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Between Folk Medicine and Pharmacological Risk: Non-Conventional Food Plants in Cancer-Associated Thrombosis

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Systematic Review

Keywords: Cancer-associated thrombosis, Non-Conventional Food Plants (NCFP), Petiveria alliacea, quercetin, bioaccessibility, herb-drug interactions

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11535337/v1

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Additional Declarations: No competing interests reported.

Abstract

Cancer-associated thrombosis (CAT) is the second leading cause of mortality in patients with active malignancy, driven by tumor-induced hypercoagulability and amplified by tyrosine kinase inhibitors (TKIs). Many oncology patients self-medicate with Non-Conventional Food Plants (NCFP) attributed with anticancer properties in Latin American popular medicine, an unstudied issue in anticoagulated oncology patients. Using *Petiveria alliacea* L. as a case study, this critical review evaluates herb-drug interaction evidence for NCFP bioactives against anticoagulants and anticancer therapies, with attention to INFOGEST 2.0 bioaccessibility. Evidence is classified into clinical, preclinical, and hypothesis tiers, which are often conflated. Clinically, isoquercetin reduced CAT biomarkers in a phase II trial, the only direct human evidence for antithrombotic activity of a quercetin-class compound in cancer patients. Preclinically, quercetin-rich NCFP species show antiplatelet mechanisms in vitro and in animal models, mechanistically consistent with that clinical result. *P. alliacea* shows an asymmetric profile: in vitro cytotoxicity and a recruiting phase Ib/II trial, against mutagenicity, genotoxicity, and no safety data, with safety prioritized. At the hypothesis tier, structural homology between *P. alliacea* dibenzyl trisulfide (DTS) and antiplatelet garlic organosulfurs suggests an untested hemostatic mechanism, and quercetin- and DTS-mediated inhibition of cytochrome P450 (CYP) and P-glycoprotein could alter TKI and anticoagulant exposure. Near-total absence of bioaccessibility data for NCFP infusions or decoctions remains the barrier to real-world exposure estimates. NCFP use during anticoagulation for CAT is a plausible but undocumented safety question rather than a demonstrated risk; priorities include bioaccessibility studies, standardized *P. alliacea* characterization, and culturally competent screening tools.

1. Introduction

Cancer-associated thrombosis (CAT) has emerged as one of the most clinically significant and underappreciated complications in oncology. Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, together with arterial thromboembolic events (ATE), represents the second leading cause of mortality in patients with active cancer, surpassed only by cancer progression itself [1]. The epidemiological burden of CAT is substantial: the 12-month incidence among unselected cancer patients ranges from approximately 3% to 5%, rising to 6–8% in those with advanced disease undergoing systemic therapy [2]. The incidence varies considerably according to tumor type, disease stage, treatment regimen, and individual thrombotic risk. Moreover, CAT is increasingly recognized not merely as a complication but as a potential marker of tumor progression, associated with thrombotic recurrence, poorer therapeutic outcomes, and reduced survival [3].

The pathophysiology of CAT is multifactorial and incompletely understood. Tumor cells drive a hypercoagulable state through the overexpression of tissue factor (TF) and cancer procoagulant (CP), the shedding of procoagulant microvesicles, and complex interactions with platelets, endothelial cells, monocytes, and neutrophils, an interaction mediated in part by neutrophil extracellular traps (NETs) [1, 4]. This prothrombotic milieu is further amplified by anticancer therapies, particularly tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) [3, 5].

Against this backdrop, a substantial proportion of cancer patients self-medicate with herbal and plant-based remedies alongside conventional oncological treatment. The pooled global prevalence has been estimated at approximately 22–23%, with reported rates varying widely from 3.5% to 90% [6]. Non-Conventional Food Plants (NCFP; known in the Brazilian literature as *Plantas Alimentícias Não Convencionais*) occupy a particularly ambiguous position in this landscape [8]. Several NCFP species, including *Petiveria alliacea* L. (piriri), *Tropaeolum majus* L. (capuchinha), *Rumex acetosa* L. (azedinha), and *Pereskia aculeata* Mill. (ora-pro-nóbis), contain bioactive compounds with documented or plausible activity on coagulation pathways, platelet aggregation, endothelial function, or tumor cell biology [9].

When a patient undergoing TKI therapy or anticoagulation with LMWH or DOACs simultaneously consumes preparations of *P. alliacea* as a folk anticancer remedy, the potential for clinically significant pharmacodynamic and pharmacokinetic interactions is pharmacologically plausible, though it has not been directly demonstrated in cancer patients and remains poorly characterized [11]. This gap is compounded by the near-total absence of bioaccessibility data for NCFP species consumed as infusions or decoctions [8, 12]. The present review critically examines this pharmacological intersection, aiming not to dismiss traditional botanical knowledge, which constitutes an irreplaceable dimension of food sovereignty and cultural heritage, but to articulate the evidence requirements and safety frameworks necessary for its responsible integration into the care of thrombosis-prone cancer patients. To our knowledge, no previous review has integrated current evidence on cancer-associated thrombosis, non-conventional food plants, herb-drug interactions with anticoagulants and anticancer therapies, and the impact of gastrointestinal bioaccessibility within a single clinically oriented framework.

This review deliberately integrates evidence from three literatures, cancer pathophysiology, food science, and pharmacology, that are rarely read together despite converging on a single clinical scenario. That breadth is a design choice rather than a drift in scope: assessing whether NCFP consumption is a plausible safety concern for a patient with CAT requires first establishing which hemostatic pathways anticancer therapy already perturbs (Section 3), then asking whether NCFP bioactives act on the same pathways (Sections 4 to 6). To keep this breadth from blurring the strength of the underlying evidence, every major claim from Section 4 onward is classified as clinical, derived

from trials or observational data in humans, preclinical, derived from in vitro or animal data, or hypothesis, a mechanistic inference not yet directly tested, using the explicit tiering scheme defined in Section 2.4. The second and third tiers should be read as generating questions for future research, not as demonstrated clinical risk.

2. Methodology

This work was conducted as a critical narrative review, selected in preference to a systematic review because the central question does not lend itself to a standardized PICO formulation or quantitative synthesis, given the marked heterogeneity in study designs, biological models, plant preparations, and outcomes across the relevant literature [13].

2.1 Conceptual Framework and Scope

The review was structured around a dual axis: (i) the mechanistic pathways of CAT and the hemostatic toxicities of anticancer therapies, particularly TKIs and ICIs; and (ii) the pharmacological profiles of NCFP species most commonly consumed by oncology patients in Latin American popular medicine, with a focus on compounds with documented or plausible activity on coagulation, platelet function, endothelial biology, fibrinolysis, and pharmacokinetic drug interactions. A secondary focus is the methodological gap in bioaccessibility data for NCFP species, assessed against the INFOGEST 2.0 standard as the internationally adopted benchmark for gastrointestinal bioavailability simulation of food bioactive compounds [8, 12].

Because this review spans mechanistic pharmacology, food science, and clinical hematology-oncology, an explicit evidence-tiering scheme, defined in Section 2.4, is applied consistently from Section 4 onward to keep the strength of each claim commensurate with its supporting data.

2.2 Literature Search Strategy

A structured literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science between May and June 2026, with no lower date restriction on foundational references. Search terms were organized into three thematic blocks:

Block A (CAT mechanisms and anticancer therapies): ("Cancer-associated thrombosis" OR "cancer AND thrombosis" OR "venous thromboembolism AND malignancy" OR "tyrosine kinase inhibitors AND thrombosis" OR "immune checkpoint inhibitors AND thrombosis") AND ("tissue factor" OR "platelets" OR "neutrophil extracellular traps" OR "extracellular vesicles" OR "endothelial dysfunction").

Block B (NCFP, ethnopharmacology, and hemostasis): ("Non Conventional food plants" OR "PANC" OR "*Petiveria alliacea*" OR "*Tropaeolum majus*" OR "*Rumex acetosa*" OR "*Pereskia aculeata*" OR "*Stachys byzantina*" OR "unconventional food plants") AND ("antiplatelet" OR "anticoagulant" OR "coagulation" OR "thrombosis" OR "hemostasis" OR "platelet aggregation" OR "tissue factor").

Block C (flavonoids, organosulfur compounds, and hemostasis): ("quercetin" OR "flavonoids" OR "polyphenols" OR "organosulfur" OR "dibenzyl trisulfide" OR "allicin") AND ("antiplatelet" OR "anticoagulant" OR "thrombosis" OR "coagulation" OR "platelet").

