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Food as a Therapeutic Agent, Antagonist, and Enabler of Pharmacotherapy: A Clinical and Mechanistic Review

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ABSTRACT: Food intake is usually addressed in pharmacotherapy as a dosing condition or a source of food–drug interactions, yet this view treats food largely as a passive background exposure. To address the separation between therapeutic nutrition and food–drug interaction management, this narrative review proposes a clinically applicable role-based framework that classifies food as a therapeutic agent, an antagonist of pharmacotherapy, or an enabler of treatment according to the dietary exposure, drug and formulation, disease state, timing, and clinical intent. In this framework, food may function as a therapeutic agent, an antagonist of pharmacotherapy, or an enabler of treatment, depending not on the food itself but on the clinical context in which it is consumed. Therapeutic roles include dietary patterns, medically tailored meals, nutrients, and food-derived bioactive compounds that support disease control, symptom relief, nutritional rehabilitation, or treatment responsiveness. Antagonistic roles occur when food reduces efficacy, increases toxicity, or destabilizes response through altered absorption, metabolism, transport, pharmacodynamics, adherence, or food-access constraints. Enabling roles occur when meal timing, composition, or nutritional support increases or stabilizes drug exposure (exposure enablement), reduces gastrointestinal or other treatment-related adverse effects (tolerability enablement), or improves adherence and dosing feasibility (adherence/feasibility enablement). Mechanisms include gastrointestinal physiology, formulation behavior, enzyme and transporter activity, nutrient–drug pharmacodynamics, microbiome effects, and artificial nutrition. Applying this framework requires structured dietary assessment, explicit prescribing instructions, diet-sensitive medication review, and interprofessional care. By classifying food roles conditionally rather than assigning fixed properties to foods, this framework can support more precise prescribing, safer food–drug management, food/formulation design, and patient-centered care.

Keywords: Food-drug interactions; food effect; pharmacotherapy; therapeutic nutrition; pharmacokinetics; medication adherence

1. Introduction

Food intake exerts reproducible and often clinically important effects on the pharmacokinetics and pharmacodynamics of many orally administered drugs, influencing absorption, bioavailability, exposure variability, therapeutic response, and toxicity risk^[1]. These effects arise from food-induced changes in gastrointestinal physiology, luminal composition, gastric emptying, bile secretion, and splanchnic blood flow,

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as well as from direct interactions between nutrients or bioactive dietary constituents and drug-metabolizing enzymes or transporters^[2]. Despite decades of work on food effects in biopharmaceutics and physiologically based pharmacokinetic modeling, these phenomena are often treated as technical considerations for drug development, product labeling, or dosing instructions rather than as integral determinants of therapeutic strategy in routine clinical care^[3].

In parallel, two largely separate bodies of literature and practice have developed. One centers on “food as medicine” and therapeutic nutrition, emphasizing dietary patterns, medically tailored meals, and functional foods as disease-modifying interventions^[4]. The other focuses on food-drug interactions as safety or efficacy concerns, emphasizing discrete pharmacokinetic or pharmacodynamic interactions that should be avoided, separated, monitored, or managed^[5]. This division creates a conceptual and clinical gap: food is often framed either as a therapeutic intervention or as a source of interaction risk, rather than as a context-dependent component of pharmacotherapy itself. It also obscures an important clinical principle: the same food exposure may function as a therapeutic agent, an antagonist of pharmacotherapy, or an enabler of drug action, depending on the drug, disease state, patient context, timing, and care setting^[6]. A unified framework is therefore needed to integrate diet and pharmacotherapy across clinical care, research, and regulatory decision-making.

In this review, we propose a mechanistic and clinically applicable framework that uses this separation between therapeutic nutrition and food-drug interaction management as its organizing rationale. The framework classifies food as a therapeutic agent, a pharmacotherapeutic antagonist, or a pharmacotherapeutic enabler. We use this framework to organize representative clinical and mechanistic evidence across these roles, including areas where roles overlap or change over time. For the purposes of this review, “food” includes composite meals, dietary patterns, macronutrients, micronutrients, and defined bioactive dietary constituents. Supplements, botanical or mineral products, and enteral or parenteral nutrition are considered related nutrition exposures rather than foods per se; collectively, these are referred to as “food and nutrition exposures” where appropriate. “Pharmacotherapy” includes systemic and locally acting medicinal products administered in outpatient, inpatient, and long-term care settings. We focus primarily on oral and enteral therapies in adult and pediatric populations, with emphasis on therapeutic areas where food-pharmacotherapy interplay is clinically consequential, including cardiometabolic disease, oncology, infectious diseases, gastrointestinal disorders, and conditions requiring artificial or medically tailored nutrition.

2. Literature search and narrative scope

This narrative review synthesizes clinical, pharmacokinetic, mechanistic, regulatory, and implementation evidence on how food influences pharmacotherapy. The review supports a role-based framework in which food may function as a therapeutic agent, an antagonist of pharmacotherapy, or an enabler of drug action, depending on mechanism, timing, formulation, disease context, patient characteristics, and clinical intent.

A structured literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar from database inception to August 2026. Additional sources included Food and Drug

Administration (FDA) and European Medicines Agency (EMA) regulatory reports, prescribing information, clinical pharmacology documents, professional guidelines, and reference lists of relevant reviews and primary studies. Search terms were combined using Boolean operators and included “food-drug interaction,” “drug-food interaction,” “food effect,” “oral drug absorption,” “bioavailability,” “pharmacokinetics,” “pharmacodynamics,” “drug metabolism,” “drug transporters,” “CYP3A,” “P-glycoprotein,” “OATP,” “gut microbiome,” “therapeutic nutrition,” “food as medicine,” “medically tailored meals,” “dietary intervention,” “meal timing,” “enteral nutrition,” “parenteral nutrition,” “medication adherence,” and “precision nutrition.”

Sources were selected when they addressed dietary interventions used for disease management; food or nutrient effects on drug absorption, metabolism, transport, exposure, efficacy, or toxicity; meal-linked dosing or nutritional support used to improve drug exposure, tolerability, adherence, or feasibility; or clinical, regulatory, and interprofessional strategies for managing food-pharmacotherapy relationships. Priority was given to human studies, regulatory labeling, controlled pharmacokinetic or pharmacodynamic studies, randomized trials, systematic reviews, and meta-analyses. Mechanistic, *in vitro*, animal, microbiome, omics, and computational studies were included when they clarified biological plausibility or emerging research directions.

The review mainly examines oral and enteral pharmacotherapy, where composition of meals, gastrointestinal physiology, luminal solubility, enzyme and transporter activity, gut microbiota and artificial nutrition have the most direct impact on drug performance. Most references were published from 2016 onward. Older studies were included only when foundational. Current recommendations were supported by recent reviews, regulatory documents, prescribing information, or contemporary clinical studies.

3. Conceptual and classification framework

3.1 Primary role definitions

Food may function as a therapeutic agent when whole diets, specific foods, or isolated food-derived constituents produce clinically meaningful effects on disease risk, disease progression, symptom control, or treatment-related vulnerability, either independently of pharmacologic therapy or in synergy with it^[7]. This role includes disease-targeted dietary patterns and medically tailored meals used as structured interventions, as well as bioactive compounds such as flavonoids and other phytochemicals that have been characterized mechanistically and investigated as therapeutic or adjunctive candidates^[5,8]. In this context, food is not treated as passive background exposure but as a modifiable treatment modality with potentially definable dose-response relationships, mechanisms of action, and measurable clinical endpoints^[5].

By contrast, food acts as an antagonist of pharmacotherapy when its consumption reduces drug efficacy, increases toxicity risk, or destabilizes drug exposure or response through pharmacokinetic, pharmacodynamic, or behavioral mechanisms. Canonical examples include nutrient or food-matrix effects that impair absorption or bioavailability, modulation of drug-metabolizing enzymes or transporters by specific dietary components, and nutrient-drug opposition at shared molecular or physiological targets, such as vitamin K counteracting vitamin K antagonist anticoagulants^[9]. Antagonism may also arise indirectly when dietary prescriptions,

irregular meal patterns, food insecurity, or culturally patterned eating behaviors undermine medication adherence or promote physiological states that oppose the intended pharmacologic effect^[6,9].

In a third role, food can function as an enabler of pharmacotherapy by improving the performance, feasibility, or tolerability of a drug regimen. For conceptual and clinical clarity, this role can be subdivided into three mechanistically distinct forms: exposure enablement, tolerability enablement, and adherence/feasibility enablement. Exposure enablement occurs when food intentionally increases or stabilizes systemic or local drug exposure, including increased bioavailability or reduced exposure variability^[1]. Tolerability enablement occurs when food reduces gastrointestinal or other treatment-related adverse effects without necessarily increasing drug exposure, whereas adherence/feasibility enablement occurs when meal-linked administration, dietary support, or reliable food access facilitates consistent and sustainable medication use^[5]. These subcategories may coexist within the same regimen but should be distinguished according to the primary mechanism and clinical objective. Many orally administered agents exhibit clinically important food effects whereby co-administration with meals increases bioavailability or stabilizes pharmacokinetic profiles, and some are explicitly labeled for administration with food to achieve adequate or consistent exposure^[10]. In addition, the use of meals to mitigate gastrointestinal or other adverse effects may foster adherence to the therapy, making food intake an operational component of safe and effective pharmacologic treatment, rather than a neutral backdrop^[5]. The proposed role-based classification of food exposure in pharmacotherapy is illustrated in Fig. 1.

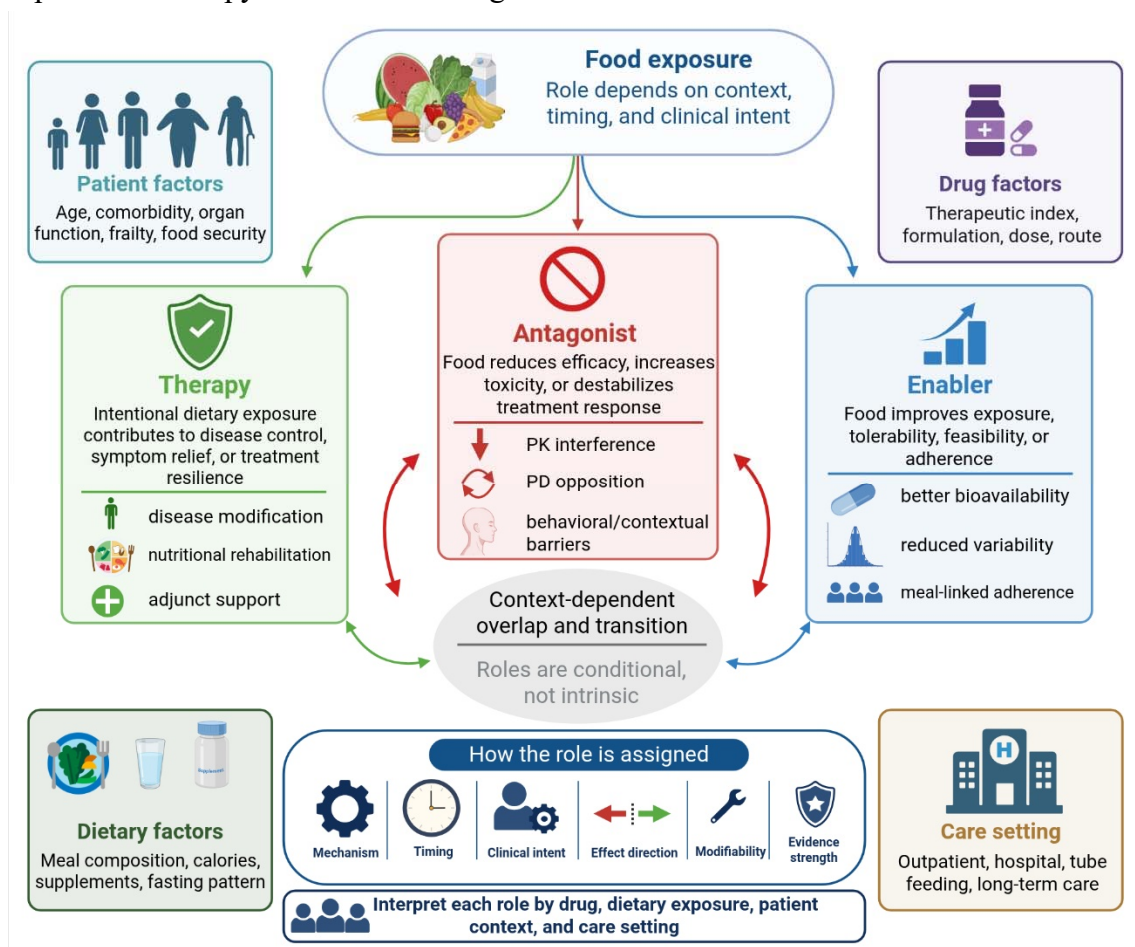


Fig. 1. Role-based framework for food exposure in pharmacotherapy.

3.2 Classification dimensions

Food–pharmacotherapy relationships can be classified along three complementary dimensions: mechanism, time scale, and clinical actionability/evidence (Box 1). The mechanistic dimension distinguishes whether food modifies drug response through pharmacokinetic, pharmacodynamic, or behavioral/contextual pathways. Pharmacokinetic effects influence the rate, extent, or consistency of systemic exposure after oral or enteral administration by altering processes such as dissolution, solubility, gastrointestinal transit, enzymatic metabolism, or transporter-mediated flux^[1]. Pharmacodynamic effects occur when nutrients, foods, or dietary constituents act on shared targets, signaling pathways, or physiological endpoints, whereas behavioral and contextual effects capture real-world factors such as adherence, meal timing, food access, and cultural eating patterns that may alter treatment effectiveness outside controlled pharmacology settings^[9,11]. The temporal dimension separates acute meal-related effects from longer-term dietary or nutritional-state effects^[10]. Acute effects are typically captured in fasted/fed crossover studies and physiologically based pharmacokinetic simulations, whereas chronic dietary exposures may influence enzyme and transporter expression, gut microbiota composition, body composition, cardiometabolic status, and baseline pharmacokinetic or pharmacodynamic behavior in ways that short-term studies may miss^[7,12]. The clinical actionability/evidence dimension determines whether a food–pharmacotherapy relationship should lead to counseling, dose separation, meal standardization, monitoring, dietary support, formulation adjustment, or intentional use of food to improve treatment performance^[6]. In the accompanying tables, evidence labels describe the primary evidence basis for each example rather than a formal risk-of-bias assessment or certainty rating. Together, these dimensions provide a structured basis for deciding whether food functions as a therapeutic agent, antagonist, or enabler in a defined pharmacotherapeutic context.

Box 1. Three-axis framework for classifying food–pharmacotherapy relationships.

Classification axis	Key question	Practical use
Mechanism	How does food modify drug response?	Identify whether the relationship is mainly pharmacokinetic, pharmacodynamic, behavioral/contextual, or mixed.
Time scale	Is the effect acute or chronic?	Distinguish single-meal or short-term effects from longer-term effects of habitual diet, nutritional status, microbiome changes, or disease-state modification.
Clinical actionability/evidence	Should this change clinical management?	Evaluate magnitude, direction, modifiability, and evidence strength to decide whether to avoid, separate, standardize, monitor, counsel, or intentionally use the food exposure.

3.3 Role overlaps, transitions, and conflicts

Food exposures rarely occupy a single, static role in relation to pharmacotherapy. The same food, meal pattern, or dietary intervention may shift between therapeutic, antagonistic, and enabling functions as the disease state, drug regimen, patient context, and time horizon change^[6,7]. For operational classification, the primary role should reflect the dominant clinically actionable consequence in the specific drug–patient–timing context: therapy when food is used to modify disease or symptoms, antagonist when it reduces efficacy or increases risk, and enabler when it improves drug exposure, tolerability, or treatment feasibility. When roles overlap, the role most relevant to immediate clinical management should be primary, with safety risks taking precedence. For example, a diet rich in green leafy vegetables and other vitamin K-containing foods may

support cardiometabolic health and overall dietary quality, but in patients treated with vitamin K antagonist anticoagulants, unstable vitamin K intake can antagonize drug effect and destabilize anticoagulation control unless intake is consistent and dosing is appropriately adjusted^[9]. Similarly, grapefruit and other furanocoumarin-containing foods may be consumed as part of an otherwise healthful dietary pattern, but in patients receiving susceptible CYP3A-substrate drugs they can inhibit intestinal CYP3A and transporter pathways, producing unsafe or unpredictable increases in systemic exposure and toxicity risk rather than clinically controlled pharmacotherapeutic enablement^[6,9]. This distinction is important because increased exposure alone does not define food as an enabler; the effect should be intentional, predictable, clinically useful, and incorporated into dosing instructions. Medically tailored, energy-dense meals illustrate another form of role transition: they may function as therapy for malnutrition or frailty and may also enable oral regimens that require co-administration with food, but they may conflict with weight-loss or glycemic-control objectives if energy content, timing, and macronutrient composition are not aligned with pharmacologic goals^[5].

