



Review

Annurca Apple-Derived Polyphenols, Bioactive Fractions and By-Products as Context-Dependent Redox Modulators: Molecular Mechanisms and Nutraceutical Perspectives—A Narrative Review

Stefania D'Angelo 

Department of Medical, Human Movement, and Well-Being Sciences (DiSMMeB), University of Naples "Parthenope", 80133 Naples, Italy; stefania.dangelo@uniparthenope.it

Abstract

Annurca apple (*Malus domestica* cv. *Annurca*) is a traditional Southern Italian cultivar increasingly recognized as a polyphenol-rich food matrix with functional and nutraceutical relevance. Its distinctive post-harvest reddening process, together with tissue-specific differences among flesh, peel and core, influences its phytochemical profile, antioxidant capacity and biological activity. In addition, *Annurca* apple by-products, including peel and core fractions, are emerging as sustainable sources of food-derived bioactives. This review critically summarizes current evidence on *Annurca* apple-derived polyphenols, bioactive fractions and by-products, focusing on their molecular mechanisms, context-dependent redox behavior and translational potential. Available studies indicate that *Annurca*-derived compounds and matrices should not be interpreted merely as antioxidant sources but rather as modulators of redox-sensitive cellular pathways whose effects depend on fruit fraction, ripening stage, extract composition, dose, biological model and cellular context. In normal cellular models, *Annurca*-derived extracts and fractions have shown cytoprotective effects against oxidative damage, mercury-induced erythrocyte alterations, phosphatidylserine externalization, advanced glycation end product (AGE)-induced cytotoxicity and oxidative stress-induced senescence. These effects involve mechanisms related to ROS modulation, erythrocyte membrane homeostasis, calcium-dependent PLSCR1 regulation, antiglycative activity, endothelial protection and senescence-associated pathways. Conversely, in cancer cell models, *Annurca* polyphenols may exert pro-oxidant and pro-apoptotic effects, mainly involving ROS/JNK signaling, inhibition of cell survival, modulation of epithelial–mesenchymal plasticity and reduced migration. Additional evidence on lipid metabolism, skin and hair biology, neuroprotective targets and by-product valorization supports broader functional and nutraceutical applications. However, most evidence remains preclinical and often relies on concentrated extracts or specific formulations. Future studies should address extract standardization, phytochemical fingerprinting, bioaccessibility, gut microbiota metabolism, circulating metabolites, dose relevance and clinical validation to clarify whether *Annurca*-derived bioactives can be developed as evidence-based functional ingredients or nutraceutical candidates.



Academic Editor: Miquel Mulero

Received: 14 August 2026

Revised: 11 September 2026

Accepted: 17 September 2026

Published: 1 October 2026

Copyright: © 2026 by the author.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and

conditions of the [Creative Commons](#)

[Attribution \(CC BY\)](#) license.

Keywords: *Annurca* apple; apple polyphenols; bioactive fractions; apple by-products; redox signaling; oxidative stress; advanced glycation end products; erythrocyte membrane homeostasis; cellular senescence; nutraceuticals

1. Introduction

Apples are among the most widely consumed fruits worldwide and represent an important dietary source of polyphenols, dietary fiber, vitamins, minerals and other phytochemicals. Their phenolic profile includes flavan-3-ols, flavonols, phenolic acids, dihydrochalcones, procyanidins and quercetin derivatives, although the relative abundance of these compounds varies markedly according to cultivar, fruit tissue, ripening stage, post-harvest handling and processing conditions [1–5]. This variability is particularly relevant because apple peel and flesh differ substantially in polyphenol composition, and evidence obtained from generic apple cultivars cannot be automatically extrapolated to specific local varieties [2,4,6]. Moreover, the biological relevance of apple-derived polyphenols depends not only on their native concentration in the fruit but also on food matrix interactions, gastrointestinal bioaccessibility, metabolism and gut microbial transformation [5,7–10].

Within this broad field, *Annurca* apple (*Malus domestica* cv. *Annurca*) is a traditional cultivar from Southern Italy and represents a distinctive Mediterranean food matrix. Its relevance is linked not only to its geographical and sensory identity but also to its characteristic post-harvest reddening process, tissue-dependent phytochemical composition and documented richness in bioactive polyphenols [11–21]. Recent studies have further extended interest in *Annurca* apple to peel, core and other usually discarded fractions, which may contain relevant amounts of phenolic compounds and display antioxidant and antiglycative properties [11,22]. These findings support the potential valorization of *Annurca* apple by-products as sustainable sources of food-derived bioactives while also highlighting the need to distinguish the edible flesh from true by-products such as peel, core and pomace. This distinction is important because apple by-products may differ markedly from whole fruit and edible flesh in terms of phenolic concentration, fiber-associated matrix components, processing stability and technological applicability [23–25].

Research on *Annurca* apple has progressively moved beyond the general concept of antioxidant capacity toward the investigation of molecular mechanisms in cellular and translational models. Available studies have examined *Annurca*-derived extracts, polyphenol-rich fractions, by-products and nutraceutical formulations in relation to erythrocyte oxidative damage, mercury-induced membrane alterations, advanced glycation end product-related cytotoxicity, lipid metabolism, skin and hair biology, cellular senescence, neuroprotective targets and cancer cell redox signaling [22,26–44]. Taken together, these studies suggest that *Annurca*-derived bioactives should not be interpreted simply as generic antioxidants but rather as context-dependent modulators of redox-sensitive pathways whose effects may vary according to fruit fraction, extract composition, dose, biological model and cellular redox status. However, chemical antioxidant assays such as DPPH, ABTS, FRAP and total antioxidant capacity should be interpreted as screening tools for redox-related chemical reactivity and not as direct evidence of physiological antioxidant effects or health benefits [45,46].

Despite this growing body of evidence, several issues remain unresolved. First, many studies rely on native extracts or concentrated polyphenol-rich preparations tested directly in vitro, whereas the compounds reaching target tissues after oral intake may be digestion-derived products, phase II conjugates or gut microbiota-derived metabolites [7–10]. Second, the polyphenol profile, bioaccessibility, gut microbiota metabolism and circulating metabolites of *Annurca*-derived preparations remain insufficiently characterized. Third, the available evidence includes different matrices, including whole fruit, edible flesh, peel, core, by-products, polyphenol-rich extracts and nutraceutical formulations, which should not be treated as interchangeable [11,22,25,31–36]. Finally, although human data are available for lipid metabolism and hair-related outcomes, much of the evidence on erythrocyte protection, antiglycative activity, senescence modulation, neuroprotective targets and

cancer cell redox modulation remains preclinical or exploratory [22,26–30,37–44]. These limitations are particularly relevant because apple polyphenols may interact with the gut microbiota, and microbial metabolism may influence their bioactivity, systemic exposure and interindividual variability [5,7,10,47].

For these reasons, a critical review specifically focused on *Annurca* apple-derived polyphenols, bioactive fractions and by-products is warranted. Previous literature has generally addressed apple polyphenols, apple by-products, polyphenol bioavailability or gut microbiota interactions in broader terms [1,5,25,47], whereas an integrated evaluation of *Annurca*-specific evidence in relation to redox modulation, fruit-fraction specificity, by-product valorization and nutraceutical translation is still lacking. The novelty of this review lies in integrating *Annurca*-specific phytochemical, preclinical and translational evidence within a single critical framework centered on fruit-fraction specificity, context-dependent redox modulation, by-product valorization and nutraceutical development. This review therefore aims to critically summarize current evidence on *Annurca* apple-derived polyphenols, bioactive fractions and by-products, with emphasis on phytochemical determinants, molecular mechanisms, antioxidant and antiglycative activity, erythrocyte membrane homeostasis, cellular senescence, lipid metabolism, neuroprotective potential, cancer-related redox signaling and sustainable nutraceutical applications. Particular attention is given to the strength and limitations of the evidence, including extract heterogeneity, tissue- and ripening-dependent variability, bioavailability, gut microbiota metabolism, dose relevance and the need for standardized preparations and clinical validation.

2. Literature Search Strategy and Review Framework

This article was designed as a critical narrative review rather than as a systematic review or meta-analysis. A narrative approach was chosen because the available evidence on *Annurca* apple is heterogeneous and includes phytochemical studies, antioxidant assays, in vitro cellular models, enzyme assays, by-product characterization, nutraceutical formulations, clinical trials and mechanistic studies on redox-sensitive pathways. The aim was not to address a narrowly defined intervention question but to integrate different levels of evidence into a coherent molecular nutrition and nutraceutical framework [48,49].

A structured literature search was performed using PubMed/MEDLINE, Scopus, Web of Science Core Collection and Google Scholar. The search covered publications from database inception to September 2026. Additional records were identified by screening the reference lists of relevant articles and reviews. The search focused on three main areas: (i) *Annurca* apple, *Annurca* apple polyphenols, bioactive fractions, fruit fractions, by-products and nutraceutical formulations; (ii) apple polyphenols, apple by-products, polyphenol bioavailability, gut microbiota metabolism and food-derived bioactives; and (iii) mechanistic literature on oxidative stress, redox signaling, glycation, erythrocyte membrane homeostasis, cellular senescence, lipid metabolism, neuroprotective targets and cancer cell stress responses.

The main search terms included the following: “*Annurca* apple”, “*MelAnnurca*”, “*Malus domestica* cv. *Annurca*”, “*Annurca* polyphenols”, “*Annurca* apple extract”, “*Annurca* by-products”, “*Annurca* peel”, “*Annurca* flesh”, “*Annurca* core”, “apple polyphenols”, “apple peel polyphenols”, “apple by-products”, “apple pomace”, “procyanidins”, “chlorogenic acid”, “quercetin derivatives”, “bioavailability”, “gut microbiota”, “polyphenol metabolites”, “oxidative stress”, “redox signaling”, “antiglycation”, “advanced glycation end products”, “erythrocytes”, “phosphatidylserine externalization”, “PLSCR1”, “cellular senescence”, “lipid metabolism”, “cholesterol absorption”, “keratin”, “hair growth”, “acetylcholinesterase”, “monoamine oxidase”, “neuroprotection”, “ROS/JNK signaling”, “breast cancer cells”, “thyroid cancer cells” and “nutraceuticals”. Search terms were used

alone and in Boolean combinations, including “*Annurca* apple” AND “polyphenols”, “*Annurca* apple” AND “by-products”, “*Annurca*” AND “oxidative stress”, “*Annurca*” AND “cholesterol”, “apple polyphenols” AND “bioavailability”, “apple by-products” AND “polyphenols”, “polyphenols” AND “gut microbiota”, “polyphenols” AND “advanced glycation end products” and “polyphenols” AND “ROS/JNK”.

Studies were considered eligible if they met at least one of the following criteria: (i) they specifically investigated *Annurca* apple, *Annurca*-derived polyphenols, fruit fractions, by-products, extracts or nutraceutical formulations; (ii) they provided relevant information on apple polyphenols, apple by-products, bioavailability, gut microbiota metabolism or food matrix effects useful for contextualizing *Annurca*-specific evidence; or (iii) they addressed molecular mechanisms directly relevant to the interpretation of *Annurca*-derived bioactivity, including oxidative stress, glycation, erythrocyte membrane alterations, cellular senescence, lipid metabolism, neuroprotective targets or cancer-related redox signaling.

Exclusion criteria included studies not related to apples, polyphenols, food-derived bioactives or nutraceutical mechanisms; articles focused exclusively on agronomic or technological aspects without relevance to phytochemical composition or biological activity; studies lacking sufficient methodological or mechanistic information; non-peer-reviewed sources; conference abstracts without full text; and duplicate records. Because this was a critical narrative review, no formal meta-analysis, PRISMA flow diagram or quantitative risk-of-bias assessment was performed. However, priority was given to peer-reviewed original articles, clinical trials, mechanistic studies and authoritative reviews directly relevant to the scope of the manuscript.

The selection and critical appraisal of the literature were performed by the author. To reduce selective interpretation, the evidence was organized according to a translational hierarchy. Human intervention studies were considered separately from preclinical, in vitro/ex vivo and chemical assay-based studies. Chemical antioxidant assays, including DPPH, ABTS, FRAP and total antioxidant capacity assays, were interpreted as screening tools for redox-related chemical reactivity and not as direct evidence of physiological antioxidant effects or health benefits. In vitro findings were considered mechanistic and hypothesis-generating unless supported by human or in vivo evidence.

Particular attention was paid to distinguishing whole fruit, edible flesh, peel, core, true by-products, concentrated polyphenol-rich extracts, isolated or enriched bioactive fractions and nutraceutical formulations because these matrices may differ substantially in phytochemical profile, bioavailability, dose relevance and biological effects. The review was organized around the concept of context-dependent redox modulation. According to this framework, *Annurca* apple-derived polyphenols, bioactive fractions and by-products were not interpreted simply as antioxidant sources but as food-derived bioactive matrices and compounds whose effects may depend on fruit fraction, ripening stage, extract composition, biological model, cellular redox status and dose. This framework was used to critically evaluate the strength and limitations of the evidence across phytochemical, preclinical, clinical and translational domains.

