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Royal jelly fatty acids as emerging anticancer agents: integrative mechanisms and translational perspectives

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ABSTRACT

Royal jelly (RJ), a nutrient-rich secretion from the hypopharyngeal and mandibular glands of worker bees (*Apis mellifera*), has gained significant attention as a natural source of bioactive compounds with therapeutic potential. Among its various constituents, medium-chain fatty acids (MCFAs), notably 10-hydroxy-2-decenoic acid (10-HDA), 10-hydroxydecanoic acid (10-HDAA), and sebacic acid (SA), exhibit potent antioxidant, anti-inflammatory, immunomodulatory, and antimicrobial properties. In recent years, 10-HDA has emerged as the primary anticancer agent in RJ, demonstrating the ability to modulate key oncogenic pathways, including the induction of apoptosis, cell cycle arrest, and inhibition of angiogenesis and metastasis. This review provides a comprehensive analysis of the chemical composition, biosynthetic origin, and extraction techniques of RJ fatty acids (RJFAs), with a critical focus on their molecular mechanisms of anticancer action, including modulation of cell signaling pathways, DNA repair mechanisms, and immune response. We further explore their metabolic stability, bioavailability, and synergistic potential with conventional chemotherapeutics in models of lung cancer, breast cancer, liver cancer, and melanoma. Although promising, current limitations, including challenges in standardization, pharmacokinetics, and formulation, warrant further investigation. Future directions emphasize omics-driven approaches, such as genomics, proteomics, and metabolomics, as well as translational research to optimize the clinical applicability of RJFAs. Collectively, these insights position RJFAs, particularly 10-HDA, as compelling candidates for adjunctive cancer therapy and integrative oncology.

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1. Introduction

Cancer remains a leading cause of global mortality, despite advances in therapeutic approaches such as surgery, chemotherapy, radiotherapy, molecular targeted therapy, and immunotherapy^[1-4]. For patients with advanced or metastatic tumors, systemic therapies

often yield limited improvements in survival and are frequently accompanied by severe adverse effects, particularly in elderly populations^[5-7]. These challenges have intensified the demand for alternative or complementary treatment strategies that offer enhanced efficacy with fewer side effects. Natural products, with their broad pharmacological activities, accessibility, and relatively favorable safety profiles, have gained substantial attention as potential candidates^[8-10].

Royal jelly (RJ), a complex bioactive secretion produced by the hypopharyngeal and mandibular glands of young worker bees (*Apis mellifera*), has emerged as a promising compound in this

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context^[11–12]. Historically, RJ has served as the exclusive nutrient for honeybee queens, enabling their remarkable longevity (approximately 5 years) and reproductive capacity (approximately 2 500 eggs/day), while worker bees, deprived of RJ after the first 3 days of life, survive only approximately 45 days^[13–14]. This striking disparity underscores the profound influence of RJ on gene expression and physiological development, driven by its unique composition of bioactive compounds, including 10-hydroxy-2-decenoic acid (10-HDA) and major RJ proteins (MRJPs)^[13,15].

RJ is composed primarily of water (60%–70%), proteins (9%–18%), lipids (3%–8%), carbohydrates, minerals, vitamins, and a diverse array of fatty acid compounds, which are depicted in Fig. 1^[16–17]. Its protein fraction is dominated by MRJPs, particularly those that account for over 80% of total protein content^[18–21]. The lipid component is especially rich in medium-chain fatty acids (MCFAs), most notably 10-HDA, a unique and biologically active marker compound that can reach up to 2%–3% (*m/m*) in RJ, along with other fatty acids such as 10-hydroxydecanoic acid (10-HDAA) and sebacic acid (SA)^[22–23]. Carbohydrates are primarily composed of glucose and fructose, with minor contributions from oligosaccharides, which are influenced by botanical and environmental factors^[24]. RJ also contains trace steroid hormones (e.g., testosterone, estradiol)^[25–26], essential minerals (e.g., Ca, Zn, Fe, Mg), polyphenols, vitamins, and enzymes^[27–28].