Role conflicts can also arise when a dietary pattern supports one therapeutic objective while undermining another, or when it facilitates the safe use of one drug while complicating the management of another within the same patient^[6,7]. Meals with higher fat content, for instance, can enhance the bioavailability and reduce exposure variability of selected lipophilic oral anticancer, antiviral, or psychotropic drugs that are labeled for administration with food, thereby enabling more reliable pharmacokinetics. However, repeated reliance on energy-dense or high-fat meals may conflict with cardiometabolic treatment goals in patients with obesity, dyslipidemia, insulin resistance, or cardiovascular disease^[1]. Likewise, strict therapeutic diets, such as very low-sodium regimens or highly restrictive elimination diets, may be beneficial as food-based therapy for selected conditions but can reduce appetite, meal regularity, social acceptability, or enjoyment of eating. These effects may indirectly undermine adherence to multi-dose oral regimens and create behavioral antagonism^[5]. Recognizing these overlaps, transitions, and conflicts is essential for applying a role-based framework in practice. It requires clinicians and researchers to evaluate food-pharmacotherapy relationships at the level of the whole patient, including the relevant drug, dietary exposure, disease target, feasibility of implementation, and competing treatment goals, rather than treating individual foods or drugs in isolation^[6,9].

4. Food as therapeutic agent

4.1 Evidence for diet as primary or co-primary therapy

Dietary interventions can function as primary or co-primary therapies in cardiometabolic, gastrointestinal, hepatic, and renal disorders, particularly when they influence pharmacologic management. Guideline-endorsed dietary patterns, including Mediterranean, DASH, and structured low-fat diets, improve blood pressure, lipid profiles, and glycemic control, which can reduce the need for antihypertensives, lipid-lowering agents, or glucose-lowering medications in high-risk populations. Structured dietary programs with behavioral support have been shown to modify disease trajectory and reduce all-cause mortality and non-fatal myocardial infarction, highlighting their direct interaction with pharmacotherapy planning^[13-15].

In gastrointestinal, hepatic, and renal disease, diet can modulate symptom burden and treatment tolerability, thereby affecting drug choice, dosing, or safety. Examples include low-FODMAP diets in irritable bowel syndrome, selective elimination diets in inflammatory bowel disease, protein and electrolyte modifications in chronic kidney disease, and structured dietary approaches in non-alcoholic fatty liver disease. These interventions may influence the use of diuretics, renin-angiotensin-aldosterone system blockers, or glucose-lowering agents, and are most effective when delivered through individualized medical nutrition therapy and dietitian-led programs^[14,16,17].

In patients with malnutrition and sarcopenia, particularly older adults and those with chronic organ disease, nutritional therapy is often required before pharmacotherapy can be safely and effectively administered. Energy- and protein-dense diets, oral nutritional supplements, and targeted micronutrient repletion improve lean mass, functional status, and physiological reserve, thereby influencing eligibility for and response to treatments such as chemotherapy, heart-failure therapies, antihypertensives, and anticoagulants. In these cases, diet shapes the biological context in which drugs act, functioning as a planned clinical intervention rather than a general lifestyle measure^[16,18].

4.2 Medically tailored nutrition interventions

The concept of food as therapy is implemented in clinical practice through the careful alignment of meals, food prescriptions, and dietary counseling with each patient's diagnoses, biomarkers, treatment objectives, and pharmacotherapy plan^[19,20]. Medically tailored meals are usually pre-prepared, condition-specific meals prescribed or recommended within healthcare settings and planned by registered dietitians for patients with conditions such as heart failure, diabetes, chronic kidney disease, cirrhosis, and cancer^[21,22]. Related food prescription programs provide vouchers, subsidies, or directed access to healthier foods, such as fruits, vegetables, and whole grains, often through clinical or community partnerships^[19,23]. Across these models, structured counseling is essential because it adapts the intervention to cultural food practices, household resources, meal timing, and concomitant medication requirements^[20].

Clinical evidence suggests that medically tailored nutrition interventions may improve disease control, nutritional status, and selected healthcare outcomes, although effects vary by population, intervention design, and endpoint^[19,21]. In recently hospitalized adults with heart failure, diabetes, or chronic kidney disease, a 10-week medically tailored meal program did not significantly reduce all-cause rehospitalization at 90 days, but exploratory analyses suggested possible reductions in mortality and heart failure-related hospitalizations^[21]. In cirrhosis with hepatic encephalopathy, high-protein medically tailored meals have shown feasibility and potential benefits for protein intake, physical function, and quality of life, supporting their use in nutritionally vulnerable patients whose clinical stability affects drug tolerance and treatment continuity^[22]. Ongoing and planned trials in type 2 diabetes and food insecurity are evaluating whether medically tailored meals plus nutrition therapy improve glycemic control, food security, patient-reported outcomes, medication intensification or de-escalation, and healthcare costs^[19,20,23]. Thus, medically tailored nutrition should be framed not only as supportive care but as a structured intervention that can modify the clinical conditions under which pharmacotherapy is initiated, adjusted, or maintained.

4.3 Food-derived bioactive compounds

Food-derived bioactive compounds, beyond their conventional nutritional roles, exert pharmacologically relevant effects by regulating receptors, enzymes, transporters, oxidative stress pathways, inflammatory signaling, gut barrier integrity, microbiota composition, and immune responses^[24,25]. Functional foods enriched with bioactives and isolated compounds such as polyphenols, carotenoids, phytochemicals, and bioactive peptides have demonstrated enzyme-inhibitory, receptor-modulating, antioxidant, anti-inflammatory, antihypertensive, anti-hyperuricemic, and skeletal or metabolic effects in preclinical studies and selected early clinical investigations^[26-28]. Recent systematic reviews further highlight that fermented foods, probiotics, and co-assembled plant compounds significantly modulate gut microbiota and systemic metabolic pathways^[28,29]. Food-derived bioactive peptides have received particular attention, as several are linked to defined molecular targets, including angiotensin-converting enzyme, xanthine oxidase, and pathways involved in bone and cardiometabolic regulation^[25,26,30]. However, most bioactive compounds should be interpreted as therapeutic adjuncts rather than substitutes for approved pharmacotherapy unless supported by standardized dosing, adequate bioavailability, target engagement, and controlled human outcome data^[24,31,32].

A central consideration is whether the observed effect occurs at a nutrient-level exposure achievable through habitual diet or at a pharmacologic-level exposure, which requires concentrated ingredients, specialized formulations, or supplement-like dosing^[25,33]. Nutrient-level exposure, typically derived from whole foods, produces modest, cumulative effects, whereas functional-food or supplement-like exposures enable higher, targeted doses and enhanced bioavailability, supporting more robust modulation of physiological pathways^[28,34,35]. While nutrient-level effects are generally subtle and embedded within broader dietary patterns, pharmacologic-level effects require reproducible dose-response relationships, in vivo target engagement, clinically relevant biomarker or endpoint changes, and evidence from controlled human studies^[25,26,30].

Regulatory context is therefore important. Compounds delivered within foods or supplements are often evaluated under nutrition or structure-function frameworks, whereas those producing drug-like effects may require medicinal product evaluation, particularly when they can interact with concomitant drugs through shared pharmacokinetic or pharmacodynamic pathways^[25,33]. Within this framework, food-derived bioactives are best viewed as food-based therapeutic candidates, with clinical relevance dependent on dose, formulation, evidence strength, and interaction potential. Accordingly, evidence for isolated food-derived bioactive compounds is generally less clinically mature than evidence for structured dietary interventions unless supported by standardized dosing, human exposure data, target engagement, and controlled clinical outcomes. Emerging studies also emphasize that bioavailability can be enhanced through nano-encapsulation, co-delivery strategies, and optimized functional-food matrices, improving the potential for clinical translation^[28,35,36].

4.4 Interaction with pharmacotherapy

Therapeutic diets can influence drug selection, dosing, monitoring, and decisions to escalate or de-escalate pharmacotherapy over time^[14,15]. In anticoagulation, variation in vitamin K intake from vegetable-rich diets is a recognized determinant of warfarin dose requirements and international normalized ratio (INR) stability. Therefore, the choice between warfarin and direct oral anticoagulants, as well as warfarin dose adjustment, should account for the patient's usual dietary pattern and its expected stability^[9]. In obesity and type 2 diabetes, intensive energy-restricted diets and bariatric surgery-linked dietary interventions can produce substantial weight loss, improve cardiometabolic risk factors, and alter hepatic or intestinal drug-metabolizing enzyme activity, including pathways such as CYP3A and CYP2C19^[16,37]. As blood pressure, glycemia, and lipid profiles improve, the need for antihypertensive, glucose-lowering, or lipid-lowering therapy may decrease, whereas incomplete dietary response may prompt pharmacologic intensification^[14,15]. Representative examples are summarized in Table 1, highlighting food-based interventions with direct implications for medication reduction, treatment substitution, and monitoring, while distinguishing randomized trial-supported interventions from observational or hypothesis-generating evidence.

Table 1. Representative examples of food as therapy and pharmacotherapy implications

Condition	Therapeutic food / diet	Role	Main mechanism	Key clinical evidence and effect	Pharmacotherapy implication	Evidence	Reference
Type 2 diabetes	Total diet replacement, food reintroduction, and weight-maintenance support	Therapy	Negative energy balance; major weight loss; reduced liver/pancreatic fat; restored glycemic control	Cluster-randomized primary-care trial in adults with type 2 diabetes ≤ 6 years, BMI 27 to 45 kg/m ² , not using insulin. Intervention used drug withdrawal, 825 to 853 kcal/day formula diet for 3 to 5 months, food reintroduction, and maintenance support. At 12 months, remission was 46% vs 4%; weight loss ≥ 15 kg was 24% vs 0%.	Requires proactive deprescribing and monitoring of glucose-lowering and antihypertensive drugs during rapid metabolic improvement.	B	[38]
Type 2 diabetes	Pharmacist-led low-carbohydrate, energy-restricted diet	Therapy + medication enabler	Lower glycemic load; energy deficit; weight loss; reduced insulin demand; improved cardiometabolic risk	Pragmatic randomized trial in 12 community pharmacies; 188 adults randomized to Pharm-TCR or usual care. Diet was < 50 g carbohydrate/day and about 850 to 1100 kcal/day for 12 weeks. 35.7% discontinued all glucose-lowering drugs vs 0%; HbA1c fell by 1.4 percentage points, weight by 12.0 kg, and systolic BP by 13 mmHg.	Supports active medication de-intensification, especially insulin and secretagogues; hypoglycemia risk increases if drugs are not reduced promptly.	B	[39]
Type 2 diabetes	Monthly fasting-mimicking diet program	Therapy + medication enabler	Periodic energy restriction; reduced glucose, insulin, and IGF-1 signaling; improved metabolic flexibility; weight loss	Randomized, assessor-blinded trial in 100 adults with type 2 diabetes using metformin only and/or diet. Five-day fasting-mimicking cycles monthly for 12 months vs usual care. Medication effect score improved by -0.3 ; HbA1c by -0.3 percentage points; weight by -3.6 kg; glycemic management improved in 53% vs 8%.	May reduce glucose-lowering medication burden while maintaining or improving glycemia in selected patients with earlier-stage disease.	B	[40]
Type 2 diabetes	Whole-food, plant-based intensive lifestyle intervention with moderate exercise	Therapy + medication enabler	Improved insulin sensitivity; lower energy density; higher fiber; reduced inflammatory burden; weight loss	Randomized trial in 169 adults with type 2 diabetes in the Marshall Islands; plant-based diet plus exercise vs standard care for 24 weeks. Additional HbA1c reduction was -1.3 percentage points at 12 weeks and -0.7 at 24 weeks. 63% reduced glucose-lowering drugs vs 24%; 23% of selected participants achieved remission.	Supports review and down-titration of diabetes and cardiovascular medications during intensive dietary-lifestyle therapy.	B	[41]

Irritable bowel syndrome	FODMAP-lowering diet through a smartphone app	Therapy	Reduced fermentable carbohydrate intake; less fermentation, gas, and symptom-triggering distension Exclusion of components linked to dysbiosis, barrier dysfunction, and inflammation; partial enteral nutrition supports intake	Pragmatic randomized primary-care trial in 459 IBS patients; diet app vs otilonium bromide 40 mg three times daily for 8 weeks. Responder rate was 71% vs 61%; in Rome IV-positive patients, 77% vs 62%. Adherence was 94% vs 73%.	Dietary strategy can serve as a first-line alternative to spasmolytics in primary-care IBS, with drugs reserved for nonresponders or adjunctive use.	B	[42]
Pediatric Crohn's disease	Crohn's Disease Exclusion Diet plus partial enteral nutrition	Therapy, microbiome/barrier-directed		Randomized pediatric trial of CEDED plus PEN vs exclusive enteral nutrition in mild-to-moderate Crohn's disease over 12 weeks. Tolerance was 97.5% vs 73.6%. Corticosteroid-free sustained remission at week 12 was 75.6% vs 45.1%, with lower CRP, fecal calprotectin, and fecal Proteobacteria.	Supports dietary therapy as an induction strategy that may reduce reliance on corticosteroids in selected pediatric patients.	B	[43]
Drug-resistant epilepsy in infants	Classic ketogenic diet	Therapy	Ketone-based brain fuel; altered neuronal excitability and seizure threshold	Phase 4 multicenter randomized trial in 136 infants aged 1 to 24 months with drug-resistant epilepsy after ≥ 2 antiseizure medicines. Ketogenic diet vs further antiseizure medication. Median seizures/day during weeks 6 to 8 were 5 vs 3; IRR 1.33, 95% CI 0.84 to 2.11. Efficacy and tolerability did not differ significantly.	May be considered in specialist care as a therapeutic option for selected infants, but this trial did not show superiority over further antiseizure medication.	B	[44]
Hyperlipidemia	Dietary portfolio: plant sterols, soy protein, viscous fiber, and nuts	Therapy	Reduced cholesterol absorption; increased bile acid loss; improved lipid metabolism; synergistic LDL-lowering	Multicenter randomized trial in 351 adults with hyperlipidemia; dietary portfolio with routine or intensive counseling vs low-saturated-fat control diet for 6 months. LDL-C fell by -13.8% with intensive portfolio, -13.1% with routine portfolio, and -3.0% with control.	Supports food-based LDL reduction as an adjunct or earlier step before escalation of lipid-lowering pharmacotherapy in suitable patients.	B	[45]
CKD-related metabolic acidosis	Base-producing fruits and vegetables	Therapy / pharmacologic alternative	Lower dietary acid load; improved bicarbonate balance; favorable kidney and cardiovascular effects	Randomized trial in 108 patients with macroalbuminuric nondiabetic CKD and metabolic acidosis; fruits and vegetables vs sodium bicarbonate vs usual care for 5 years. Plasma total CO_2 improved with fruits/vegetables and bicarbonate. Five-year eGFR decline was lower with fruits/vegetables, $-10.0 \text{ mL/min/1.73 m}^2$, and bicarbonate, -12.3 , than usual care, -18.8 . Fruits/vegetables also improved systolic	Food can function as a therapeutic alternative or complement to alkali pharmacotherapy, with potentially broader cardiometabolic benefit.	B	[46]

Major depressive disorder	Mediterranean-style structured dietary improvement program	Adjunctive therapy	Improved diet quality may affect inflammation, oxidative stress, gut-brain pathways, and neuroplasticity	BP and cardiovascular risk indicators more than bicarbonate. Single-blind randomized trial in 67 adults with moderate-to-severe depression; seven dietitian sessions vs social support for 12 weeks. Most participants were receiving psychotherapy and/or pharmacotherapy. MADRS improved more with diet; Cohen's $d = -1.16$. Remission was 32.3% vs 8.0%; NNT 4.1.	Supports diet as an adjunct to antidepressant and psychotherapeutic care, not as a replacement for indicated psychiatric treatment.	B	[47]
High-risk non-muscle-invasive bladder cancer receiving BCG	Higher leafy green vegetable intake and higher zinc/magnesium intake	Hypothesis-generating supportive therapy	Possible immune, inflammatory, and treatment-microenvironment modulation	Prospective exploratory cohort in patients receiving BCG; 46 enrolled and 41 evaluable for recurrence. Nominal inverse associations with 1-year recurrence were observed for leafy greens, zinc, and magnesium, but none remained significant after false-discovery-rate correction.	No current basis for changing BCG or oncologic therapy. Best interpreted as a research hypothesis for nutrition-immunotherapy interactions.	C	[48]

Evidence: A, regulatory labeling or controlled human PK/PD evidence; B, randomized trial, systematic review, meta-analysis, or major guideline; C, observational clinical evidence; D, case report, pharmacovigilance, or expert opinion; E, preclinical, in vitro, animal, microbiome, omics, or computational evidence.

