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The impact of single nucleotide polymorphisms on the absorption, distribution, metabolism, and excretion of dietary (poly)phenols: a critical systematic review

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Response to (poly)phenol intake is highly variable among subjects, and genetic variants may contribute to such variability. However, evidence addressing this assumption is currently lacking. To address such shortcomings, we systematically reviewed the current literature and selected twelve studies looking at associations between the inter-individual variability in (poly)phenol bioavailability and metabolism and single nucleotide polymorphisms (SNPs) in candidate genes involved in (poly)phenol ADME (absorption, distribution, metabolism, and excretion). In total, 88 SNPs in 33 genes were studied, of which slightly more than half (n = 17) were related to drug/xenobiotic metabolism. More specifically, two were involved in absorption, seven in phase I metabolism, four in phase II metabolism, and four in excretion. The remaining 16 genes were related to steroid hormone metabolism and activity. Considering genes specifically related to (poly)phenol ADME, 16 SNPs showed significant modifying effects on urinary and/or plasma levels of phenolic metabolites and/or on their kinetic parameters. However, it was not possible to associate a particular genetic variant with a change in (poly)phenol-related ADME. Only a few studies applied stringent statistical criteria and recruited sufficiently large and diverse samples to reach solid and reliable conclusions. As such, studies employing larger samples, leveraging integrative bioinformatics approaches and genome-wide linkage, are warranted.

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1. Introduction

(Poly)phenols are a large family of phytochemicals comprising over 8000 heterogeneous compounds that can be found in a variety of beverages and foods of plant origin.[1–3] They are characterised by the presence of at least one phenolic group and are usually classified as flavonoids and non-flavonoids.[1] A growing body of scholarly research suggests that high (poly)phenol intake and supplementation may protect against non-communicable chronic diseases, including cardiovascular, neurodegenerative, and metabolic diseases.[4–6] However, evidence is not compelling yet, due to the high heterogeneity in the results from different studies.[7–10]

Contrasting findings reported in the literature derive from the influence of various factors leading to high inter-individual variability in (poly)phenol bioavailability,[11,12] which is the main determinant of their effectiveness and physiological response, influencing health outcomes. Factors determining differences in the absorption, distribution, metabolism, and excretion (ADME) process can be exogenous, including the variability of (poly)phenol content in foods,[13] the high degree of diversification of chemical structures,[14,15] and the complex interplay of (poly)phenols with other components of the diet (fibre, proteins, *etc.*), as well as the food matrix.[16] However, endogenous/individual factors are considered the principal source of heterogeneity: among them, personal characteristics (age, sex, ethnicity), lifestyle (dietary habits, smoking, physical activity, medication), pathophysiological status, gut microbiota, and genetic background.[17–20]

In the case of the bioavailability and metabolism of (poly)phenols, genetic variations and microbiota composition and activity are the major contributors to variability.[11,12] Single

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Nucleotide Polymorphisms (SNPs) represent a source of genetic variation that may, at least partially, explain differences in the response to dietary (poly)phenol exposure.[21] A further layer of variability is related to the gut microbiota, which can be considered a key player in a variety of individual physiological processes and an important determinant of metabolic phenotypes (also known as metabotypes).[22,23] The human microbiome has been linked with host genetic variants, and dysbiosis has been associated with several diseases. As such, human genetic variants are expected to play a relevant role in explaining various complex and overlapping (patho)physiological phenomena, ranging from food intake to the composition of the microbiome and their impacts on food metabolism and human health.[24] However, to the best of our knowledge, information is scarce concerning the influence of genetic variants on the bioavailability and metabolism of dietary (poly)phenols and consequently on the response to dietary (poly)phenol exposure.

Often found in glycosylated forms, (poly)phenols are partially hydrolyzed by human enzymes in the upper gastrointestinal tract, releasing aglycones that can be absorbed and conjugated by phase II enzymes in enterocytes and hepatocytes.[1–3] However, most (poly)phenols are not absorbed in the small intestine and reach the colon intact, where they are modified by the gut microbiota into smaller catabolites. Gut microbial catabolites are more easily absorbed and can be conjugated by phase II enzymes in colonocytes and hepatocytes.[1–3] As such, the molecules present in the circulation and potentially bioavailable for target tissues are phase II metabolites of both human and microbial-human origin, which are finally excreted through urine. SNPs in genes involved in (poly)phenol ADME, including transporters, glycosidases, and phase II enzymes (sulfotransferases or SULTs, UDP-glucuronosyltransferases or UGTs, and catechol-*O*-methyltransferase or COMT), could have an impact on the amount and type of metabolites excreted[18] (Fig. 1).

A better understanding of the genetic component would enable and enhance the translation of our current knowledge about these bioactive compounds into more effective and personalised dietary advice. A recently published review found that more research on the factors that underlie the differences in the response to (poly)phenol exposure is urgently needed.[10] Therefore, the present study was undertaken to fill this knowledge gap, with the aim of systematically identifying and appraising genetic factors associated with the inter-individual variability in (poly)phenol ADME after their dietary intake and assessing their causal relationships with (poly)phenol bioavailability and metabolism.

2. Material and methods

2.1 Study protocol

An *a priori* study protocol was devised and registered within the "International Prospective Register of Systematic Reviews" (PROSPERO, Centre for Reviews and Dissemination (CRD), University of York, York, UK) with the registration code CRD42023416767 (accessible at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=416767).

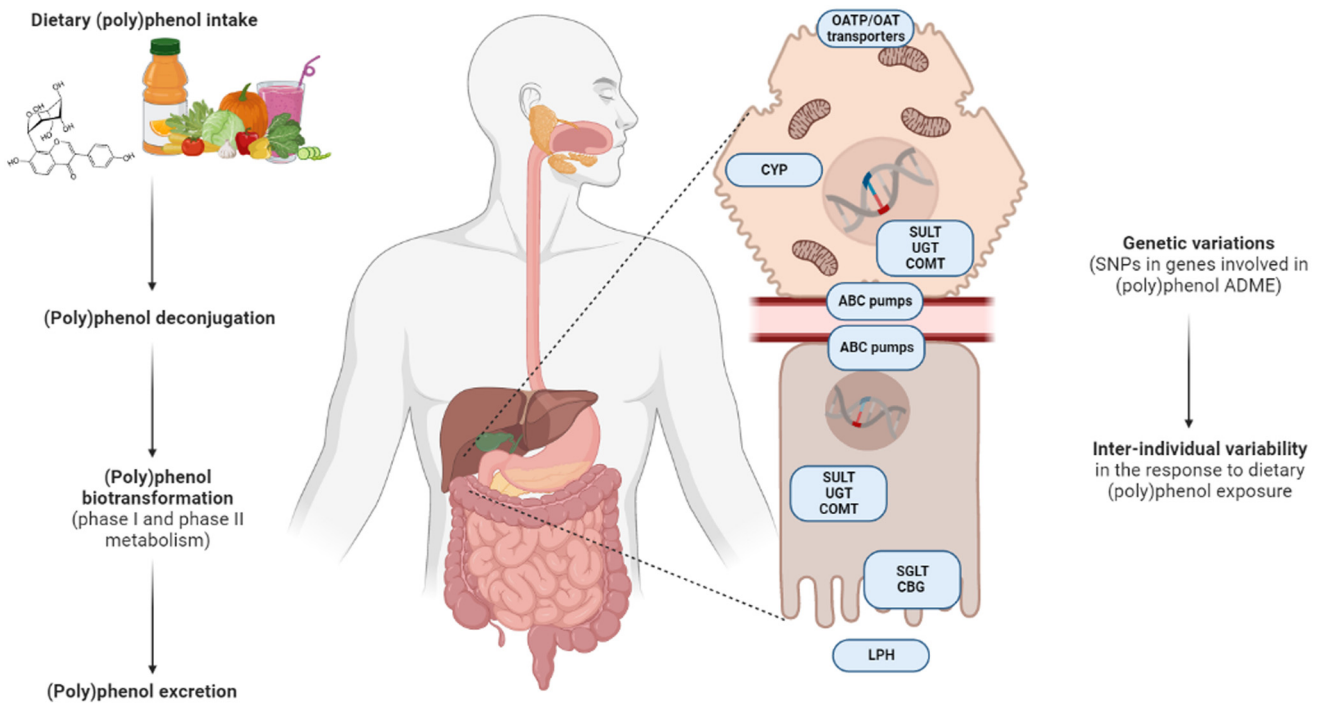

Fig. 1 Representation of the process of (poly)phenol absorption, distribution, metabolism and excretion, and indication of genes carrying genetic variations that can determine the inter-individual variability in the response to dietary (poly)phenol intake.

2.2 Literature search

A comprehensive literature search was performed with a string of keywords consisting of four broad components ((poly) phenols, dietary exposure/intake, human metabolism, and SNPs) on five major scholar databases: namely, MEDLINE (*via* its freely accessible PubMed interface), Scopus, Web of Science (WoS), EMBASE, and "Chemical Abstracts Service" (CAS), a database of the "American Chemical Society" (ACS).

The "Medical Subject Headings" (MeSH) thesaurus, a controlled, hierarchically-organised vocabulary produced by the National Library of Medicine (NLM), was leveraged. When appropriate, the wild-card option (*i.e.*, truncated words) was used. (Poly)phenol compound names were obtained from Phenol-Explorer, the most comprehensive database on (poly) phenols.[25] (Poly)phenol metabolite names were obtained from PhytoHub, a freely available electronic database containing detailed information about dietary phytochemicals and their human and animal metabolites. The full string, which was modified and adapted according to each database, is reported in SI Table 1. Moreover, the "Human Genome Epidemiology Literature Finder" (HuGE Navigator Database) based at the "Public Health Genomics and Precision Health Knowledge Base" (PHGKB v8.5) was mined. Extensive cross-referencing was applied. Finally, target journals were hand-searched: these journals were selected because they represent the most frequently publishing outlets in the fields of nutritional genomics, nutrikinetics, and (poly)phenol research. Their inclusion ensured that our manual search complemented database screening and minimized the risk of missing relevant studies at the intersection of (poly)phenol metabolism and genetics. The literature search was conducted by two researchers independently and is updated as of September 24, 2023. Further details are reported in Table 1 and SI Table 1.

2.3 Inclusion and exclusion criteria

Inclusion and exclusion criteria were pre-defined and devised according to the population – intervention/exposure – comparators/comparisons – outcomes – study design (PICOS/PECOS) criteria. Original studies (S) investigating populations (P) consisting of humans undergoing dietary interventions with (poly)phenols (I) or exposed (E) to dietary (poly)phenols, stratified according to their genotype status (C, comparators/comparisons), and for whom (poly)phenol-related plasma and/or urinary metabolites (O, outcomes) were quantified (*i.e.*, characterised and measured by means of any methodology/technique of analytical chemistry), and reported, were deemed eligible for inclusion.

