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Natural compounds for non-small cell lung cancer treatment: focus on the EGFR signaling pathway

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The EGFR signaling pathway is a critical driver in the occurrence and development of non-small cell lung cancer (NSCLC). However, the inevitable development of acquired resistance to EGFR tyrosine kinase inhibitor (TKI) poses a major therapeutic challenge. Natural compounds, with their intrinsic multi-target capabilities and favorable safety profiles, represent a promising strategy for overcoming this resistance. This review provides a critical synthesis of current evidence for over 33 representative natural compounds—spanning alkaloids, terpenoids, flavonoids, and polyphenols—with a focus on their mechanisms for enhancing TKI efficacy. These include direct inhibition of EGFR activation, regulation of key downstream signaling pathways, and induction of programmed cell death. Furthermore, it also examines how emerging approaches such as nano-delivery systems can overcome the pharmacokinetic limitations of these compounds. Ultimately, this review provides a novel, strategy-oriented perspective by framing natural compounds not merely as standalone agents, but as essential components of rational combination therapies, thereby offering a fresh roadmap for their clinical translation in precision oncology for NSCLC.

KEYWORDS

drug resistance, EGFR signaling pathway, natural compounds, NSCLC, precision therapy

1 Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases (Jeon et al., 2025; Huang et al., 2025). The discovery of activating mutations in the epidermal growth factor receptor (EGFR) gene, such as exon 19 deletions and the L858R point mutation, has transformed the therapeutic landscape. EGFR tyrosine kinase inhibitors (TKIs), including gefitinib, erlotinib, and osimertinib, have become the standard first-line therapy for patients with EGFR-mutant NSCLC, demonstrating remarkable clinical efficacy (Zhou et al., 2025).

However, the long-term benefit of EGFR-TKIs is invariably limited by the development of acquired resistance, which now represents a paramount clinical challenge (Riely et al., 2024; Bouchard and Daaboul, 2025). Resistance mechanisms are complex and heterogeneous, encompassing on-target secondary EGFR mutations (e.g., T790M, C797S), activation of bypass signaling pathways (e.g., MET, AXL), and phenotypic transformations such as epithelial-mesenchymal transition (EMT). This complexity underscores the limitations of sequential single-target therapies and creates an urgent need for innovative strategies that can simultaneously address multiple facets of the resistance network.

In this context, plant-derived natural compounds emerge as a compelling source of novel therapeutic agents. Their diverse chemical structures, intrinsic multi-target

capabilities, and generally favorable safety profiles position them as ideal candidates for developing rational combination therapies aimed at overcoming TKIs resistance (Wang et al., 2016; Andrés et al., 2024; Imtiaz et al., 2025). Rather than acting as mere substitutes for existing TKIs, their strategic value may lie in their ability to modulate the core EGFR pathway alongside its crosstalk networks, thereby resensitizing resistant tumors.

To systematically evaluate this potential, a structured literature search was conducted following a predefined strategy. Databases including PubMed, Google Scholar, and Web of Science were queried for publications from January 2010 to June 2025, using a search strategy that combined key terms from three conceptual groups: (1) disease context (“non-small cell lung cancer” OR “NSCLC”), (2) molecular target/pathology (“EGFR” OR “epidermal growth factor receptor” OR “tyrosine kinase inhibitor resistance”), and (3) intervention (“natural compound” OR “phytochemical” OR “alkaloid” OR “terpenoid” OR “flavonoid” OR “polyphenol”). Studies were screened according to predefined inclusion criteria—original research or seminal reviews focusing on defined natural compounds and their effects on EGFR signaling or TKI resistance in NSCLC—and exclusion criteria, such as non-English publications, studies on other cancer types without direct NSCLC relevance, and reports on uncharacterized herbal mixtures. Eligible studies were critically appraised based on model systems, experimental robustness, mechanistic clarity, and translational relevance, thereby informing a synthesis that highlights both the promise and limitations of the current evidence.

This review, therefore, is framed around a central strategic perspective: to critically assess the evidence for natural compounds—spanning alkaloids, terpenoids, flavonoids, and polyphenols—as multi-targeted partners in combination regimens designed to prevent or reverse EGFR TKI resistance. By synthesizing their mechanisms of action and translational challenges, we aim to provide a roadmap for integrating these promising agents into the precision oncology paradigm for NSCLC.

2 EGFR signaling pathway and its role in NSCLC resistance

The EGFR pathway is a central regulator of cellular growth and survival, and its dysregulation is a principal oncogenic driver in NSCLC. Therapeutic targeting of mutant EGFR with TKIs initially yields high response rates, but the inevitable emergence of acquired resistance remains a major clinical challenge. This section provides a focused overview of EGFR signaling, highlighting the structural and regulatory features most relevant to NSCLC pathogenesis and the development of TKI resistance.

2.1 Key features of EGFR structure and oncogenic mutations

EGFR is a transmembrane receptor with an extracellular ligand-binding domain, a transmembrane anchor, and an intracellular tyrosine kinase domain (Figure 1). Oncogenesis in NSCLC is frequently driven by activating mutations within the kinase domain, most commonly exon 19 deletions and the L858R point mutation, which confer constitutive signaling and sensitivity to first-

and second-generation TKIs (Bellevicine et al., 2014; Castellanos et al., 2017; Rossi and Galetta, 2022). The acquisition of secondary mutations, such as T790M, restores ATP affinity and is a classic mechanism of resistance, later targeted by third-generation TKIs like osimertinib.

2.2 Core signaling cascades and dysregulation in resistance

Ligand binding induces EGFR dimerization and autophosphorylation, recruiting adaptor proteins to activate downstream pathways critical for tumor survival: the RAS/RAF/MEK/ERK (MAPK) and PI3K/Akt/mTOR pathways (Wang et al., 2020; Murphrey et al., 2025) (Figure 2). In the context of resistance, these cascades can be reactivated despite EGFR inhibition. For instance, mutated EGFR variants often exhibit impaired endocytosis, leading to prolonged receptor retention at the membrane and sustained downstream signal output (Sorkin and Duex, 2010; Wee and Wang, 2017). Moreover, persistent activation of pathways like JAK/STAT can promote the expression of anti-apoptotic genes, further contributing to treatment evasion.

2.3 Mechanisms of signal attenuation and their failure

Under physiological conditions, EGFR signaling is precisely controlled through a multi-layered attenuation system to prevent sustained proliferative signaling (Schultz et al., 2023). The primary mechanism involves receptor downregulation via clathrin-mediated endocytosis, where activated EGFR is internalized and sorted for either recycling to the membrane or degradation in lysosomes following ubiquitination by E3 ligases like Cbl (Salih et al., 2025). This degradation pathway, mediated by the ESCRT complex, can shorten EGFR's half-life to under 1 h, providing a rapid termination mechanism for mitogenic signals. Concurrently, protein tyrosine phosphatases (PTPs) function as critical negative regulators by directly dephosphorylating activated EGFR and its downstream effectors, thereby resetting the signaling cascade (Figure 2). Furthermore, intrinsic negative feedback loops—such as ERK-mediated inhibition of upstream SOS and EGFR, or mTORC1/S6K1-induced suppression of IRS1—create self-limiting circuits that maintain signaling homeostasis.

In NSCLC, particularly in the context of TKI resistance, these regulatory mechanisms are frequently subverted. Mutant EGFR variants often exhibit impaired endocytic trafficking and defective ubiquitination, leading to prolonged membrane retention and constitutive signaling (Xia et al., 2025). The tumor microenvironment (TME) may further suppress PTP activity or expression, disrupting the phosphorylation-dephosphorylation balance. Additionally, chronic TKI exposure can dysregulate feedback mechanisms, enabling adaptive survival signaling through alternative nodes. This collective failure of endogenous attenuation not only contributes to oncogenic progression but also establishes a permissive landscape for resistance, wherein tumor cells evade pharmacological inhibition through reinforced signaling networks. Understanding these compromised regulatory checkpoints is therefore essential for designing strategies to restore pathway control.