Abbreviations: BCG, Bacillus Calmette–Guérin; BMI, Body Mass Index; BP, Blood Pressure; CDED, Crohn's Disease Exclusion Diet; CI, Confidence Interval; CKD, Chronic Kidney Disease; CRP, C-Reactive Protein; FODMAP, Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols; IBS, Irritable Bowel Syndrome; IGF, Insulin-like Growth Factor; IRR, Incidence Rate Ratio; IV, Intravenous; LDL, Low-Density Lipoprotein; MADRS, Montgomery–Åsberg Depression Rating Scale; NNT, Number Needed to Treat; PEN, Partial Enteral Nutrition; Pharm-TCR, Pharmacist-led Therapeutic Carbohydrate Restriction.

Food-as-therapy can also modify the benefit-risk profile of concurrent medications by changing body composition, organ function, comorbidity burden, and susceptibility to adverse effects^[16,49]. Nutritional rehabilitation in malnourished or sarcopenic patients may improve physiological reserve, albumin status, hepatic and renal function, and hemodynamic stability, thereby improving tolerance to chemotherapy, heart-failure therapies, anticoagulants, or antihypertensives^[16,49]. Conversely, therapeutic diets that restrict sodium, fluid, potassium, protein, or specific macronutrients may enhance the intended effects of diuretics, renin-angiotensin-aldosterone system inhibitors, or glucose-lowering drugs, but may also increase the risk of hypotension, electrolyte disturbances, renal impairment, or hypoglycemia^[14,16]. In chronic liver disease, high-protein medically tailored diets used to treat sarcopenia and reduce hepatic encephalopathy risk may improve function and resilience, while also influencing diuretic, lactulose, and rifaximin regimens through effects on nitrogen balance, volume status, bowel function, and gut microbiota^[16,22]. These bidirectional effects require drug choice, dose adjustment, and monitoring plans to be calibrated to the patient's nutritional treatment plan rather than managing pharmacotherapy and nutritional intervention as separate therapeutic domains.

5. Food as antagonist of pharmacotherapy

5.1 Pharmacokinetic antagonism

5.1.1 Absorption and bioavailability

Food can antagonize oral pharmacotherapy by altering the gastrointestinal conditions that determine drug dissolution and absorption, particularly gastric pH, gastric emptying, luminal binding, and bile-mediated solubilization^[1,2]. In the fed state, gastric pH rises and becomes more variable, which can reduce dissolution of weakly basic drugs or increase degradation of acid-labile compounds, leading to delayed or reduced absorption unless the formulation or dosing strategy compensates for these changes^[1,50]. Experimental and modeling studies show that meal-related or acid-reducing changes in gastric pH can alter dissolution-precipitation behavior, especially for poorly soluble drugs in biopharmaceutics classes II and IV^[1,50,51]. Food-induced slowing of gastric emptying may also delay absorption or prolong exposure to unfavorable gastric conditions, although the direction and magnitude of this effect depend on the drug, formulation, and absorption window^[1,52]. Meal composition further modifies absorption through chelation, sequestration, and changes in luminal solubilization^[1,53]. Divalent and trivalent cations in dairy products, supplements, and fortified foods can bind tetracyclines, fluoroquinolones, and levothyroxine, forming poorly soluble complexes that reduce systemic exposure despite correct medication intake^[1,9]. Viscous fibers and some food matrices may sequester drugs or slow diffusion toward the absorptive surface, reducing apparent permeability and flattening exposure profiles^[2]. Although bile secretion and lipid incorporation into mixed micelles can enhance absorption of some poorly water-soluble lipophilic drugs, the same fed-state processes may antagonize other drugs by shifting the site or timing of dissolution, promoting precipitation, or increasing

variability^[1,53]. Thus, ordinary meals can reduce the fraction of an oral dose that reaches systemic circulation in a timely and predictable manner, making absorption and bioavailability central mechanisms of food-mediated pharmacokinetic antagonism^[1,2].

5.1.2 Metabolic modulation

Dietary components can antagonize pharmacotherapy by inducing or inhibiting hepatic and intestinal drug-metabolizing enzymes, thereby altering systemic exposure, clearance, or bioactivation of co-administered drugs at fixed doses^[6,9]. Plant-derived constituents, including flavonoids, terpenes, and other non-nutrient phytochemicals, have been shown mainly in vitro and in animal models to modulate cytochrome P450 enzymes and phase II conjugating pathways through direct enzyme inhibition or activation of xenobiotic-sensing nuclear receptors such as pregnane X receptor (PXR) and aryl hydrocarbon receptor (AhR)^[54]. For example, quercetin and related polyphenols can alter the expression or activity of CYP isoforms and other biotransformation pathways in experimental models, suggesting that high supplemental or concentrated intakes may affect the clearance of susceptible drugs^[54]. Essential oil constituents, including β -caryophyllene, β -caryophyllene oxide, and α -humulene, have also demonstrated inhibitory effects on major human and rat drug-metabolizing enzymes in vitro, supporting a plausible interaction risk when such compounds are consumed in concentrated forms^[55]. Some ethnobotanical preparations used as dietary supplements may produce more complex patterns of metabolic modulation. *Phyllanthus amarus* extracts, for instance, have been reported in humanized hepatocyte models to activate PXR and AhR, increase CYP3A4 and CYP1A2 mRNA expression, and simultaneously inhibit CYP3A4 enzyme activity, suggesting that the net effect on CYP3A4 substrates may depend on dose, duration of exposure, and timing relative to drug administration^[56]. Clinically, these mechanisms are most relevant for drugs with narrow therapeutic indices, extensive first-pass metabolism, or exposure-dependent toxicity. Thus, specific foods, botanicals, and especially concentrated extracts can act as metabolic antagonists when they reduce active drug exposure, increase parent-drug accumulation, or enhance toxic metabolite formation^[6,9,56,57].

5.1.3 Transporter-mediated effects

Food constituents can antagonize pharmacotherapy by modulating uptake and efflux transporters that regulate drug movement across the intestinal epithelium, hepatocytes, renal tubules, and other tissues^[58]. Many cardiovascular drugs, statins, anticancer agents, antivirals, and other therapies are substrates of ATP-binding cassette transporters, including P-glycoprotein and breast cancer resistance protein, as well as solute carrier transporters such as organic anion transporting polypeptide (OATP), organic cation transporter (OCT), and organic anion transporter (OAT) families^[58,59]. Dietary compounds and natural products that inhibit or compete for these systems can alter absorption, hepatic uptake, biliary excretion, renal clearance, or tissue distribution, thereby increasing toxicity risk or reducing active drug exposure depending on the transporter, substrate, and site of action^[58]. Evidence from natural product-drug interaction studies, particularly in cardiovascular pharmacotherapy, shows that plant-derived constituents can inhibit or compete for clinically relevant transporters, challenging standard dosing assumptions when exposure is high, repeated,

or combined with narrow-therapeutic-index drugs^[58]. Emerging biomarker-based approaches also indicate that changes in transporter activity can be detected through endogenous or metabolomic markers, supporting the clinical relevance of transporter modulation as a mechanism of altered drug disposition^[60]. Recent experimental studies further characterize transporter effects of specific food-derived compound classes, although most findings remain preclinical and should be interpreted cautiously. Flavonoids found in foods and herbal products have been identified as inhibitors of organic cation transporter 1, with some molecules showing low-micromolar inhibitory potency and effects on uptake or toxicity of OCT1 substrate drugs in cellular and animal models^[61]. Similarly, selected alkaloids have been reported to inhibit the hepatic uptake transporter OATP1B1, reducing transporter-mediated uptake of methotrexate and other substrates and modifying susceptibility to bosentan-related liver injury in experimental systems^[62]. Together with regulatory analyses showing increasing recognition of transporter-mediated interactions in drug labeling, these data support the concept that food constituents can act as transporter-level antagonists of pharmacotherapy, particularly when consumed as concentrated extracts, supplements, or high-exposure dietary products, and especially in patients receiving transporter-dependent drugs with narrow safety margins^[59].

5.2 Pharmacodynamic antagonism

Pharmacodynamic antagonism occurs when nutrients, foods, or dietary patterns oppose drug action at the level of targets, pathways, or integrated physiological responses, even when drug absorption and systemic exposure are adequate^[9,14]. A classic example is vitamin K intake in patients receiving vitamin K antagonist anticoagulants. Higher or unstable intake of green leafy vegetables and other vitamin K-rich foods can counteract warfarin's inhibition of the vitamin K cycle, reduce anticoagulant effect, and destabilize INR control despite unchanged dosing^[9]. Similar opposition can occur when dietary electrolytes or macronutrients influence the same physiological systems targeted by drugs. High sodium intake may blunt the blood pressure-lowering effect of antihypertensives by promoting volume expansion and vascular stiffness, while high potassium intake can increase hyperkalemia risk in patients receiving renin-angiotensin-aldosterone system inhibitors^[14]. In these examples, food does not primarily antagonize therapy by impairing absorption, but by shifting the physiological set point that pharmacotherapy is intended to modify.

Whole dietary patterns can also reduce the net clinical effect of pharmacotherapy, particularly in chronic cardiometabolic disease^[14,15]. Diets high in sodium, excess energy, saturated fat, refined carbohydrates, or ultra-processed foods can increase blood pressure, worsen insulin resistance, promote weight gain, and raise triglyceride concentrations, thereby limiting the therapeutic impact of antihypertensive, glucose-lowering, and lipid-lowering drugs^[14,16]. In heart failure, excessive sodium and fluid intake can counteract the decongestive and symptom-relieving effects of diuretics and neurohormonal therapies, contributing to persistent congestion and avoidable treatment escalation^[16]. Likewise, dietary patterns that perpetuate dyslipidemia or weight gain may reduce the absolute risk reduction achievable with statins or other lipid-lowering drugs, even when pharmacologic exposure is adequate^[14,15]. These examples show that pharmacodynamic antagonism often reflects opposition at shared physiological endpoints, including coagulation, vascular tone, fluid balance,

electrolyte homeostasis, glycemic control, and lipid metabolism. Without addressing the relevant dietary driver, pharmacotherapy may be forced to operate against a persistent counter-regulatory nutritional exposure^[9,14].

5.3 Behavioral and contextual antagonism

Behavioral and contextual antagonism occurs when dietary prescriptions, meal patterns, or food access constraints reduce the feasibility of pharmacotherapy, most often by increasing treatment burden or undermining adherence^[63,64]. Strict therapeutic diets, including intensive hypocaloric regimens in obesity, multi-step elimination diets in gastrointestinal disease, or tightly timed meal requirements, can complicate daily routines and make medication use harder to sustain^[63,65]. Food-linked dosing instructions, such as “take with food” or “take on an empty stomach,” may also be difficult to follow consistently, particularly when meal timing is irregular or the regimen is complex. In antiretroviral therapy, deviations from food-related dosing instructions have been associated with poorer virological or clinical responses even when other adherence measures appear acceptable^[64]. Similar challenges occur in pediatric hypertension, where families must integrate dietary change, medication schedules, school routines, and behavioral support without overwhelming the patient or caregiver^[66].

Socioeconomic and cultural factors can further antagonize pharmacotherapy by limiting which foods are available, affordable, acceptable, and compatible with medication timing^[5,67]. Food insecurity, irregular meals, and reliance on low-cost, energy-dense foods are common in populations with high burdens of diabetes and cardiovascular disease, and can make it difficult to follow therapeutic diets or take medications that require synchronization with meals^[5,68]. Cultural food practices and religious observances may also alter meal composition and timing in clinically relevant ways; prolonged fasting periods or large festival meals, for example, can destabilize glucose control, blood pressure management, and medication routines unless treatment plans are adapted^[67]. Studies of diet prescription adherence in type 2 diabetes and hypertension indicate that motivation alone is often insufficient when competing demands, limited access to recommended foods, and social norms constrain daily eating behavior^[67]. In these settings, food acts as a behavioral and contextual antagonist not primarily because of its molecular composition, but because the social organization of eating is misaligned with the requirements of pharmacotherapy^[5,63].

5.4 Clinical exemplars

Clinical exemplars of food-mediated antagonism show how common eating behaviors can undermine pharmacotherapy despite appropriate prescribing and apparent medication adherence^[1,9]. Levothyroxine is a prototypical example: co-ingestion with meals, coffee, soy products, dairy, fiber, and calcium or iron supplements can reduce bioavailability through delayed gastric emptying, altered gastric pH, and luminal complexation, leading to suboptimal thyroid control and unnecessary dose escalation when fasting administration is not followed^[69,70]. These interactions support recommendations to take levothyroxine on an empty stomach, 30 to 60 minutes before breakfast or at bedtime, while liquid and soft-gel formulations may reduce susceptibility to food-related malabsorption in selected patients^[69,71]. Similarly, tetracyclines and

fluoroquinolones can form insoluble chelates with divalent or trivalent cations present in dairy products, antacids, supplements, and fortified foods, reducing absorption and risking therapeutic failure; separation from calcium-, magnesium-, iron-, or aluminum-containing products is therefore a key counseling point^[9].

Other examples illustrate pharmacodynamic antagonism or unsafe exposure increases rather than reduced absorption alone^[6,9]. In patients receiving warfarin, high or unstable intake of vitamin K-rich foods can counteract vitamin K cycle inhibition, destabilize INR control, and increase thromboembolic risk, so management should emphasize consistent vitamin K intake rather than indiscriminate avoidance of vegetables^[9]. Grapefruit juice and related furanocoumarin-containing products inhibit intestinal CYP3A and some transport pathways, increasing exposure and toxicity risk for susceptible CYP3A substrates such as selected calcium channel blockers, statins, antiarrhythmics, and immunosuppressants^[6,9]. Abiraterone illustrates a distinct antagonistic food effect: high-fat meals can increase bioavailability several-fold, but because this effect is variable and may increase toxicity risk, administration under fasting conditions is recommended to maintain controlled exposure^[1]. Together, these examples show that clinically important food-drug antagonism may occur through impaired absorption, pharmacodynamic opposition, or unsafe overexposure, and should therefore be addressed explicitly during prescribing, medication review, and patient counseling^[1,9,69]. Representative examples of food-mediated antagonism are summarized in Table 2, including interactions supported by controlled human pharmacokinetic studies, systematic reviews, clinical observational evidence, and selected case-based or expert-guidance evidence.

Table 2. Representative examples of food as antagonist of pharmacotherapy.

