



Ferulic Acid: A Natural Phenolic Compound with Anticancer Activity — A Comprehensive Review

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ABSTRACT :

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a ubiquitous hydroxycinnamic acid derivative found abundantly, in both free and bound forms, in the cell walls of cereals, fruits, vegetables, seeds and several medicinal plants. Beyond its long-recognised antioxidant, anti-inflammatory, antimicrobial and hepatoprotective properties, a substantial and rapidly growing body of preclinical evidence now supports a meaningful anticancer role for this compound across a wide range of tumour types, including breast, colon, lung, liver, prostate, cervical, pancreatic, esophageal and renal cancers. Ferulic acid exerts these effects through multiple, often interconnected, molecular mechanisms: scavenging of reactive oxygen species, induction of mitochondria-mediated intrinsic apoptosis, arrest of the cell cycle at the G0/G1, S or G2/M checkpoints, modulation of the PI3K/Akt, MAPK, NF-κB and STAT3 signalling cascades, activation of autophagic and ferroptotic cell death, and suppression of angiogenesis, invasion and metastasis. It further sensitises malignant cells to conventional chemotherapeutic agents while sparing normal tissue, an attribute of considerable translational interest. Nevertheless, its poor aqueous solubility, extensive first-pass metabolism and short plasma half-life continue to restrict its clinical applicability, prompting the development of nanoparticulate, liposomal, self-emulsifying and polymer-conjugated delivery systems designed to enhance bioavailability and tumour-selective delivery. This review consolidates current knowledge of the chemistry, natural occurrence, pharmacokinetics, molecular anticancer mechanisms, structure-activity relationships, combinatorial strategies, delivery innovations, safety profile and translational challenges associated with ferulic acid, and outlines the research priorities that must be addressed before this dietary phenolic compound can be advanced towards clinical oncology.

Keywords: Ferulic acid; phenolic acid; anticancer; apoptosis; oxidative stress; nanoformulation; chemoprevention

1. INTRODUCTION

Cancer remains among the foremost causes of morbidity and mortality worldwide, and despite considerable advances in surgery, radiotherapy, cytotoxic chemotherapy and targeted biological agents, the disease continues to impose a heavy clinical and economic burden. Conventional chemotherapeutic regimens are frequently limited by dose-dependent systemic toxicity, the emergence of multidrug resistance and a narrow therapeutic index, which has directed sustained scientific attention towards naturally occurring phytochemicals as adjuvant, chemopreventive or lead compounds for the development of safer anticancer agents. Plant-derived polyphenols, in particular, have attracted interest because epidemiological studies consistently associate diets rich in fruits, vegetables and whole grains with a reduced incidence of several malignancies.

Ferulic acid (FA), chemically designated 4-hydroxy-3-methoxycinnamic acid, is one of the most abundant hydroxycinnamic acids in the plant kingdom. It was first isolated from the resin of *Ferula* species in the nineteenth century and has since been identified as a structural component of plant cell walls, where it cross-links lignin, arabinoxylans and other polysaccharides to confer rigidity and mechanical strength. Dietary sources such as wheat bran, rice bran, oats, corn, coffee, citrus fruits, tomatoes and numerous traditional Chinese medicinal herbs (including *Angelica sinensis*, *Ligusticum chuanxiong* and *Cimicifuga* species) contribute meaningful quantities of FA to the human diet, with average intake estimated in the range of 150 to 250 milligrams per day.

Ferulic acid is pharmacologically versatile, exhibiting antioxidant, anti-inflammatory, antimicrobial, antiviral, antiallergic, neuroprotective, hepatoprotective, antidiabetic and cardioprotective activities. Of growing translational significance, however, is the expanding evidence that FA also possesses direct antiproliferative, pro-apoptotic, anti-angiogenic and anti-metastatic activity against a broad panel of human cancer cell lines and animal

tumour models. Unlike many synthetic cytotoxic agents, FA appears to act preferentially on malignant cells while exerting comparatively little toxicity on normal, non-transformed cells, a selectivity that is central to its appeal as a candidate chemopreventive or adjuvant anticancer molecule.

This review synthesises the current understanding of ferulic acid as an anticancer phytochemical. It begins with an overview of its chemistry, natural sources and pharmacokinetic behaviour, before examining in detail the molecular mechanisms through which it exerts antitumour effects, the evidence available across individual cancer types, its structure-activity relationships and derivatives, its synergistic interactions with established chemotherapeutic drugs, and the nanotechnology-based delivery strategies being explored to overcome its principal pharmacokinetic limitation — poor oral bioavailability. The review concludes with a discussion of safety considerations and the research gaps that must be bridged before ferulic acid can be meaningfully translated into clinical oncology practice.