Studies were excluded if studying non-human populations (P), *i.e.*, if designed as *in vitro* models (like cellular models), animal models, or *in silico*/computational models. Also, articles were not retained in the present review if study subjects were exposed (E) to dietary compounds other than (poly) phenols or if, in the case of exposure to dietary (poly)phenols, (poly)phenol-related metabolites were not analytically characterised/measured (O). Another cause of exclusion was given by other studied outcomes, including changes in dietary habits and eating patterns (*e.g.* energy intake), anthropometric characteristics (body weight, body mass index (BMI), waist circumference), or metabolic responses (for instance, glucose and insulin levels, or circulating leptin, ghrelin, or adiponectin). Finally, studies were excluded if designed as technical notes reporting new methodologies or advancements in techniques of analytical chemistry but narrowly focused on the technical aspects, letters to the editor, editorials, commentaries, and expert opinions, or not containing sufficient quantitative details (S). Reviews (of any type, narrative, systematic, or meta-analysis) were also excluded but were, however,

Table 1 Overview of the search strategy adopted in the present systematic review

Search items	Details
Search string components	(Poly)phenols Dietary exposure/intake Human metabolism SNPs
Databases/registries/repositories mined/searched	PubMed/MEDLINE, Scopus, WoS, EMBASE, CAS/ACS, HuGE Navigator Database (PHGKB v8.5)
Inclusion criteria	P (humans) I/E (exposed to dietary (poly)phenols) C (stratified according to their genotype status) O (quantification of (poly)phenol-related plasma and/or urinary metabolites by any separation methodology/technique of analytical chemistry) S (any original study, observational/interventional, retrospective/prospective, cross-sectional/longitudinal, randomised/non-randomised, parallel/cross-over, placebo/non-placebo-controlled, pilot, *etc.*)
Exclusion criteria	P (*in vitro* studies- cellular-, *in silico*/computational studies) I/E (exposed to nutrients other than (poly)phenols) C (not providing information about genotype status) O (not quantifying (poly)phenol-related metabolites) S (reviews of any type)
Time filter	None applied
Language filter	None applied
Target journals hand-searched	*Biochem. Pharmacol.*; *Br. J. Nutr.*; *Cancer Epidemiol. Biomarkers Prev.*; *Eur. J. Pharmacol.*; *Genes Nutr.*; *Int. J. Mol. Epidemiol. Genet.*; *Mol. Nutr. Food Res.*; *Nutrients*; *PLoS One*

scanned to increase the chance of not missing content relevant to the present review.

2.4 Data extraction

The following data were extracted: study authors (in particular, the surname of the first author), study year, study country, study design, sample size, sample characteristics (mean age, sex/gender distribution, BMI, and ancestry, level of physical activity practiced, smoking status, alcohol intake, use of drugs, contraceptives, and hormone therapy, dietary habits and how the dietary assessment was performed), SNPs and related genes, information related to genotyping technique, allele frequencies, and possible deviations from Hardy–Weinberg equilibrium, type of genetic modelling conducted, statistical analysis carried out and statistical threshold adopted, goodness-of-fit evaluation and validation, type and source of dietary (poly)phenol intervention/exposure, intervention duration and timepoints, assessment of adherence to the intervention protocol, metabolites searched in biological samples, technique of analytical chemistry utilised for metabolite sand quantification, and impact of the SNP on dietary (poly)phenol ADME. Finally, study strengths and limitations were also recorded, along with trial registration (only if the study was designed as a randomised trial), funding/sponsoring and its role (if any), and whether a checklist for findings reporting was followed.

A specifically designed Excel spreadsheet was utilised. Two researchers independently extracted the data. Further details about the search strategy adopted in the present systematic review are reported in Table 1 and SI Table 1.

2.5 Methodological assessment

As foreseen by the PRISMA methodology,[26] study quality appraisal was evaluated by applying the framework for evaluating scientific validity in nutritional genomics developed by Keathley *et al.*[27] This framework consists of several items related to various dimensions (namely, study design and quality, generalisability, directness, consistency, precision, confounding, effect size, biological plausibility, publication/funding bias, allele and nutrient dose–response, and summary levels of evidence).

2.6 Bioinformatics analysis

The retrieved lists of genes and related SNPs associated with (poly)phenol metabolism was extensively annotated using a wide range of bioinformatics tools. Genes were functionally annotated using Gene Ontology (GO) along its three major domains (biological processes, molecular functions, and cellular components). The web browser located at the Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey, USA, accessible at https://go.princeton.edu/cgi-bin/GOTermFinder (last access September 24, 2023), was utilised. GO terms were visualised employing the "Reduce plus visualize Gene Ontology" (REVIGO) tool (freely available at https://revigo.irb.hr/) (last accessed September 24, 2023). Briefly, the list of GO terms associated in a statistically significant fashion with the genes involved in (poly)phenol metabolism was transformed into a matrix of the GO term pairwise semantic similarities. Then, Multidimensional Scaling (MDS) was applied to reduce the dimensionality of the matrix. Semantically similar GO terms are displayed together in the plot along the axes of the semantic space. The SNPs were annotated using the SNPinfo Web Server, accessible at https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html (last accessed September 24, 2023). Locations of SNPs along the human genome were displayed using the PhenoGram plot (accessible at https://visualization.ritchielab.org/phenograms/plot) (last accessed September 24, 2023). Finally, the overlapping genes and SNPs involved in (poly)phenol ADME were visualised through network-based representations in R, employing the *tidyverse*, *igraph*, and *ggraph* packages.

3. Results

3.1 Literature search

The initial literature search yielded a pool of 23 513 items, which remained at 5310 after removing the duplicates. A total of 5288 items were discarded based on title and/or abstract. Twenty-two studies were scrutinised in full text. Based on the inclusion and exclusion criteria mentioned above, ten studies[28–37] were "excluded with reason" (SI Table 2). Finally, twelve studies were retained in the present systematic review, overviewed in Table 2 and detailed in SI Tables 3 and 4.[38–49] The flowchart adopted to manage the study retrieval and inclusion/exclusion is depicted in Fig. 2.

3.2 Overview of the studies included: sample features

Articles were published between 2010[42] and 2023.[46] Sample sizes ranged from 20[44] to 16 672[46] subjects (median 74), totalling 19 413 participants. The age of the participants varied from 18[44] to 75 years.[39] Five studies[38,39,42,45,49] recruited populations consisting of males[38,42,45] or females[39,49] only. In the remaining seven studies,[40,41,43,44,46–48] the percentage of male subjects ranged from 35.7%[48] to 70.0%.[44] Of note, only two studies[46,48] reported and analysed data stratified according to sex/gender.

Most studies (67%) were conducted in Europe – five in the UK,[38,44–46,49] two in Germany,[43,48] and one in France.[47] Two studies were carried out in the Americas – one in the USA[39] and one in Brazil[40] – and two in Asia, one in China,[42] and one in South Korea.[41] As such, information was primarily provided for European/Caucasian ancestry, with only one study investigating African ancestry along with Caucasian ancestry[39] and other two focusing exclusively on Asiatic ancestry.[41,42]

Concerning BMI, no information was provided in four studies.[42,43,46,47] When reported, BMI ranged from 18.5 to 38.0 kg m^{-2}, meaning that a range of populations – normal weight, overweight, and obese – have been investigated in the studies included in the present systematic review, with a higher representation of the latter.

Table 2 Overview of the studies included in the present systematic review

Study	Study design	Country	Sample size	SNPs	Dietary (poly) phenols	(Poly)phenol source	Intervention duration	Impact of SNPs
Brown *et al.* (2011) [38]	Single-centre, placebo-controlled, double-blinded, cross-over study with age- and BMI-matched groups	UK	64 subjects aged 40–69 years, 100% males, overweight or obese	COMT (rs4680)	Flavan-3-ols (mainly catechins and gallocatechins)	Green tea	6 weeks	Lower concentrations in homozygous GG individuals
Chang *et al.* (2019) [39]	Randomised cross-over study	USA	252 subjects aged 59.4 ± 6.2 years, 100% females, BMI 30.5 ± 7.6	60 functional SNPs in 29 genes (ARPC1A, BAIAP2L1, BMF, COMT, CYP17A1, CYP19A1, CYP1A1, CYP1B1, CYP3A4, CYP3A5, ESR1, GCKR, HHEX, HSD17B1, JMJD1C, LHCGR, NR2F2, PRMT6, SHBG, SLCO1B1, SULT1A1, TDGF3, TSPYL5, UGT1A1, ZBTB10, ZKSCAN5, ZNF652)	Lignans	Ground brown flaxseed	6 weeks	Impact of SNPs on enterolactone excretion
Fraga *et al.* (2022) [40]	Non-randomised, pre-post design study	Brazil	46 subjects aged 26.26 ± 4.50 years [19–38 years], 20 males (43.5%) and 26 females (56.5%), BMI 23.23 ± 2.54 [18.50–29.9]	SULT1A1 (rs3760091, rs4788068), SULT1C4 (rs1402467), ABCC2 (rs8187710)	Flavanones (mainly hesperetin and naringenin)	Pasteurised orange juice (*Citrus sinensis*)	24 hours	Significant ($p < 0.05$) relationship between SNPs and high excretion of phase II flavanone metabolites
Hong *et al.* (2012) [41]	Cross-sectional, ancillary sub-analysis of a population-based study	South Korea	1391 healthy subjects aged 52.0 years, 758 males (54.5%) and 633 females (45.5%), BMI 24.9	HACE1 (rs6927608, rs4946645, rs11759010, rs17065302, and rs4245525)	Equol	Soy	Not applicable – observational	Significant effects of five SNPs clustered in the 6q21 region, the most significant of which was rs6927608 (allele A>C)
Inoue-Choi *et al.* (2010)[42]	Cross-sectional sub-analysis nested within the Shanghai Cohort Study	China	660 subjects aged 56.7 ± 5.0 years, 100% males	COMT (rs4680)	Flavan-3-ols (mainly catechins and gallocatechins)	Green tea	Not applicable – observational	Urinary tea catechins were lower by 35–45% among men carrying the LL genotype (p = 0.007). When consuming greater amount of green tea (≥5 g day^{-1}), urinary tea catechins did not differ according to COMT genotype
Lorenz *et al.* (2014)[43]	Non-randomised, pre-post design study	Germany	24 subjects, 10 males (41.7%) and 14 females (58.3%)	COMT (rs6269, rs4633, rs4680, rs4818)	EGCG	Pure compound	2 hours	None
Miller *et al.* (2012)[44]	Pilot, non-placebo-controlled trial	UK	20 overweight and obese individuals, aged 54.6 ± 3.2 years [18–70 years], 14 males (70.0%) and 6 females (30.0%)	COMT (rs4680)	Flavan-3-ols (mainly catechins and gallocatechins)	Green tea	8 hours	None

Table 2 *(Contd.)*

Study	Study design	Country	Sample size	SNPs	Dietary (poly) phenols	(Poly)phenol source	Intervention duration	Impact of SNPs
Miller *et al.* (2012)[45]	Randomised, double-blinded, placebo-controlled, crossover trial, with age- and BMI-matched groups	UK	47 overweight/obese adults, 100% males	COMT (rs4680)	Flavan-3-ols (mainly catechins and gallocatechins)	Green tea	24 hours	None
Momma *et al.* (2023)[46]	Cross-sectional, ancillary sub-analysis of a population-based study	UK	16 672 subjects, 9020 females (54.1%) and 7652 males (45.9%)	PON1 (rs662, rs854560, rs705379, rs705381, and rs854572)	Flavan-3-ols	Diet (not better characterised)	Not applicable – observational	No differences in the sum of 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-sulfate and 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-glucuronide metabolites in men, and only small differences among rs662 and rs705381 alleles in women with no clinical and physiological impact
Muhrez, *et al.* (2017)[47]	Metabolomics study	France	53 subjects aged 23 years [20–59 years], 24M males (45.3%) and 29 females (54.7%)	ABCC2/MRP2 (rs717620, rs3740066, rs2273697)	NA	Free diet	Not applicable – observational	SNPs associated with some (poly)phenol low-molecular weight urinary metabolites
Scholl *et al.* (2018)[48]	Population-based, open, one-arm nutrikinetic study	Germany	84 subjects aged 24.5 ± 3.9 years [19–49 years], 30 males (35.7%) and 54 females (64.3%), BMI 22.7 ± 2.6	MRP2/ABCC2 (rs2273697, rs3740066, rs717620, rs8187710), OATP1B1/SLCO1B1 (rs4149056, rs2306283, rs11045819), Pgp/ABCB1 (rs1045642, rs1128503, rs2032582), COMT (rs4680), SULT1A1 (rs750155), UGT1A1 (rs8175347)	Flavan-3-ols (mainly catechins and gallocatechins)	Green tea	5 days	Impact of SNPs of MRP2 and OATP1B1
Wakeling and Ford (2012)[49]	Non-randomised, pre-post design study	UK	100 subjects aged 33.0 ± 9.3 years [18–50 years], 100% females, BMI 23.4 ± 3.4	UGT1A1 (rs8175347), CBG (rs358231), ABCG2 (rs2231142), and ABCC2 (rs2273697), LPH (rs3754689)	Isoflavones (mainly glycitein, daidzein and genistein)	Soy	24 hours	Impact of SNPs on isoflavone excretion

BMI indicates body mass index (kg m^{-2}).

