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Review

Polyscias fruticosa (L.) Harms as a Functional Botanical Resource: A Quality-Gated Framework Linking Phytochemistry, Extraction Engineering, Bioactivity, and Application-Specific Development

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Abstract

Polyscias fruticosa (L.) Harms is consumed as food and used traditionally in Southeast Asia, but reproducible ingredient development requires the alignment of raw material identity, chemical specification, processing, exposure, safety, and claims. This critical narrative review integrates species-specific studies with analytical, engineering, and regulatory considerations within a five-stage translational framework, with safety considered throughout. Findings support *P. fruticosa* saponin as a candidate quantitative anchor alongside complementary markers and document laboratory extraction optimization, mechanism-linked cellular responses, and animal proof-of-concept studies. However, direct biological studies remain predominantly preclinical, while bioaccessibility, pharmacokinetics, metabolite profiling, tissue distribution, target engagement, and controlled human validation remain limited or absent. Animal studies also report reproductive and gestational safety findings that warrant product-specific evaluation of concentrated or repeated-exposure materials. Credible scale-up requires predefined specifications, delivered-energy characterization, solvent recovery, and process designs that preserve product quality. Stronger physiological or therapeutic claims require substantiation through release, exposure, stability, efficacy, and safety data. The literature supports application-specific development of *P. fruticosa* for food, nutraceutical, topical, and pharmaceutical products, with claim strength constrained by the least validated element across material identity, specification, processing, exposure, safety, and finished product performance. This framework distinguishes reported findings from transferable guidance and identifies priorities for reproducible development.

Keywords: *Polyscias fruticosa*; triterpenoid saponins; botanical authentication; multi-marker analytical control; cross-study transferability; bioaccessibility; safety assessment; quality by design

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1. Introduction

Polyscias fruticosa (L.) Harms (hereafter, *P. fruticosa*) is a shrub of the family Araliaceae, widely used across Southeast Asia as both a food source and traditional medicinal plant. In Vietnam, where it is commonly known as đinh lăng, the leaves are consumed as food or

prepared as teas, whereas the roots are primarily used in decoctions and alcoholic preparations [1–4]. The species is also known as "Vietnamese ginseng", but taxonomic recircumscription and family-wide transcriptomic analyses distinguish the *Polyscias–Pseudopanax* lineage from *Panax* [5,6]. This commercial designation should not be interpreted as demonstrating chemical, pharmacological, or therapeutic equivalence with *Panax* species. Accordingly, traditional-use records are primarily used to identify the source, preparation techniques, and exposure conditions. In contrast, enriched extracts, purified fractions, and concentrated modern products require consistent specifications and specific data regarding their dosage, efficacy, and safety [7,8].

A central challenge is the limited transferability of findings across non-equivalent *P. fruticosa* materials. Roots, leaves, cultivars, cultured biomass, crude extracts, fractions, isolated compounds, formulations, and finished products can vary in their chemical composition, processing characteristics, levels of exposure, and claim boundaries. Direct studies have shown that variations in saponins, phenolics, lipophilic constituents, and biological responses depend on the organ, production system, and cultivar [9–12]. Findings should remain linked to the specific material, process, or product combination, rather than being conveyed solely through the botanical name. This aligns with established principles of botanical authentication, marker traceability, and quality control within the value chain [7,13,14].

Isolated *P. fruticosa* saponin (PFS) demonstrates both the strengths and limitations of compound-based interpretation. It has been shown to inhibit porcine pancreatic α-amylase and yeast α-glucosidase and to decrease glucose levels in an acute sucrose test in nondiabetic mice [15,16]. Structure-specific activity highlights the importance of compound-resolved control, as related saponins exhibit varied effects on enzyme inhibition, redox activity, antimicrobial activity, and cytotoxicity across different studies [12,15]. Similarly, defined leaf extracts and lipophilic fractions have been reported to modulate osteoclastogenic, redox, and inflammatory pathways in cellular and animal systems [10,17]. Conversely, a methanolic leaf extract showed no meaningful inhibition of nuclear factor κB in RAW 264.7 cells under the reported screening conditions [18]. Collectively, these findings indicate that the bioactivity of *P. fruticosa* is specific to material, constituent, process, dose, and model factors, rather than representing a general saponin effect or a universal pharmacological profile for the species.

The principal translational priority is to connect defined *P. fruticosa* constituents with biological exposure and response. Therefore, species-specific evaluation must consider bioaccessibility, pharmacokinetics, metabolite formation, tissue distribution, and target engagement. Additionally, findings from related saponin systems show that factors such as gastrointestinal transformation, sugar chain structure, interactions with gut microbiota, and formulation attributes can significantly affect both local and systemic exposure [19–21]. Therefore, marker levels in the raw material or extract should be considered alongside their bioaccessible concentration and exposure at the target site. To date, no eligible controlled human intervention study evaluating a chemically characterized *P. fruticosa* material or finished product was identified by the literature search. Currently, the literature provides chemical, mechanistic, and animal findings that support biological plausibility, while exposure-based and controlled human validation remain key steps to advance to the next stage of translation.

Previous reviews have primarily summarized the phytochemical diversity, traditional uses, biotechnology, biological activities, and potential applications of *Polyscias* and *P. fruticosa* [1–3]. The present review addresses a complementary question: how far findings obtained from non-equivalent materials can be transferred across analytical, processing, exposure, safety, and application contexts. It links material-specific findings with analytical

continuity, process engineering, exposure, safety, and application-specific claim boundaries rather than treating reported biological activity alone as product-level validation. This distinction is important because transferring findings across organs, cultivars, extraction systems, formulations, and routes depends on comparable composition, exposure, and product performance. Extraction and processing influence the recovery, preservation, transformation, and loss of bioactives. Therefore, extraction methods such as conventional, intensified, or alternative approaches should be assessed not only by yield and speed but also by the chemical and functional criteria of the final product [22–24]. To develop a clearer pathway from phytochemical characterization to practical application, it is essential to integrate authenticated raw materials with appropriate analytical controls and maintain specifications throughout processing. Exposure, route-specific safety, and finished-product performance should then be evaluated.

This review combines species-specific findings on *P. fruticosa* with analytical, processing, exposure, safety, and regulatory factors to assess its suitability for various product applications. The available literature is examined across five interconnected stages: chemical and preliminary biological screening, mechanism-linked cellular findings, animal proof-of-concept, exposure support, and human validation, with safety considerations incorporated throughout the development pathway. These five stages were selected to distinguish successive translational questions concerning screening, mechanism, organism-level response, exposure, and human validation. Particular emphasis is placed on identifying where findings can reasonably be transferred across materials and applications and where additional validation is required. On this basis, the review proposes that the strength of claims for *P. fruticosa* should be aligned with the least validated component of the validation chain. Its materials should also be considered within distinct development pathways for food, nutraceutical, topical, and pharmaceutical applications rather than as a single universal medicinal extract.

2. Literature Search and Study Evaluation

A structured literature search was conducted to identify studies relevant to the botanical identity, phytochemistry, analytical characterization, extraction and processing, biological activity, exposure, safety, and potential applications of *Polyscias fruticosa*. Searches of Web of Science Core Collection, Scopus, and PubMed were conducted without date restriction and were rerun during revision through 22 September 2026. Google Scholar was used as a supplementary source to identify records not readily captured by the indexed databases, together with backward and forward citation tracking of key primary studies and previous reviews. The primary search used the species name together with historical names, spelling variants, and common names, including "*Polyscias fruticosa*", "*Panax fruticosus*", "*Nothopanax fruticosus*", "*Aralia fruticosa*", "*Tieghemopanax fruticosus*", "*Polyscias fructicosa*", "*Polyscias fruticose*", "*Polyscias fruticosum*", and "Ming aralia". Additional searches combined this species block with terms related to phytochemistry, saponins, phenolics, flavonoids, extraction, processing, biological activity, pharmacology, pharmacokinetics, bioavailability, safety, toxicity, formulation, and clinical evaluation. Representative Boolean combinations included ("*Polyscias fruticosa*" OR "*Panax fruticosus*" OR "*Nothopanax fruticosus*" OR "*Aralia fruticosa*" OR "*Ming aralia*") AND (saponins OR phenolics OR flavonoids OR extraction OR processing OR pharmacokinetics OR bioavailability OR safety OR toxicity OR formulation OR clinical evaluation). These domain-focused searches were used to confirm coverage rather than to restrict the species-level search. Duplicate records identified across databases were removed during record consolidation.

Studies were considered for inclusion when they addressed at least one review domain and provided sufficient information to identify the plant material tested, constituent,

process, experimental model, or application. Records were not used for species-specific synthesis when the identity of *P. fruticosa* could not be established, or its contribution could not be distinguished from other taxa or undefined botanical mixtures. Records with insufficient information to interpret the relevant outcome were also excluded from species-specific synthesis. No language restrictions were applied. Peer-reviewed journal articles formed the main literature base, while conference proceedings were retained when they reported directly relevant experimental data with sufficient methodological detail. No theses or preprints were retained in the final reference set. Authoritative botanical databases and guidance documents from international or regulatory organizations were used only to support taxonomy, analytical quality control, safety assessment, or regulatory context.

To distinguish demonstrated species-specific findings from transferable information, the literature was organized into three source categories: direct *P. fruticosa* studies, related botanical-system studies, and general engineering–regulatory guidance. The direct category comprised studies conducted with identifiable plant materials, cultured biomass, extracts, fractions, isolated constituents, formulations, or products derived from this species. The related category comprised studies of other botanicals, saponins, or chemically comparable systems used to inform mechanistic, physicochemical, or processing interpretation where direct species-specific data were limited. General engineering–regulatory guidance included studies, standards, and guidance documents addressing extraction engineering, scale-up, analytical control, quality assurance, safety assessment, or regulatory principles that were not specific to *P. fruticosa*. These categories were used differently in the synthesis: direct studies supported species-specific conclusions; related studies informed interpretation and transferability; and general engineering–regulatory guidance supported process, quality, safety, and regulatory interpretation. Neither external category was used to infer that the same outcome had been demonstrated in *P. fruticosa*.

The five-stage framework was developed during synthesis of the retrieved literature, rather than prospectively prespecified before literature collection, to organize findings according to translational position. It was used as an organizing framework rather than as a mandatory sequential progression, a regulatory classification, or a numerical ranking of methodological quality or overall scientific support. Operational criteria for Stages I–V are summarized in Table 1. Findings were assigned according to the experimental question directly addressed by each study component. When a study contributed findings relevant to more than one stage, individual findings were interpreted at their corresponding stages rather than assigning the entire study to the highest stage reached. The translational stage was evaluated separately from methodological confidence. Methodological appraisal considered the definition and chemical characterization of the test material, appropriateness of experimental controls, replication or sample size, and dose selection and justification. Additional criteria included randomization or blinding where relevant, exposure characterization, reporting consistency, and independent replication with chemically comparable material where available. Features not reported in the original study were recorded as not reported rather than assumed to be absent. Safety was evaluated across all translational stages, with interpretation constrained by the tested material, dose, route of administration, and exposure duration. Knowledge gaps were described only in relation to the defined search process. Statements of absence indicate that no eligible study was identified within the defined search, rather than asserting an absolute absence from the literature.

Table 1. Operational definitions of the five translational stages used in this review.

Stage	Study Type Represented	Minimum Basis for Assignment	Main Interpretive Boundary
I	Chemical assays and preliminary biological or hazard screening	Defined test material and an analytical, functional, or screening outcome	Does not establish physiological efficacy or mechanism
II	Mechanism-linked biochemical or cellular findings	Defined material or constituent linked to a specific molecular, biochemical, or cellular response	Does not establish whole-organism efficacy or exposure
III	Whole-organism proof-of-concept	Defined administered material, dose/route, and organism-level outcome	Does not establish human efficacy or exposure unless directly measured
IV	Exposure–response data	Administered dose and formulation linked to transformation or bioaccessibility, systemic or target-site exposure, and biological response	Remains material-, formulation-, and model-specific
V	Human validation	Controlled human evaluation using a chemically characterized material or finished product	Conclusions remain specific to the tested product, dose, population, and use

Note: The translational stage indicates the experimental question addressed and does not represent methodological quality or overall strength of support. Safety was evaluated across all stages.

3. Raw Material Identity and Variability as the First Quality Gate

Raw material qualification is an essential first step, as every downstream comparison depends on a clearly defined starting material. This does not require the same biomass in every batch; instead, it specifies material attributes and acceptable ranges to ensure comparability and consistent processing. The findings can be reliably compared and applied provided that the plant material is clearly characterized, including its identity, organ, accession or cultivar, developmental stage, growing conditions, crop health, and postharvest history. Acceptable variability within a scientifically justified limit may be managed prospectively through predefined specifications, batch control, and appropriate process standardization. However, differences that compromise material identity or safety, or that cause critical quality attributes or key chemical constituents to fall outside predefined acceptance ranges, should be segregated or rejected rather than being addressed solely through downstream process modifications [7,8,13].

3.1. Botanical Identity, Nomenclature, and Accession-Level Comparability

Polyscias fruticosa (L.) Harms is the accepted botanical name [25]. Historical synonyms include *Panax fruticosus* (L.), *Nothopanax fruticosus* (L.) Miq., and *Aralia fruticosa* (L.) L.H. Bailey. The 2010 recircumscription acknowledged 159 *Polyscias* species, whereas family-wide transcriptomics distinguishes the *Polyscias–Pseudopanax* lineage from *Panax* [5,6]. These results confirm that *P. fruticosa* should be regarded as a separate taxonomic entity from Panax, especially under the commercial name "Vietnamese ginseng". However, comparisons at the compound level need direct analytical verification.

