal digestion on the bioactivity of (poly)phenol-containing foods ("Increase" bioactivity: 37.9 %, *versus* "Decrease" bioactivity: 22.7 %), although a notable proportion of studies showed a highly variable bioactivity profile depending on several sample and digestion-related factors (39.4 %). The combination of different and complementary antioxidant assays alongside the comparison of data from undigested and digested samples is prompted as a necessary approach to further elucidate the potential health effects of food-derived (poly)phenols.

3.3.2. *In vitro* antioxidant activity determined by using cellular models

The potential impact of antioxidant research has exponentially expanded in the last years and consequently a wide variety of antioxidant biochemical assays have been developed, as can be noticed in subsection 3.3.1. However, more physiological data derived from cell-based models are prompted to evaluate the functional properties of antioxidant phenolic compounds. These cellular approaches provide physiological relevance (membrane transport, metabolism, subcellular localization of antioxidants) and mechanistic insights (direct and indirect antioxidant effects, modulation of antioxidant enzymes, redox signaling pathways, *etc.*), considering also the bioavailability and metabolism of the bioactive compounds. Consequently, further studies using *in vivo* models and clinical trials are additionally required to validate antioxidant potential (Cheli & Baldi, 2011; Granato et al., 2018).

For example, it has been found that digested fractions from coffee pulp (flour and extract) displayed antioxidant effect by the ABTS and FRAP methods and scavenge reactive oxygen and nitrogen species, but also, enhanced cellular protection against oxidative stress induced by *tert*-butyl hydroperoxide (t-BOOH) in intestinal epithelial IEC-6 and hepatic HepG2 cells (Cañas, Rebollo-Hernanz, Martín-Trueba, et al., 2023). On the other hand, other authors used intestinal Caco-2 cells exposed to pro-oxidant t-BOOH and treated with the bioaccessible fractions of chickpea flours (Delgado-Andrade et al., 2024). They found that cellular antioxidant activity measured by the generation of reactive

oxygen species (ROS) did not always correlate with the biochemical antioxidant capacity analyzed by ABTS and FRAP assays.

3.3.3. Other in vitro activities

In addition to the antioxidant determinations, some of the studies illustrated in Table 3 contemplated the evaluation of complementary bioactivities such as: anti-inflammatory (10/76, 13.2 %), hypoglycemic (6/76, 7.9 %), antiproliferative (5/76, 6.6 %), antimicrobial (4/76, 5.3 %), antihypertensive (2/76, 2.6 %), and probiotic, hypolipidemic, antilarval, and immune-modulatory effects (1/76, 1.3 %). This fact emphasized the potential multifunctional role attributed to the health benefits of (poly)phenols (Fraga et al., 2019), although its presence in the literature is much less noticeable in comparison with their antioxidant effect.

In this regard, most of the studies which additionally evaluated the anti-inflammatory activity applied some cell-based methods cultured in the presence of a pro-inflammatory agent (*e.g.* bacterial LPS). Interestingly, these studies illustrated the biological effects as response of cellular molecules including nitric oxide, different interleukins, and/or inflammation-mediators at mRNA or protein levels (Table 3). Regarding hypoglycemic activity, most works focused on the ability of (poly)phenols to inhibit enzymes such as α-glucosidase and α-amylase (Demir et al., 2023; Mashiane et al., 2021). Moreover, other studies investigated their capacity to reduce glucose uptake in Caco-2 cells, as well as their effect on the expression of glucose transporters (Zhao et al., 2024). Antiproliferative and antimicrobial activities were assessed using tumor cell lines and microbiological assays, respectively (Bochnak-Niedzwiecka et al., 2022; Majumder et al., 2024). Additionally, antihypertensive activity was reported -although in only two studies- by demonstrating that digested (poly)phenol-rich matrices were able to inhibit angiotensin-converting enzyme (ACE) activity (Ayyash et al., 2022; Demir et al., 2023).

Together with the significant lack of studies focusing on non-antioxidant properties, the absence of *in vivo* research -whether in animal models or clinical trials- remains a major limitation in understanding the biological effects of (poly)phenols after human digestion.