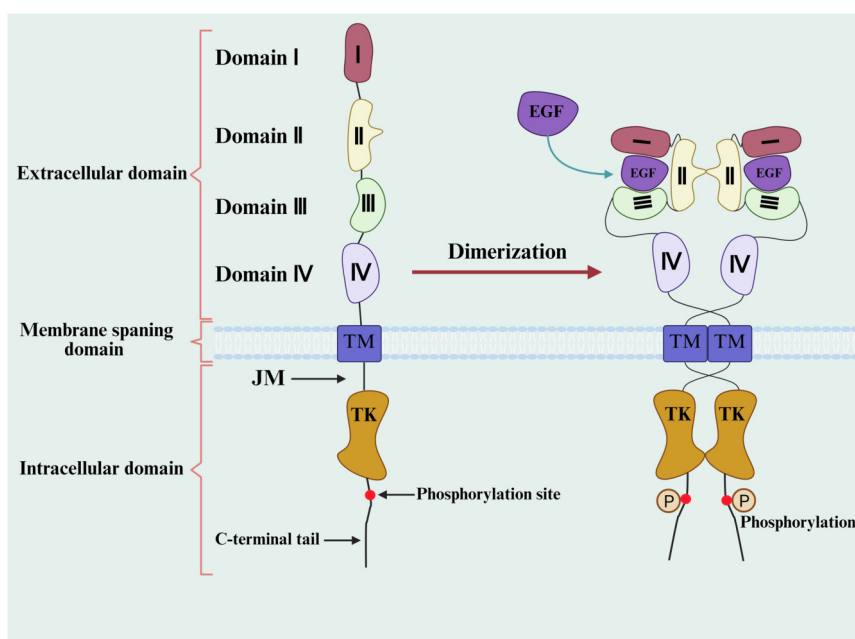


FIGURE 1
The structure of EGFR and activated EGFR.

2.4 Crosstalk with bypass pathways: the nexus of resistance

A primary cause of TKI failure is the activation of alternative signaling networks that bypass EGFR dependence. The MET pathway, through amplification or overexpression, reactivates the shared PI3K/Akt and MAPK cascades, sustaining survival signals independently of EGFR inhibition (Breindel et al., 2013; Reznik et al., 2008). Simultaneously, dynamic crosstalk with the TME establishes a resilient pro-tumorigenic loop: EGFR signaling upregulates immune checkpoint molecules such as PD-L1 to facilitate immune evasion, while inflammatory cytokines from the TME reciprocally enhance EGFR pathway activity, further entrenching therapeutic resistance (Gu et al., 2025). Furthermore, under TKI-induced stress, tumor cells may activate protective autophagy as an adaptive survival mechanism, revealing another actionable axis for therapeutic intervention (Zaryouh et al., 2022). Collectively, this network of bypass signaling, microenvironmental interplay, and stress adaptation constitutes a multifaceted barrier to durable EGFR inhibition. It thus provides a compelling biological rationale for pursuing multi-target therapeutic strategies—including natural compounds with polypharmacological profiles—capable of concurrently suppressing EGFR along with these key resistance axes (Jänne et al., 2015; Soria et al., 2018).

3 Therapeutic challenges and strategic opportunities: rationale for novel interventions

EGFR-TKIs represent a landmark achievement in the precision therapy of EGFR-mutant NSCLC. However, as delineated in Section

2, the long-term efficacy of these agents is universally compromised by the emergence of acquired resistance. This resistance is not monolithic but manifests as a complex network encompassing on-target secondary mutations, activation of bypass tracks, phenotypic transformation, and adaptive remodeling of the tumor microenvironment. This multifaceted nature means that sequential targeting of single resistance mechanisms often leads only to the emergence of the next.

Consequently, next-generation synthetic TKIs and combination regimens, while advancing the field, frequently encounter inherent limitations. These include a narrow spectrum of activity against specific resistance mechanisms, the potential to inadvertently select for novel resistant clones, and the compounded systemic toxicities associated with targeted drug combinations. There exists, therefore, a clear and pressing therapeutic gap: the need for agents capable of concurrently modulating multiple nodes within the oncogenic signaling network to preempt or overcome polyclonal resistance, all while maintaining a manageable safety profile.

This gap presents a strategic opportunity for natural compounds. Inherently equipped with polypharmacological profiles, these plant-derived molecules can simultaneously influence multiple pathways—such as the core EGFR axis, its key downstream effectors, and critical bypass signals. Coupled with their historically favorable toxicity profiles, natural compounds offer a compelling rationale as backbone agents or sensitizers in next-generation combination strategies aimed at durable resistance control. Therefore, rather than presenting a mere catalog of compounds, the following sections are organized to critically evaluate each major class (alkaloids, terpenoids, flavonoids, and polyphenols) through a resistance-centric lens. We will focus on their documented abilities to: (1) co-target core EGFR signaling and key resistance-associated bypass pathways; and (2) synergize with existing

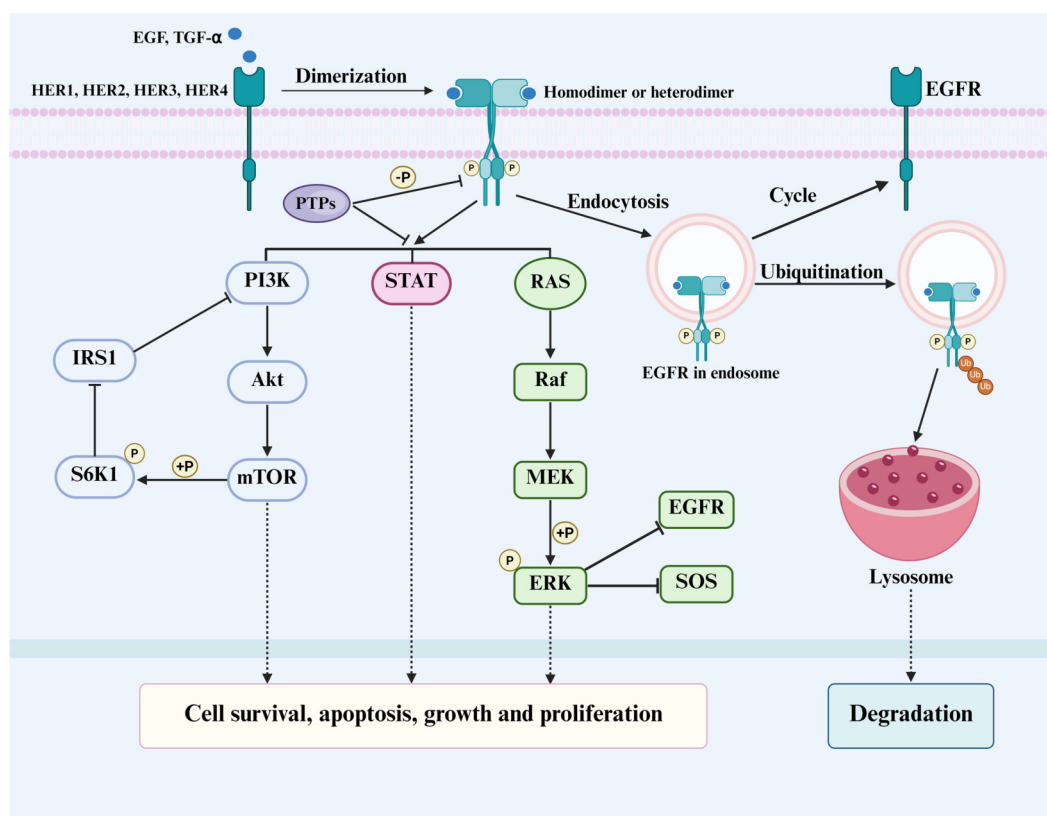


FIGURE 2
The composition, activation, and negative regulation of the EGFR signaling pathway.

