



Exploring the antitumorigenic properties of agro-food byproducts: A comprehensive scientific review

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ABSTRACT

Natural byproducts have garnered significant attention for their potential antitumorigenic properties. The current scenario sketched by the goals of circular economy approaches the research towards the utilization of agro-waste biomasses as valuable source of biological active metabolites. This comprehensive scientific review explores the various mechanisms through which these natural compounds exert anticancer effects, including apoptosis induction, cell cycle arrest, inhibition of angiogenesis, and suppression of metastasis. The review highlights key bioactive molecules such as polyphenols, flavonoids, alkaloids, and terpenoids, examining their molecular interactions with cancer cells. Furthermore, the potential of these natural byproducts as adjuvant therapies in combination with conventional treatments is discussed. By summarizing recent advancements and identifying future research directions, this review underscores the promise of natural byproducts from as a source of novel anticancer agents. A specific section is dedicated to outline the role of innovative materials, such as nanoparticles, hydrogels, and biopolymers, that are being developed to enhance the delivery and efficacy of active components. These carriers offer improved stability, targeted delivery, and controlled release of natural compounds, maximizing their therapeutic potential while minimizing side effects.

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the continuous search for effective treatments. Traditional cancer therapies, such as chemo- and radiotherapy, while often effective, are accompanied by severe side effects and the potential for resistance development. Consequently, there has been growing interest in the exploration of natural byproducts as potential antitumorigenic agents [1]. The investigation into natural byproducts as antitumor agents is driven by several factors. First, many of these substances have been used in traditional medicine for centuries, suggesting their potential efficacy and safety. Second, natural byproducts often contain a complex mixture of compounds that can target multiple pathways involved in cancer development and progression, thereby reducing the likelihood of resistance [2]. Third, the rise of

biotechnological advancements has facilitated the extraction, purification, and characterization of these bioactive compounds, enabling more rigorous scientific evaluation of their antitumorigenic potential. A well acknowledged source of natural bioactive molecules is represented by the organic residual biomasses deriving from the agro-food value chains. Biopolymers, primary and secondary metabolites preserved in fresh and processed organic residues, are regarded as worthy ingredients for medical treatments and pharmaceutical development [3]. The valorization of natural products for health care strategy is stressed by the recent proposal to revise the Pharmaceutical legislation adopted by European Commission aimed at combining the priorities outlined in the European Green Deal Europe's and Beating Cancer Plan to support sustainable pharmaceutical development for Europe (*Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive*

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2001/83/EC and Directive 2009/35/EC COM). This literature review wishes to provide a comprehensive overview of the current state of research on the antitumorogenic properties of natural byproducts. By synthesizing the existing knowledge, this review seeks to underscore their potential as a valuable addition to the arsenal of cancer therapeutics [4]. The purpose is to pave the way for future research that could lead to the development of novel, more effective, and less toxic cancer treatments derived from nature's bounty. Natural byproducts offer a promising alternative and complementary approach to traditional cancer therapies. Their potential lies not only in their bioactivity but also in their structural diversity, which often surpasses that of synthetic compounds [5]. This structural complexity allows natural byproducts to interact with a variety of biological targets, potentially leading to more effective and multifaceted antitumorogenic effects. Additionally, the use of natural byproducts aligns with the growing trend towards integrative medicine, which combines conventional medical treatments with natural and holistic approaches. Patients and healthcare providers alike are increasingly interested in treatments that are perceived as more natural and less toxic. Natural byproducts can fulfill this role, affording a real reduction and well perceived side effects compared to conventional chemotherapeutic agents. While the potential of natural byproducts is significant, several challenges must be addressed to fully realize their therapeutic benefits [6]. One of the primary concerns is the complexity of natural extracts, made up by multiple bioactive compounds that may act synergistically or antagonistically. Isolating and identifying the specific functional groups responsible for anticancer activity is a critical step requiring sophisticated analytical techniques and bioassays [7]. Another demanding issue is the variability in the attainment of these compounds, influenced by environmental factors, geographical location, and the method of extraction. Standardizing the production and quality control of natural byproducts is essential to ensure consistent efficacy and safety [8]. Moreover, the pharmacokinetics and bioavailability of natural compounds can pose significant hurdles. Many natural compounds are poorly soluble in water, have limited absorption, or are rapidly metabolized and excreted from the body [9]. Advancements in drug delivery systems, such as nanotechnology and encapsulation, are being explored to overcome these limitations and enhance the therapeutic potential of natural byproducts [10].

2. Agro-food residues

In recent years, the valorization of agro-food residues has been deemed as a valid, sustainable and cost-effective alternative source of bioactive compounds, including antitumorogenic molecules. Agro-food residues, which are the byproducts of agricultural and food processing industries, are often considered residual wastes and pose environmental disposal challenges [11]. However, these residues retain a wide variety of phytochemicals, such as polyphenols, flavonoids, alkaloids, and terpenoids, which have displayed strong anticancer activities in various studies. The exploitation of agro-food residues not only addresses waste management issues but also provides an economically viable source of natural compounds for cancer therapy [12]. Grape pomace, a byproduct of the wine industry, contains high levels of resveratrol and quercetin which have been extensively investigated for their anticancer properties [13]. Resveratrol has been shown to induce apoptosis, inhibit cell proliferation, and suppress metastasis in various cancer cell lines. Similarly, citrus peels, which are often discarded during juice production, are a rich source of flavonoids such as naringenin and hesperidin. These compounds have demonstrated significant anticancer effects by inducing cell cycle arrest, promoting apoptosis, and inhibiting angiogenesis [14]. Tomato scraps from agro-industrial processing, may provide a large amount of preserved lycopene, a carotenoid with strong antioxidant capability that has been linked to reduced risks of prostate, breast, and lung cancers [15]. Furthermore, the use of agro-food residues aligns with the principles of green chemistry and circular economy, promoting the efficient use of natural resources reducing the use of

chemicals and the environmental impact [16]. Although the potential of agro-biomasses as a source of antitumorogenic molecules is a cutting-edge methodology, their integration into cancer therapy requires further research and development. Challenges such as variability in bioactive compound content, stability, and bioavailability need to be faced. Comprehensive studies on pharmacokinetics, toxicity, and efficacy of these compounds in clinical settings are essential to establish their therapeutic potential [14,17,18]. Many natural compounds have poor solubility in water, limited absorption in the gastrointestinal tract, or are rapidly metabolized and excreted from the body. Enhancing the bioavailability and stability of these compounds through techniques such as nanotechnology, encapsulation, and structural modification could significantly improve their therapeutic potential [19]. Exhaustive preclinical and clinical studies are also necessary to establish the safety and efficacy of these compounds. Understanding the pharmacokinetics, toxicity, and potential side effects of these compounds is a paramount step for their successful integration into cancer treatment regimens [20].

3. Bioactive compounds from vegetable processing wastes and by-products

Vegetable processing generates significant amounts of waste and by-products, embedded with reactive compounds with potential health benefits extended to antitumorogenic implementation. These fractions include polyphenols, flavonoids, carotenoids, glucosinolates, and dietary fibers, which retain various biological activities such as antioxidants, anti-inflammatory, and anticancer effects (see Table 1) [21]. The value of vegetable waste not only provides a sustainable solution to waste management but also offers a valuable source of natural compounds for the development of novel therapeutic agents [22]. For instance, onion skins contain high levels of quercetin, a flavonoid with potent anticancer activities which has been shown to induce apoptosis, inhibit cell proliferation, and suppress metastasis in various cancer cell lines [23]. Correlated investigations have unveiled the precise molecular mechanisms underlying the anticancer empowerment of curcumin and epigallocatechin gallate (EGCG), elucidating their roles in the dampen action on tumor cell proliferation and actuation of apoptosis [24]. Potato peels are rich in chlorogenic and caffeic acids, which delivered anticancer effects through the modulation of oxidative stress and inhibition of tumor growth. The polyunsaturated homologues of the carotenoid family, (e.g. beta-carotene, lycopene, and lutein), represent another group of bioactive integrators found in green biomasses. Tomato pomace serves as an excellent source of lycopene, a carotenoid recognized for its latent antioxidant and anticancer attributes, acting as cells proliferation inhibitor of cancer, and apoptosis enabler, thus owning the risk threshold of various diseases, including prostate, breast, and lung cancers [25]. Carrot peels, rich in beta-carotene, also possess anticancer potential through their ability to scavenge free radicals and modulate cellular signaling pathways. Glucosinolates are sulfur-containing compounds found in significant amounts in discarded cruciferous vegetables remains. For instance, sulforaphane, which is derived from glucoraphanin found in broccoli residues, has been extensively investigated for its ability to induce phase II detoxifying enzymes, inhibit histone deacetylase, and modulate various signaling pathways involved in cancer prevention and treatment. Vegetable wastes are also a rich source of dietary fibers, which play a crucial role in maintaining gut health and preventing cancer [26]. The fermentation of dietary fibers like pea pods and carrot peels, by gut microbiota produces short-chain fatty acids (SCFAs) exemplified by butyrate, an apoptosis primer and cell proliferation inhibitor, which modulates immune responses in the gut, thereby contributing to colorectal cancer restraint. Glucosinolates, found in cruciferous vegetables, yield bioactive isothiocyanates like sulforaphane, which induce detoxifying enzymes and modulate signaling pathways critical in cancer development.