Accurate identification of material for extraction requires voucher-backed botanical characterization, accession or cultivar details, and molecular and chemical validation. Internal transcribed spacer analyses of Vietnamese *Polyscias* samples identified different genotypes but also showed inconsistencies between initial morphological classifications and sequence-based clustering [26,27]. Molecular interpretation also depends on locus selection and reference quality. Authentication should combine voucher deposition, accession or

cultivar designation, provenance, macro- and microscopic examination, and molecular confirmation. Once comminution or extraction reduces morphological information, a source-appropriate chemical fingerprint becomes essential [13,28,29]. DNA barcoding should support, not replace, botanical and chemical authentication.

3.2. Ethnobotanical Use as a Record of Source, Preparation, and Exposure

Ethnobotanical records are most useful for understanding traditional sources, preparation methods, and exposure rather than for supporting modern therapeutic claims. Vietnamese records describe leaves as foods, teas, or topical materials, whereas roots are used mainly in decoctions and alcoholic preparations [1,3,4]. These records specify relevant organs and exposure scenarios, while concentrated ingredients should be evaluated separately for composition, dose, exposure, efficacy, and safety.

Aqueous preparations facilitate evaluation of water-compatible constituents and oral safety. Alcoholic preparations enable hydroethanolic extraction only under controlled residual solvent levels, extract concentrations, and exposure routes. Traditional-use information should align with the original route. Enriched extracts, purified fractions, and high-dose formulations need product-specific safety assessments for oral or topical use [7,8]. Findings of the traditional use remain relevant only when the modern material is chemically and operationally connected to the historical source, preparation, and exposure route.

3.3. Plant Part, Developmental State, Cultivar, and Production System

Roots, leaves, cultivars, and cultured biomass should be considered distinct starting materials. Direct studies report different saponin, phenolic, and lipophilic profiles across these materials [9–11]. The cultivar *P. fruticosa* "Hawaiiana Ming" produced four confirmed oleanane glycosides, including a serratagenic-acid glycoside that was not previously reported in the genus [12]. Accordingly, cultivar and organ identity should be explicitly incorporated into the test-material definition to support reproducible comparison across studies.

Plant-part differences also influence the choice and efficacy of extraction approaches. Lignified roots and flexible leaves are heterogeneous porous matrices that differ in swelling, liquid retention, suspension behavior, and resistance to mass transfer. These attributes govern effective diffusion, interfacial area, acoustic attenuation, and the energy required to recover a specified marker profile. Ultrasound-based extraction further depends on particle size distribution, solids loading, solvent properties, acoustic field distribution, and reactor geometry [23,30–32]. Accordingly, meaningful comparison of extraction severity across organs requires consideration of organ-specific material properties, delivered energy, solids loading, and reactor geometry in addition to treatment time and nominal power.

Developmental state is an important material attribute. The available root study is based on six-year-old material [33], while systematic marker-profile comparisons across different root ages and leaf developmental stages provide a clear next step for defining harvest windows. Production systems may also influence material characteristics. For example, a salinity biochar experiment used the ornamental dwarf cultivar *P. fruticosa* "Elegans", which limits the applicability of the findings to authenticated medicinal accessions [34]. Nanofertilizers, elicitors, and reactor configurations have also altered biomass production or marker-related responses [11,35,36], positioning residue safety, marker-yield stability, and product equivalence as separate qualification targets.

Controlled culture may offer greater control over material supply and production of targeted compounds. Its equivalence to field-grown plant materials can be established through matched chemical fingerprints, marker ratios, impurity and medium-residue profiles, batch stability, and route-specific safety [7,8,11,37].

3.4. Postharvest Definition and the Material Design Space

Postharvest conditions are also important for defining the material used for extraction. A direct study of hot-air and microwave drying quantified drying kinetics and energy consumption in *P. fruticosa* leaves [38]. Drying, storage, residual moisture, oxygen, light, temperature, and comminution can alter oxidation, pigments, matrix integrity, microbial stability, and extractability. A 30-day study of microwave-dried leaves yielded model-derived chlorophyll half-lives that extended far beyond the observation period [39]. Therefore, the findings are best interpreted as a chlorophyll retention model that requires additional validation of microbiological and sensory quality, marker stability, packaging performance, and finished-product stability.

Residual moisture and particle size distribution affect both microbial stability and the physicochemical environment of extraction. Endogenous water changes the effective solvent-to-solid ratio, wetting, swelling, diffusional path length, rheology, and solid–liquid separation. In deep eutectic solvent and natural deep eutectic solvent systems, total water content can modify viscosity, polarity, hydrogen-bond interactions, and solute transfer [40–42]. Water associated with plant tissue may not behave identically to water added during solvent preparation; both gravimetric moisture and final plant–solvent composition should be reported.

Pretreatment remains inconsistently documented. For example, Chuyen [33] reported freeze-drying to 3.5% residual moisture, storage at −18 °C, and particles below 0.5 mm. In contrast, Koffuor [43] did not report residual moisture or particle-size distribution. Pretreatment conditions should be reported comprehensively to permit reproducible comparison of extraction yield, marker recovery, assay responses, and process-energy metrics.

Minimum qualification should document identity, provenance, developmental state, crop health, drying, residual moisture or water activity, particle size distribution, packaging, and storage [8,13,44]. Additional testing should follow source vulnerabilities and intended use. Reports of plant pathogens and a location-specific radionuclide survey highlight the importance of considering source-specific risks, while numerical safety or release limits must be validated for the specific product and its intended use [45–47].

Raw material qualification should establish a justified range of acceptable material characteristics rather than a single fixed composition. Within that design space, solvent composition, solids loading, energy density, residence time, or downstream conditions may be adjusted prospectively to maintain the required product. Such adaptation requires predefined relationships among critical material attributes, critical process parameters, and product-specific critical quality attributes. These relationships should be used to maintain product quality rather than compensate for variations in extraction yield. Numerical release limits should be established using validated methods and product-, route-, and formulation-specific justification [7,8,14]. Once the acceptable characteristics of the starting material are established, analytical controls can identify the chemical attributes that should remain traceable through processing.

4. From Chemical Diversity to Fit-for-Purpose Analytical Control

Once the acceptable characteristics of the raw material have been defined, analytical control should determine whether processing produces an extract with a reproducible chemical composition. For *P. fruticosa*, this requires confirmation of identity, quantification of intended constituents, and detection of process-induced changes, degradation products, and safety-relevant impurities. A product-specific marker panel, combined with a complementary chemical fingerprint, may provide a more reliable quality assessment than any universal assay [7,8,13,14,48].

4.1. Chemical Space and Confidence of Identification

Direct studies identify *P. fruticosa* constituents as amphiphilic oleanane-type saponins, mid-polarity phenolics and flavonoids, nonpolar sterols and polyacetylenes, and volatile terpenoids [3,10,12,49]. These chemically diverse constituents can be characterized through complementary liquid- and gas-chromatographic techniques supported by high-resolution structural analysis. High-performance liquid chromatography (HPLC) is suitable for non-volatile polar and semipolar constituents, whereas gas chromatography (GC) is suitable for volatile or derivatized lipophilic compounds. High-resolution mass spectrometry (MS) and nuclear magnetic resonance (NMR) provide stronger structural confirmation than colorimetric responses or spectral-library matches alone [13,29,50,51]. Reported metabolite counts do not necessarily represent complete or comparable chemical profiles, as they depend on plant organ, accession, extraction selectivity, detector response, data-processing rules, database quality, and identification confidence [1,2,10]. Accordingly, the chemical profile reported for *P. serrata* should be considered as supportive until the relevant compounds are confirmed in the intended *P. fruticosa* material [52].

Figure 1 illustrates representative structures reported directly for *P. fruticosa*, while Table 2 organizes the main analytical findings according to their practical quality-control function. Species-specific saponin studies provide the strongest quantitative foundation. *P. fruticosa* saponin (PFS) has the strongest current species-specific analytical support as a candidate quantitative anchor, and complementary oleanane glycosides have been reported across field-grown and culture-derived materials [2,11,15,16,53–55]. Phenolic and flavonoid studies identify quercitrin, afzelin, and related compounds as complementary analytical targets, while total phenolic and flavonoid assays are primarily useful for comparative process screening [17,36,56–58]. Lipophilic and volatile studies extend the analytical space to phytosterols, polyacetylenes, oleanolic acid, and source-dependent terpenoids [10,49,51,59–61]. Controlled-culture studies further demonstrate the value of PFS, ladyginoside A, and polyscioside E as production-monitoring markers [11,37], while elicited in vitro roots show that total-content indices can support comparative culture-response screening [36]. These studies support a hierarchical analytical strategy combining a quantitative anchor, matrix- and process-specific complementary markers, and an overall chemical fingerprint.

Table 2. Direct phytochemical markers, quantitative data, analytical basis, and current interpretive limits in *P. fruticosa* materials.

Chemical Domain	Material/Representative Marker(s)	Reported Quantitative Data	Analytical Method/Validation	Analytical Status/Main Limitation	Literature Basis/Ref.
Saponin	Leaves and roots: PFS and complementary oleanane glycosides; cultivar-specific leaf glycosides	PFS: 1300 µg/g DW in leaves and 570 µg/g DW in roots	PFS: HPLC–DAD, linear range 10–300 µg/mL (r^2 = 0.9996), LOD 2.5 and LOQ 7.0 µg/mL; complementary glycosides characterized by MS/NMR	PFS is a candidate quantitative anchor with the strongest current species-specific analytical support, but is not a validated release specification or potency marker. Biological activity is compound-specific, and no quantitative PFS content–exposure–response relationship has been established	D: [12,15,16,53–55]

Table 2. *Cont.*

Chemical Domain	Material/Representative Marker(s)	Reported Quantitative Data	Analytical Method/Validation	Analytical Status/Main Limitation	Literature Basis/Ref.
Phenolic/flavonoid	Leaves: quercitrin; leaf, root, and in vitro root materials: TPC/TFC as comparative indices	Quercitrin: 0.13–0.32% in leaves. TPC/TFC values are assay-, material-, and process-dependent and are not compound-resolved concentrations	HPLC–DAD for quercitrin; colorimetric assays for TPC/TFC	Quercitrin is a candidate quantitative leaf marker requiring broader material validation. TPC/TFC support matched-condition screening but do not establish identity or batch equivalence	D: [17,36,56–58,62]
Lipophilic constituents	Nonpolar leaf fractions/materials: phytosterols, 22-dehydro-24-isopropylcholesterol, oleanolic acid, polyacetylenes, fatty-acid derivatives, and related constituents	71 constituents were GC–MS annotated in leaf lipophilic fractions; absolute concentrations of individual constituents were not validated	GC–MS profiling; selected sterol and oleanolic-acid structures confirmed by orthogonal structural methods	Supports fraction-specific fingerprinting; most GC–MS assignments remain tentative and no constituent is established as a universal quantitative or potency marker	D: [10,49]
Volatile constituents	Hydrodistilled fresh-leaf oils: α-bergamotene, γ-elemene, germacrene D and other source-dependent terpenoids	Oil yield 0.1384%; α-bergamotene 20.25%, γ-elemene 15.28%, germacrene D 13.29%; two major peaks (25.19% and 14.53%) remained unidentified	Hydrodistillation + GC–MS profiling	Useful for source/chemotype comparison; geographic/source dependence and incomplete structural confirmation preclude a universal volatile specification	D: [59–61]
Culture-derived metabolites	Suspension cells and in vitro roots: PFS, ladyginoside A, polyscioside E, oleanolic acid; TPC/TFC/TSC as culture-response indices	Flask, day 20: PFS 0.50 ± 0.05 and ladyginoside A 0.22 ± 0.01 mg/g DW; 20 L bioreactors: 0.91 ± 0.12 and 0.73 ± 0.07 mg/g DW, respectively	UPLC–ESI–MS for PFS/ladyginoside A; targeted and total-content analyses in additional culture studies	Suitable for culture-process monitoring; metabolite abundance depends on culture system, elicitation, and line history. Equivalence to field-grown organs has not been demonstrated	D: [11,36,37,63,64]
Pigments/carotenoids	Leaves: chlorophyll a, chlorophyll b, lutein	Chlorophyll a: up to 5.48 mg/g; chlorophyll b: up to 2.81 mg/g; lutein: 592.95 ± 2.13 mg/kg DW under the reported extraction conditions	MAE-based chlorophyll quantification; lutein quantified spectrophotometrically after n-hexane UAE	Direct quantitative processing markers, but values are method- and condition-specific rather than universal compositional specifications; lutein requires chromatographic confirmation for stronger marker use	D: [65,66]

Note: D, direct *P. fruticosa* studies. Quantitative values are reported only where directly available for identifiable *P. fruticosa* materials; values not reported by the primary study were not inferred. TPC, TFC, and TSC are retained only as comparative screening indices and are not interpreted as compound-resolved concentrations. Related botanical-system studies (R) and general engineering–regulatory guidance (G) are not used to establish constituent occurrence or abundance in this table. Reported occurrence or quantification does not by itself establish a validated release specification or potency marker. DW, dry weight; GC–MS, gas chromatography–mass spectrometry; HPLC–DAD, high-performance liquid chromatography with diode-array detection; LOD, limit of detection; LOQ, limit of quantification; MAE, microwave-assisted extraction; NMR, nuclear magnetic resonance; PFS, *Polyscias fruticosa* saponin; TFC, total flavonoid content; TPC, total phenolic content; TSC, total saponin content; UAE, ultrasound-assisted extraction; UPLC–ESI–MS, ultra-performance liquid chromatography–electrospray ionization mass spectrometry.