2. CHEMISTRY AND PHYSICOCHEMICAL PROPERTIES

Ferulic acid (molecular formula C₁₀H₁₀O₄; molecular weight 194.18 g/mol) belongs to the hydroxycinnamic acid family of phenolic compounds, sharing the cinnamic acid backbone substituted with a hydroxyl group at the para position and a methoxy group at the meta position of the aromatic ring, together with an α,β -unsaturated carboxylic acid side chain. Biosynthetically, FA is derived from the phenylpropanoid pathway via methylation of caffeic acid by caffeate O-methyltransferase, and it exists in plants predominantly in trans (E) configuration, which is thermodynamically more stable and biologically more active than the cis (Z) isomer.

The compound is only sparingly soluble in water but readily soluble in polar organic solvents such as ethanol, methanol and dimethyl sulfoxide, a physicochemical characteristic that has important implications for its oral bioavailability and pharmaceutical formulation. The conjugated aromatic ring and the phenolic hydroxyl group confer strong free-radical scavenging capacity, allowing FA to donate a hydrogen atom to stabilise reactive oxygen and nitrogen species, while the extended conjugation of the acrylic acid side chain further delocalises the resulting phenoxyl radical, enhancing antioxidant stability relative to simpler phenolics. In plants, FA rarely occurs in the free form; it is more commonly esterified to arabinoxylans, pectins, lignin, polyamines and hydroxy fatty acids, and it also serves as a biosynthetic precursor of vanillin, coniferyl alcohol, sinapic acid, diferulic acid and, indirectly, curcumin.

From a medicinal chemistry standpoint, the FA scaffold is considered highly "druggable" because it offers three independently modifiable sites: the carboxylic acid, which is amenable to esterification, amidation and metal coordination; the phenolic hydroxyl, which can be alkylated, glycosylated or acylated to modulate antioxidant strength and membrane permeability; and the vinylic double bond, which can undergo Michael-type addition or serve as a synthetic handle for polymer conjugation. This structural versatility explains the very large number of semi-synthetic FA derivatives that have been synthesised and screened for anticancer activity over the past two decades, several of which are discussed in Section 8.

3. NATURAL SOURCES AND DIETARY INTAKE

Ferulic acid is one of the most abundant phenolic acids in the human diet. Cereal brans (wheat, rice, oat and corn) are particularly rich sources, where FA is esterified to arabinoxylan side chains within the aleurone and pericarp layers. Substantial quantities are also present in coffee beans, citrus fruits, tomatoes, spinach, beetroot, sugar beet pulp, bamboo shoots and numerous nuts and seeds. Several herbs used extensively in traditional Chinese and Ayurvedic medicine, notably *Angelica sinensis* (Dong quai), *Ligusticum chuanxiong*, *Cimicifuga heracleifolia* and *Ferula* species, contain particularly high concentrations of FA and its esters, which is thought to contribute to the antitumour reputation of these botanicals in traditional pharmacopoeias.

Because FA is largely bound to structural polysaccharides in cereal brans, its release and subsequent bioavailability are strongly influenced by food processing, fermentation and the activity of esterase enzymes produced by colonic microbiota. Wholegrain diets, fermented foods and processed cereal products such as bread and beer therefore differ considerably in the proportion of free versus bound FA that they deliver to the gastrointestinal tract, which in turn affects systemic exposure following ingestion.

4. PHARMACOKINETICS, METABOLISM AND BIOAVAILABILITY

Following oral ingestion, ferulic acid is absorbed along the entire length of the gastrointestinal tract, with evidence indicating that a portion is absorbed directly in the stomach. Bound forms of FA are liberated in the small and large intestine through the action of feruloyl esterases produced by gut microbiota, after which free FA is absorbed by passive diffusion and, to a lesser extent, by monocarboxylic acid transporters. Human studies using tomato-derived FA have shown that peak urinary excretion occurs at approximately seven hours after ingestion, with cumulative recovery of free FA and feruloyl glucuronide in urine accounting for roughly eleven to twenty-five percent of the ingested dose, reflecting extensive first-pass metabolism rather than incomplete absorption.