3. *Annurca* Apple as a Fruit-Fraction-Specific Bioactive Matrix

Annurca apple (*Malus domestica* cv. *Annurca*) is a traditional cultivar from Southern Italy and represents one of the most distinctive fruit products of the Campania region [15–17]. Its functional relevance is not limited to geographical origin or sensory identity but derives from the interaction among cultivar-specific traits, post-harvest reddening, fruit-fraction composition and bioactive potential [11–21]. The recognition of “*MelAnnurca* Campana” as a Protected Geographical Indication further supports the close relationship between this fruit, its production area and traditional post-harvest practices [15].

A defining feature of *Annurca* apple is the post-harvest reddening process, traditionally carried out in the *melaio* [15,18]. During this phase, fruits are exposed after harvest to promote the development of the characteristic red skin coloration while preserving firmness, crispness and sensory quality [17,18]. From a molecular nutrition perspective, this process is relevant because reddening-ripening may affect antioxidant properties, phenolic composition and tissue-specific bioactive potential [11–13]. Therefore, the post-harvest phase should not be considered only an aesthetic or commercial step but also a biological determinant that may influence the phytochemical profile and reproducibility of *Annurca*-derived preparations [11,12,18,19].

The phytochemical profile of *Annurca* apple is shaped by cultivar identity, ripening stage, fruit tissue and post-harvest or processing conditions. Apples contain several classes of phenolic compounds, including flavan-3-ols, flavonols, phenolic acids, dihydrochalcones and procyanidins, but their relative abundance varies markedly among cultivars and fruit fractions [1–5,50]. In *Annurca* apple, early evidence showed that reddening-ripening modifies the antioxidant activity of polyphenol-rich extracts [12], while phytochemical studies identified specific antioxidant compounds in the peel, including E- and Z-p-coumaroyl fatty acid esters [13]. The broader apple literature also indicates that peel and flesh differ substantially in total and individual phenolic compounds, supporting the need to interpret *Annurca* apple bioactivity according to fruit fraction rather than as a generic property of the whole fruit [2,4,6].

This fruit-fraction specificity is central to the interpretation of the available evidence. The peel is generally considered a phenolic-rich outer fraction, directly exposed to light, environmental stimuli and pigmentation-related metabolic changes [2,4,6,13]. The flesh represents the main edible fraction and has been used in several studies on *Annurca*-derived biophenols, oxidative stress, skin-related cellular responses, neuroprotective targets and cancer cell redox modulation [20,21,26,27,37–44]. The core and other usually discarded fractions may retain phenolic compounds, antioxidant activity and fiber- or pectin-associated components, supporting their potential inclusion in by-product valorization strategies [11,22–25,51,52]. Importantly, flesh should be distinguished from true by-products: peel, core and pomace may be considered by-products when discarded or generated during processing, whereas flesh remains the principal edible matrix.

The interpretation of *Annurca*-derived bioactivity also depends on the type of preparation tested. Whole fruit, edible flesh, peel, core, by-product extracts, polyphenol-rich fractions and nutraceutical formulations cannot be considered interchangeable. Concentrated extracts may contain higher levels of bioactive compounds than those achievable through habitual fruit consumption, and their biological effects may depend on extraction procedure, dose, matrix composition and cellular model [11,14,22,26–36]. Similarly, chemical antioxidant assays such as DPPH, ABTS, FRAP and total antioxidant capacity are useful for preliminary screening of redox-related chemical reactivity, but they do not directly demonstrate physiological antioxidant effects or health benefits [45,46].

Overall, *Annurca* apple should be interpreted as a fruit-fraction-specific bioactive matrix rather than as a uniform source of antioxidant compounds. Its biological relevance depends on cultivar identity, reddening-ripening, peel–flesh–core distribution, extract standardization, dose relevance and bioavailability. The fruit-fraction distribution, phytochemical features, evidence type and critical limitations of *Annurca* apple-derived matrices are summarized in Table 1.

Table 1. Fruit-fraction distribution and phytochemical profile of *Annurca* apple-derived bioactives.

Fruit Fraction/Matrix	Main Phytochemical Features	Representative Compounds or Classes	Evidence Type	Biological Relevance	Critical Interpretation/Limitations	Refs.
Whole <i>Annurca</i> apple	Cultivar-specific Mediterranean food matrix influenced by reddening, ripening stage and post-harvest conditions	Flavan-3-ols, flavonols, phenolic acids, dihydrochalcones, procyanidins and other apple phytochemicals	<i>Annurca</i> -specific and broader apple literature	Provides the food-matrix background for interpreting <i>Annurca</i> -derived bioactivity	Whole-fruit effects cannot be directly extrapolated from concentrated extracts or isolated fractions	[1–4,6,12,14–21,50]
Peel	Phenolic-rich outer fraction, strongly influenced by light exposure, pigmentation and reddening-ripening	Flavonols, quercetin derivatives, procyanidins, phenolic acids, E- and Z-p-coumaryl fatty acid esters	Mainly phytochemical and chemical antioxidant evidence	Relevant source of redox-active compounds; potentially important for by-product valorization	Most evidence is based on chemical assays; antioxidant capacity does not directly demonstrate physiological efficacy	[2,6,11,13]
Flesh	Main edible fraction and commonly investigated source of <i>Annurca</i> -derived biophenols	Flavan-3-ols, phenolic acids, dihydrochalcones, procyanidin-rich fractions and other biophenols; non-phenolic components such as TLP1a may also contribute	<i>Annurca</i> -specific cellular and mechanistic studies	Used in studies on oxidative stress, skin-related models, neuroprotective targets and cancer cell redox modulation	Flesh-derived extracts are not equivalent to whole-fruit intake; extract dose, composition and bioavailability require clarification	[20,21,26,27,37–44]
Core	Usually discarded internal fraction with potential residual phenolic content	Phenolic acids, flavan-3-ols, procyanidins and fiber/pectin-associated matrix components	Emerging <i>Annurca</i> -specific by-product evidence	Potential source of bioactives for circular valorization strategies	Direct biological evidence remains limited; core should be distinguished from edible flesh and from processed pomace	[11,22–25,51,52]
Peel/core by-products	Usually discarded fractions with ripening- and tissue-dependent phenolic content	Total polyphenols, flavonoids, ortho-diphenols and antioxidant fractions; fiber- and pectin-associated components	<i>Annurca</i> -specific by-product studies and broader by-product literature	Antioxidant and antiglycative activity; inhibition of AGE formation and protection against AGE-induced cytotoxicity in preclinical models	Mainly chemical and in vitro evidence; safety, contaminants, digestion, bioaccessibility and batch reproducibility need assessment	[11,22–25,51,52]
Polyphenol-rich extracts/bioactive fractions	Concentrated preparations obtained from defined or partially defined fruit matrices	Procyanidin-rich components, flavan-3-ols, flavonols, phenolic acids and other extractable polyphenols	<i>Annurca</i> -specific mechanistic studies	Redox-related cytoprotection, erythrocyte membrane protection, lipid metabolism, senescence marker modulation and cancer cell stress responses	Concentrated extracts may not reflect dietary exposure; native compounds may differ from circulating metabolites after digestion and microbiota metabolism	[5,7–10,12,14,20,21,26–34,37–42,53–55]
<i>Annurca</i> -based nutraceutical formulations	Enriched or standardized formulations based on <i>Annurca</i> apple polyphenolic extracts	Polyphenol-enriched preparations, usually formulation-specific	Human intervention studies and mechanistic studies	Evidence for lipid-profile modulation and hair/keratin-related outcomes	Findings are formulation-specific and should not be automatically extrapolated to whole-fruit consumption or non-standardized extracts	[31–36]

Note: This table distinguishes edible fruit fractions, usually discarded fractions and formulated preparations. Peel, core and pomace may be considered by-products when discarded or generated during processing, whereas flesh represents the main edible fraction. Chemical antioxidant assays should be interpreted as preliminary screening tools and not as direct evidence of physiological efficacy or health benefits. Abbreviations: AGE, advanced glycation end products; TLP1a, thaumatin-like protein 1a.

4. Annurca Apple By-Products and Sustainable Valorization

The valorization of fruit by-products has become a central issue in food science, nutrition and circular bioeconomy. Apple processing residues, including peels, cores, seeds and pomace, may retain dietary fiber, pectin, minerals and phenolic compounds, together with antioxidant activity and technological functionality [23–25,51,52]. Therefore, apple by-products are increasingly considered potential sources of functional ingredients for food, nutraceutical and cosmeceutical applications rather than simple waste streams.

In this framework, *Annurca* apple by-products are of particular interest because their phytochemical and functional properties depend on fruit fraction, ripening stage and post-harvest conditions [11]. Recent evidence showed that peel, flesh and core from *Annurca* apples at different ripening stages differ in total polyphenols, flavonoids, ortho-diphenols and antioxidant capacity, with peel emerging as a particularly phenolic-rich fraction [11]. However, it is important to distinguish edible fruit fractions from true by-products: flesh represents the main edible matrix, whereas peel, core and pomace may be considered by-products when discarded or generated during processing.

Importantly, *Annurca* apple by-products have been investigated not only for chemical antioxidant capacity but also for their activity in glycoxidative stress models. By-products obtained at different ripening stages were reported to inhibit advanced glycation end product formation and protect against AGE-induced cytotoxicity in cellular models [22]. These findings suggest that *Annurca* residues may contain bioactive compounds able to interfere with oxidative and glycative stress pathways. Nevertheless, this evidence remains mainly chemical and in vitro and should not be interpreted as direct proof of physiological or clinical efficacy.

The sustainable exploitation of *Annurca* by-products requires careful standardization. Several variables may affect the final composition and biological activity of recovered extracts, including cultivar identity, fruit fraction, ripening stage, reddening conditions, agronomic practices, storage, drying method, extraction solvent and analytical procedure [4,11,19,25]. Future studies should therefore report detailed phytochemical fingerprints, marker compounds and extraction conditions to improve comparability and reproducibility.

Another critical aspect concerns translation into food, nutraceutical or cosmeceutical applications. The physiological relevance of *Annurca* by-product extracts depends on bioaccessibility, digestive stability, intestinal absorption, microbiota-mediated metabolism and dose compatibility with realistic exposure conditions [7,53,56]. In addition, safety issues, including pesticide residues, microbial contamination and batch-to-batch variability, should be addressed before these materials are proposed for human use.

Overall, *Annurca* apple by-products represent a promising but still preliminary model of circular valorization. Their development as sustainable functional ingredients will require standardized preparation, safety assessment, bioaccessibility studies and validation under physiologically relevant conditions. The fruit-fraction specificity of *Annurca* apple bioactives, together with the distinction between edible fractions and true by-products, is summarized in Figure 1.

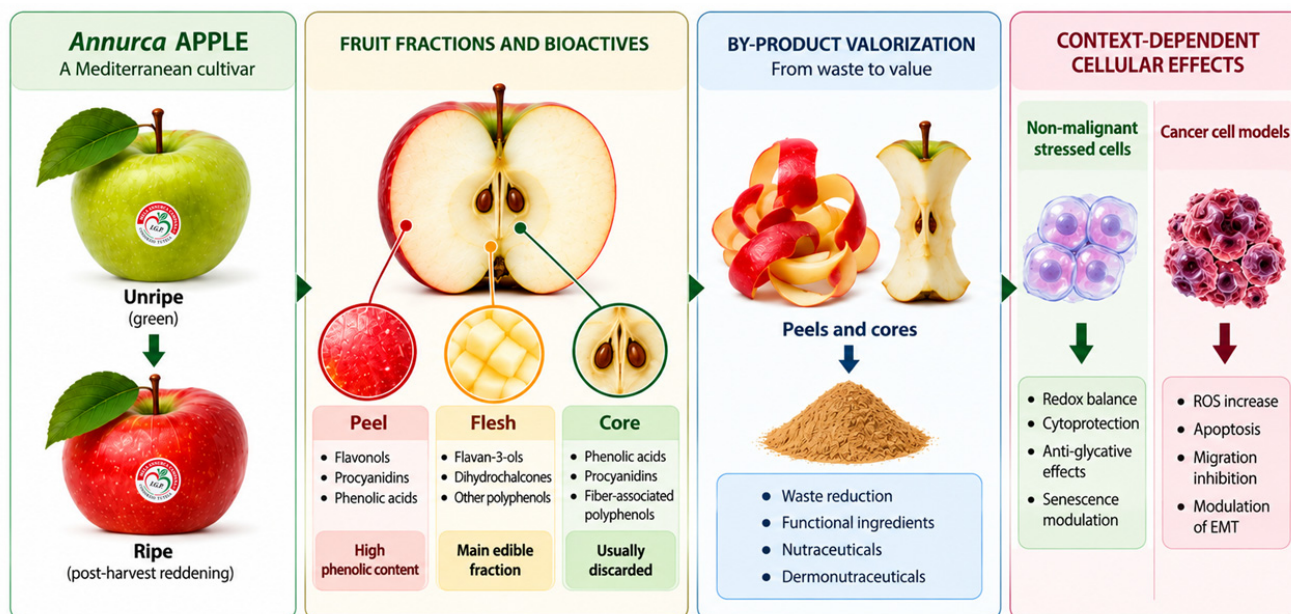


Figure 1. Fruit-fraction specificity of *Annurca* apple bioactives. *Annurca* apple bioactivity depends on fruit fraction, ripening stage and extract composition. The peel is generally enriched in phenolic compounds, including flavonols, quercetin derivatives, procyanidins and specific antioxidant secondary metabolites. The flesh represents the main edible matrix and has been used in several studies on *Annurca*-derived biophenols and bioactive preparations. The core and other usually discarded fractions may contribute to by-product valorization as sources of phenolic-rich and fiber-associated matrices. This figure distinguishes edible fruit fractions from true by-products and highlights that chemical antioxidant capacity should be interpreted as preliminary evidence rather than direct proof of physiological efficacy.