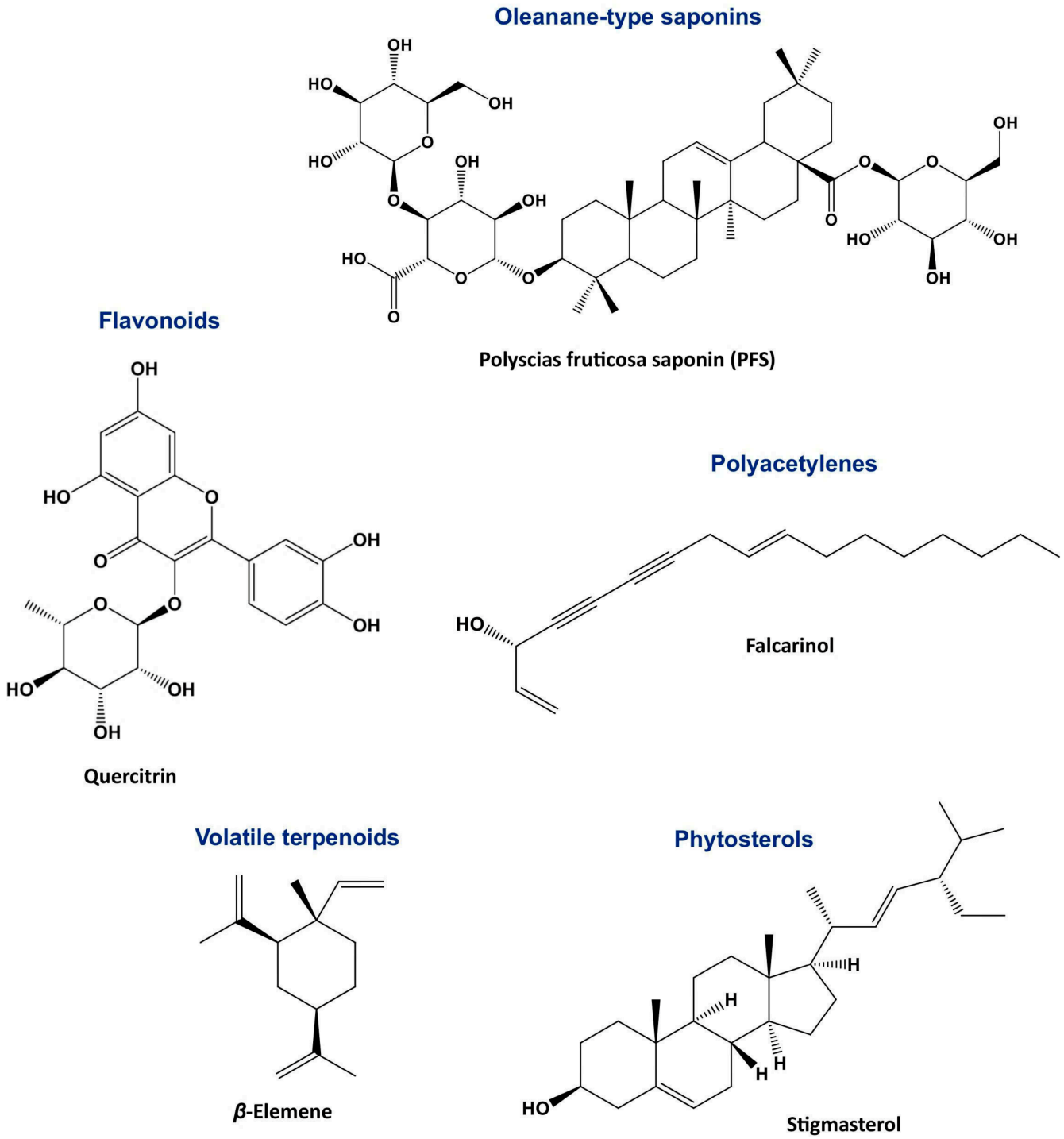


Figure 1. Representative structures of constituents reported or tentatively annotated in *P. fruticosa*. Selected examples span oleanane-type saponins, flavonoids, polyacetylenes, phytosterols, and volatile terpenoids. The panel illustrates chemical-space diversity; inclusion does not imply universal occurrence, abundance, validated marker status, or confirmed biological activity across organs, accessions, production systems, or processing histories.

4.2. Polyscias fruticosa Saponin as a Candidate Quantitative Anchor for Saponin-Oriented Control

Oleanane-type saponins provide the strongest basis for saponin-oriented standardization. Among these, *P. fruticosa* saponin (PFS) currently has the strongest species-specific analytical support as a candidate quantitative anchor for saponin-oriented materials. Earlier isolation studies established a broader series of oleanane-type saponins in *P. fruticosa* [54],

with later work reporting polysciosides J and K from the leaves [55]. The reported HPLC method with diode-array detection showed linearity over the range of 10–300 μg/mL (r^2 = 0.9996), with limits of detection and quantification of 2.5 and 7.0 μg/mL, respectively [53]. These results support laboratory quantification of PFS, but routine use across cultivars, laboratories, processing conditions, and matrices requires further validation of recovery, precision, robustness, sample stability, and matrix selectivity. Detection at 205 nm may also have limited specificity in complex botanical matrices [8,13,29,53]. PFS has biological relevance in addition to its analytical value. It inhibited α-amylase and α-glucosidase and reduced glucose excursion in an acute sucrose-challenge model [15,16]. However, the related saponins did not exhibit the same enzyme inhibitory activity, whereas other oleanane glycosides showed distinct redox, antimicrobial, and cytotoxic activities [12,15]. Accordingly, whole-extract control should combine PFS quantification with broader saponin profiling rather than relying on either total saponin content or PFS alone. Processing-related modifications should also be considered. The defined search identified no direct study demonstrating ultrasound-induced degradation of PFS under reported *P. fruticosa* processing conditions. However, intensified processing can alter several phytochemical classes through thermal, radical-mediated, or oxidative pathways [22]. HPLC–MS could be used to monitor PFS, complementary saponins, aglycones, and emerging products as functions of temperature and energy inputs. PFS represents a candidate quantitative anchor with the strongest current species-specific analytical support, but its use across materials and laboratories requires further fit-for-purpose validation. Whole-extract control should additionally incorporate complementary saponin profiling and a broader chemical fingerprint [7,8,48].

4.3. Phenolic and Flavonoid Control

Phenolic-oriented materials require an analytical strategy different from saponin control. Folin–Ciocalteu and aluminum-chloride assays can be used to compare matched treatments, but their results depend on reaction chemistry, reference standard, matrix interference, and reporting unit. Extraction conditions, plant organ, and elicitation have influenced these responses across direct *P. fruticosa* studies [36,56,57]. Total phenolic and flavonoid contents should be considered process-screening indices rather than compositional specifications. Higher total-content results may reflect improved release, altered extractability, matrix disruption, or chemical transformation rather than increased recovery of intact target compounds. DPPH, ABTS, FRAP, and related assays also measure different simplified redox reactions. These assays serve primarily for comparative redox assessment, whereas identification of the compounds responsible for these responses, assessment of their structural stability, and comparison between batches require compound-specific chromatographic analysis [67,68]. Processing-related variation should be evaluated by chromatographically monitoring selected markers and the appearance of new peaks.

Greater interpretive value arises when identified compounds are connected to a defined material and biological response. In one ethanol leaf extract, PFS and quercitrin reproduced part of the inhibition of osteoclast differentiation [17]. Candidate phenolic markers should be selected for their characteristic occurrence, detectability, process sensitivity, and ingredient relevance, then interpreted within a validated chemical fingerprint [29,48,50]. One comparative study reported inconsistent GAE/QE terminology, a weak calibration curve, and an ambiguous assignment of rutin. Although these findings may support comparative screening, reference marker contents, universal plant organ specifications, and quantitative activity relationships require stronger analytical validation [58].

4.4. Lipophilic and Volatile Constituents

Lipophilic and volatile materials require a distinct analytical approach. GC–MS annotated 71 constituents in hexane and dichloromethane leaf fractions, largely through library matching [10]. By contrast, nuclear magnetic resonance, high-resolution mass spectrometry, and X-ray diffraction confirmed 22-dehydro-24-isopropylcholesterol and oleanolic acid in one nonpolar material [49]. Each proposed marker should carry an explicit identification-confidence level based on spectra, retention behavior, authentic standards, and orthogonal structural confirmation.

Library matches remain tentative without retention indices, standards, or complementary structural methods. A Nigerian hydrodistilled leaf oil was reported to contain capsaicin, zingerone, and γ-sitosterol, but these unusual assignments remain unconfirmed and insufficient to establish a geographical chemotype [61]. Phytosterol methods should likewise be selected according to matrix, analyte form, oxidation risk, sensitivity, and intended use [51].

Earlier studies on oils also showed source-dependent profiles. One early volatile-oil study reported an oil yield of 0.1384%, with α-bergamotene, γ-elemene, and germacrene D among the major identified constituents, together with two abundant unidentified peaks. The oil showed no meaningful DPPH activity but exhibited P388 cytotoxicity under preliminary screening conditions [59]. This is a screening-level activity and hazard signal, not indicative of anticancer activity. Further characterization of provenance, distillation conditions, quantitative calibration, retention data, and structural confirmation is required before concluding on markers, chemotypes, preservatives, topical applications, or biological activity [59–61].

4.5. Hierarchical Marker Panels and Analytical Continuity

An effective analytical system should assign each element a defined function. Identity markers provide the characteristic occurrence; quantitative markers support reproducible assays; process-sensitive and degradation markers detect changes during processing or storage; and safety markers monitor hazardous constituents or impurities. Potency-linked markers additionally require demonstrated relationships with biological response and relevant exposure. Abundance, analytical convenience, or isolated in vitro activity alone is insufficient [7,8,20,48]. At present, no marker has been validated as a potency-linked marker for a finished *P. fruticosa* ingredient. Although PFS has analytical utility and compound-specific biological relevance, enzyme inhibition and an acute animal response do not establish a quantitative relationship between PFS content, product exposure, and biological performance. A multicomponent extract requires PFS measurement alongside complementary markers and fingerprint information. Marker ratios and complementary chemical fingerprints preserve whole-profile information, while total-content assays remain useful for matched-process screening. Claims of additive or synergistic mixture effects should be supported by controlled comparisons between the mixture and its components using an explicit additivity model.

Targeted assays and fingerprints serve complementary functions. Quantitative methods measure specific markers, whereas orthogonal techniques like HPLC–MS, GC–MS, NMR, high-performance thin-layer chromatography (TLC), or validated spectroscopic fingerprints identify unusual profiles, adulteration, and process variations. Chemometrics can define multivariate acceptance regions only when preprocessing procedures, reference populations, acceptance criteria, and external validation are predetermined [13,29,50]. Metabolomics, correlation analysis, network pharmacology, and docking are best used to prioritize candidates, with causality, direct target engagement, and product efficacy established through dedicated experimental validation. Controlled-culture biomass requires

the same hierarchy but should retain a distinct reference profile. PFS, ladyginoside A, and polyscioside E have been detected in culture-derived materials, yet accumulation varied with culture system and line history [11,37]. Such materials require dedicated chemical fingerprints, marker ratios, stability monitoring, medium-residue control, and demonstration of chemical comparability with the intended reference material before equivalence is assumed.

Deep eutectic solvents and natural deep eutectic solvents impose analytical constraints due to their viscosity, water content, polarity, and nonvolatile components [40,42,69]. Direct injection, cleanup, or dilution cannot be prescribed universally. A low-viscosity ternary natural deep eutectic solvent permitted direct ultra-high-performance liquid chromatography (UPLC) with diode-array detection only after system-specific validation of rheology, recovery, precision, and matrix effects [70]. Conversely, a natural deep eutectic solvent-labeled microextraction still relied on chloroform, showing that analytical compatibility and environmental benefits should be evaluated for the complete solvent–method system [71].

Each *P. fruticosa* solvent system should be validated for analyte recovery, matrix effects, stability, residual analyte interference, instrument compatibility, and bioassay interference. Natural deep eutectic solvent-only, pH-matched, and conventional-solvent controls should be included where the solvent could influence the measured response [72]. Analytical continuity should encompass extraction, clarification, concentration, enrichment, drying, storage, and formulation. To ensure that successive outputs stay chemically comparable, marker continuity, fingerprint similarity, impurity control, and stability-indicating analysis should be evaluated [7,8,14]. This approach allows processing performance to be evaluated against the specified chemical material it is intended to deliver.

5. From Extraction Yield to Specification-Preserving Processing

Extraction converts a qualified raw material into an extract with a distinct chemical composition, and the available studies on *P. fruticosa* show that different chemical targets require different processing routes. Conventional hydroethanolic extraction has been used mainly for root phenolics, flavonoids, and saponins [33,56], whereas probe and bath UAE provide laboratory-scale data for saponin and phenolic recovery [9,57]. External saponin studies further show that extraction optima can differ across marker and product-function endpoints [73–75]. Leaf studies have investigated aqueous or acetone MAE for phenolic/chlorophyll targets and nonpolar UAE for lutein [65,66,76]. DES/NADES studies provide prospective solvent-design benchmarks [40–42,69,77–79], while pilot-scale ultrasound studies define the energy and geometry descriptors needed for scale transfer [23,31,32,80,81]. Green process and life-cycle assessments should consider product quality and yield together with solvent recovery, energy use, water consumption, and waste generation [24,82–85]. Figure 2 integrates these extraction routes into a specification-preserving process framework, while Table 3 distinguishes direct species-specific extraction findings from transferable engineering requirements for scale-up and manufacturing comparison.