By harnessing the rich reservoir of bioactive compounds found in agro-industrial wastes, researchers can develop targeted interventions

Table 1

Bioactive Compounds in Vegetable Processing Wastes and Their Anticancer Properties. This table illustrates the main classes of compounds derived from vegetable processing waste, summarizing their sources, key therapeutic components as anti-cancer agents, mechanisms of action, and relevant literature.

Compound	Source	Key Bioactive Components	Mechanism of Action	Reference
Flavonoids	Onion Skins	Quercetin	Induces apoptosis, inhibits cell proliferation, suppresses metastasis	Buljeta et al., 2023 (https://doi.org/10.3390/cim45020052)
	Potato Peels	Chlorogenic Acid, Caffeic Acid	Modulates oxidative stress, inhibits tumor growth	Chadorshabi et al., 2022 (https://doi.org/10.1016/j.foodchem.2022.132737)
Carotenoids	Tomato Pomace	Lycopene	Inhibits cancer cell proliferation, induces apoptosis, reduces risk of prostate, breast, and lung cancers	Eslami et al., 2023 (https://doi.org/10.1016/j.jclepro.2023.138996)
	Carrot Peels	Beta-Carotene	Scavenges free radicals, modulates cellular signaling pathways	Akhtar et al., 2017 (https://doi.org/10.1016/j.tifs.2017.05.004)
Glucosinolates	Cruciferous Vegetable Residues	Sulforaphane	Induces phase II detoxifying enzymes, inhibits histone deacetylase, modulates cancer signaling pathways	Buitrón et al., 2021 (https://doi.org/10.3390/fermentati9020122); Bidkar et al., 2025
Dietary Fibers	Pea Pods, Carrot Peels	Various Fibers	Fermented to SCFAs (e.g., butyrate), which induce apoptosis, inhibit cell proliferation, improve gut health	Khan et al., 2022 (https://doi.org/10.3390/ijerph19053042)

that not only mitigate cancer risk but also enhance the effectiveness of existing therapies. The exploration of natural organic molecules encompasses a broad spectrum of scientific inquiry, ranging from elucidating specific mechanisms of action to optimizing extraction techniques and fostering interdisciplinary collaboration [27]. This convergence of food science, pharmacology, and oncology steps up the advancement in cancer prevention and treatment strategies, ultimately improving patient outcomes and public health. Moreover, formulation studies aiming to create precision interventions, such as dietary supplements containing sulforaphane and lycopene, may unfold tailored approaches in cancer prevention and treatment [28]. The present engagement is devoted to the development of novel formulations designs, to enhance the bioavailability and targeted delivery of natural molecules to cancer cells [29,30]. Lastly, interdisciplinary collaboration has emerged as a cornerstone in advancing cancer research, as evidenced by the growing body of literature on co-implementation of diverse disciplines in tackling complex challenges in oncology.

4. Molecular action and cellular target of bioactive compounds

In recent years, there has been growing interest in elucidating the molecular actions and cellular targets of agro-food waste, including by-products from food processing industries and agricultural residues, driven by their potential therapeutic applications and sustainability benefits [31](see Table 2). The relationship between bioactive compounds and anti-tumorigenic agents is complex, as their unique structures influence various cellular functions through multiple mechanisms [32–36] (Fig. 1).

Polyphenols found in fruit pomace and vegetable peels, for example, have been shown to interact with important signaling molecules like nuclear factor-kappa B (NF- κ B) and mitogen-activated protein kinases (MAPKs). These bioactive compounds have been studied for their ability to influence cellular processes that regulate tumor growth and cell death, positioning them as potential candidates for cancer prevention and therapeutic strategies. For instance, curcumin has been extensively researched for its ability to suppress NF- κ B activation by inhibiting the I κ B kinase (IKK) complex, which prevents the nuclear translocation of NF- κ B and consequently reduces the expression of pro-inflammatory and anti-apoptotic genes. This ability to modulate key signaling pathways has made curcumin a subject of great interest in the development of anti-inflammatory and anticancer therapies. Similarly, epigallocatechin gallate (EGCG), a powerful polyphenol found in green tea, has been shown to block NF- κ B signaling by specifically targeting the phosphorylation of p65, a subunit of NF- κ B. This action results in the suppression of cancer cell proliferation and an increase in apoptosis, further supporting the potential of EGCG as a therapeutic agent in cancer treatment [37,38]. Quercetin-3-methyl ester (Q3ME), a flavonoid compound, directly interacts with key proteins in the MAPK signaling pathway, such as ERK1 and ERK2, by binding to their ATP-binding sites. This binding inhibits the enzymatic activity and function of these proteins, which are critical for regulating cell proliferation and survival. By disrupting the MAPK pathway, Q3ME has the potential to exert significant anti-cancer effects. Moreover, it has been demonstrated that Q3ME also binds to AKT, another critical kinase involved in cell growth and survival, inhibiting the phosphorylation of downstream targets like c-Jun and RSK2. This dual action on both the MAPK and AKT pathways underscores the compound's ability to modulate key cellular processes involved in tumorigenesis [39]. Moreover, several researchers have emphasized the numerous health benefits of quercetin as an antimicrobial agent due to its ability to inhibit the growth of various bacterial strains. Studies have demonstrated that quercetin from onion skins works by disrupting the integrity of bacterial cell membranes, which compromises the cells' structural stability and leads to their eventual destruction [40]. In addition to their direct anti-cancer effects, these compounds have demonstrated anti-angiogenic properties, meaning they can inhibit the formation of new blood vessels (angiogenesis) that are essential for tumor growth and metastasis. By preventing the development of a blood supply to tumors, these compounds can hinder their ability to expand and spread, further highlighting their potential as therapeutic agents in cancer treatment. Hydroxytyrosol, a compound found in olive mill wastewater, a byproduct of olive oil production, has been shown to inhibit key steps of angiogenesis. It influences endothelial cell cycle progression, particularly by altering the cell cycle distribution. This alteration disrupts the normal proliferation and migration of endothelial cells, both of which are necessary for the formation of new blood vessels necessary for tumor growth [41]. Notable examples of agro-food waste with significant health benefits are mango seed kernels and pomegranate peels. These bioproducts are rich in mangiferin and ellagitannins, respectively, polyphenolic compounds with potent antioxidant properties. Research has shown that both mangiferin and ellagitannins can protect neuronal cells from oxidative damage by activating the Nrf2 pathway, which in turn upregulates the expression of antioxidant enzymes like heme oxygenase-1 (HO-1) and superoxide dismutase (SOD) [41,42]. Additionally, mangiferin has been found to

Table 2

Therapeutic Potential and Biomolecular Actions of Bioactive Compounds from Agro-Food Wastes. The table illustrates the most common bioproducts derived from food processing industries and agricultural residues, highlighting their potential therapeutic applications and sustainability benefits. The unique mechanisms of action associated with each bioproduct are also presented, along with relevant literature references.