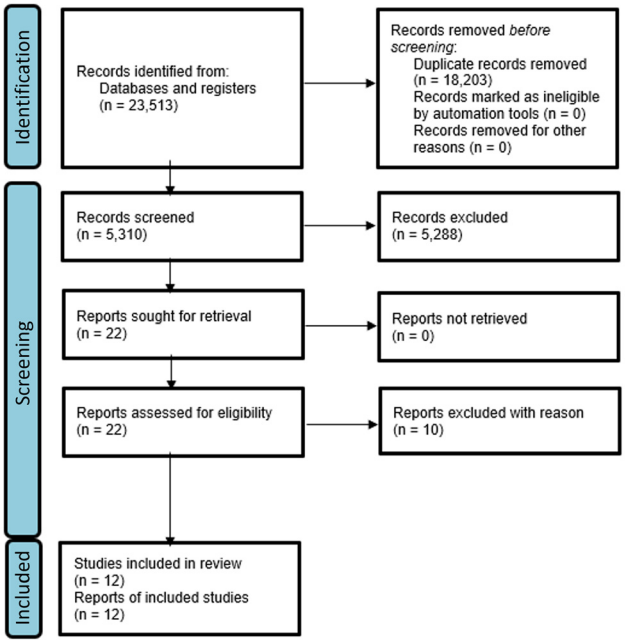

Fig. 2 Pictorial flow-chart of the search strategy adopted in the present systematic review.

3.3 Overview of the studies included: study design

Most studies were interventional, except for four,[41,42,46,47] which were designed as observational – three[41,42,46] were ancillary, cross-sectional sub-analyses nested within population-based, prospective investigations, and one[47] was a "real-life" metabolomics study. However, most subjects included in the review—16 672 out of approximately 19 500—come from a single observational study.[46] Additionally, a significant portion (1391 participants) were recruited from another observational study.[41] Of the interventional studies, only three[38,39,45] were randomised, double-blinded, cross-over investigations. Furthermore, four studies[40,43,44,49] were single acute intake, one-arm, non-placebo-controlled investigations. Another study[48] was designed as a population-based, open, one-arm nutrikinetic study. Finally, the duration of the dietary intervention varied from a few hours/one day[40,49] to six weeks,[38,39] thus including both acute and chronic trials.

3.4 Overview of the studies included: confounders and mediators/moderators of dietary (poly)phenol metabolism

Several variables, including behavioural lifestyles (smoking, drugs, alcohol intake, and exercise/physical activity), are known to potentially confound or interact with – mediate/moderate – dietary (poly)phenol metabolism. Despite the importance of these variables, high heterogeneity in their reporting was found.

Concerning smoking status, no information was provided for three studies.[43,46,47] Four studies[39,41,42,48] included smokers, whereas all the other studies excluded smokers from enrolment. When reported/recruited, the rate of current smokers varied considerably from 19.8%[39] to 60%.[42] Regarding alcohol intake, no information was provided for five studies.[39,43,46,47,49] When reported, the rate of habitual alcohol consumers ranged from 5.9%[41] to 89.3%.[48] All the other studies excluded alcohol consumers or asked participants to refrain from alcohol consumption from 24[44] to 48 hours[45] before the investigation. Concerning exercise and physical activity, no information was provided for eight studies.[39,41–44,46,47,49]

Finally, there was a considerable degree of heterogeneity also in the reporting of drugs and contraceptives/hormone therapy. Information about the former variable was not disclosed in five studies,[41–43,46,47] whereas all the other studies excluded patients on drugs from enrolment. Concerning the latter variable, only one study[48] considered this parameter, with 44.0% and 56.0% of the sample recruited ever and never using contraceptives, respectively. Of note, the use of contraceptives was found to impact dietary (poly)phenol metabolism.

3.5 Sources and classes of dietary (poly)phenols

Six studies[38,42–45,48] studied the effects of genetic variations on the metabolism of green tea flavan-3-ols. Another study focused on flavan-3-ol metabolites deriving from a free diet.[46] Two studies[41,49] focused on isoflavone metabolites, while another study[40] explored the association between genetic variations and phase II metabolites of flavanones contained in orange juice. One study[39] assessed the effects of SNPs on the metabolism of flaxseed-derived lignans. Finally, one study[47] explored the impact of genetic variations on the levels of some (poly)phenol metabolites derived from a free diet, including 3′,4′-dihydroxycinnamic acid, 3′,4′-dihydroxyphenylacetic acid, benzene-1,3-diol, and 4′-hydroxyhippuric acid. Sources and classes of dietary (poly)phenols are pictorially shown in Fig. 3.

3.6 Adherence to the study protocol

Only a few studies explicitly reported whether and how they monitored compliance with the study protocol: by pill count,[38] asking the participant to return unconsumed food/beverage (*i.e.*, uneaten flaxseed),[39] or *via* an investigator-led 24-hour dietary recall to monitor compliance with low-flavonoid diet.[45]

3.7 Dietary assessment and dietary habits

Only two studies[42,48] explored participants' dietary habits, especially in terms of (poly)phenol intake. These studies included a variety of green tea drinkers, categorised according to their green tea drinking habits in terms of the range in the amount consumed per day or simply dichotomised in habitual/non-habitual green tea consumers. On the contrary, none of the other studies reported any information concerning dietary habits and usual (poly)phenol exposure/intake. All studies excluded per *protocol* habitual consumers of (poly)phenol-rich foods and beverages and included populations naive to dietary (poly)phenols and/or on low/very-low (poly)phenol diets.

Dietary assessment was performed mainly by carrying out a 24-hour dietary recall. In one study,[39] a series of 12 telephone-administered 24-hour dietary recalls were assigned randomly

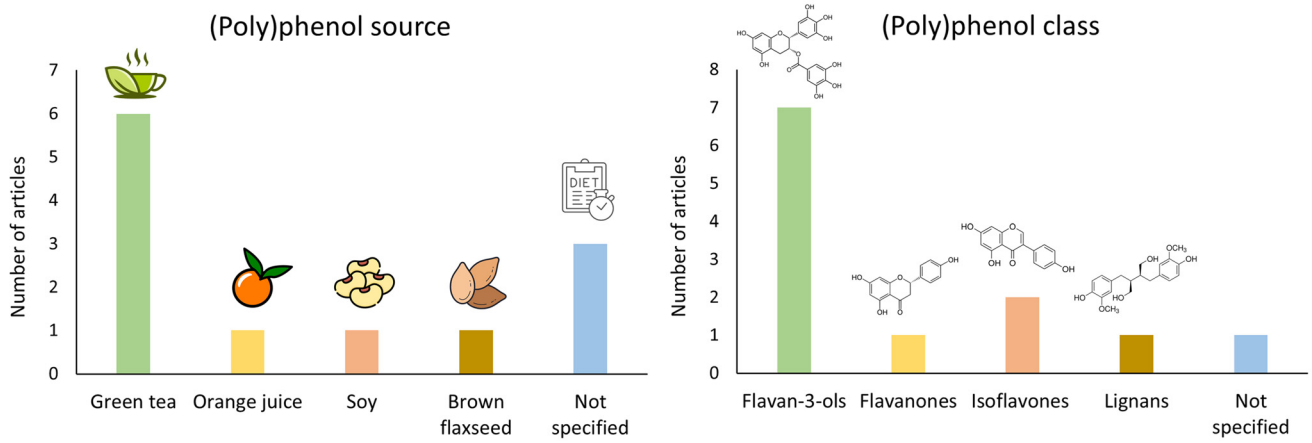

Fig. 3 Number of studies investigating a certain (poly)phenol source (on the left) or (poly)phenol class (on the right).

throughout the 5-month active intervention period. Only one study,[42] which was observational, utilised a "Food Frequency Questionnaire" (FFQ) that included 45 food groups or items representing commonly consumed local foods to assess eating habits in terms of dietary patterns. Of note, only in one study[38] participants were prospectively required to record dietary and daily activity information.

3.8 Biological samples and chemical characterisation analysis

Four studies[41,43,44,48] collected only blood samples and one study[46] collected only urine samples, whilst all the other studies collected both blood and urine. Samples were analysed using chromatographic separation techniques coupled with detection methods based on mass spectrometry (MS) or ultraviolet/visible spectroscopy. High-performance liquid chromatography (HPLC) was employed in seven studies:[38,40,42–44,48,49] three studies coupled it with mass spectrometry,[38,40,48] one with ultraviolet/visible (UV/VIS) detectors[49] and the remaining three with electrochemical detectors.[42–44] One study[41] employed liquid chromatography (LC) coupled with mass spectrometry and three studies[44–46] employed ultra-performance liquid chromatography (UPLC) coupled with mass spectrometry. Further two studies[39,47] analysed samples by gas chromatography (GC) coupled with mass spectrometry.

3.9 Genetic variations, genotyping, and features of the genes and related SNPs studied

The SNPs retrieved in the present systematic review and related genes are reported in SI Tables 5–8. Overall, 88 SNPs in 33 genes were studied.

A median value of 1 gene per study was investigated: the range of genes under study went from one[38,42–47] to 25.[39] Seven studies[38,42–47] explored one single gene, one study[40] three genes, another study[49] five genes, and a further study[48] six genes. Finally, one study[39] appraised 25 genes. Of note, a single study[39] was responsible for most (76%) of the genes investigated, and, despite some degree of overlapping, no gene was studied by all the articles included in the present systematic review (Fig. 4). It is worth stressing that a study[41] did not adopt the candidate gene approach, adopting, instead, a genome-wide exploration unbiased from an *a priori* selection of any preferential gene.

Of the 33 genes studied, slightly more than half (n = 17, 51.5%) were related to drug/xenobiotic metabolism (Table 3). More specifically, two (11.8%; 6.1% of the entire set of genes) were involved in absorption, seven (41.2%; 21.2% of the overall set of genes) in phase I metabolism, four (23.5%; 12.1% of all genes) in phase II metabolism, and four (23.5%; 12.1% of the entire list of genes) in excretion. The remaining 16 genes (48.5%) were related, to varying degrees, to steroid hormone metabolism and activity (Fig. 5).

A median value of 5 SNPs per study was analysed: the range of SNPs went from one SNP[38,42,44] to sixty.[39] Three studies[38,42,44] studied the impact of a single SNP, one study[47] the effects of three SNPs, two studies,[40,43] and four studies[41,45,46,49] of five SNPs. Finally, one study[48] and a further study[39] explored the effects of panels of 13 and 60 SNPs, respectively. Of note, a single study[39] was responsible for the majority (68%) of the SNPs investigated among 9 genes (Fig. 6). Considering genes specifically related to (poly)phenol ADME, 16 SNPs showed significant modifying effects on urinary and/or plasma levels of phenolic metabolites and/or on their kinetic parameters (Table 4).