5. Redox-Related Cytoprotection and Erythrocyte Membrane Homeostasis

Oxidative stress is a central mechanism involved in cellular dysfunction, aging and several pathological processes [57]. In nutritional research, however, the biological relevance of food-derived bioactives cannot be inferred only from radical-scavenging capacity or chemical antioxidant assays. It should also be evaluated through cellular models able to assess redox balance, membrane integrity, viability and stress-related functional endpoints [26,28–30]. In this context, *Annurca*-derived polyphenols and extracts have been investigated in non-malignant cellular models exposed to oxidative or toxicant-induced stress.

Human erythrocytes represent one of the earliest models used to evaluate the cytoprotective properties of *Annurca* apple polyphenols. Red blood cells are highly exposed to oxygen, contain abundant hemoglobin and polyunsaturated membrane lipids and are particularly sensitive to oxidative damage because of their limited biosynthetic and repair capacity [58]. In this model, *Annurca* apple extract was reported to protect human erythrocytes against oxidative damage, suggesting a possible role in preserving membrane and cellular integrity under oxidative challenge [26]. This evidence provided the basis for later studies focused on toxicant-induced erythrocyte stress and membrane asymmetry.

Mercury-induced erythrocyte damage represents one of the most specific mechanistic areas of *Annurca* apple research. Inorganic mercury compounds such as mercury chloride (HgCl₂) can impair erythrocyte homeostasis by increasing oxidative and nitrosative stress, promoting hemoglobin oxidation, reducing glutathione content and altering membrane-associated proteins [59–61]. A relevant consequence of erythrocyte stress is the disruption of membrane phospholipid asymmetry, particularly the externalization of phosphatidylserine,

a hallmark of eryptosis-like processes that may be triggered by oxidative stress, calcium influx and activation of phospholipid scrambling pathways [62,63].

Within this framework, *Annurca* apple polyphenol-rich extracts were shown to counteract HgCl_2 -induced oxidative stress in human erythrocytes [28]. A subsequent study further linked this protective effect to phosphatidylserine externalization, intracellular calcium homeostasis and phospholipid scramblase 1 (PLSCR1) regulation [29]. Since phosphatidylserine exposure is controlled by a complex network of flippases, scramblases and ion-dependent mechanisms, these findings should be interpreted cautiously. They suggest that *Annurca*-derived polyphenols may contribute to the preservation of erythrocyte membrane asymmetry through redox- and calcium-sensitive pathways, but they do not yet establish the contribution of individual compounds or direct in vivo relevance [29,62–65].

The Ca^{2+} /PLSCR1/phosphatidylserine axis provides a biologically plausible link between oxidative stress, membrane remodeling and erythrocyte dysfunction. Increased intracellular calcium can promote phospholipid scrambling and phosphatidylserine exposure, potentially contributing to altered hemorheology, macrovesicles formation and procoagulant activity [62,63]. The observation that *Annurca* apple polyphenols may attenuate HgCl_2 -induced phosphatidylserine externalization therefore supports a mechanistic interpretation that extends beyond generic antioxidant activity [28,29]. Similar experimental approaches have also been applied to other Mediterranean plant matrices, suggesting that polyphenol-rich foods may differentially modulate toxicant-induced erythrocyte stress depending on their phytochemical profile [66].

Other non-malignant cellular models have also been used to explore the cytoprotective potential of *Annurca*-derived polyphenols. In human HaCaT keratinocytes, *Annurca* apple polyphenols were reported to influence cell proliferation, suggesting an interaction with epithelial cell responses [27]. More recent evidence in human dermal fibroblasts showed that polyphenol-rich extracts from *Annurca* apple can modulate oxidative stress-induced senescence-associated markers [30]. These findings are consistent with a redox-related cytoprotective profile, but they remain preclinical and should not be interpreted as direct evidence of anti-aging efficacy in humans.

Overall, the available evidence suggests that *Annurca*-derived polyphenols and extracts may exert redox-related cytoprotective effects in non-malignant cellular models, particularly in erythrocytes exposed to oxidative or mercury-induced stress [26,28,29]. The most distinctive mechanistic evidence concerns preservation of erythrocyte membrane homeostasis, including modulation of oxidative damage, calcium-related events, PLSCR1-associated responses and phosphatidylserine externalization. However, most findings derive from in vitro or ex vivo models using concentrated extracts. Future studies should therefore evaluate standardized preparations, physiologically relevant concentrations, digested extracts, circulating metabolites and in vivo biomarkers of erythrocyte redox and membrane status.

6. AGE-Related Injury and Endothelial Cell Protection

Advanced glycation end products (AGEs) are heterogeneous compounds generated through non-enzymatic reactions between reducing sugars or reactive carbonyl intermediates and amino groups of proteins, lipids or nucleic acids [67]. Their formation is accelerated by hyperglycemia, oxidative stress and carbonyl stress and contributes to protein cross-linking, inflammation, tissue dysfunction and vascular aging [67,68]. In endothelial cells, AGE accumulation may activate receptor for advanced glycation end products (RAGE)-related pathways, leading to oxidative stress amplification, reduced nitric oxide bioavailability, inflammatory signaling and cellular dysfunction [68–70].

Polyphenols have been investigated as potential antiglycative agents because they may interfere with several stages of the glycation process, including oxidative reactions, reactive carbonyl species, metal-dependent oxidation and AGE-RAGE-associated redox signaling [71]. However, the antiglycative effects of polyphenol-rich matrices depend on chemical structure, extract composition, concentration, bioaccessibility and cellular context [7,53,71]. Therefore, evidence obtained with complex fruit-derived extracts should be interpreted cautiously and within the limits of the experimental model used.

In this context, *Annurca* apple by-products have recently been investigated for their ability to inhibit AGE formation and counteract AGE-induced cellular injury [22]. By-products obtained from *Annurca* apples at different ripening stages were reported to reduce protein glycation and protect against AGE-induced cytotoxicity through antioxidant-related mechanisms [22]. This finding extends the relevance of *Annurca* by-products beyond conventional antioxidant assays and suggests that these matrices may interfere with glycoxidative stress pathways in cellular models.

The endothelial component of this evidence is particularly relevant because AGE-induced endothelial injury represents a model in which oxidative stress, inflammation and cellular dysfunction converge [67–70]. The reported protective effect of *Annurca* by-products against AGE-induced cytotoxicity suggests a possible interaction with vascular-relevant stress pathways [22]. Nevertheless, this evidence remains preclinical and should not be interpreted as direct proof of vascular protection or clinical cardiometabolic benefit.

Several limitations should be considered. Most antiglycative assays are performed under simplified in vitro conditions that do not reproduce digestion, absorption, metabolism or tissue exposure to circulating metabolites [7,53,71]. In addition, the concentration required to inhibit AGE formation in vitro may not correspond to those achievable after dietary intake. Since *Annurca* by-products are chemically complex matrices, their activity may also depend on synergistic interactions among phenolic and non-phenolic constituents rather than on a single compound [11,22]. Future studies should therefore evaluate digested extracts, circulating metabolites, carbonyl-trapping capacity, RAGE-related signaling and endothelial biomarkers under physiologically relevant conditions.

Overall, the available evidence supports AGE-related injury modulation as a distinct but still preliminary mechanistic domain of *Annurca* apple research. *Annurca* by-products may interfere with AGE formation and AGE-induced cellular damage, but further standardized and physiologically relevant studies are needed before translational or clinical conclusions can be drawn.

7. Lipid Metabolism and Cardiometabolic Evidence

Cardiometabolic health represents one of the most translationally relevant areas of *Annurca* apple research. Dyslipidemia, particularly increased low-density lipoprotein cholesterol (LDL-C), is a major causal factor in atherosclerotic cardiovascular disease, and dietary strategies aimed at improving lipid homeostasis remain central to prevention-oriented nutrition [72]. Apples and apple-derived polyphenols have been investigated in this context because they contain fiber, pectin and phenolic compounds that may influence cholesterol absorption, bile acid metabolism, oxidative stress and lipid handling [3,73]. Within this broader field, *Annurca* apple has attracted specific attention because of its polyphenol-rich profile and its potential effects on plasma cholesterol balance [14,31–34].

The strongest level of evidence derives from human intervention studies. A randomized clinical trial reported that *Annurca* apple intake improved plasma cholesterol parameters, supporting the hypothesis that this cultivar may have cardiometabolic relevance beyond its general nutritional value [31]. Subsequently, an *Annurca* apple-based nutraceutical formulation was evaluated in a randomized trial and was reported to improve

lipid-profile parameters, including LDL-C and HDL-C [32]. These studies are important because they provide human evidence; however, they should be interpreted cautiously because whole-fruit intake, concentrated polyphenolic extracts and nutraceutical formulations are not equivalent interventions [31,32].

Mechanistic studies suggest that *Annurca*-derived preparations may influence lipid metabolism through intestinal and hepatic pathways. At the intestinal level, cholesterol absorption depends on micellar solubilization, transporter-mediated uptake and chylomicron assembly [74,75]. Niemann–Pick C1-like 1 (NPC1L1) is a key transporter involved in intestinal cholesterol uptake and is also relevant to hepatic cholesterol trafficking [74]. *Annurca*-based nutraceutical formulations have been reported to affect intestinal cholesterol absorption, suggesting that reduced intestinal cholesterol availability or uptake may contribute to their cholesterol-lowering effect [33]. At the hepatic level, *Annurca* apple polyphenols have been associated with modulation of hepatic cell metabolism and mitochondrial activity in experimental models, indicating a possible interaction with cellular energy metabolism and cholesterol-related pathways [34].

The cardiometabolic evidence is consistent with the phytochemical profile of *Annurca* apple. Procyanidins, flavan-3-ols, flavonols and phenolic acids have been implicated in lipid metabolism, oxidative stress modulation and inflammation-related pathways [3,14,73]. However, the biological activity of *Annurca*-derived preparations may vary according to fruit fraction, ripening stage, extraction procedure and degree of standardization [11,14]. This distinction is particularly important for nutraceutical formulations, in which the final effect depends on the composition, dose and reproducibility of the polyphenolic fraction.

Several limitations should be considered. Although the lipid-related evidence includes human intervention studies, the number of trials remains limited, and some findings refer to specific nutraceutical formulations rather than to habitual whole-fruit consumption [31–33]. Therefore, the results cannot be generalized to all forms of *Annurca* intake. In addition, the effective doses of concentrated preparations may differ from those achievable through dietary consumption, and the contribution of individual compounds, whole-food matrix effects, digestion, bioaccessibility and gut microbiota metabolism remains incompletely defined [7,53,56,76].

Future studies should clearly distinguish food-based from supplement-based evidence. Whole *Annurca* apple provides polyphenols together with fiber, sugars, organic acids and other matrix components, whereas nutraceutical formulations may deliver enriched and standardized polyphenolic fractions [31–33]. These interventions may differ in mechanisms, bioavailability and physiological effects. Future trials should therefore define the intervention matrix, polyphenol dose, marker compounds, background diet, participant metabolic status and lipid endpoints. Ideally, clinical studies should also include mechanistic biomarkers, such as cholesterol absorption markers, bile acid metabolism, oxidative stress indices, endothelial function and circulating phenolic metabolites.

Overall, lipid metabolism represents one of the most promising translational domains of *Annurca* apple research because it includes human intervention evidence. Nevertheless, the cardiometabolic potential of *Annurca* apple should be considered promising but not definitive. Current data support possible effects on plasma lipid profile, intestinal cholesterol handling and hepatic metabolism, but further controlled studies are needed to clarify dose relevance, matrix specificity, bioavailability and long-term clinical significance.

8. Skin, Hair and Senescence-Related Evidence

Cellular senescence is a stress-response program characterized by stable proliferative arrest, metabolic remodeling and acquisition of a senescence-associated secretory phenotype [77,78]. Although senescence contributes to tissue repair and tumor suppression, the

chronic accumulation of senescent cells may promote inflammation, impaired regenerative capacity and aging-related tissue dysfunction [77,78]. Oxidative stress is one of the major triggers of senescence and links redox imbalance to mitochondrial dysfunction, DNA damage responses, inflammatory signaling and extracellular matrix remodeling [77–79].

The skin represents a relevant model for studying redox-sensitive aging mechanisms because chronological aging and photoaging affect both epidermal and dermal compartments, leading to altered keratinocyte function, dermal matrix remodeling, collagen degradation and impaired fibroblast activity [80–82]. In this context, *Annurca*-derived polyphenols have been investigated in skin-related cellular models. In human HaCaT keratinocytes, *Annurca* apple polyphenols were reported to influence cell proliferation, suggesting an interaction with epidermal cellular responses [27]. More recent evidence showed that polyphenol-rich extracts from *Annurca* apple can modulate oxidative stress-induced senescence-associated responses in human dermal fibroblasts [30].