Bioproduct waste sources	Bioactive Compounds	Therapeutic Applications	Mechanisms of Action	References
Onion Skins	Quercetin	Antimicrobial, Antitumorogenic	Disrupts bacterial cell membranes, induces apoptosis in cancer cells	Stoica et al., 2023 (https://doi.org/10.1016/j.tifs.2023.104173)
Pomegranate Peels	Ellagitannins	Cardiovascular Health	Enhances Nrf2 signaling, reduces oxidative stress and inflammation	Stoica et al., 2023 (https://doi.org/10.1016/j.tifs.2023.104173)
Potato Peels	Phenolic Compounds	Anti-Diabetic	Modulates insulin signaling pathway, enhances glucose uptake	Zafar et al., 2022 (https://doi.org/10.3390/app12125811)
Mango Seed Kernels	Mangiferin	Neuroprotective, Anti-Inflammatory	Activates Nrf2 pathway, upregulates antioxidant enzymes, inhibits inflammatory cytokines	Vučić et al., 2019 (https://doi.org/10.2174/1381612825666190708183941); Aggarwal et al., 2011 (https://doi.org/10.2174/138945011798109464)
Tomato Pomace	Lycopene	Cancer Prevention	Neutralizes free radicals, inhibits IGF/PI3K/Akt pathway, induces apoptosis	Salman et al., 2007 (https://doi.org/10.1016/j.biopha.2007.02.015); Viuda-Martos et al., 2014 (https://doi.org/10.1080/10408398.2011.623799)
Banana Peels	Catecholamines	Wound Healing, Anti-Inflammatory	Promotes collagen synthesis, fibroblast proliferation, TGF- β /Smad signaling	Zaini et al., 2022 (https://doi.org/10.1016/j.jff.2022.105054)
Cereal Bran	Dietary Fibers	Gut Health, Nutrient Absorption	Binds to receptors in gastrointestinal tract, influences gut microbiota	Gasparrini et al., 2021 (https://doi.org/10.33594/000000441)
Fruit Pomace	Polyphenols, Flavonoids	Antioxidant, Anti-Inflammatory	Modulates NF- κ B, MAPK pathways, scavenges free radicals	Frigerio et al., 2021 (https://doi.org/10.3389/fphar.2021.726199)
Vegetable Peels	Polyphenols, Flavonoids	Antioxidant, Anti-Cancer	Interacts with NF- κ B and MAPK pathways, reduces oxidative stress	Castrica et al., 2019 (https://doi.org/10.1080/1828051X.2018.1529544); Ratu et al., 2023 (https://doi.org/10.3390/agriculture13081559)
Terpenoids, Alkaloids	Various	Cancer Cell Proliferation, Apoptosis	Regulates cell cycle, induces apoptosis, targets intracellular signaling pathways	Chiocchio et al., 2021 (https://doi.org/10.3390/molecules26020495)

have anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines, such as TNF- α and IL-6, through the suppression of the NF- κ B signaling pathway. These combined actions position mango seed kernels and pomegranate peels as promising candidates for the development of neuroprotective and anti-inflammatory nutraceuticals [43]. Another compelling example of agro-food waste with health benefits is tomato pomace, which is rich in lycopene, a potent antioxidant carotenoid. Lycopene has been extensively studied for its ability to neutralize free radicals and protect against oxidative stress. Lycopene modulates the expression of crucial proteins such as p53 and p21, which control the cell cycle and apoptosis, thereby inhibiting cancer cell proliferation. It also inhibits angiogenesis by reducing the expression of growth factors like VEGF, preventing new blood vessel formation necessary for tumor growth. Lycopene's antioxidant activity combats oxidative stress, reduces ROS, and protects against DNA damage, thus preventing mutations that can contribute to cancer development. Additionally, lycopene has been shown to reduce the mutagenic and genotoxic effects caused by H₂O₂ exposure in various cell models [44,45]. Furthermore, lycopene enhances the body's antioxidant defense mechanisms by increasing the activity of enzymes such as glutathione peroxidase and catalase. Similarly, banana peels and tomato pomace, often discarded as waste, are rich in phenolic compounds like catecholamines, which have shown potential in wound healing applications. These compounds accelerate the wound healing process by promoting collagen synthesis and enhancing the proliferation and migration of fibroblasts through the TGF- β /Smad signaling pathway

[46]. The anti-inflammatory and antimicrobial properties of banana peel extracts further contribute to their effectiveness in treating wounds and skin infections. Flavonoids, including quercetin, silibinin, and genistein, also play an essential role in regulating miRNA expression, which affects critical processes such as apoptosis, cell proliferation, migration, and invasion. These flavonoids modulate proteins like Caspase-3, Caspase-9, Bcl-2, p21, p27, and PTEN, inducing conformational changes that alter cellular dynamics. This modulation impacts key signaling pathways such as NOTCH and PI3K/Akt, transforming cancer cell behavior. For example, quercetin influences miR-145 expression in ovarian cancer cells, promoting apoptosis and inhibiting cell growth, while genistein reduces miR-27a expression, inhibiting proliferation and migration in ovarian cancer cells [47]. In addition to their anti-cancer properties, natural compounds, specifically products extracted from potato peels, have shown promise in managing chronic diseases. These compounds possess anti-diabetic properties that help regulate blood glucose levels through multiple mechanisms: i) by improving insulin sensitivity, which is essential for maintaining proper blood glucose levels; ii) enhancing glucose uptake in muscle cells, which is particularly beneficial for individuals with insulin resistance. Muscle tissue is a major site for glucose utilization, and by improving glucose uptake in this tissue, these compounds can contribute to better blood sugar control and overall metabolic health. This dual action makes potato peel extracts a valuable source for people managing type 2 diabetes, offering a potential alternative or complementary strategy to traditional therapies [48]. Similarly, dietary fibers derived from cereal bran and fruit pulp have