Beyond its ecological role, RJ has long been used in traditional medicine, particularly in Asia and regions such as ancient Egypt, and is now widely applied in functional foods and nutraceuticals^[29–30]. Its broad pharmacological profile, including antioxidant, immunomodulatory, antimicrobial, hepatoprotective, and antidiabetic activities, positions RJ as a multifunctional natural product with therapeutic potential. However, compositional variability driven by geographic origin and collection methods remains a key challenge for standardization and clinical translation^[31].

The emerging anticancer potential of RJ has attracted increasing scientific attention, with evidence showing that its components, particularly 10-HDA, exert tumor-inhibitory effects through mechanisms including the induction of apoptosis, the suppression of angiogenesis, and the arrest of the cell cycle^[32–33]. Preclinical studies demonstrate that RJ and its constituents can enhance the efficacy of chemotherapeutics (e.g., cisplatin and 5-fluorouracil (5-FU)) while attenuating chemotherapy-related toxicities^[33–34]. For instance, RJ has been shown to reduce cyclophosphamide-induced genotoxicity and lower the half-maximal inhibitory concentration (IC₅₀) of 5-FU in cancer models^[33,35]. These synergistic interactions suggest that RJ fatty acids (RJFAs) are promising adjuvants in oncology, aligning with the growing demand for natural compounds that can address chemotherapy resistance and mitigate polypharmacy risks^[20,36].

This review presents a comprehensive synthesis of the anticancer potential of RJFAs, with particular emphasis on 10-HDA and 10-HDAA. It critically evaluates their chemical composition, extraction techniques, and biological activities, focusing on their roles in regulating oxidative stress, inflammation, and tumorigenic signaling pathways. In addition, the review highlights their synergistic interactions with conventional anticancer therapies, identifies key limitations in current research, and outlines future directions to facilitate the clinical translation of these therapies. By integrating evidence from preclinical studies and uncovering emerging

mechanistic insights, this review aims to bridge the gap between fundamental research and translational oncology, thereby supporting the development of RJFA-based therapeutic strategies.

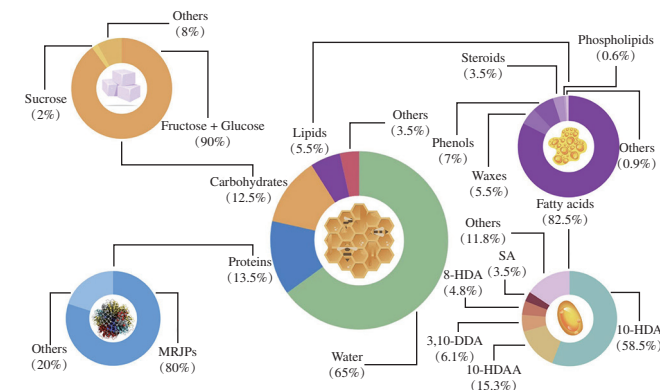


Fig. 1 Hierarchical composition of RJ and its bioactive constituents. The schematic illustrates the major chemical components of RJ, including water, carbohydrates, proteins, and lipids, together with their principal sub-fractions. Carbohydrates are predominantly composed of glucose and fructose, with minor amounts of sucrose and other sugars. Proteins are mainly represented by MRJPs, with smaller contributions from other protein fractions. The lipid component is dominated by fatty acids, notably 10-HDA, along with 10-HDAA, SA, 3,10-dihydroxydecanoic acid (3,10-DDA), and 8-hydroxydecanoic acid (8-HDA), as well as minor waxes, phenols, steroids, and phospholipids. Insets depict the relative composition of each fraction, highlighting 10-HDA as the predominant RJFAs^[15,37].