Once absorbed, FA undergoes extensive phase II biotransformation in the liver and intestinal mucosa, chiefly via glucuronidation, sulfation and, to a lesser extent, methylation, generating conjugated metabolites such as feruloyl glucuronide and ferulic acid sulfate. A minor fraction is reduced to dihydroferulic acid or further catabolised by colonic microbiota to smaller phenolic acids, including 3-hydroxyphenylpropionic acid, which has been identified as a major urinary metabolite in some animal studies. The overall biological activity attributed to dietary FA intake is therefore determined not only by the parent compound but also by the specific profile of circulating metabolites generated, which can vary considerably between individuals as a function of age, sex, gut microbial composition and hepatic enzyme activity.

From a pharmaceutical development perspective, the principal limitation of FA is not its intestinal absorption but its pharmacokinetic disposition after entering the systemic circulation: it is characterised by a short plasma half-life, rapid conjugative clearance and, owing to its limited aqueous solubility, dose-dependent and incomplete absorption at higher oral doses. These properties collectively constrain the plasma concentrations of free,

pharmacologically active FA that can be sustained after oral administration, and they constitute the principal rationale for the nanoformulation and prodrug strategies discussed later in this review.

5. ANTIOXIDANT BASIS OF ANTICANCER ACTION

Chronic oxidative stress, arising from an imbalance between reactive oxygen species (ROS) production and antioxidant defence, is intimately linked to carcinogenesis through DNA damage, activation of oncogenic signalling and promotion of a pro-inflammatory tumour microenvironment. As a potent chain-breaking antioxidant, ferulic acid scavenges superoxide, hydroxyl and peroxy radicals, chelates transition metal ions that catalyse Fenton-type radical generation, and upregulates endogenous antioxidant defences, including superoxide dismutase, catalase and glutathione peroxidase, partly through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway.

Paradoxically, at the elevated intracellular concentrations achievable within malignant cells, FA has also been shown to act as a pro-oxidant, triggering a marked and selective rise in intracellular ROS that overwhelms the comparatively weaker antioxidant capacity typical of cancer cells and thereby initiates mitochondrial dysfunction and apoptotic signalling. This dual, concentration- and context-dependent antioxidant/pro-oxidant behaviour is now recognised as a central feature underlying the tumour-selective cytotoxicity of FA, and it distinguishes its mechanism of action from that of simple free-radical scavengers.

6. MOLECULAR MECHANISMS OF ANTICANCER ACTION

6.1 INDUCTION OF APOPTOSIS

Induction of programmed cell death is the most extensively documented anticancer mechanism of ferulic acid. In human breast cancer MDA-MB-231 cells, FA derived from corn husk has been shown to elevate intracellular ROS, trigger mitochondria-dependent apoptosis and inhibit cell migration through coordinated activation of the MAPK, STAT3 and NF- κ B signalling pathways. Complementary work using isolated FA against the same cell line demonstrated classical morphological hallmarks of apoptosis, including cell shrinkage and membrane blebbing, alongside an increase in early and late apoptotic populations on Annexin V/propidium iodide flow cytometry, internucleosomal DNA fragmentation, upregulation of the pro-apoptotic genes BAX and TP53, and downregulation of the anti-apoptotic gene BCL-2, indicating engagement of a p53-dependent intrinsic apoptotic pathway.

Similar pro-apoptotic effects have been reported in prostate cancer. In LNCaP cells, FA treatment reduced BCL-2 gene and protein expression while increasing expression of cytochrome c (CYCS), consistent with mitochondrial outer membrane permeabilisation and cytochrome c release into the cytosol, a decisive step in intrinsic apoptosis. Analogous shifts in the balance of pro- and anti-apoptotic Bcl-2 family proteins have been documented in renal carcinoma (ACHN) cells, where FA exposure reduced BCL-2 expression while increasing BAX expression. Across multiple tumour types, FA and its derivatives have also been reported to increase the BAX/BCL-2 ratio and inhibit PI3K/Akt signalling in a dose-dependent manner, reinforcing apoptotic commitment.

6.2 CELL CYCLE ARREST

Ferulic acid arrests the cancer cell cycle at multiple checkpoints depending on cell type, dose and duration of exposure. In colon cancer Caco-2 cells, treatment with FA at higher micromolar concentrations has been shown to prolong the S phase and induce S-phase arrest, thereby limiting DNA replication and clonal expansion. In other tumour models, FA-based treatment regimens have produced G0/G1 arrest through downregulation of the JNK, AKT/mTOR and MEK/ERK signalling cascades, while in breast cancer cells increasing exposure duration to FA has been associated with a progressive rise in the proportion of cells arrested in G2/M phase, accompanied by suppression of phosphorylated AKT and of cyclin-dependent kinase-related proteins. Mechanistically, FA and its structural derivatives have been reported to reduce the expression of cyclin-dependent kinases CDK2, CDK4 and CDK6, disrupting the cyclin-CDK complexes required for progression through the G1/S and G2/M transitions.