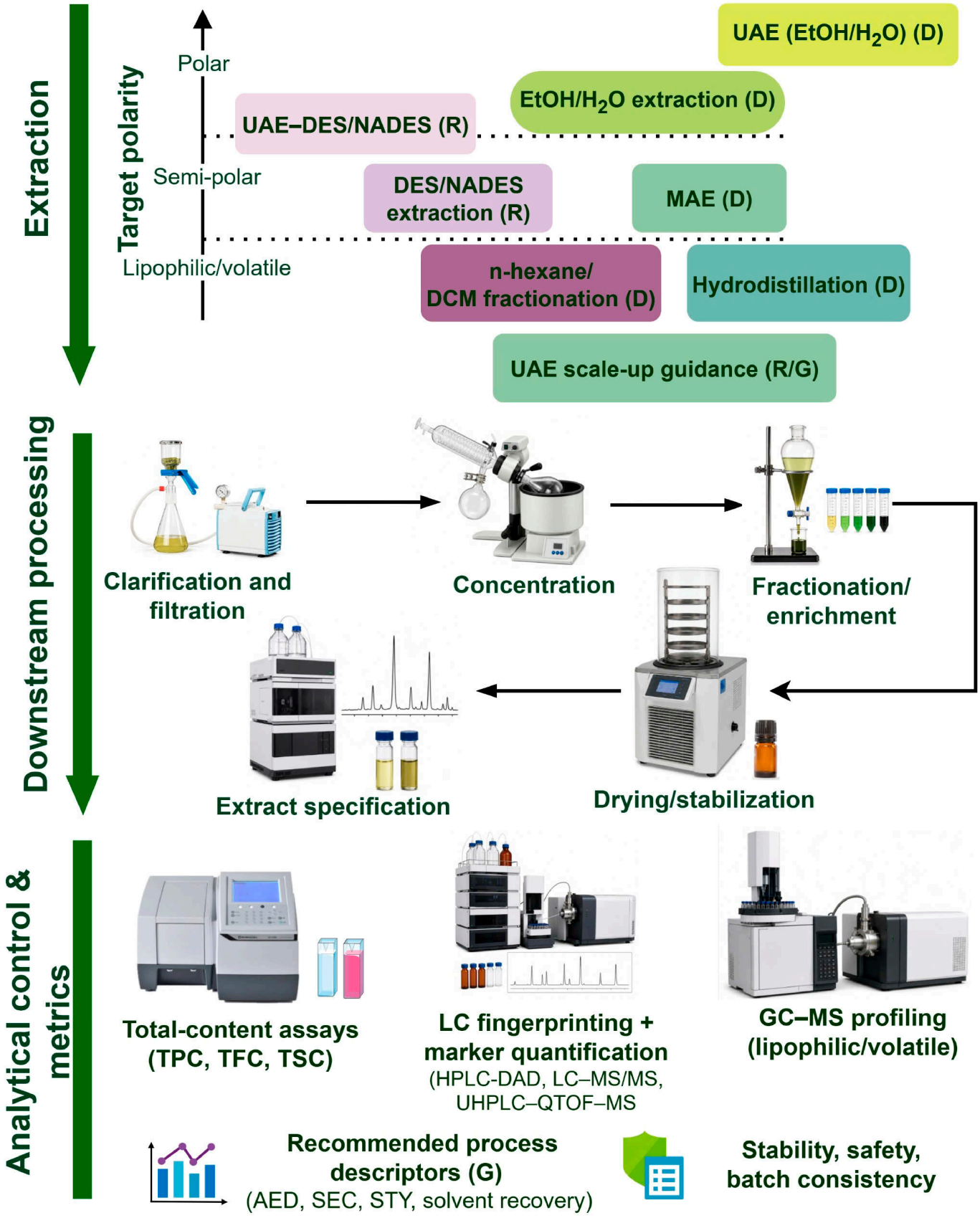


Figure 2. Specification-preserving processing framework for *P. fruticosa*. Extraction routes are positioned according to target chemical space and labeled by literature basis: D, direct *P. fruticosa* studies; R, related botanical/process-system studies; and G, general engineering guidance. Cross-cutting

UAE scale-up guidance, together with related-system studies and general engineering guidance, identifies prospective process options and validation requirements but does not demonstrate process performance in *P. fruticosa*. Downstream operations, analytical controls, and recommended process descriptors indicate the steps needed to evaluate whether an extract remains chemically defined and specification-compliant during further development. Abbreviations: AED, acoustic energy density; DCM, dichloromethane; DES, deep eutectic solvent; HPLC–DAD, high-performance liquid chromatography with diode-array detection; LC–MS/MS, liquid chromatography–tandem mass spectrometry; MAE, microwave-assisted extraction; NADES, natural deep eutectic solvent; SEC, specific energy consumption; STY, space–time yield; TFC, total flavonoid content; TPC, total phenolic content; TSC, total saponin content; UAE, ultrasound-assisted extraction; UHPLC–QTOF–MS, ultra-high-performance liquid chromatography–quadrupole time-of-flight mass spectrometry.

Table 3. Extraction conditions, quantitative outputs, and validation gaps for *P. fruticosa* and transferable process approaches.

Extraction Route/Target	Material and Key Conditions	Reported Quantitative Output	Analytical Basis	Interpretation/ Main Gap	Literature Basis/ Citation
Conventional extraction/phenolics and saponins	• Root phenolics: 90% EtOH, 1:20 g/mL, 30 °C, 3 h. • Root saponins: 40% EtOH, 50 °C, 90 min; 20 mL/g recommended after testing 5–80 mL/g. Leaf saponins: MeOH, 1:12, 70 °C, 4 h	• Root phenolics: TPC 96.09 µg GAE/mg extract; TFC 58.30 µg QE/mg dry extract • Leaf saponins: TSC 8.12 ± 0.59 mg/mL; DPPH IC_{50} 17.14 µg/mL • Named phenolic/saponin recovery was not reported	• UV–Vis/ colorimetric TPC, TFC and TSC assays • DPPH/ABTS as applicable	Demonstrates target- and condition-dependent laboratory extraction, but not marker-controlled recovery, batch reproducibility, downstream mass balance, or solvent-recovery performance	D: [33,56,86]
Root UAE/saponins and phenolics	• Probe: 70% EtOH, 20:1 solvent/material, 60 °C, 185 W, 65 min • Bath: 40% EtOH, 50 mL/g, 45 °C, 20 min; bath rated at 550 W	• Probe: yield 14.51 ± 1.15%; TSC 41.24 ± 1.68 mg OAE/g dry material • Bath: TPC 2.13 ± 0.02 mg GAE/g DW; DPPH response 78.13 ± 0.25%	• Probe: UV–Vis TSC + RSM • Bath: Folin–Ciocalteu, DPPH, SEM	Direct laboratory optimization/screening. PFS or other named markers, delivered acoustic energy, degradation, SEC/STY, solvent recovery, and scale transfer remain unvalidated	D: [9,57]
Leaf intensified extraction/phenolics, pigments, and lutein	• Aqueous MAE: 1:25 *w*/*v*, 210 W, 25 s • Acetone MAE: 80% acetone, 1:40–1:80 g/mL, 300–600 W, 15 min; lutein UAE: n-hexane + 0.1% BHT, 20.16:1 *v*/*w*, 249.38 W, 31.6 min	• Aqueous MAE: TPC 35.1 mg GAE/g; TFC 22.0 mg QE/g; DPPH 79.6% • Acetone MAE: model-derived chlorophyll a 5.48 and b 2.81 mg/g. UAE: lutein 592.95 ± 2.13 mg/kg DW	• Colorimetric TPC/TFC • UV–Vis chlorophyll kinetics • UV–Vis lutein + RSM	Demonstrates that extraction conditions are target-specific. Compound-resolved phenolics, absorbed energy, degradation, chromatographic confirmation of lutein, food-grade solvent substitution, and scale-up remain unresolved	D: [65,66,76]
Ethanol extraction + low-polarity fractionation	Dried leaves; 95% EtOH, 1:10 *w*/*v*, 2 × 24 h at room temperature; crude extract subsequently partitioned with n-hexane and DCM	100 g leaves → 13.46 ± 2.03 g crude extract; 10 g crude → 1.61 ± 0.31 g hexane and 1.11 ± 0.49 g DCM fractions; 71 constituents GC–MS annotated	Gravimetric fraction recovery; GC–MS spectral-library profiling	Demonstrates discovery-scale lipophilic fractionation; most assignments remain tentative and complete mass balance, chemotype reproducibility, safer-solvent substitution, recycling, and manufacturing performance remain unresolved	D: [10]

Table 3. *Cont.*

Extraction Route/Target	Material and Key Conditions	Reported Quantitative Output	Analytical Basis	Interpretation/ Main Gap	Literature Basis/ Citation
Hydrodistillation/volatile profiling	Fresh leaves. Ogwuche et al. [61]: 250 g + 500 mL water, 4 h. Other studies used independent leaf-oil preparations	Kawaree et al. [59]: oil yield 0.1384%; α-bergamotene 20.25%, γ-elemene 15.28%, germacrene D 13.29%. Ogwuche et al. [61]: 23 tentative constituents; oil yield NR	GC–MS profiling, predominantly library-based assignment	Confirms source-dependent volatile profiles; incomplete structural confirmation, variable provenance, and limited quantitative replication preclude a universal volatile specification	D: [59–61]
DES/NADES/ prospective solvent systems	No direct *P. fruticosa* DES/NADES extraction study identified. External systems vary in HBA/HBD composition, molar ratio, water content, viscosity, temperature, UAE conditions, and recovery strategy	No species-specific quantitative output	External physicochemical, extraction and analytical studies	Prospective only. Marker recovery/integrity, viscosity and filtration, solvent retention/recovery, whole-mixture safety, sensory compatibility, and scale performance require direct validation	R: [40–42,69, 77,78]
Scale-up and sustainable-process assessment	External continuous/pilot UAE and general green-extraction/LCA literature; no direct *P. fruticosa* scale-up, LCA, or techno-economic study identified	No species-specific quantitative output	Scale-up descriptors, process inventory, LCA and sustainability assessment	Nominal power/time or higher yield alone do not establish scalability or greenness. AED, geometry, residence time, SEC, STY, solvent recovery, product specification, energy/water use, waste, and functional unit require direct evaluation	R: [31,80,81] G: [23,24, 32,82–85]

Note: D, direct *P. fruticosa* studies; R, related botanical/process-system studies; G, general engineering guidance; NR, not reported. Quantitative outputs are reproduced using the reporting basis of the original studies and are not directly comparable across different materials, assays, extraction conditions, or units. TPC, TFC, and TSC are total-content indices rather than compound-resolved marker concentrations. Reported ultrasonic or microwave power should not be interpreted as delivered or absorbed energy unless experimentally determined. External R/G sources identify prospective process requirements but do not demonstrate equivalent performance in *P. fruticosa*. Absence statements in this table refer to the defined literature search described in Section 2. AED, acoustic energy density; BHT, butylated hydroxytoluene; DCM, dichloromethane; DW, dry weight; GAE, gallic acid equivalents; LCA, life-cycle assessment; MAE, microwave-assisted extraction; OAE, oleanolic acid equivalents; QE, quercetin equivalents; RSM, response surface methodology; SEC, specific energy consumption; SEM, scanning electron microscopy; STY, space–time yield; TFC, total flavonoid content; TPC, total phenolic content; TSC, total saponin content; UAE, ultrasound-assisted extraction.

5.1. Product Definition Before Process Optimization

Process optimization should begin with a predefined ingredient profile. A saponin-oriented root extract, phenolic beverage ingredient, chlorophyll-rich leaf material, lutein fraction, and volatile oil require different markers, solvents, stability targets, safety constraints, and downstream operations. Direct root studies show that extraction conditions depend on the measured response. Phenolic and flavonoid indices favored a high-ethanol system, whereas saponin-related responses favored lower ethanol concentrations and different extraction durations [33,56]. These findings identify target-specific laboratory-scale conditions rather than a single transferable process.

The same principle applies to intensified extraction. A response-surface optimum for total saponin content may not maximize PFS recovery, preserve complementary saponins, or minimize degradation. External studies show that individual saponins may require different solvents and temperature conditions, while product properties such as surface activity or foaming may need simultaneous optimization [73–75]. These studies consequently provide transferable process-design context and reinforce the need to define the

response before optimization. Marker-resolved recovery should provide the chemical basis for process comparison. Specific energy consumption (SEC), space–time yield (STY), solvent recovery, stability, and batch reproducibility should then be evaluated relative to the amount of extract that meets the required specification, rather than to the total extract mass. Environmental comparison should similarly use a clearly defined functional unit and system boundary, considering solvent production, energy and water use, downstream operations, recovery, waste treatment, and relevant upstream inputs [24,82–85].

5.2. Hydroethanolic Extraction and Ultrasound-Assisted Extraction Scale-Up

Hydroethanolic extraction remains the most directly supported approach for recovering polar and amphiphilic constituents of *P. fruticosa*. However, available studies rely mainly on total-content indices and chemical antioxidant assays rather than compound-resolved markers. Conventional root studies have described the effects of ethanol concentration, liquid loading, temperature, and extraction time on phenolic, flavonoid, saponin, soluble solids, and chemical antioxidant responses [33,56]. A heated-methanol leaf study likewise identified preferred laboratory conditions through sequential screening, rather than through a food-grade process based on specific chemical markers [86]. Such studies provide useful experimental ranges, but further evaluation with specific markers is needed to assess the overall chemical profile. Probe and bath UAE have been evaluated under distinct laboratory conditions [9,57]. However, the effective acoustic treatment of a heterogeneous suspension is governed by delivered power, frequency, amplitude, pulse mode, solids loading, rheology, temperature history, reactor geometry, and field distribution [23,30–32].