2. Composition, biosynthesis, and extraction of RJFAs

2.1 Lipids and fatty acids content

Lipids constitute approximately 3%–8% of the composition of RJ and are dominated by unique MCFAs, notably hydroxy fatty acids and dicarboxylic acids^[11]. The majority of lipids (80%–90%) are free fatty acids, with few being esterified^[13]. Approximately 90% of RJ lipids fall within the 8–12 carbon range, with 10-HDA as the most bioactive and abundant RJ lipid, more than 50% of the free fatty acids, and approximately 3.5% of the freeze-dried RJ^[13,22]. The lipid content predominantly consists of fatty acids, followed by phenols (4%–10%), waxes (5%–6%), steroids (3%–4%), and phospholipids (0.4%–0.8%). The fatty acid profile of RJ is predominantly composed of MCFAs, with 10-HDA, SA, and 9-hydroxy-2-decenoic acid being among the most abundant constituents^[13,18,38]. Additional bioactive fatty acids include 10-HDAA, 2-decenoic-1,10-dioic acid, 9-hydroxy-2(*E*)-decenoic acid (9-HAD), 3-hydroxydecanoic acid (3-HDA), 8-hydroxyoctanoic acid, and 3,10-DDA, which contribute to the pharmacological complexity of RJ^[23,39]. Structurally, RJFAs are distinguished by hydroxyl and carboxyl functional groups located at the chain termini^[12–13]. The chemical composition of RJFAs and their activities are detailed in Table 1.

In summary, the lipid fraction of RJ is unique and biologically significant, characterized by a dominance of MCFAs, particularly 10-HDA, whose abundance, chemical stability, and bioactivity not only define the therapeutic potential of RJ but also serve as critical markers of its quality and authenticity in both commercial and clinical applications.

Table 1
Major fatty acids in RJ and their pharmacological activities.

Fatty acid	Chemical structure	Pharmacological activity	Reference
10-HDA	$\text{CH}_3(\text{CH}_2)_6\text{CH}=\text{CHCH}_2\text{OH}$	Anti-inflammatory	[40-42]
		Immunoregulation	[43-44]
		Antimicrobial	[45-47]
		Antioxidant	[43,47-49]
		Neuroprotective	[50-52]
		Glucose homeostasis	[44]
SA	$\text{HOOC}-(\text{CH}_2)_8-\text{COOH}$	Antimicrobial	[44]
		Glucose homeostasis	[44]
		Anti-inflammatory	[44,53-55]
		Neuroprotective	[44,56]
		Immunoregulation	[44]
		Anti-inflammatory	[55,57-59]
10-HDAA	$\text{CH}_3(\text{CH}_2)_7\text{CH}(\text{OH})\text{COOH}$	Neuroprotective	[59]
		Immunoregulation	[58,60]
		Anti-inflammatory	[12,38,61-62]
		Antimicrobial	[13,55]
		Antioxidant	[62-63]
		Antimicrobial	[64-65]
3-HDA	$\text{CH}_3-(\text{CH}_2)_5-\text{CH}(\text{OH})-\text{COOH}$	Anticancer	[66]
		Anti-fungal	[67]
		Immunoregulation	[68]
3,10-DDA	$\text{CH}_3-(\text{CH}_2)_7-\text{CH}(\text{OH})-(\text{CH}_2)_6-\text{CH}(\text{OH})-\text{COOH}$	Immunoregulation	[69]
		Anticancer	[38]
8-Hydroxyoctanoic acid	$\text{CH}_3-(\text{CH}_2)_6-\text{CH}(\text{OH})-\text{COOH}$	Anticancer	[70]

2.2 Biosynthesis of RJFAs

2.2.1 Mandibular gland biosynthesis in *A. mellifera*

In *A. mellifera* (honeybee), the biosynthesis of 10-HDA and related fatty acids begins with *de novo* fatty acid synthesis. The process is catalyzed by enzymes such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), which produce palmitoyl-acyl carrier protein (ACP)^[71]. This precursor undergoes elongation to stearoyl-CoA by elongases and reductases, followed by ω -hydroxylation of stearic acid by cytochrome P450 enzymes to form ω -hydroxystearic acid. The final step in the biosynthetic pathway involves β -oxidation and $\Delta 11$ -desaturation, resulting in the formation of 10-HDA^[71-72]. This pathway is crucial for the formation of RJFAs, and a variety of metabolic enzymes regulate it.

Recent studies have utilized isotope tracer experiments, and the functional annotation of the honeybee mandibular glands has elucidated this complex pathway, further clarifying the enzymatic steps involved in the biosynthesis of RJFAs^[71-72]. These insights contribute to a better understanding of the molecular mechanisms underlying RJ production and its associated fatty acids.