The functional annotation of SNPs and related genes in terms of biological processes, molecular functions, and cellular components is pictorially shown in SI Fig. 1 and 2. Forty-five biological processes (SI Table 5 and SI Fig. 1), 19 molecular functions (SI Table 6 and SI Fig. 2), and one cellular component (SI Table 7) could be identified. The locations of SNPs along the human genome are displayed in Fig. 7 and SI Table 8.

In most cases, SNPs had been chosen and tested by the authors based on knowledge derived from previous *in vitro*, animal or *in silico*/computational studies or from clinical/epidemiological studies. Only one study[39] devised a systematic methodology for selecting SNPs, integrating data-mining (by

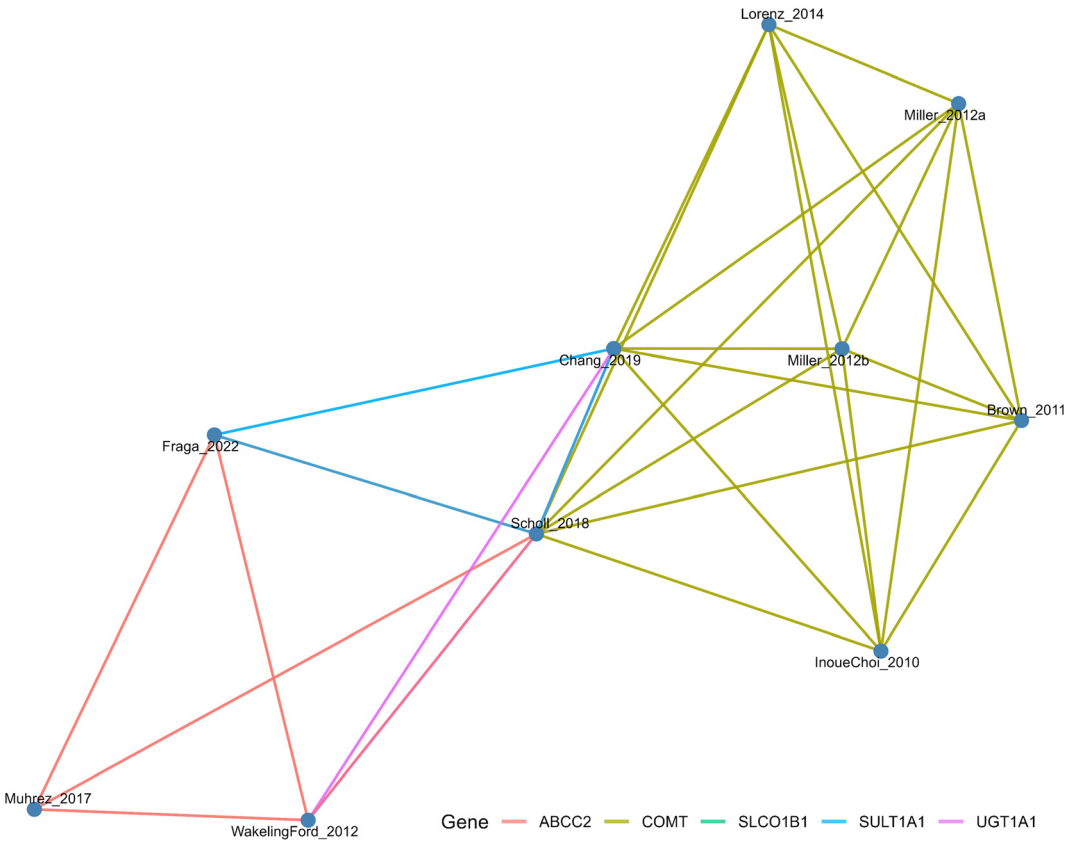

Fig. 4 Network-based representation of the overlapping genes involved in (poly)phenol adme among studies included in the present systematic review. Only interconnected genes are shown.

surveying the HuGE Navigator Database) and text mining (by comprehensively looking for all published genome-wide association studies, GWAS, of genes coding proteins involved in the metabolism of endo- and xenobiotics, across any phenotype).

In most studies,[42–45,47–49] genotyping was carried out by TaqMan assay, which utilises the 5′ nuclease activity of Taq polymerase to generate a fluorescent signal during polymerase chain reaction (PCR), or similar techniques. In one study,[40] "Kompetitive Allele Specific" PCR (KASP) and agarose gel electrophoresis were utilised, which enabled a fast, cheap, but high-quality and highly reliable bi-allelic SNP characterisation. In another study,[38] genotyping was conducted by direct sequencing. Finally, one study[39] genotyped by multiplexing (utilizing the MassARRAY technology and iPLEX Gold assay). Of note, only one study[41] performed a GWAS. Only one study[46] did not provide any detail about the genotyping technique.

3.10 *A priori* sample size and power analysis

Formal *a priori* sample size and power analyses were conducted only in one study,[38] even if this study conducted such analyses but for their primary (and not secondary) outcome (changes in blood pressure and not the impact of the genetic variant).

3.11 Data quality check, dealing with missing data, and data pre-processing/transformation

Only a few studies explicitly reported the procedures followed to ensure data quality, deal with missing data, and perform data pre-processing/transformation. For instance, one study[38] log-transformed post-intervention analytical values of urinary metabolites. Similarly, two other studies[42,46] log-transformed the values of all urinary metabolites, the distributions of which exhibited a markedly skewed trend toward high values. As such, all formal statistical tests were carried out on logarithmically transformed values of urinary (poly)phenol metabolites, presenting geometric (and not arithmetic) means. Furthermore, in one of these two studies,[42] the authors computed within-batch coefficients of variations on duplicate samples, which were found to vary from 5.8% to 24.6%. Another study[49] checked for normality of urinary metabolite values using the Kolmogorov–Smirnov test and non-normally distributed data were transformed by ranking according to Blom. Also, the authors reported mean intra-assay (9.1%) and inter-assay (13.4%) CVs and, after quality checks, removed 3 subjects from their analyses. In a "real-life" metabolomic study,[47] 217 metabolites were initially identified, and, after quality checks, 108 metabolites entered the multivariate analyses (Principal Component Analysis, PCA) to check for hom-

Table 3 List of genes related to (poly)phenol ADME, with their coded proteins and SNPs

Gene	Protein	Function	SNP	Study
CBG/GBA3	Cytosolic β-glucosidase	Deglycosilation – absorption	**rs358231**	49
LCT	Lactase-phlorizin hydrolase		rs3754689	49
ABCC2/MRP2	ATP-binding cassette C2/multidrug resistance-associated protein 2	Efflux – excretion	**rs2273697**	47–49
			rs717620	47 and 48
			rs3740066	47 and 48
			rs8187710	40 and 48
ABCG2/BCRP	ATP-binding cassette G2/breast cancer resistance protein		**rs2231142**	49
ABCB1/PGP/ MDR1	ATP-binding cassette B1/P-glycoprotein 1/multidrug resistant-associated protein 1		rs1045642	48
			rs1128503	48
			rs2032582	48
OATP1B1/ SLCO1B1	Organic anion transporting polypeptide 1B1/solute carrier organic anion transporter 1B1	Uptake – excretion	**rs4149056**	39 and 48
			rs11045819	48
			rs2306283	48
COMT	Catechol-*O*-methyltransferase	Methylation – phase II metabolism	**rs4680**	38, 39, 42–45 and 48
			rs6269	39 and 43
			rs4633	39 and 43
			rs4818	43
			rs4646312	39
UGT1A1	UDP-glucuronosyltransferase 1A1	Glucuronidation – phase II metabolism	**rs8175347**	48 and 49
			rs4124874	39
			rs10929302	39
			rs887829	39
			rs6742078	39
SULT1A1	Sulfotransferase 1A1	Sulfation – phase II metabolism	rs26528	39
			rs8049439	39
			rs4788068	40
			rs3760091	40
			rs750155	48
SULT1C4	Sulfotransferase 1E1		**rs1402467**	40
PON1	Paraoxonase 1	Hydrolysis – phase I metabolism	**rs662**	46
			rs854560	46
			rs705379	46
			rs705381	**46**
			rs854572	46

SNPs that have a significant modifying effect on (poly)phenol ADME are in bold. The study analysing each SNP is also indicated.

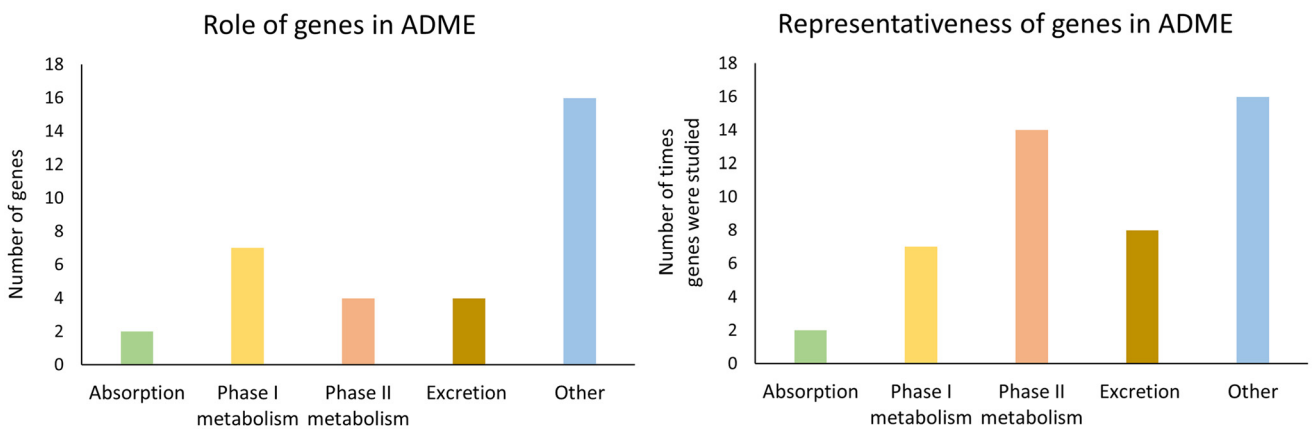

Fig. 5 Number of genes with a certain role in (poly)phenol ADME or other roles (on the left), and times that genes with a certain role were studied (on the right).

ogeneity and reproducibility of the dataset and identify eventual outliers. "Orthogonal projections to latent structure discriminant analysis" (OPLS-DA) was carried out to maximise the separation between genotypic classes.