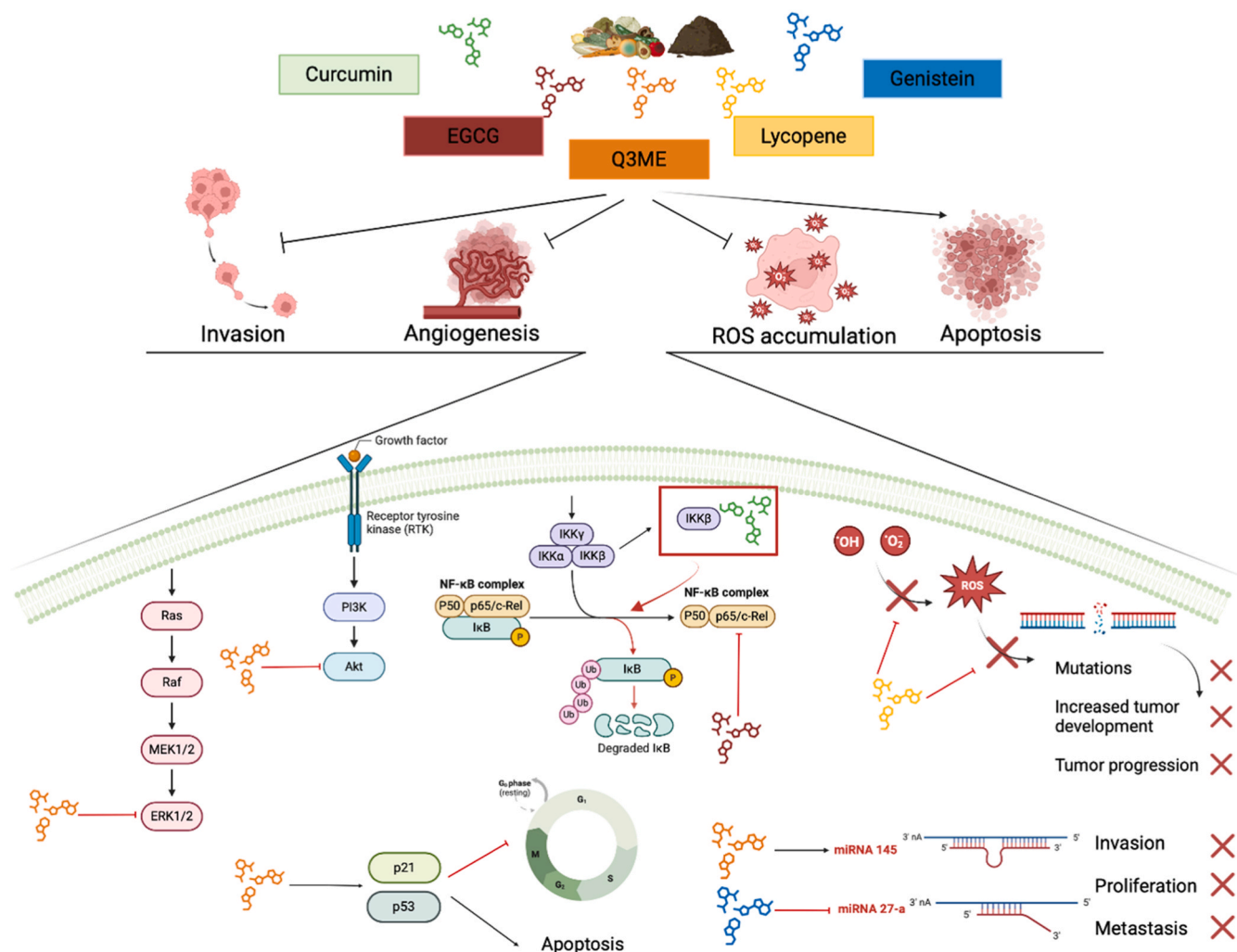


Fig. 1. Molecular mechanism behind the anti-cancer effects of bioactive compounds. Graphical abstract illustrating the impact of bioactive molecules derived from bioproduct waste source on cancer biology (*Upper panel*). This overview highlights the key molecular mechanisms through which these compounds inhibit cancer cell invasion, angiogenesis, ROS accumulation, and DNA damage, while also promoting apoptosis in cancer cells: a) **Quercetin-3-methyl ester (Q3M3)** targets the MAPK pathway, specifically inhibiting ERK1/2, thereby reducing cell proliferation. b) **Quercetin** is known to target AKT, limiting cell invasion, migration and angiogenesis. c) **Curcumin** suppresses NF-κB activation by inhibiting IκB kinase (IKK), preventing the nuclear translocation of NF-κB. This inhibits pro-inflammatory and anti-apoptotic gene expression. NF-κB signalling pathway inhibition via **epigallocatechin gallate (EGCG)**, through targeting p65, reduces cancer cell proliferation and promoting apoptosis. d) **Quercetin-3-methyl ester (Q3M3)** induces p21 and p53 activation, inhibiting cell cycle and influencing cell state dynamics. e) **Lycopene** promotes miR-145 expression in ovarian cancer cells, inducing apoptosis and inhibiting cell growth, while **Genistein** reduces miR-27a expression and inhibits migration in ovarian cancer cells. f) **Lycopene** exerts significant antioxidant activity, counteracting oxidative stress and reducing reactive oxygen species (ROS), thus protecting against DNA damage and preventing mutations that contribute to cancer development. Additionally, lycopene has been shown to mitigate the mutagenic and genotoxic effects caused by H₂O₂ exposure in various cell models (*Lower panel*). This figure was partly created using Biorender.com.

been shown to have significant health benefits, particularly in the context of chronic disease management. These natural fibers can bind to cell surface receptors in the gastrointestinal tract, influencing various physiological processes, such as nutrient absorption and gut microbiota composition. By interacting with these receptors, dietary fibers can regulate the release of digestive enzymes, which in turn helps to slow down the digestion and absorption of carbohydrates. This slower absorption can contribute to better glycemic control, making these fibers particularly useful in the management of conditions like diabetes and metabolic syndrome [49,50]. Their broad spectrum of benefits highlights their promise as integral components of functional foods, dietary supplements, or nutraceuticals aimed at preventing and managing chronic diseases.

However, while many bioactive compounds exhibit promising anti-cancer properties, their safety profiles must be carefully evaluated, particularly regarding potential toxicity at high doses or with long-term use [51]. For example, flavonoids such as quercetin and catechins have

been shown to exhibit cytotoxic effects at high concentrations, potentially inducing oxidative stress or mitochondrial dysfunction in normal cells [52]. Similarly, certain alkaloids, such as berberine, can exhibit hepatotoxicity or cardiotoxicity when consumed in high doses [53]. Therefore, a balanced approach to the application of bioactive phytochemicals is crucial to harness their therapeutic potential while mitigating risks associated with toxicity. The efficacy of flavonoids, phenolic acids, and alkaloids depends on factors such as dosage, bioavailability, metabolism, and individual patient variability. Controlled and optimized dosing is essential, as excessive concentrations can lead to unintended cytotoxicity, oxidative stress, or mitochondrial dysfunction, as observed with quercetin and catechins. Alkaloids like berberine, despite their antimicrobial and metabolic benefits, may induce hepatotoxicity or cardiotoxicity at high doses [54]. To ensure safe and effective use, research should focus on pharmacokinetics, synergistic interactions with other compounds, and targeted delivery systems that enhance bioavailability while reducing systemic toxicity. Techniques such as

encapsulation or nanoparticle formulations may enhance therapeutic outcomes while minimizing adverse effects (see Chapter 7) [55]. Regulatory oversight, evidence-based guidelines, and interdisciplinary collaboration will be crucial in translating these compounds into safe and effective treatments for human diseases [56]. Further elucidation of their precise mechanisms of action and validation through preclinical and clinical studies are warranted to fully harness their therapeutic potential. Continued research efforts should focus on identifying specific bioactive compounds within agro-food wastes responsible for their antitumorogenic effects and elucidating their pharmacokinetic profiles and bioavailability to optimize therapeutic efficacy. Moreover, investigating the synergistic interactions between different components present in agro-food wastes and conventional cancer therapies could provide valuable insights into combination treatment strategies that enhance efficacy while minimizing adverse effects. Furthermore, the development of innovative extraction and purification techniques to concentrate bioactive compounds from agro-food wastes, along with the formulation of stable delivery systems, will be instrumental in translating these findings into clinically viable therapies.

5. Supplementary antitumorogenic resource from natural organic materials: humic substances

An approachable complementary asset for the development of pharmacological formulates from natural organic compounds is represented by the exploitation of bio-stimulant activity of the so-called humic substances (HS) [57]. HSs, are the larger organic carbon pool in the biosphere found in soils, sediments and natural water environments, derived from biological transformation of plant, microbial and animal inputs. The water dispersive form is achieved by high reproducible stages, starting with alkaline solubilization, back titration to neutral pH, dialysis and final freeze drying, achieving a pliable material suitable to be arranged in countless accurate dilution doses. HSs are collection of polydisperse molecules assembled in micelle-like aggregates of polar and apolar components with variable molecular weight distribution and wide array of reactive functional groups. The colloidal characteristic, conformational flexibility and broad spectrum of active sites make the HS as versatile components for biobased applications [58, 59]. In the context of technological breakthrough defined by the objectives of Green Deal plan the use of recycled agro-food wastes as

valuable sources of humic materials is a further progress in the definition of affordable eco-friendly strategies in different fields including pharmacological sector [60,61]. Although the scientific surveys specifically linking HSs to antitumorogenic effects are limited (see Table 3), some studies indicate their potential anti-inflammatory and immunomodulatory capacity [62] to counteract tumor growth and metastasis, as well as implementing immune responses to cancer. The proposed antitumorogenic mechanism implicates the antioxidant functions, as humic components can scavenge free radicals and reduce oxidative stress [63]. By mitigating oxidative damage to cells and DNA, these substances may prevent the initiation and progression of cancer. Additionally, HSs may exert immunomodulatory effects, thus consolidating the body's immune response to cancer cells. This modulation of the immune system could encompass the stimulation activity of immune T cells and natural killer cells, which play crucial roles in recognizing and eliminating cancerous cells. The anti-inflammatory response affects the antitumorogenic impacts of HS by reducing chronic inflammation, which is associated with an increased risk of cancer development [64]. The cytotoxic activity of immune cells raised by HS, include the natural killer cells and cytotoxic T lymphocytes, against pancreatic cancer cells *in vitro*. The microbial interactions facilitated by HSs, through their diverse microbial community, may influence the gut microbiota and immune function, potentially impacting cancer progression [65]. Although definite pathways underlying the antitumorogenic effects of HSs remain to be fully elucidated, their antioxidant, immunomodulatory, anti-inflammatory, and microbial interactions represent practicable operative progress for further investigation in cancer prevention and treatment [61,66]. Recent researchers outlined the cytotoxic effects of humic materials against breast cancer cells *in vitro*, promoting apoptosis and thwarting cell proliferation. This cytotoxicity was attributed to HS ability to generate ROS and disrupt mitochondrial function, leading to cellular stress and death. Similar studies have investigated the effects of humic materials on tumor growth in either a *vitro* model of lung cancer, murine model of melanoma and mouse model of breast cancer [67]. The researchers found limited tumor growth and metastasis in treated cells compared to control. Mechanistic analysis revealed that humic acids enhance immune cell infiltration into tumors and promote an anti-tumor immune response characterized by increased cytokine production and cytotoxic T cell activity [68]. Further insight on humic activity pointed out the downregulation of key signaling pathways involved in tumor cell

Table 3

Antitumorogenic Effects of Humic Substances. This table highlights the use of recycled agro-food wastes as valuable sources of humic substances, supporting objectives to promote eco-friendly and sustainable anticancer strategies. It explores the potential and mechanisms of action of these humic materials in the treatment of various solid tumors.