6.3 MODULATION OF PI3K/AKT, MAPK, NF-KB AND STAT3 SIGNALLING

A recurring theme across the anticancer literature on ferulic acid is its capacity to interfere with the prosurvival signalling networks that malignant cells depend upon for proliferation, survival and evasion of apoptosis. FA has been shown to suppress activation of the PI3K/Akt/mTOR axis, a pathway frequently hyperactivated in human tumours and strongly implicated in resistance to apoptosis; inhibition of this pathway by FA reduces phosphorylated Akt levels and downstream mTOR signalling, thereby restoring the cell's sensitivity to apoptotic stimuli. Concurrently, FA modulates mitogen-activated protein kinase (MAPK) signalling, engaging ERK, JNK and p38 MAPK branches in a manner that, in the context of malignant cells, tips the balance towards pro-apoptotic and anti-proliferative outcomes rather than survival.

Nuclear factor kappa B (NF- κ B), a transcription factor central to inflammation-associated carcinogenesis and to the expression of anti-apoptotic and pro-metastatic genes, is likewise downregulated by FA in several tumour models, contributing to reduced cell viability and enhanced chemosensitivity. Signal transducer and activator of transcription 3 (STAT3), which drives proliferation and immune evasion in many solid tumours, is similarly suppressed by FA-mediated signalling, and the combined inhibition of MAPK, STAT3 and NF- κ B has been proposed as a coordinated mechanism underlying the ROS-triggered mitochondrial apoptosis observed in FA-treated breast cancer cells.

6.4 AUTOPHAGY AND FERROPTOSIS

Beyond classical apoptosis, ferulic acid engages additional programmed cell death modalities, including autophagy and, in more recent reports, ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation. In several tumour cell models, FA treatment has been found to elevate markers of autophagic flux, including beclin-1 and the lipidated form of light chain 3 (LC3-II), alongside mitophagy-associated proteins PINK1 and Parkin, indicating that FA can promote clearance of damaged mitochondria as a component of its cytotoxic action. Ferulic acid derivatives, such as tributyltin(IV) ferulate, have produced comparable increases in autophagy-related proteins, including LC3-II and the autophagy receptor p62, in colon cancer cell lines. The relative contribution of apoptosis, autophagy and ferroptosis to the overall cytotoxic profile of FA appears to be context-dependent, varying with cell type, concentration and duration of exposure, and represents an active area of ongoing mechanistic investigation.

6.5 ANTI-ANGIOGENIC AND ANTI-METASTATIC EFFECTS

Tumour progression depends on the capacity of malignant cells to recruit new blood vessels (angiogenesis) and to invade surrounding tissue and disseminate to distant sites (metastasis). Ferulic acid has been reported to suppress both processes. In vitro, FA reduces cancer cell migration and invasion, effects that in breast cancer models have been linked mechanistically to suppression of MAPK signalling. FA also downregulates matrix metalloproteinases, in particular MMP-2 and MMP-9, which degrade basement membrane components and facilitate tumour cell invasion, while additionally reducing expression of pro-angiogenic mediators such as vascular endothelial growth factor. Collectively, these anti-invasive and anti-angiogenic properties complement the pro-apoptotic and antiproliferative actions of FA, positioning it as a multi-targeted rather than single-pathway anticancer agent.

7. EVIDENCE ACROSS SPECIFIC CANCER TYPES

7.1 BREAST CANCER

Breast cancer is among the most extensively studied malignancies in the context of FA pharmacology. Multiple independent studies using the triple-negative MDA-MB-231 cell line have demonstrated selective cytotoxicity of FA towards malignant cells relative to normal epithelial or oral cells, mitochondria-mediated apoptosis via ROS-dependent MAPK/STAT3/NF- κ B signalling, G2/M cell cycle arrest, and inhibition of migratory capacity. In vivo, nanoparticulate formulations of FA combined with doxorubicin have shown enhanced antitumour efficacy in breast cancer models compared with either agent alone, supporting a combinatorial therapeutic rationale that is discussed further in Section 9.

7.2 COLORECTAL CANCER

In colon cancer cell lines, including Caco-2, HCT116 and HT-29, FA and its metal-conjugated derivatives have been shown to arrest the cell cycle, most notably by prolonging S phase, and to activate autophagy-associated pathways. Poly(ferulic acid), a polymeric nanocarrier synthesised by polycondensation of FA monomers, has itself been reported to possess intrinsic anticancer activity against colorectal cancer cells while simultaneously functioning as a biodegradable, pH-responsive carrier for co-delivered chemotherapeutic payloads, illustrating a dual therapeutic-plus-delivery role that is relatively unusual among phytochemical-based nanocarriers.