Additional targeted searches were performed for individual NCFP species combined with pharmacological outcome terms, and for herb-drug interactions with anticoagulants and anticancer agents. Reference lists of included reviews were manually screened. Full-text assessment was conducted in English.

Given the narrative rather than systematic design of this review, no formal record of the number of citations screened, included, or excluded at each stage was retained; this limits the reproducibility of the selection process and is acknowledged explicitly in Section 7.3.

2.3 Inclusion and Exclusion Criteria

Studies were included if they reported original data or reviewed evidence on CAT mechanisms, pharmacological data on NCFP species with hemostatic relevance, herb-drug interactions relevant to oncological care, or bioaccessibility of plant bioactive compounds using in vitro digestion models. Studies were excluded if they addressed only agricultural, purely structural-phytochemical, or botanical identification aspects without pharmacological outcomes, or were based solely on conference abstracts. Methodological limitations are explicitly appraised and summarized in Tables 1 and 2.

2.4 Evidence Appraisal and Synthesis

Evidence was appraised according to study level, in vitro, animal model, clinical trial, or clinical observation, preparation type, and translational relevance. To prevent the conflation of mechanistic plausibility with demonstrated clinical effect, three explicit evidence tiers are used consistently from Section 4 onward.

Clinical tier. Findings from randomized trials, prospective clinical trials, or observational studies conducted in human patients. Within this review, only the isoquercetin phase II trial in CAT biomarkers [15] and the ex vivo blast correlation study using patient-derived cells [16] meet this standard directly; the *P. alliacea* phase Ib/II trial (PA001) is a registered protocol without reported efficacy or safety results and is discussed as an indicator of the field's trajectory, not as clinical evidence [17].

Preclinical tier. In vitro (cell-based, enzymatic, biochemical) or animal-model findings describing a documented biological effect that has not been tested in cancer patients, for example the antiplatelet mechanisms of quercetin described in Section 4.2 or the murine antitumor data for *P. alliacea* in Section 5.2.

Hypothesis tier. Mechanistic inferences constructed by the authors from structural, pharmacokinetic, or biochemical analogy, without direct experimental testing of the specific interaction proposed, for example the DTS-garlic organosulfur structural parallel in Section 5.4 and the constructed clinical scenarios in Section 6.4.

Given the absence of randomized controlled trials on NCFP-hemostasis interactions in oncological patients, most of the synthesis in Sections 5 and 6 sits at the preclinical or hypothesis tier and is presented accordingly, as hypothesis-generating rather than as demonstrated clinical risk. Reporting follows the Scale for the Assessment of Narrative Review Articles (SANRA) criteria [13]; the tiering scheme above is offered as a supplementary transparency measure appropriate to a critical narrative review, whose source selection and synthesis are inherently more subjective than those of a systematic review, a limitation discussed further in Section 7.3.

2.5 Use of Generative Artificial Intelligence

The authors used artificial intelligence-assisted tools (Claude, Anthropic) during the preparation of this manuscript to support literature synthesis, structural editing, and language refinement. All AI-generated content was critically reviewed, verified against primary sources, and substantially revised by the authors. The authors take full responsibility for the integrity, accuracy, and originality of all content presented. AI tools were not used for data analysis, figure generation, or the formulation of scientific conclusions.

3. Pathomechanisms of Cancer-Associated Thrombosis

3.1 The Hypercoagulable State: Virchow’s Triad Revisited

The conceptual framework for understanding thrombosis in cancer patients remains anchored in Virchow’s triad, the concurrence of endothelial injury, blood flow stasis, and hypercoagulability, with malignancy perturbing all three components simultaneously and synergistically [1, 5]. Cancer creates a systemic pro-thrombotic milieu of extraordinary complexity that varies across tumor types, disease stages, and therapeutic contexts [3].

3.2 Tissue Factor, Cancer Procoagulant, and Procoagulant Extracellular Vesicles

Tissue factor (TF) is aberrantly overexpressed on tumor cells across multiple cancer types, frequently driven by oncogenic signaling including KRAS activating mutations and PTEN loss [1, 3]. Cancer procoagulant (CP) sustains low-grade coagulation cascade activation independently of TF [4]. Tumor-derived extracellular vesicles (EVs), encompassing microvesicles (100–1000 nm) and exosomes (30–100 nm), disseminate procoagulant cargo including TF, phosphatidylserine, and polyphosphates into systemic circulation, activating multiple coagulation branches simultaneously [1, 18].

3.3 Platelet Activation, NETs, and Endothelial Dysfunction

Tumor cells activate platelets through ADP/TXA2 secretion, TF-driven thrombin generation, direct receptor–ligand interactions, and engagement of podoplanin with the platelet receptor CLEC-2 [4, 19]. NETs promote thrombosis by activating FXII, degrading TFPI via elastase and cathepsin G, directly activating platelets, providing a structural scaffold that traps procoagulant cells, and promoting endothelial damage [1, 18]. Tumor-derived VEGF, TNF-α, IL-1, and reactive oxygen species induce endothelial dysfunction characterized by upregulation of TF, vWF, and adhesion molecules, and downregulation of thrombomodulin and endothelial protein C receptor [1]. Reciprocally, activated platelets provide tumor cells with PDGF, TGF-β, and VEGF, reinforcing the cancer–platelet–thrombosis loop [20].

3.4 Anticancer Therapies as Amplifiers of Thrombotic Risk

BCR-ABL inhibitors (nilotinib, ponatinib) elevate ATE risk through endothelial dysfunction, impaired NO-mediated vasodilatation, accelerated atherosclerosis, and platelet hyper-reactivity. VEGFR-TKIs (sunitinib, sorafenib, regorafenib) suppress endothelial PGI2 and NO synthesis while upregulating endothelin-1. BTK inhibitors (ibrutinib) cause paradoxical bleeding through GPVI/GPIb platelet dysfunction while increasing atrial fibrillation risk [2, 5]. ICIs establish persistent inflammatory–prothrombotic cycles with cumulative VTE incidence up to 24%

at 48 months [3]. The shift toward ATE-prone agents requires expanding CAT management beyond the VTE-centric paradigm, precisely the context in which NCFP self-medication potentially acquires clinical significance.

4. NCFP with Pharmacological Relevance to Hemostasis and Coagulation

4.1 Defining the Pharmacological Interface

Non-Conventional Food Plants (NCFP; known in the Brazilian literature as *Plantas Alimentícias Não Convencionais*, or NCFP) constitute a broad and heterogeneous group of plant species with one or more edible parts that, despite their nutritional and pharmacological potential, remain outside mainstream food production and distribution systems [8]. From a pharmacognostic perspective, a fundamental question remains: what chemical entity is the patient consuming? The limited chemical standardization of most NCFP preparations further complicates interpretation of the available evidence. Variations in botanical authentication, plant organ, geographical origin, genotype or chemotype, harvest season, post-harvest processing, extraction procedure, and analytical characterization can markedly alter phytochemical composition and, consequently, biological activity. Moreover, most pharmacological studies evaluate chemically insufficiently characterized extracts rather than standardized botanical preparations, limiting reproducibility and translational relevance, a limitation the botanical natural product field has itself flagged as a barrier to interpretable research [21]. Therefore, extrapolation from experimental studies to real-world dietary exposure should be performed with great caution. A subset contains bioactive compounds, primarily flavonoids, organosulfur compounds, polyphenols, terpenes, and lectins, whose pharmacological properties intersect directly with the hemostatic mechanisms described in Section 3.

4.2 Flavonoids: The Best-Characterized NCFP Antiplatelet Agents

Among the flavonoids relevant to this discussion, quercetin occupies a central position because it is consistently identified across several NCFP species and represents one of the best-characterized natural modulators of hemostatic function. Beyond its antiplatelet and anticoagulant activities, quercetin exhibits pleiotropic pharmacological effects, acting as a systems-level modulator of oxidative stress, inflammation, apoptosis, and cellular metabolism in cardiovascular, neurological, and metabolic disorders [22]. This broad pharmacological profile, together with its occurrence in multiple NCFP species, makes quercetin the principal flavonoid linking NCFP consumption to potential hemostatic outcomes considered in the present review.

4.2.1 Quercetin and its glycosides

Quercetin and its glycosides, present e.g. in *Tropaeolum majus* L., *Rumex acetosa* L., and *Pereskia aculeata* Mill., and widely distributed among NCFP species, are the best comprehensively characterized flavonoids with relevance to hemostatic regulation [9, 23].