Drug or class	Food or dietary exposure	Mechanism	Key quantitative effect	Recommended management	Evidence	References
Levothyroxine tablets	Coffee, espresso, cow's milk, calcium-rich foods, soy, calcium/iron supplements, enteral nutrition	Reduced dissolution and absorption; binding or complexation with calcium, fiber, soy proteins, and enteral formulas	Coffee reduced maximal serum T4 rise by 14% to 49% and overall T4 rise by 23% to 55%. Milk reduced total T4 AUC from 73.5 ± 17.0 to 67.3 ± 12.1 , $p = 0.02$. Systematic review found reduced absorption with coffee, soy, fiber, calcium, iron, and enteral nutrition. Fed arm: 14/25 had no measurable exposure; remaining 11 had limited exposure. Fasting vs reference increased AUC and C_{max} by about 40%, $p = 0.082$ and 0.080. Longer post-dose fasting increased exposure, $p < 0.001$. Population PK estimated bioavailability at 0.8% under recommended conditions.	Take with water on an empty stomach, usually 30 to 60 min before breakfast. Separate calcium, iron, multivitamins, and high-fiber supplements by about 4 h. Consider liquid or soft-gel formulation if absorption failure persists.	A/B	[69,72,73]
Oral semaglutide	Food before or soon after dosing; large water volume	Food and gastric contents disrupt SNAC-mediated gastric absorption	Fasted simultaneous dosing reduced bicitegravir AUC_{inf} by 79% with Al/Mg antacid, 33% with calcium, and 63% with iron. Fed calcium dosing mitigated the effect, AUC_{inf} ratio 103.3%. Fed iron reduced C_{max} to 75.1%. Bicitegravir 2 h before Al/Mg antacid gave AUC_{inf} ratio 86.7%; 2 h after antacid gave 47.7%.	Take after overnight fast with ≤ 120 mL water. Wait at least 30 min before food, drink, or other oral medicines.	A	[74,75]
Bicitegravir and other INSTIs	Al/Mg antacids; calcium carbonate; ferrous fumarate; mineral supplements; multivitamins	Chelation with polyvalent cations reduces absorption	Fasted simultaneous dosing reduced bicitegravir AUC_{inf} by 79% with Al/Mg antacid, 33% with calcium, and 63% with iron. Fed calcium dosing mitigated the effect, AUC_{inf} ratio 103.3%. Fed iron reduced C_{max} to 75.1%. Bicitegravir 2 h before Al/Mg antacid gave AUC_{inf} ratio 86.7%; 2 h after antacid gave 47.7%.	Avoid fasted simultaneous dosing with polyvalent cations. Calcium or iron may be taken with bicitegravir with food. Give bicitegravir at least 2 h before Al/Mg antacids; avoid taking it 2 h after antacid.	A	[76]
Dolutegravir	Calcium carbonate, ferrous fumarate, multivitamins, Al/Mg antacids	Chelation with polyvalent cations	Fasted calcium reduced AUC, C_{max} , and C_{24} by 39%, 37%, and 39%. Ferrous fumarate reduced C_{max} , AUC, and C_{min} by 57%, 54%, and 56%. Simultaneous antacid reduced exposure by about 74%. Food counteracted calcium/iron interaction.	Give dolutegravir 2 h before or 6 h after cation products. Calcium or iron may be taken simultaneously if taken with food.	A	[77]
Fluoroquinolones: ciprofloxacin, levofloxacin, norfloxacin,	Al/Mg antacids, iron, calcium, zinc, milk, yogurt, calcium-fortified orange juice	Chelation reduces free drug and absorption	Systematic review/meta-analysis: ciprofloxacin with Al/Mg antacids reduced AUC by 85% and C_{max} by 81%; iron reduced AUC by 55% and C_{max} by 48%; calcium reduced AUC by about 35%. Milk and	Avoid coadministration with dairy alone, mineral supplements, or antacids. For ciprofloxacin-type regimens, separate from cations by at least 2 h before or 4 to 6 h after,	B	[78]

delafloxacin			calcium-fortified juice reduced exposure in multiple studies.	depending on label and infection severity.		
Tetracyclines: tetracycline, doxycycline, demeclocycline, omadacycline	Milk, dairy, iron, calcium, magnesium, aluminum antacids, high-fat meals with or without dairy	Chelation with divalent/trivalent cations; food-related absorption reduction	Systematic review found significant reduction of tetracycline absorption with antacids and minerals. Omadacycline: high-fat non-dairy meal 2 h before dosing reduced $C_{\max}$ and AUC by 40% and 42%; high-fat meal with dairy reduced $C_{\max}$ and AUC by 59% and 63%.	Use water. Avoid dairy and polyvalent cations around dosing. For omadacycline, fast 4 h before and avoid food for 2 h after; avoid dairy, antacids, and iron for at least 4 h after.	A/B	[79,80]
β -lactams: penicillin V, penicillin G, cefalexin, cefradine, cefdinir, cefpodoxime proxetil	Milk, food, iron salts, antacids, mineral supplements	Reduced absorption; cation binding or formulation-related food effects	Systematic review/meta-analysis: milk reduced extent of absorption by >40% for cefalexin, cefradine, penicillin G, and penicillin V. Antacids or minerals reduced bioavailability for 4/13 β -lactams; cefdinir with iron had the largest negative effect.	For β -lactams with known food/mineral sensitivity, give with water and avoid milk or minerals near dosing when high exposure is needed. Use drug-specific instructions because some β -lactams have neutral or positive food effects.	B	[81]
Alendronate and oral bisphosphonates	Breakfast, coffee, orange juice, milk, mineral water, calcium supplements	Very low baseline bioavailability; food/beverages further reduce absorption by binding and impaired dissolution	Coffee or orange juice reduced alendronate bioavailability by about 60%. Absorption is nearly negligible when taken with or soon after breakfast.	Take immediately after waking with plain water only. Wait at least 30 min before food, beverages, or other medicines. Remain upright for at least 30 min.	A	[82]
Warfarin	Variable vitamin K intake; leafy greens; broccoli, spinach, kale; natto; vitamin K-containing nutrition drinks/supplements	Pharmacodynamic opposition through vitamin K-dependent clotting factor carboxylation	Usual vitamin K intake ≥ 250 $\mu\text{g/day}$ was associated with decreased warfarin sensitivity, lower day-5 INR, and higher steady-state dose needs. Abrupt change or variability is the main clinical issue.	Do not advise vegetable avoidance. Maintain consistent vitamin K intake and adjust warfarin to the stable diet. Recheck INR after major diet changes, nutrition drinks, or supplements.	B/C	[83,84]
Phenytoin via feeding tube	Continuous enteral nutrition; protein-containing tube feeds; nasogastric tubing	Binding to formula/tubing; poor solubility and delivery reduce absorbed dose	Case series: 5 ICU patients switched from IV to nasogastric phenytoin had serum concentrations fall below assay sensitivity; 2/5 had seizures. Evidence review found decreased concentrations with feeds, although prospective RCT evidence is limited.	Prefer alternative route or antiseizure drug if feasible. If enteral phenytoin is necessary, hold feeds around dosing, flush tube, and monitor total and free phenytoin levels.	C/D	[85,86]
Voriconazole	High-fat meals; routine dosing with food	Food lowers and delays absorption	Multiple-dose oral voriconazole 200 mg twice daily with food reduced AUC_{τ} by about 22%. High-fat meals reduced $C_{\max}$ by 34% and AUC by 24%.	Give oral voriconazole at least 1 h before or 1 h after meals. Consider therapeutic drug monitoring for invasive fungal infection, toxicity, hepatic impairment, or variable	A	[87,88]

Abiraterone acetate	Low-fat meal, high-fat meal, inconsistent timing	Food increases and destabilizes absorption, causing unsafe exposure	markedly and	Healthy males: low-fat meal increased $C_{\max}$ and AUC about 7-fold and 5-fold; high-fat meal increased $C_{\max}$ and AUC about 17-fold and 10-fold. In metastatic CRPC, high-fat meal increased AUC about 2-fold.	intake. Take fasting. No food for at least 2 h before and 1 h after dosing. Do not use food boosting outside a controlled protocol.	A	[89]
Nilotinib capsules	Light meal, high-fat meal, grapefruit products	Food increases exposure and toxicity risk; grapefruit may further increase CYP3A-mediated exposure		High-fat breakfast 30 min before nilotinib increased AUC by 82% and $C_{\max}$ by 112%. Light breakfast increased AUC by 29% and $C_{\max}$ by 55%.	Avoid food for 2 h before and 1 h after dosing. Avoid grapefruit products. Food-based reduced dosing should be considered only under specialist oversight with therapeutic drug monitoring.	A	[90,91]
Lapatinib	Low-fat breakfast, high-fat breakfast, inconsistent meal timing	Food increases solubilization and absorption, causing overexposure		Low-fat breakfast increased AUC by 167%, equivalent to 2.67-fold. High-fat breakfast increased AUC by 325%, equivalent to 4.25-fold, and $C_{\max}$ by 203%.	Take consistently according to label, typically at least 1 h before or 1 h after food. Avoid ad hoc meal-based dose changes.	A	[92]
Pazopanib	Low-fat meal, high-fat meal	Food increases absorption and toxicity risk		Low-fat meal increased $C_{\max}$ and AUC by 1.9-fold and 2.1-fold; high-fat meal increased $C_{\max}$ and AUC by 2.1-fold and 2.3-fold. High-fat AUC0-72 increase was 2.34-fold.	Take without food, at least 1 h before or 2 h after meals. Avoid inconsistent meal timing.	A	[93,94]
CYP3A-sensitive substrates: simvastatin, lovastatin, felodipine, some calcineurin inhibitors and antiarrhythmics OATP substrates: fexofenadine, aliskiren, celiprolol, atenolol in selected contexts	Grapefruit juice, grapefruit, Seville orange, pomelo	Furanocoumarin-mediated intestinal CYP3A inhibition increases exposure and toxicity		One glass grapefruit juice daily increased simvastatin AUC0-24 by 3.6-fold and simvastatin acid AUC by 3.3-fold. Grapefruit juice approximately doubled felodipine AUC.	Avoid grapefruit, Seville orange, and pomelo with sensitive CYP3A substrates, especially narrow-therapeutic-index drugs. Use noninteracting alternatives when possible.	A	[95]
	Apple juice, orange juice, grapefruit juice	Inhibition of intestinal uptake transporters, especially OATP1A2 and OATP2B1		Fexofenadine AUC decreased to 26.9%, 30.6%, and 36.7% of water control with apple, orange, and grapefruit juice. Grapefruit juice reduced aliskiren $C_{\max}$ by 81%; orange/apple juice reduced $C_{\max}$ by about 80% and AUC by about 63%.	Take with water. Avoid apple, orange, and grapefruit juice around dosing, commonly for 2 to 4 h, or follow product-specific guidance.	A	[96-98]
Irreversible nonselective MAO	Aged cheese, cured meats, fermented soy products, spoiled	MAO-A inhibition prevents tyramine degradation; tyramine		Older dietary pharmacology data: 6 mg tyramine may cause mild crisis; 10 to 25 mg may cause severe headache and intracranial	Provide a practical low-tyramine diet. Avoid aged, fermented, cured, spoiled, or improperly stored	A/D	[99,100]

inhibitors: phenelzine, tranylcypromine, isocarboxazide	protein foods, some beers and wines	releases norepinephrine and raises BP	hemorrhage risk in susceptible MAOI-treated patients.	high-protein foods. Continue restrictions after stopping according to half-life and label guidance.		
ACE inhibitors, ARBs, and antiproteinuric RAAS blockade	High-sodium diet; processed foods; restaurant meals; salt-preserved foods	Sodium and volume expansion blunt RAAS blockade and reduce antiproteinuric and antihypertensive response	High salt intake >14 g/day blunted ACE inhibitor antiproteinuric effect and increased ESRD risk independent of BP control. Sodium restriction increased RAAS blockade efficacy in diabetic nephropathy studies.	Assess sodium intake before escalating therapy for resistant hypertension or persistent proteinuria. Use structured sodium reduction and monitor BP, albuminuria/proteinuria, potassium, and kidney function.	B/C	[101-103]
Antihypertensives, diuretics, mineralocorticoid antagonists, digoxin-sensitive patients	Licorice root; glycyrrhizin-containing candies, teas, supplements, herbal products	Glycyrrhizic acid inhibits 11 β -HSD2, causing apparent mineralocorticoid excess, sodium retention, potassium wasting, and BP elevation	2024 meta-analysis of 8 RCTs, 541 participants: SBP increased by 3.48 mmHg and DBP by 1.27 mmHg. 2024 low-dose RCT found BP effects with 100 mg glycyrrhizic acid/day.	Avoid glycyrrhizin-containing licorice in uncontrolled hypertension, heart failure, CKD, hypokalemia, and patients using diuretics, digoxin, or mineralocorticoid antagonists. Monitor BP and potassium if exposure occurs.	B	[104,105]
Empagliflozin 10 mg	High-fat diet/meal before dosing	Food-related changes in gastric emptying, transit, and absorption reduce exposure in recent single-dose data	Healthy Chinese volunteers: fasting/fed 90% CIs were 152.29% to 178.77% for C _{max} and 127.21% to 147.29% for AUC _{0-t} , outside 80% to 125%. This corresponds to fed C _{max} about 40% lower and AUC about 27% lower than fasting. Urine glucose increased after dosing in both states: fasting 70.9 $\pm$ 29.9 vs 0.3 $\pm$ 0.2 mmol/L; fed 89.6 $\pm$ 35.4 vs 0.3 $\pm$ 0.3 mmol/L, p < 0.001.	Do not overstate as a universal fasting requirement because data are single-dose healthy-volunteer data. Use consistent administration and consider recent high-fat intake when interpreting unexpected PK/PD response.	A	[106]

Evidence: A, regulatory labeling or controlled human PK/PD evidence; B, randomized trial, systematic review, meta-analysis, or major guideline; C, observational clinical evidence; D, case report, pharmacovigilance, or expert opinion; E, preclinical, in vitro, animal, microbiome, omics, or computational evidence.

Magnitude is reported as pharmacokinetic change when available; for pharmacodynamic interactions, the most clinically relevant response marker is shown. For drugs such as abiraterone, nilotinib, lapatinib, pazopanib, and grapefruit-sensitive CYP3A substrates, food-mediated antagonism reflects unsafe or unpredictable overexposure rather than reduced efficacy.

Abbreviations: ACE, Angiotensin-Converting Enzyme; AUC, Area Under the Concentration–Time Curve; AUC₀, Area Under the Curve from Time 0; BP, Blood Pressure; C_{max}, Maximum Plasma Concentration; CKD, Chronic Kidney Disease; CRPC, Castration-Resistant Prostate Cancer; DBP, Diastolic Blood Pressure; ESRD, End-Stage Renal Disease; HSD2, 11 β -Hydroxysteroid Dehydrogenase Type 2; ICU, Intensive Care Unit; INR, International Normalized Ratio; IV, Intravenous; MAO, Monoamine Oxidase; MAOI, Monoamine Oxidase Inhibitor; OATP, Organic Anion Transporting Polypeptide; ON, Oral Nutrition; PD, Pharmacodynamics; PK, Pharmacokinetics; RAAS, Renin-Angiotensin-Aldosterone System; RCT, Randomized Controlled Trial; SBP, Systolic Blood Pressure; SNAC, Sodium N-[8-(2-Hydroxybenzoyl) Amino] Caprylate.

6. Food as enabler of pharmacotherapy

6.1 Exposure enablement

6.1.1 Increased bioavailability

Food can enable pharmacotherapy when administration with a meal increases oral bioavailability in a predictable and clinically useful manner, thereby improving drug exposure without changing the nominal dose^[1,107]. This effect is most relevant for poorly soluble, lipophilic, or permeability-limited drugs, for which meals, particularly moderate- or high-fat meals, can increase maximum plasma concentration ($C_{\max}$) and area under the concentration-time curve (AUC) through enhanced dissolution, bile salt-lipid micellar solubilization, and prolonged residence in absorptive regions of the gastrointestinal tract^[1,53]. Such food-enhanced absorption has informed formulation strategies, including lipid-based dispersions, solid lipid nanoparticles, and micellar systems designed either to mimic fed-state solubilization or to reduce dependence on meal composition for drugs such as fenofibrate and other poorly soluble compounds^[108,109]. In vitro gut models and gut-on-a-chip platforms further support this approach by allowing controlled assessment of how food-like luminal environments influence dissolution, permeability, and intestinal absorption^[110,111]. For drugs with steep exposure-response relationships, food-dependent increases in bioavailability can be clinically decisive and may be incorporated into dosing recommendations^[1,107]. Regulatory food-effect studies commonly use controlled fed conditions, including high-fat meals, to identify changes in exposure that may justify “take with food” labeling when adequate or consistent concentrations are needed^[1,112]. Selected food components may also influence intestinal transport or membrane permeability, as shown experimentally for compounds such as vanillin, although these findings remain more mechanistic than routinely actionable in clinical prescribing^[113].

Within the present framework, increased bioavailability should be classified as enabling only when the effect is intentional, sufficiently predictable, safe, and incorporated into dosing instructions or clinical management; otherwise, uncontrolled food-related overexposure is better understood as antagonism through toxicity risk^[1,107]. Recent controlled human studies provide empirical support for this boundary: DFV890, an oral NLRP3 inhibitor, showed a 1.49–2.05-fold increase in systemic exposure under fed conditions compared with fasting^[114], while the novel antimalarial MMV367 exhibited 1.3–1.6-fold increased bioavailability in postprandial conditions^[115]. These findings reinforce that elevated drug exposure is clinically enabling only when predictable, safe, and explicitly incorporated into dosing guidance, rather than assumed beneficial solely based on absolute plasma concentrations.

6.1.2 Reduced inter- and intra-individual variability

Standardized meal conditions can enable pharmacotherapy by reducing inter- and intra-individual variability in drug exposure. For drugs with large food effects or sensitivity to prandial state, dosing with a consistent meal can reduce variability in gastrointestinal pH, gastric emptying, bile secretion, luminal

solubilization, and first-pass conditions at the time of administration^[1,107]. This is clinically relevant because lower variability in C_{max} , trough concentrations, or total exposure may keep more patients within the intended therapeutic window at a fixed dose. Antimalarial regimens provide one example: studies of piperaquine and dihydroartemisinin-piperaquine show that food can increase bioavailability and improve the predictability of exposure, supporting attention to meal timing and composition during treatment^[116]. For narrow-therapeutic-index drugs such as tacrolimus, inconsistent dietary or supplement use may contribute to within- and between-patient variability, and reviews emphasize standardizing food intake and avoiding interacting foods to stabilize trough concentrations and reduce rejection or toxicity risk^[117]. In practice, consistent food instructions function as a form of exposure control. Regulatory food-effect studies use defined meal conditions to quantify not only mean changes in exposure but also the variability introduced or reduced by the fed state^[1,107]. The same principle applies clinically when patients are instructed to take a medication “with the main meal” or “with a similar meal each day,” because this reduces day-to-day variation in the dosing environment and supports more predictable drug response. Emerging continuous-monitoring studies also suggest that structured dietary patterns can reduce short-term variability in physiological markers such as glucose, which indirectly supports synchronizing selected glucose-lowering therapies with stable eating patterns to avoid excessive pharmacodynamic fluctuation^[1,107,118]. Thus, food can enable pharmacotherapy not only by increasing average bioavailability, but also by making exposure and response more reproducible across doses, days, and patients^[1,118].