TKIs to restore therapeutic sensitivity. This analytical framework directly addresses the multifaceted resistance network outlined above, providing a strategic assessment of their translational potential.

4 Natural compounds targeting the EGFR signaling pathway in NSCLC therapy

The inherent polypharmacology of natural compounds offers a unique strategic advantage against the multifaceted network of EGFR TKI resistance. Unlike single-target synthetic drugs, these molecules can simultaneously modulate the core EGFR pathway and its key bypass tracks, positioning them as ideal candidates for rational combination therapies. This section moves beyond a mere cataloging of effects to provide a critical synthesis of the major classes of natural compounds—alkaloids, terpenoids, flavonoids, and polyphenols—evaluating their mechanisms, preclinical evidence, and most importantly, the translational challenges that must be addressed to realize their clinical potential in NSCLC. A comparative overview of representative compounds, their primary resistance targets, and evidence levels is provided in Table 1.

4.1 Alkaloids

Berberine (BBR) has demonstrated the ability to inhibit the EGFR pathway and synergize with EGFR-TKIs in preclinical

NSCLC models (Cuan et al., 2023; Chen et al., 2021; Chen et al., 2022). However, it is crucial to note that these promising results are largely derived from *in vitro* and animal studies. A significant translational challenge for BBR is its poor oral bioavailability and rapid systemic elimination, which may limit its effective concentration at the tumor site. While some studies report low cytotoxicity in certain normal cells (Zhang et al., 2025), a systematic and comprehensive toxicity profile, including potential hepatotoxicity or gastrointestinal effects at therapeutic doses, has not been fully established in the context of NSCLC treatment. Furthermore, its potential interactions with co-administered drugs via cytochrome P450 enzymes warrant investigation. Therefore, despite its promising multi-target mechanism, BBR's clinical application in NSCLC is contingent upon overcoming these pharmacokinetic hurdles and obtaining robust safety data from well-designed clinical trials.

Piperlongumine (PL) has emerged as a candidate with a dual mechanism against EGFR TKI resistance, functioning as a direct inhibitor of both wild-type and mutant EGFR while concurrently promoting the degradation of the anti-apoptotic protein Mcl-1 via the Akt/GSK3 β axis to induce mitochondrial apoptosis (Liu et al., 2025). Preclinical studies indicate that PL synergizes with gefitinib or erlotinib and demonstrates antitumor activity in osimertinib-resistant xenograft models (Wang S. et al., 2025; Modi and Andey, 2024). However, this promising preclinical profile must be critically evaluated: its efficacy in animal models does not guarantee human translational success, as critical

TABLE 1 Natural compounds targeting the EGFR signaling pathway in NSCLC therapy.

No.	Compound name	Formula	Classification	Evidence level	Upregulates targets	Downregulates targets	Main effects	Effects on EGFR TKI resistance	References
1	Berberine	C ₂₀ H ₁₈ NO ₄ ⁺	Alkaloid	<i>In vitro</i> and <i>in vivo</i>	EMT.	p-EGFR, p-Akt and p-mTOR.	Inhibits proliferation, migration, invasion; induces autophagy or apoptosis	Synergistic sensitization; reversal resistance caused by MET amplification	Chen et al. (2021), Zhang et al. (2025), Ming et al. (2024)
2	Piperlongumine	C ₁₇ H ₁₉ NO ₅	Alkaloid	<i>In vitro</i> and <i>in vivo</i>	Mcl-1 ubiquitination	EGFR mutants, EGFR and PI3K/Akt	Induces apoptosis	Synergistic sensitization; overcoming resistance caused by T790M mutations	Liu et al. (2025), Wang S. et al. (2025)
3	Matrine	C ₁₅ H ₂₄ N ₂ O	Alkaloid	<i>In vitro</i> and <i>in vivo</i>	—	IL-6, JAK1 and STAT3	Induces apoptosis	Synergistic sensitization	Chen et al. (2017)
4	Oxymatrine	C ₁₅ H ₂₄ N ₂ O ₂	Alkaloid	<i>In vitro</i> and <i>in vivo</i>	—	p-EGFR, p-Akt and p-ERK.	Induces cell cycle arrest	Synergistic sensitization	Li W. et al. (2018)
5	Sanguinarine	C ₂₀ H ₁₄ NO ₄ ⁺	Alkaloid	<i>In vitro</i> and <i>in vivo</i>	NOX3	MsrA	Promote oxidation and degradation of EGFR T790M mutant	Overcomes TKIs resistance, notably by reversing the T790M-mediated mechanism	Leung et al. (2016), Saini et al. (2022)
6	Griffithazanone A	C ₁₄ H ₁₁ NO ₄	Alkaloid	<i>In vitro</i> and <i>in vivo</i>	—	PIM1	Induces apoptosis	Synergistic sensitization; reversal of Osimertinib resistance	Xiao et al. (2024)
7	Celastrol	C ₂₉ H ₃₈ O ₄	Triterpenoid	<i>In vitro</i> and <i>in vivo</i>	—	EGFR, PI3K/Akt and RAS/ MAPK.	Induces EGFR degradation; inhibits proliferation; induces apoptosis	Synergistic sensitization; overcomes TKIs resistance	Xu et al. (2016), Dai et al. (2021), Wang et al. (2018), Lee et al. (2019)
8	Ginsenoside Rg3	C ₄₂ H ₇₂ O ₁₃	Triterpenoid	<i>In vitro</i> , <i>in vivo</i> and clinical	—	PD-L1 glycosylation and HIF-1α/ VEGF/EGFR.	Induces autophagy; inhibits proliferation	Synergistic sensitization; overcomes osimertinib resistance	Wang X. J. et al. (2019), Liang et al. (2021), Wang et al. (2024a)
9	β-elemene	C ₁₅ H ₂₄	Triterpenoid	<i>In vitro</i> and <i>in vivo</i>	AMPK/MAPK.	EZH2, lncRNA H19 and TFEB.	Inhibits proliferation; induces apoptosis; induces ferroptosis and autophagy	Synergistic sensitization; reversal of TKIs resistance	Wang et al. (2021), Xu et al. (2023), Zhang R. et al. (2024), Zhao et al. (2024)
10	Ursolic acid	C ₃₀ H ₄₈ O ₃	Triterpenoid	<i>In vitro</i> , <i>in vivo</i> and clinical	—	β-catenin/TCF4/CT45A2, EGFR and JAK2/STAT3	Induces apoptosis; inhibits proliferation, migration and invasion	Synergistic sensitization; overcomes TKIs resistance	Yang et al. (2019), Kang et al. (2021)
11	Betulinic acid	C ₃₀ H ₄₈ O ₃	Triterpenoid	<i>In vitro</i>	—	EGFR and PI3K/Akt/mTOR.	Inhibits proliferation; induces autophagy and apoptosis; induces cell cycle arrest	Synergistic sensitization; overcomes TKIs primary resistance	Ko et al. (2018), Torres-Martinez et al. (2023), Wang H. et al. (2024)
12	Oleanolic acid	C ₃₀ H ₄₈ O ₃	Triterpenoid	<i>In vitro</i>	—	PI3K/Akt/mTOR.	Induces apoptosis	—	Zhou et al. (2024), Chen et al. (2019a)

(Continued)