A probe introduces energy locally into the slurry, producing steep spatial gradients near the sonotrode. In an ultrasonic bath, energy is transferred through the bath liquid and vessel wall, with additional effects from bath loading, vessel position, liquid depth, and container geometry. Accordingly, comparison between probe and bath systems should be based on delivered energy, reactor geometry, thermal history, and suspension conditions rather than nominal wattage and treatment time alone.

Scanning electron microscopy was used in the direct bath-UAE study to examine structural changes in the extracted residues, while acoustic dose equivalence and marker preservation were not established [57]. Future studies should use matched non-sonicated controls to distinguish ultrasound-specific effects from those caused by temperature, agitation, and solvent contact. Scale-up may further change attenuation, mixing, particle shielding, and residence-time distribution. External pilot studies show that acoustic intensity or power density often requires retuning across reactor sizes and flow configurations [31,80,81]. These studies provide useful guidance for reporting and process evaluation rather than directly transferable operating conditions. Cross-scale comparison should consider comparable starting materials, chemical profiles, delivered power, reactor geometry, thermal profile, SEC, STY, and solvent recovery. Cross-technology comparisons should also standardize solvent composition, solids loading, temperature, and downstream concentration before attributing performance to cavitation mode [87]. Current UAE studies provide a laboratory-scale optimization and screening basis but progression toward pilot and industrial scales requires confirmation of marker recovery and stability, characterization of delivered energy, and assessment of solvent recovery.

5.3. Complementary Routes for Distinct Chemical Targets

Microwave-assisted extraction, nonpolar UAE, solvent fractionation, and hydrodistillation have been investigated for chemically distinct targets that may not be efficiently recovered by hydroethanolic extraction. Direct leaf studies have used aqueous MAE for total phenolic and flavonoid extraction, acetone-based MAE for chlorophyll, and *n*-hexane

UAE for lutein recovery [65,66,76]. These studies demonstrate that suitable extraction conditions depend on the target compounds rather than suggesting that one extraction technology can be applied universally.

The direct MAE studies demonstrate rapid extraction of phenolic/flavonoid and chlorophyll targets under their respective conditions [65,76]. Further validation should include direct measurement of sample temperature, absorbed microwave energy, compound-specific recovery, marker stability, and scale-up performance. The lutein extraction method used n-hexane containing butylated hydroxytoluene (BHT), with quantification using ultraviolet–visible (UV–Vis) spectrophotometry. The study reported lutein recovery but does not establish a validated food-grade process. Further studies should include chromatographic confirmation, degradation monitoring, evaluation of safer solvents, energy consumption relative to target-compound recovery, and downstream solvent recovery. Sequential ethanol extraction followed by *n*-hexane and dichloromethane partitioning has been used for lipophilic profiling and evaluation of biological activities [10]. Hydrodistillation similarly isolates a volatile product rather than saponin or phenolic domains [59–61]. These extraction approaches produce chemically distinct fractions that require application-specific evaluation. Further development for production requires consideration of safer solvents, complete mass balances, residue control, solvent recycling, chemotype reproducibility, and storage stability.

5.4. DES/NADES as Prospective Process Systems

No eligible direct *P. fruticosa* DES/NADES extraction study meeting the search criteria was identified; these systems are considered prospective rather than established extraction routes for this species. Deep eutectic solvents (DES) are mixtures that exhibit a pronounced melting-point depression relative to their individual components through composition-dependent interactions, often involving hydrogen bonding and charge delocalization. Natural deep eutectic solvents (NADES) are prepared from naturally occurring constituents, but their origin and liquid appearance do not themselves confirm eutectic phase behavior, safety, or environmental advantages. Their composition, molar ratio, water content, temperature, viscosity, polarity, and phase behavior should be experimentally characterized [40,41,69,79,88]. Water content can alter viscosity, polarity, hydrogen-bond interactions, solute diffusion, and overall mass transfer; at high levels, the system may increasingly behave as an aqueous solution. It should be treated as a critical process parameter rather than simply a co-solvent. For *P. fruticosa*, the suitability of these solvents depends on their ability to recover bulky oleanane glycosides and other target compounds while minimizing hydrolysis, chemical composition changes, solvent residues, and downstream processing challenges. Food-grade hydroethanol currently provides a practical reference for comparison because it is supported by direct *P. fruticosa* studies, although this does not imply that it is universally optimal. Candidate DES/NADES systems should be compared directly with hydroethanol for marker recovery, product quality, and downstream performance. Their evaluation should include marker integrity, kinetics, filtration, solvent retention and recovery, downstream yield, SEC, reuse, whole-mixture toxicity, and overall resource use.

DES/NADES systems may also interfere with chromatographic analysis and bioassays. NADES-only, pH-matched, solvent-concentration-matched, and conventional-solvent controls are needed when the solvent may influence detector response, microbial growth, cytotoxicity, or assay chemistry [42,72]. These controls should be complemented by residual analysis, mass balance, and route-specific safety testing. External studies show that molecular modeling and spectroscopic characterization provide a rational basis for solvent selection, while recovery, scale-up, and sustainability are resolved through process-level

experimental assessment [77,78]. External studies further show that solvent recovery may require additional downstream operations and that extraction performance can decline during reuse [77,78]. The environmental advantages of DES/NADES should be evaluated across the entire process, including solvent recovery, reuse, downstream processing, energy and water consumption, and waste generation, rather than being assumed from the nature of the solvent or extraction yield alone [85,89].

5.5. Marker Continuity Through Downstream Processing

Process evaluation should extend beyond extraction. Clarification, filtration, concentration, fractionation, solvent removal, drying, storage, and formulation can remove, concentrate, transform, or degrade constituents. Saponin-oriented processes should monitor PFS and complementary saponins, while phenolic, pigment, lipophilic, and volatile products require their own appropriate marker sets. Total-content assays may support in-process screening, while chemical profile preservation should be verified through marker-resolved and fingerprint-based analysis. A complete mass balance should distinguish target-marker recovery, extract or fraction recovery, solvent recovery, intermediate losses, and waste. Stability-indicating methods should separate physical loss from chemical degradation, while marker ratios and fingerprint similarity should be monitored across unit operations. Biological testing should use material that represents the intended final product. An external study on saponin-rich material combined LC–MS/MS characterization, administered dose, preliminary safety, and animal response, providing a more complete link between chemical characterization and biological evaluation than extraction yield alone [90]. However, because the process remained at the discovery scale, it provides transferable methodological guidance rather than a directly transferable manufacturing process.

Variability in qualified raw materials may be managed within a validated design space when relationships among material characteristics, processing conditions, and product quality are clearly established. Solvent composition, residence time, energy density, and downstream conditions can then be adjusted as needed to maintain the required product quality rather than simply compensate for changes in crude extraction yield. A validated process for the intended product should reproducibly produce *P. fruticosa* material with the intended chemical composition while maintaining acceptable energy use, solvent consumption, downstream processing feasibility, stability, safety, and application performance. Material produced under these defined conditions can then be used for subsequent evaluation of biological activity, exposure, and claims.

6. Translational Position and Methodological Appraisal of Biological Findings

Reliable interpretation of biological activity requires well-characterized test materials along with appropriate experimental models, relevant exposure levels, measured responses, and safety assessment. Different *P. fruticosa* materials have been investigated across redox/oxidative-stress, inflammatory, metabolic, bone-related, neurological, antimicrobial, reproductive, and cytotoxic endpoints. Translational stage and methodological confidence were evaluated as separate dimensions. Stage indicates the translational question addressed by a finding, whereas confidence depends on factors including test-material characterization, analytical specificity, experimental controls, and replication or sample size. Additional considerations include dose justification, bias-relevant reporting, exposure characterization, and independent replication where available. Accordingly, advancement to a higher translational stage should not, in itself, be taken to imply greater strength or reliability of the underlying scientific support. Stages I–V are applied according to the operational definitions in Table 1. The level of scientific support required depends on

the intended application and the strength of the proposed claim. Traditional food use does not require a pharmaceutical development package, whereas concentrated products and stronger health claims require progressively stronger data on exposure, safety, and efficacy. Safety should be considered throughout all stages. Figure 3 summarizes the current translational landscape of the biological findings. Table 4 synthesizes the findings by biological domain, highlighting the highest demonstrated translational stage, major methodological limitations, and priorities for further validation. Supplementary Table S1 provides study-component-level information on test materials, doses, outcomes, and methodological appraisal. Direct *P. fruticosa* studies extend from preliminary chemical and biological screening to mechanism-linked biochemical or cellular studies and selected whole-organism proof-of-concept models. However, the depth of support and independent replication are uneven across biological domains, and several areas are represented by only one or a few studies using chemically non-equivalent materials. The number of reported activities should not be interpreted as equivalent depth of support or reproducibility.

Table 4. Biological-domain synthesis of *P. fruticosa* findings, translational position, major methodological limitations, and next validation priorities.

Biological Domain	Best Direct *P. fruticosa* Finding	Highest Demonstrated Stage	Material Definition and Principal Limitation	Next Decisive Validation	Refs.
Redox and oxidative-stress responses	Cell-free responses varied by material; lipophilic leaf fractions and PFS modulated ROS-related macrophage responses, and leaf extracts improved selected oxidative-stress outcomes in Drosophila	III	Non-equivalent materials/models; incomplete marker definition and compound attribution for several multicomponent materials, with limited chemically comparable independent replication	Test a marker-defined material in a dose–response mammalian model with exposure and safety characterization	[10,12,33,36,56,57,59,91–93]
Metabolic/glucose regulation	PFS inhibited α-amylase/α-glucosidase and reduced glucose excursion in an acute sucrose-challenge mouse model	III	Defined compound (PFS); acute nondiabetic model (n = 6/group); no exposure data or independent in vivo replication	Establish bioaccessibility/PK, disease-model dose–response, and repeated-dose safety	[15,16,91]
Inflammation, analgesia, and antipyresis	Leaf fractions/extracts showed macrophage effects and reduced edema, writhing, and pyrexia in rodents; a separate NF-κB screen was negative	III	Cellular and animal materials were not chemically comparable; the historical fraction was poorly resolved, with no exposure data or chemically comparable independent replication	Bridge a standardized marker-defined material from mechanistic assays to bias-controlled animal studies with exposure and safety endpoints	[10,18,94]
Osteoclast/bone	An ethanol leaf extract inhibited osteoclastogenesis in vitro and reduced LPS-induced bone loss in mice; PFS and quercitrin partly reproduced the cellular response	III	Leaf extract linked to PFS/quercitrin; single integrated study; no PK/bone exposure, longer-term testing, or independent replication	Confirm a standardized extract in a chronic dose–response bone model with exposure and longer-term safety	[17]

Table 4. *Cont.*

Biological Domain	Best Direct *P. fruticosa* Finding	Highest Demonstrated Stage	Material Definition and Principal Limitation	Next Decisive Validation	Refs.
Neurological/ neuronal-injury models	A root extract showed HT22-cell protection and short-term benefit after cerebral ischemia in gerbils; leaf extracts improved selected outcomes in Drosophila neurotoxicity models	III	Heterogeneous root/leaf materials and models; small animal studies; no brain exposure or chemically comparable independent replication	Use standardized chemistry, brain PK, dose–response mammalian testing, and independent replication.	[95–97]
Respiratory/ asthma-related responses	Ethanol leaf extract improved selected inflammatory, bronchospasm, cough, and mucus endpoints; ex vivo ileum and mast-cell assays provided mechanistic support	III	Incompletely marker-defined leaf extract; small studies largely from one research program; no PK bridge or independent replication	Repeat with a standardized batch, bias controls, exposure assessment, broader repeated-dose toxicology, and independent replication	[43,98,99]
Antimicrobial	Culture extract, isolated oleanane glycosides, and leaf oil showed strain-dependent antimicrobial screening responses	I	Non-equivalent, partly characterized materials; tentative oil assignments; no chemically comparable replication, host cell safety, MBC, or matrix/infection-model validation	Confirm chemistry, MIC/MBC, host cell selectivity, matrix performance, then a relevant infection/preservation model	[11,12,61]
Cytotoxicity/hazard screening	Root extract, volatile oil, and isolated constituents produced variable cytotoxicity findings; one root-extract study contains conflicting IC_{50} units	I	Heterogeneous materials and characterization; unit discrepancy, limited normal-cell selectivity, and no chemically comparable replication preclude reliable potency or safety-margin inference	Verify units and assay conditions, add normal-cell controls, identify causal constituents, and establish tolerable in vivo exposure	[9,12,58,59, 100]
Reproductive and general safety (cross-cutting)	Rat studies reported mixed reproductive/endocrine findings; at 500 mg/kg, gestational studies reported post-implantation loss, and one study also reported two maternal deaths. Acute and 28-day studies provide only limited tolerability information	Cross-cutting; findings reach Stage III models	Non-standardized leaf extracts, small groups, source-reporting inconsistencies, no exposure data, and limited independent confirmation with standardized material; no general NOAEL or reproductive-safety conclusion	Conduct product- and route-specific repeated-dose and reproductive/developmental toxicology with standardized material and exposure-based safety margins	[43,94,98, 101–103]