Study	Humic Substance	Cancer Model	Key Findings	Mechanism of Action
Zolghadr et al., 2023 (https://doi.org/10.1007/s12649-022-01863-1)	Humic Acid	Breast Cancer (<i>In vitro</i>)	Induced apoptosis, inhibited cell proliferation. Cytotoxic effects through ROS generation and mitochondrial disruption	Enhanced oxidative stress, disrupted mitochondrial function
Lee et al., 2009 (https://doi.org/10.1136/thx.2007.093872)	Humic Acid	Lung Cancer (<i>In vitro</i>)	Reduced tumor growth and metastasis. Increased immune cell infiltration, enhanced cytokine production, and T cell activity	Enhanced anti-tumor immune response, increased cytokine production and T cell activity
Taherkhani et al., 2023 (https://doi.org/10.32598/JID.26.4.3)	Humic Acid	Melanoma (<i>In vitro</i> and <i>In vivo</i>)	Inhibited tumor growth and metastasis. Downregulated PI3K/Akt and MAPK pathways, induced apoptosis	Downregulated key signaling pathways, activated caspase cascades, and induced DNA damage
Song et al., 2020 (https://doi.org/10.1007/s12672-022-00495-0)	Humic Substances	Pancreatic Cancer (<i>In vitro</i> and <i>In vivo</i>)	Reduced tumor growth and metastasis. Inhibited NF- κ B signaling, enhanced cytotoxic activity of immune cells	Suppressed inflammation and angiogenesis, enhanced NK and T cell cytotoxicity
Kordestani et al., 2024 (https://jkm.kmu.ac.ir/10.34172/jkm.2024.12)	Humic Substances	Breast Cancer (<i>In vitro</i> and <i>In vivo</i>)	Reduced tumor volume and metastasis. Inhibited NF- κ B signaling, promoted M1 macrophage differentiation	Inhibited inflammatory cytokine production, promoted anti-tumoral macrophage phenotype
Vallinas et al., 2013 (https://doi.org/10.1111/nure.12051)	Compost Tea	Ovarian Cancer (<i>In vitro</i>)	Decreased cell proliferation, increased apoptosis. Modulated gene expression related to cell cycle and apoptosis	Altered gene expression for cell cycle regulation and apoptosis
Parish et al., 2023 (https://doi.org/10.3390/cancers15030862)	Compost Tea	Ovarian Cancer (<i>In vitro</i>)	Enhanced antitumor effects similar to compost tea, showing potential as a natural therapeutic agent	Modulated cell cycle and apoptosis pathways, contributing to decreased proliferation and increased apoptosis

proliferation and survival, such as the PI3K/Akt and MAPK pathways [69]. Humic acid may trigger apoptosis in melanoma cells by activating caspase cascades and inducing DNA damage [70]. The use of HS, in a liver cancer preclinical model, prevents the NF- κ B signaling pathway, thereby suppressing inflammation and angiogenesis within the tumor microenvironment. Likewise, the HS activated the differentiation of tumor-associated macrophages towards an anti-tumoral M1 phenotype, supporting the tumor suppression [71]. These findings outline the various types of mechanisms underlying the subsidiarity of HSs as immunomodulatory agents in cancer therapy. and substantiate their prospective formulations as natural therapeutic agents in cancer treatment [72].

The main challenges in the application of humic materials are the current gap on univocal and clear representation of structural activity relationship among molecular characteristics and bioactive effects. The self-assembling behavior and conformational dynamic determine their ability to act as carrier of bioactive components and interact with cell membrane. The comprehensive knowledge of humic equilibria, solubility and bio-persistence in formulation is unavoidable requirement for biomedical applications, where stability, selectivity, and predictable performance are essential. The detailed characterization is a preliminary requisite to determine the involved components to achieve a better understanding of mechanisms and tailored application of humic materials of different origin [73].

6. Valorization technologies for agro-food wastes

Processing technologies play a pivotal role in transforming agro-waste into valuable reservoir of bioactive compounds as anti-tumorigenic complements. The conversion of agricultural residues into high-value products involves a variety of advanced extraction and purification techniques designed to maximize the yield and efficacy of bioactive compounds while ensuring sustainability and environmental safety [74]. Advances in extraction and purification have played a critical step to boosting the feasible recovery of high-purity constituents from structurally weathered agro-food leftover. The adoption of supercritical fluid (SFE), microwave-assisted (MAE) and ultrasound-assisted extraction (UAE) techniques raised the yield and quality of released compounds, counteracting the use of harmful solvents. SFE is highly efficient for extracting bioactive compounds while minimizing solvent usage. However, it is typically optimized for use with fresh samples, as its effectiveness relies on the ability of the fluid to penetrate the sample and the volatility of the compounds being extracted [75]. Many agricultural and food by-products, such as citrus peels and grape pomace, can be processed immediately after production or stored under controlled conditions, such as freeze-drying or vacuum-sealing, to maintain their freshness and biochemical integrity [76]. Emerging techniques, such as low-temperature SFE and co-solvent modifications, have been demonstrated to enhance the stability and recovery of sensitive compounds, including essential oils and polyphenols, despite the potential degradation of some volatile components over time. Although SFE typically results in smaller extract volumes compared to conventional methods, process optimization strategies—such as scaling up extraction conditions or employing sequential fractionation—can effectively increase output without compromising quality. Additionally, integrating SFE with complementary techniques like UAE can enhance overall efficiency and extract yield, thereby ensuring sufficient material is available for pharmacological testing [77,78]. SFE brings the fluids above the phase separation critical physico-chemical point, to isolate bioactive metabolites from biomasses. The exceeding of critical temperature and pressure limits, confer to the fluid (most commonly carbon dioxide CO₂) physical-chemical metastable conformation between those of a liquid and a gas, which allows it to penetrate solid matrices like a gas and dissolve compounds like a liquid [79]. The SFE is particularly advantageous for its adaptability to solvent requirements, environmental consistency, and the ability to extract thermally labile compounds