TABLE 1 Continued

No.	Compound name	Formula	Classification	Evidence level	Upregulates targets	Downregulates targets	Main effects	Effects on EGFR TKI resistance	References
13	Oridonin	C ₂₀ H ₂₈ O ₆	Triterpenoid	<i>In vitro</i> and <i>in vivo</i>	—	EGFR/ERK/MMP-12 and CIP2A/PP2A/Akt	Inhibits proliferation	Overcomes Gefitinib resistance	Xiao et al. (2016)
14	Cucurbitacin B	C ₃₂ H ₄₆ O ₈	Triterpenoid	<i>In vitro</i> and <i>in vivo</i>	—	p-EGFR, PI3K/mTOR and STAT3	Inhibits proliferation; induces apoptosis	—	Khan et al. (2017), Liu et al. (2019)
15	Dihydroartemisinin	C ₁₅ H ₂₄ O ₅	Triterpenoid	<i>In vitro</i> and <i>in vivo</i>	ROS degradation	—	Induces ferroptosis	Overcomes EGFR TKI resistance	Cai et al. (2021), Lai et al. (2023)
16	Costunolide	C ₁₅ H ₂₀ O ₂	Triterpenoid	<i>In vitro</i>	—	MEK1 and AKT1/2	—	Overcomes osimertinib resistance	Tian et al. (2022)
17	Quercetin	C ₁₅ H ₁₀ O ₇	Flavonoid	<i>In vitro</i> and <i>in vivo</i>	—	EGFR, ERK/MEK, Akt/S6K NF-κB and multi-targets RTKs (c-Met, Her-2, AXL, IGF1R)	Inhibits proliferation; induces apoptosis and autophagy	Synergistic sensitization; reversal of TKIs resistance	Ge et al. (2023), Chan et al. (2023), Jiao et al. (2023), Alam et al. (2022), Ramirez et al. (2021)
18	Hyperoside	C ₂₁ H ₂₀ O ₁₂	Flavonoid	<i>In vitro</i> and <i>in vivo</i>	FoxO1	lncRNA CCAT1	Inhibits proliferation; induces apoptosis	—	Hu Z. et al. (2020)
19	Luteolin	C ₁₅ H ₁₀ O ₆	Flavonoid	<i>In vitro</i> and <i>in vivo</i>	—	EGFR, ERK, Akt/mTOR and NF-κB	Induces apoptosis and autophagy	Synergistic sensitization; overcomes TKIs resistance	Zhang J. et al. (2024), Zhang et al. (2022), Ambrose et al. (2018), Hong et al. (2014), Huang G. et al. (2023), Ganthala et al. (2022)
20	Apigenin	C ₁₅ H ₁₀ O ₅	Flavonoid	<i>In vitro</i> and <i>in vivo</i>	—	p-EGFR, EGFR, HIF-1α, c-Myc, PI3K/Akt and RAS/RAF/MEK/ERK.	Inhibits proliferation, migration, invasion; induces apoptosis	Synergistic sensitization; overcomes resistance caused by L858R/T790M mutations	Chang et al. (2018), Chen et al. (2019b)
21	Dihydromyricetin	C ₁₅ H ₁₂ O ₈	Flavonoid	<i>In vitro</i> and <i>in vivo</i>	—	EGFR, Akt, survivin	Induces apoptosis	Overcomes TKIs resistance	Li et al. (2023)
22	Hydroxygenkwanin	C ₁₆ H ₁₂ O ₆	Flavonoid	<i>In vitro</i> and <i>in vivo</i>	EGFR ubiquitination and degradation	STAT3, Akt and ERK.	Induces apoptosis	Overcomes TKIs resistance	Leu et al. (2020)
23	Curcumin	C ₂₁ H ₂₀ O ₆	Polyphenol	<i>In vitro</i> and <i>in vivo</i>	—	EGFR, ERK/MEK, Akt/S6K and multi-targets RTKs (c-Met, Her-2, AXL, IGF1R)	Inhibits proliferation; induces apoptosis and autophagy	Synergistic sensitization; reversal of TKIs resistance	Ye et al. (2012), Chen P. et al. (2019), Zhang et al. (2019), Li et al. (2013), Wada et al. (2015)
24	Resveratrol	C ₁₄ H ₁₂ O ₃	Polyphenol	<i>In vitro</i>	AMPK.	p-EGFR, EGFR, ERK/MEK, PI3K/Akt and Akt/mTOR.	Inhibits proliferation; induces apoptosis, autophagy and senescence	Synergistic sensitization; reversal of TKIs resistance	Li W. et al. (2016), Zhu et al. (2015), Lu et al. (2019), Zhao et al. (2023), Fan et al. (2015)
25	EGCG	C ₂₂ H ₁₈ O ₁₁	Polyphenol	<i>In vitro</i> and <i>in vivo</i>	EGFR degradation	MAPK, PI3K/Akt and STAT3	Inhibits proliferation, migration; induces cell cycle arrest and apoptosis	Synergistic sensitization; reversal of TKIs resistance	Minnelli et al. (2020), Meng et al. (2019), Minnelli et al. (2021), Polonio-Alcalá et al. (2025)

(Continued)

TABLE 1 Continued

No.	Compound name	Formula	Classification	Evidence level	Upregulates targets	Downregulates targets	Main effects	Effects on EGFR TKI resistance	References
26	Gallic Acid	C ₇ H ₆ O ₅	Polyphenol	<i>In vitro</i> and <i>in vivo</i>	EGFR degradation	p-EGFR, PI3K/Akt and RAS/ERK.	Inhibits proliferation; induces apoptosis	Overcomes TKIs resistance	Kang et al. (2020), Wang and Bao (2020), Phan et al. (2016)
27	Ellagic Acid	C ₁₄ H ₆ O ₈	Polyphenol	<i>In vitro</i> and <i>in vivo</i>	—	EGFR.	Inhibits proliferation; induces apoptosis	Synergistic sensitization; reversal of TKIs resistance	Ayaz et al. (2022), Xie et al. (2020b)
28	Shikonin	C ₁₆ H ₁₆ O ₅	Others	<i>In vitro</i> and <i>in vivo</i>	ROS and EGFR degradation	PI3K/Akt and MEK/ERK	Induces apoptosis	Synergistic sensitization	Li et al. (2017), Hsieh et al. (2017), Hu et al. (2020b)
29	Silibinin	C ₂₅ H ₂₂ O ₁₀	Others	<i>In vitro</i> and <i>in vivo</i>	—	EGFR, EMT, PI3K/Akt and JAK/STAT.	Inhibits proliferation, migration and invasion	Synergistic sensitization; overcomes acquired resistance	Wang (2025), Rugamba et al. (2021)
30	Psorachromene	C ₂₀ H ₁₈ O ₄	Others	<i>In vitro</i>	—	EGFR.	Inhibits proliferation	—	Wang et al. (2022)
31	Xanthohumol	C ₂₁ H ₂₂ O ₅	Others	<i>In vitro</i> and <i>in vivo</i>	Ets-1 ubiquitination	c-Met.	Inhibits proliferation	Overcomes Osimertinib resistance	Ma et al. (2024)
32	Genipin	C ₁₁ H ₁₄ O ₅	Others	<i>In vitro</i>	—	EGFR/JAK1/STAT3	Inhibits migration and invasion; induces apoptosis	—	Kim et al. (2025)
33	α-Mangostin	C ₂₄ H ₂₆ O ₆	Others	<i>In vitro</i>	—	EGFR/STAT3	Inhibits proliferation	—	Wang J. et al. (2025)

pharmacokinetic parameters—including bioavailability, tissue distribution, and human-specific metabolism—remain largely uncharacterized. Furthermore, claims of favorable tolerability are based on limited short-term animal observations and do not constitute a comprehensive safety assessment, leaving potential organ toxicity and off-target effects unexamined. Thus, while PL represents a mechanistically compelling preclinical lead, its advancement as a viable clinical strategy necessitates rigorous pharmacologic and toxicologic investigation to address these fundamental translational hurdles.