Its antiplatelet mechanisms include: (i) inhibition of platelet activation and aggregation through modulation of the PI3K/Akt and MAPK signaling pathways; (ii) inhibition of integrin αIIbβ3 (GPIIb/IIIa) activation; (iii) dense granule secretion inhibition; (iv) calcium mobilization suppression; and (v) PDE2/PDE5 inhibition, elevating intraplatelet cAMP and cGMP [24]. Beyond platelet effects, quercetin inhibits thrombin and FXa activity and reduces endothelial TF expression under inflammatory conditions [9]. These multiple targets suggest that quercetin modulates several components of Virchow's triad rather than platelet activation alone [25]. *In vivo* activity operates primarily through circulating metabolites isorhamnetin and tamarixetin [23]. In *P. aculeata* leaves, rutin (quercetin-3-*O*-rutinoside) has been identified as the dominant flavonoid by UHPLC-ESI-Q-TOF-MS/MS [26]. Importantly, the biological relevance of rutin differs substantially from that of quercetin aglycone because its gastrointestinal absorption depends on microbial hydrolysis of the rutinose moiety, an aspect discussed in Section 4.5. Antiplatelet, anticoagulant, and fibrinolytic potential is not unique to quercetin but extends across the flavonoid class more generally, acting on multiple receptors and enzymes across a wide range of experimentally tested concentrations (typically 2 -300 μM), although clinical evidence beyond in vitro and in silico models remains scarce [27].

4.2.2 Kaempferol, luteolin, and isoquercetin

Kaempferol, present in *T. majus* and *Stachys byzantina* K. Koch, inhibits collagen-induced platelet activation through NADPH-dependent ROS suppression and GPVI signaling inhibition [9]. Luteolin, abundant in *S. byzantina*, attenuates pro-inflammatory cytokine secretion from endothelial cells and macrophages. Although direct antiplatelet evidence remains limited, attenuation of endothelial inflammation may indirectly reduce tissue factor expression and thrombo-inflammatory activation. Isoquercetin (quercetin-3-*O*-glucoside), the only flavonoid to enter clinical investigation specifically for CAT prevention, significantly reduced plasma TF-positive EV levels, D-dimer, platelet-dependent thrombin generation, and soluble P-selectin in a multicenter phase II trial in solid tumor patients (1000 mg/day for 56 days; D-dimer reduction − 21.9%, P = 0.0002) [15], the single clinical-tier finding on which the reasoning below rests. Although isoquercetin and rutin differ in their gastrointestinal absorption and bioavailability, discussed in Section 4.5, both yield quercetin aglycone upon hydrolysis. As rutin is the

predominant flavonoid identified in *P. aculeata* [26], a pharmacological link between NCFP consumption and antithrombotic bioactivity is mechanistically plausible at the hypothesis tier defined in Section 2.4, but remains to be experimentally and clinically validated.

4.3 Organosulfur Compounds: High Potency, High Complexity

Allium species consumed as NCFP exhibit multiple hemostatic effects involving three complementary mechanisms: (i) inhibition of platelet TXA2 formation and ADP-induced aggregation (DATS > DADS in potency); (ii) prolongation of PT and aPTT associated with inhibition of coagulation factors V, VII, VIII, IX, and X; and (iii) enhancement of fibrinolysis through t-PA stimulation and PAI-1 suppression [28]. Allicin is heat-labile, meaning hemostatic impact depends critically on processing and preparation method [29]. Roots and leaves of *Petiveria alliacea* L. are characterized by a complex phytochemical profile dominated by organosulfur compounds, including dibenzyl trisulfide (DTS), together with flavonoids (astilbin, engeletin, myricitrin) and triterpenes (isoarborinol, β-sitosterol), but controlled studies investigating its effect on hemostasis are virtually absent [10, 30], and are discussed in detail in Section 5. The well-characterized hemostatic effects of *Allium*-derived organosulfur compounds provide a mechanistic reference framework for evaluating the largely unexplored hemostatic potential of structurally related organosulfur constituents in *P. alliacea*, although such extrapolation remains, at this stage, a hypothesis rather than a tested effect, and requires direct experimental validation before it can inform clinical guidance.

It should be emphasized that these pharmacological data are derived predominantly from isolated compounds, whereas NCFP are consumed as complex phytochemical matrices in which interactions among flavonoids, phenolic acids, terpenoids, and other metabolites may influence bioaccessibility and pharmacological activity.

4.4 Systematic Overview

Table 1
Non-Conventional Food Plants with Pharmacological Relevance to Hemostasis and Coagulation in the Context of Cancer-Associated Thrombosis: Principal Bioactive Compounds, Mechanistic Targets, Evidence Levels, and Critical Gaps

NCFP Species	Common Name (BR)	Key Bioactive Compounds	Documented Hemostatic Effect	Mechanism	Study Level	Evidence Gap	Ref.
Tropaeolum majus L.	Capuchinha	Quercetin, kaempferol, isorhamnetin, isothiocyanates	Antiplatelet, anti-inflammatory	GPIIb/IIIa inhibition, PDE2/5 inhibition, TF↓	*In vitro*, animal	No clinical data; bioaccessibility unknown	[9, 24]
Rumex acetosa L.	Azedinha	Quercetin glycosides, catechins, oxalic acid	Antiplatelet, antithrombotic	PI3K/Akt/ERK/Src inhibition in platelets	*In vitro*, animal (rat)	Form of consumption not studied	[9, 24]
Pereskia aculeata Mill.	Ora-pro-nóbis	Rutin, quercetin derivatives, kaempferol, mucilage	Antioxidant, putative antiplatelet	Quercetin-class mechanism (indirect)	*In vitro* (antioxidant only)	Hemostatic studies absent; bioaccessibility under investigation	[26]
Stachys byzantina K. Koch	Peixinho	Luteolin, apigenin, terpenes, steroids	Anti-inflammatory, endothelial protection	NF-κB↓, cytokine↓	*In vitro* (macrophage model)	No platelet/coagulation data	[9]
Petiveria alliacea L.	Pirirí/Guiné	DTS, organosulfurs, astilbin, myricitrin, β-sitosterol	Cytotoxic (in vitro), putative antiplatelet	CYP1A1 inhibition, ERK1/2; organosulfur mechanism (inferred)	*In vitro* (cytotoxicity only)	MAJOR GAP: no hemostatic, bioaccessibility, or clinical data	[10, 30]
Allium ursinum L.	Alho-do-mato	Allicin, DADS, DATS, ajoene	Antiplatelet, anticoagulant, profibrinolytic	TXA2↓, PT/aPTT prolongation, t-PA↑, PAI-1↓	*In vitro*, animal, limited human	Heat-labile; form-dependent activity	[28]
Xanthosoma sagittifolium (L.) Schott	Taioba	C-glycosylated flavones (apigenin, luteolin)	Anti-inflammatory, putative antiplatelet	NF-κB pathway, endothelial protection	*In vitro*	No hemostatic or CAT-specific data	[31]
Hibiscus sabdariffa L.	Vinagreira	Anthocyanins (delphinidin, cyanidin), hibiscus acid	Antiplatelet, antihypertensive	COX/TXA2↓, platelet aggregation↓	*In vitro*, limited animal	Bioavailability poor; clinical data limited to CV endpoints	[32]

Note: DTS = dibenzyl trisulfide; DADS = diallyl disulfide; DATS = diallyl trisulfide; TXA2 = thromboxane A2; PAI-1 = plasminogen activator inhibitor-1; t-PA = tissue-type plasminogen activator; TF = tissue factor.

4.5 The Central Methodological Problem: From Extract to Exposure

The lack of standardized INFOGEST 2.0-based bioaccessibility studies for NCFP species as actually consumed, as aqueous infusions or decoctions, represents the most important methodological limitation in the evidence base reviewed in Table 1 [8, 12]. The extraction solvents used in experimental pharmacology frequently differ from the aqueous preparations consumed, resulting in substantially different phytochemical profiles and limiting translational relevance. The overwhelming majority of pharmacological studies use organic solvent extracts at concentrations bearing no relationship to systemic exposure achievable through consumption of an aqueous infusion or fresh leaf. This limitation is not merely quantitative but fundamentally qualitative, because gastrointestinal digestion transforms plant-derived compounds through several barriers before any systemic absorption can occur.