3.12 Genetic modelling and genetic assumptions

In most studies, genotypes were simply grouped based on the presence of the minor allele. Only a few studies[38,40] performed

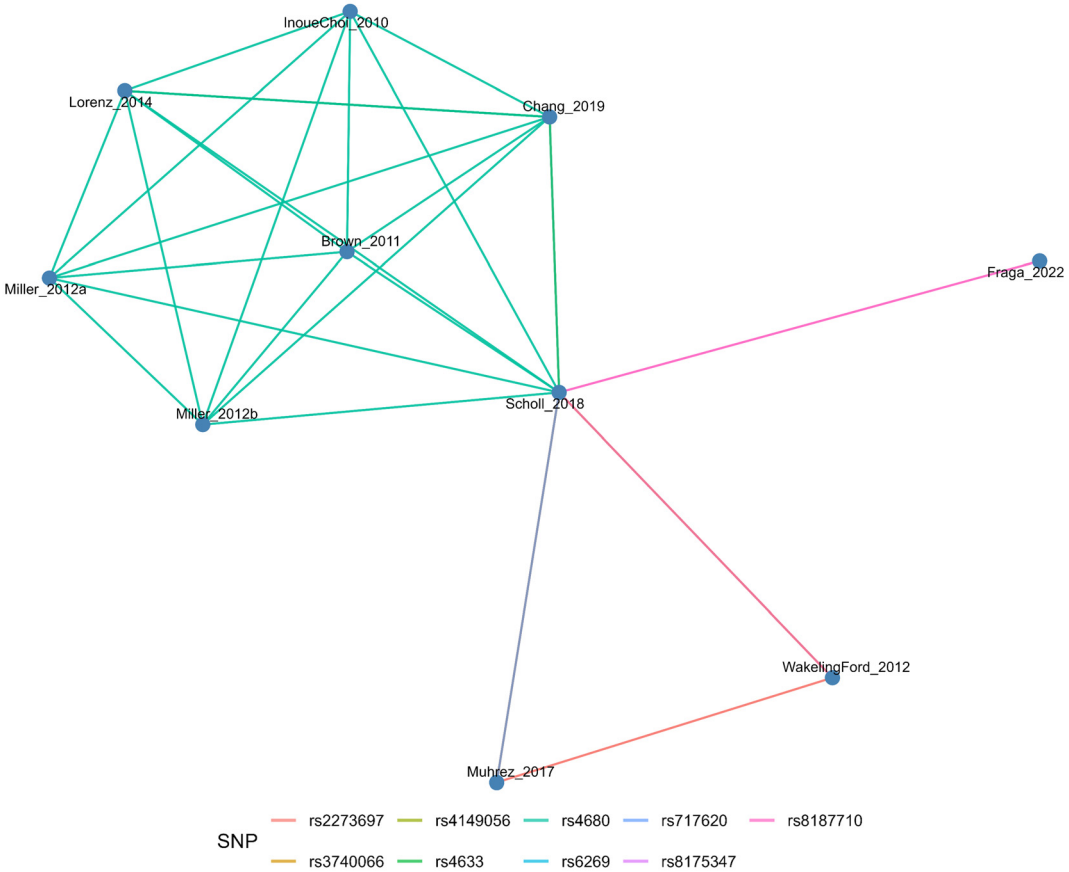

Fig. 6 Network-based representation of the overlapping SNPs involved in (poly)phenol adme among studies included in the present systematic review. Only interconnected SNPs are shown.

extensive and comprehensive genetic modelling. One study[38] conducted four genetic analyses, comparing dominant, recessive, and additive models and model-free or non-parametric computation, not assuming a specific genetic model and relying on statistical methods to identify associations between genetic markers and traits. Another study[40] tested five genetic models (namely, dominant, co-dominant, over-dominant, recessive, and log-additive). Of note, only one study[40] performed a haplotype analysis, which involved the study of the combination of alleles inherited together from a single parent to understand patterns of genetic variation, inheritance, and their association with the excretion of flavanone metabolites.

Furthermore, two studies[44,45] included only homozygous variant individuals for a specific variant of the COMT gene, excluding those heterozygous. Finally, concerning genetic assumptions, they were generally met. Only two studies[40,43] found evidence of linkage disequilibrium and violation of the Hardy–Weinberg equilibrium, at least for a SNP and in a subgroup of the population recruited.

3.13 Analysis of the impact of the SNP on dietary (poly) phenol metabolism: model building

Only a few studies explicitly reported the statistical procedure followed to build their model. A study[44] performed a three-way interaction analysis (SNP genotype, treatment, and time). One study[47] leveraged non-targeted metabolomics, whilst two studies[44,48] utilised pharmacokinetics/nutrikinetics modelling. In the metabolomic study,[47] subsets of metabolites significantly contributing to the discrimination between genetic groups were identified by iteratively performing a stepwise removal of the less contributing metabolites, according to coefficient plots and values of the variable importance on projection. In one of the two nutrikinetics studies,[44] mean catechin concentrations at each time point stratified by SNP (more specifically, COMT genotype) were modelled using cubic spline interpolation, and pharmacokinetic parameters were estimated. In the other nutrikinetics study,[48] catechin concentrations were modelled using non-compartmental analyses and population pharmacokinetic methods (including linear trapezoidal-linear interpolation to estimate the area under the ROC curve, area under the time-concentration curve (AUC), correlational analyses, and non-linear mixed-effects modelling techniques).

3.14 Statistical analysis, threshold for statistical significance, goodness-of-fit statistics, and model evaluation and validation

Most studies carried out multivariate statistical analyses, except for a single study.[43] Most studies did not utilise strin-

Table 4 List of genes related to (poly)phenol ADME, with the SNPs having a statistically significant influence on phenolic metabolite levels and/or kinetic parameters

Gene	SNPs	Impact of SNPs	Study
COMT	rs4680	Lower 24 h urinary excretion of EGC, EC, 4′-*O*-methyl-EGC, 3′,4′-diHPVL, 3′,4′,5′-triHPVL in AA genotype group (low activity COMT)	42
COMT	rs4680	Lower 24 h urinary excretion of EGC and 4′-*O*-methyl-EGC in GG genotype group (high activity COMT)	38
COMT	rs4680	Higher urinary excretion of 4′-*O*-methyl-EGC in GG genotype group (high activity COMT) during the first 5.5 h	44
SLCO1B1	rs4149056, rs2306283	Plasma pharmacokinetics and/or relative bioavailability of EGCG and EGC	48
COMT	rs4680		
MRP2	rs717620, rs3740066		
UGT1A1	rs8175347		
SULT1A1	rs4788068, rs3760091	Higher urinary excretion of phase II conjugates of hesperetin and naringenin	40
SULT1C4	rs1402467		
MRP2	rs8187710		
UGT1A1	rs8175347	Relative/absolute, individual/total urinary excretion of isoflavone metabolites, and/or sulfate-to-glucuronide ratio	49
CBG	rs358231		
MRP2	rs2273697		
BCRP	rs2231142		
MRP2	rs717620, rs3740066, rs2273697	Urinary excretion of 1,3-dihydroxybenzene, 2-(3′,4′-dihydroxyphenyl)acetic acid, 3′,4′-dihydroxycinnamic acid, 3-(3′-hydroxyphenyl)propanoic acid, 4′-hydroxyhippuric acid	47
SLCO1B1	rs4149056	Urinary excretion of enterolactone, with an effect depending on ethnicity (European or African ancestry women)	39
COMT	rs4633		
PON1	rs661, rs705381	Urinary excretion of the sum of sulfated and glucuronidated forms of 3′,4′-dihydroxyphenyl-γ-valerolactone in women	46

gent statistical criteria. Of note, only two studies[39,47] performed corrections for multiple testing, specifically applying Bonferroni correction. Interestingly, the only performed GWAS[41] adopted a p-value $<1 \times 10^{-5}$, not reaching the standard genome-wide significance threshold (*i.e.* p-value $<5 \times 10^{-8}$) and choosing to use a suggestive threshold. On the other hand, they could still avoid type II errors and screen genetic variants with minor effects on the trait of interest (*i.e.*, the equol-producing phenotype).

Goodness-of-fit statistics were rarely reported.[47,48] In one study,[47] the goodness of fit of the models was estimated by computing R^2 and Q^2 by 7-fold internal cross-validation, and the analysis of variance (ANOVA) of the cross-validated residuals (or CV-ANOVA). In a pharmacokinetics/nutrikinetics study,[48] model selection was based on the objective function value, several goodness-of-fit indicators and plots, and a visual predictive check. A stepwise covariate model-building strategy was leveraged by utilising forward inclusion of covariates followed by backward elimination.

3.15 Major findings

In the following sections, the major findings of the studies retained in the present systematic review are overviewed and compared (see also Table 2). Full details of the outcomes are reported in SI Table 3.

3.16 Impact of genetic variations on green tea flavan-3-ol metabolism

Green tea is a source of flavan-3-ol monomers, including epigallocatechin-3-*O*-gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), and epicatechin-3-*O*-gallate (ECG), collectively known also as (gallo)catechins. (Gallo)catechins absorbed in the small intestine can undergo sulfation, glucuronidation, and methylation by phase II enzymes in enterocytes and hepatocytes before entering the systemic circulation. In particular, monomers with a 3-*O*-galloyl moiety are quite resistant to sulfation and glucuronidation and are found in plasma mainly in a free form, being excreted mainly through the biliary system.[50–52] EGCG can be metabolised through methylation, producing 4′-*O*-methyl EGCG, 4″-*O*-methyl EGCG and 4′,4″-*O*-dimethyl-EGCG. Also, EGC can be methylated in position 4′, giving origin to 4′-methyl-*O*-EGC, which can be found in plasma and urine. The fraction of (gallo)catechins that are not absorbed in the smaller intestine (70% of catechins and 90% of gallocatechins) reach the colon and are catabolised to phenyl-γ-valerolactones (PVLs) and smaller phenolic acids by the gut microbiota, which are absorbed through passive diffusion, conjugated by phase II enzymes, and excreted through urine.[53,54]

The enzyme catechol-*O*-methyltransferase (COMT), encoded by a gene located at 22q11.21 (genomic coordinates, 22: 19 941 772–19 969 975), is responsible for catalysing a major metabolic pathway of flavonoids and their gut microbiota metabolites, namely their *O*-methylation, which is the transfer of a methyl group from *S*-adenosylmethionine (SAM) to one of the hydroxyl groups of catechols, to produce *O*-methylated catechols and *S*-adenosyl-L-homocysteine (SAH). This biotransformation mainly occurs in the intestinal tract, liver, and kidney.[55] Two isoforms of COMT have been demonstrated to exist: a soluble form of the protein, which is the predominant one in most tissues, and a membrane-bound form. The genetic polymorphism rs4680 is a common missense variant (G to A base change), resulting in a valine-to-methionine amino acid substitution at position 108 in the soluble protein

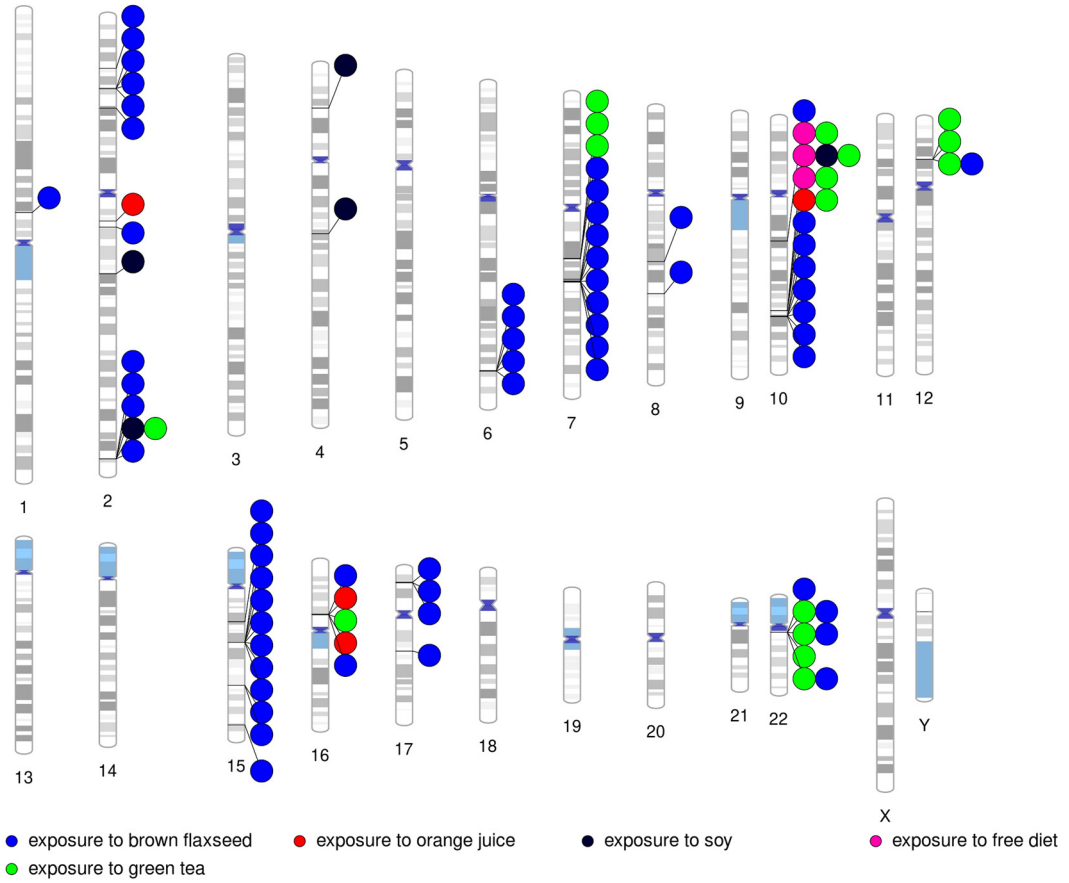

Fig. 7 Locations of SNPs involved in (poly)phenol ADME along the human genome.