Matrine, oxymatrine, sanguinarine, and griffithazanone A exemplify the diverse mechanisms through which alkaloids may counteract EGFR TKI resistance. Matrine appears to modulate the tumor microenvironment and apoptosis in T790M-mutant cells by reducing IL-6 and downregulating Bcl-2 via the JAK1/STAT3 pathway, demonstrating preclinical synergy with afatinib (Chen et al., 2017). Oxymatrine directly suppresses phosphorylation of diverse EGFR forms (wild-type, L858R/T790M, Ex19del) and their downstream Akt/ERK activity, leading to cell cycle arrest (Li W. et al., 2018). Sanguinarine employs a redox-based strategy, inducing ROS to specifically degrade the EGFR T790M mutant (Leung et al., 2016), and computational studies suggest high-affinity binding to EGFR (Saini et al., 2022). Griffithazanone A, although not a direct EGFR inhibitor, targets the upstream kinase PIM1 to enhance apoptosis and shows synergistic effects with gefitinib and osimertinib (Xiao et al., 2024). However, the translational potential of these compounds is constrained by significant gaps in characterization. For matrine and oxymatrine, promising *in vivo* efficacy and reported low toxicity in xenograft models remain preliminary, as critical pharmacokinetic parameters—including oral bioavailability and human metabolic profiles—are undefined, and their long-term safety is unestablished. Sanguinarine's ROS-mediated mechanism raises inherent safety concerns regarding potential off-target oxidative damage to normal tissues, a risk not yet rigorously evaluated. Its computationally predicted high binding affinity also requires empirical validation in relevant biological systems. Similarly, griffithazanone A's action through PIM1 inhibition may lead to broader signaling perturbations with unknown systemic consequences. Collectively, while these alkaloids present mechanistically compelling preclinical leads, their progression is hindered by a lack of comprehensive drug-like property assessment and safety pharmacology, underscoring the necessity of addressing these fundamental gaps prior to clinical development.

4.2 Terpenoids

Celastrol, a natural triterpene, demonstrates a multi-mechanistic approach to overcoming EGFR TKI resistance in preclinical NSCLC models by inducing EGFR degradation to suppress downstream PI3K/Akt and RAS/MAPK signaling, thereby inhibiting proliferation and promoting apoptosis (Xu et al., 2016; Dai et al., 2021). It exhibits synergistic effects with gefitinib or osimertinib, enhancing tumor growth suppression *in vivo* (Wang et al., 2018; Lee et al., 2019; Fan et al., 2014), and operates through additional pathways including autophagy regulation and downregulation of the resistance-linked protein SHOC2 (Xu et al., 2016; Terai et al., 2021). Advanced delivery strategies, such as glutathione-responsive

nano-drug systems co-delivering celastrol and gefitinib, have been developed to concurrently target Hsp90 and degrade client proteins like EGFR and Akt, showing promise against resistant cells in preclinical settings (Xie X. et al., 2020). However, the translation of celastrol faces a critical barrier rooted in its well-documented narrow therapeutic index and associated systemic toxicity concerns, including potential hepatotoxicity and cardiotoxicity. While innovative nano-formulations aim to mitigate these risks by improving tumor targeting, they remain at an early experimental stage. Consequently, celastrol exemplifies a potent natural lead compound whose clinical advancement is contingent not merely on its multi-target efficacy but on the successful development of delivery platforms that can decisively separate its antitumor activity from its adverse safety profile in humans.

Ginsenoside Rg3 represents a notable case where a natural compound has generated both preclinical mechanistic insights and preliminary clinical observations in NSCLC. A clinical retrospective study reported that combining EGFR-TKIs with Rg3 significantly prolonged progression-free survival (PFS) and improved objective response rates (ORR), suggesting a potential sensitizing effect in patients (Li Y. et al., 2016). Mechanistically, preclinical research indicates Rg3 operates through multiple avenues: it enhances TKI sensitivity by inhibiting protective autophagy, directly suppresses EGFR-mediated proliferation signals, modulates the tumor immune microenvironment by inhibiting PD-L1 glycosylation, and when formulated as a nano-drug with osimertinib, targets the HIF-1 α /VEGF/EGFR axis to overcome resistance (Wang X. J. et al., 2019; Liang et al., 2021; Wang W. et al., 2024; Jiang et al., 2025). Furthermore, Rg3 has been shown to reduce EGFR gene copy number and protein expression in mutant cells (Lv et al., 2025). While the clinical data provides a valuable signal, it originates from a retrospective analysis and requires prospective validation. The major impediment to Rg3's translation is its exceptionally poor oral bioavailability, which severely limits the clinical relevance of its preclinical activity. Although innovative nano-formulations represent a promising solution to this pharmacokinetic challenge, they are not yet clinically established (Wang W. et al., 2024). Therefore, the future of Rg3 depends on successfully addressing its delivery limitations through pharmaceutical engineering and confirming its synergistic benefits in controlled clinical trials.

β -Elemene demonstrates a multi-pathway approach to overcoming EGFR TKI resistance in preclinical NSCLC models. Research indicates its activity is mediated through the downregulation of EZH2 to enhance gefitinib's effects, activation of AMPK and MAPK pathways to promote apoptosis in resistant cells, and modulation of lncRNA H19 to induce ferroptosis and suppress protective autophagy, thereby increasing erlotinib sensitivity (Cheng et al., 2018; Wang et al., 2021; Xu et al., 2023; Zhang R. et al., 2024). A distinct mechanism involving TFEB-mediated GPX4 degradation has also been identified, suggesting potential utility in EGFR-wildtype contexts (Zhao et al., 2024). Despite promising *in vitro* synergy, β -Elemene's translation faces defined challenges. Its established clinical use as an intravenous emulsion for palliative care underscores its poor pharmacokinetic properties, including negligible oral bioavailability. The relevance of its diverse cellular mechanisms to human tumors, and its safety profile in combination with targeted therapies, remain unvalidated.

Thus, while mechanistically interesting, β -Elemene requires advanced formulation strategies and rigorous clinical evaluation to assess its utility in modern TKI-based regimens.

Ursolic acid (UA) demonstrates multi-target activity against EGFR TKI resistant NSCLC in preclinical studies. It shows specificity against T790M-mutant cells by downregulating the β -catenin/TCF4/CT45A2 pathway to induce apoptosis (Yang et al., 2019), directly binds to EGFR to inhibit its phosphorylation and downstream JAK2/STAT3 signaling, concurrently reducing PD-L1 expression, and has been engineered into nano-formulations for combination with chemotherapeutics or erlotinib to enhance delivery and efficacy (Yang et al., 2019; Kang et al., 2021; Fu et al., 2022; Wang Z. et al., 2025). The multi-mechanistic profile of UA is pharmacologically promising, yet its development is constrained by inherent physicochemical and pharmacokinetic limitations. As a typical pentacyclic triterpenoid, UA suffers from extremely low aqueous solubility and poor oral bioavailability, which fundamentally restrict its effective *in vivo* application. The reported nano-formulations represent essential but early-stage solutions to this delivery problem (Fu et al., 2022; Wang Z. et al., 2025). Furthermore, while UA appears to modulate immune checkpoints like PD-L1, the functional consequences and potential immunomodulatory risks of this effect in a therapeutic context are unexplored (Kang et al., 2021). Therefore, UA exemplifies a compound whose translational path is unequivocally dependent on pharmaceutical innovation to overcome delivery barriers, and whose promising multi-target pharmacology requires validation in models that account for its formulated pharmacokinetics.

Betulinic acid (BA) exhibits promising anti-NSCLC activity through EGFR pathway modulation. Preclinical studies indicate BA enhances apoptosis and autophagy in TKI-resistant cells when combined with EGFR-TKIs (Ko et al., 2018). A BSA-based nanocarrier co-delivering BA and doxorubicin showed synergistic effects and EGFR downregulation (Torres-Martinez et al., 2023). Notably, a 2024 study combining molecular docking and experimental validation demonstrated that BA directly binds to the ATP-binding site of wild-type EGFR, inhibiting its autophosphorylation and downstream PI3K-Akt-mTOR signaling, thereby synergizing with TKIs to overcome primary resistance in wt-EGFR models (Wang H. et al., 2024). While BA's mechanism of action—particularly its direct binding to wt-EGFR—is mechanistically compelling, its clinical translation faces defined pharmacokinetic hurdles. Like many triterpenoids, BA is expected to have poor aqueous solubility and suboptimal bioavailability, which are not adequately addressed in the current literature. The demonstrated nano-formulation is a necessary but preliminary step (Torres-Martinez et al., 2023). Furthermore, the specificity of its binding to wt-EGFR over mutant forms, and the potential for off-target effects given its multi-pathway activity, require careful evaluation. Therefore, BA represents an advanced preclinical lead whose value hinges on concurrent progress in pharmaceutical formulation to enable reliable systemic delivery and thorough investigation of its selectivity and safety profile in relevant *in vivo* models.