6.2 Tolerability enablement

Tolerability enablement occurs when food is used primarily to reduce treatment-related adverse effects or improve treatment acceptability, rather than to increase systemic drug exposure. Food can enable pharmacotherapy by improving tolerability, particularly for drugs limited by gastrointestinal irritation, nausea, dyspepsia, or appetite-related adverse effects^[1]. Taking nonsteroidal anti-inflammatory drugs, metformin, and many oral anticancer agents with meals is common clinical practice to reduce upper gastrointestinal symptoms and support persistence with therapy, even when the pharmacokinetic effect of food is modest^[1,119,120]. For selected oral targeted therapies, food instructions can also improve exposure consistency or tolerability, but these instructions must remain product-specific because meals may either enable therapy or produce unsafe overexposure depending on the drug and formulation^[121]. Similar principles apply to neuropsychiatric and obesity pharmacotherapy, where meal structuring and nutritional counseling may help manage appetite changes, nausea, diarrhea, constipation, sleep disturbance, or weight-related concerns, thereby improving treatment acceptability and continuity^[65,122].

6.3 Adherence and feasibility enablement

Adherence and feasibility enablement occurs when food-related dosing conditions facilitate consistent, practical, and sustainable medication use. Meal-linked dosing instructions, such as taking a drug with the main meal, may reduce the cognitive and logistical burden of treatment compared with regimens that require fasting windows, complex timing rules, or multiple unsynchronized doses^[68]. In chronic conditions such as diabetes,

hypertension, and pediatric hypertension, aligning medication schedules with meals, family routines, or school schedules can support both dietary and pharmacologic adherence when counseling is individualized and feasible^[66,68]. In ADHD and other neuropsychiatric conditions, coordinating medication timing with meals may help balance symptom control, appetite, and sleep, making long-term therapy more acceptable to patients and caregivers^[122]. Thus, food can enable pharmacotherapy not only by altering exposure, but also by reducing adverse effects, standardizing dosing conditions, and anchoring medication use to sustainable daily behavior^[65,68].

6.4 Enabling in vulnerable populations

Food security and meal regularity determine whether food-dependent regimens are feasible in vulnerable populations, including patients with low income, chronic illness, unstable housing, or complex treatment burdens. Population-based studies from Canada and the United States show that adults in food-insecure households have higher rates of cost-related medication nonadherence than food-secure adults, indicating that limited food access and competing financial demands can directly undermine consistent medication use^[123,124]. Among people living with HIV, cohort and daily-diary studies show that food insufficiency and hunger are associated with missed antiretroviral doses, with substance use further amplifying the negative effect on adherence^[125,126]. In these settings, instructions such as “take with a substantial meal” or “take with the largest meal of the day” may be impractical when meals are skipped, delayed, or nutritionally inadequate, converting an intended enabling condition into a barrier to adequate exposure and adherence^[123,125].

For vulnerable populations, food-dependent prescribing should therefore be paired with assessment of food access, meal timing, and nutrition support needs^[5,123]. In people living with HIV, addressing food insufficiency through meal programs, food vouchers, or linkage to community resources can support antiretroviral adherence and should be considered part of treatment implementation rather than an ancillary social service^[125,126]. Similar principles apply to patients prescribed food-dependent antivirals, oncology agents, psychotropics, or other oral therapies: referral to food assistance, medically tailored meals, or dietitian-led services may help ensure that appropriate meals are available at dosing times and reduce exposure variability caused by erratic intake^[5,21]. In this context, food functions as an enabling co-therapy only when patients can reliably access and consume the meals required by the regimen; otherwise, the food requirement becomes a structural constraint on safe pharmacotherapy^[123,125].

6.5 Clinical exemplars

Lurasidone is a clear example of meal-dependent dosing in psychopharmacology. Its labeling specifies administration with at least 350 kcal to achieve adequate and consistent exposure, and clinical pharmacology data show that food increases oral bioavailability several-fold compared with fasting conditions^[1,127]. Pooled double-blind trials in schizophrenia further support efficacy and tolerability at 40 to 160 mg/day under fed-state dosing conditions^[127]. In clinical practice, the meal is therefore an enabling co-factor: patients who take lurasidone consistently with an adequate meal are more likely to achieve therapeutic exposure, whereas inconsistent meal intake may cause underexposure despite correct milligram dosing^[1,127]. Other psychotropic

agents may have smaller food effects, but meal-linked dosing can still improve exposure consistency or tolerability in selected cases^[1].

Food also enables pharmacotherapy for selected oncology, antiviral, and anti-infective agents with label-relevant food effects^[1,128]. Dedicated food-effect studies of agents such as presatovir and acebilustat have quantified meal-related changes in $C_{\max}$, AUC, and $T_{\max}$, showing that some drugs require or benefit from fed-state dosing to reach target exposure, while others show delayed absorption without clinically meaningful loss of total exposure^[129,130]. Ensitrelvir provides a more moderate example, in which a standard meal modestly increases exposure without compromising safety, supporting flexible administration in either fasted or fed conditions while acknowledging a small food-related pharmacokinetic effect^[131]. Similar principles apply to selected oral anticancer and metabolic agents, where food may improve bioavailability, reduce variability, or align peak concentrations with periods of greatest therapeutic need^[132]. Together, these examples show that food functions as an enabler when its effect on exposure is intentional, predictable, safe, and incorporated into dosing instructions or clinical management^[1,127,128]. Representative examples of food-enabled pharmacotherapy are summarized in Table 3, most of which are supported by controlled human food-effect studies, regulatory labeling, or both.

Table 3. Representative examples of food as enabler of pharmacotherapy

Drug or class	Enabler subcategory and meal requirement	Key food effect	Clinical recommendation	Evidence	References
Rivaroxaban 15 mg and 20 mg	Ensures adequate exposure; take with food, preferably a main meal	20 mg fasting bioavailability is about 66%; food increases 20 mg AUC by 39% and C_{max} by 76%.	Take 15 mg and 20 mg doses with food, especially for AF and VTE treatment dosing.	A	[133,134]
Lurasidone	Ensures adequate exposure; take with at least 350 kcal	Food increases C_{max} about 3-fold and AUC about 2-fold vs fasting; exposure is not meaningfully increased further by 350 to 1000 kcal or higher fat content.	Take once daily with at least 350 kcal. Avoid fasting dosing.	A	[135,136]
Ziprasidone	Ensures adequate and reproducible exposure; take with at least 500 kcal	Meals ≥ 500 kcal produce exposures similar to high-calorie meals; 250 kcal meals produce exposures about 60% to 90% lower and approach fasting exposure.	Take every oral dose with a real meal, not only a snack. Meal fat is less important than calories.	A	[137-139]
Rilpivirine	Ensures antiretroviral exposure; take with a meal	Fasting AUClast ratio was 0.57 and protein drink ratio was 0.50 vs normal-fat breakfast; high-fat breakfast was similar to normal-fat breakfast, ratio 0.92.	Take with a meal. Do not replace the meal with a protein drink or shake.	A	[140]
Etravirine	Ensures antiretroviral exposure; take after a meal	Fasted dosing caused 51% lower mean exposure than dosing after a standard breakfast.	Take after meals. Avoid fasting dosing.	A	[141]
Darunavir with ritonavir or cobicistat	Ensures protease inhibitor exposure; take with food	Fasted darunavir/ritonavir decreased C_{max} and AUClast by about 30% vs fed dosing.	Take with food. Meal type can be flexible, but fasting dosing should be avoided.	A	[142]
Atazanavir with ritonavir or cobicistat	Increases exposure and reduces variability; take with or after food	Light meal increased AUC by 33%, C_{max} by 40%, and 24 h concentration by 40%. With ritonavir, meals reduced AUC and C_{max} variability by about 25% vs fasting.	Take with food, especially when adherence or gastric-acid modification may threaten exposure.	A	[143,144]
Elvitegravir/cobicistat/emtricitabine/tenofovir DF	Ensures integrase inhibitor and booster exposure; take with food	Fasting reduced elvitegravir C_{max} and AUC _{inf} by approximately 55% and 50%, respectively, versus a standard breakfast, whereas exposure with a protein-rich drink was comparable to that with the standard breakfast.	Take with food; the cited study found that a protein-rich nutritional drink provided exposure comparable to a standard breakfast.	A	[145]
Ivacaftor and ivacaftor-containing CFTR modulators	Ensures CFTR modulator exposure; take with fat-containing food	Fat-containing food increases ivacaftor AUC by about 2.5- to 4.0-fold.	Take each dose with fat-containing food; this is exposure-critical.	A	[146,147]
Atovaquone and atovaquone/proguanil	Enables antiparasitic exposure; take with food or milky drink, preferably fat-containing	Dietary fat increases atovaquone AUC 2- to 3-fold and C_{max} about 5-fold; high-fat meal increased AUC 3.3-fold and C_{max} 5.3-fold.	Take with food or milky drink. Follow product-specific redosing guidance if vomiting occurs.	A	[148,149]
Artemether-lumefantrine	Enables antimalarial exposure; take with food or milk as soon as tolerated	High-fat food increased artemether bioavailability >2-fold and lumefantrine about 16-fold; soya milk increased lumefantrine exposure >5-fold.	Give with food or milk, especially because malaria often causes anorexia or vomiting.	A	[150,151]

Albendazole systemic infection	for helminth	Increases systemic exposure; take with fatty meal	High-fat breakfast increased albendazole and albendazole sulfoxide AUC and $C_{\max}$ about 2-fold vs low-fat breakfast.	For systemic infections, take with a fatty meal. For luminal intestinal parasites, apply indication-specific guidance.	A	[152]
Praziquantel		Increases antiparasitic exposure; take with meals	High-lipid meal increased $C_{\max}$ by 243% and AUC0-8h by 180%; high-carbohydrate meal increased $C_{\max}$ by 515% and AUC0-8h by 271%.	Take with meals for schistosomiasis and systemic trematode or cestode infections.	A	[153]
Posaconazole suspension	oral	Enables antifungal exposure; take with full meal, high-fat meal, or nutritional supplement if unable to eat	High-fat meal increased suspension AUC0-72h and $C_{\max}$ by about 400% vs fasting.	Take suspension with a full meal when possible. If unable to eat, use nutritional supplement or acidic beverage per product guidance. Do not generalize this to delayed-release tablets.	A	[154,155]
Itraconazole capsules		Enables antifungal exposure; take capsules immediately after a full meal	Mean $C_{\max}$ was 140 ng/mL fasting vs 239 ng/mL after a standard meal; fasting $C_{\max}$ was about 59% of fed $C_{\max}$.	Take capsules after a full meal. Do not apply this to itraconazole oral solution, which has different food instructions.	A/D	[156]
Alectinib		Enables ALK inhibitor exposure; take with food and avoid low-fat yogurt alone	High-fat/high-calorie meal increased combined alectinib plus M4 exposure about 3.1-fold; low-fat yogurt produced clinically relevant lower trough concentrations.	Take with a real meal. Low-fat yogurt alone is inadequate in patients near the exposure threshold.	A	[157]
Ceritinib		Enables lower, better-tolerated dosing; approved lower-dose fed strategy, typically 450 mg with food	Low-fat meal increased AUC0-inf by 58%; high-fat meal by 73%. ASCEND-8 showed 450 mg with food achieved similar exposure and improved GI tolerability vs 750 mg fasting.	Use approved fed regimen where applicable. Food is part of dose optimization, not optional advice.	A/B	[158]
Neratinib		Supports labeled exposure; take with food consistently	High-fat meal increased $C_{\max}$ by 70% and AUC _{inf} by 120%; standard breakfast increased $C_{\max}$ by 20% and AUC _{inf} by 10%.	Take with food. Avoid irregular high-fat boosting. Maintain consistent dosing and manage diarrhea prophylactically when indicated.	A	[159,160]
Nintedanib		Improves tolerability and modestly increases exposure; take with food and liquid	Food increased exposure by about 20% and delayed median $T_{\max}$ from about 2.00 h fasting to 3.98 h fed.	Take twice daily with food. This is mainly a tolerability and consistency instruction.	A	[161,162]
Pirfenidone		Improves tolerability by lowering peak concentration; take with food	Food had modest effect on total exposure but lowered peak concentrations; FDA review notes reduced nausea and dizziness, with $C_{\max}$ reduction around 40% to 50%.	Take with food to improve tolerability. The effect is mainly lower peak-related adverse effects rather than exposure enhancement.	A	[120,163]
Metformin extended-release		Supports exposure and GI tolerability; take with meals, often evening meal for once-daily XR	Food increased metformin XR AUC by about 50%; $C_{\max}$ and $T_{\max}$ were not substantially affected.	Take with meals to support tolerability and product-specific exposure.	A/D	[119,164]
Pretomanid		Ensures antitubercular exposure; take with food	High-fat/high-calorie meal increased $C_{\max}$ by 76% and AUC _{inf} by 88% vs fasting.	Take with food in multidrug-resistant TB regimens.	A	[165,166]

Conventional and formulation-dependent isotretinoin products	Increases absorption and reduces underexposure; conventional products should be taken with food, preferably fat-containing	Older data found relative bioavailability about 1.5- to 2-fold greater with food. For micronized isotretinoin, fed-to-fasted ratios were 125.0% for AUC _{0-t} , 123.5% for AUC _{0-inf} , and 110.3% for C _{max} .	Conventional isotretinoin should be taken with food. For newer formulations, use product-specific guidance because food dependence is smaller but not identical.	A	[167,168]
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Evidence: A, regulatory labeling or controlled human PK/PD evidence; B, randomized trial, systematic review, meta-analysis, or major guideline; C, observational clinical evidence; D, case report, pharmacovigilance, or expert opinion; E, preclinical, in vitro, animal, microbiome, omics, or computational evidence.

Abbreviations: AF, Atrial Fibrillation; ALK, Anaplastic Lymphoma Kinase; AUC, Area Under the Concentration–Time Curve; AUC₀, Area Under the Curve from Time 0; C_{max}, Maximum Plasma Concentration; CFTR, Cystic Fibrosis Transmembrane Conductance Regulator; Tenofovir DF = Tenofovir disoproxil fumarate; FDA, Food and Drug Administration; GI, Gastrointestinal; T_{max}, Time to Maximum Plasma Concentration; TB, Tuberculosis; VTE, Venous Thromboembolism; XR, Extended Release.

7. Mechanistic integration across roles

7.1 Gastrointestinal physiology and luminal environment

Gastrointestinal physiology and the luminal environment provide a common mechanistic basis through which food can function as therapy, antagonist, or enabler of pharmacotherapy. Meal intake changes gastric pH, gastric emptying, luminal viscosity, osmolarity, bile acid secretion, and intestinal fluid composition. These changes influence disintegration, dissolution, precipitation, diffusion, and absorption of orally administered drugs along the gastrointestinal tract^[169]. Meal composition is also important. High-fat and high-fiber meals can slow gastric emptying and modify small intestinal transit, thereby altering contact time with absorptive surfaces and exposure to presystemic metabolism. The clinical direction of this effect depends on drug solubility, formulation, permeability, absorption window, and site of action^[170,171].

Clinical evidence illustrates how these gastrointestinal mechanisms translate into clinically relevant food–drug effects. In patients receiving levothyroxine tablets, Benvenga et al.^[72] reported eight clinical cases in which concomitant coffee or espresso intake was associated with inappropriately high or nonsuppressed thyroid-stimulating hormone concentrations; subsequent absorption testing demonstrated reduced thyroxine exposure when levothyroxine was taken with coffee, supporting temporal separation of the drug from interfering beverages. Oral semaglutide provides a formulation-dependent example: in a controlled clinical pharmacokinetic study, administration in the fed state resulted in limited or no measurable semaglutide exposure, whereas fasting administration with up to 120 mL of water and at least 30 min of post-dose fasting produced clinically relevant exposure^[74]. Conversely, rivaroxaban illustrates food-mediated enablement, as the absorption of the 15- and 20-mg doses is reduced under fasting conditions, whereas administration with food achieves high oral bioavailability ($\geq 80\%$), supporting the recommendation that these doses be taken with food^[133]. Together, these examples demonstrate that changes in the gastrointestinal and luminal environment can either impair or facilitate drug absorption depending on the physicochemical and formulation characteristics of the drug.