and at position 158 in the membrane-bound form. The allele rs4680-A, which can be found in insulin-resistant and type 2 diabetics, seems to alter the function of the COMT enzyme by decreasing its thermostability and resulting in a 30–40% reduction of its activity.[55]

Six studies[38,42–45,48] explored the impact of COMT-related genetic variations on the metabolism of green tea (gallo)catechins. In the study by Brown *et al.*,[38] the authors recruited 83 subjects who consumed decaffeinated green tea extract (about six to eight cups of moderate-strength green tea daily). Plasma concentrations of EGCG were undetectable at baseline and remained undetectable after dietary supplementation in the placebo group but increased in the experimental group. Urinary excretion over 24 h of EGC and 4′-*O*-methyl-EGC was similar for the two groups at baseline, but post-intervention increased in the experimental group by 28-fold and 34-fold, respectively. Mean urinary concentrations of EGC and 4′-*O*-methyl-EGC were significantly lower ($p < 0.01$) in individuals homozygous for the high-activity COMT G-allele (rs4680-G), potentially reflecting increased metabolic flux and a more rapid turnover and conversion to downstream metabolites compared to individuals carrying at least one copy of the low-activity COMT A-allele.

In the study by Inoue-Choi *et al.*,[42] 660 subjects, self-identified as daily green tea drinkers, were recruited from four small, geographically defined communities from the Greater Shanghai metropolitan area, and stratified according to COMT genotypes (rs4680): 343 carried the homozygous wild-type genotype (GG), 49 the homozygous variant genotype (AA), and 268 the heterozygous genotype (GA). The enrolled subjects not only geographically but also genetically belonged to the Asian area, in accordance with frequencies reported in the database (f(G) = 0.72 and f(A) = 0.27). Comparing the three COMT genotype groups, nominal statistically significant differences could be found for the five (poly)phenol metabolites under study when considering each one individually (EGC, EC, 4′-*O*-methyl-EGC, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone, 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone). Considering all the metabolites altogether, the difference was highly significant ($p = 0.007$). More specifically, the authors found that those carrying the homozygous low-activity genotype had lower urinary levels of five tea (poly)phenol metabolites by 35–45%, compared to those with the wild type high-activity genotype or the heterozygous variant genotype (who had, on the contrary, comparable levels of urinary metabolites). The authors speculated that carriers of the homozygous genotype could retain more green tea (poly)phenols in their bodies and benefit more from green tea intake. Of note, when stratifying according to daily green tea consumption, low green tea consumers (<5 g day^{-1}) had lower

urinary metabolite concentrations in both homozygous low-activity and heterozygous genotype groups, compared with the high-activity homozygous wild-type genotype, whilst the difference between high- and intermediate-activity COMT genotypes (genotypes GG and GA) tended to disappear with increasing green tea consumption ($p = 0.18$).

Conversely, Lorenz *et al.*[43] found no impact of COMT genotype on EGCG plasma levels. The authors explored the enzymatic activities of four functional COMT SNPs determined in red blood cells in a sample of 24 healthy human volunteers supplemented with pure EGCG. The analysed SNPs were rs4680 (472G>A, Val158Met), rs6269 (1-98A>G), rs4633 (186C>T, His62=) and rs4818 (408C>G, Leu136=). EGCG plasma levels and COMT enzyme activities in erythrocytes were measured before and two hours after intervention. While enzymatic COMT activities were affected by the COMT SNPs ($p < 0.001$), EGCG plasma levels significantly increased after the intervention and were not influenced by any of the COMT SNPs and different enzyme activities. Furthermore, EGCG ingestion did not result in impairment of COMT activity, which significantly increased by 24% after EGCG consumption.

Similarly, the study by Miller *et al.*[44] found no influence of COMT genotype. The authors recruited 20 participants who were exposed to decaffeinated green tea extract. Maximum plasma concentrations of 1.09 μM, 405, 331, 160, and 77.1 nM were reached for EGCG, EGC, EC, ECG, and 4′-*O*-methyl EGCG at 81.5, 98.5, 99.0, 85.5 and 96.5 min, respectively. Bimodal and single-peaked curves could be observed for the non-gallated and gallated green tea catechins, respectively, probably reflecting a meal effect from the high-carbohydrate breakfast administered 1 hour after the capsule consumption. It is hypothesised that galloylated species, different from non-galloylated ones, may form complexes with the food components, resulting in a single peak being observed. Other possible explanations could be a depletion in glucuronidation precursors in the fasted status. No statistically significant differences based on COMT genotype could be found in terms of maximum concentration, time to reach maximum concentration, AUC, EGCG half-life absorption, and EGCG half-life elimination. However, a trend towards a greater maximum concentration and AUC response in the plasma concentration curve for 4′-*O*-methyl-EGCG in the COMT AA genotype group could be noted. Also, a tendency towards a higher maximum plasma concentration for the AA genotype for EC, EGC and ECG was detected, along with higher median concentrations of 4″-*O*-methyl-EGCG, which was detected and quantified only in a few samples.

The authors were able to replicate their findings in another, more extensive study[45] with 47 participants. A genotypic effect was observed for urinary 4′-*O*-methyl-EGC during the first 5.5 h, with the COMT GG group exhibiting a greater concentration ($p = 0.049$) than the other 2 genotypes, even if marginally. No differences could be found for the remaining 18.5 h collection or for total EGC during the 5.5 h and 18.5 h collections. Finally, no difference in concentrations of plasma metabolites (C, EC, EGC, ECG, EGCG, 4′-*O*-methyl-EGCG, 4″-*O*-methyl EGCG, 4′,4″-*O*-dimethyl-EGCG) could be detected. According to the authors, these findings are coherent with the hypothesis of a slower methylation enzymatic function in the COMT AA genotype individuals, as well as with a differential preference for methylation position ("regioselectivity") induced by the genetic variation, which could explain why, in the COMT GG group, secondary and tertiary methylation products, such as 4′,4″-*O*-dimethyl EGCG and 3′,4′,4″-*O*-trimethyl EGCG, are more likely to be detected with respect to primary methylation products.[44,45] On the other hand, all these differences are, overall, slight and not statistically significant, suggesting that green tea (gallo)catechins, having low bioavailability and being poorly absorbed in the small intestine and quickly eliminated, may have better enzyme–substrate interactions and binding affinity than endogenous substrates, which could counteract, at least partly, the effects of the polymorphisms.

Whilst COMT genotype as a potential genetic factor mediating green tea exposure/intake and metabolic response has been the most investigated, other studied SNPs are related to genes coding members of the family of drug transporters, which include uptake (Organic Anion Transporting Polypeptide type 1B1, SLCO1B1) and efflux (Multi-drug Resistance-associated Protein type 2, ABCC2) transporters.[56] The former is specifically expressed in the liver, on the basolateral membrane of hepatocytes, whereas the latter is an ATP-binding cassette protein and is expressed in several human tissues, being of particular importance for intestinal drug absorption and hepatic drug elimination.

In the nutrikinetics study by Scholl *et al.*,[48] 84 healthy participants took green tea extract capsules for 5 days. On day 5, plasma profiles for EGCG, EGC and ECG were obtained by collecting venous blood samples 0.5, 1, 2, 3, 4, 5, 7, and 9 hours after the last green tea extract capsule consumption. A substantial between-subject variability in pharmacokinetics was found, with maximum plasma concentrations varying more than 6-fold (6.1, 7.7 and 6.6-fold for EGCG, EGC and ECG, respectively). For EGCG and ECG, the highest inter-individual variabilities concerned the zero-and first-order absorption processes, whilst for EGC, the highest interindividual variability regarded the central volume of distribution and the intercompartmental distribution. The AUCs of EGCG, EGC and ECG were 877.9 (360.8–1576.5), 35.1 (8.0–87.4), and 183.6 (55.5–364.6) μg $L^{-1} \times h$ respectively, and the elimination half-lives were 2.6 (1.8–3.8), 3.9 (0.9–10.7) and 1.8 (0.8–2.9) hours, respectively. Metabolite concentrations were found to decline in a biexponential fashion. Genetic polymorphisms in genes of the drug transporters ABCC2 and SLCO1B1 were found to explain, at least partly, the high variability in pharmacokinetic parameters. More specifically, carriers of the C allele of ABCC2 rs717620 (-24C>T) exhibited 26% less EGCG relative bioavailability than carriers of the variant allele T ($p = 0.00721$). Additionally, total body clearance of EGCG was lower in carriers of the C allele of rs4149056 (521T>C, Val174Ala) ($p = 0.01212$). Concerning EGC, its pharmacokinetics was affected by MRP2 rs3740066 (3972C>T, Ile1324=) ($p = 0.00153$, a higher

intercompartmental clearance in carriers of the C allele), OATP1B1 rs2306283 (388A>G, Asn130Asp) (p = 0.00163, a 35% reduction in total body clearance in carriers of the A allele), ACBC2 rs717620 (-24C>T) (p = 0.01654, a reduction in central volume of distribution in carriers of the T allele), UGT1A*28 or rs8175347 (p = 0.01795, a 26% reduction in total body clearance in wildtype carriers), and COMT rs4680 (p = 0.02350, a 24% reduction in relative bioavailability in carriers of the low-activity AA genotype). Of note is that habitual tea drinking was not found to impact the kinetics of any of the metabolites measured.

3.17 Impact of genetic variations on flaxseed lignan metabolism

Flaxseed is a source particularly rich in lignans, especially secoisolariciresinol-diglucoside, which is poorly absorbed in the smaller intestine and reaches the lower part of the gastrointestinal tract, where it is deglycosylated to secoisolariciresinol and converted by the intestinal microbiota to the enterolignans enterodiol and enterolactone.[57,58] Enterodiol is, in turn, rapidly converted to enterolactone, which is, therefore, the predominant circulating lignan metabolite. The effects of enterolignans are complex in that they can have both estrogenic and anti-estrogenic actions, depending on their concentration and individual factors, including age and the reproductive/menopausal status of the subject.[59–62]

In the study by Chang *et al.*,[39] ground brown flaxseed consumption for 6 weeks in post-menopausal women resulted in increased urinary enterolactone excretion, which was higher in European ancestry women. Associations between urinary phytoestrogen enterolactone excretion and 70 functional polymorphisms in 29 steroid hormone metabolizing genes, including genes putatively involved in (poly)phenol excretion and phase II metabolism (SLCO1B1, COMT, UGT1A1, SULT1A1), were explored. In women of European ancestry, 12% and 17% of the variation in baseline and post-intervention excretion levels was explained by genetic variants. In African ancestry women, this percentage was 16% and 13%, respectively. These associations were more marked among women of African ancestry than among those of European ancestry. However, these associations were only nominal ($p < 0.05$), failing to achieve the statistical significance threshold after correction for multiple comparisons. Of note, no SNPs were associated in both ethnic groups.