A range of terpenoids—including Oleanolic Acid, Oridonin, Cucurbitacin B, Dihydroartemisinin, and Costunolide—demonstrate the ability to counteract EGFR TKI resistance through distinct

mechanisms in preclinical NSCLC models. These include direct pathway inhibition (e.g., PI3K-Akt-mTOR suppression by Oleanolic Acid), multi-target blockade (e.g., concurrent MEK1 and Akt1/2 inhibition by Costunolide), and induction of alternative cell death modalities such as ferroptosis by Dihydroartemisinin (Silva et al., 2015; Yan et al., 2018; Gao et al., 2024; Zhou et al., 2024; Chen et al., 2019a; Xiao et al., 2016; Khan et al., 2017; Liu et al., 2019). While this group of compounds exemplifies the rich mechanistic diversity within terpenoids, their collective translation is hindered by shared and compound-specific challenges. A principal barrier is the typically unfavorable pharmacokinetic profile common to many terpenoids, characterized by poor solubility, rapid metabolism, and limited bioavailability. With the exception of the semi-synthetic artemisinin derivative Dihydroartemisinin, most remain far from clinical evaluation for NSCLC. Furthermore, strategies like ferroptosis induction or dual kinase inhibition, though mechanistically novel, carry undefined risks of off-target toxicity and systemic metabolic disruption that have not been adequately assessed (Cai et al., 2021; Lai et al., 2023; Tian et al., 2022). Therefore, these compounds largely represent early-stage chemical probes that illuminate resistance biology; their advancement into therapeutics would require substantial medicinal chemistry optimization and comprehensive preclinical safety studies tailored to their specific mechanisms.

4.3 Flavonoids

Quercetin demonstrates a broad-spectrum, multi-target approach to overcoming EGFR TKI resistance in preclinical models. It directly inhibits EGFR phosphorylation and downstream ERK/MEK and Akt/S6K pathways, induces autophagy-dependent cell death, and concurrently blocks key bypass receptors such as c-Met, Her-2, AXL, and IGF1R (Ge et al., 2023; Chan et al., 2023; Jiao et al., 2023; Alam et al., 2022). This multi-pronged action translates to synergistic cytotoxicity and apoptosis with erlotinib in resistant cells (Ramirez et al., 2021). To address its primary pharmacokinetic flaw of extremely low bioavailability, advanced formulations like anti-EGFR antibody-conjugated nanovesicles have been developed, which improve targeting and efficacy in animal models (Huang et al., 2021; Cui et al., 2022). The derivative hyperoside also shows activity against T790M-positive cells via the FoxO1/CCAT1 axis (Hu Z. et al., 2020). Quercetin epitomizes the classic challenge in natural product drug development: potent and mechanistically diverse *in vitro* activity that is rendered almost irrelevant by abysmal pharmacokinetic properties. Its well-documented negligible oral bioavailability and rapid systemic clearance mean that the effective concentrations used in cellular studies are pharmacologically unachievable in humans via conventional administration. The sophisticated nano-formulations reported are not mere improvements but essential prerequisites for any serious therapeutic consideration, yet they remain in early preclinical testing (Huang et al., 2021; Cui et al., 2022). Furthermore, its inhibition of a wide array of RTKs, while beneficial for overcoming resistance, significantly increases the risk of unpredictable off-target effects and drug-drug interactions (Alam et al., 2022). Therefore, quercetin serves as a compelling proof-of-concept molecule for multi-target therapy, but its future

lies not in the compound itself, but in the successful clinical translation of the advanced delivery technologies designed to rescue it.

Luteolin demonstrates a multi-modal mechanism against EGFR TKI resistance in preclinical NSCLC models. It directly binds to and inhibits EGFR activation, blocking downstream ERK/MEK and Akt/mTOR pathways, while also modulating apoptosis regulators and inducing autophagy (Zhang J. et al., 2024; Zhang et al., 2022; Ambrose et al., 2018; Hong et al., 2014; Huang G. et al., 2023). These actions contribute to its synergistic effects with erlotinib in resistant cells (Ganthala et al., 2022). Computational studies support its direct interaction with EGFR, and network pharmacology analyses suggest broader effects on pathways like PI3K-Akt/MDM2-p53 (Jiao et al., 2023; Maiti et al., 2021; Yi et al., 2022; Ye et al., 2023). Despite its promising multi-target profile *in vitro*, luteolin's therapeutic potential is critically limited by its extremely poor bioavailability, a characteristic flaw of many flavonoids. The effective concentrations used in mechanistic studies are pharmacologically unachievable with conventional oral dosing due to rapid metabolism and clearance. While its binding to EGFR is computationally validated, this interaction must be confirmed in physiologically relevant systems that account for its pharmacokinetic behavior. Furthermore, its broad effects on multiple core pathways increase the risk of unpredictable biological consequences and potential toxicity when combined with TKIs (Yi et al., 2022; Ye et al., 2023). Therefore, luteolin primarily serves as a valuable tool compound for validating multi-target inhibition strategies; its development as a drug requires prior solutions to its inherent delivery challenges through advanced formulation or prodrug strategies.

Apigenin demonstrates a multi-target mechanism against EGFR TKI resistant NSCLC in preclinical models. It inhibits EGFR phosphorylation and downstream PI3K/Akt and MAPK pathways, while also suppressing EMT mediators like Snail/Slug (Chang et al., 2018). In combination with gefitinib, apigenin disrupts metabolic (HIF-1 α , c-Myc) and autophagic adaptations in L858R/T790M-mutant cells to induce apoptosis (Chen et al., 2019b). As a key component of the compound Feiyaning, it has also been shown to reverse resistance by targeting the IGF1R-PI3K-Akt axis (Han et al., 2025). Apigenin's promising preclinical synergy is overshadowed by the severe pharmacokinetic limitations common to its flavonoid class, including negligible oral bioavailability and rapid systemic elimination. The effective concentrations required to observe its multi-pathway effects *in vitro* are unlikely to be achieved or sustained in human tumors. Furthermore, its activity against targets like IGF1R, while mechanistically valuable for overcoming resistance, expands its pharmacological footprint and raises concerns about off-target effects and an increased risk of drug-drug interactions in a clinical combination setting (Han et al., 2025). Therefore, apigenin exemplifies a compound whose translational feasibility is currently low, serving more as a mechanistic blueprint for multi-pathway inhibition than as an immediate drug candidate. Its potential utility would depend on the development of formulations that dramatically enhance its bioavailability and stability.

Dihydromyricetin (DHM) and hydroxygenkwanin (HGK) represent flavonoids that target EGFR stability to overcome resistance. DHM promotes the ubiquitin-mediated degradation of

survivin, suppressing signaling from both wild-type and mutant EGFR (Li et al., 2023). HGK induces apoptosis by promoting EGFR ubiquitination and degradation, concurrently inhibiting downstream STAT3, Akt, and ERK pathways, with transcriptomic data supporting its role in modulating ubiquitination networks (Leu et al., 2020). Preclinical models report antitumor activity for both compounds. While the mechanism of inducing EGFR degradation is pharmacologically attractive, the development of DHM and HGK is constrained by the same critical limitations that plague most flavonoids: very poor bioavailability and uncharacterized human pharmacokinetics. Claims of "low cytotoxicity to normal cells" are based on limited *in vitro* assays and do not constitute an adequate safety profile for therapeutic development. Promoting protein degradation via the ubiquitin-proteasome system, as both compounds appear to do, carries a non-specific risk of disrupting the degradation of essential cellular proteins, a potential toxicity that has not been evaluated. Therefore, DHM and HGK are early-stage tool compounds that validate EGFR degradation as a resistance strategy; their advancement would require extensive medicinal chemistry to improve drug-like properties and thorough investigations into degradation selectivity and systemic safety.