lessening the uncontrolled modifications. The SFE was employed for suitable isolation of polyphenols, flavonoids, and other phytochemicals from fresh residues such as grape pomace, citrus peels, and tomato skins [80]. MAE leverages microwave energy to heat the solvent and plant material, significantly reducing extraction time and solvent usage compared to conventional methods. The rapid heating provided by microwaves disrupts plant cell walls, facilitating the release of intracellular compounds. MAE has been successfully applied to extract a wide range of metabolic substances, including phenolic compounds and naringenin, hesperidin and antioxidants, from various agro-wastes [81]. UAE employs ultrasonic waves to create cavitation bubbles in the solvent, which collapse and generate localized high temperatures and pressures. This process set a fast mass transfer and disrupts cell walls, improving the extraction efficiency of bio-labile derivatives), matched by low energy consumption and reduced extraction times. Enzymatic hydrolysis involves the selective and mild breakdown performed by specific enzymes to convert the complex matrices and larger molecules of agro-waste into simpler units, thereby preserving the intrinsic bioactivity [82]. Pressurized liquid extraction (PLE), also known as accelerated solvent extraction (ASE), syncs temperatures and pressures to speed up the extraction time and regulate the solvent consumption while improving yield of carotenoids, polyphenols and other heat-stable compounds, from agro-waste like tomato pomace and grape seeds. Fermentation is a biological valorization process accomplished by microorganisms, (e.g. bacteria, yeast, or fungi), to convert agro-waste into biological active by-products [83]. The membrane separation technologies, comprising ultrafiltration and nanofiltration, purify and concentrate the agro-waste extracts with high selective and performing workflow, ensuring an optimal transfer of target compounds [84]. The ability to operate at ambient temperatures also helps to preserve the stability of heat-sensitive bioactive molecules. Integrated extraction technologies combine multiple extraction methods (e.g. SFE+UAE, enzymatic hydrolysis+ MAE) to maximize both the detachment of bound elements from plant tissues and the purity of released fractions. Despite the advancements in valorization technologies, several challenges remain in the large-scale application of these methods [85]. The variability in the composition of agro-waste can affect the consistency and reproducibility of the extraction process. Standardizing the processing conditions and developing robust protocols are essential to address this issue. Another challenge is the scalability of the extraction technologies. While many methods have shown perspective outcomes at laboratory scale, scaling up to high TRL levels requires careful optimization to maintain technical efficiency, biological activity and cost-effectiveness. Research and development efforts should focus on optimizing process parameters, reducing energy consumption, and ensuring the economic viability of large-scale operations, the regulatory framework for the use of natural organic materials derived from agro-waste in pharmaceuticals and nutraceuticals needs to be investigated [86]. Warranting the safety and quality of natural ingredients is crucial for their acceptance and viable integration into therapeutic applications. Comprehensive toxicological and pharmacological studies are necessary to establish the healthy profiles of these compounds.

7. Bioactives molecules from agro-wastes: new formulation

The formulation of bioactive molecules derived from agro-wastes into functional products involves several critical steps to ensure their stability, bioavailability, and efficacy. The stability of bioactive compounds from agro-wastes is a key factor influencing their functional efficacy and shelf life in formulated products. These compounds are often susceptible to degradation due to environmental factors such as temperature, pH, light exposure, and oxidative conditions. High temperatures can accelerate chemical reactions, leading to the breakdown of bioactive molecules, while extreme pH levels may induce structural changes that reduce their bioactivity. Light exposure, particularly to UV radiation, can trigger photodegradation, affecting both potency and

functionality. Moreover, oxidative stress caused by oxygen and ROS can lead to the deterioration of sensitive compounds like polyphenols and flavonoids [87]. To preserve the stability and activity of the natural bioproducts, strategies like encapsulation (e.g., nanoencapsulation, microencapsulation, and liposomal formulations), the use of stabilizing agents, and optimized storage conditions are employed. Encapsulation in biopolymeric matrices (such as chitosan or alginate) has been shown to protect these bioactives, enhancing their stability and bioavailability [87,88]. Once extracted, bioactive compounds are often encapsulated to prevent degradation and ensure proper delivery. Various encapsulation methods, such as nanoencapsulation, liposomal encapsulation, and spray drying, are used to improve the solubility and absorption of bioactive compounds in the human body. These compounds are incorporated into carrier systems like tablets, capsules, beverages, or food matrices, while advanced techniques ensure sustained release and maximized health benefits [89]. For example, polyphenols from grape pomace have been encapsulated in nanoemulsions to improve their stability and bioavailability. Nanoemulsions, which have a small droplet size, offer a large surface area that enhances absorption and allows targeted delivery of bioactives to tumor sites streamlines the penetration across biological barriers, such as cell membranes and the blood-brain barrier. Similarly, flavonoids from agro-waste residues like citrus peels and tea leaves exhibit antioxidant, anti-inflammatory, and anticancer properties when formulated into nanoemulsions. These formulations can also modulate cancer-related signaling pathways, providing multiple antitumor effects [90,91]. Nanoparticles, such as those loaded with curcumin from turmeric waste, can solve issues related to the low solubility and bioavailability of certain bioactive compounds. Additionally, silver nanoparticles synthesized from banana peels and solid lipid nanoparticles (SLNs) loaded with resveratrol enhance the stability and controlled release of these compounds, offering benefits such as antioxidant protection and anti-aging effects. [92].

Liposomes are another carrier system that improves the delivery and stability of bioactive compounds, such as flavonoids from citrus peels. These lipid-based vesicles protect the bioactive compounds from degradation, enhance intestinal absorption, and allow for targeted delivery to tumor sites. Liposomes can also encapsulate chemotherapeutic drugs, improving their pharmacokinetics and reducing systemic toxicity, which can lead to better cancer treatment outcomes [93]. In the case of dietary fibers from apple pomace, spray drying has been employed to create a fine powder that can be easily added to various food products, such as baked goods and snacks. This solution not only raises the fiber content but also leverages the prebiotic effects of the fibers, promoting gut health. One of the key advantages of liposomal technologies is their contingent feature to wrap a wide range of metabolites, including chemotherapeutic drugs, nucleic acids, peptides, besides typical antioxidants like polyphenols, flavonoids, and terpenoids [94]. Natural anticancer products, like curcumin, resveratrol, and EGCG, have been successfully linked to liposomes structure to regulate their bioavailability and therapeutic goals. Several chemotherapeutic drugs, such as doxorubicin, paclitaxel, and cisplatin, inserted in liposomes, extend their circulation time in the bloodstream and gain accumulation chances at tumor sites through the prolonged permeability and retention (EPR) effect, thus intensifying the performances against various types of cancer, including breast, lung, and ovarian cancer [95]. Liposomal formulations of these drugs can improve their pharmacokinetics, reduce off-target effects, and overcome drug resistance, leading to better patient recovery outcomes. These liposomal formulations, when combined with chemotherapeutic agents, can selectively deliver bioactive compounds to tumor cells, where they exert their antitumor effects. The flexible structure of liposomes can be engineered to target specific tumor markers or overexpressed receptors on cancer cells, thereby enhancing their ability to target tumors more effectively. [96]. Pectin polymer extracted from citrus peels is a valis component in controlled release within tablet formulations. The self-gelling behavior of pectin produces a matrix capable to display a slow and sustained

release of active ingredients, making it an ideal nutraceutical bio-composite to improve digestive health. An emerging area of interest is the use of hydrogels derived from agro-waste components in 3D printing technology for biomedical applications. Cellulose extracted from sugarcane bagasse can be modified to produce hydrogels suitable for 3D bioprinting. These hydrogels can be loaded with bioactive molecules to create 3D-printed scaffolds for tissue engineering. The scaffolds provide a supportive matrix that mimics the natural extracellular matrix, promoting cell adhesion, proliferation, and differentiation. Overall, these technologies enable the effective transformation of agro-waste bioactives into nutraceuticals and functional foods, offering a sustainable way to promote human health while reducing environmental impact. A synthesis of several extraction and encapsulation techniques are reported in Table 4.

8. Multifunctional hybrid materials for the valorization of humic substances

A forefront methodology to deal with the operative drawbacks related to variable structural composition of HSs is based on the conjugation with complementary matrix consisting of either organic or inorganic materials. The hybridization of HSs is an exploitable path to sharpen their bioavailability, stability, and efficacy [97]. Nanotechnology-based approaches, such as the development of humic nanoparticles, nanoemulsions, and nanocomposites, display innovative scenario to progress ahead in respect to conventional formulations. Inorganic nanoparticles have been identified as useful biointerfaces due to their biocompatibility and their tunable size, shape and porosity, which allows functional versatility. Consequently, they are well positioned as a viable option for the development of multifunctional nanomaterials. The nanotechnology offers innovative solutions for

Table 4

Innovative Extraction and Encapsulation Techniques. This table provides an overview of innovative extraction and encapsulation techniques used for the derivation of natural products. It summarizes various methods, their applications, and the potential advantages they offer. These techniques are designed to enhance the bioavailability, stability, and controlled release of natural compounds, making them more effective in diverse fields such as pharmaceuticals, nutraceuticals, and cosmetics.