These findings suggest that *Annurca*-derived polyphenols may influence skin-related stress responses beyond simple chemical antioxidant activity. However, the evidence remains preclinical and should be interpreted cautiously. Keratinocyte and fibroblast models are useful for mechanistic investigation, but they do not reproduce the full complexity of human skin, including interactions among epidermal cells, fibroblasts, immune cells, extracellular matrix, vascular components and environmental exposures [80–82].

A more translational area concerns hair and keratin biology. *Annurca*-based nutraceutical formulations have been reported to enhance keratin expression in a human skin model and to improve hair growth-related parameters in a randomized clinical trial [35]. Mechanistic studies also suggested that *Annurca* apple polyphenols may stimulate keratin production in hair follicles through metabolic remodeling involving the pentose phosphate pathway and amino acid oxidation [36]. These findings support a possible role for standardized *Annurca*-based formulations in hair-related outcomes, but they should be considered formulation-specific and not automatically extrapolated to whole-fruit consumption.

Several limitations remain. The concentrations used in vitro may not correspond to the levels of *Annurca*-derived metabolites reaching skin tissues after ingestion [7,53]. Moreover, whole fruit, polyphenol-rich extracts and nutraceutical formulations differ in dose, matrix composition, bioavailability and standardization [35,36]. Future studies should therefore integrate standardized extracts, simulated digestion, metabolite profiling, advanced skin models and well-defined clinical endpoints related to skin barrier function, dermal matrix remodeling, oxidative biomarkers and hair biology.

Overall, the available evidence suggests that *Annurca*-derived polyphenols and formulations may modulate skin- and hair-related biological responses, including keratinocyte function, fibroblast senescence-associated markers and keratin metabolism [27,30,35,36]. However, only hair-related outcomes include clinical formulation-based evidence, whereas senescence and skin-aging mechanisms remain mainly preclinical. Therefore, this field should be presented as promising but still requiring mechanistic and clinical validation.

9. Exploratory Neuromodulatory and Neuroprotective Targets

Neurodegenerative processes are associated with oxidative stress, mitochondrial dysfunction, impaired proteostasis, neuroinflammation and altered neurotransmitter metabolism [83]. In this context, dietary polyphenols have been investigated for their ability to modulate redox-sensitive signaling, inflammatory responses, mitochondrial function and enzymes involved in neurotransmitter regulation [84,85]. However, evidence on *Annurca*-derived bioactives in this field remains limited and should be considered exploratory.

The first line of evidence concerns the modulation of enzymes involved in neurotransmitter metabolism. *Annurca* apple polyphenol extract was reported to affect the

in vitro activity of acetylcholinesterase and monoamine oxidase [43]. Acetylcholinesterase is involved in acetylcholine hydrolysis, whereas monoamine oxidases are mitochondrial enzymes involved in the oxidative deamination of monoamine neurotransmitters [86,87]. These findings suggest that *Annurca*-derived compounds may interact with neurochemical targets, but in vitro enzyme modulation does not imply therapeutic efficacy in vivo.

A second line of evidence concerns the identification of neuroprotective properties of thaumatin-like protein 1a (TLP1a) in *Annurca* flesh-derived preparations [44]. This finding is relevant because it broadens the interpretation of *Annurca* bioactivity beyond polyphenols alone, indicating that non-phenolic components may also contribute to the biological effects of this food matrix [44]. Therefore, future studies should clarify the relative contribution of phenolic and non-phenolic constituents and determine whether their effects are additive, synergistic or independent.

Several limitations should be emphasized. The available studies are mainly preclinical and mechanistic, and they do not establish clinical neuroprotective efficacy [43,44]. Moreover, the biological relevance of native extracts or isolated components depends on digestion, metabolism, blood–brain barrier permeability, tissue distribution and achievable concentrations [7,53,84]. Direct evidence linking *Annurca*-derived metabolites to brain outcomes is still lacking.

Future research should evaluate digested extracts, circulating metabolites, neuronal and glial models, blood–brain barrier permeability, mitochondrial endpoints, neuroinflammatory markers and protein aggregation-related pathways [83–85]. The role of TLP1a and other non-phenolic components should also be investigated alongside polyphenols rather than attributing *Annurca* bioactivity to a single class of compounds [44].

Overall, the available evidence suggests that *Annurca*-derived bioactives may interact with neuromodulatory and neuroprotective targets, including acetylcholinesterase, monoamine oxidase and TLP1a-related mechanisms [43,44]. However, this field remains exploratory and hypothesis-generating, and further mechanistic and translational studies are required before any neuroprotective claim can be proposed.

10. Cancer Cell Redox Modulation: In Vitro Evidence

The biological activity of dietary polyphenols in cancer models cannot be interpreted exclusively through the classical antioxidant paradigm. Cancer cells often display altered redox homeostasis, increased basal reactive oxygen species production, mitochondrial dysfunction and adaptive antioxidant responses, which may contribute to proliferation, survival and therapeutic resistance [88,89]. Under these conditions, additional oxidative pressure may exceed the cellular tolerance threshold and promote cell cycle arrest, apoptosis or other stress-related responses [88,89]. Therefore, polyphenol-rich extracts may produce different outcomes depending on cellular redox status, metabolic phenotype and stress-response capacity.

This concept is relevant for *Annurca* apple polyphenols. While *Annurca*-derived extracts have shown cytoprotective effects in non-malignant models exposed to oxidative, toxicant-induced, glycative or senescence-related stress [26,28–30], several studies have reported pro-oxidant, pro-apoptotic and anti-migratory effects in cancer cell models [37–42]. This apparent dual behavior should not be interpreted as contradictory but as a context-dependent response influenced by basal redox state, extract composition, dose and cellular model.

The main evidence derives from breast cancer models. *Annurca* apple polyphenol extract was reported to induce pro-oxidant and pro-apoptotic effects in human breast cancer cells [37]. Subsequent studies showed that *Annurca* polyphenols can modulate breast cancer cell viability, growth and survival pathways [38,39]. In MDA-MB-231 triple-negative breast

cancer cells, *Annurca* apple polyphenol extract was reported to promote ROS generation, sustained JNK activation and inhibition of cell growth and survival [39]. Since JNK is a stress-activated pathway whose outcome depends on signal intensity, duration and cellular context, these findings should be interpreted as mechanistic in vitro evidence rather than as direct evidence of anticancer efficacy [39,90].

Additional evidence suggests that *Annurca* polyphenol extract may influence phenotypic plasticity and migration-related processes in triple-negative breast cancer cells. In this model, the extract was reported to promote mesenchymal-to-epithelial transition and inhibit migration through ROS/JNK signaling [40]. This finding is biologically relevant because epithelial–mesenchymal transition and its reverse process are involved in cancer cell plasticity, invasion and metastatic potential [91,92]. However, these results remain limited to cell-based models and require validation in more complex experimental systems.

Other cancer models have broadened this field. *Annurca* apple biophenols were investigated in combination with cisplatin in A549 lung cancer cells, suggesting a possible interaction with chemotherapy-induced cellular stress [41]. *Annurca* flesh apple polyphenols were also studied in human thyroid cancer cell lines, supporting the extension of this research to endocrine cancer models [42]. Although these studies differ in cell type, extract preparation and endpoints, they collectively indicate that *Annurca*-derived polyphenols may interfere with redox-sensitive pathways involved in cancer cell survival, apoptosis and migration [37–42].

Several limitations are essential for interpretation. Most studies were performed in vitro using concentrated extracts, and the concentrations required to induce pro-oxidant or pro-apoptotic responses may not correspond to levels achievable through dietary intake [37–42]. Cancer cell lines are simplified systems that do not reproduce tumor microenvironment complexity, immune interactions, stromal components, pharmacokinetics or systemic metabolism [91]. In addition, extract composition, fruit fraction, ripening stage, extraction procedure and analytical standardization may strongly influence the observed redox behavior [11,12,14]. Therefore, these findings should not be presented as evidence that *Annurca* apple has anticancer effects in humans.

Overall, cancer cell models provide one of the clearest examples of context-dependent redox modulation by *Annurca*-derived polyphenols. Available in vitro studies suggest that these extracts may increase redox pressure and modulate ROS/JNK-dependent pathways involved in apoptosis, survival and migration in selected cancer models [37–42]. However, this evidence remains preclinical and hypothesis-generating. Future studies should use standardized extracts, digested or metabolized preparations, physiologically relevant concentrations, normal/cancer cell comparisons and more complex tumor models before any translational conclusion is proposed.

Figure 2 conceptually summarizes the context-dependent redox behavior of *Annurca* apple bioactives, highlighting their cytoprotective effects in non-malignant stressed models and their redox stress-modulating activity in cancer cell models.

To complement this conceptual scheme, Table 2 provides a comparative overview of the main biological domains, experimental models, *Annurca*-derived materials, reported effects and critical limitations across the available evidence.

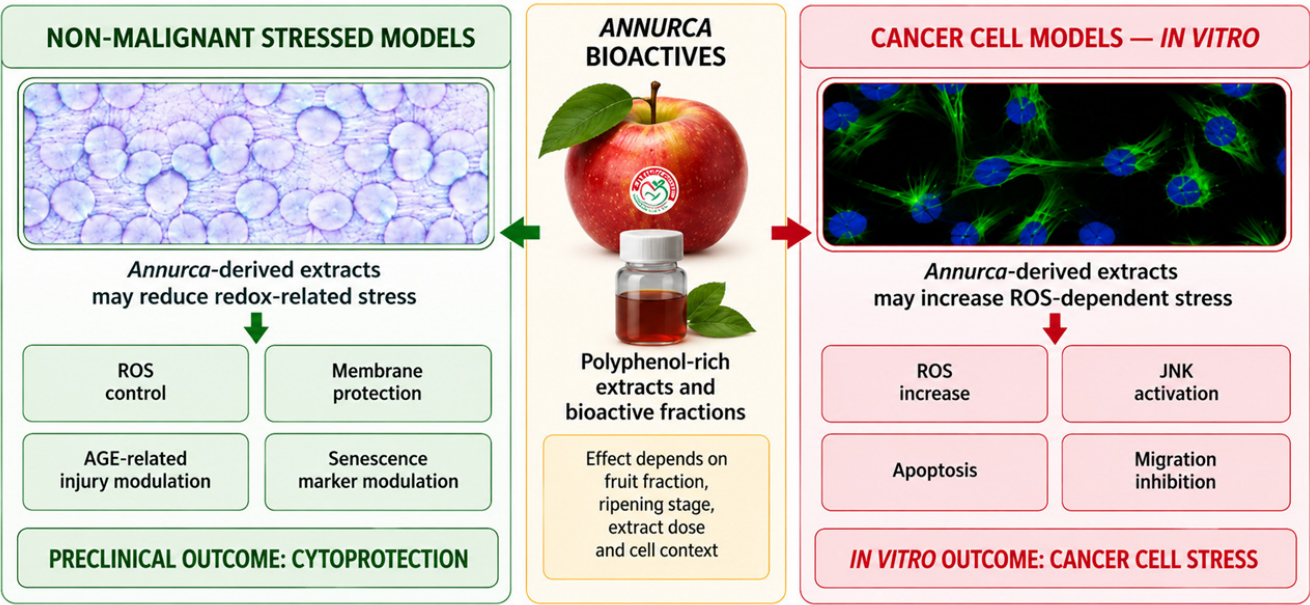


Figure 2. Context-dependent redox behavior of *Annurca* apple-derived bioactives. *Annurca*-derived polyphenol-rich extracts and bioactive fractions may reduce redox-related stress in non-malignant stressed models, with effects involving ROS control, membrane protection, AGE-related injury modulation and senescence marker modulation. In cancer cell models, available in vitro evidence suggests that these extracts may increase ROS-dependent stress and modulate JNK activation, apoptosis and migration. These findings support the interpretation of *Annurca*-derived bioactives as context-dependent redox modulators rather than simple antioxidants, but cancer-related effects should be considered preclinical and hypothesis-generating.

Table 2. Biological effects of *Annurca*-derived bioactives: evidence strength and limitations.