4.4 Polyphenols

Curcumin, extensively studied for its broad multi-target activity, shows preclinical promise in countering EGFR TKI resistance by inhibiting EGFR phosphorylation, downstream ERK/MEK and Akt/S6K pathways, and concurrently blocking bypass receptors such as c-Met, Her-2, and AXL (Ye et al., 2012). These mechanisms contribute to its synergistic induction of apoptosis and autophagy-dependent cell death in combination with erlotinib in resistant models (Chen P. et al., 2019; Zhang et al., 2019; Li et al., 2013). To overcome its well-documented pharmacokinetic deficiencies—negligible oral bioavailability, rapid metabolism, and poor stability—research has advanced along two parallel paths: the development of synthetic analogs and hybrids (e.g., WZ35, CP compounds) with enhanced potency and stability, and the design of sophisticated nano-delivery systems (e.g., antibody-conjugated nanovesicles) that improve targeted delivery and *in vivo* efficacy (Chen P. et al., 2019; Zhang et al., 2019; Li et al., 2013). Computational studies further support its direct binding to EGFR mutants, and additional mechanisms such as Ca²⁺/calmodulin-mediated EGFR degradation have been identified (Rajeev et al., 2025; Li et al., 2025). Curcumin exemplifies a natural compound whose compelling multi-target pharmacology *in vitro* is fundamentally disconnected from clinical feasibility due to intrinsic pharmacokinetic failures. Consequently, the translational focus has shifted decisively from the native molecule toward second-generation engineered analogs and advanced delivery platforms that aim to preserve its polypharmacological logic while conferring drug-like properties. Claims regarding its safety profile in animal models are thus largely incidental, as the parent compound cannot achieve pharmacologically relevant exposures in humans (Wang S. et al., 2025). The future of curcumin-based intervention in NSCLC therefore rests not on curcumin itself, but on these rationally designed successors that seek to transform its mechanistic promise into a therapeutically viable entity.

Resveratrol demonstrates multi-modal activity against EGFR TKI resistance in preclinical NSCLC models. It directly inhibits EGFR phosphorylation and downstream ERK/MEK and Akt/mTOR pathways, while also modulating cell death and senescence through calcium-mediated SERCA inhibition, ER stress, and AMPK activation (Li W. et al., 2016; Zhu et al., 2015; Lu et al., 2019). These actions contribute to its synergistic effects with gefitinib, partly by inhibiting drug efflux transporters. To overcome its poor bioavailability, derivatives with improved potency (e.g., TMS, DMU-212, YI-12) have been developed, as well as nano-formulations for co-delivery with chemotherapy (Zhao et al., 2023; Soonthonsrima et al., 2025; Song et al., 2018). Despite its well-characterized multi-target pharmacology, resveratrol's therapeutic potential is critically constrained by its unfavorable pharmacokinetics, including low oral bioavailability, rapid conjugation, and short half-life. The promising activities observed *in vitro* and in animal models often employ concentrations or formulations not attainable in humans via conventional administration. The development of more potent derivatives and advanced delivery systems is a direct and necessary response to these limitations. However, these optimized variants themselves remain in early preclinical stages. Furthermore, resveratrol's pleiotropic effects—such as SERCA inhibition and transporter modulation—while mechanistically valuable, introduce a significant risk of off-target physiological disruption and complex drug interactions. Therefore, resveratrol serves primarily as a pharmacophore for drug design; its clinical translation in oncology depends on the success of its engineered successors in achieving a favorable balance between multi-target efficacy and pharmacokinetic/safety profiles.

Epigallocatechin gallate (EGCG) is a well-characterized polyphenol that directly targets the EGFR ATP-binding site, leading to receptor internalization and degradation, and suppression of downstream MAPK, PI3K/Akt, and STAT3 pathways (Minnelli et al., 2020; Meng et al., 2019). It inhibits proliferation, induces apoptosis, and shows anti-metastatic activity across multiple NSCLC cell lines (Minnelli et al., 2021; Polonio-Alcalá et al., 2025). EGCG synergizes with EGFR-TKIs and antibodies to overcome resistance, and derivatives such as PBOG, EGCG-erlotinib conjugates have been designed for improved targeting (Wang J. et al., 2019; Zhou et al., 2023; Sun et al., 2022; Zi et al., 2025). Computational studies support its binding to EGFR and guide analog design (Alam et al., 2022; Bommu et al., 2019). Despite its clear mechanistic rationale and promising preclinical data, EGCG's clinical development for NSCLC faces substantial hurdles. Its low oral bioavailability, extensive metabolism, and instability at physiological pH severely limit the achievable systemic concentrations, making the effective doses used in many *in vitro* studies pharmacologically irrelevant in humans. While combination studies in mice show promise, these models often use non-physiological administration routes or doses (Meng et al., 2019; Huang Y. et al., 2023). The reported “favorable safety profile” in limited trials pertains to its consumption as a dietary component, not to the high-dose, targeted therapeutic regimens required for oncology, where toxicity concerns (e.g., hepatotoxicity at high doses) emerge. Furthermore, its direct EGFR binding may be compromised by common resistance mutations (Minnelli et al., 2020). Therefore, EGCG currently serves as a lead compound

demonstrating the feasibility of natural product-based EGFR inhibition; its therapeutic future likely depends on the development of bioavailable analogs or prodrugs that overcome its pharmacokinetic shortcomings while maintaining target specificity.

Gallic acid (GA) demonstrates a multi-mechanistic profile against EGFR TKI resistance, including direct inhibition of EGFR phosphorylation and downstream PI3K/Akt and RAS/ERK pathways, specific blockade of Src-Stat3 signaling, and promotion of EGFR degradation via the proteasome in mutant cells (Kang et al., 2020; Wang and Bao, 2020; Phan et al., 2016; Nam et al., 2016). It also modulates immune-related pathways by upregulating p53/miR-34a and downregulating PD-L1 (Kang et al., 2020). Preclinical xenograft models support its antitumor efficacy (Phan et al., 2016). While GA's diverse mechanisms are pharmacologically appealing, its development is constrained by incomplete pharmacokinetic characterization and unaddressed delivery challenges. As a small phenolic acid, its absorption, distribution, metabolism, and excretion (ADME) properties in the context of cancer therapy are poorly defined, making it unclear whether effective *in vivo* concentrations can be achieved. Furthermore, its activity in promoting EGFR degradation and modulating PD-L1, while mechanistically synergistic, increases the risk of unintended biological effects and potential immune-related adverse events that have not been evaluated (Zhou et al., 2025; Nam et al., 2016). Therefore, GA remains an early-stage compound whose translational potential depends on comprehensive ADME studies, safety pharmacology assessments, and potentially formulation strategies to ensure targeted delivery and minimize systemic toxicity.