Technology	Key Features	Applications	Advantages
Supercritical Fluid Extraction (SFE)	Uses supercritical CO ₂ to extract bioactive compounds	Polyphenols, flavonoids, phytochemicals	Environmental friendly, preserves compounds
Microwave-Assisted Extraction (MAE)	Uses microwave energy to heat solvent and plant material	Phenolics, antioxidants	Reduces extraction time and solvent usage
Ultrasound-Assisted Extraction (UAE)	Uses ultrasonic waves to create cavitation bubbles	Lycopene, resveratrol	Low energy consumption, efficient extraction
Enzymatic Hydrolysis	Uses specific enzymes to break down complex molecules	Phenolic acids, flavonoids	Highly selective, preserves bioactive molecules
Pressurized Liquid Extraction (PLE)	Uses high temperatures and pressures to enhance extraction	Carotenoids, polyphenols	High efficiency, scalable for industrial use
Membrane Separation	Uses ultrafiltration and nanofiltration to purify and concentrate compounds	Polyphenols, flavonoids	High selectivity, preserves heat-sensitive molecules
Integrated Extraction Technologies	Combines multiple extraction methods	Various bioactive compounds	Synergistic benefits, optimized recovery

converting biowastes (BWs) into hybrid functional materials with modifiable conformations. The possibility to integrate bio-derived organic components with inorganic nanoparticles at the molecular level represents an efficacious technology to boost the intrinsic quality of both the organic and inorganic phases while selectively directing their functions [98]. At the same time, this approach may face the inherent limitations of these organic fractions, concerning low stability, rapid conformational dynamics, and high reactivity in aqueous media, which may override the applicative benefits. Following this aim, bioactive features of HSs can be significantly primed by a fine combination with an inorganic nanostructured phase, like the ceramic templated implements. Specifically, the molecular integration of such heterogeneous moieties with an inorganic matrix (e.g., SiO₂, TiO₂, ZnO) has been identified as a viable workflow to mitigate the degradation of organic moieties in aqueous environments. Moreover, this method improves the physicochemical stability, heightening the specific features of HSs in the resulting hybrid nanostructured materials [12].

The first devising of ceramic templated approach to modify industrially derived HSs, pointed out the viability to produce reproducible and hybrid systems with outstanding biocidal action, even using less refined industrial bio-waste [99,100]. The electrospinning technology enables to design of bioactive nanocomposite films for food packaging applications, made from electrospun biodegradable and bio-derived Poly(3-Hydroxybutyrate-co-3-Hydroxyvalerate) (PHBV) and hybrid nanostructured HSs-based materials. The current trend is the achievement of bio-composite made by organic matrix and biowaste components, avoiding the use of non-degradable inorganic nanostructures. The mix of HSs with a bio-based and a biodegradable support, such as PHBV, appears as practical technical proceeding to attain stability and functionality of natural bioproducts, providing for a feasible valorisation route, which concurrently improve the overall circular index of obtained materials [101]. Other synthesis pathways employ these biomolecules as functional cross-linking agent in gelatine hydrogels [99], leading to the formation of hybrid –3D HS networks with suitable rheological feedback and significant biological antimicrobial and antioxidant efficacy, suitable for a wide range of biotechnological deployments.

Furthermore, HSs can be encapsulated within nanoparticles or conjugated onto nanofibers to facilitate their transport to specific tissues or cells. This targeted delivery system allows for precise dosing and controlled release of substances, minimizing systemic side effects and maximizing therapeutic outcomes [102]. By incorporating HSs into scaffolds or matrices, nanocomposites can mimic the natural

extracellular environment and promote cell adhesion, proliferation, and differentiation. This solution may suit the settlement in wound healing, bone regeneration, and organ transplantation, where the regenerative properties of HSs can accelerate tissue repair and regeneration. Besides therapeutic handling, nanotechnologies can also be employed for diagnostic purposes. Nanoparticles functionalized with HSs can work as contrasting agents for imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) [103]. These nanoparticle-based composites can broaden the visualization of specific tissues or organs, aiding in the early detection and monitoring of diseases.

A schematic representation of HS customized materials is depicted in Fig. 2.

The proper health fitting of HS-loaded liposomes is in the field of antioxidant therapy. The storing of HSs within liposomes is suitable for controlled release and prolonged antioxidant performance for the mitigation of oxidative damage associated with aging, inflammation, and chronic diseases, offering potential benefits for overall health and well-being [28]. Furthermore, the liposomes lining can be explored for the inherent inhibition of pro-inflammatory cytokines provided by HS and the modulation of immune responses [104]. The liposomal frame may direct the delivery to inflamed tissues or target immune cells with positive therapeutic outcomes for inflammatory conditions such as arthritis, asthma, or inflammatory bowel disease. The HS-loaded liposomes may find applications in skincare formulations. HSs have been reported to promote skin health by priming collagen synthesis, improving skin hydration, and protecting against UV-induced damage. Liposomal encapsulation of HSs can facilitate their penetration into the deeper layers of the skin, where they can exert their beneficial effects on cellular function and tissue regeneration [105]. In summary, the integration of HSs with liposome technologies offers exciting opportunities for advancing human health and wellness [106]. The encapsulation fit and delivery capabilities of liposomes, could be effectively channeling the HSs to target tissues, affording antioxidant and anti-inflammatory benefits. Further research and development in this area have the potential to unlock new therapeutic methodologies and improve patient outcomes across a range of health needs. The complementary incorporation of HSs within hydrogel carriers offers several advantages, tailoring their therapeutic peculiarities and bioavailability [107]. Hydrogels, with their high-water content and biocompatibility, provide an excellent platform for the controlled release of HSs, allowing for sustained delivery and improved efficacy. The formulation process

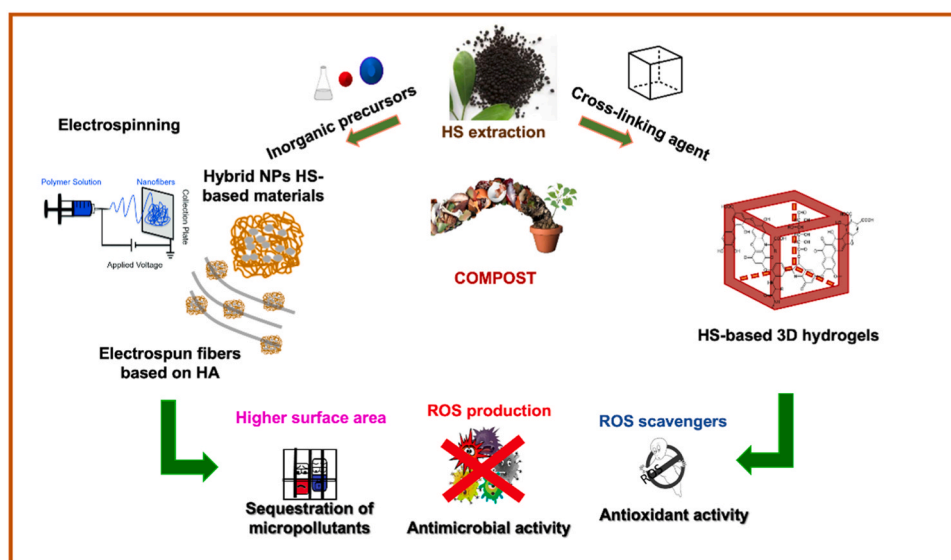


Fig. 2. Sustainable multifunctional materials from valorized humic substances.

typically involves the encapsulation of humic fractions inside hydrogel matrices, such as polymeric networks of alginate, chitosan, or hyaluronic acid. These hydrogels can be designed to gradually release humic constituent with specific molecular size, providing a steady supply of bioactive compounds to target tissues or organs. Moreover, the inherent biocompatibility of hydrogels reduces the risk of adverse reactions, making them suitable for various biomedical applications [108]. In wound healing process, the framed humic-hydrogels blends can accelerate the regeneration of skin tissue, promote collagen synthesis, and reduce inflammation, leading to faster wound closure and improved healing success. The formulation process involves the dispersion of HSs within hydrogel precursors, followed by crosslinking to form stable hydrogel networks. Various biodegradable polymers, such as chitosan and alginate, can be used as hydrogel matrices for HS encapsulation. HS-loaded hydrogels can be formulated for transdermal drug delivery applications [109]. By incorporating therapeutic ingredients into the hydrogel matrix along with HSs, these hydrogels can facilitate the controlled, targeted release of embedded drugs through the skin, materials offering targeted and steady lasting delivery. In the field of regenerative medicine, HS-hydrogels blends can be utilized for bone tissue engineering, operating as biomimetic environments that support bone regeneration and repair. The HSs can stimulate osteogenic differentiation of mesenchymal stem cells, enhance extracellular matrix production, and promote vascularization, leading to improved bone healing and regeneration in cases of fractures, defects, or bone diseases [110]. These biosynthetic carriers may be conceived as tools to tackle interventions in neurological disorders. The hydrogel-based humic systems may penetrate the blood-brain barrier and deliver neuroactive compounds to affected brain regions, thereby mitigating neurodegeneration and promoting neuronal repair and regeneration [110]. The formulation of HSs into hydrogels presents an innovative approach for prospective antitumorogenic care. The delivery of HS to tumor sites can be optimized, for surgical and consistent interaction within the tumor microenvironment to attain a prolonged exposure to tumor cells while minimizing systemic toxicity.