Quercetin-*O*-glucosides (monosaccharide-conjugated) are hydrolyzed by brush-border lactase-phlorizin hydrolase (LPH) and cytosolic β-glucosidase, then absorbed directly in the small intestine. Rutin (quercetin-3-*O*-rutinoside), bearing a disaccharide moiety, resists this hydrolysis and passes intact into the colon, where it depends on microbiota-derived α-rhamnosidase and β-glucosidase for conversion to the aglycone, at approximately 80% lower absorption efficiency than the small-intestinal route [33]. Because rutin is the dominant flavonoid identified in *Pereskia aculeata* leaves [26], this lower-efficiency, microbiota-dependent route, rather than the higher-efficiency route shown on the left, is the one most relevant to NCFP infusion consumption.

This glycoside-specific difference in gastrointestinal fate, summarized in Fig. 3, has direct bearing on pharmacological claims for rutin-rich NCFP species such as *Pereskia aculeata*: because rutin, rather than free quercetin or quercetin-*O*-glucosides, is its dominant flavonoid [26], it

is the lower-efficiency, microbiota-dependent colonic route, not the small-intestinal route, that governs how much quercetin aglycone actually becomes bioaccessible from an aqueous infusion of this species [33].

This glycoside-specific absorption profile has two direct implications for pharmacological risk assessment. First, in vitro pharmacological assays using quercetin aglycone or ethanolic extracts may substantially overestimate the systemic exposure achievable from rutin-rich NCFP preparations consumed as aqueous infusions; the bioaccessible fraction of rutin from *P. aculeata* tea is unknown but likely to be substantially lower than ethanolic extract studies would imply. Second, colonic microbiota composition, profoundly affected by antibiotic use and chemotherapy-induced dysbiosis (both common in oncological patients), means that the already-low colonic conversion of rutin to quercetin aglycone is additionally variable in the very patient population for whom pharmacological risk is most salient [33]. Without standardized INFOGEST 2.0 digestion models combined with colonic fermentation and phytochemical characterization of population-relevant preparations, meaningful extrapolation from NCFP consumption to systemic exposure and hemostatic pharmacological effects remains impossible. Importantly, bioaccessibility represents only the first step toward systemic exposure and should not be equated with bioavailability, which is further influenced by intestinal absorption. Phase I/II metabolism, microbial biotransformation, and tissue distribution.

5. Critical Appraisal of Anticancer Claims: as Paradigm Case

5. Critical Appraisal of Anticancer Claims: *Petiveria alliacea* as Paradigm Case

5.1 The Problem of Ethnopharmacological Anticancer Claims

The general pattern across the ethnopharmacological literature on anticancer plants is well characterized and sobering: while a large proportion of traditionally used species exhibit cytotoxic activity against cancer cell lines in vitro, the vast majority have never been tested in animals at clinically relevant doses, and fewer still have entered clinical trials [35]. Of those that reach clinical investigation, most fail to demonstrate efficacy at non-toxic doses, reflecting both the nonselective cytotoxicity common to many plant secondary metabolites and the profound difference between eliminating cells in a petri dish and treating a patient with a solid tumor. *Petiveria alliacea* exemplifies this pattern with particular acuity, but with sufficient complexity, including a recently initiated phase I/II clinical trial, to merit detailed, nuanced analysis.

5.2 Preclinical and Early Clinical Evidence

Petiveria alliacea L., known in Brazil as piriri, guiné, or mucura-caá, is the NCFP species most widely attributed with anticancer properties in popular medicine across Latin America and the Caribbean [30, 36]. At the preclinical tier, ethanolic, aqueous, and standardized extracts have demonstrated antiproliferative and cytotoxic activity against a range of cancer cell lines, with IC50 values ranging from approximately 18 to 440 µg/mL [10, 37]. A standardized aqueous extract reduced tumor burden, decreased metastasis, and modulated peripheral immune responses in an orthotopic murine AML model [37].

Bridging the preclinical and clinical tiers, an ex vivo study using primary blast cells from 32 acute leukemia patients found a correlation between ex vivo response to *P. alliacea* extract and clinical response to induction chemotherapy, with good responders achieving a median overall survival of 12.5 months versus 7.23 months [16]. This is a translational, hypothesis-generating association rather than a demonstration that *P. alliacea* itself produced the survival difference, since the extract was tested on isolated cells rather than administered to the patients.

At the clinical tier proper, PA001, a phase Ib/randomized double-blind phase II study, began enrolling patients with metastatic gastrointestinal tumors and acute leukemias in 2023 [17]. As of this review, PA001 remains in recruitment, and no efficacy or safety results have been reported. It therefore does not yet constitute clinical evidence for anticancer activity in humans; it is discussed here only as an indicator that formal clinical evaluation of *P. alliacea* has begun.

5.3 Safety Signals That Warrant Greater Weight Than the Anticancer Claim

Four limitations qualify the preclinical and early clinical picture described above. They are presented here in the order of the weight this review assigns them when interpreting *P. alliacea*'s therapeutic potential for an oncology patient, rather than in the order in which they typically appear in the primary literature.

The mutagenicity and genotoxicity signal. Multiple studies have documented mutagenic effects of *P. alliacea* extracts, including DNA damage through sister chromatid exchanges in human lymphocytes in vitro and in mouse bone marrow cells in vivo [36]. A 2022 study confirmed mutagenic effects of ethanolic fractions on *Saccharomyces cerevisiae* DNA repair-deficient (ogg1) strains [39]. Chronic and subchronic exposure induces moderate-to-high toxicity, including mutagenicity and genotoxicity [36, 40]. In a cancer patient with potentially

compromised DNA repair capacity, whether from the malignancy itself or from concurrent genotoxic chemotherapy, chronic consumption constitutes a risk that is biologically plausible, replicated across at least two independent experimental systems, and clinically unstudied. Because this signal is both consistent and mechanistically coherent with the patient population most likely to use *P. alliacea*, this review treats it as the finding that should weigh most heavily in any risk-benefit assessment, ahead of the unproven anticancer signal described in Section 5.2.

The cytotoxicity and selectivity problem. DTS affects normal cells at concentrations only modestly higher than tumor cells in most assays, producing a therapeutic window too narrow for safe clinical application without purification and dose optimization [10, 40].

The standardization problem. The pharmacological and toxicological profiles of *P. alliacea* depend critically on plant part, solvent, preparation method, and chemotype, which varies geographically across its range [30]. Popular consumption uses aqueous infusions of variable strength with no standardization, a substantially different pharmacological profile from the standardized ethanolic extracts used in published research; this discrepancy affects both the anticancer and the toxicological data equally and is not specific to either.

The absence of clinical efficacy data. Memorial Sloan Kettering Cancer Center states explicitly that *Petiveria alliacea* has not been shown to treat cancer in humans, and notes that in vitro and in vivo assays indicate mutagenic effects [40]. As established in Section 5.2, PA001 was still in recruitment at the time of this review; it marks the beginning, not the end, of the clinical evidence pathway, and no clinical efficacy claim for *P. alliacea* can currently be supported by direct human data.

Taken together, these four points indicate that the safety evidence against *P. alliacea* is more mature, more consistently replicated, and more directly relevant to a cancer patient's immediate clinical situation than the evidence in favor of its anticancer use. This asymmetry, not the anticancer signal in isolation, should guide clinical counseling until PA001 or comparable trials report results.

5.4 A Structural Hypothesis for Hemostatic Activity of *Petiveria alliacea*: DTS and the *Allium* Parallel

The mechanism proposed in this section is a hypothesis derived from structural analogy, as defined in Section 2.4. It has not been directly tested in *P. alliacea* and should not be read as an established pharmacological effect.

A persistent and underappreciated dimension of the hemostatic risk profile of *P. alliacea* concerns its organosulfur compounds, principally DTS and related thiosulfinate-like species, in relation to platelet function. The structural analogy between DTS and the antiplatelet-active organosulfurs of garlic (*Allium sativum*) is pharmacologically suggestive, though it remains untested for DTS specifically.

In garlic, the antiplatelet activity of diallyl trisulfide (DATS) and allicin operates primarily through (i) inhibition of thromboxane A2 (TXA2) biosynthesis via suppression of COX-1 and thromboxane synthase activity, and (ii) direct inhibition of platelet aggregation through reduction of intracellular calcium mobilization and interference with ADP-P2Y12 receptor signaling [28]. The structural feature responsible for this activity, the reactive polysulfide bond (S-S-S in DATS, S-S in allicin) capable of forming mixed disulfides with protein thiols and disrupting platelet signal transduction, is shared by DTS, which contains a benzyl-trisulfide core. This structural homology makes antiplatelet activity through an analogous thiol-reactive mechanism pharmacologically plausible for DTS, though it has never been directly tested in platelet aggregometry assays [10].