7.3 PROSTATE AND RENAL CANCER

In androgen-sensitive LNCaP and androgen-independent PC-3 prostate cancer cell lines, FA reduces cell viability in a dose-dependent manner, downregulates BCL-2 and increases cytochrome c expression, and inhibits PI3K/Akt signalling, collectively favouring an intrinsic apoptotic outcome. Comparable shifts in the BAX/BCL-2 balance have been reported in ACHN renal carcinoma cells, suggesting that the pro-apoptotic mechanism of FA is broadly conserved across genitourinary malignancies, even though the magnitude of the effective concentration required differs between cell lines.

7.4 HEPATOCELLULAR, LUNG AND ESOPHAGEAL CANCER

Ferulic acid and its conjugated derivatives, when co-delivered with other natural anticancer agents such as diosgenin using functionalised carbon nanotube carriers, have produced a more pronounced growth-inhibitory effect on HepG2 hepatocellular carcinoma cells than on A549 lung cancer or MCF7 breast cancer cells, with modulation of long non-coding RNAs, microRNAs and epithelial-mesenchymal transition-related proteins such as E-cadherin and TGF- β . In esophageal cancer models, extracts rich in ferulic acid-related phenolics derived from *Ferula* species have been shown to induce apoptosis via combined mitochondrial and PI3K/Akt/Bad signalling, underscoring the relevance of the PI3K/Akt axis across multiple gastrointestinal and thoracic malignancies.

7.5 PANCREATIC CANCER

Pancreatic ductal adenocarcinoma is notoriously refractory to conventional chemotherapy, which has prompted interest in chemopreventive combination strategies. Chitosan-coated solid lipid nanoparticles co-encapsulating FA with aspirin have been shown to reduce the effective cytotoxic dose of both agents severalfold in MIA PaCa-2 and Panc-1 pancreatic cancer cells relative to the free drug combination, while increasing the apoptotic fraction. In

xenograft models, oral administration of this nanoparticulate FA-aspirin combination reduced expression of the proliferation markers PCNA and MKI67 in tumour tissue while increasing expression of apoptosis-associated proteins, supporting the chemopreventive potential of nanoencapsulated FA combinations in a highly aggressive tumour type.

7.6 CERVICAL AND OTHER MALIGNANCIES

Additional evidence, though generally less extensive than for the tumour types described above, points to antiproliferative and pro-apoptotic activity of FA in cervical, gastric and skin cancer cell models, generally converging on the same core mechanisms of oxidative stress induction, mitochondrial apoptosis and interference with prosurvival kinase signalling. The consistency of these mechanistic findings across histologically diverse cancers supports the concept of FA as a broadly acting, multi-target phytochemical rather than a tumour type-specific agent.

Table 1 summarises representative preclinical findings on the anticancer activity of ferulic acid across the principal cancer types discussed above, together with the predominant molecular mechanisms reported and the corresponding experimental models used.

Table 1. Summary of representative preclinical anticancer evidence for ferulic acid.

Cancer type	Cell line / model	Predominant mechanism(s)	Key outcome
Breast	MDA-MB-231	ROS-mediated MAPK/STAT3/NF- κ B apoptosis; G2/M arrest; reduced migration	Decreased viability, increased apoptosis
Prostate	LNCaP, PC-3	PI3K/Akt inhibition; $\downarrow$ BCL-2, $\uparrow$ cytochrome c	Dose-dependent cytotoxicity
Renal	ACHN	$\downarrow$ BCL-2, $\uparrow$ BAX	Increased apoptotic index
Colorectal	Caco-2, HCT116, HT-29	S-phase arrest; autophagy activation	Reduced proliferation
Hepatocellular	HepG2	lncRNA/miRNA modulation; E-cadherin/TGF- β	Enhanced apoptosis with co-delivery
Pancreatic	MIA PaCa-2, Panc-1	Synergy with aspirin; $\downarrow$ PCNA, $\downarrow$ MKI67	Reduced tumour growth in vivo
Esophageal	EC cell lines / Ferula extract	Mitochondrial + PI3K/Akt/Bad pathway	Apoptosis induction

8. STRUCTURE-ACTIVITY RELATIONSHIPS AND SEMI-SYNTHETIC DERIVATIVES

The anticancer potency of ferulic acid is closely tied to specific structural features: the free phenolic hydroxyl group is essential for radical scavenging and redox-modulating activity, the methoxy substituent contributes to lipophilicity and membrane permeability, and the α,β -unsaturated carboxylic acid side chain provides a site for Michael addition reactions with cellular nucleophiles as well as a convenient handle for chemical derivatisation. Esterification, amidation or metal complexation of the carboxylic acid group has been widely explored to improve lipophilicity, membrane permeability and target selectivity while retaining or enhancing anticancer potency.