Table 4. *Cont.*

Biological Domain	Best Direct *P. fruticosa* Finding	Highest Demonstrated Stage	Material Definition and Principal Limitation	Next Decisive Validation	Refs.
Exposure and human validation	No eligible study meeting the search criteria through 22 September 2026 met Stage IV criteria, and no controlled human intervention study using a chemically characterized *P. fruticosa* material or finished product was identified	IV: not demonstrated; V: not demonstrated	Species-specific bioaccessibility, PK, metabolite, tissue-exposure, and target-engagement data remain unavailable within the defined search	Perform product-matched release/bioaccessibility, PK, metabolite/tissue distribution, target-engagement, response, and safety studies before controlled human evaluation	No D; external context (R): [19–21,104–109]

Note: Stage indicates translational position, not methodological quality. Safety is cross-cutting. Literature basis: D, direct *P. fruticosa* studies; R, related botanical/saponin-system studies; G, general engineering–regulatory guidance. All biological findings are D unless explicitly marked otherwise; R/G inform interpretation and gap definition only and do not advance the species-specific stage. Detailed study-level appraisal is provided in Table S1. Abbreviations: AAE, ascorbic acid equivalents; AIF, apoptosis-inducing factor; AKT, protein kinase B; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); AChE, acetylcholinesterase; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; DPPH, 2,2-diphenyl-1-picrylhydrazyl; DW, dry weight; EC_{50}, half-maximal effective concentration; GAE, gallic acid equivalents; GC–MS, gas chromatography–mass spectrometry; GSH, glutathione; IC_{50}, half-maximal inhibitory concentration; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; M-CSF, macrophage colony-stimulating factor; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MS, mass spectrometry; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NADPH, nicotinamide adenine dinucleotide phosphate; NFATc1, nuclear factor of activated T cells 1; NMR, nuclear magnetic resonance; NOAEL, no-observed-adverse-effect level; PBMC, peripheral blood mononuclear cell; PFS, *Polyscias fruticosa* saponin; qPCR, quantitative polymerase chain reaction; QE, quercetin equivalents; RANKL, receptor activator of nuclear factor κB ligand; ROS, reactive oxygen species; TAC, total antioxidant capacity; TEAC, Trolox equivalent antioxidant capacity; TFC, total flavonoid content; TPC, total phenolic content; TRAP, tartrate-resistant acid phosphatase; TSC, total saponin content; TLC, thin-layer chromatography; UHPLC–QTOF–MS/MS, ultra-high-performance liquid chromatography–quadrupole time-of-flight tandem mass spectrometry; XTT, 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide.

6.1. Stage I: Preliminary Screening and Hazard Assessment

Chemical antioxidant and total-content assays provide simplified measures of structurally diverse constituents, and their results remain sensitive to assay conditions, standards, matrices, and reporting units [67,68]. Direct *P. fruticosa* studies have shown substantial variation depending on the extraction conditions and material source, with no single set of optimal conditions across the measured responses [33,36,56,57]. A comparative *Polyscias* study further showed species- and organ-dependent differences in phenolic profiles, antioxidant responses, and A549-cell inhibition [58]. A four-component formulation containing 10% *P. fruticosa* supported mixture-level optimization rather than species-specific activity [110]. Relative screening studies reported chemical antioxidant responses and α-glucosidase inhibition, whereas a methanolic leaf extract was inactive in the NF-κB screening model under the reported conditions [18,91]. These findings demonstrate that preliminary screening results depend strongly on the test material and experimental model.

Broad cytotoxicity and antimicrobial assays also remain Stage I unless selectivity, mechanism, and host cell tolerability are established. Inconsistencies in the reported source and units limit the root-extract study to qualitative interpretation of cytotoxicity [9]. Suspension-cell extracts exhibited strain-dependent antibacterial activity, whereas essential-oil effects were observed mainly at high concentrations and were associated with tentatively identified constituents [11,61]. Stage I is therefore most appropriate for comparing pro-

cessing conditions, selecting promising candidates, and identifying potential hazards, but physiological or therapeutic conclusions require further experimental validation.

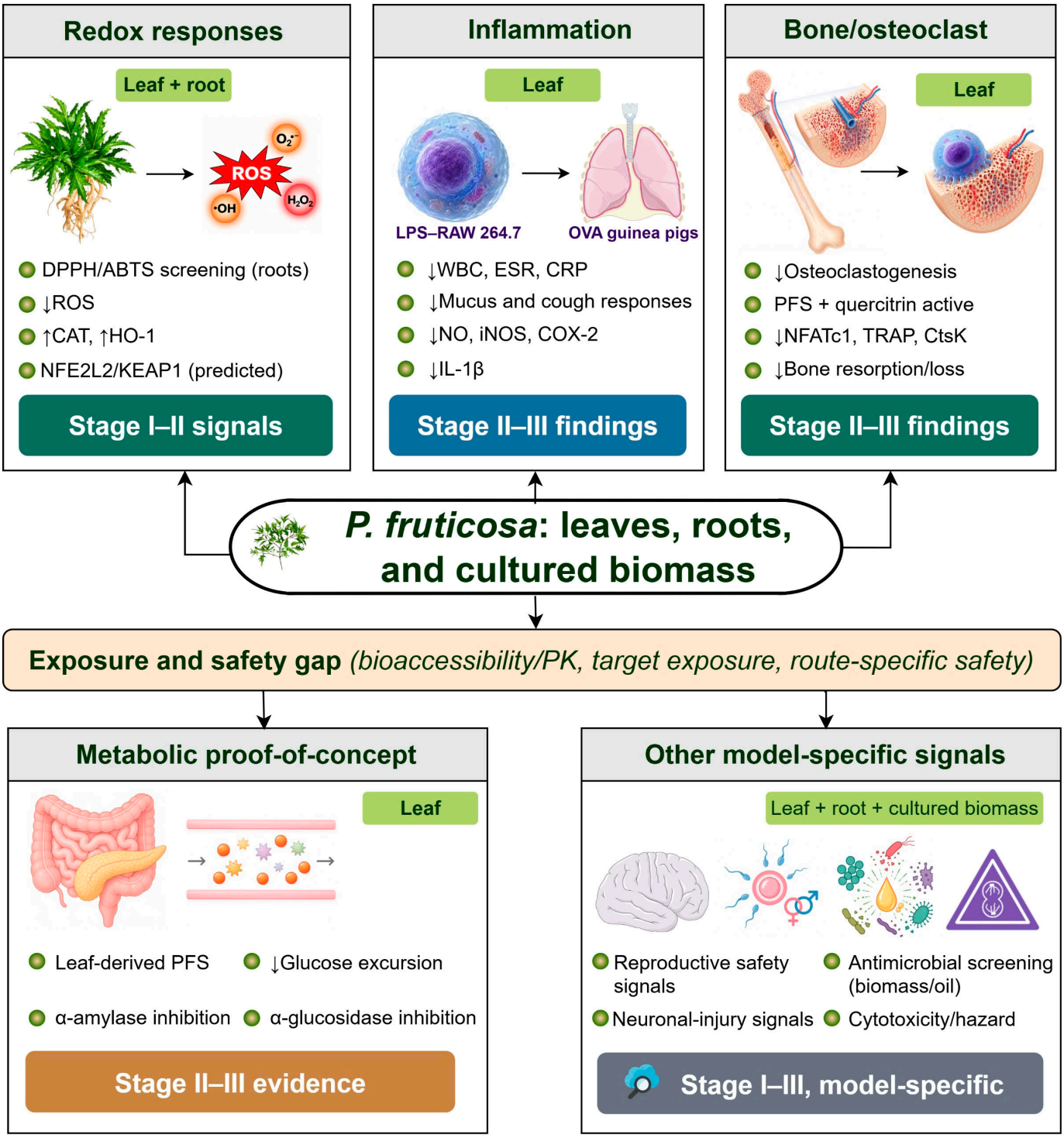


Figure 3. Translational landscape of direct biological studies for *P. fruticosa*. Species-specific findings span Stage I chemical or hazard screening, Stage II mechanism-linked biochemical or cellular responses, and selected Stage III whole-organism proof-of-concept studies. The depth of support and independent replication vary among biological domains. No eligible direct Stage IV exposure–response study or Stage V controlled human study was identified within the defined search. Exposure and safety remain major constraints on further translation. Upward and downward arrows (↑ and ↓) indicate reported increases and decreases, respectively; black connecting arrows indicate conceptual

relationships among the material source, response domains, and exposure/safety gap rather than causal pathways. Abbreviations: ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); CAT, catalase; COX-2, cyclooxygenase-2; CRP, C-reactive protein; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ESR, erythrocyte sedimentation rate; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; KEAP1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; NFE2L2/NRF2, nuclear factor erythroid 2-related factor 2; NFATc1, nuclear factor of activated T cells 1; OVA, ovalbumin; PFS, *Polyscias fruticosa* saponin; PK, pharmacokinetics; RANKL, receptor activator of nuclear factor κB ligand; ROS, reactive oxygen species; TRAP, tartrate-resistant acid phosphatase; WBC, white blood cell count.

6.2. Stage II: Biochemical and Cellular Mechanisms

Stage II includes biochemical or cellular responses linked to plausible mechanisms, with cell-based interpretation requiring concentrations compatible with cell viability. Lipophilic leaf fractions affected redox and inflammatory markers in lipopolysaccharide-stimulated macrophages [10]. However, most GC–MS annotations and computationally predicted targets remain provisional. Further mechanism-linked studies should assess host cell viability alongside pathway-specific responses to distinguish specific biological effects from those associated with cytotoxicity. Studies on structurally confirmed oleanane glycosides show that biological activity varies among individual saponins. PFS reduced lipopolysaccharide-induced NADPH oxidase activity and intracellular reactive oxygen species, whereas ladyginoside A showed greater cytotoxicity and only weak antimicrobial activity [12]. PFS also inhibited α-amylase and α-glucosidase, whereas polysciosides D and I were inactive [15,16]. These findings demonstrate that the activities of individual saponins should be evaluated separately rather than generalized across the entire class of compounds. An ethanol leaf extract inhibited osteoclast differentiation and resorption, with PFS and quercitrin partially reproducing the response [17]. A 75% ethanol root extract reduced glutamate-induced oxidative stress and apoptosis-related signaling in HT22 cells [95]. These findings identify specific extracts and compounds for further investigation, although the observed responses remain dependent on the test materials and experimental models used.

6.3. Stage III: Organism-Level Proof-of-Concept

Stage III evaluates whole-organism responses, with interpretation depending on model relevance, test-material standardization, exposure, study duration, and replication. Oral administration of PFS reduced glucose excursion in an acute sucrose-challenge study in non-diabetic mice [16]. This demonstrates an acute response under the tested conditions, while evaluation of longer-term efficacy requires repeated-dose studies in appropriate disease models, together with characterization of systemic exposure. An ethanol leaf extract also reduced bone loss in a short-term lipopolysaccharide-induced mouse model [17]. Earlier work using a poorly resolved n-butanol, saponin-rich leaf fraction reported effects in rodent paw edema, acetic acid writhing, and vaccine-induced pyrexia models. Given the limited chemical characterization and insufficient information on potential bias, exposure, and repeated-dose safety, these findings represent preliminary whole-organism signals that require further validation using well-characterized materials and appropriate experimental controls [94].

Leaf extracts are also reported to improve neurological or redox outcomes in specialized *Drosophila* models, while a 75% ethanol root extract reduced neuronal degeneration after transient cerebral ischemia in gerbils [93,95–97]. These studies provide model-specific neurological and neuroprotection-related signals, but further investigation requires well-characterized and standardized materials, assessment of brain exposure, longer-term safety studies, confirmation in appropriate mammalian models, and independent replication.

Guinea-pig studies reported improvements in respiratory endpoints, whereas a 28-day assessment found no significant changes in measured body weight, hematological indices, or routine liver or kidney measures [43,98,99]. These findings provide dose- and endpoint-specific 28-day tolerability data, while a general no-observed-adverse-effect level, comprehensive safety assessment, and clinical respiratory efficacy require broader evaluation. In a male-rat study, the leaf extracts increased sperm counts at selected doses, whereas mean serum testosterone was lower in the treated groups without a statistically significant between-group difference. Primary-spermatocyte vacuolation was reported across groups rather than as a treatment-specific lesion [101]. These mixed findings do not support a fertility-enhancement claim and instead identify male reproductive function as an endpoint requiring further safety evaluation. Two additional rat studies reported female reproductive and gestational findings. At 500 mg/kg, one gestational study reported two maternal deaths and increased post-implantation loss, while a separate study also reported post-implantation loss [102,103]. Interpretation is constrained by small pregnancy subgroups and inconsistencies in the reporting of some experimental details. Considered together, the available studies identify reproductive and developmental safety as a priority for further evaluation of orally administered leaf extracts, particularly under repeated exposure and pregnancy-related use.