If this hypothesis were confirmed, a patient consuming daily *P. alliacea* infusions while receiving LMWH or a DOAC for CAT would be simultaneously exposed to factor Xa or IIa inhibition from the prescribed anticoagulant, potential thiosulfinate-mediated antiplatelet activity from DTS, and possible CYP-mediated pharmacokinetic alteration of the anticoagulant's metabolism. Whether this additive antiplatelet component would be clinically relevant, particularly in the context of tumor-associated thrombocytopenia, cannot currently be assessed. Systematic platelet aggregometry studies using standardized *P. alliacea* aqueous extracts at bioaccessibility-adjusted concentrations are needed before this hypothesis can be considered a plausible clinical risk rather than a structural inference.

5.5 Three Registers of Risk, Presented as Hypotheses for Future Testing

Sections 5.3 and 5.4 describe three distinct, currently untested categories of risk that could, in principle, operate simultaneously in a single patient. They are presented separately because each rests on a different type of evidence and would require a different study design to confirm.

Register 1, direct hemostatic risk

organosulfur-containing NCFP may exert antiplatelet or anticoagulant effects additive with prescribed antithrombotic therapy (LMWH, DOACs), increasing bleeding risk. The DTS-*Allium* structural parallel described in Section 5.4 lends mechanistic plausibility to this register,

but its direction and magnitude are unknown because hemostatic studies on *P. alliacea* in anticoagulated patients are absent.

Register 2, pharmacokinetic drug interaction risk

DTS and CYP1A1/1A2-inhibitory compounds in *P. alliacea* may alter the metabolism of TKIs and other CYP-metabolized anticancer drugs, modifying plasma drug levels and either reducing efficacy or increasing toxicity [10].

Register 3, direct genotoxic risk

chronic consumption of mutagenic *P. alliacea* preparations by patients with potentially compromised DNA repair capacity introduces a risk of secondary genotoxic injury, the register with the strongest existing preclinical support, as discussed in Section 5.3.

Whether these three registers would in fact operate simultaneously in a patient consuming *P. alliacea* during active oncological treatment and anticoagulation therapy, a scenario that is plausible though not yet documented in Latin American oncology practice, is an open empirical question. This review treats their possible co-occurrence as a hypothesis that current clinical monitoring systems are not equipped to detect, rather than as an established risk of demonstrated magnitude, and proposes the studies outlined in Section 7.2 as the means of testing it.

6. Herb-Drug Interactions in Oncological Patients: NCFP, Anticoagulants, and Anticancer Therapies

6.1 The Magnitude of the Problem

Drug–drug interactions (DDIs) are common and clinically consequential in cancer management, complicating the already challenging choice of anticoagulation strategy in CAT [4, 41]. A retrospective cohort study in patients with CAT on concurrent anticoagulation and anticancer therapy found a high incidence of DDIs with anticoagulants, 41.6% of patients had at least one Lexicomp® interaction risk C, D, or X, with a higher incidence with DOACs than LMWH [42]. Critically, this analysis did not consider herb–drug interactions (HDIs), a category operating through identical pharmacokinetic and pharmacodynamic mechanisms as conventional DDIs, but systematically absent from drug interaction databases and clinical monitoring systems [11]. More than eight out of ten cancer patients who use herbal medicines do so concomitantly with prescribed anticancer drugs without informing their healthcare team [11].

DOACs, rivaroxaban, apixaban, and edoxaban, the three agents with randomized clinical trial evidence in CAT, are substrates of CYP3A4, P-glycoprotein (P-gp), and/or BCRP [41]. Any plant compound that inhibits or induces these enzymes and transporters will alter DOAC plasma levels, potentially reducing antithrombotic efficacy or increasing hemorrhagic risk. LMWH, while less susceptible to CYP-based interactions, remains vulnerable to pharmacodynamic interactions with plant compounds that have additive antiplatelet or anticoagulant activity.

6.2 Pharmacokinetic Interactions: NCFP Bioactives as CYP and Transporter Modulators

6.2.1 Quercetin and the CYP3A4/P-gp axis

Quercetin, the dominant or co-dominant flavonoid in multiple NCFP species including *T. majus*, *R. acetosa*, and *P. aculeata*, inhibits CYP3A4 in a concentration-dependent manner with an IC50 of 1.97 μM in rat liver microsomes, and is a documented inhibitor of P-glycoprotein-mediated efflux transport [43]. Virtually all TKIs are substrates of CYP3A4, and most are also P-gp substrates. A clinical proof-of-concept exists: St. John's wort, a flavonoid-rich preparation acting as a CYP3A4 inducer, increased imatinib clearance by 43% and decreased its AUC and Cmax by 30% and 29%, respectively, in human subjects [43]. Quercetin's dual inhibitory effect on CYP3A4 and P-gp predicts the opposite direction: increased TKI exposure with potential for dose-dependent toxicity. For DOACs, imatinib has been shown to increase rivaroxaban Cmax by 90.43% and AUC by 119.96% in rats through CYP2J2, CYP3A4, BCRP, and P-gp inhibition [44]. Quercetin's CYP-inhibitory profile extends beyond CYP3A4: in human liver microsomes, it acts as a potent competitive inhibitor of both CYP1A2 (Ki = 0.93 μM) and CYP2C9 (Ki = 1.67 μM) [45], the latter being directly relevant to warfarin metabolism and reinforcing the plausibility of quercetin-mediated interference with vitamin K antagonist anticoagulation discussed in Section 6.2.3.

A critical qualification regarding clinical achievability. Quercetin aglycone plasma concentrations in human subjects after dietary ingestion of quercetin-rich foods typically reach 0.1–0.5 μM, while supplemental quercetin at 500–1000 mg/day can achieve peak plasma concentrations of approximately 0.7–1.5 μM of total quercetin metabolites. The CYP3A4 IC50 for quercetin of 1.97 μM [43] is therefore at or above the upper end of achievable dietary plasma concentrations for the aglycone, meaning that CYP3A4 inhibition of clinical significance likely requires supplemental quercetin doses rather than typical dietary consumption of *P. aculeata* leaves as an infusion.

However, two caveats prevent complete dismissal of the clinical interaction risk at NCFP consumption levels. First, as established in Section 4.5, rutin from *P. aculeata* is absorbed via the colonic route [33], but the fraction absorbed as quercetin aglycone in the small intestinal wall, where CYP3A4 is most abundant, may create local concentrations at the enterocyte surface substantially higher than systemic plasma concentrations, and the "intestinal wall inhibition" effect for P-gp and CYP3A4 can meaningfully affect oral bioavailability of co-administered drugs even when systemic quercetin plasma levels are modest [43]. Second, patients who consume NCFP as multi-species preparations, a common practice in Brazilian popular medicine, may have additive flavonoid loads that cumulatively exceed individual thresholds. These considerations underscore that the interaction risk, while unlikely to be clinically significant at typical single-species dietary consumption, cannot be ruled out at the medicinal supplementation doses adopted by some patients, and requires prospective evaluation [33].

6.2.2 DTS and CYP1A1/1A2 inhibition

DTS from *P. alliacea* is a documented inhibitor of CYP1A1 and CYP1A2 [10]. CYP1A1 inhibition may reduce the bioactivation of chemotherapeutic prodrugs, potentially reducing anticancer efficacy; CYP1A2 inhibition may increase plasma levels of drugs metabolized by this pathway, including nilotinib, generating unpredictable effects on both anticoagulation control and drug efficacy.

6.2.3 Garlic organosulfurs and CYP2C9

Garlic-derived organosulfur compounds have been associated with CYP2C9 inhibition in vitro, raising concerns for patients on warfarin (primarily metabolized by CYP2C9) [46]. Clinical case reports of garlic–warfarin interactions resulting in INR elevation and bleeding have been documented [46].