Biological Domain	Model/Evidence	<i>Annurca</i> -Derived Material	Main Reported Effects	Evidence Strength/Critical Limitations	Refs.
Redox-related cytoprotection	Human erythrocytes and non-malignant cellular models	<i>Annurca</i> apple extract/polyphenol-rich extracts	Reduced oxidative damage; preservation of membrane integrity and cellular viability	Mainly in vitro/ex vivo evidence using concentrated extracts; physiological relevance depends on dose, digestion and metabolites	[26–28]
Mercury-induced erythrocyte damage	Human erythrocytes exposed to HgCl ₂	Polyphenol-rich extracts	Modulation of ROS, Ca ²⁺ homeostasis, PLSCR1 and phosphatidylserine externalization	Mechanistically relevant ex vivo model; in vivo relevance and contribution of individual compounds remain unclear	[28,29]
Skin-related responses and senescence markers	HaCaT keratinocytes; dermal fibroblasts	Polyphenols/polyphenol-rich extracts	Modulation of keratinocyte responses and oxidative stress-induced senescence markers	Preclinical cellular evidence; not proof of anti-aging efficacy in humans	[27,30]
AGE-related injury	AGE formation assays; AGE-stressed endothelial cells	<i>Annurca</i> apple by-products	Inhibition of AGE formation and protection against AGE-induced cytotoxicity	Mainly chemical and in vitro evidence; does not directly demonstrate clinical vascular benefit	[22]
Lipid metabolism	Human trials; intestinal and hepatic models	Whole <i>Annurca</i> apple; nutraceutical formulations; polyphenols	Improvement of plasma lipid profile; effects on cholesterol handling and hepatic metabolism	Includes human data, but trials are limited and often formulation-specific	[31–34]
Hair and keratin biology	Human skin model; clinical trial; hair follicle-related models	<i>Annurca</i> -based nutraceutical formulations/polyphenols	Enhanced keratin expression and improvement of hair growth-related parameters	Includes formulation-based clinical evidence; findings are product- and dose-specific	[35,36]
Neuromodulatory targets	Enzyme assays; preclinical models	Polyphenol extract; <i>Annurca</i> -derived TLP1a	Modulation of AChE, MAO and non-phenolic neuroprotective components	Exploratory preclinical evidence; brain bioavailability and physiological relevance remain unclear	[43,44]

Table 2. Cont.

Biological Domain	Model/Evidence	<i>Annurca</i> -Derived Material	Main Reported Effects	Evidence Strength/Critical Limitations	Refs.
Cancer cell redox modulation—in vitro	Breast, triple-negative breast, lung and thyroid cancer cell models	Polyphenols/polyphenol-rich extracts/biophenols	ROS/JNK modulation, apoptosis, survival inhibition, EMT/MET modulation and reduced migration	In vitro and hypothesis-generating only; not evidence of anticancer efficacy in humans	[37–42]
By-product bioactivity	Peel, flesh and core at different ripening stages	<i>Annurca</i> apple by-products	Identification of antioxidant and antiglycative bioactive reservoirs	Mainly chemical and in vitro evidence; safety, bioaccessibility and batch reproducibility require assessment	[11,22]

Note: Evidence includes chemical assays, in vitro/ex vivo models, preclinical studies and human intervention studies. Reported effects should be interpreted according to the *Annurca*-derived material tested, fruit fraction, ripening stage, extraction procedure, dose and biological model. Chemical antioxidant assays should be considered screening tools and not direct evidence of physiological efficacy or health benefits. Abbreviations: AChE, acetylcholinesterase; AGE, advanced glycation end products; EMT, epithelial–mesenchymal transition; HgCl₂, mercury chloride; JNK, c-Jun N-terminal kinase; MAO, monoamine oxidase; MET, mesenchymal-to-epithelial transition; PLSCR1, phospholipid scramblase 1; ROS, reactive oxygen species; TLP1a, thaumatin-like protein 1a.

11. Bioavailability, Gut Microbiota and Translational Bottlenecks

The biological interpretation of *Annurca*-derived polyphenols, bioactive fractions and by-products requires careful consideration of bioavailability, gastrointestinal transformation and gut microbiota metabolism. Although many in vitro studies report antioxidant, antiglycative, cytoprotective or cancer cell redox-modulating effects, the compounds tested in cellular models may differ substantially from the molecular forms generated after ingestion, digestion, absorption, phase II metabolism and microbial transformation [5,7–10,53–55]. Therefore, the transition from experimental extract bioactivity to nutritional or nutraceutical relevance represents one of the major translational challenges in this field.

Dietary polyphenols generally show limited and variable bioavailability, depending on chemical structure, degree of polymerization, glycosylation pattern, food matrix, dose and individual metabolic capacity [8,9,53,54]. Low-molecular-weight polyphenols may be absorbed in the small intestine and undergo glucuronidation, sulfation or methylation, whereas larger compounds, including oligomeric and polymeric procyanidins, often reach the colon and are transformed by the gut microbiota into smaller phenolic acids and related catabolites [7,10,54,55]. This is particularly relevant for apple polyphenols, which include flavan-3-ols, procyanidins, chlorogenic acid, flavonols and dihydrochalcones, each with distinct digestive and metabolic behavior [3–5,47].

In the case of *Annurca* apple, many biological studies have used concentrated polyphenol-rich extracts from flesh, peel, core, by-products or nutraceutical formulations [11,26–44]. These preparations are useful for mechanistic investigation, but they may not reproduce the forms, concentrations and kinetics of compounds circulating after whole-fruit consumption or intake of standardized formulations. Native polyphenols, digestion-derived products, phase II conjugates and gut microbiota-derived catabolites may differ in cellular uptake, redox behavior and molecular targets [5,8–10,54,55]. Consequently, effects observed in erythrocytes, endothelial cells, fibroblasts, keratinocytes, neuronal models or cancer cells should be interpreted as mechanistic evidence rather than direct proof of in vivo efficacy.

The gut microbiota is a key determinant of polyphenol bioactivity. Microbial enzymes can transform complex phenolic structures into metabolites that may be more absorbable or biologically active than the parent compounds [7,10,54,55]. At the same time, polyphenols and their metabolites may influence microbial ecology and microbial metabolite production, supporting the concept of a bidirectional gut microbiota–polyphenol axis [7,10,55,56]. For

Annurca apple, direct evidence linking specific microbial catabolites to biological outcomes remains limited. Future studies should therefore test not only native extracts, but also digested extracts, colonic fermentation products and representative circulating metabolites.

The food matrix is another relevant variable. Whole *Annurca* apple provides polyphenols together with fiber, pectin, sugars, organic acids, minerals and other phytochemicals, whereas nutraceutical formulations deliver enriched and often standardized polyphenolic fractions [3,5,31–36,73]. These matrices may differ in release, stability, bioaccessibility and biological activity. This distinction is essential when interpreting clinical studies on lipid metabolism or hair-related outcomes, because results obtained with standardized formulations cannot be automatically extrapolated to habitual fruit consumption. Recent evidence on *Annurca*-based nutraceutical products also supports the need to consider processing-related changes in phenolic bioaccessibility [76].

Another major bottleneck is standardization. *Annurca* apple bioactivity may be influenced by cultivar identity, ripening stage, reddening conditions, fruit fraction, extraction method and storage [4,11–13,19]. Without detailed phytochemical fingerprints, marker compounds and dose definition, comparison among studies remains difficult. Standardization should therefore be combined with simulated digestion, metabolite profiling and physiologically relevant concentrations, especially for by-products or concentrated extracts intended for nutraceutical or functional food development [7,11,22–25,51–53].

Individual variability represents an additional translational challenge. Differences in gut microbiota composition, diet, age, metabolic status, medication use and genetic background may influence polyphenol metabolism and biological responsiveness [7,10,55,56,93]. Gut microbial metabolotypes may affect the ability to generate specific bioactive metabolites, contributing to heterogeneous outcomes in dietary polyphenol interventions [93]. Future *Annurca* clinical studies should therefore consider participant phenotype, baseline cardiometabolic status, gut microbiota composition, microbial metabolotype and circulating phenolic metabolites.

Overall, bioavailability and gut microbiota metabolism are essential bottlenecks for translating *Annurca* apple research from cellular models to human nutrition. Current evidence supports a promising molecular profile, but the physiological relevance of *Annurca*-derived extracts and preparations depends on the identification of bioaccessible compounds, circulating metabolites, microbial catabolites and realistic exposure conditions [5,7–10,53–55,93]. Addressing these gaps will be crucial for developing standardized functional ingredients or nutraceutical candidates with reproducible biological effects.

12. Critical Appraisal and Future Perspectives

The available evidence indicates that *Annurca*-derived polyphenols, bioactive fractions and by-products represent a promising food-derived bioactive system with cytoprotective, antiglycative, cardiometabolic, skin- and hair-related, neuromodulatory and cancer cell redox-modulating properties [11,26–34,37–44]. However, several methodological and translational limitations should be considered before drawing firm conclusions. Many studies have been performed in vitro using concentrated extracts, whereas fewer studies have evaluated physiologically relevant concentrations, digested fractions, circulating metabolites or clinical outcomes [5,7–10,53–55]. Therefore, much of the available evidence should be interpreted as mechanistic and hypothesis-generating rather than as definitive proof of health efficacy.

A major limitation concerns extract heterogeneity. *Annurca*-derived preparations differ according to fruit fraction, ripening stage, reddening conditions, extraction protocol, solvent system, concentration procedure and analytical characterization [11–13,22,30,31]. These variables may influence phytochemical profile and biological response. Therefore,

the term “*Annurca* apple polyphenol extract” should not be used generically unless the source material, fruit fraction, ripening stage and chemical fingerprint are clearly defined.

A second critical point is phytochemical standardization. Future studies should report total phenolics, flavonoids, ortho-diphenols, procyanidins, chlorogenic acid, quercetin derivatives and other relevant marker compounds [2,4,11,13]. Targeted and untargeted metabolomic approaches may further improve comparability among studies and help identify compound classes associated with biological activity [94]. This is particularly important for by-products, whose development as functional ingredients requires reproducible composition, batch-to-batch stability and quality-control criteria [23–25,51,52].

Bioavailability remains one of the main translational bottlenecks. Many *Annurca* studies test native extracts directly on cells, but after oral intake, polyphenols undergo digestion, intestinal transformation, phase II metabolism and gut microbiota-mediated catabolism [5,7–10,53–55]. As a result, target tissues may be exposed to conjugated metabolites or microbial catabolites rather than to the native compounds present in the original fruit or extract. Future studies should therefore include standardized simulated digestion protocols, such as INFOGEST-based models, to evaluate bioaccessibility and digestive stability before biological testing [95,96].

Dose relevance is another key issue. Concentrations used in vitro may exceed those achievable through habitual whole-fruit consumption or nutraceutical supplementation [8,9,53,54]. This is particularly important for cancer cell models, where pro-oxidant and pro-apoptotic responses may require concentrations not attainable in vivo [37–42]. Future studies should justify the concentrations used, compare native extracts with physiologically plausible metabolites and avoid extrapolating preclinical findings to human health claims.

The current evidence is also uneven across biological domains. The strongest human data concern lipid metabolism and hair-related nutraceutical formulations [31–36]. In contrast, evidence on erythrocyte protection, mercury-induced membrane damage, AGE-related injury, senescence modulation, neuromodulatory targets and cancer cell redox modulation remains largely preclinical or in vitro [22,26–30,37–44]. Clinical studies are therefore needed to clarify whether the molecular mechanisms observed experimentally translate into measurable outcomes in humans. Such trials should define primary and secondary endpoints, include appropriate controls and assess relevant biomarkers [97].

Whole-fruit intake and nutraceutical formulations should also be clearly distinguished. Whole *Annurca* apple provides polyphenols within a complex food matrix containing fiber, pectin, sugars, organic acids and other constituents, whereas nutraceutical formulations may deliver enriched and standardized polyphenolic fractions [31–36,73]. These interventions may differ in dose, bioavailability, mechanism and biological effect and should not be considered interchangeable.

Future research should therefore move toward a more integrated translational pipeline. Standardized *Annurca*-derived preparations should be obtained from clearly defined fruit fractions and ripening stages; native extracts should be compared with digested extracts, post-fermentation fractions and circulating metabolites. In addition, mechanistic studies should use physiologically relevant concentrations and validated biomarkers of oxidative stress, glycation, senescence, lipid metabolism, endothelial function and inflammatory signaling. For by-products, this pipeline should also include raw material selection, extraction optimization, safety assessment, contaminant monitoring, bioaccessibility testing and technological stability [11,22–25,51,52,95,96].

Overall, the main strength of the *Annurca* apple literature is the coherence of a research trajectory linking cultivar specificity, post-harvest reddening, fruit-fraction bioactivity, by-product valorization and molecular mechanisms of cellular stress modulation [11,12,26–34,37–44]. Its main weakness is the still limited translational evidence connecting these mechanisms to hu-

man bioavailability and clinical outcomes. Addressing this gap will determine whether *Annurca*-derived polyphenols, bioactive fractions and by-products can progress from promising experimental matrices to standardized functional food ingredients or nutraceutical candidates with reproducible biological effects.

The proposed translational pathway linking *Annurca* apple matrix characterization, extract standardization, bioavailability, metabolism and translational validation is summarized in Figure 3.