Ellagic acid (EA) shows a distinct profile in countering EGFR TKI resistance. It exhibits strong binding affinity for EGFR, reportedly exceeding some standard therapies, to directly inhibit its activity (Ayaz et al., 2022). Notably, EA displays selective anti-proliferative effects against TKI-resistant NSCLC cells while sparing sensitive ones. Its combination with erlotinib demonstrates synergistic antitumor activity in both cellular and xenograft models of EGFR-mutant NSCLC (Xie C. et al., 2020). EA's promising selectivity and synergy *in vitro* are offset by significant and poorly characterized pharmacokinetic barriers. As a high-molecular-weight polyphenol, it is expected to have very low oral bioavailability, and its absorption, metabolism, and tissue distribution in the context of cancer treatment have not been systematically studied. The claim of superior binding affinity requires validation in physiologically relevant systems (Ayaz et al., 2022). Furthermore, its selective activity against resistant cells, while intriguing, raises questions about the underlying mechanism and whether this selectivity translates to a therapeutic window *in vivo*, or if it merely reflects differential baseline metabolic or uptake properties (Xie C. et al., 2020). Therefore, EA represents an interesting but early-stage candidate whose development necessitates thorough pharmacokinetic investigation and mechanistic deconvolution of its observed selectivity before its adjuvant potential can be realistically assessed.

4.5 Others

Shikonin (a naphthoquinone) and silibinin (a flavonolignan), along with other compounds like xanthohumol, represent diverse

chemical classes with activity against EGFR TKI resistance. Shikonin induces ROS-mediated apoptosis and EGFR degradation, showing synergy with TKIs in both mutant and wild-type EGFR contexts (Li et al., 2017; Hsieh et al., 2017; Hu X. et al., 2020; Tang et al., 2018; Li B. et al., 2018; Li Y. L. et al., 2018). Silibinin inhibits EGFR downstream pathways (PI3K/Akt, JAK/STAT) and reverses EMT by modulating specific microRNAs, with its bioavailability improved by formulation as silibinin-meglumine (Wang, 2025; Rugamba et al., 2021; Hou et al., 2018; Cufi et al., 2013a; Cufi et al., 2013b; Corominas-Faja et al., 2013). Other agents, such as xanthohumol, target bypass resistance by promoting Ets-1 degradation to disrupt c-Met signaling (Ma et al., 2024). The promising multi-target activities of these compounds are counterbalanced by significant and often unaddressed developmental challenges. For shikonin, its potent ROS induction is a double-edged sword, posing a clear risk of off-target toxicity and oxidative damage to normal tissues—a safety concern that has not been adequately evaluated in preclinical models. While silibinin-meglumine addresses solubility, the broader pharmacokinetic profile, long-term safety, and optimal dosing for combination therapy with TKIs remain undefined (Corominas-Faja et al., 2013). Many of the other mentioned compounds such as psorachromene and genipin derivatives are at an early proof-of-concept stage with no available data on absorption, metabolism, or toxicity (Wang et al., 2022; Kim et al., 2025). Therefore, this group of compounds collectively illustrates a spectrum of interesting mechanistic leads; however, their progression beyond basic research requires dedicated investigation into their drug-like properties, selectivity, and safety, moving from phenotypic observations to thorough translational pharmacology.

5 Discussion

The extensive preclinical evidence synthesized in this review underscores the compelling rationale for exploring natural compounds as strategic partners to overcome EGFR TKI resistance in NSCLC. Their inherent polypharmacology enables the simultaneous targeting of the core EGFR pathway and its key resistance-associated bypass tracks, a theoretical advantage over sequential single-target therapies. However, the translation of this mechanistic promise into clinical practice is fraught with systemic challenges. This discussion moves beyond reiterating mechanisms to critically evaluate the primary translational barriers and propose a strategic roadmap for future development.

5.1 The translational chasm: systemic barriers beyond efficacy

The principal obstacle to clinical translation lies not in a lack of *in vitro* efficacy, but in a pervasive disconnect between promising cellular activity and viable drug-like properties. Most compounds reviewed—particularly flavonoids, polyphenols, and many terpenoids—suffer from extremely poor oral bioavailability, owing to low aqueous solubility, rapid phase II metabolism, and swift systemic clearance (Smeu et al., 2025). Consequently, effective concentrations demonstrated in cell culture are often pharmacologically unattainable in human plasma using the native

compounds, rendering much reported *in vitro* synergy clinically irrelevant without deliberate pharmaceutical intervention. Furthermore, claims of “favorable safety profiles” are typically based on limited acute toxicity assays or historical use, rather than rigorous, oncology-focused toxicology studies. Critical gaps persist concerning chronic toxicity, organ-specific liabilities such as hepatotoxicity from high-dose EGCG or celastrol, and mechanism-based risks—including off-target oxidative damage induced by ROS-promoting agents like shikonin and dihydroartemisinin, or disruption of the ubiquitin-proteasome system by compounds that enhance protein degradation. Additionally, the potential for drug-drug interactions with concurrently administered TKIs, often mediated through CYP450 enzyme modulation, remains largely uncharacterized. Beyond these scientific hurdles, the development of complex natural products also faces unique regulatory challenges, including batch-to-batch variability, precise quantification of active constituents, and demonstration of pharmacokinetic reproducibility—complications that are exacerbated when the active moiety includes metabolites or multiple synergistic components.

5.2 Strategic pathways to clinical translation

To bridge this translational chasm, future research must pivot decisively from descriptive mechanism-finding to problem-solving engineering and rigorous clinical science. Overcoming pharmacokinetic limitations is non-optional and should be prioritized through two main engineering strategies. First, the development of advanced drug delivery systems, particularly nanotechnology-based platforms such as ligand-targeted nanoparticles and exosomes, is essential. These systems can enhance solubility, protect compounds from metabolism, promote tumor-selective delivery, and enable the controlled co-delivery of natural compound-TKI combinations, as evidenced in preliminary studies with celastrol and Rg3. Second, medicinal chemistry-driven optimization represents a more direct developmental path, involving the creation of synthetic analogs or prodrugs (e.g., curcumin hybrid CP, resveratrol derivative TMS) that retain the core multi-target pharmacophore while significantly improving chemical stability, potency, and overall pharmacokinetic properties.

Concurrently, the field must generate robust, translational evidence beyond model system observations. This necessitates hierarchical preclinical validation using pharmacologically relevant models—such as a “resistance model repository” of patient-derived organoids and xenografts—that employ the intended clinical formulations. Furthermore, early-phase trials must be meticulously designed with the primary objectives of establishing the pharmacokinetic profile and maximum tolerated dose of novel formulations in combination with standard TKIs. Promising candidates with preliminary clinical signals, like Ginsenoside Rg3, warrant prospective, biomarker-driven phase I/II trials to formally assess combination safety and efficacy.

Finally, leveraging enabling technologies is crucial for precise target and patient selection. Artificial intelligence and computational tools can accelerate the identification and ADMET prediction of natural product-inspired leads, guiding rational design. Complementing this, the development of

mechanistic biomarkers—such as specific mutation profiles or expression levels of bypass proteins—is vital for enriching clinical trials with patients most likely to benefit from a given natural compound combination, steering the field towards a more personalized therapeutic approach.

5.3 Future perspective

Natural compounds offer a rich repository of molecular templates for designing multi-targeted interventions against the complex network of EGFR TKI resistance. Their future in NSCLC therapy, however, does not lie in their direct application as dietary supplements or crude extracts. The path forward requires a strategic convergence: integrating the nuanced biological insights gained from natural products with the precision-driven disciplines of medicinal chemistry, advanced drug delivery, and rigorous clinical oncology. Ultimate success will be measured by the development of engineered therapeutic agents—whether as optimized synthetic analogs or sophisticated nano-formulations—capable of reliably translating multi-target potential into clinical benefit for patients, thereby expanding the therapeutic arsenal against EGFR-TKI-resistant NSCLC.

6 Conclusion

This review establishes that natural compounds, by virtue of their inherent multi-target capabilities, represent a unique strategic avenue to overcome the complex challenge of EGFR TKI resistance in NSCLC. Their ability to simultaneously modulate the core EGFR axis and key resistance pathways provides a strong rationale for their development as sensitizing agents in rational combination therapies. However, this significant preclinical promise must now be bridged to clinical reality through rigorous pharmaceutical optimization and dedicated clinical trials. Therefore, the future of this field lies in translating these multifaceted mechanistic insights into clinically validated, next-generation combination regimens for the benefit of patients.

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