6.3 Pharmacodynamic Interactions: Additive Hemostatic Effects

Quercetin and its glycosides, allicin/DATS, and β-sitosterol independently reduce platelet aggregation through distinct mechanisms. When consumed concomitantly with LMWH or DOACs, these compounds potentially produce additive anticoagulation. In patients with tumor-associated thrombocytopenia, this additive antiplatelet burden may be clinically significant even at subthreshold concentrations in non-thrombocytopenic patients [9, 28]. Clinical case reports have associated perioperative garlic supplementation with excessive bleeding [46]. A less frequently considered risk operates in the opposite direction: dose-response relationships for some flavonoids are nonlinear, with compounds exhibiting pro-aggregatory effects at low concentrations through partial agonism at platelet receptors [47], creating theoretical scenarios where fluctuating plasma concentrations of metabolites from unstandardized NCFP infusions could shift hemostatic balance unpredictably.

6.4 Clinically Relevant Interaction Scenarios

The following constructed (non-empirical) scenarios illustrate, rather than document, the convergence of the mechanisms described in the preceding sections. None corresponds to an actual patient, case report, or clinical observation; no CONSORT, STROBE, or CARE reporting applies, as no real-world patient data are involved. Each scenario is a deliberately simplified composite designed to translate isolated pharmacokinetic and pharmacodynamic findings into a single clinically recognizable configuration, for the sole purpose of orienting future empirical study, and should not be read as evidence that the described interaction has occurred or been observed in practice.

Scenario A, patient on TKI and ora-pro-nóbis tea: A patient with chronic myeloid leukaemia (CML) on imatinib (CYP3A4/P-gp substrate) is modeled as consuming daily aqueous infusions of *P. aculeata* leaves. Rutin undergoes colonic hydrolysis to quercetin aglycone; quercetin inhibits intestinal CYP3A4 and P-gp, potentially increasing imatinib bioavailability. *Clinical significance qualification*: risk is most plausible at medicinal supplementation doses rather than typical dietary consumption (see Section 6.2.1). Evidence level: in vitro + animal; not studied clinically for *P. aculeata* specifically [26, 43].

Scenario B, patient on apixaban and piriri tea: A patient with pancreatic cancer on apixaban for VTE is modeled as consuming *P. alliacea* aqueous infusion daily as a folk anticancer remedy. DTS inhibits CYP1A1/1A2 and possibly CYP3A4; organosulfur compounds (structural homologs of garlic DATS) may add antiplatelet activity to factor Xa inhibition (see Section 5.4). Predicted consequence: potential bleeding risk amplification; possible altered apixaban metabolism; genotoxic risk at chronic doses. Evidence level: PD mechanism plausible; PK extrapolated from CYP inhibition data; no clinical data [10, 39].

Scenario C, patient on LMWH and garlic-family NCFP: A patient with lung adenocarcinoma on tinzaparin for PE is modeled as consuming *Allium ursinum* (alho-do-mato) regularly. DATS inhibits TXA2 formation and platelet aggregation; fibrinolysis is enhanced via t-PA stimulation. Predicted consequence: additive antiplatelet and potentially profibrinolytic effects; risk amplified in patients with mucosal tumors. Evidence level: in vitro, limited human antiplatelet data; one perioperative bleeding case report [28, 46].

6.5 Drug Interaction Overview (Table 2)

Table 2

Principal pharmacokinetic and pharmacodynamic interactions identified between NCFP bioactives and the anticancer and anticoagulant therapies most commonly used in the management of CAT, with their predicted clinical effects and current evidence levels. Evidence levels reflect the hierarchy from preclinical *in vitro* data to clinical observations; absence of clinical evidence does not preclude clinical significance.

NCFP / Bioactive	Anticancer Drug	Anticoagulant	Interaction Mechanism	Predicted Effect	Evidence Level	Ref.
Quercetin (T. majus, R. acetosa, P. aculeata)	Most TKIs (CYP3A4/P-gp substrates: imatinib, sorafenib, nilotinib)	Rivaroxaban, apixaban (CYP3A4/P-gp substrates)	CYP3A4 inhibition (IC_{50} 1.97 μM) + P-gp inhibition	Increased plasma TKI and DOAC concentrations; elevated toxicity and bleeding risk	In vitro + animal; clinical relevance at dietary doses uncertain, see Section 6.2.1	[43]
Allicin / DATS (Allium NCFP)	General (no specific TKI data)	LMWH, DOACs, warfarin	Additive antiplatelet (TXA2 inhibition) + fibrinolysis enhancement	Potentiated anticoagulation; increased bleeding risk	In vitro, limited human; one perioperative bleeding case report	[28, 46]
DTS (Petiveria alliacea)	CYP3A4 and CYP1A1/1A2 substrates: nilotinib, imatinib, sorafenib	No data	CYP1A1/1A2 inhibition; potential CYP3A4 modulation	Altered TKI metabolism; unpredictable plasma levels; prodrug activation impaired	In vitro (CYP inhibition); no clinical interaction data	[10]
Rutin / isoquercetin (P. aculeata)	Doxorubicin (P-gp substrate)	Factor Xa inhibitors (CYP3A4 substrates)	P-gp inhibition; CYP3A4 modulation	Increased doxorubicin cytotoxicity; increased anticoagulant exposure	In vitro + rat PK studies; not studied in cancer/CAT patients	[26, 43]
Luteolin / apigenin (S. byzantina, taioba)	TKIs (multiple CYP substrates)	Warfarin (CYP2C9 substrate)	CYP2C9 and CYP3A4 modulation	Possible warfarin INR elevation; TKI level changes unpredictable	In vitro; no clinical data	[48]
Organosulfurs (general NCFP)	Platinum compounds (ROS modulation)	LMWH	Additive antithrombotic: fibrinolysis + antiplatelet + ROS effects on endothelium	Enhanced bleeding in surgical/oncological context	Preclinical only; mechanistic inference	[28]

Note: PK = pharmacokinetic; PD = pharmacodynamic; CYP = cytochrome P450; P-gp = P-glycoprotein; BCRP = breast cancer resistance protein; DTS = dibenzyl trisulfide; TKI = tyrosine kinase inhibitor; DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin. Absence of clinical evidence does not preclude clinically significant interactions.

6.6 Clinical Implications and the Non-Disclosure Problem

The clinical management implications of the interaction landscape described above are directly constrained by a fundamental epidemiological reality: the majority of cancer patients who self-medicate with herbal preparations do not disclose this use to their oncologists or hematologists [7, 11]. Widely used clinical decision support tools contain limited or no data on species like *Petiveria alliacea*, *Pereskia aculeata*, or *Rumex acetosa*, even where mechanistic plausibility for clinically significant interactions is high. It should be stressed that, as of this review, no herb-drug interaction between an NCFP species and an anticoagulant or anticancer therapy has been directly documented in a cancer patient; the clinical decision support gap described here concerns preparedness for a plausible interaction, not a confirmed one. The development of evidence-based, culturally sensitive patient counseling tools addressing NCFP use during oncological treatment and anticoagulation therapy remains a priority once the preclinical evidence in Section 7.2 has been generated.

7. Conclusions and Research Agenda

7.1 Principal Conclusions

This critical narrative review has mapped the pharmacological intersection of cancer-associated thrombosis and self-medication with Non-Conventional Food Plants among oncological patients in Latin America, with *Petiveria alliacea* L. as the principal case study, and has classified the underlying evidence into clinical, preclinical, and hypothesis tiers throughout, as defined in Section 2.4. Five conclusions follow from this classification.

First, the hemostatic relevance of several NCFP species is pharmacologically plausible but remains largely at the preclinical tier. Quercetin-rich species including *T. majus*, *R. acetosa*, and *P. aculeata* contain bioactive compounds with antiplatelet mechanisms documented in vitro and in animal models, directly relevant to CAT pathophysiology [9, 23]. The phase II clinical evidence for isoquercetin in reducing CAT biomarkers [15] is the only finding in this review that reaches the clinical tier for a quercetin-class compound, and it lends indirect, not direct, pharmacological plausibility to NCFP species with high rutin or quercetin content.

Second, the ethnopharmacological anticancer claims for *P. alliacea* rest on an asymmetric and predominantly preclinical evidence base. Substantial in vitro cytotoxicity [10, 37] and an emerging in vivo preclinical signal [37] are set against documented mutagenicity and genotoxicity [36, 39], high nonselective cytotoxicity of DTS [10], profound preparation heterogeneity, and a complete absence of clinical efficacy or safety data in humans [40]. The first clinical trial, PA001, remains in recruitment and has not yet reported results [17]; until it does, this review treats the mutagenicity and genotoxicity signal, not the anticancer signal, as the finding that should carry the most weight in clinical counseling, for the reasons detailed in Section 5.3. The structural analogy between DTS and garlic antiplatelet organosulfurs (Section 5.4) is a testable mechanistic hypothesis, not an established hemostatic risk, and should guide future platelet aggregometry studies rather than clinical recommendations.