2.2.2 Microbial biosynthesis of RJFAs

Microbial biosynthesis of RJFAs, particularly 10-HDA, has emerged as an attractive alternative to traditional extraction

methods, offering benefits in terms of scalability, process control, and sustainability^[73-74]. Advances in synthetic biology have enabled the engineering of strains such as *Escherichia coli* to produce RJ-specific fatty acids. Key enzymes involved in this bioconversion include cytochrome P450 monooxygenases (CYP), acyl-CoA synthetases, acyl-CoA dehydrogenases, and acyl-CoA thioesterases, which collectively facilitate the transformation of decanoic acid into hydroxylated fatty acids such as 10-HDA and 10-HDAA^[73-74]. For example, decanoic acid is first activated to decanoyl-CoA by acyl-CoA synthetase, desaturated to *trans*-2-decenoic acid by acyl-CoA dehydrogenase, and then hydroxylated by cytochrome P450 enzymes to yield 10-HDA. In *Pseudomonas putida* KT2440, a similar pathway leads to the production of *trans*-2-decenoic acid from decanoic acid^[75-77].

However, challenges such as the low solubility of decanoic acid and its cytotoxicity at high concentrations hinder microbial growth and enzyme activity, thereby limiting the overall efficiency of the bioprocess^[73,78]. To overcome these limitations, synthetic biology approaches have been employed to engineer strains of *E. coli* with enhanced productivity. Notably, an engineered *E. coli* strain co-expressing the native acyl-CoA synthetase (*FadE*), malonyl-CoA synthetase (*Macs*), thioesterase (*YdiI*), and CYP genes, while deleting competing pathway genes such as *FadB*, *FadJ*, and *FadR*, achieved a remarkable conversion efficiency of 75.6% from decanoic acid to 10-HDA, yielding 0.628 g/L within 10 h^[79]. This genetic modification directed metabolic flux toward the desired product, minimizing the formation of undesired by-products.

2.2.3 Chemical synthesis of RJFAs

In addition to microbial biosynthesis, chemical synthesis methods have been developed to produce RJFAs, particularly 10-HDA. The synthesis of 10-HDA typically involves a multistep process, including acetylation, α -bromination, and elimination reactions to yield the unsaturated hydroxylated decenoic acid^[44]. While these chemical routes can achieve satisfactory yields, the presence of residual solvents, reagents, and by-products often renders these products unsuitable for food applications^[11]. Similarly, SA, though synthesized efficiently through chemical processes, is not suitable for food use due to the involvement of toxic solvents and by-products^[80]. However, when adequately purified and industrially synthesized, MCFAs such as 10-HDA and SA show potential for use in pharmaceuticals and functional foods^[11,81].

2.3 Extraction methods for RJFAs

The extraction of RJFAs is essential not only for its pharmaceutical, nutraceutical, and therapeutic applications but also for ensuring the quality control of RJ-based products. Historically, traditional methods, including ethanol precipitation, ether extraction, and ethanol extraction, have been commonly employed^[82-83]. However, these methods are often inefficient, offer low specificity, and lack scalability, prompting the development of more advanced techniques designed to improve yield, selectivity, and environmental sustainability^[23].

2.3.1 Traditional extraction methods

Solvent extraction remains one of the most widely used methods for RJFA isolation due to its operational simplicity, reproducibility,

and compatibility with a variety of solvents^[84]. Mixed solvent systems, such as chloroform/methanol (2:1, *V/V*) and diethyl ether/isopropanol (50:1, *V/V*), have demonstrated superior extraction efficiencies, yielding more than 95% total lipids, with diethyl ether/isopropanol showing enhanced recovery of fatty acids^[85-86]. Soxhlet extraction, a continuous solid-liquid extraction process conducted under reflux, provides consistent solvent-matrix interactions and high reproducibility. However, prolonged exposure to high temperatures can degrade thermolabile fatty acids, and the use of organic solvents limits its applicability for food-grade or pharmaceutical-grade applications^[87-88].