3.18 Impact of genetic variations on isoflavone metabolism

Soy is a source particularly rich in isoflavones, with daidzein, genistein and glycitein being the major representatives and occurring *in planta* predominantly as β-glucosides. Their absorption involves a preliminary step of hydrolysis catalysed by intestinal enzymes, including cytosolic-β-glucosidase (CGG) and lactase-phlorizin hydrolase (LPH). Then they are conjugated by human SULTs and UGTs, forming phase II metabolites, with glucuronides in excess of sulphates.[63] A common genetic variation consisting in the presence of an additional TA repeat in a TA-repeat region ($(TA)_7$ compared with $(TA)_6$) of the promoter of the human UGT1A1 gene results in reduced expression of UGT1A1.[64]

Wakeling and Ford[49] recruited a sample of 100 pre-menopausal women. The participants in the "Soy Isoflavone Metabolism Study" consumed a commercial soy supplement as a single bolus dose. The authors measured the urinary levels of isoflavone metabolites (aglycones, 7-glucuronides, and sulfates of genistein, daidzein, and glycitein) and their relationships with UGT1A1*28 promoter polymorphism and SNPs in other genes involved in absorption and excretion (GBA3, LCT, ABCC2, and ABCG2). ABCG2/BCRP (Breast Cancer Resistance Protein) is an efflux transporter belonging to the ATP-binding cassette family and is present in the luminal membrane of the intestine. Urine was collected over 24 h. Large inter-individual differences in isoflavone recovery (mean 39% [range 11–89%], eightfold variation) and metabolites could be observed, with glucuronides representing the primary metabolites (72% of total). No statistically significant association between the UGT1A1*28 polymorphism (rs8175347) and net recovery in the urine of any individual isoflavone metabolite under study could be detected. However, the polymorphism showed other significant associations. In more detail, the UGT1A1*28 minor allele was found to be positively associated with the percentage of glycitein excreted in urine as sulfate (p = 0.046), and, after excluding 5 participants with both minor alleles (A allele) of GBA3 and ABCG2, due to a statistically significant interaction (p = 0.025), it was positively associated with the percentage of glycitein as sulfate in urine (p = 0.014), negatively with percentage of glycitein as glucuronide (p = 0.028), positively with combined isoflavones as sulfate (p = 0.035), and positively with sulphate-to-glucuronide ratio for combined isoflavones (p = 0.036). Finally, SNPs in GBA3 (rs358231), ABCG2 (rs2231142), and ABCC2 (rs2273697) were also found to correlate with differences in isoflavone metabolites in urine. In detail, GBA3 rs358231 (1368T>A, Tyr456SeM) was associated with the percentage of total isoflavone recovered in urine as glucuronide (p = 0.035), ABCG2 rs2231142 (421C>A, Lys141Gln) was negatively associated with the percentage of total isoflavone recovered in urine as glucuronide (p = 0.042), and ABCC2 rs2273697 (1249C>A, Val141Ile) was associated with total glycitein excretion (p = 0.034) and total genistein excretion (p = 0.019).

Equol, or 4′,7-isoflavandiol, is a nonsteroidal estrogen derived from the metabolism of isoflavones by the gut microbiota.[65] Equol production occurs in approximately 25–30% of the adult population of Western countries, while this percentage reaches 50–60% when considering adults from Japan, China, and Korea or Western adult vegetarians. These differences are due to variations in the intestinal bacterial composition,[66] whereas the contribution of the genetic makeup of the individual is less known. Inter-individual differences in equol production could explain the differential impact of soy intake on health-related outcomes, especially cardiovascular health.[65,67,68] Hong *et al.*[41] attempted to fill in this knowledge gap, by performing a GWAS of the equol-producing phenotype in a sample of 1391 Koreans in the context of free diet. In the

study population, 70.1% of the participants were equol-producers and exhibited significantly lower blood pressure than non-producers. Five SNPs identified in the HACE1 gene (HECT Domain And Ankyrin Repeat Containing E3 Ubiquitin Protein Ligase 1) were significantly associated with equol production, the most significant of which was rs6927608: more specifically, individuals with a minor allele of this SNP (allele C) were less likely to produce equol and displayed more elevated systolic blood pressure values. HACE1 plays a crucial role in a variety of biological functions and processes, including tumour suppression, by hindering tumour cell proliferation and facilitating the programmed cell death of tumour cells.[69] Moreover, it safeguards the heart, mitigates against oxidative stress, and regulates cellular dynamics.[70] The authors speculated that HACE1 could be involved in host intestinal immune responses and the maintenance of the pool of equol-producing bacteria, thus mediating the impact of the equol-producing phenotype on heart health.[41]

3.19 Impact of genetic variations on orange flavanone metabolism

Citrus fruits and drinks are major sources of dietary flavanones, including hesperetin, naringenin and their respective glycosides. After ingestion, flavanone glucosides and other glycosides are hydrolysed in the small intestine and in the colon, respectively, and the released aglycones are conjugated by intestinal and hepatic phase II enzymes forming glucuronides, sulfates, sulfo-glucuronides, and diglucuronides.[71]

Fraga and coauthors[40] investigated the impact of four SNPs in three genes involved in phase II metabolism or excretion (SULT1A1, SULT1C4, ABCC2). A total of 46 volunteers ingested a single dose of orange juice. Based on the urinary excretion of phase II hesperetin and naringenin metabolites, 25 and 21 subjects were categorised as high- and low-excretors, respectively. A positive, statistically significant relationship between three out of the four SNPs under study (SULT1A1 rs4788068, SULT1C4 rs1402467 and ABCC2 rs8187710) and the excretion of phase II flavanone metabolites was found.

3.20 Impact of genetic variations on the metabolism of (poly)phenols derived from free diet

Muhrez *et al.*[47] explored the impact of genetic variations affecting the gene coding for ABCC2 (rs717620, rs2273697 and rs3740066) by leveraging a metabolomics-based approach. The authors recruited 53 individuals, exposed to dietary (poly) phenols ingested under uncontrolled, real-world conditions (free diet). A total of 108 urinary metabolites were monitored, including some low-molecular weight phenolics which can derive from dietary (poly)phenols, belonging to the classes of benzenes and phenolic acids (phenylpropanoic, phenylhydracrylic, phenyllactic, phenylacetic, mandelic, cinnamic and benzoic acids). A set of 37, 33 and 35 urinary metabolites was identified to vary significantly in association with SNPs rs717620, rs2273697 and rs3740066, respectively. Out of these metabolites, 7 exhibited an opposite excretion pattern between subjects carrying alleles associated with decreased function and carriers of alleles associated with increased function. When analysed simultaneously, metabolites showing the highest discriminatory power were identified as potential biomarkers of MRP2 function and potential substrates of this transporter. Of note, 5 out of these 8 metabolites were (poly) phenol metabolites: 1,3-dihydroxybenzene (benzene-1,3-diol or resorcinol), 2-(3′,4′-dihydroxyphenyl)acetic acid, 3′,4′-dihydroxycinnamic acid (caffeic acid), 3-(3′-hydroxyphenyl)propanoic acid, and 4′-hydroxyhippuric acid.

Another study[46] explored the impact of polymorphisms in the gene PON1 on the performance of an emerging biomarker of flavan-3-ol intake, namely the sum of two gut microbial metabolites specific for this class of flavonoids: 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-sulfate and 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-glucuronide. The authors hypothesised the role of a family of human serum proteins known as paraoxonases (PONs) in catalysing the hydrolysis of PVLs into phenylvaleric acids (PVAs), thus affecting the levels of circulating PVLs and so their suitability as nutritional biomarkers. The study first consisted of a single acute intake, single arm, non-randomised intervention part, in which 13 healthy male volunteers were recruited and administered a flavan-3-ol-containing drink consisting of a fruit-flavoured beverage mix prepared with a flavan-3-ol-containing cocoa extract. A rapid transformation of PVLs into PVAs could be observed in serum samples collected *ex vivo*, with a half-life of approximately 9.8 ± 0.3 minutes. This conversion was mediated by the PON1 and PON3 isoforms, with PON enzymes also involved in processing the phase II metabolites of PVLs. This evidence was confirmed collecting and analysing urine samples: the majority of PVAs metabolites were conjugated in the same positions and with the same moieties (methyl groups, sulfates, and glucuronides) as their PVL precursors. In the second part of the study, an ancillary analysis of the EPIC-Norfolk cohort study, five common PON1 genetic variations (rs662, rs854560, rs705379, rs705381, rs854572) were investigated to determine their impact on the urinary levels of a specific biomarker of flavan-3-ol intake (in a context of free diet), showing a limited influence on the inter-individual variations in biomarker levels. Although two SNPs were found to contribute to inter-individual differences, the overall genetic variation did not affect the performance of the biomarker, suggesting that the benefits of considering PON1 SNPs are negligible. As pointed out by the authors, further studies are needed to better understand the role of PON in flavan-3-ol metabolism and assess the impact of genetic variants on PVL excretion. Such studies should consider the great inter-individual variability in flavan-3-ol metabolism and in the subsequent PVL production, as reported in the literature.[72–75]

When considering observational studies or studies performed in a context of free diet, the association between (poly) phenol metabolites and specific SNPs could be affected by some biases, including the background diet, the time of urinary collection, and the convergence between metabolic pathways of (poly)phenols and other endogenous and exogenous aromatic compounds. Regarding background diet, a correction

for (poly)phenol intake should be considered, since it can influence metabolite excretion hiding potential associations between metabolites and SNPs. Another potential bias could emerge when the urine collection time (with respect to the time of (poly)phenol exposure) is not clearly assessed. Finally, when evaluating the excretion of low-molecular weight microbial metabolites, their heterogeneous origin should be pointed out, since they can derive from endogenous and exogenous sources other than (poly)phenols,[76] potentially influencing the relationship between their levels in biological fluids and the presence of genetic variants. Therefore, the best way to assess the association between (poly)phenol ADME and genetic background is to perform controlled intervention trials assessing the participants' diet and collecting 24 h urine samples, which are more informative than morning spot urine.

3.21 Trial registration, funding/sponsorship

Only one trial[39] was registered. Only two studies[39,48] reported their findings adhering to consolidated checklists (namely, the CONSORT and the TREND checklists, respectively).

Finally, concerning funding/sponsorship, no information was provided for one study.[48] For the remaining studies, funding/sponsorship was provided by national councils/institutes,[40,42,43,49] non-profit/public organisations,[47] or companies with significant commercial interests in food products and/or beverages.[38,44–46] In a study,[39] one of the authors served as a consultant/advisory board member of the council of a body/institution with significant commercial interests in food products and/or beverages.