Metal-based ferulate complexes, including organotin(IV) ferulates such as tributyltin(IV) ferulate, have demonstrated markedly enhanced potency against colon cancer cell lines relative to the parent compound, with a distinct capacity to activate autophagy-related pathways. Polymeric derivatives, most notably poly(ferulic acid) formed by oxidative or enzymatic polycondensation of FA monomers, retain intrinsic cytotoxic activity against colorectal cancer cells while additionally functioning as a self-therapeutic, biodegradable nanocarrier platform. These structure-activity insights indicate that rational chemical modification of the FA scaffold offers a promising route towards next-generation derivatives with improved potency, selectivity and pharmaceutical developability.

9. SYNERGISTIC COMBINATION WITH CONVENTIONAL CHEMOTHERAPEUTIC AGENTS

One of the most clinically appealing properties of ferulic acid is its capacity to sensitise malignant cells to established cytotoxic drugs, potentially allowing dose reduction and consequent mitigation of systemic toxicity. In breast cancer models, nanoparticulate FA co-administered with doxorubicin has produced enhanced antitumour efficacy compared with doxorubicin alone, consistent with a chemosensitising role for FA. In pancreatic cancer, combination of FA with aspirin, delivered via chitosan-coated solid lipid nanoparticles, achieved synergistic reductions in cell viability at markedly lower doses of each agent than were required when using the free drugs individually, with corresponding increases in apoptotic markers both in vitro and in xenograft tumour tissue.

Dual-loaded nanocarrier systems combining FA with other natural anticancer agents, such as diosgenin delivered via functionalised carbon nanotubes, have likewise produced additive-to-synergistic cytotoxicity in hepatocellular carcinoma cells, although antagonistic interactions have been observed at

higher concentrations in some cell lines, underscoring the importance of careful dose-ratio optimisation when designing combination regimens. Collectively, these findings support further systematic investigation of FA as a chemosensitising adjuvant across a range of standard-of-care chemotherapeutic and chemopreventive regimens.

10. NANOTECHNOLOGY-BASED DELIVERY STRATEGIES

The principal barrier to clinical translation of ferulic acid as an anticancer agent is not a lack of biological activity but its unfavourable pharmaceutical properties, namely poor aqueous solubility, rapid phase II metabolism and a short plasma half-life, which together limit the systemic exposure achievable after oral administration. To address this, a range of nanoparticulate and colloidal delivery systems has been developed and evaluated.

Solid lipid nanoparticles, particularly when surface-modified with chitosan to confer mucoadhesive and positively charged characteristics, have achieved high encapsulation efficiencies for FA (in the region of 80 percent) alongside favourable particle size and zeta potential profiles, translating into markedly improved *in vitro* cytotoxicity and *in vivo* antitumour activity at substantially reduced doses compared with free FA. Polymeric nanocarriers, including poly(ferulic acid) itself and functionalised carbon nanotubes, have been used both to improve FA solubility and stability and to enable co-delivery of a second therapeutic payload with controlled, often glutathione- or pH-responsive, release kinetics suited to the reducing, mildly acidic tumour microenvironment.

Other approaches reported in the literature include self-microemulsifying drug delivery systems (SMEDDS), which improve oral absorption by dispersing FA within a lipidic microemulsion that bypasses some of the solubility-limited absorption seen with the free acid, as well as liposomal and niosomal encapsulation strategies originally developed to improve delivery of related phenolic acids and now being extended to FA. Across these platforms, the consistent finding is that nanoencapsulation permits equivalent or superior anticancer efficacy at a fraction of the dose required for free FA, while potentially conferring a degree of passive tumour targeting through the enhanced permeability and retention effect characteristic of solid tumours.

From a formulation-science perspective, several design variables recur across these delivery platforms as determinants of performance: particle size and surface charge (zeta potential), which govern cellular uptake and colloidal stability; the choice of coating polymer (commonly chitosan, polyethylene glycol or bovine serum albumin), which influences mucoadhesion, circulation time and immune recognition; and the release trigger built into the carrier, whether pH-, enzyme-, redox- or temperature-responsive, which determines whether payload release is confined preferentially to the tumour microenvironment. Rigorous physicochemical characterisation of these systems, including particle sizing, zeta potential measurement, encapsulation efficiency determination and *in vitro* release-kinetics modelling, remains essential to establishing a reliable structure-performance relationship before any FA nanoformulation can be considered for further preclinical development.