6.4. Stage IV: Bioaccessibility and Exposure

No eligible direct *P. fruticosa* study identified by the literature search and subsequent update through 22 September 2026 linked an administered material or dose to bioaccessibility, pharmacokinetics, or metabolite formation. Species-specific data on systemic or tissue exposure and target engagement were also not identified. Chemical marker abundance should be linked directly to local or systemic exposure. This gap is critical for PFS because gastrointestinal conditions, the microbiota, the matrix, and the formulation can alter saponin stability, hydrolysis, absorption, and local activity [19,20,106]. Studies on other saponins provide useful information on factors that should be investigated directly for *P. fruticosa*. Saikosaponin A exhibited very low oral bioavailability, whereas intravenous administration caused hemolysis in rats [104]. Saponins in *Panax japonicus* extract exhibited distinct plasma and tissue distribution profiles [107]. These values serve as external exposure benchmarks rather than quantitative estimates for PFS. Safety assessments require consideration of compound-specific characteristics, including the aglycone scaffold, sugar architecture, polarity, and molecular configuration. A related-system study of triterpenoid saponins and sapogenins demonstrated marked structure dependence of hemolytic activity, with oleanane-type compounds generally showing stronger effects than ursane- or dammarane-type comparators [109]. These findings provide a structure-dependent safety benchmark for saponin-rich materials but do not provide quantitative hemolysis data for PFS or *P. fruticosa* extracts.

Formulation may also modify exposure. In a related formulation system, tea-saponin-stabilized albendazole nanocrystals increased intestinal permeability and systemic exposure to albendazole sulfoxide relative to albendazole alone [108]. This finding illustrates formulation-dependent exposure but does not provide exposure data for PFS or *P. fruticosa*. Carrier-specific evaluation and carrier-only controls are essential when assessing saponin delivery systems [21,105]. Stage IV should establish the relationships among administered dose, compound release or transformation, local or systemic exposure, target engagement, biological response, and safety.

6.5. Stage V: Human Studies and Safety Considerations

No eligible controlled human intervention study evaluating a chemically characterized *P. fruticosa* material or finished product was identified within the defined search. Stage V therefore remains reserved for controlled human validation of the intended *P. fruticosa* product. Findings from *Panax*, other saponins, or multi-botanical products may provide supporting information but cannot substitute for direct studies of *P. fruticosa*. This absence of controlled intervention studies should not be interpreted as an absence of human exposure. Traditional dietary and medicinal use provides historical exposure information, but it does not establish controlled efficacy, dose–response, or product-specific safety.

Safety operates as a cross-cutting consideration across all translational stages. Direct *P. fruticosa* studies have reported material- and dose-specific safety findings, including cytotoxicity or hazard signals for selected extracts and isolated saponins [9,12,58,59,100] and reproductive or gestational findings in rat studies [101–103]. These observations do not establish a uniform toxicity profile for the species. They nevertheless support product-specific evaluation of dose, duration, route of exposure, reproductive and developmental endpoints, and appropriate safety margins for concentrated or repeated-exposure products.

Safety assessment should use authenticated materials with batch consistency and include appropriate control of contaminants and residual solvents, along with toxicity testing relevant to the intended route of use. Cell-based studies should include appropriate vehicle, interference, normal-cell, and selectivity controls [72]. Depending on the intended dose, route, duration, and population, saponin-rich products intended for systemic exposure may additionally require assessment of hemolysis, repeated-dose toxicity, genotoxicity, reproductive toxicity, potential interaction testing, and exposure-based safety-margin assessment. Topical products require a safety assessment of the final product for dermal use [8,13,111,112]. Further biological and clinical evaluation should consider material identity and composition, as well as exposure, biological response, and safety. The specific requirements will depend on the intended application of the *P. fruticosa* product.

7. Application Pathways and Translational Priorities

The diverse phytochemical composition and reported biological activities of *P. fruticosa* have been investigated across several application areas, including nutraceuticals, food and beverage products, topical and cosmetic formulations, and pharmaceutical-oriented development. Controlled culture is considered separately as an alternative supply platform. Each application involves a distinct material–process–product combination, with specific quality attributes, exposure routes, safety considerations, regulatory requirements, and claim boundaries. Accordingly, the application potential of *P. fruticosa* should be evaluated in the context of the intended finished product rather than solely based on botanical identity, extraction yield, marker concentration, or a positive bioassay. Figure 4 presents this application-bounded portfolio. Direct product-oriented studies currently include food processing and prototype development [39,113], supported by broader functional-food design considerations [114]. Topical and cosmetic translation relies on preliminary species-specific screening and transferable formulation studies [10,115–119]. Controlled-culture studies further support cell-suspension systems as alternative supply platforms [63,64], while broader guidance on herbal-product quality reinforces product-specific regulatory qualification across application routes [120].

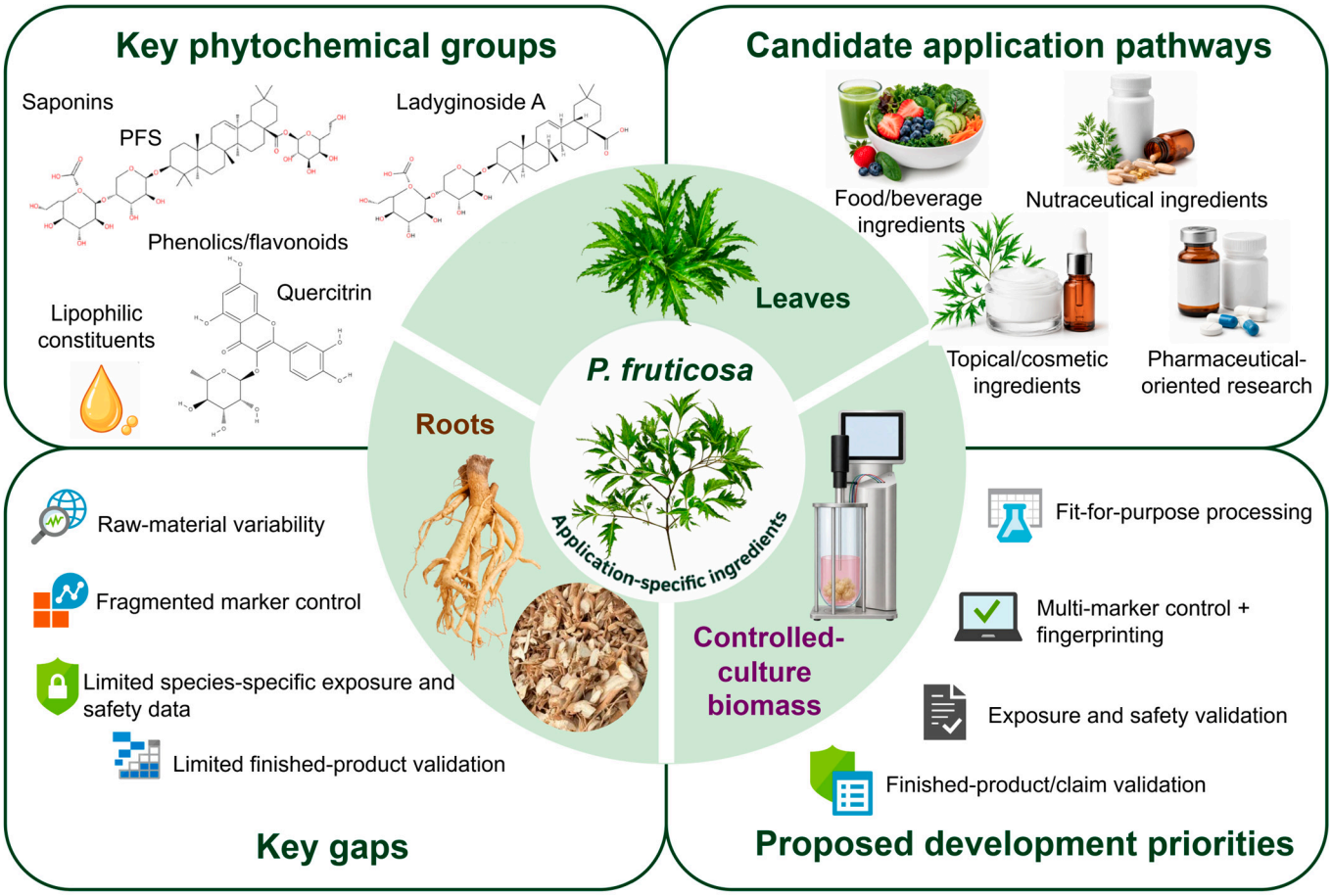


Figure 4. Application-bounded portfolio and proposed development priorities for *Polyscias fruticosa*. Leaves, roots, and controlled-culture biomass support distinct candidate food, nutraceutical, topical, and pharmaceutical-oriented product concepts. Current species-specific findings define the direct literature base, whereas related-system studies and general guidance inform proposed validation priorities. Controlled bioproduction is an alternative supply platform rather than a product category. Each pathway requires product- and route-specific quality, exposure, safety, stability, and claim validation. Abbreviation: PFS, *Polyscias fruticosa* saponin.

7.1. Functional Food and Beverage Ingredients

Traditional leaf consumption provides the most direct history-of-use basis for food-oriented development of *P. fruticosa*. Candidate formats include authenticated leaf powders, infusions, tea-like preparations, and aqueous or food-grade hydroethanolic leaf extracts. This history of use should not be extrapolated automatically to concentrated leaf or root extracts, enriched fractions, or isolated saponins, which represent compositionally and quantitatively different exposure scenarios. Reproductive and gestational findings reported for orally administered leaf extracts in rats [101–103] further support product-specific exposure and safety assessment for concentrated or compositionally modified ingredients.

Direct studies currently provide preliminary processing windows rather than demonstrating finished-food efficacy. Studies on *P. fruticosa* root extraction show that solvent composition, temperature, time, and liquid loading alter total-content and chemical-antioxidant responses [33,56]. Although these findings provide transferable process principles, their applicability to food development should be interpreted cautiously as leaf-based materials may differ in composition and processing behavior. A tea-bag study identified a preferred drying and brewing condition within the tested design [113], providing direct prototype support for subsequent sensory, microbial, packaging, bioaccessibility, and shelf-life valida-

tion. The 30-day chlorophyll-retention model should likewise be treated as preliminary stability data requiring finished-product validation [39].

Food-oriented development of *P. fruticosa* ultimately depends on its performance within the intended food matrix, including dispersibility, precipitation behavior, color, odor, taste, preparation stability, packaging compatibility, and exposure under realistic serving conditions [114]. Food-oriented qualification should also incorporate source-relevant contaminant surveillance, as illustrated by the location-specific radionuclide assessment of *P. fruticosa* and other vegetables [47]. Findings from dietary Drosophila studies further provide organism-level oxidative-stress proof-of-concept [93], while the tea-bag and chlorophyll-retention studies provide the strongest species-specific support for processing and prototype development [39,113]. For mixed-botanical formulations, biological effects should be attributed carefully to individual components; the formulation containing 10% *P. fruticosa* supports mixture-level optimization, but species-specific efficacy would require component-resolved validation [110]. The available findings support food-prototype development and compositional or technological positioning of *P. fruticosa*, whereas physiological benefit claims require product-specific substantiation at the appropriate translational stage.

7.2. Nutraceutical Ingredients

Nutraceutical development requires more concentrated, reproducible, and dose-defined materials. Potential product formats include saponin-oriented extracts, marker-controlled powders, and finished dosage forms. Isolated PFS, enriched fractions, and whole extracts must remain separate product hypotheses.

For saponin-oriented products, PFS is the candidate quantitative anchor with the strongest current species-specific analytical support. However, the available assay data do not establish PFS as a validated release specification or potency marker, and a single constituent cannot represent the chemical complexity of whole extracts. PFS should be evaluated alongside complementary saponins, process-sensitive or degradation markers, and a chromatographic fingerprint to support extract identity, consistency, and stability [7,48,53].

PFS has been reported to inhibit digestive enzymes and to reduce glucose excursion in an acute mouse model, while related saponins showed structure-dependent differences in activity [15,16]. Direct UAE work further provides a laboratory route to saponin-rich root extracts [9]. Gastrointestinal, pharmacokinetic, tissue-distribution, and formulation studies in related saponin systems define the exposure variables that concentrated *P. fruticosa* products should address [19,104,107,108]. These findings support formulation-matched preclinical structure–function research and repeated-dose efficacy, exposure–response characterization, and dose selection for future human studies as subsequent validation steps.

Development must connect dosage-form release with gastrointestinal transformation, bioaccessibility, metabolites, systemic or local exposure, and safety. Enhanced delivery may increase both activity and interaction or toxicity risks [20,21]. For concentrated oral products, development should establish a justified daily intake and an exposure-based safety margin and, where warranted by composition and intended use, assess hemolytic potential, repeated-dose toxicity, and reproductive and developmental safety. Direct reproductive and gestational findings reported for *P. fruticosa* leaf extracts in rats [101–103] reinforce the need for this product-specific assessment.

7.3. Topical and Cosmetic Ingredients

P. fruticosa has been investigated for topical and cosmetic applications, but species-specific studies remain largely at the preformulation and comparative-screening stages. Lipophilic leaf fractions modulated macrophage redox and inflammatory responses but

were not evaluated in skin cells or dermal systems [10]. A comparative elastase screen included *P. fruticosa* root but advanced *Rosa damascena* for further development, positioning the *P. fruticosa* result as preliminary comparative screening rather than finished-product anti-wrinkle substantiation [115].

The finished formulation becomes the main basis for evaluating performance and safety. Extract identity and marker retention must be linked to pH, rheology, phase stability, oxidative and photostability, odor, color, preservative compatibility, and packaging. Dermal retention or penetration, irritation, sensitization, phototoxicity, microbial challenge, and real-time stability must be measured in the intended product [116–119]. Broader cosmetic literature reinforces this product-level approach by linking botanical-ingredient performance to extract standardization, antioxidant delivery, vehicle design, formulation stability, skin compatibility, and microbiological performance [121–124].

Carrier and vehicle effects should be evaluated alongside extract-specific performance. Current findings support preformulation and cosmetic research, while finished-product appearance, photoprotection, wound-healing, or therapeutic claims require formulation-specific validation.