4. Conclusions, current limitations and future perspectives

This review evidenced the significant impact of gastrointestinal digestion on the stability, BA and biological activities of food phenolic compounds. The use of INFOGEST 2.0 method has facilitated the analysis of different classes of phenolic compounds under simulated digestive conditions. As a major advantage, the harmonized nature of this protocol allows reproducibility and comparison between the published literature; this could be used by the scientific community as a meaningful tool to ascertain the behavior of food compounds during gastrointestinal digestion. However, as previously stated, the interplay between (poly)phenols and gut microbiota remains a challenge for this method as INFOGEST 2.0 does not include colonic stage to study the metabolization of non-absorbed phenolic compounds and their 'expanded BA'. Although many studies applied subsequent models that included colonic fermentation of food samples, a harmonized and standardized protocol should be designed.

Several studies reported TPC BA values above 100 % due to the release of phenolics from cell structures or complexes with macromolecules during digestion. However, the quantification of TPC in undigested samples remains a challenge; consequently, underestimation of TPC counts in pre-digested samples might occur, which affects BA calculation and misinterpretation of current data. Therefore, the optimization of food matrices pretreatment, as well as the adaptation of quantification procedures -often linked to spectrophotometric technologies- to complex samples is crucial to obtain reliable results.

Despite some food matrices showed low BAs, some researchers achieved TPC improvements through technological approaches such as encapsulation or microbial fermentation. On the other hand, remarkable differences regarding what authors considered the bioaccessible fraction were identified across studies. This fact is highlighted as a current limitation; a standardization of sample procedure following simulated digestion is prompted.

Specific phenolic compounds or (poly)phenolic groups were identified by liquid chromatography coupled to different detectors, and phenolic acids and flavonoids stand out as the most representative in digestion studies. BA indexes were highly variable, but generally, BAs bellow 100 % were more frequent for individual (poly)phenols than for TPC. Many transformation reactions have been identified in digestion studies including polymerization, depolymerization, isomerization, hydrolysis and binding to macromolecules, which affected individual phenolic compounds. Moreover, although BA values illustrate the theoretical fraction available for intestinal absorption, complementary bioavailability studies should be carried out. They are outside the scope of the present review but were virtually missed in our bibliography search. Thus, this kind of studies are still needed to evaluate whether phenolics will be further modify and/or reach their targets to effectively exert their bioactivities.

Regarding (poly)phenols biological activity, more than half of the identified studies also performed *in vitro* activity evaluation of digested samples. However, a clear predominance of articles based on antioxidant activity can be observed, mostly using biochemical assays. In this sense, this review reinforces the consideration of using a combination of different biochemical-based antioxidant methodologies for the same sample and, preferably, cellular models providing physiological relevance to the results.

Moreover, further evaluation of additional biological activities is required, since the potential of digested phenolic compounds as anti-inflammatory, immunomodulatory, antiproliferative, or hypocholesterolemic molecules has been much less explored. The combination of INFOGEST 2.0 digestion method couple to cellular models could notably reinforce the knowledge on this scientific field.

The review also allowed us to shed some light on the comparison of bioactivity of (poly)phenol-rich foods before and after simulated digestion. The reviewed literature suggested that in general terms gastrointestinal digestion might beneficially affect the biological activity of food phenolics, particularly in those studies identifying parallel higher BA values (TPC >100 %). Although, it has been also proved that a significant proportion of studies found a decrease or a mixed profile in bioactivity after digestion. Hence, additional studies establishing correlations between specific individual phenolics and biological activities, and characterizing their mechanistic effects, are encouraged. Finally, since most of the summarized works applied biochemical (and cellular, only in some cases) methods, *in vivo* models must be used to validate the promising *in vitro* results. Animal models and clinical trials are crucial to elucidate the real impact of gastrointestinal digestion on phenolics bioactivity.

CRediT authorship contribution statement

Diego Morales: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Amaia Iriondo-DeHond:** Writing – original draft, Investigation, Data curation, Conceptualization. **Samuel Fernández-Tomé:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Funding

This research received no external funding.

Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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