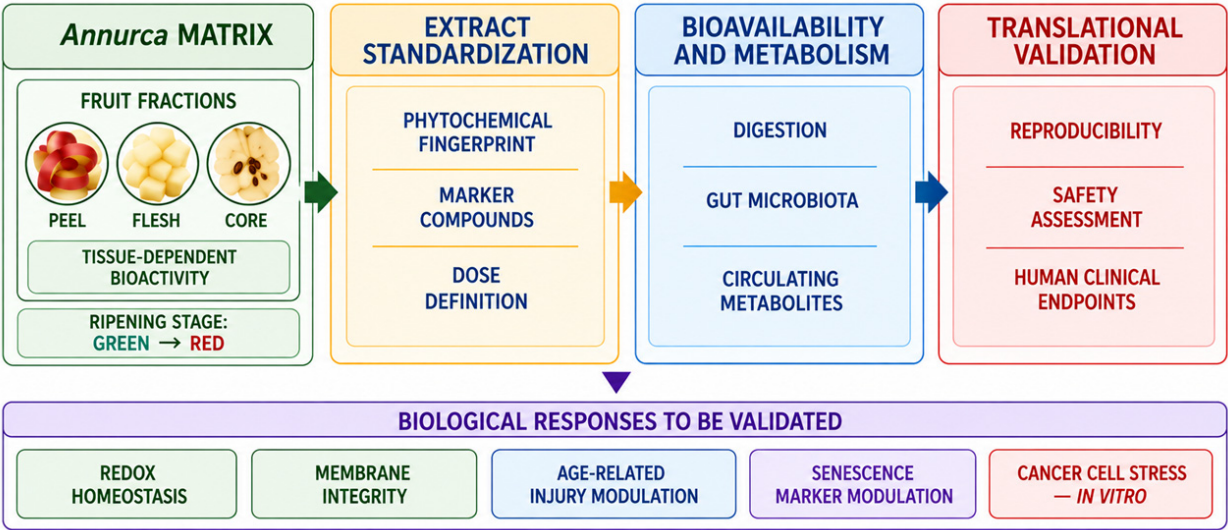


Figure 3. Translational pathway for *Annurca* apple-derived bioactives. The figure summarizes the proposed translational pathway from *Annurca* apple matrix characterization to biological and clinical validation. Fruit fraction, ripening stage and tissue-dependent bioactivity influence extract standardization, phytochemical fingerprinting, bioavailability, gut microbiota metabolism and circulating metabolites. These steps are essential before attributing reproducible biological effects to *Annurca*-derived bioactives. The reported responses, including redox homeostasis, membrane integrity, AGE-related injury modulation, senescence marker modulation and cancer cell stress, require validation under physiologically relevant conditions; cancer-related effects should be interpreted as in vitro and hypothesis-generating.

The main limitations and future research priorities for *Annurca*-derived polyphenols, bioactive fractions and by-products are summarized in Table 3.

Table 3. Translational challenges and future research priorities for *Annurca*-derived bioactives.

Area	Translational Relevance	Main Limitations	Future Priorities	Refs.
Phytochemical profile and standardization	Defines the bioactive basis of <i>Annurca</i> -derived preparations and explains differences between peel, flesh, core and ripening stages	Extract heterogeneity; incomplete marker-compound reporting; limited comparability among preparations	Standardized phytochemical fingerprints; marker compounds; targeted and untargeted metabolomic profiling	[2,4,11–14,50]
By-product valorization	Supports peel, core and usually discarded fractions as sustainable sources of functional ingredients	Variability due to ripening, processing and extraction; safety, stability and batch-to-batch issues	Optimized extraction; safety assessment; contaminant control; batch reproducibility; functional ingredient development	[11,22–25,51,52]
Oxidative, glycativ and toxicant-induced stress	Shows cytoprotection in erythrocytes, endothelial cells and other stress-related models	Mostly in vitro/ex vivo evidence; use of concentrated extracts; uncertain physiological dose relevance	Digested extracts; circulating metabolites; validated redox, glycation and erythrocyte membrane biomarkers	[22,26–30,57–71,79]
Cardiometabolic effects	Includes human data on lipid profile and mechanistic evidence related to cholesterol handling	Limited number of trials; formulations differ from whole-fruit intake; incomplete mechanistic biomarker assessment	Larger RCTs; comparison of whole fruit vs. formulations; cholesterol absorption, bile acid and circulating metabolite biomarkers	[31–34,72–75]

Table 3. Cont.

Area	Translational Relevance	Main Limitations	Future Priorities	Refs.
Skin, hair and senescence	Supports dermonutraceutical potential through keratinocyte, fibroblast, senescence and hair-related evidence	Limited clinical mechanistic validation; variable formulations; uncertain tissue exposure to active metabolites	3D skin models; standardized dermonutraceutical trials; senescence, extracellular matrix and oxidative stress biomarkers	[27,30,35,36,77,78,80–82]
Neuroprotective potential	Suggests modulation of AChE, MAO and <i>Annurca</i> -derived TLP1a-associated neuroprotective activity	Exploratory evidence; uncertain brain bioavailability; unclear contribution of phenolic vs. non-phenolic components	Neuronal/glia models; blood–brain barrier studies; mitochondrial and neuroinflammatory endpoints; phenolic vs. non-phenolic mechanisms	[43,44,83–87]
Cancer cell redox modulation	Demonstrates context-dependent pro-oxidant effects in selected cancer cell models	In vitro evidence only; no clinical anticancer evidence; dose and bioavailability concerns	Normal vs. cancer cell comparisons; metabolite-based studies; complex tumor models; distinction between nutraceutical research and anticancer therapy	[37–42,88–92]
Bioavailability, gut microbiota and microbial metabolites	Essential for translating extract bioactivity into nutritional relevance and for explaining interindividual variability	Limited <i>Annurca</i> -specific data on digestion, absorption, microbial metabolism and responder profiles	INFOGEST digestion; colonic fermentation; metabolomics; circulating metabolites; microbial metabolite characterization; precision nutrition approaches	[5,7–10,53–56,93–96]

Note: This table summarizes the main translational challenges that should be addressed before *Annurca*-derived polyphenols, bioactive fractions and by-products can be developed as standardized functional ingredients or nutraceutical candidates. Abbreviations: AChE, acetylcholinesterase; MAO, monoamine oxidase; RCTs, randomized controlled trials; TLP1a, thaumatin-like protein 1a.

13. Conclusions

Annurca apple represents a distinctive Mediterranean food matrix in which cultivar identity, post-harvest reddening, ripening stage and fruit fraction contribute to shaping phytochemical composition and biological activity [1–4,6,11–22,50]. The available evidence indicates that *Annurca*-derived polyphenols, bioactive fractions and by-products should not be interpreted merely as generic antioxidant sources but as complex food-derived matrices whose effects depend on fruit fraction, extract composition, dose, biological model and cellular context [11,26–30,37–44].

Current findings support several biological domains of interest. In non-malignant cellular and ex vivo models, *Annurca*-derived extracts have shown cytoprotective effects against oxidative damage, mercury-induced erythrocyte alterations, phosphatidylserine externalization, AGE-induced cytotoxicity and oxidative stress-induced senescence-associated responses [22,26–30]. These effects involve redox balance, erythrocyte membrane homeostasis, calcium/PLSCR1-related mechanisms, antiglycative activity and senescence-related pathways. In parallel, lipid metabolism and hair-related outcomes represent the most translationally advanced areas because they include human intervention studies using whole-fruit intake or standardized *Annurca*-based nutraceutical formulations [31–36].

Evidence on neuromodulatory targets remains exploratory, involving in vitro modulation of acetylcholinesterase and monoamine oxidase and the identification of non-phenolic components such as TLP1a with potential neuroprotective relevance [43,44]. Cancer-related evidence is also limited to in vitro models. In these systems, *Annurca* apple polyphenols and polyphenol-rich extracts have been reported to modulate ROS/JNK-related signaling, apoptosis, survival and migration-related processes [37–42]. These findings are mechanistically interesting but should not be interpreted as evidence of anticancer efficacy in humans.

The valorization of *Annurca* apple by-products further expands the relevance of this field. Peel, core and other usually discarded fractions may represent sources of phenolic compounds with antioxidant and antiglycative activity, supporting their possible use within circular bioeconomy strategies [11,22–25,51,52]. However, their development as functional ingredients or nutraceutical candidates requires standardized extraction, phyto-

chemical characterization, safety assessment, bioaccessibility studies and validation under physiologically relevant conditions.

Important limitations remain. Much of the available evidence is based on native extracts tested in vitro, whereas fewer studies have evaluated digestion-derived products, circulating metabolites, gut microbiota transformation, microbial metabolites or clinical outcomes [5,7–10,53–55,93]. Future research should therefore move toward standardized, metabolite-informed and clinically relevant approaches, with attention to fruit fraction, ripening stage, extraction method, marker compounds, dose relevance, bioavailability, gut microbiota interactions and interindividual variability.

Overall, *Annurca*-derived polyphenols, bioactive fractions and by-products provide a valuable model for studying how a traditional Mediterranean food matrix may influence oxidative, glycative, toxicant-induced, senescence-related and cancer cell stress responses. Their potential lies not only in chemical antioxidant activity but in their ability to modulate redox-sensitive molecular pathways according to biological context. Establishing whether these mechanisms translate into reproducible nutritional or nutraceutical benefits will require standardized preparations, physiologically relevant models, metabolite-based studies and well-designed clinical investigations.

Funding: This study received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: During the preparation of this manuscript, the author used GPT-5.5 version (OpenAI, San Francisco, CA, USA) to assist with figure development. All outputs were reviewed, verified and edited by the author, who takes full responsibility for the content of this publication.

Conflicts of Interest: The author declares no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AGE	Advanced glycation end products
AChE	Acetylcholinesterase
EMT	Epithelial–mesenchymal transition
HDL-C	High-density lipoprotein cholesterol
HgCl ₂	Mercury chloride
JNK	c-Jun N-terminal kinase
LDL-C	Low-density lipoprotein cholesterol
MAO	Monoamine oxidase
MET	Mesenchymal-to-epithelial transition
NPC1L1	Niemann–Pick C1-like 1
PLSCR1	Phospholipid scramblase 1
PS	Phosphatidylserine
RAGE	Receptor for advanced glycation end products
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype
TLP1a	Thaumatococcus-like protein 1a

References

1. Mierczak, K.; Garus-Pakowska, A. An Overview of Apple Varieties and the Importance of Apple Consumption in the Prevention of Non-Communicable Diseases—A Narrative Review. *Nutrients* **2024**, *16*, 3307. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Tsao, R.; Yang, R.; Young, J.C.; Zhu, H. Polyphenolic Profiles in Eight Apple Cultivars Using High-Performance Liquid Chromatography. *J. Agric. Food Chem.* **2003**, *51*, 6347–6353. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Boyer, J.; Liu, R.H. Apple Phytochemicals and Their Health Benefits. *Nutr. J.* **2004**, *3*, 5. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Francini, A.; Sebastiani, L. Phenolic Compounds in Apple (*Malus × domestica* Borkh.): Compounds Characterization and Stability during Postharvest and after Processing. *Antioxidants* **2013**, *2*, 181–193. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Jakobek, L.; Matić, P. Phenolic Compounds from Apples: From Natural Fruits to the Beneficial Effects in the Digestive System. *Molecules* **2024**, *29*, 568. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Drogoudi, P.D.; Michailidis, Z.; Pantelidis, G. Peel and Flesh Antioxidant Content and Harvest Quality Characteristics of Seven Apple Cultivars. *Sci. Hortic.* **2008**, *115*, 149–153. [\[CrossRef\]](#)
7. Tomás-Barberán, F.A.; Selma, M.V.; Espín, J.C. Interactions of Gut Microbiota with Dietary Polyphenols and Consequences to Human Health. *Curr. Opin. Clin. Nutr. Metab. Care* **2016**, *19*, 471–476. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Rémésy, C. Bioavailability and Bioefficacy of Polyphenols in Humans. I. Review of 97 Bioavailability Studies. *Am. J. Clin. Nutr.* **2005**, *81*, 230S–242S. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J.P.E.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (Poly)phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects against Chronic Diseases. *Antioxid. Redox Signal.* **2013**, *18*, 1818–1892. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Espín, J.C.; González-Sarriás, A.; Tomás-Barberán, F.A. The Gut Microbiota: A Key Factor in the Therapeutic Effects of (Poly)phenols. *Biochem. Pharmacol.* **2017**, *139*, 82–93. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Perrone, P.; Palmieri, S.; Piscopo, M.; Lettieri, G.; Eugelio, F.; Fanti, F.; D’Angelo, S. Antioxidant Activity of Annurca Apple By-Products at Different Ripening Stages: A Sustainable Valorization Approach. *Antioxidants* **2025**, *14*, 941. [\[CrossRef\]](#) [\[PubMed\]](#)
12. D’Angelo, S.; Cimmino, A.; Raimo, M.; Salvatore, A.; Zappia, V.; Galletti, P. Effect of Reddening–Ripening on the Antioxidant Activity of Polyphenol Extracts from cv. ‘Annurca’ Apple Fruits. *J. Agric. Food Chem.* **2007**, *55*, 9977–9985. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Cefarelli, G.; D’Abrosca, B.; Fiorentino, A.; Izzo, A.; Monaco, P. Isolation, Characterization, and Antioxidant Activity of E- and Z-p-Coumaryl Fatty Acid Esters from cv. Annurca Apple Fruits. *J. Agric. Food Chem.* **2005**, *53*, 3525–3529. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Tenore, G.C.; Campiglia, P.; Stiuso, P.; Ritieni, A.; Novellino, E. Nutraceutical Potential of Polyphenolic Fractions from Annurca Apple (*M. pumila* Miller cv. Annurca). *Food Chem.* **2013**, *140*, 614–622. [\[CrossRef\]](#) [\[PubMed\]](#)
15. European Commission. Commission Regulation (EC) No. 417/2006 of 10 March 2006 Supplementing the Annex to Regulation (EC) No. 2400/96 as Regards the Entry of Certain Names in the Register of Protected Designations of Origin and Protected Geographical Indications: Melannurca Campana (PGI). *Off. J. Eur. Union* **2006**, *L72*, 8–9.
16. Iannaccone, M.; Palumbo, D.; Ventimiglia, I.; Patocchi, A.; Spigno, P.; Capparelli, R. Use of Molecular Markers and Flow Cytometry to Preserve Ancient Annurca Apple Germplasm. *Biotechnol. Lett.* **2007**, *29*, 279–284. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Lo Scalzo, R.; Testoni, A.; Genna, A. ‘Annurca’ Apple Fruit, a Southern Italy Apple Cultivar: Textural Properties and Aroma Composition. *Food Chem.* **2001**, *73*, 333–343. [\[CrossRef\]](#)
18. Corrado, G.; Mataffo, A.; Scognamiglio, P.; Teobaldelli, M.; Basile, B. Resolving the Texture–Flavor Trade-Off in ‘Annurca’ Apples with an Integrated Postharvest System. *Foods* **2025**, *14*, 3554. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Graziani, G.; Ritieni, A.; Cirillo, A.; Cice, D.; Di Vaio, C. Effects of Biostimulants on Annurca Fruit Quality and Potential Nutraceutical Compounds at Harvest and during Storage. *Plants* **2020**, *9*, 775. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Tenore, G.C.; Calabrese, G.; Stiuso, P.; Ritieni, A.; Giannetti, D.; Novellino, E. Effects of Annurca Apple Polyphenols on Lipid Metabolism in HepG2 Cell Lines: A Source of Nutraceuticals Potentially Indicated for the Metabolic Syndrome. *Food Res. Int.* **2014**, *63*, 252–257. [\[CrossRef\]](#)
21. Vuoso, D.C.; Porcelli, M.; Cacciapuoti, G.; D’Angelo, S. Biological Activity of MelAnnurca Flesh Apple Biophenols. *Curr. Nutr. Food Sci.* **2020**, *16*, 1149–1162. [\[CrossRef\]](#)
22. Liccardo, M.; Perrone, P.; Perrella, S.; Sirangelo, I.; D’Angelo, S.; Iannuzzi, C. Annurca Apple By-Products at Different Ripening Stages Inhibit AGE Formation and Protect against AGE-Induced Cytotoxicity through Antioxidant Activity. *Antioxidants* **2026**, *15*, 200. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Schieber, A.; Stintzing, F.C.; Carle, R. By-Products of Plant Food Processing as a Source of Functional Compounds—Recent Developments. *Trends Food Sci. Technol.* **2001**, *12*, 401–413. [\[CrossRef\]](#)
24. Bhushan, S.; Kalia, K.; Sharma, M.; Singh, B.; Ahuja, P.S. Processing of Apple Pomace for Bioactive Molecules. *Crit. Rev. Biotechnol.* **2008**, *28*, 285–296. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Perussello, C.A.; Zhang, Z.; Marzocchella, A.; Tiwari, B.K. Valorization of Apple Pomace by Extraction of Valuable Compounds. *Compr. Rev. Food Sci. Food Saf.* **2017**, *16*, 776–796. [\[CrossRef\]](#) [\[PubMed\]](#)