11. SAFETY, TOXICITY AND PRECLINICAL CONSIDERATIONS

Ferulic acid is generally regarded as a compound of low toxicity, consistent with its long history of dietary consumption and its established use as a cosmetic antioxidant and food preservative in some regulatory jurisdictions. Preclinical studies examining FA and its nanoparticulate formulations have generally reported minimal cytotoxicity towards normal, non-transformed cells at concentrations that are effective against malignant cells, a selectivity window that is central to its appeal as an adjuvant or chemopreventive agent. Nonetheless, comprehensive dose-ranging toxicological data, particularly for the higher systemic exposures that might be achieved using nanoformulations designed to overcome its native bioavailability limitations, remain comparatively limited, and long-term and reproductive toxicity data specific to sustained high-dose administration are not yet extensive.

12. CLINICAL TRANSLATION: CHALLENGES AND FUTURE PERSPECTIVES

Despite consistent and mechanistically coherent preclinical evidence, no ferulic acid-based anticancer formulation has yet progressed to routine clinical oncology practice. Several interconnected challenges account for this translational gap. First, the pharmacokinetic limitations discussed in Section 4 mean that oral administration of native FA is unlikely to achieve or sustain the micromolar tissue concentrations shown to be cytotoxic *in vitro*, necessitating either high or repeated dosing, or reliance on the nanoformulation strategies described in Section 10, most of which remain at an early, largely preclinical stage of development.

Second, much of the existing mechanistic evidence derives from *in vitro* cell culture and rodent xenograft studies, and confirmatory data from larger animal models and, ultimately, controlled human trials are needed before firm conclusions can be drawn regarding clinical efficacy and dosing. Third, standardisation of extraction, purity and formulation across studies is inconsistent, which complicates direct comparison of reported potencies and effective concentrations between research groups. Future research priorities include well-designed pharmacokinetic and dose-escalation studies of optimised FA nanoformulations, systematic head-to-head evaluation of FA in combination with standard-of-care chemotherapeutics across multiple tumour types, deeper mechanistic dissection of the relative contributions of apoptosis, autophagy and ferroptosis in a cell type-specific manner, and, ultimately, carefully controlled early-phase clinical trials in appropriately selected patient populations.

13. CONCLUSION

Ferulic acid, a naturally abundant and dietarily ubiquitous phenolic acid, has emerged over the past decade as a scientifically well-substantiated anticancer phytochemical, with activity documented across breast, colorectal, prostate, renal, hepatic, pancreatic, esophageal and other malignancies. Its anticancer effects are mediated through a convergent set of mechanisms, including selective pro-oxidant induction of mitochondrial apoptosis, cell cycle arrest, modulation of the PI3K/Akt, MAPK, NF- κ B and STAT3 signalling networks, activation of autophagy and ferroptosis, and suppression of angiogenesis and metastasis, alongside a favourable capacity to sensitise malignant cells to conventional chemotherapeutic agents. The principal obstacle to clinical

translation remains its poor pharmacokinetic profile, an issue that nanotechnology-based delivery platforms are increasingly well positioned to address. With continued mechanistic, pharmacokinetic and clinical investigation, ferulic acid holds meaningful promise as an adjuvant, chemosensitising or chemopreventive agent in future oncology practice. Bridging the gap between extensive preclinical characterisation and clinical application will require sustained, multidisciplinary collaboration between phytochemists, pharmaceutical formulation scientists, pharmacologists and clinical oncologists, but the consistency and mechanistic depth of the evidence accumulated to date provide a strong rationale for continuing to pursue ferulic acid, and its rationally designed derivatives and delivery systems, as candidate anticancer therapeutics.