Habitual diet further modifies the gastrointestinal environment through effects on gut motility, mucosal function, bile acid metabolism, and the gut microbiota. Diet-responsive microbial communities can alter luminal metabolism, redox conditions, and the biotransformation of nutrients and drugs^[172]. Emerging evidence indicates that the gut microbiome also contributes to variability in drug absorption, metabolism, and exposure, reinforcing the mechanistic link between diet, microbes, and pharmacotherapy^[173,174]. Dysbiosis has been associated with altered gastrointestinal motility and metabolic disease states that may secondarily affect drug handling, while selected microbial enzymes can activate, inactivate, or degrade specific orally administered agents^[175,176]. These mechanisms help explain why the same dietary pattern may support disease control, impair the activity of some drugs, and improve exposure or tolerability of others. For example, a diet that improves glycemic control or bowel function may act therapeutically, but the same pattern may also

modify drug absorption or microbial drug metabolism in ways that are clinically favorable or unfavorable depending on the compound.

The gastrointestinal lumen also functions as a nutrient-sensing and signaling interface. Enteroendocrine cells express nutrient-sensitive G protein-coupled receptors and transporters that detect glucose, amino acids, lipids, bile acids, and microbial metabolites such as short-chain fatty acids. These signals regulate gastric emptying, insulin secretion, appetite, intestinal secretion, and inflammatory tone^[176,177]. The magnitude and timing of these luminal signals can also be shaped by the post-swallow structural trajectory of the food matrix, because cellular integrity, particle size, viscosity, gel mechanics, emulsion stability, and gastric disintegration influence when, where, and in what physical form nutrients and fermentable substrates become available during gastrointestinal transit^[178]. Several of these pathways overlap with pharmacologic targets for antidiabetic, anti-obesity, and prokinetic drugs. Nutrient-driven signaling may therefore reinforce, oppose, or buffer drug effects at the level of gastrointestinal motility, secretion, and metabolic regulation^[121,175,177].

Experimental systems, including dynamic gastrointestinal simulators and microbiome-informed models, allow controlled assessment of how diet, luminal conditions, and microbial activity jointly influence drug dissolution, permeability, and presystemic metabolism^[175,179]. Recent human-relevant studies using gut-on-a-chip and physiologically based pharmacokinetic (PBPK) models provide further mechanistic insight into the interaction between diet, luminal environment, and oral drug absorption^[1,180]. These models are useful for hypothesis generation and formulation development, but their clinical interpretation still requires confirmation in human pharmacokinetic or pharmacodynamic studies. Overall, the gastrointestinal tract should be viewed not as a passive conduit for oral medications, but as a diet-responsive organ system in which pH, transit, secretion, bile acids, mucosal signaling, and microbial metabolism jointly determine whether food acts as therapy, antagonist, or enabler in a given pharmacotherapeutic context^[169,170].

7.2 Solubility, dissolution, and formulation interactions

Solubility and dissolution in the gastrointestinal lumen are major determinants of whether food antagonizes or enables oral pharmacotherapy. These effects depend on the drug's physicochemical properties, dose, formulation, and the luminal conditions created by fasting or fed states^[181]. Poorly water-soluble and lipophilic drugs, particularly many biopharmaceutics classification system class II and some class IV compounds, often depend on bile salts, dietary lipids, mixed micelles, and adequate residence time in the upper small intestine for dissolution and absorption. In such cases, a meal, especially one containing fat, may increase apparent solubility and systemic exposure, thereby enabling pharmacotherapy when the effect is predictable and incorporated into dosing instructions^[1,182]. By contrast, food may antagonize pharmacotherapy when fed-state changes reduce dissolution or promote precipitation. This is particularly relevant for drugs whose solubility decreases as gastric or intestinal pH rises, or for formulations whose release characteristics are sensitive to meal-induced changes in pH, fluid volume, viscosity, or transit time^[170].

Formulation design can either reduce or intentionally use food-related effects. Solid dispersions, crystalline form optimization, hydrophilic carriers, and other formulation approaches can improve dissolution

in biorelevant media and reduce dependence on variable luminal conditions. Experimental work with drugs such as celecoxib, naproxen, and phenytoin illustrates how changes in crystalline structure and dispersion systems may accelerate dissolution and partially limit negative food effects, although translation to clinical exposure depends on the specific formulation and in vivo conditions^[183]. Similarly, excipients such as surfactants, polymers, and pore-forming agents can improve wetting, inhibit precipitation, or maintain supersaturation in intestinal fluids, thereby reducing the need for a high-fat meal to achieve adequate exposure for selected poorly soluble drugs^[184].

Advanced delivery systems may also smooth differences between fasted and fed states^[185]. Nanosuspensions, solid lipid systems, and polymeric nanoparticle formulations can improve apparent solubility and dissolution rate across a range of luminal conditions, potentially reducing exposure variability related to meal composition^[186]. However, these technologies should not be assumed to eliminate clinically relevant food effects without direct pharmacokinetic evidence. Conversely, some lipid-based formulations are designed to perform best in the presence of bile secretion and dietary lipids, making co-administration with food an intentional enabling strategy rather than an incidental interaction^[108,182].

Thus, solubility, dissolution, and formulation are not only pharmaceutical development considerations; they are clinical determinants of how food should be classified for a given oral drug. Food acts as an enabler when it reproducibly improves dissolution, absorption, or exposure within a safe therapeutic range. It acts as an antagonist when it reduces bioavailability, increases variability, or produces unsafe exposure changes. The same meal-related mechanism may therefore support or impair pharmacotherapy depending on drug properties, formulation design, dosing instructions, and patient adherence to the required prandial conditions^[186].

7.3 Enzyme and transporter networks

Enzyme and transporter networks provide a mechanistic link between diet and drug disposition, allowing the same dietary exposure to increase, reduce, or have little effect on drug exposure depending on the compound and clinical context^[169,187]. Food-derived constituents can modulate cytochrome P450 enzymes, UDP-glucuronosyltransferases, and other biotransformation pathways, as well as intestinal, hepatic, and renal transporters such as P-glycoprotein, BCRP, OATP1B1, OCTs, and OATs^[187,188]. Recent human quantitative proteomics and functional studies confirm that these enzymes and transporters are variably expressed in the jejunum and ileum, with interindividual differences that can influence drug absorption and exposure^[189,190]. These effects may alter intestinal absorption, first-pass extraction, hepatic uptake, biliary excretion, renal clearance, and tissue distribution. Their clinical importance is greatest for drugs with narrow therapeutic indices, steep exposure-response relationships, extensive presystemic metabolism, or dependence on specific uptake or efflux transporters.

As discussed earlier, several food-derived or botanical constituents have been shown to affect drug-metabolizing enzymes and transporters, although much of this evidence remains experimental. Flavonoids and alkaloids can inhibit transporters such as OCT1 or OATP1B1 in cellular and animal models,

while ethnobotanical extracts such as *Phyllanthus amarus* may produce mixed effects by inducing CYP expression through nuclear receptor pathways while also inhibiting enzyme activity^[56,61,62]. High intake of quercetin and its conjugates has been shown to inhibit CYP3A4, OATP1B1, and BCRP in human in vitro and ex vivo studies, suggesting potential clinical relevance when combined with sensitive drug substrates^[191]. Such findings support biological plausibility, but they should not be interpreted as direct clinical dosing guidance without human exposure and outcome data. The interaction risk is more credible when intake involves concentrated extracts, supplements, or repeated high exposure, and when the affected drug depends strongly on the enzyme or transporter pathway involved.

Diet may also influence drug disposition indirectly by modifying bile acid metabolism, intestinal barrier function, inflammation, and the expression of nutrient and xenobiotic transport systems. Experimental models show that dietary factors can alter bile acid synthesis and transport, including pathways such as Cyp7a1 and ileal bile acid transporters, which may affect drugs undergoing biliary excretion or enterohepatic recycling^[192]. Other preclinical studies suggest that dietary interventions can modify intestinal nutrient transporters, tight junction proteins, and permeability, with potential downstream effects on absorption of drugs or prodrugs that share related uptake pathways^[193,194]. Emerging human evidence indicates that gut microbiota can regulate intestinal drug transporters, including P-gp, BCRP, and OATPs, through metabolites such as SCFAs and secondary bile acids, impacting interindividual pharmacokinetic variability^[195]. These observations are mechanistically informative but remain context dependent, and their clinical relevance should be assessed according to the drug substrate, dose, formulation, and patient risk profile.

Within the proposed framework, enzyme and transporter modulation can place food in different roles. Food acts as an antagonist when it induces clearance, increases efflux, reduces uptake, or otherwise lowers active drug exposure, or when it increases systemic exposure to a toxic range. It acts as an enabler when a predictable effect on metabolism or transport improves bioavailability, reduces variability, or supports therapeutic exposure within a safe range. It may contribute therapeutically when sustained dietary change improves endogenous metabolic or transport pathways relevant to disease control, although this role should be distinguished from short-term pharmacokinetic modulation^[169,196]. Mapping diet-responsive enzyme and transporter pathways to specific drugs, formulations, and patient contexts is therefore essential for determining whether a food exposure should be avoided, standardized, monitored, or intentionally used to support pharmacotherapy.

7.4 Nutrient–drug pharmacodynamics

Nutrient–drug pharmacodynamics occurs when nutrients, foods, or food-derived constituents influence the same physiological targets or pathways as pharmacotherapy, independent of changes in drug exposure^[9,197]. These interactions may be synergistic, antagonistic, or context dependent. Classic examples include vitamin K intake opposing warfarin activity through the gamma-carboxylation pathway, sodium intake attenuating the effect of antihypertensive therapy through effects on volume status and vascular tone, and potassium intake increasing hyperkalemia risk in patients receiving renin-angiotensin-aldosterone system

inhibitors^[9,14,198]. In each case, the nutrient modifies the same biological endpoint targeted by the drug, so clinical response may change even when pharmacokinetic exposure is unchanged.

Micronutrient status may also influence pharmacodynamic response in selected therapeutic areas. Vitamin D metabolism, for example, involves intestinal and hepatic pathways that overlap with drug-handling systems, and vitamin D deficiency or high-dose supplementation may modify responses to therapies acting on bone, mineral metabolism, or related endocrine pathways^[199]. In older adults, polypharmacy and altered micronutrient intake may interact at shared biological systems, including saliva composition, mineralization, bone health, and mucosal integrity, with potential consequences for treatment outcomes and adverse effects^[200]. Recent studies also highlight the role of gut microbiota in modulating nutrient-pharmacodynamic interactions, such as vitamin K synthesis affecting warfarin anticoagulation and short-chain fatty acids influencing immune or metabolic drug targets^[201,202]. These examples support a clinically relevant distinction: nutrients may not only affect drug disposition, but may also alter the physiological state in which drug action occurs.

Food-derived constituents and diet-responsive metabolites can also influence central nervous, endocrine, metabolic, and immune pathways that are pharmacologic targets. For example, bergamot essential oil has shown anxiolytic-like effects in preclinical and mechanistic studies involving serotonergic 5-HT_{1A} signaling and olfactory-cortical circuits, but these findings should be interpreted as early mechanistic evidence rather than proof of clinical substitutability for established anxiolytic therapy^[203,204]. Similarly, gut microbiota-derived metabolites, including short-chain fatty acids and secondary bile acids, can influence immune and metabolic pathways relevant to immunotherapies, antidiabetic agents, and lipid-lowering drugs^[173,175,205]. Interindividual differences in diet-microbiome metabolism may therefore contribute to variability in pharmacodynamic response at similar drug exposures.

The interaction is bidirectional. Drugs can also modify nutrient handling by inhibiting or altering intestinal transporters for glucose, folate, bile acids, or other endogenous substrates, thereby changing the nutritional and metabolic context in which other therapies act^[206]. Within the proposed framework, nutrient-drug pharmacodynamics places food in different roles according to intent and effect. Food acts as therapy when nutrient or dietary modulation supports disease control, as an antagonist when it opposes the intended pharmacologic response or increases toxicity risk, and as an enabler when it improves the physiological conditions required for safe or effective drug action. Clinical interpretation should therefore focus on the shared endpoint, the magnitude of the effect, the stability of the dietary exposure, and the vulnerability of the patient rather than on the presence of a nutrient-drug overlap alone^[9,173,207].

7.5 Systems and data-driven approaches

The integration of chemical, pharmacologic, dietary, microbiome, clinical, and pharmacovigilance datasets enables systems-based and data-driven approaches to predict, classify, and prioritize food–drug relationships. Graph-based and machine-learning models increasingly represent drugs, food constituents, enzymes, transporters, adverse events, and interaction endpoints as connected nodes within knowledge

networks built from sources such as DrugBank, FAERS, curated food composition databases, and natural-language-processed literature^[208,209]. These models can identify candidate drug-food interactions, predict potential mechanisms, and prioritize interactions for further study, including effects on absorption, metabolism, transport, or toxicity^[173,210]. However, their outputs should be considered hypothesis-generating unless supported by experimental validation, human pharmacokinetic data, or clinical outcome evidence. High internal model performance does not by itself establish clinical actionability, especially when dietary exposure, dose, formulation, and patient context are incompletely captured.

Quantitative systems pharmacology and pharmacometric models provide a complementary approach by incorporating food, nutrient exposure, meal timing, body composition, microbiome-related variables, or disease-specific nutritional states as covariates in pharmacokinetic/pharmacodynamic (PK/PD) models^[211,212]. These approaches enable simulation of how diet or specific food constituents may alter exposure-response relationships, toxicity risk, or the likelihood that a food exposure functions as therapy, antagonist, or enabler^[175,213]. Their main value is in prioritizing mechanisms for targeted clinical evaluation, informing food-effect study design, and identifying patients or regimens that may require labeling, monitoring, or dietary counseling^[214].

Multi-omics and systems biology approaches extend this framework by linking dietary exposures to molecular phenotypes that can be mapped onto drug targets and pathways^[215]. Metabolomics, transcriptomics, and proteomics can identify circulating and gut-derived metabolites associated with dietary patterns, while network analyses map these metabolites to pharmacologic pathways involved in efficacy or toxicity. Integration with microbiome data (pharmacomicrobiomics) allows prediction of interindividual variability in drug response based on diet-microbiome interactions^[216,217]. These approaches may eventually support patient stratification according to diet-microbiome-drug response profiles, but current use remains mainly investigational and should not replace established clinical monitoring.

Pharmacovigilance and real-world data systems are also relevant to this framework. Spontaneous reporting systems, electronic health records, dispensing data, and dietary information can be combined to detect potential food-drug safety signals, examine whether suspected interactions occur in routine care, and refine risk estimates across patient subgroups^[218]. Such signals require careful interpretation because confounding, incomplete diet documentation, recall bias, and under-reporting are common. Overall, systems and data-driven methods are best viewed as tools for prioritization, prediction, and signal detection. The clinical value of these approaches depends on transparent models, external validation, standardized dietary exposure data, and prospective studies that demonstrate whether model-informed dietary recommendations improve drug efficacy, safety, or adherence^[219,220]; biological plausibility and predictive performance should therefore be distinguished from clinical actionability.

8. Clinical application of the framework

8.1 Integration into prescribing and medication review

Applying the proposed framework in clinical practice begins with making food-related instructions explicit during prescribing and medication review. For each clinically relevant drug-diet relationship, food can be documented according to its intended role: therapeutic agent, antagonist, or enabler. Therapeutic roles include structured dietary interventions used to support disease control, such as sodium restriction in heart failure or dietary modification in metabolic dysfunction-associated steatotic liver disease. Antagonistic roles include foods or nutrients that reduce efficacy or increase toxicity, such as unstable vitamin K intake during warfarin therapy or grapefruit products with susceptible CYP3A substrates. Enabling roles include food intake required or recommended to improve drug exposure, tolerability, or adherence, such as administration with a meal for drugs with clinically important fed-state absorption^[59,200,221]. A practical workflow for assessing and managing food-informed pharmacotherapy is presented in Fig. 2.