Another viable procedure to combine bioavailability and retention time within the tumor microenvironment is the encapsulation of humic materials in nano particles. Nanotechnologies offer strategies to focus the intracellular delivery of HSs to tumor cells, enabling the unfolding of bioactive properties associated with inflammatory cytokines, immunomodulatory response, apoptosis priming, cell cycle arrest, and inhibition of angiogenesis. These examples illustrate the versatility of humic hybrid blends in addressing a wide range of human health challenges. The leveraging of unique properties of HSs and the tunable characteristics of carrier matrices, are conducive for innovative therapeutic strategies to match patient outcomes and quality of life. Further research and development in this area have the potential to unlock new therapeutic applications and enhance the effectiveness of HSs in improving human health and well-being [111].

9. Future prospective and limitations

The utilization of agro-food wastes for their potential anti-tumorogenic activities holds great promise for both the pharmaceutical and food industries. As research in this field continues to advance, several prospects emerge. Firstly, there is a growing interest in identifying and characterizing specific bioactive compounds present in agro-food waste that exhibit anti-tumorogenic properties. Understanding the mechanisms of action and the synergistic interactions among these compounds could lead to the development of targeted therapies against various types of cancer [112–114]. The study of bioactive compounds from agricultural and food by-products inherently requires the integration of multiple disciplines, including food science, pharmacology, and oncology, each contributing unique methodologies and insights. In food science, advanced extraction techniques such as ultrasound-assisted extraction UAE and SFE optimize the isolation of

bioactive compounds while preserving their structural integrity and bioactivity [30]. Natural products are poised to play a crucial role in the future of nutraceutical formulation, as they provide a rich source of bioactive compounds that can be utilized for their therapeutic benefits. Nutraceuticals, which are food-derived products that offer health benefits beyond basic nutrition, include supplements, functional foods, and fortified beverages that aim to improve health, prevent chronic diseases, or support bodily functions providing a wide range of health benefits, such as anti-inflammatory, antioxidant, and immune-boosting effects. Natural products due to their therapeutic properties, are becoming integral to the development of nutraceuticals that support overall wellness, improve quality of life, and offer a safer, more natural alternative to synthetic pharmaceuticals. Their natural origin also aligns with the increasing consumer demand for sustainable and organic solutions [115, 116]. With ongoing research into the therapeutic and functional properties of natural compounds, they are expected to continue transforming also the cosmetic industry by offering more effective, environmentally friendly, and skin-safe alternatives to traditional formulations. In cosmetic applications, natural products offer a diverse range of plant-based and bioactive ingredients that provide numerous benefits for skin health and beauty. These natural compounds are increasingly sought after because they tend to be gentler on the skin compared to synthetic chemicals, reducing the risk of irritation or allergic reactions. Many plant-derived ingredients, such as Aloe vera, chamomile, and tea tree oil, are rich in vitamins, antioxidants, and essential fatty acids that nourish, hydrate, and protect the skin. In addition to their skin-friendly properties, natural ingredients often possess anti-aging, anti-inflammatory, and healing qualities, which make them highly effective in a variety of cosmetic products, from moisturizers to anti-wrinkle creams. The rising consumer demand for clean beauty products further fuels the relevance of natural compounds, as they are perceived as safer, more sustainable, and better for both personal health and the environment making them an eco-conscious choice for eco-aware consumers [117]. Moreover, natural compounds isolated and characterized from agro-food sources or HSs derived from biomass degradation will continue to play a key role in oncology research. The translational oncology research seeks to connect laboratory discoveries with clinical applications, including the development of new molecules, validation of their therapeutic effects, and pharmacological studies. The new molecules identified will be evaluated for their anti-tumor activity using a multidisciplinary approach, starting with *in vitro* 2D models. However, due to the limited ability of these models to represent tumor complexity, 3D models—such as patient-derived organoids and tumor spheroids—are increasingly used, as they mimic stromal interactions, oxygen gradients, and drug penetration dynamics [118,119]. These platforms are complemented by *in vivo* models like patient-derived xenografts (PDX) and genetically engineered mouse models (GEMMs), which recapitulate the primary tumor complex ecosystem and the progression to metastatic disease [120,121]. The molecular mechanism underlines the anti-tumor activity of the compounds, will be also deciphered through *in vitro* biochemical and biological assays. If these new compounds are suitable to be considered for clinical trials, pharmacological studies will be performed to determine bioactive compounds' bioavailability, metabolism, and safety profiles. This integrated approach ensures a seamless progression from compound isolation to clinical validation, fostering a robust and efficient pipeline for therapeutic development. As reported in Table 5, significant efforts have been made to develop novel extraction and purification techniques from agro-food wastes, as well as to establish delivery systems that enhance their efficacy and improve their distribution within the human body. However, several limitations must be addressed to fully realize the potential of natural compounds for several human applications. One major challenge is the variability in the composition and bioactivity of agro-food wastes and HSs, which can depend on factors such as seasonal variations, agricultural practices, and post-harvest handling. Standardization of extraction protocols and quality control measures are needed to ensure

Table 5

Emerging Trends and Future Directions. This table outlines emerging trends and future directions for the application of natural bioproducts highlighting key developments in the integration of natural bioproducts into various industries such as agriculture, environmental sustainability and healthcare.

Trend	Description	Innovative Aspects	Potential Impact
Sustainable Materials	Use of agro-wastes and natural materials.	Reduced environmental impact, innovative use of byproducts.	Promotes environmental sustainability.
Targeted Drug Delivery	Precision delivery of bioactives to specific sites.	Nanoparticles, liposomes, targeted formulations.	Enhanced therapeutic efficacy, reduced side effects.
Combination Therapies	Integrating multiple bioactives or therapies.	Synergistic effects, multi-target approaches.	Improved treatment outcomes, reduced drug resistance.
Advanced Diagnostic Applications	Utilizing nanotechnologies for diagnostics.	Functionalized nanoparticles for imaging.	Improved disease detection and monitoring.
Regenerative Medicine	Use of bioactive-loaded hydrogels in tissue engineering.	3D bioprinting, scaffold-based therapies.	Innovations in tissue repair and organ regeneration.

consistency and reproducibility in the bioactive content of agro-food waste-derived products. Additionally, regulatory and safety considerations must be addressed to ensure the safe use of agro-food waste-derived products in cancer therapy. Comprehensive toxicological studies are necessary to evaluate the safety profile and potential side effects of these products, particularly when administered at high doses or in combination with other drugs.

10. Conclusions

The exploration of agro-food wastes for their potential anti-tumorigenic properties represents a promising frontier in oncology research and medicine. The rich reservoir of bioactive compounds within agro-food wastes, including polyphenols, flavonoids, and dietary fibers exhibit anti-cancer properties through mechanisms such as inhibition of cell proliferation, apoptosis induction, and regulation of cancer-related cellular pathways. Cutting-edge extraction techniques and nanotechnology applications – including nanoparticle engineering, liposome encapsulation, and hydrogel-based delivery systems – are revolutionizing how these compounds are harnessed. These innovations enhance targeted delivery to cancerous cells while improving compound stability and absorption, potentially reducing side effects through precise therapeutic action. However, the development of standardized methods for waste processing and bioactive compound isolation remains crucial, as does addressing challenges like material variability and regulatory requirements for clinical applications. By advancing research in waste valorization, could impact cancer treatment paradigms – offering cost-effective therapies with dual environmental and public health benefits. Sustained interdisciplinary efforts may ultimately yield safer, more sustainable anticancer strategies while reducing agricultural waste burdens.

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Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

No data was used for the research described in the article.

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