7.4. Pharmaceutical-Oriented Development

P. fruticosa has also been investigated in pharmaceutical-oriented research, with studies reporting metabolic, osteoclastogenic, respiratory, and neurological activities [16,17,43,95–97]. However, progression from preliminary biological activity to therapeutic development requires substantially greater control over material identity, composition, exposure, efficacy, and safety [8,20]. Chemically defined extracts require validated fingerprints and marker ranges, while purified fractions or compounds additionally require assay, purity, related-substance limits, and stability-indicating methods. Enzyme, cellular, and animal studies help identify candidate mechanisms and disease-related biological endpoints. Their translational value depends on demonstrating that the material can be consistently produced and that the biologically active constituents reach relevant sites of action at an effective and safe exposure [8,20]. Accordingly, pharmaceutical-oriented development of *P. fruticosa* should progress through product-matched exposure, toxicology, and controlled human evaluation before therapeutic or disease-prevention claims are advanced.

7.5. Controlled Bioproduction as an Alternative Supply Platform

Controlled culture systems offer an alternative approach for producing *P. fruticosa*-derived biomass and bioactive materials, particularly where consistent raw-material supply and greater control over production conditions are desired. Culture conditions, carbon source, elicitation, reactor configuration, and line history affect biomass and metabolite accumulation, including oleanolic acid and saponin-related responses [2,11,36,37,63,64]. In suspension-cultured *P. fruticosa* cells, auxin composition has also been shown to affect biomass accumulation, rhizogenesis, and somatic embryogenesis [125], further demonstrating that culture conditions are integral attributes of the source material. These findings support the optimization of controlled-culture processes and identify PFS productivity, whole-profile stability, and equivalence to field-grown organs as the principal qualification targets.

Before culture-derived materials can be considered suitable alternatives to conventional plant sources, their identity, consistency, and chemical performance must be adequately established. Key considerations include cell-line identity, genetic and metabolic stability, marker productivity, batch reproducibility, medium-residue control, microbial quality, and downstream stability [13,28]. Culture-derived materials should retain distinct reference fingerprints unless equivalence has been demonstrated. Their exposure and safety requirements follow the final food, nutraceutical, topical, or pharmaceutical pathway.

7.6. Cross-Route Qualification and Regulatory Positioning

The regulatory and development position of *P. fruticosa* depends largely on how its derived material is processed, formulated, administered, and intended to be used, rather than on botanical identity alone. Differences in composition, concentration, fractionation, purification, dosage form, route of exposure, target population, and intended claims may result in substantially different product categories and corresponding qualification requirements. All development pathways share several core requirements: authenticated raw material, traceable manufacture, fit-for-purpose marker control, chromatographic fingerprinting, contaminant and process-residue limits, dosage-form performance, packaging, and stability [7,8]. Batch consistency should be assessed through a justified multi-marker profile supported by a chromatographic fingerprint rather than relying on a single marker. A Quality by Design (QbD) framework should connect critical material attributes (CMAs) and critical process parameters (CPPs) with product-specific critical quality attributes (CQAs). Chemometrics may support fingerprint comparison and detection of process drift only when reference populations, preprocessing, criteria, and validation are predefined [14,29,50].

The regulatory requirements and level of scientific support needed for product development remain dependent on the product category, route of administration, dose, intended claims, target population, and jurisdiction [8,120]. Within this review, the term "supportable claims" refers to the strongest claims supportable by the evaluated findings, not automatic legal authorization or prohibition. Claim substantiation should remain relevant to the material, dose, route, intended use, and claim strength. The framework complements rather than replaces jurisdiction-specific regulatory assessment. Likewise, "nutraceutical" is used in this review as a descriptive development category rather than a harmonized legal classification. Table 5 summarizes the current species-specific findings, principal unresolved gaps, and proposed next validation priorities for each application pathway.

Table 5. Application-specific status, major gaps, and proposed next validation priorities for *P. fruticosa* development.

Application Pathway	Current Direct *P. fruticosa* Findings	Major Unresolved Gap	Proposed Next Validation Priority	Literature Basis/Refs.
Functional food and beverage	• Local use of leaves as a vegetable • Dried-leaf storage and tea-processing studies • Reproductive/gestational signals from oral leaf extracts	Finished-product exposure/bioaccessibility, sensory acceptance, shelf life, and safety of concentrated products	• Define product and serving exposure • Validate sensory, microbial and shelf-life performance • Targeted safety assessment and claim-relevant validation	D: [4,39,101–103,113]. R/G: [114,120]
Nutraceutical ingredients	• PFS quantified by HPLC-DAD • Enzyme inhibition and acute mouse glucose response • UAE optimization of root saponin extraction • Oral reproductive/gestational signals	• Limited cross-study material comparability • No direct PK/exposure–response, validated potency marker, chronic efficacy, or human validation.	• Marker/fingerprint-defined product • Bioaccessibility and PK • Repeated dose and reproductive/developmental safety • Product-matched efficacy	D: [9,15,16,53,101–103] R/G: [7,19,20,104]
Topical and cosmetic ingredients	• Leaf fractions showed non-dermal cellular redox/inflammatory effects • Root was included in comparative elastase screening	No direct dermal safety, penetration, or finished-product validation.	• Defined formulation • Stability and dermal exposure • Irritation/sensitization assessment • Human-use validation	D: [10,115]. R: [116,119]

Table 5. *Cont.*

Application Pathway	Current Direct *P. fruticosa* Findings	Major Unresolved Gap	Proposed Next Validation Priority	Literature Basis/Refs.
Pharmaceutical-oriented development	• Defined extracts/compounds show metabolic, bone, respiratory and neurological preclinical effects • Reproductive/developmental safety signals are also reported	Product-matched PK/PD, target exposure, comprehensive toxicology, robust disease-model efficacy, and controlled human data	• Define investigational product; establish PK/PD and target exposure • Route-specific toxicology and disease-model validation • Controlled human evaluation	D: [16,17,43,95–97,101–103]. R/G: [8,20]

Note: D, direct *P. fruticosa* studies; R, related botanical/saponin-system studies; G, general engineering–regulatory guidance; PFS, *Polyscias fruticosa* saponin; UAE, ultrasound-assisted extraction; PK, pharmacokinetics; PD, pharmacodynamics. R/G sources inform interpretation and proposed validation priorities but do not demonstrate equivalent performance in *P. fruticosa*. Statements of unavailable direct data refer to the defined literature search described in Section 2. Safety is considered across all application pathways. Proposed priorities are scientific development recommendations rather than universal regulatory requirements and should be adapted to the intended product, exposure, population, claim, and jurisdiction. Controlled bioproduction is treated as an alternative supply platform rather than a separate application pathway.

7.7. Research Priorities and Integrated Development Pathway

The current literature highlights five closely related research priorities. First, comparative studies should define which plant organs, accessions, developmental states, and production systems belong within one material design space. Second, multi-marker and stability-indicating specifications should combine PFS with complementary saponin, phenolic, lipophilic, degradation, and safety markers. Third, scale-up studies should evaluate maintenance of the required chemical profile in relation to delivered energy, reactor geometry, temperature profiles, SEC, STY, solvent recovery, and downstream processing. Once pilot-scale data meeting the required product specifications become available, techno-economic assessment should be integrated with life-cycle assessment using a common functional unit to determine the production benefits of process intensification [84,85]. Fourth, exposure and safety studies using the intended formulation should evaluate compound release, gastrointestinal or dermal transformation, bioaccessibility, metabolites, pharmacokinetics, tissue distribution, target engagement, and route-specific toxicity. Fifth, finished-product validation should reflect the intended application. Traditional leaf consumption provides the most direct history-of-use basis for food-oriented development, although concentrated or compositionally modified ingredients require product-specific exposure and safety assessment. Other application pathways likewise require product-specific validation aligned with route, dose, formulation, intended population, and claim strength.

Together, these priorities define an iterative QbD pathway in which product requirements guide raw-material selection, analytical specifications, and processing conditions, while subsequent findings are used to refine the design space. Further development and the strength of product claims should reflect the level of validation achieved across material quality, chemical specifications, processing, exposure, safety, and finished-product performance.

8. Limitations of the Review

This review has several limitations. The available literature is heterogeneous with respect to plant organ, accession or cultivar, extraction procedure, analytical characterization, experimental model, dose, and outcome reporting, which limits direct comparison among studies. Several biological domains are supported by only one or a few studies, and independent replication using chemically comparable *P. fruticosa* materials remains uncommon. Given this limited and uneven literature, publication and selective reporting

biases cannot be excluded, and the number of reported activities should not be taken to indicate independent replication or reproducibility. Data on bioaccessibility, pharmacokinetics, tissue exposure, and repeated-dose safety are limited or absent, and no eligible controlled human intervention study was identified within the literature search and subsequent update through 22 September 2026. Related botanical-system studies and general engineering–regulatory guidance were used to interpret mechanisms and define development gaps where direct *P. fruticosa* data were unavailable. These sources were not treated as substitutes for species-specific validation. Accordingly, the framework presented here should be interpreted as a structured synthesis of the current literature and its limitations rather than as a regulatory classification or quantitative ranking of development status.

9. Conclusions

The reviewed literature indicates that *Polyscias fruticosa* (L.) Harms materials differ across plant organs, cultivars, and production systems in chemical composition, processing behavior, and reported biological responses. Major reported chemical domains include oleanane-type saponins, phenolic and flavonoid constituents, lipophilic and volatile compounds, and leaf pigments and carotenoids. Representative quantitative data include PFS at 1300 μg/g DW in leaves and 570 μg/g DW in roots and quercitrin at 0.13–0.32% in leaves; these values are material- and method-specific rather than universal compositional specifications. *Polyscias fruticosa* saponin remains a candidate quantitative anchor with the strongest current species-specific analytical support, while whole-extract control requires complementary markers and chemical fingerprints. Targeted chromatographic methods support quantitative marker analysis, whereas LC–MS, NMR, and GC–MS provide broader structural or compositional characterization; total-content and chemical redox assays remain more appropriate for comparative screening than for compound-resolved specification or physiological inference.

Direct biological studies currently extend from Stage I screening through Stage II mechanism-linked findings to selected Stage III whole-organism proof-of-concept studies, but do not establish product-level efficacy. Representative Stage II–III findings include PFS inhibition of α-amylase and α-glucosidase with reduced glucose excursion in an acute sucrose-challenge model; an ethanol leaf extract showing PFS/quercitrin-linked inhibition of osteoclast differentiation and short-term bone-loss proof-of-concept; and model-specific inflammatory, respiratory, and neurological responses. No eligible direct Stage IV exposure–response study or Stage V controlled human study meeting the search criteria was identified through 22 September 2026, and important gaps remain in bioaccessibility, pharmacokinetics, metabolite profiling, tissue distribution, target engagement, and repeated-dose safety. Reproductive and gestational findings in animal studies also warrant product-specific evaluation of concentrated or repeated-exposure materials. Food, nutraceutical, topical, and pharmaceutical-oriented applications should be considered as distinct material–process–product pathways. Future work should prioritize reproducible material definition, fit-for-purpose multi-marker specifications, marker recovery and stability during processing, exposure characterization, route-specific safety, and finished-product validation. Linking botanical identity, analytical characterization, processing, exposure, safety, and biological response will be essential for developing scientifically supportable application-specific products and claims.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app16209990/s1. Table S1: Study-level translational assignment and concise methodological appraisal of principal direct *P. fruticosa* findings contributing to the biological synthesis.

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Abbreviations

AAE	Ascorbic acid equivalents
ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AChE	Acetylcholinesterase
AED	Acoustic energy density
BHT	Butylated hydroxytoluene
CMAs	Critical material attributes
CPPs	Critical process parameters
CQAs	Critical quality attributes
DCM	Dichloromethane
DES	Deep eutectic solvent
DPPH	2,2-diphenyl-1-picrylhydrazyl
DW	Dry weight
EC_{50}	Half-maximal effective concentration
FRAP	Ferric reducing antioxidant power
GAE	Gallic acid equivalents
GC–MS	Gas chromatography–mass spectrometry
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSH	Glutathione
HPLC	High-performance liquid chromatography
HPLC–DAD	High-performance liquid chromatography with diode-array detection
HR–ESI–MS	High-resolution electrospray-ionization mass spectrometry
IC_{50}	Half-maximal inhibitory concentration
LC–MS	Liquid chromatography–mass spectrometry
LC–MS/MS	Liquid chromatography–tandem mass spectrometry
LPS	Lipopolysaccharide
MAE	Microwave-assisted extraction
M-CSF	Macrophage colony-stimulating factor
MDA	Malondialdehyde
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
NADES	Natural deep eutectic solvent
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance
PBMC	Peripheral blood mononuclear cell
PFS	*Polyscias fruticosa* saponin
qPCR	Quantitative polymerase chain reaction

QbD	Quality by design
QE	Quercetin equivalents
RANKL	Receptor activator of nuclear factor κB ligand
SEC	Specific energy consumption
SEM	Scanning electron microscopy
STY	Space–time yield
TAC	Total antioxidant capacity
TEAC	Trolox equivalent antioxidant capacity
TFC	Total flavonoid content
TPC	Total phenolic content
TRAP	Tartrate-resistant acid phosphatase
TSC	Total saponin content
TSS	Total soluble solids
UAE	Ultrasound-assisted extraction
UHPLC–QTOF–MS/MS	Ultra-high-performance liquid chromatography–quadrupole time-of-flight tandem mass spectrometry
UV–Vis	Ultraviolet–visible spectroscopy
XTT	2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide

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