In comparison, ethanol-based extraction under mild temperature conditions has been successfully used to isolate 10-HDA, achieving a purity of up to 62.44%^[44]. Despite its lower purity compared to some modern methods, this approach provides a balance between efficiency and safety for large-scale applications. However, the extraction efficiency of ethanol-based methods is still unquantified, and further optimization is required to improve yields and specificities for bioactive fatty acids^[85].

2.3.2 Advanced extraction methods

Recent advancements have focused on improving extraction efficiency, selectivity, and scalability for industrial applications. Reverse-phase column chromatography (RPC), which utilizes hydrophobic interactions between non-polar stationary phases and analytes, has proven effective for isolating RJFAs with minimal interference from polar contaminants^[89]. This method, renowned for its high purity and reproducibility, enables the separation of structurally similar lipophilic compounds, making it ideal for applications that require high precision and accuracy. However, the scalability of the method is limited by the need for expensive equipment and materials.

Macroporous resins, such as X-5, have also been used for adsorption-based recovery, offering significant advantages in terms of scalability. These resins exhibit excellent adsorption-desorption properties, making them suitable for large-scale industrial applications, particularly due to their chemical stability and reusability^[90]. In comparison with solvent extraction, these advanced methods offer higher operational efficiency, reproducibility, and compliance with current good manufacturing practices (cGMP), making them more suitable for pharmaceutical and nutraceutical applications.

Homogeneous liquid-liquid extraction (h-LLE), using water-miscible solvents such as acetonitrile, has emerged as a greener alternative to traditional solvent extraction. This technique improves extraction efficiency while minimizing environmental impact by reducing solvent use^[85,91]. However, achieving optimal extraction

requires careful optimization of solvent-agent compatibility, temperature, and pH to maximize efficiency. Furthermore, deep eutectic solvents and ionic liquids hold promise for further enhancing the environmental benefits of h-LLE^[92].

Among the most promising green technologies is ultrasound-assisted extraction (UAE), which has garnered significant attention due to its eco-friendliness, efficiency, and reduced solvent consumption. The novel UAE protocol optimized for RJFA extraction yields a substantial 16.48% with a 10-HDA content of 4.12%. This method outperforms conventional solvent extraction by demonstrating higher bioactivity and lower solvent usage, making it an attractive option for industrial applications^[23]. Compared to traditional solvent extraction, UAE provides a higher yield in a shorter time, making it more suitable for large-scale applications in the pharmaceutical, food, and nutraceutical industries. The comparison of RJFA extraction is summarized in Table 2.

In conclusion, the extraction and quantification of RJFA have evolved from traditional methods, such as solvent extraction, to more advanced, environmentally sustainable techniques, including UAE and h-LLE. Specifically, while traditional methods offer simplicity and reproducibility, modern methods provide enhanced yield, specificity, and scalability, making them more suitable for large-scale industrial applications. Future research should focus on optimizing these advanced methods to further reduce environmental impact, improve efficiency, and refine selectivity, particularly for bioactive fatty acids such as 10-HDA. Continued development of greener, more sustainable extraction technologies is crucial for the broader therapeutic application of RJFAs.

3. Anticancer activities of RJFAs in various human cancer types

RJ and its principal fatty acids, particularly 10-HDA and 10-HDAA, have demonstrated broad anticancer activity across multiple organ systems, including the respiratory, digestive, urinary, and integumentary systems, as well as hormone-responsive malignancies such as breast cancer^[12]. Accumulating evidence suggests that these bioactive lipids exert pleiotropic effects on cancer cells by coordinating the modulation of redox balance, inflammatory signaling, apoptotic and cell-cycle machinery, metastatic programs, metabolic reprogramming, hormone-responsive pathways, and epigenetic regulation^[32-33,100].

Rather than acting through a single dominant pathway, RJFAs influence cancer progression in a context-dependent manner that reflects tumor origin, molecular subtype, and microenvironmental cues^[101]. In epithelial malignancies such as lung, colorectal, and liver cancers, RJFAs predominantly suppress proliferation and metastatic potential through reactive oxygen species (ROS)-dependent apoptosis, inhibition of pro-survival signaling cascades,

Table 2
Comparison of traditional and advanced extraction techniques for RJFA.