Third, the pharmacokinetic interaction risk between NCFP bioactives and CAT-associated therapies is mechanistically plausible in preclinical models, but its clinical relevance at typical dietary NCFP consumption doses is uncertain and concentration-dependent [33, 43]. The qualification established in Section 6.2.1, that CYP3A4/P-gp inhibitory effects of quercetin are most plausible at supplemental rather than typical dietary doses, though intestinal first-pass effects may operate at lower concentrations, should be incorporated into any future clinical guidance rather than treated as a settled risk.

Fourth, the pharmacodynamic interaction risk, additive antiplatelet activity from NCFP consumption on top of LMWH, DOAC, or antiplatelet therapy, is a preclinical inference that would, if confirmed, be most clinically significant in patients with tumor-associated thrombocytopenia or mucosal tumors at high gastrointestinal bleeding risk [9, 28]; no clinical data currently confirm or exclude this effect in cancer patients.

Fifth, and most fundamentally, the bioaccessibility gap, the near-complete absence of INFOGEST 2.0-based data on the fraction of pharmacologically active compounds in NCFP species that survives gastrointestinal digestion when consumed as infusions or decoctions, means that essentially all pharmacological inference in this review, drawn from organic solvent extract studies, remains uncertain with respect to real-world human exposure [8, 12]. The profoundly different gastrointestinal fate of rutin versus quercetin aglycone (Section 4.5), and the role of colonic microbiota in rutin biotransformation [33], constitute a methodological barrier that food-science-based bioaccessibility studies, conducted on NCFP species as actually consumed, are needed to resolve before any of the preceding four conclusions can be tested clinically.

7.2 Research Agenda: Seven Priorities

Priority 1, INFOGEST 2.0-based bioaccessibility characterization of hemostatic bioactives in key NCFP species. Systematic application of the INFOGEST 2.0 protocol [12] to aqueous infusions and fresh preparations of *Petiveria alliacea*, *Tropaeolum majus*, *Rumex acetosa*, *Pereskia aculeata*, and *Allium* NCFP is the foundational prerequisite for all subsequent pharmacological and clinical risk assessment, and is directly within the competencies of the NCFP/food science research community [8].

Priority 2, hemostatic characterization of standardized Petiveria alliacea preparations. Controlled in vitro hemostatic studies, platelet aggregometry (light transmission aggregometry with ADP, collagen, and thrombin agonists), PT/aPTT assays, TF expression in endothelial cells, and fibrinolysis assays, using standardized aqueous extracts of *P. alliacea* at bioaccessibility-adjusted concentrations. These studies should use the route of popular consumption (aqueous infusion) rather than organic solvent extraction, and should test the structural homology hypothesis with garlic DATS proposed in Section 5.4.

Priority 3, CYP and transporter interaction profiling at population-relevant concentrations. *In vitro* characterization of CYP1A1, CYP1A2, CYP2C9, CYP3A4, and P-gp modulation by bioaccessibility-adjusted concentrations of DTS, quercetin, allicin/DATS, and other major NCFP bioactives, specifically including intestinal model systems (Caco-2 monolayers) that reflect the intestinal first-pass inhibition scenario identified as the most clinically plausible route of interaction at dietary doses (Section 6.2.1).

Priority 4, genotoxicity assessment of Petiveria alliacea at population-relevant doses. The mutagenic signal identified in Section 5.3 [36, 39] requires evaluation at doses achievable through typical popular-medicine preparation, in human cell models with normal and chemotherapy-impaired DNA repair capacity, given the priority this review assigns to the safety signal over the anticancer signal.

Priority 5, cross-sectional epidemiology of NCFP use in Brazilian and Latin American oncology cohorts. A structured questionnaire study in Brazilian oncology centers would characterize the prevalence, frequency, preparation methods, and co-administration patterns of NCFP

use among cancer patients receiving anticoagulation therapy.

Priority 6, pharmacovigilance signal detection. Retrospective analysis of pharmacovigilance databases (VigiBase, FDA FAERS, ANVISA) for signals of unusual bleeding or thrombotic events in patients from regions with high NCFP consumption receiving anticoagulation therapy.

Priority 7, culturally competent clinical guidance development. Co-designed with community knowledge holders and patients, validated, culturally sensitive screening tools and counseling frameworks for NCFP use during oncological treatment and anticoagulation therapy are essential for translating pharmacological risk assessment into clinical practice, once Priorities 1 through 4 have produced the underlying data.

7.3 Limitations of This Review

This critical narrative review has limitations that should be acknowledged.

Its scope is deliberately broad, spanning cancer pathophysiology, food science, and pharmacology, in order to bring together literatures that are otherwise read separately. This breadth necessarily comes at the cost of depth in any single sub-area, and a reader seeking an exhaustive treatment of, for example, TKI-associated bleeding mechanisms or NCFP ethnobotany specifically should consult the dedicated reviews cited in Sections 3 and 4. The evidence-tiering scheme introduced in Section 2.4 was adopted specifically to keep this breadth from obscuring the strength of any individual claim, but it is a transparency measure, not a substitute for the quantitative synthesis that a systematic review or meta-analysis would provide, and it was applied by the authors' own judgment rather than by an independent or blinded process.

As a narrative rather than systematic review, source selection and synthesis carry an inherent degree of subjectivity that the search strategy described in Section 2.2 only partly mitigates: no formal record of records screened, included, or excluded was retained, and reviewer disagreement was not formally adjudicated. The search was restricted to PubMed/MEDLINE, Scopus, and Web of Science; grey literature repositories, including the Brazilian Digital Library of Theses and Dissertations (BDTD/IBICT), SciELO Brasil, institutional repositories, and national databases of food composition (TACO, TBCA) and ethnobotanical surveys (DATAPLAMT, RENISUS), may contain relevant primary data on NCFP hemostatic activity, traditional use patterns, and phytochemical composition not captured here.

The pharmacological inference from in vitro CYP inhibition data to clinically significant drug interactions in living patients involves substantial uncertainty, and the qualification added in Section 6.2.1 reflects this epistemic caution. The bioaccessibility gap discussed in Section 4.5 means that many of the pharmacological claims made for NCFP bioactives rest on extrapolation from extract concentrations that may not reflect achievable human plasma levels. Finally, and most directly relevant to clinical application, the evidence base for every NCFP species discussed here, including *P. alliacea*, remains insufficient to support formal clinical risk classification under established pharmacovigilance frameworks; the risk registers proposed in Section 5.5 are hypotheses intended to orient future research, not a validated risk stratification tool.

7.4 Critical View and Concluding Statement

Cancer-associated thrombosis represents a life-threatening complication arising at the intersection of tumor biology, treatment toxicity, and host hemostatic response. The parallel use of Non-Conventional Food Plants, particularly species attributed with anticancer properties in Latin American popular medicine, by patients navigating this intersection creates a pharmacological interface that is mechanistically plausible, currently undocumented in cancer populations, and largely invisible to existing clinical monitoring systems. This review has attempted to make that interface visible, to classify its principal claims by evidence tier with explicit epistemic caution regarding the limits of preclinical extrapolation, and to propose a research agenda for converting pharmacological plausibility into evidence-based clinical guidance. Future pharmacological evaluation of NCFP intended for human consumption should integrate rigorous phytochemical characterization, standardized INFOGEST 2.0 digestion models, colonic fermentation, and pharmacokinetic assessment before mechanistic findings are extrapolated to clinically relevant exposure and safety recommendations. The goal is not to erect barriers between patients and their cultural healing traditions, but to ensure that those traditions can be integrated with conventional oncological care without amplifying the hemostatic risks that current evidence, though still largely preclinical, suggests may accompany the cancer-associated thrombosis landscape.

Abbreviations

ADP, adenosine diphosphate.

AI, artificial intelligence.

AML, acute myeloid leukemia.

ATE, arterial thromboembolism.

AUC, area under the concentration-time curve.

BCRP, breast cancer resistance protein.

BTK, Bruton tyrosine kinase.

CAT, cancer-associated thrombosis.

CLEC-2, C-type lectin-like receptor 2.

COX, cyclooxygenase.

CV, cardiovascular.

CYP, cytochrome P450.

DADS, diallyl disulfide.

DATS, diallyl trisulfide.

DDIs, drug-drug interactions.