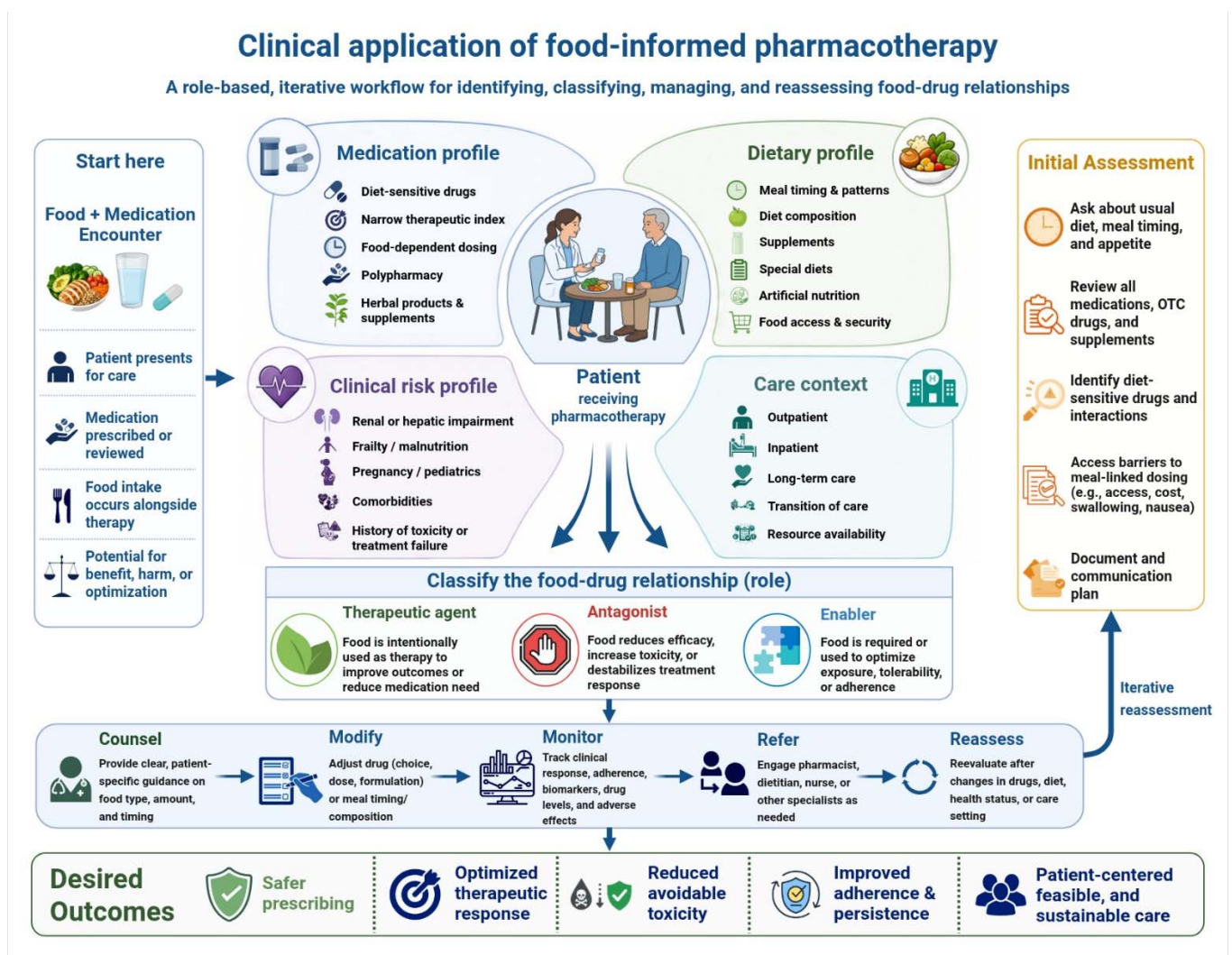


Fig. 2. Food-informed pharmacotherapy assessment and management workflow.

This role-based information can be incorporated into prescribing systems, pharmacy records, and medication lists as structured instructions rather than nonspecific free text. Existing regulatory and labeling practices already classify many interaction risks according to mechanism, including CYP3A inhibition, transporter involvement, dose limits, contraindications, and monitoring requirements^[59,221,222]. A similar approach can be applied to food-drug relationships by specifying the relevant dietary exposure, the

mechanism, the clinical consequence, and the required action. Examples include “take with a meal,” “take consistently with respect to food,” “avoid grapefruit products,” or “maintain consistent vitamin K intake.” Embedding these instructions in computable fields could improve consistency across prescribers and care settings, although implementation should be guided by evidence strength and clinical importance to avoid excessive alerts^[221,223,224].

Medication reconciliation provides a practical point for applying this framework, particularly in patients with polypharmacy, multimorbidity, restrictive diets, or irregular meal patterns^[218,223]. During reconciliation, clinicians and pharmacists can compare each medication with the patient’s usual diet, supplement use, food access, and meal timing. This process can identify antagonistic exposures, such as high sodium intake in patients treated for hypertension or heart failure, interacting supplements, or inconsistent vitamin K intake during warfarin therapy. It can also identify underused enabling strategies, such as failure to take food-dependent drugs with an adequate meal or missed opportunities to use meals to reduce gastrointestinal intolerance^[200,218].

In medication optimization, the framework can guide coordinated changes to drug choice, dose, timing, monitoring, and dietary counseling. High-risk food-drug relationships should be prioritized when the drug has a narrow therapeutic index, a steep exposure-response relationship, serious toxicity, or strong dependence on meal conditions. Lower-risk relationships may require counseling and follow-up rather than immediate regimen change. Similarly, examples supported by regulatory labeling, controlled human PK/PD studies, randomized trials, systematic reviews, or consistent clinical evidence should be prioritized for direct prescribing instructions, counseling, or monitoring, whereas lower-certainty signals require individualized interpretation or further validation. Color-coded or tiered decision-support approaches, similar to those used in pharmacogenomic-assisted prescribing, may help distinguish interactions requiring urgent action from those requiring monitoring or patient education^[225]. In this way, food-related considerations become part of routine pharmacotherapy management rather than a separate nutritional issue addressed only after treatment failure or toxicity occurs.

8.2 Structured dietary assessment and patient counseling

Structured dietary assessment for pharmacotherapy does not require a comprehensive nutritional work-up in every patient. A focused minimum data set can capture the dietary variables most likely to affect drug exposure, response, safety, or adherence^[226,227]. Key elements include habitual intake of salt, alcohol, grapefruit and related citrus products, green leafy vegetables, protein and total energy, fiber, and over-the-counter supplements. Meal timing should also be assessed, including fasting practices, skipped meals, night eating, shift work, and irregular eating patterns. Special diets, such as ketogenic, very-low-calorie, plant-based, elimination, or medically prescribed diets, should be documented because they may alter drug absorption, pharmacodynamics, or regimen feasibility^[227,228].

Brief diet screeners can support this process in routine care. Validated food-based questionnaires and structured diet history tools can identify high-risk dietary patterns without requiring a full dietetic assessment

at every encounter^[226,228,229]. Web-based and mobile tools, including electronic food frequency questionnaires and meal-based diet history instruments, may further improve capture of meal composition and timing, especially when linked to medication review or electronic prescribing systems^[230-232]. In settings where digital tools are unavailable, a focused verbal or paper checklist using the same core elements can still standardize dietary assessment during prescribing, reconciliation, and follow-up^[226-228].

Patient counseling should then be organized according to the role of food in the patient's regimen. When food functions as therapy, counseling should emphasize preserving or implementing the beneficial dietary pattern, such as a Mediterranean-style dietary pattern for cardiovascular prevention or adequate protein and energy intake in patients at risk of malnutrition^[227,228,233]. When food functions as an antagonist, counseling should quantify the relevant exposure and provide specific, feasible changes. Examples include stabilizing vitamin K intake during warfarin therapy, avoiding grapefruit products with susceptible CYP3A substrates, limiting excessive sodium intake in hypertension or heart failure, or separating interacting supplements from drugs affected by chelation. This approach is preferable to broad prohibitions because it links the dietary advice to a defined clinical mechanism and patient-specific behavior^[226,228,234]. When food functions as an enabler, counseling should specify the timing, amount, and type of food needed for the medication to work as intended. Instructions such as "take with food" are often too vague. More actionable counseling may state whether the drug should be taken with the main meal, with a meal containing fat, with a minimum caloric intake, or consistently in relation to meals. Aligning these instructions with the patient's usual eating pattern can improve feasibility and adherence, particularly for patients with irregular schedules, low appetite, food insecurity, or complex regimens^[229,230,234].

Dietary assessment should be repeated when medications are started, stopped, dose-adjusted, or when disease control changes unexpectedly. Follow-up using brief screeners or targeted questions allows clinicians to determine whether the intended dietary behavior has been adopted and whether pharmacotherapy should be adjusted. In this way, diet is treated as a dynamic component of the treatment plan rather than a static background exposure^[228,229,235].

8.3 Interprofessional workflows

Interprofessional workflows are essential for managing food-pharmacotherapy relationships because clinically relevant issues often span diagnosis, prescribing, dispensing, dietary assessment, and patient behavior. Effective implementation requires shared protocols and clear communication among prescribers, pharmacists, dietitians, nurses, and other members of the care team^[236,237]. Prescribers define therapeutic priorities, select pharmacotherapy, and identify patients in whom diet is likely to alter efficacy or safety, such as those with multimorbidity, polypharmacy, malnutrition, obesity, renal or hepatic impairment, restrictive diets, stimulant therapy, or weight-loss pharmacotherapy^[236,238]. Their role includes recognizing when food is part of treatment, when it may oppose drug action, and when it is required to enable adequate drug exposure or tolerability.

Pharmacists are central to identifying and managing pharmacokinetic and pharmacodynamic food-drug interactions. They can review medication lists for drugs affected by meal timing, gastric pH, chelation, CYP enzymes, transporters, alcohol, grapefruit products, vitamin K, and dietary supplements. They are also well positioned to translate interaction information into practical recommendations, including dose timing, separation from interacting foods or supplements, monitoring plans, and escalation to the prescriber when drug choice or dose adjustment is required^[236,237]. Dietitians contribute by assessing habitual intake, food access, meal timing, nutritional status, and feasibility of dietary advice. They can design dietary plans that support therapeutic goals while minimizing antagonistic interactions and enabling medications that require food for absorption or tolerability^[122,236].

Operationalizing this approach requires structured workflows rather than informal consultation. Key transition points include hospital admission, discharge, initiation of high-risk medications, medication reconciliation, oncology or transplant reviews, anticoagulation visits, and management of patients with complex metabolic or gastrointestinal disease. At these points, pharmacists can screen for high-risk food-drug issues and document them in the electronic record, while dietitians can conduct focused dietary assessment and provide patient-specific meal or supplementation guidance^[218,235,237]. Prescribers can then adjust drug selection, dosing, monitoring, or referral plans based on the combined pharmacologic and nutritional assessment.

Shared documentation should specify the food role, the mechanism, the clinical risk, and the required action. For example, the record should distinguish “maintain consistent vitamin K intake during warfarin therapy,” “avoid grapefruit products with this CYP3A substrate,” and “take this medication with the main meal to ensure adequate exposure.” This level of specificity reduces conflicting advice and supports consistent counseling across clinicians, pharmacists, and dietitians. Multidisciplinary meetings, virtual case conferences, or embedded pharmacist-dietitian review models may be especially useful for patients with severe obesity, eating disorders, complex neuropsychiatric treatment, frailty, cancer therapy, transplant regimens, or advanced kidney, liver, or heart disease^[122,236]. In this model, food-pharmacotherapy management becomes a shared clinical responsibility, with each profession contributing to a unified treatment plan rather than addressing diet and medication as separate domains.

8.4 Special clinical scenarios

Polypharmacy and multimorbidity create a high-risk context in which food-pharmacotherapy relationships are more numerous, less visible, and more clinically consequential^[239]. Patients with advanced age, cancer, diabetes, infectious disease, chronic kidney disease, frailty, or functional decline commonly receive multiple concurrent medications and are at increased risk of adverse drug reactions, drug-drug interactions, and dosing complexity. These same patients often have diet-related vulnerabilities, including malnutrition, obesity, altered appetite, renal or hepatic impairment, and limited food access. As a result, food may simultaneously function as therapy, antagonist, and enabler within the same regimen. Examples include protein and energy support as therapy for frailty or malnutrition, excess sodium intake as an antagonist of heart

failure or antihypertensive therapy, and meal intake as an enabler for drugs requiring fed-state administration. In these settings, dietary factors should be incorporated into structured medication review, deprescribing, and individualized pharmacotherapy management rather than addressed separately^[240-243]. Review protocols should identify diet-sensitive drugs, including anticoagulants, diuretics, renin-angiotensin-aldosterone system inhibitors, glucose-lowering agents, antimicrobials, immunosuppressants, and drugs with narrow therapeutic indices or strong food effects. For each drug, clinicians should determine whether current dietary intake supports therapy, opposes the intended pharmacologic effect, or is needed to optimize exposure or tolerability. This role-based approach can help prioritize which food-drug issues require immediate intervention, laboratory monitoring, patient counseling, or regimen simplification, especially when clinical time and patient capacity are limited^[239,240,244].

Special diets add another layer of complexity because they intentionally alter nutrient exposure, body weight, gastrointestinal physiology, or metabolic status^[227,241]. Very-low-calorie, ketogenic, elimination, plant-based, and other restrictive diets may be used for obesity, diabetes, epilepsy, gastrointestinal disease, or patient-directed health goals. These diets can change glycemic control, blood pressure, volume status, electrolyte balance, renal function, hepatic metabolism, and medication adherence. In patients receiving glucose-lowering drugs, antihypertensives, diuretics, anticoagulants, or psychotropic medications, rapid dietary change may therefore require closer monitoring and possible dose adjustment^[243-246]. The goal is not to discourage therapeutic diets, but to align dietary change with medication safety and treatment intent.

Artificial nutrition requires specific attention in patients receiving complex pharmacotherapy. In critically ill and nutritionally vulnerable patients, clinical assessment may identify the need for enteral or parenteral nutritional support^[227]. Medication management in these settings should consider organ function, route and timing of administration, and potential incompatibilities, particularly in older patients with multimorbidity and polypharmacy^[240,241]. Enteral feeding may also interfere with selected orally administered drugs; for example, tube feeds containing divalent cations can reduce fluoroquinolone absorption, requiring appropriate separation between feeding and drug administration^[241].

Across these scenarios, the framework helps clinicians map how diet, special nutrition plans, and artificial nutrition intersect with complex medication regimens. The practical task is to define the food role, identify the mechanism, assess patient-specific risk, and implement a monitoring or adjustment plan. This approach supports proactive management of food-pharmacotherapy interactions instead of reacting only after treatment failure, toxicity, or intolerance occurs.

8.5 Life-stage and special-population considerations

Life stage and physiological status can alter how food functions within pharmacotherapy. In children, older adults, and pregnant women, differences in physiology, meal patterns, formulation use, supplement exposure, and monitoring needs may determine whether food acts as therapy, antagonist, or enabler. These populations therefore require explicit, individualized classification within the proposed framework.

In children, food-pharmacotherapy relationships are shaped by developmental stage, caregiver-administered dosing, acceptability of formulations, school or family meal routines, and frequent use of liquids, dispersible tablets, crushed tablets, or food vehicles to support administration. Food may function therapeutically when dietary strategies directly modify disease activity or reduce the need for pharmacologic escalation. For example, Crohn's Disease Exclusion Diet combined with partial enteral nutrition induced corticosteroid-free sustained remission in children with mild-to-moderate Crohn's disease, while ketogenic dietary therapy has been tested against further antiseizure medication in infants with drug-resistant epilepsy^[43,44]. Food may also enable pharmacotherapy by improving palatability, tolerability, and adherence when administration is aligned with feeding routines. However, it may antagonize therapy when drugs are mixed with unsuitable foods, administered with mineral-containing products, or given alongside feeds that alter absorption. This is particularly relevant for chelation-sensitive antimicrobials, integrase inhibitors, thyroid hormone, and drugs administered through enteral feeding schedules^[76,77,80]. Pediatric food-related instructions should therefore specify the formulation, timing, acceptable administration vehicle, feeding schedule, and caregiver role.

Older adults require special attention because food-pharmacotherapy relationships often occur in the context of polypharmacy, multimorbidity, frailty, sarcopenia, dysphagia, cognitive impairment, renal impairment, food insecurity, and frequent use of non-prescription products or dietary supplements^[239-247]. The gastrointestinal physiological state of older adults can further modify the role of food in oral pharmacotherapy. Advanced age is associated with substantial interindividual variability in gastrointestinal conditions relevant to drug absorption, including gastric motility and emptying, luminal fluid volume and composition, and intestinal permeability, while comorbidities, frailty, atrophic gastric disorders, and concomitant medications may further modify these processes. Consequently, meal-induced changes in gastric emptying, luminal pH, bile secretion, and intestinal solubilization may influence drug dissolution and absorption differently in older adults than in younger populations^[248,249]. These effects are particularly relevant for drugs with pH- or food-dependent absorption, limited solubility, narrow absorption windows, or narrow therapeutic indices. Food may therefore act as an enabler when fed-state conditions improve dissolution, absorption, or tolerability, but as an antagonist when altered gastrointestinal conditions delay, reduce, or destabilize drug exposure. Food-related dosing instructions in older adults should thus be interpreted in conjunction with gastrointestinal function, comorbidities, formulation characteristics, and concomitant medications rather than on chronological age alone. In this population, food may act therapeutically when medically tailored meals, protein-energy support, or structured dietary interventions improve nutritional reserve, functional status, metabolic control, or treatment tolerance^[21,22]. Food may also enable drug therapy by anchoring medication use to regular meals or reducing gastrointestinal intolerance. Conversely, food may antagonize pharmacotherapy when irregular intake destabilizes anticoagulation, high sodium intake blunts antihypertensive or heart-failure therapy, oral nutritional supplements alter mineral exposure, or botanical products affect drug metabolism and blood pressure^[83,84,101-105]. Older adults also frequently receive drugs

with clinically important food-dependent dosing requirements, making relatively small changes in meal composition or timing clinically meaningful. Medication review in this group should therefore include usual meal timing, appetite, swallowing ability, dietary supplements, oral nutritional products, food access, kidney function, and the feasibility of fasting or fed-state dosing instructions.