3.22 Summary of the findings and quality appraisal

The overall quality of the studies overviewed here appears to be low-medium, showing a weak methodological strength, statistical robustness, reproducibility, and generalisability (SI Table 9). Out of the 12 studies assessed, only 1 [39] (8.3%) reached a high overall level of evidence, while 6 [38,40,41,43,45,48] (50.0%) were moderate and 5 [42,44,46,47,49] (41.7%) low. In terms of methodological quality, 2 [39,48] (16.7%) studies were rated high, 9 [38,40–47] (75.0%) moderate, and 1 [49] (8.3%) low, whereas for study design, 4 [38,39,41,45] (33.3%) were considered high, 5 [40,43,44,48,49] (41.7%) moderate, and 3 [42,46,47] (25.0%) low. Population directness and generalizability were high in 1 [46] (8.3%), moderate in 6 [39–41,43,45,48] (50.0%), and low in 5 [38,42,44,47,49] (41.7%) of the studies. Regarding study directness (relatedness), 8 [38–40,42,44,45,48,49] (66.7%) showed a high degree of relevance and 4 [41,43,46,47] (33.3%) a moderate one. Statistical precision was high in 3 [39,41,46] (25.0%), moderate in 6 [38,40,42,47–49] (50.0%), and low in 3 [43–45] (25.0%) of the studies, while consistency of results was uniformly moderate across all studies (12/12; 100%). Correction for plausible confounding was high in 5 [38–40,45,48] (41.7%), moderate in 2 [42,43] (16.7%), and low in 5 [41,44,46,47,49] (41.7%), whereas effect sizes were moderate in 7 [38–41,47–49] (58.3%) and low in 5 [42–46] (41.7%), with no study achieving a high effect size. Publication or funding bias was moderate in 5 [38,39,44–46] (41.7%) and low in the remaining 7 [40–43,47–49] (58.3%). Biological plausibility was consistently moderate across all studies (12/12; 100%). Nutrient–dose response was low in 11 [38–41,43–49] (91.7%) and moderate in only 1 [42] (8.3%), while allele–dose response was moderate in 4 [38,40,48,49] (33.3%) and low in 8 [39,41–47] (66.7%).

4. Discussion

Genetic variations are becoming increasingly recognised as an essential modifier of the impact of environmental exposures, including diet, on human physiology and physiopathology. Despite an increasing body of scholarly investigations on (poly)phenols and their dietary intake, still very little is known about the effects of SNPs on (poly)phenol bioavailability in the human body. The present systematic review has synthesised 12 articles that explored the impact of genetic variations on the ADME of dietary (poly)phenols. The inter-individual variability in the plasma circulating levels and in the urinary excretion of (poly)phenol metabolites was hypothesised to be influenced, at least partly, by SNPs in the genes encoding for influx and efflux transporters, and phase I and phase II metabolism enzymes.

Half of the studies investigated green tea flavan-3-ol ADME, using green tea, green tea extract, or pure EGCG as sources. Other studies explored the bioavailability and metabolism of flavanones, isoflavones, and lignans, present in orange juice, soy supplement, and ground brown flaxseed, respectively. Only one study analysed the impact of an unrestricted diet on the phenolic metabolome, and two other studies investigated the metabolism of flavan-3-ols and isoflavones deriving from a free diet, considering their specific gut microbial metabolites. These findings indicate that the investigation of the association between the variability in (poly)phenol ADME and genetic differences is limited and needs more research, focusing on other classes. Moreover, gallocatechins, flavanones, isoflavones, and lignans are not ubiquitous classes but characterize specific foods, being their intake in the daily diet restricted, suggesting that the sources considered in the present review are not so representative from a dietary point of view. Therefore, the study of (poly)phenol ADME and related SNPs should be widened by considering other classes, including flavan-3-ols of different origin from green tea, flavonols, and cinnamic acids, among others.

A total of 88 SNPs in 33 different genes were studied, a half of them related to xenobiotic metabolism and the remaining ones related to steroid hormone metabolism/activity and analysed in relation to phytoestrogens. In particular, two genes are involved in absorption (CBG/GBA and LCT), seven in phase I metabolism (PON1, CYP1A1, CYP1B1, CYP3A4, CYP3A5, CYP17A1, CYP19A1), four in phase II metabolism (COMT, UGT1A1, SULT1A1, SULT1C4) and four in excretion (ABCC2/MRP2, ABCG2/BCRP, ABCB1/PGP/MDR1, OATP1B1/SCLO1B1). Considering the genes analysed in the studies and their role in ADME process, phase I metabolism was the most representative phase (7 genes), followed by excretion (4 genes) and phase II metabolism (4 genes). This was unexpected as phase I

metabolism is a very limited pathway when it comes to (poly) phenol metabolism, driven mainly by microbial catabolism and phase II conjugations.[1–3] Going into detail, 6 genes coding for isoforms of cytochrome P450 were analysed in a single study[39] investigating the impact of SNPs on phytoestrogen levels after lignan consumption. Taking into account the number of times a gene was studied in all works, the most studied phase resulted to be phase II metabolism, followed by excretion and phase I metabolism. Absorption was the least represented and studied phase, with only two genes studied in one work. These results are consistent with the crucial role of conjugation in the metabolism of (poly)phenols.

Considering the metabolites that were influenced by genetic variability, many of them were phase II conjugates, including methylated forms of gallocatechins (4′-*O*-methyl-EGC), sulfated and glucuronidated forms of isoflavones (glycitein, genistein, and daidzein), and sulfated, glucuronidated, sulfo-glucuronidated, and diglucuronidated forms of flavanones (naringenin and hesperetin). Other metabolites included algycones of (gallo)catechins (EGCG, EGC, EC) and isoflavones (glycitein, genistein, and daidzein), phenolic acids (3′,4′-dihydroxycinnamic acid, 4′-hydroxyhippuric acid), and gut microbiota catabolites (5-(3′,4′-dihydroxyphenyl)-γ-valerolactone, 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone, 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-sulfate, 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-glucuronide, enterolactone, equol, 3′,4′-dihydroxyphenylacetic acid, benzene-1,3-diol).

A total of 16 SNPs in genes involved in (poly)phenol ADME showed a significant modifying effect on urinary and/or plasma levels of phenolic metabolites and/or on their kinetic parameters. Regarding phase II metabolism, COMT genetic variants were analysed mainly in relation to gallocatechins, UGT1A1 genetic variants were associated with isoflavone phase II metabolites, and SULT1A1/SULT1C4 were explored together with flavanone phase II metabolites. The most studied genetic variation was rs4680 in the COMT gene. Glucosidases involved in (poly)phenol absorption (GBA3 and LCT) were analysed only in relation to soy isoflavones, while influx/efflux transporters involved in (poly)phenol excretion were investigated with all sources of (poly)phenols, suggesting their importance in determining (poly)phenol bioavailability. Finally, genetic variations of *PON1* were analysed to determine their impact on the urinary levels of the two most important phenyl-gamma-valerolactone conjugates, used as biomarkers of flavan-3-ol intake. However, there was no consensus among studies allowing the association of a particular genetic variant with a reduction/increase of a specific metabolite in urine or plasma or with kinetic parameters.

The findings are conflicting and can only be partially reconciled by considering differences in methods and protocols. Most studies were conducted in controlled settings to minimize biases and confounders, but these do not always reflect real-world conditions, particularly in eating patterns. For example, Inoue-Choi *et al.*[42] captured the wide variability in green tea consumption, with urinary samples timed based on pharmacokinetic studies rather than laboratory schedules. Other studies in this review may lack ecological validity. Additionally, some had small sample sizes, lacked replication, and did not adjust for confounders like seasonal food intake. SNP variations by ethnicity suggest more diverse populations are needed, with systems genetics or GWAS approaches offering promise.

Our understanding of how genetic variations influence the metabolism of dietary (poly)phenols is limited due to the lack of studies and knowledge about the functional effects of relevant SNPs. Specifically, we still do not fully grasp the extent of phase II metabolism, both locally within enterocytes and systemically in the liver. Given the complexity of dietary exposure, reductionist approaches fail to capture its heterogeneity. New integrative methodologies, combining *in vivo* and *in vitro* studies, wet-lab and computational techniques, nutritional epidemiology, and mathematical modelling (pharmacokinetics/nutrikinetics), are needed.[77] These approaches can help uncover how specific genotypes affect the metabolism and health outcomes of ingested (poly)phenols, enabling personalized dietary recommendations.[78,79] Most studied polymorphisms have shown minimal impact on metabolism, and polygenic scores may help clarify ADME genotypes. Additionally, differences in gastrointestinal motility and gut microbiota likely contribute to variability in plasma concentrations and urinary excretion of (poly)phenols.

The present systematic review has several strengths, including (i) high methodological rigor, (ii) transparency and reproducibility, (iii) extensive, comprehensive literature search conducted on several databases enhanced by cross-referencing and target journal hand-search, a critical approach, quality appraisal, and (iv) complemented by bioinformatics analyses. On the other hand, it has a few shortcomings that should be properly acknowledged, including the relatively small number of studies included and the high degree of heterogeneity that hinders a meta-analysis. Additionally, exploring the connection between genetic variants and (poly)phenol bioavailability is difficult for several reasons: (i) the absence of validated and reliable biomarkers of intake for most classes of (poly) phenols, which makes it hard to identify key phenolic metabolites that explain how genetics contribute to the variability in their bioavailability; (ii) the presence of confounding factors, such as gut microbiota composition and activity, which can affect the variation in (poly)phenol ADME among individuals, especially when considering gut microbial metabolites; and (iii) the fact that personalized nutrition approaches with (poly) phenols should not only consider genetics but also incorporate other factors influencing variability like age, sex, gut microbiota, dietary habits, and more. In particular, the gut microbiota composition and activity in the main determinant of the heterogeneity in (poly)phenol colonic catabolism, acting as a possible confounder when analysing associations between SNPs and gut microbial metabolites.

The research in the field should be increased and improved in different ways: (i) considering (poly)phenol classes that are more representative of the population daily intake, such as flavan-3-ols, flavonols, anthocyanins and cinnamic acids; (ii) investigating less explored phases of the metabolism (absorp-

tion, distribution, excretion); (iii) increasing the sample size and exploring more diverse populations from a genetic point of view (ethnicity); (iv) considering confounding factors (sex, age, smoking, alcohol, drugs, habitual diet) and acknowledging the factors that could contribute to the inter-individual variability in (poly)phenol bioavailability (gut microbiome, lifestyle, pathophysiological status), potentially hiding associations between ADME and SNPs; (v) highlighting possible limitations that could hinder the analysis, including the lack of reliable and validated biomarkers of (poly)phenol intake for most classes; (vi) analysing more genes and SNPs in relation to a specific (poly)phenol class, also implementing untargeted approaches such as GWAS and new methodologies such as systems genetics and polygenic risk scores.

5. Conclusions

To the best of our knowledge, this is the first comprehensive investigation of the genetic factors explaining inter-individual variability in the bioavailability and metabolism of dietary (poly)phenols by conducting a systematic literature review. However, a consensus was not reached among studies allowing the association of a particular genetic variant with a change in (poly)phenol bioavailability and metabolism. Overall, the present systematic review can pave the way for further investigations that leverage bioinformatics analysis and GWAS-based approaches.

Author contributions

The conceptualization and methodology were set up by Nicole Tosi, Nicola L. Bragazzi and Pedro Mena. Investigation, formal analysis and data curation were performed by Nicole Tosi and Nicola L. Bragazzi. Cristiana Mignogna and Mirko Treccani also contributed to formal analysis. Pedro Mena and Daniele del Rio were in charge of funding acquisition, and Pedro Mena was also responsible for supervision. The first draft of the manuscript was written by Nicole Tosi and Nicola L. Bragazzi, and all authors contributed to review and editing.

Conflicts of interest

No potential conflict of interest was reported by the authors.

Data availability

This article is a review and does not include new experimental data. All data cited and discussed in the manuscript are derived from previously published studies, which are appropriately referenced throughout the text. No new datasets were generated or analyzed during the preparation of this work.

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