REFERENCES

1. Ahmed, S.M. et al. Potential therapeutic efficacy of ferulic acid and its derivatives in the management of cancers: a comprehensive analysis with mechanistic insight. *International Journal of Food Science*, 2025.
2. Sun, W., Zhang, N.D. et al. Corn husk ferulic acid induces apoptosis of breast cancer cells via ROS-mediated signaling pathways. *Journal of Food Biochemistry*, 2024.
3. Updates on the strategies to improve the anti-tumor efficacy of ferulic acid. *International Journal of Molecular Sciences*, 2026.
4. Assessment of the anticancer mechanism of ferulic acid via cell cycle and apoptotic pathways in human prostate cancer cell lines. (Eroglu et al., 2015; related review).
5. Ferulic acid: a natural phenol that inhibits neoplastic events through modulation of oncogenic signaling. *Molecules*, 2022; 27(21):7653.
6. Isolated compounds from natural extract induce apoptosis in MDA-MB-231 breast cancer cells through a p53-dependent pathway. *Artificial Cells, Nanomedicine, and Biotechnology*, 2024.
7. Bahetjan, Y., Liu, W. et al. Ferula ferulaeoides ethyl acetate extract induces apoptosis in esophageal cancer cells via mitochondrial and PI3K/Akt/Bad pathways. *Arabian Journal of Chemistry*, 2023; 16(12):105291.
8. Zhao, Z., Moghadasian, M.H. Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: a review. *Food Chemistry*, 2008; 109:691-702.
9. Bioavailability of ferulic acid from tomato consumption in humans: pharmacokinetics of excretion. *American Journal of Clinical Nutrition / related study*, 2002.
10. A critical appraisal on ferulic acid: biological profile, biopharmaceutical challenges and nano formulations. (Review), 2022.
11. Kumar, N., Pruthi, V. Potential applications of ferulic acid from natural sources. *Biotechnology Reports*, 2014; 4:86-93.
12. Mancuso, C., Santangelo, R. Ferulic acid: pharmacological and toxicological aspects. *Food and Chemical Toxicology*, 2014; 65:185-195.
13. A recent overview on the biological and pharmacological activities of ferulic acid. *PMC review article*, 2019.
14. Oral pharmacokinetics of hydroxycinnamic acids: an updated review. *PMC review article*, 2022.
15. Thakkar, A., Chenreddy, S., Wang, J., Prabhu, S. Ferulic acid combined with aspirin demonstrates chemopreventive potential towards pancreatic cancer when delivered using chitosan-coated solid-lipid nanoparticles. *Cell & Bioscience*, 2015; 5:46.
16. Functionalized carbon nanotubes for delivery of ferulic acid and diosgenin anticancer natural agents. (*Nanomedicine journal*), 2024.
17. Poly(ferulic acid) with an anticancer effect as a drug nanocarrier for enhanced colon cancer therapy. *Advanced Functional Materials*, 2019.
18. Salama, A.F., Omran, G.A., Salahuddin, A.M., Abd-El-Azim, H.M., Noreldin, A., Okda, T.M. Enhanced antitumor efficacy of ferulic acid nanoparticles in combination with doxorubicin — a promising strategy for breast cancer treatment. *Contemporary Oncology*, 2025; 29(3):297-315.
19. Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: a review. *PubMed indexed review*, 2008.
20. Self-microemulsifying drug delivery system for improved oral delivery and hypnotic efficacy of ferulic acid. *International Journal of Nanomedicine*, 2020; 15:2059-2070.
21. Graf, E. Antioxidant potential of ferulic acid. *Free Radical Biology and Medicine*, 1992; 13(4):435-448.
22. Srinivasan, M., Sudheer, A.R., Menon, V.P. Ferulic acid: therapeutic potential through its antioxidant property. *Journal of Clinical Biochemistry and Nutrition*, 2007; 40(2):92-100.
23. Zduńska, K., Dana, A., Kolodziejczak, A., Rotsztein, H. Antioxidant properties of ferulic acid and its possible application. *Skin Pharmacology and Physiology*, 2018; 31(6):332-336.
24. Ou, S., Kwok, K.C. Ferulic acid: pharmaceutical functions, preparation and applications in foods. *Journal of the Science of Food and Agriculture*, 2004; 84(11):1261-1269.
25. Rosa, L.S. et al. Anticancer properties of phenolic acids in colon cancer: a review. *Journal of Nutrition and Cancer Prevention*, 2016.
26. Karthikeyan, S. et al. Ferulic acid modulates apoptotic and inflammatory pathways in experimental hepatocellular carcinoma. *Toxicology Reports*, 2011.
27. Janicke, B. et al. Ferulic acid and its transformation into vanillin and vanillic acid: role in dietary chemoprevention. *Molecular Nutrition & Food Research*, 2005.
28. Eroglu, C. et al. Anti-cancer mechanism of ferulic acid in human prostate cancer cells. *Molecular Biology Reports*, 2015.
29. Luo, H. et al. Ferulic acid derivatives and their pharmacological activity against cancer cell lines. *Bioorganic Chemistry*, 2021.
30. Gao, J. et al. Ferulic acid induces cell cycle arrest at the S phase in Caco-2 colon cancer cells. *Anticancer Research*, 2020.