Pregnancy adds another layer of complexity because maternal disease control, fetal safety, nutritional adequacy, and drug exposure must be considered together. Food may function therapeutically by supporting maternal and fetal nutritional requirements, glycemic control, blood-pressure management, and correction of micronutrient deficiency. Clinical trials in pregnancy show that pharmacotherapy decisions for chronic hypertension and diabetes must be interpreted in relation to maternal benefit, fetal safety, and changing physiological demands^[250,251]. Food may also enable pharmacotherapy when taking medication with meals improves tolerability during nausea, vomiting, reflux, or reduced appetite. At the same time, routine use of prenatal iron, calcium, magnesium, folate, and multivitamin supplements can complicate oral drug administration, especially for drugs affected by chelation or absorption changes. Human pharmacokinetic studies showing reduced exposure of integrase inhibitors when administered with mineral supplements illustrate why supplement timing may be clinically important in pregnant patients receiving oral therapies^[76,77]. Pregnancy-related safety concerns, as shown in large antiretroviral pregnancy cohorts, further emphasize that food- and supplement-related recommendations should be evaluated within a maternal-fetal risk framework rather than by maternal pharmacokinetics alone^[252].

Across life-stage groups, clinicians should define the role of food according to the patient, drug, formulation, timing, and treatment goal. Children require caregiver-centered dosing and attention to formulation-food compatibility; older adults require nutrition, supplement, polypharmacy, renal, and adherence assessment; and pregnant women require coordination with supplement timing, nausea management, maternal nutrition, and fetal safety. This approach clarifies why the same food exposure may be therapeutic, antagonistic, or enabling depending on clinical context.

9. Implications for research, policy, and education

9.1 Standardized terminology and classification

Standardized terminology is needed to make food-pharmacotherapy interactions comparable across studies, labels, guidelines, and clinical decision-support systems. A role-based nomenclature can classify each clinically relevant food exposure in relation to a specific drug and patient context as therapy, antagonist, or enabler. “Therapy” denotes food or nutrient exposure used intentionally as part of disease management. “Antagonist” denotes food exposure that reduces efficacy, increases toxicity, or destabilizes response. “Enabler” denotes food exposure required or strongly recommended to support safe or effective drug use. Within this role, exposure enablement refers to food-mediated improvement or stabilization of drug exposure, tolerability enablement refers to reduction of treatment-related adverse effects, and adherence/feasibility enablement refers to food- or meal-related conditions that facilitate consistent and sustainable medication use. These labels should be recorded as structured attributes rather than embedded only in narrative instructions.

Role labels should be paired with mechanism-based descriptors. The primary mechanism may be pharmacokinetic, such as altered gastric emptying, solubility, CYP activity, transporter function, or absorption; pharmacodynamic, such as opposing effects on coagulation, blood pressure, glycemia, or electrolytes; microbiome-mediated; behavioral or contextual; or mixed. This approach aligns food-pharmacotherapy classification with established drug-drug interaction frameworks and with labeling approaches that already organize recommendations around mechanism, clinical severity, dose modification, contraindications, and monitoring^[59,221,222]. Classification should also specify direction of effect, magnitude, modifiability, and evidence strength. Magnitude may be graded according to exposure change, biomarker effect, clinical outcome, or toxicity risk. Modifiability should distinguish exposures that can be easily changed, standardized, separated from dosing, monitored, or are difficult to modify because of food access, culture, disease state, or artificial nutrition. Evidence level should distinguish mechanistic, preclinical, observational, randomized, labeling-based, and post-marketing evidence^[221].

A multidimensional classification would allow researchers, regulators, and clinicians to describe food-related effects on pharmacotherapy more consistently. In research reports, structured documentation of role, mechanism, magnitude, modifiability, and evidence level would improve comparability and support evidence synthesis^[253,254]. In clinical care, the same categories could be embedded into medication therapy management templates, electronic health records, pharmacy systems, and decision-support tools, extending existing documentation of drug-drug interactions, adverse effects, adherence barriers, and food-related instructions^[255]. This would help distinguish high-risk interactions requiring immediate action from lower-risk issues requiring counseling or monitoring.

At the policy level, harmonized terminology could support clearer guidance on which food-drug relationships warrant label changes, monitoring recommendations, patient education materials, or professional training^[221,255,256]. It would also support development of interoperable datasets and ontologies for pharmacovigilance, model-informed drug development, precision nutrition, and clinical decision support. The goal is not to assign permanent labels to individual foods, but to classify food roles in relation to a defined drug, mechanism, patient population, timing, and clinical intent. This context-specific classification is essential because the same food exposure may be therapeutic in one setting, antagonistic in another, and enabling in a third.

9.2 Methodological recommendations

Pharmacologic studies should report dietary context with the same consistency used for other clinically relevant covariates. At minimum, drug trials and PK/PD studies should document prespecified dietary conditions, including fasted or fed administration, meal composition, meal timing, and restrictions on key interacting foods or supplements^[257-259]. They should also report whether these instructions were implemented as planned, how adherence was assessed, and whether participants used dietary supplements, medical nutrition products, alcohol, grapefruit products, high-fat meals, or other exposures relevant to the drug under study^[227,260,261]. Brief validated screeners or food-group-based tools may be sufficient when full dietary

assessment is not feasible, provided that they capture the dietary variables most likely to alter drug exposure, pharmacodynamic response, or adherence.

Nutrition trials should apply the same principle in the opposite direction. When dietary interventions assess outcomes such as blood pressure, glycemic control, lipid levels, inflammation, adverse effects, or drug concentrations, investigators should document concurrent medications, medication changes during follow-up, and any protocolized timing between food intake and drug administration^[227,260]. Without this information, it is difficult to determine whether observed effects reflect the dietary intervention itself, changes in pharmacotherapy, or an interaction between the two. Reporting templates for “dietary context in pharmacology” and “pharmacotherapy context in nutrition” could be incorporated into CONSORT- and STROBE-style extensions to improve transparency, reproducibility, and evidence synthesis^[258,259]. Applying FAIR principles to diet and medication metadata would further support pooled analyses and secondary research by making key context variables findable, accessible, interoperable, and reusable.

Several study designs are suitable for evaluating food-pharmacotherapy relationships, but each should define the food role, mechanism, magnitude, modifiability, and evidence level in advance^[215,262]. Mechanistic crossover studies and controlled feeding trials are useful for quantifying acute pharmacokinetic or pharmacodynamic effects of defined meals, nutrients, or food constituents on specific drugs. These designs are strongest when meal composition, timing, formulation, sampling schedule, and adherence are tightly controlled. Studies of plant-derived compounds such as higenamine illustrate how standardized intake and serial sampling can clarify exposure patterns and potential interaction thresholds, although such findings require careful translation to routine clinical diets^[262].

Pragmatic randomized trials and factorial designs can then test whether dietary interventions delivered alongside usual pharmacotherapy improve clinical outcomes, tolerability, adherence, or medication requirements. These studies should record both dietary implementation and pharmacotherapy changes throughout follow-up, especially when medication escalation or de-escalation is part of usual care^[260]. Large cohorts, registries, and linked electronic health record datasets can complement trials by detecting real-world food-drug interaction signals, particularly for rare adverse events or vulnerable populations that are underrepresented in controlled trials^[261]. Nested case-control and case-crossover analyses may be especially useful when dietary exposures, medication timing, and outcome dates are sufficiently well captured.

Model-informed approaches can integrate mechanistic, clinical, and population-level data. Population PK/PD modeling, physiologically based pharmacokinetic modeling, and systems pharmacology can simulate how meal composition, dietary patterns, supplement use, nutritional status, or microbiome-related variables may alter drug exposure and response^[215]. These models are most useful for prioritizing hypotheses, identifying high-risk scenarios, and informing the design of prospective studies. They should not replace clinical validation when the proposed recommendation would change prescribing, monitoring, or dietary counseling. Future studies should aim to move promising lower-certainty food-pharmacotherapy signals toward clinically actionable evidence through controlled human PK/PD studies, pragmatic trials,

observational cohorts, and regulatory-quality dietary and medication reporting. Overall, future research should treat diet and pharmacotherapy as interacting components of the same therapeutic system, with both measured, reported, and analyzed explicitly.

9.3 Precision nutrition and individualized pharmacotherapy

Precision nutrition and individualized pharmacotherapy share a common objective: to explain and manage variability in treatment response by integrating diet, genotype, phenotype, disease state, and drug exposure^[263,264]. Large, deeply phenotyped cohorts, such as the China Precision Nutrition Biobank, are beginning to collect detailed dietary data, food challenge responses, continuous glucose monitoring, multi-omics, genomic information, and clinical outcomes in the same participants^[265]. These resources can support models that examine how dietary patterns interact with genetic and metabolic background to influence cardiometabolic risk and treatment response. Methods developed for gene-diet interaction studies, including harmonized dietary phenotypes, polygenic risk scores, causal inference, and machine learning, provide a useful template for future diet-drug-genotype analyses^[263].

Pharmacology is moving in a similar direction through genotype-informed exposure modeling. Physiologically based pharmacokinetic models that incorporate pharmacogenomic variation, such as CYP2D6 genotype-stratified models for doxepin, illustrate how genetic and clinical variables can be used to predict exposure and guide individualized dosing^[266]. Extending these models to include diet-related parameters, such as meal composition, habitual fat intake, ketogenic or very-low-calorie diets, supplement use, and microbiome-related variables, could improve prediction of food-dependent drug exposure. Experimental studies integrating diet, genotype, transcriptomics, and epigenomics in animal models also show that genetic background can modify metabolic responses to diet and pharmacologic intervention, although these findings remain primarily mechanistic and require careful translation to human care^[267,268].

Prospective studies are needed to move this field beyond retrospective subgroup analysis. In obesity, diabetes, and cardiovascular disease, trials could test whether combining specific dietary patterns with pharmacotherapies such as GLP-1 receptor agonists, SGLT2 inhibitors, statins, or antihypertensives improves outcomes when stratified by pharmacogenes, polygenic risk, baseline metabolic phenotype, or microbiome profile^[263,265]. In psychiatry and neurology, precision dosing studies could evaluate whether meal timing or meal composition modifies exposure, tolerability, or response to drugs with relevant pharmacokinetic sensitivity, while accounting for CYP genotype and patient-specific eating patterns^[266,268]. In inflammatory bowel disease and immune-mediated conditions, diet-drug-microbiome trials could examine whether dietary interventions modify response to biologics or small-molecule therapies through microbial or host metabolic pathways.

Adaptive and pragmatic trial designs may be especially useful in this area. Trials comparing standard care with precision nutrition plus individualized pharmacotherapy could embed mechanistic substudies, including pharmacokinetics, metabolomics, microbiome profiling, and transcriptomics, while still measuring clinically meaningful outcomes. Such designs would allow investigators to test whether integrated diet-drug

models improve efficacy, safety, adherence, or medication de-escalation in defined patient groups. At present, precision nutrition and individualized pharmacotherapy should be viewed as complementary but still developing fields. Their integration is promising, but clinical implementation should depend on validated predictive models, feasible dietary assessment, actionable prescribing recommendations, and evidence that the combined approach improves patient outcomes.

9.4 Education and decision support

Education and decision support are central to translating a role-based framework for food-pharmacotherapy interactions into routine care^[269]. Training for physicians, pharmacists, nurses, and dietitians should focus on a defined set of competencies: recognizing when food functions as therapy, antagonist, or enabler; understanding the main mechanisms, including absorption, CYP enzymes, transporters, microbiome effects, and pharmacodynamics; applying standardized descriptors for role, mechanism, magnitude, modifiability, and evidence level; and communicating recommendations in a way that supports adherence and shared decision making^[221,255]. Precision nutrition guidance and expert opinion surveys emphasize that training should also address variability in response related to genotype, microbiome, disease state, food access, and social context, which aligns closely with individualized pharmacotherapy^[269-271].

Educational content should be case based and clinically applied rather than limited to lists of isolated interactions. Examples such as warfarin and vitamin K, grapefruit and CYP3A substrates, food-dependent oral oncology drugs, antihypertensive therapy and sodium intake, and enteral feeding with time-sensitive medications can be used to teach role classification and management. Skills-based methods, including brief counseling, motivational interviewing, risk communication, and interprofessional simulation, may help clinicians translate complex diet-drug mechanisms into practical patient instructions^[227,272]. At undergraduate, postgraduate, and continuing professional levels, learners should be required to identify the food role, define the mechanism, assess clinical risk, recommend a management plan, and document the decision using standardized terminology.

Digital decision support is needed because the number of possible food-drug combinations exceeds what clinicians can reliably manage from memory alone^[218,273]. Building on existing interaction checkers and electronic prescribing alerts, future tools should encode food-pharmacotherapy relationships as structured data linked to drug identifiers, mechanisms, evidence strength, and patient-specific risk factors. This would allow context-specific prompts such as “avoid grapefruit products,” “maintain consistent vitamin K intake,” “take with the main meal,” or “assess food access before prescribing a food-dependent regimen”^[209,221,256]. To reduce alert fatigue, alerts should be tiered by severity, evidence level, and modifiability, with high-risk interactions prioritized for interruptive alerts and lower-risk issues directed to counseling or monitoring.

Decision support should also account for patient behavior and feasibility. Informatics and precision nutrition studies suggest that dietary patterns, meal timing, and contextual factors can be captured digitally and used to tailor recommendations, although these approaches require validation before routine clinical

deployment^[215,273]. Implementation should therefore prioritize tools that are affordable, easy to use, integrated into electronic health record and pharmacy systems, and supported by training, rather than stand-alone applications that add workload^[270]. Over time, linkage to learning health system infrastructure could allow real-world data on diet, medication use, drug exposure, adherence, adverse events, and clinical outcomes to refine interaction rules. In this way, education and decision support can connect research evidence with prescribing, dispensing, counseling, and follow-up practice.

10. Conclusion

Food-pharmacotherapy relationships should be understood as dynamic, mechanism-dependent, and clinically modifiable rather than as isolated dietary cautions. Across therapeutic areas, food may function as a therapeutic agent, an antagonist of pharmacotherapy, or an enabler of drug action. These roles depend on the drug, dietary exposure, timing, formulation, disease state, patient characteristics, food access, and clinical intent. The same food exposure may therefore support treatment in one context, impair therapy in another, or improve drug exposure and tolerability when intentionally incorporated into the regimen.

This review proposes a role-based framework that integrates pharmacokinetic, pharmacodynamic, microbiome-mediated, behavioral, and contextual mechanisms. Food can alter drug absorption through effects on gastric pH, gastric emptying, bile secretion, dissolution, and luminal binding. It can modify drug disposition through enzymes and transporters, oppose or reinforce drug effects through shared physiological pathways, and influence real-world adherence through meal timing, tolerability, cultural practices, and food security. These mechanisms provide a practical basis for classifying food as therapy, antagonist, or enabler in relation to specific drugs and patient contexts.

Clinical application of this framework requires structured dietary assessment, explicit food-related prescribing instructions, and interprofessional workflows involving prescribers, pharmacists, dietitians, and nurses. Medication review should routinely identify diet-sensitive drugs, high-risk food exposures, special diets, supplements, artificial nutrition, and barriers to meal-dependent dosing. Patient counseling should move beyond generic advice such as “take with food” or “avoid certain foods” and instead specify the mechanism, timing, amount, and clinical purpose of the recommendation.

For research and policy, standardized terminology and minimum reporting standards are needed so that dietary context and pharmacotherapy context are documented consistently in trials, observational studies, pharmacovigilance systems, and regulatory labeling. Precision nutrition, pharmacogenomics, pharmacomicrobiomics, and model-informed drug development offer promising tools for identifying patient-specific food-drug relationships, but clinical implementation should remain tied to validated evidence and measurable patient benefit. Because the supporting evidence ranges from regulatory labeling and controlled human studies to observational, mechanistic, and computational evidence, recommendations should be strongest for validated food-pharmacotherapy relationships, while emerging signals should guide monitoring, individualized judgment, or future research.

Overall, food should be conceptualized as an active component of pharmacotherapy management. Recognizing when it acts as therapy, antagonist, or enabler can improve prescribing, reduce avoidable treatment failure or toxicity, and support more individualized, feasible, and clinically coherent care.

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

No new data was generated or analyzed in this review. All information discussed in the manuscript is derived from previously published literature and publicly available sources.

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