26. D'Angelo, S.; Sammartino, D. Protective Effect of Annurca Apple Extract against Oxidative Damage in Human Erythrocytes. *Curr. Nutr. Food Sci.* **2015**, *11*, 248–256. [[CrossRef](#)]
27. D'Angelo, S.; La Porta, R.; Napolitano, M.; Galletti, P.; Quagliuolo, L.; Boccellino, M. Effect of Annurca Apple Polyphenols on Human HaCaT Keratinocytes Proliferation. *J. Med. Food* **2012**, *15*, 1024–1031. [[CrossRef](#)] [[PubMed](#)]
28. Perrone, P.; Moriello, C.; Alessio, N.; Manna, C.; D'Angelo, S. Cytoprotective Potential of Annurca Apple Polyphenols on Mercury-Induced Oxidative Stress in Human Erythrocytes. *Int. J. Mol. Sci.* **2025**, *26*, 8826. [[CrossRef](#)] [[PubMed](#)]
29. Perrone, P.; Moriello, C.; Alessio, N.; Contri, A.; Manna, C.; D'Angelo, S. Annurca Apple Polyphenols Prevent Mercury-Induced Phosphatidylserine Externalization in Human Erythrocytes via Calcium-Dependent PLSCR1 Regulation. *Front. Nutr.* **2026**, *13*, 1770188. [[CrossRef](#)] [[PubMed](#)]
30. Moriello, C.; Alessio, N.; Perrone, P.; Squillaro, T.; D'Angelo, S.; Galderisi, U.; Di Bernardo, G. Polyphenol-Rich Extracts from Annurca Apple Differentially Modulate Oxidative Stress-Induced Senescence in Human Dermal Fibroblasts. *Antioxidants* **2026**, *15*, 372. [[CrossRef](#)] [[PubMed](#)]
31. Tenore, G.C.; Caruso, D.; Buonomo, G.; D'Urso, E.; D'Avino, M.; Campiglia, P.; Marinelli, L.; Novellino, E. Annurca (*Malus pumila* Miller cv. Annurca) Apple as a Functional Food for the Contribution to a Healthy Balance of Plasma Cholesterol Levels: Results of a Randomized Clinical Trial. *J. Sci. Food Agric.* **2017**, *97*, 2107–2115. [[CrossRef](#)] [[PubMed](#)]
32. Tenore, G.C.; Caruso, D.; Buonomo, G.; D'Avino, M.; Campiglia, P.; Marinelli, L.; Novellino, E. A Healthy Balance of Plasma Cholesterol by a Novel Annurca Apple-Based Nutraceutical Formulation: Results of a Randomized Trial. *J. Med. Food* **2017**, *20*, 288–300. [[CrossRef](#)] [[PubMed](#)]
33. Tenore, G.C.; Carotenuto, A.; Caruso, D.; Buonomo, G.; D'Avino, A.M.; Brancaccio, D.; Ciampaglia, R.; Maisto, M.; Schisano, C.; Novellino, E. A Nutraceutical Formulation Based on Annurca Apple Polyphenolic Extract Is Effective on Intestinal Cholesterol Absorption: A Randomised, Placebo-Controlled, Crossover Study. *PharmaNutrition* **2018**, *6*, 85–94. [[CrossRef](#)]
34. Sommella, E.; Badolati, N.; Riccio, G.; Salviati, E.; Bottone, S.; Dentice, M.; Campiglia, P.; Tenore, G.C.; Stornaiuolo, M.; Novellino, E. A Boost in Mitochondrial Activity Underpins the Cholesterol-Lowering Effect of Annurca Apple Polyphenols on Hepatic Cells. *Nutrients* **2019**, *11*, 163. [[CrossRef](#)] [[PubMed](#)]
35. Tenore, G.C.; Caruso, D.; Buonomo, G.; D'Avino, M.; Santamaria, R.; Irace, C.; Piccolo, M.; Maisto, M.; Novellino, E. Annurca Apple Nutraceutical Formulation Enhances Keratin Expression in a Human Model of Skin and Promotes Hair Growth and Tropism in a Randomized Clinical Trial. *J. Med. Food* **2018**, *21*, 90–103. [[CrossRef](#)] [[PubMed](#)]
36. Badolati, N.; Sommella, E.; Riccio, G.; Salviati, E.; Heintz, D.; Bottone, S.; Di Cicco, E.; Dentice, M.; Tenore, G.C.; Campiglia, P.; et al. Annurca Apple Polyphenols Ignite Keratin Production in Hair Follicles by Inhibiting the Pentose Phosphate Pathway and Amino Acid Oxidation. *Nutrients* **2018**, *10*, 1406. [[CrossRef](#)] [[PubMed](#)]
37. D'Angelo, S.; Martino, E.; Ilisso, C.P.; Bagarolo, M.L.; Porcelli, M.; Cacciapuoti, G. Pro-Oxidant and Pro-Apoptotic Activity of Polyphenol Extract from Annurca Apple and Its Underlying Mechanisms in Human Breast Cancer Cells. *Int. J. Oncol.* **2017**, *51*, 939–948. [[CrossRef](#)] [[PubMed](#)]
38. D'Angelo, S.; Martino, E.; Cacciapuoti, G. Effects of Annurca Apple (*Malus pumila* cv. Annurca) Polyphenols on Breast Cancer Cells. *Curr. Nutr. Food Sci.* **2019**, *15*, 745–751. [[CrossRef](#)]
39. Martino, E.; Vuoso, D.C.; D'Angelo, S.; Mele, L.; D'Onofrio, N.; Porcelli, M.; Cacciapuoti, G. Annurca Apple Polyphenol Extract Selectively Kills MDA-MB-231 Cells through ROS Generation, Sustained JNK Activation and Cell Growth and Survival Inhibition. *Sci. Rep.* **2019**, *9*, 13045. [[CrossRef](#)] [[PubMed](#)]
40. Vuoso, D.C.; D'Angelo, S.; Ferraro, R.; Caserta, S.; Guido, S.; Cammarota, M.; Porcelli, M.; Cacciapuoti, G. Annurca Apple Polyphenol Extract Promotes Mesenchymal-to-Epithelial Transition and Inhibits Migration in Triple-Negative Breast Cancer Cells through ROS/JNK Signaling. *Sci. Rep.* **2020**, *10*, 15921. [[CrossRef](#)] [[PubMed](#)]
41. Boccellino, M.; Quagliuolo, L.; D'Angelo, S. Annurca Apple Biophenols' Effects in Combination with Cisplatin on A549 Cells. *Curr. Nutr. Food Sci.* **2021**, *17*, 111–120. [[CrossRef](#)]
42. Orlandella, F.M.; Mirabelli, P.; De Stefano, A.E.; Iervolino, P.L.C.; Luciano, N.; D'Angelo, S.; Salvatore, G. Effects of Annurca Flesh Apple Polyphenol in Human Thyroid Cancer Cell Lines. *Oxid. Med. Cell. Longev.* **2022**, *2022*, 6268755. [[CrossRef](#)] [[PubMed](#)]
43. Nasso, R.; Pagliara, V.; D'Angelo, S.; Rullo, R.; Masullo, M.; Arcone, R. Annurca Apple Polyphenol Extract Affects Acetylcholinesterase and Monoamine Oxidase In Vitro Enzyme Activity. *Pharmaceuticals* **2021**, *14*, 62. [[CrossRef](#)] [[PubMed](#)]
44. D'Errico, A.; Nasso, R.; Di Maro, A.; Landi, N.; Chambery, A.; Russo, R.; D'Angelo, S.; Masullo, M.; Arcone, R. Identification and Characterization of Neuroprotective Properties of Thaumatin-like Protein 1a from Annurca Apple Flesh Polyphenol Extract. *Nutrients* **2024**, *16*, 307. [[CrossRef](#)] [[PubMed](#)]
45. Prior, R.L.; Wu, X.; Schaich, K. Standardized Methods for the Determination of Antioxidant Capacity and Phenolics in Foods and Dietary Supplements. *J. Agric. Food Chem.* **2005**, *53*, 4290–4302. [[CrossRef](#)] [[PubMed](#)]
46. Apak, R.; Özyürek, M.; Güçlü, K.; Çapanoğlu, E. Antioxidant Activity/Capacity Measurement. 1. Classification, Physicochemical Principles, Mechanisms, and Electron Transfer (ET)-Based Assays. *J. Agric. Food Chem.* **2016**, *64*, 997–1027. [[CrossRef](#)] [[PubMed](#)]