DNA, deoxyribonucleic acid.

DOACs, direct oral anticoagulants.

DTS, dibenzyl trisulfide.

ERK, extracellular signal-regulated kinase.

EVs, extracellular vesicles.

FXa, activated coagulation factor X.

FXII, coagulation factor XII.

GPVI, glycoprotein VI.

IC50, half-maximal inhibitory concentration.

ICIs, immune checkpoint inhibitors.

INR, international normalized ratio.

LMWH, low-molecular-weight heparin.

MAPK, mitogen-activated protein kinase.

MSKCC, Memorial Sloan Kettering Cancer Center.

NCFP, Non-Conventional Food Plants.

NETs, neutrophil extracellular traps.

NO, nitric oxide.

P-gp, P-glycoprotein.

PAI-1, plasminogen activator inhibitor-1.

PD, pharmacodynamic.

PGI2, prostacyclin.

PI3K, phosphoinositide 3-kinase.

PK, pharmacokinetic.

ROS, reactive oxygen species.

SANRA, Scale for the Assessment of Narrative Review Articles.

TF, tissue factor.

TFPI, tissue factor pathway inhibitor.

TKIs, tyrosine kinase inhibitors.

TXA2, thromboxane A2.

UHPLC-ESI-Q-TOF-MS/MS, ultra-high-performance liquid chromatography coupled to electrospray ionization and quadrupole time-of-flight tandem mass spectrometry.

VEGF, vascular endothelial growth factor.

VTE, venous thromboembolism.

Declarations

Competing Interests:

The authors declare no competing financial interests.

Funding:

The authors declare that no specific grant, funding, or other support was received for the preparation of this manuscript.

Author Contribution

Conceptualization: R.A.L., D.P., and S.B.F. Literature search and evidence synthesis: D.P. (Sections 3 and 5.3, CAT mechanisms and clinical pharmacology), R.A.L. (Sections 4.5 and 7, NCFP bioaccessibility and research agenda), S.B.F. (Sections 4.2 to 4.3, phytochemistry and bioactive compounds); all authors jointly (Sections 1, 2, 5.1 to 5.2, and 6). Writing (original draft): R.A.L. Writing (review and editing): D.P. and S.B.F. All authors have read and approved the final version of the manuscript.

Acknowledgement

The authors thank Comenius University Bratislava for making this collaboration possible and for enabling the joint work presented in this manuscript.

Data Availability:

Not applicable. This narrative review synthesizes previously published studies.

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Figures

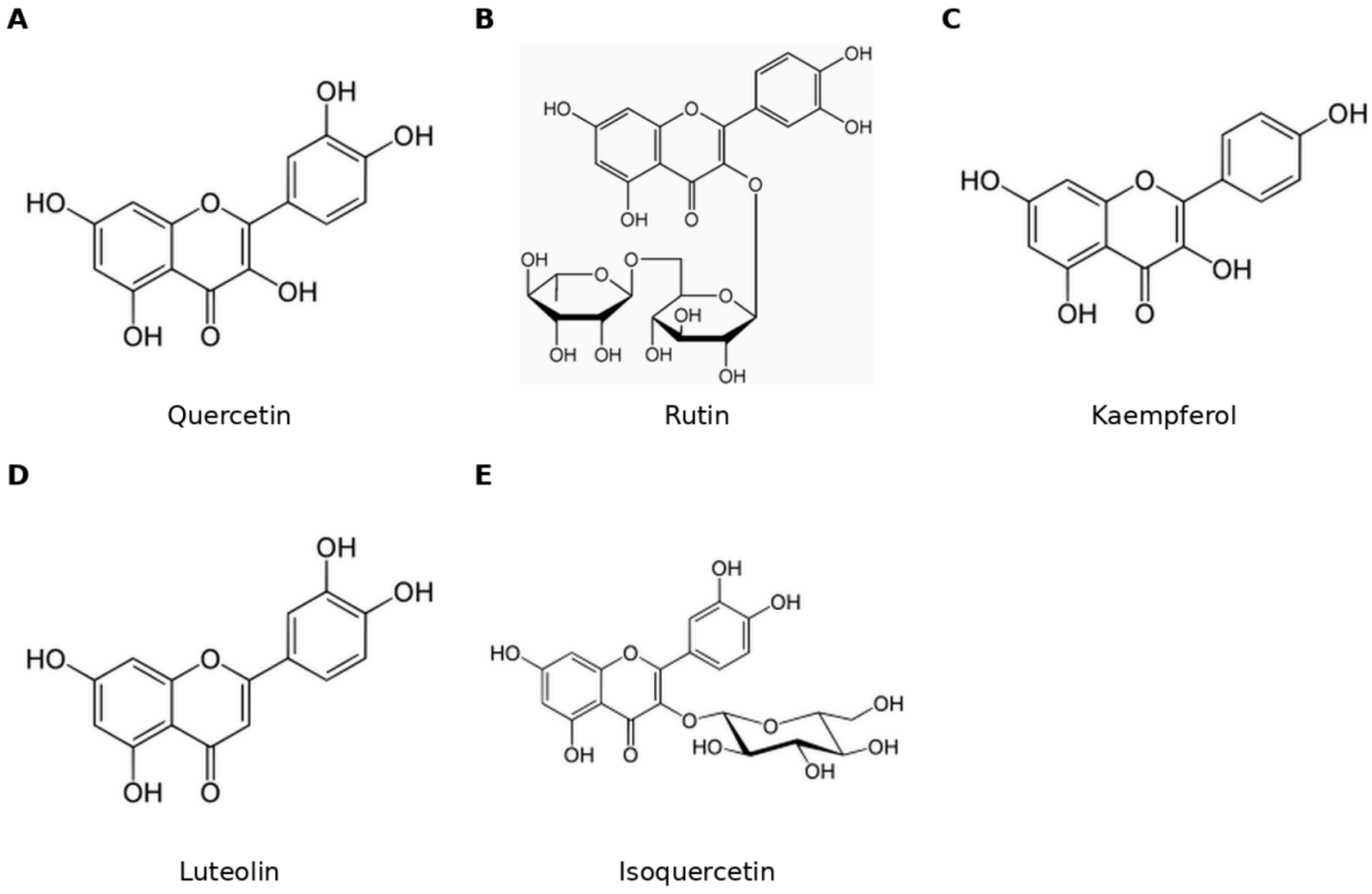


Figure 1

Chemical structures of the discussed flavonoids, NCFP antiplatelet agents. (A) Quercetin; (B) Rutin; (C) Kaempferol; (D) Luteolin; (E) Isoquercetin

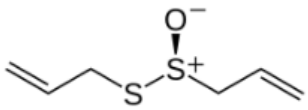


Figure 2

Structural formula of R-allicin, the principal antiplatelet organosulfur compound in *Allium*species

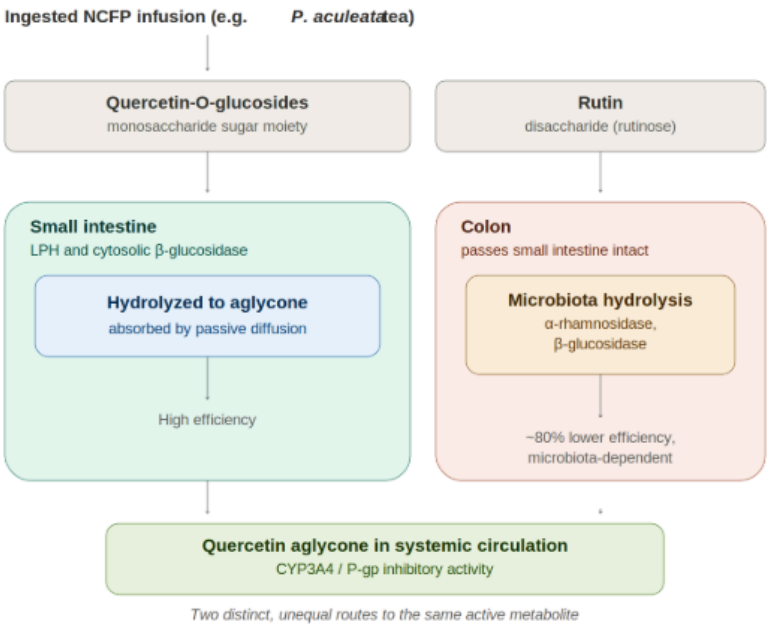


Figure 3

Two unequal gastrointestinal routes to systemic quercetin