47. Koutsos, A.; Tuohy, K.M.; Lovegrove, J.A. Apples and Cardiovascular Health—Is the Gut Microbiota a Core Consideration? *Nutrients* **2015**, *7*, 3959–3998. [[CrossRef](#)] [[PubMed](#)]
48. Green, B.N.; Johnson, C.D.; Adams, A. Writing Narrative Literature Reviews for Peer-Reviewed Journals: Secrets of the Trade. *J. Chiropr. Med.* **2006**, *5*, 101–117. [[CrossRef](#)] [[PubMed](#)]
49. Baethge, C.; Goldbeck-Wood, S.; Mertens, S. SANRA—A Scale for the Quality Assessment of Narrative Review Articles. *Res. Integr. Peer Rev.* **2019**, *4*, 5. [[CrossRef](#)] [[PubMed](#)]
50. Jakobek, L.; Barron, A.R. Ancient Apple Varieties from Croatia as a Source of Bioactive Polyphenolic Compounds. *J. Food Compos. Anal.* **2016**, *45*, 9–15. [[CrossRef](#)]
51. O'Shea, N.; Arendt, E.K.; Gallagher, E. Dietary Fibre and Phytochemical Characteristics of Fruit and Vegetable By-Products and Their Recent Applications as Novel Ingredients in Food Products. *Innov. Food Sci. Emerg. Technol.* **2012**, *16*, 1–10. [[CrossRef](#)]
52. Sudha, M.L.; Baskaran, V.; Leelavathi, K. Apple Pomace as a Source of Dietary Fiber and Polyphenols and Its Effect on the Rheological Characteristics and Cake Making. *Food Chem.* **2007**, *104*, 686–692. [[CrossRef](#)]
53. Scalbert, A.; Williamson, G. Dietary Intake and Bioavailability of Polyphenols. *J. Nutr.* **2000**, *130*, 2073S–2085S. [[CrossRef](#)] [[PubMed](#)]
54. Williamson, G.; Clifford, M.N. Role of the Small Intestine, Colon and Microbiota in Determining the Metabolic Fate of Polyphenols. *Biochem. Pharmacol.* **2017**, *139*, 24–39. [[CrossRef](#)] [[PubMed](#)]
55. Cardona, F.; Andrés-Lacueva, C.; Tulipani, S.; Tinahones, F.J.; Queipo-Ortuño, M.I. Benefits of Polyphenols on Gut Microbiota and Implications in Human Health. *J. Nutr. Biochem.* **2013**, *24*, 1415–1422. [[CrossRef](#)] [[PubMed](#)]
56. Mosca, L.; Pagano, C.; Tafuri, M.G.; Di Maio, G.; Rejano-Gordillo, C.M.; Della Marca, R.; D'Angelo, S.; Monda, M.; Messina, G.; Polito, R.; et al. The Gut Microbiota–Polyphenol–NLRP3 Inflammasome Axis: A Key Regulatory Network Linking Diet to Chronic Inflammation. *Nutrients* **2026**, *18*, 1483. [[CrossRef](#)] [[PubMed](#)]
57. Sies, H. Oxidative Stress: Concept and Some Practical Aspects. *Antioxidants* **2020**, *9*, 852. [[CrossRef](#)] [[PubMed](#)]
58. Pandey, K.B.; Rizvi, S.I. Biomarkers of Oxidative Stress in Red Blood Cells. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub.* **2011**, *155*, 131–136. [[CrossRef](#)] [[PubMed](#)]
59. Clarkson, T.W.; Magos, L. The Toxicology of Mercury and Its Chemical Compounds. *Crit. Rev. Toxicol.* **2006**, *36*, 609–662. [[CrossRef](#)] [[PubMed](#)]
60. Ahmad, S.; Mahmood, R. Mercury Chloride Toxicity in Human Erythrocytes: Enhanced Generation of ROS and RNS, Hemoglobin Oxidation, Impaired Antioxidant Power, and Inhibition of Plasma Membrane Redox System. *Environ. Sci. Pollut. Res. Int.* **2019**, *26*, 5645–5657. [[CrossRef](#)] [[PubMed](#)]
61. Piscopo, M.; Notariale, R.; Tortora, F.; Lettieri, G.; Palumbo, G.; Manna, C. Novel Insights into Mercury Effects on Hemoglobin and Membrane Proteins in Human Erythrocytes. *Molecules* **2020**, *25*, 3278. [[CrossRef](#)] [[PubMed](#)]
62. Lang, E.; Qadri, S.M.; Lang, F. Killing Me Softly—Suicidal Erythrocyte Death. *Int. J. Biochem. Cell Biol.* **2012**, *44*, 1236–1243. [[CrossRef](#)] [[PubMed](#)]
63. Bevers, E.M.; Williamson, P.L. Getting to the Outer Leaflet: Physiology of Phosphatidylserine Exposure at the Plasma Membrane. *Physiol. Rev.* **2016**, *96*, 605–645. [[CrossRef](#)] [[PubMed](#)]
64. Dal Col, J.; Lamberti, M.J.; Nigro, A.; Casolaro, V.; Fratta, E.; Steffan, A.; Montico, B. Phospholipid Scramblase 1: A Protein with Multiple Functions via Multiple Molecular Interactors. *Cell Commun. Signal.* **2022**, *20*, 78. [[CrossRef](#)] [[PubMed](#)]
65. Guo, J.; Li, J.; Xia, L.; Wang, Y.; Zhu, J.; Du, J.; Lu, Y.; Liu, G.; Yao, X.; Shen, B. Transient Receptor Potential Canonical 5-Scramblase Signaling Complex Mediates Neuronal Phosphatidylserine Externalization and Apoptosis. *Cells* **2020**, *9*, 547. [[CrossRef](#)] [[PubMed](#)]
66. Notariale, R.; Perrone, P.; Mele, L.; Lettieri, G.; Piscopo, M.; Manna, C. Olive Oil Phenols Prevent Mercury-Induced Phosphatidylserine Exposure and Morphological Changes in Human Erythrocytes Regardless of Their Different Scavenging Activity. *Int. J. Mol. Sci.* **2022**, *23*, 5693. [[CrossRef](#)] [[PubMed](#)]
67. Brownlee, M. Biochemistry and Molecular Cell Biology of Diabetic Complications. *Nature* **2001**, *414*, 813–820. [[CrossRef](#)] [[PubMed](#)]
68. Goldin, A.; Beckman, J.A.; Schmidt, A.M.; Creager, M.A. Advanced Glycation End Products: Sparking the Development of Diabetic Vascular Injury. *Circulation* **2006**, *114*, 597–605. [[CrossRef](#)] [[PubMed](#)]
69. Ramasamy, R.; Yan, S.F.; Schmidt, A.M. Receptor for AGE: Signaling Mechanisms in the Pathogenesis of Diabetes and Its Complications. *Ann. N. Y. Acad. Sci.* **2011**, *1243*, 88–102. [[CrossRef](#)] [[PubMed](#)]
70. Poulsen, M.W.; Hedegaard, R.V.; Andersen, J.M.; de Courten, B.; Bügel, S.; Nielsen, J.; Skibsted, L.H.; Dragsted, L.O. Advanced Glycation Endproducts in Food and Their Effects on Health. *Food Chem. Toxicol.* **2013**, *60*, 10–37. [[CrossRef](#)] [[PubMed](#)]
71. Yeh, W.J.; Hsia, S.M.; Lee, W.H.; Wu, C.H. Polyphenols with Antiglycation Activity and Mechanisms of Action: A Review of Recent Findings. *J. Food Drug Anal.* **2017**, *25*, 84–92. [[CrossRef](#)] [[PubMed](#)]
72. Ference, B.A.; Ginsberg, H.N.; Graham, I.; Ray, K.K.; Packard, C.J.; Bruckert, E.; Hegele, R.A.; Krauss, R.M.; Raal, F.J.; Schunkert, H.; et al. Low-Density Lipoproteins Cause Atherosclerotic Cardiovascular Disease. 1. Evidence from Genetic, Epidemiologic, and Clinical Studies. A Consensus Statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* **2017**, *38*, 2459–2472. [[CrossRef](#)] [[PubMed](#)]

73. Hyson, D.A. A Comprehensive Review of Apples and Apple Components and Their Relationship to Human Health. *Adv. Nutr.* **2011**, *2*, 408–420. [[CrossRef](#)] [[PubMed](#)]
74. Jia, L.; Betters, J.L.; Yu, L. Niemann-Pick C1-like 1 Protein in Intestinal and Hepatic Cholesterol Transport. *Annu. Rev. Physiol.* **2011**, *73*, 239–259. [[CrossRef](#)] [[PubMed](#)]
75. Wang, D.Q.H. Regulation of Intestinal Cholesterol Absorption. *Annu. Rev. Physiol.* **2007**, *69*, 221–248. [[CrossRef](#)] [[PubMed](#)]
76. Maisto, M.; Schiano, E.; Novellino, E.; Piccolo, V.; Iannuzzo, F.; Salviati, E.; Summa, V.; Annunziata, G.; Tenore, G.C. Application of a Rapid and Simple Technological Process to Increase Levels and Bioaccessibility of Free Phenolic Compounds in Annurca Apple Nutraceutical Product. *Foods* **2022**, *11*, 1453. [[CrossRef](#)] [[PubMed](#)]
77. Campisi, J. Aging, Cellular Senescence, and Cancer. *Annu. Rev. Physiol.* **2013**, *75*, 685–705. [[CrossRef](#)] [[PubMed](#)]
78. Gorgoulis, V.; Adams, P.D.; Alimonti, A.; Bennett, D.C.; Bischof, O.; Bishop, C.; Campisi, J.; Collado, M.; Evangelou, K.; Ferbeyre, G.; et al. Cellular Senescence: Defining a Path Forward. *Cell* **2019**, *179*, 813–827. [[CrossRef](#)] [[PubMed](#)]
79. Rinnerthaler, M.; Bischof, J.; Streubel, M.K.; Trost, A.; Richter, K. Oxidative Stress in Aging Human Skin. *Biomolecules* **2015**, *5*, 545–589. [[CrossRef](#)] [[PubMed](#)]
80. Rittié, L.; Fisher, G.J. Natural and Sun-Induced Aging of Human Skin. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a015370. [[CrossRef](#)] [[PubMed](#)]
81. Jenkins, G. Molecular Mechanisms of Skin Ageing. *Mech. Ageing Dev.* **2002**, *123*, 801–810. [[CrossRef](#)] [[PubMed](#)]
82. Kammeyer, A.; Luiten, R.M. Oxidation Events and Skin Aging. *Ageing Res. Rev.* **2015**, *21*, 16–29. [[CrossRef](#)] [[PubMed](#)]
83. Halliwell, B. Oxidative Stress and Neurodegeneration: Where Are We Now? *J. Neurochem.* **2006**, *97*, 1634–1658. [[CrossRef](#)] [[PubMed](#)]
84. Spencer, J.P.E. The Interactions of Flavonoids within Neuronal Signalling Pathways. *Genes Nutr.* **2007**, *2*, 257–273. [[CrossRef](#)] [[PubMed](#)]
85. Mandel, S.A.; Amit, T.; Kalfon, L.; Reznichenko, L.; Youdim, M.B.H. Targeting Multiple Neurodegenerative Disease Etiologies with Multimodal-Acting Green Tea Catechins. *J. Nutr.* **2008**, *138*, 1578S–1583S. [[CrossRef](#)] [[PubMed](#)]
86. Soreq, H.; Seidman, S. Acetylcholinesterase—New Roles for an Old Actor. *Nat. Rev. Neurosci.* **2001**, *2*, 294–302. [[CrossRef](#)] [[PubMed](#)]
87. Youdim, M.B.H.; Edmondson, D.; Tipton, K.F. The Therapeutic Potential of Monoamine Oxidase Inhibitors. *Nat. Rev. Neurosci.* **2006**, *7*, 295–309. [[CrossRef](#)] [[PubMed](#)]
88. Trachootham, D.; Alexandre, J.; Huang, P. Targeting Cancer Cells by ROS-Mediated Mechanisms: A Radical Therapeutic Approach? *Nat. Rev. Drug Discov.* **2009**, *8*, 579–591. [[CrossRef](#)] [[PubMed](#)]
89. Gorrini, C.; Harris, I.S.; Mak, T.W. Modulation of Oxidative Stress as an Anticancer Strategy. *Nat. Rev. Drug Discov.* **2013**, *12*, 931–947. [[CrossRef](#)] [[PubMed](#)]
90. Davis, R.J. Signal Transduction by the JNK Group of MAP Kinases. *Cell* **2000**, *103*, 239–252. [[CrossRef](#)] [[PubMed](#)]
91. Hanahan, D. Hallmarks of Cancer: New Dimensions. *Cancer Discov.* **2022**, *12*, 31–46. [[CrossRef](#)] [[PubMed](#)]
92. Nieto, M.A.; Huang, R.Y.J.; Jackson, R.A.; Thiery, J.P. Epithelial–Mesenchymal Transitions in Development and Disease. *Cell* **2016**, *166*, 21–45. [[CrossRef](#)] [[PubMed](#)]
93. Perrone, P.; D’Angelo, S. Gut Microbial Metabotypes Shape Polyphenol Bioactivity: Toward Precision Nutrition Strategies for Human Health. *Nutrients* **2026**, *18*, 2396. [[CrossRef](#)] [[PubMed](#)]
94. Sumner, L.W.; Amberg, A.; Barrett, D.; Beale, M.H.; Beger, R.; Daykin, C.A.; Fan, T.W.-M.; Fiehn, O.; Goodacre, R.; Griffin, J.L.; et al. Proposed Minimum Reporting Standards for Chemical Analysis. *Metabolomics* **2007**, *3*, 211–221. [[CrossRef](#)] [[PubMed](#)]
95. Minekus, M.; Alminger, M.; Alvito, P.; Ballance, S.; Bohn, T.; Bourlieu, C.; Carrière, F.; Boutrou, R.; Corredig, M.; Dupont, D.; et al. A Standardised Static In Vitro Digestion Method Suitable for Food—An International Consensus. *Food Funct.* **2014**, *5*, 1113–1124. [[CrossRef](#)] [[PubMed](#)]
96. Brodkorb, A.; Egger, L.; Alminger, M.; Alvito, P.; Assunção, R.; Ballance, S.; Bohn, T.; Bourlieu-Lacanal, C.; Boutrou, R.; Carrière, F.; et al. INFOGEST Static In Vitro Simulation of Gastrointestinal Food Digestion. *Nat. Protoc.* **2019**, *14*, 991–1014. [[CrossRef](#)] [[PubMed](#)]
97. Schulz, K.F.; Altman, D.G.; Moher, D.; CONSORT Group. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. *BMJ* **2010**, *340*, c332. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.