Method	Efficiency	Yield	Specificity (10-HDA)	Scalability	Environmental impact	Reference
Solvent extraction	Moderate	> 95% total lipids	Moderate	High (simple)	High solvent residue	[93-97]
RPC	High	High purity	High	Moderate (expensive)	Low	[89]
Macro-porous resins	High	Moderate to high	High	High (large-scale)	Low	[90,98]
h-LLE	High	High	High	Moderate	Low	[99]
UAE	High	16.48% (10-HDA)	High	High (scalable)	Very low	[23]

metabolic rewiring, and blockade of epithelial-mesenchymal transition (EMT)^[102]. In hormone-responsive cancers, such as breast cancer, RJFAs also interact with estrogen receptor (ER) signaling^[6] and nuclear histone deacetylase (HDAC)-mediated epigenetic regulation, resulting in dose- and receptor subtype-specific biological outcomes^[103]. In melanoma and renal disease-associated malignancies, RJFAs modulate lineage-specific transcriptional programs, inflammatory pathways, and oxidative stress responses that are closely linked to disease progression and therapeutic resistance.

The following subsections synthesize the anticancer effects of RJFAs according to tumor type, while maintaining a mechanism-centered perspective to highlight convergent and divergent modes of action. This structure facilitates the comparative interpretation of RJFA activity across cancer systems and provides a foundation for evaluating its translational potential as an integrative or adjunctive anticancer agent.

3.1 Lung cancer

Lung cancer remains the leading cause of cancer-related mortality worldwide, with poor prognosis primarily attributable to late-stage diagnosis, metastatic dissemination, and limited responsiveness to conventional therapies^[104–106]. Within this context, RJFAs, particularly 10-HDA, have emerged as promising natural compounds exhibiting selective anticancer activity against non-small cell lung cancer (NSCLC).

Mechanistically, 10-HDA demonstrates dose-dependent cytotoxicity against NSCLC cell lines, including A549, NCI-H460, and NCI-H23, at concentrations ranging from 1 to 100 $\mu\text{mol/L}$, while sparing normal cells such as IMR90 and L-02^[12,90]. In A549 cells, treatment with 10-HDA at 30 $\mu\text{mol/L}$ robustly activates the intrinsic (mitochondrial) apoptotic pathway, as evidenced by downregulation of the anti-apoptotic protein Bcl-2 and concomitant upregulation of pro-apoptotic markers, including cleaved Caspase-3, poly(ADP-ribose) polymerase (PARP), Bax, and cytochrome C^[102,107]. These apoptotic effects are critically dependent on ROS, as co-treatment with the antioxidant *N*-acetylcysteine (NAC) effectively abolishes apoptosis, underscoring a central role for ROS in mediating 10-HDA-induced cell death^[102,107]. At the signaling level, 10-HDA activates stress-responsive mitogen-activated protein kinase (MAPK) pathways, characterized by increased phosphorylation of p38 mitogen-activated protein kinase (p-p38) and c-Jun N-terminal kinase (p-JNK), while simultaneously suppressing pro-survival signaling mediators, including phosphorylated extracellular signal-regulated kinase (p-ERK), signal transducer and activator of transcription 3 (p-STAT3), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κB)^[102].

Beyond apoptosis, 10-HDA disrupts cell cycle progression in NSCLC cells. In A549 cells, 10-HDA induces G_0/G_1 phase arrest, which is associated with decreased expression of cyclins D1 and E, reduced levels of cyclin-dependent kinases (CDKs), such as CDK2, CDK4, and CDK6, and upregulation of cyclin-dependent kinase inhibitors (CDKIs), including p21 and p27^[102,108]. This cell cycle blockade is further linked to attenuation of Akt phosphorylation, indicating that redox-sensitive modulation of the Akt-CDK pathway contributes to the antiproliferative effects of 10-HDA, as illustrated in Fig. 2^[109–110].

In addition to its pro-apoptotic and antiproliferative actions, 10-HDA exhibits pronounced anti-metastatic effects by inhibiting the EMT. Treatment with 10-HDA increases the expression of the epithelial marker E-cadherin while suppressing mesenchymal and EMT-associated markers, including transforming growth factor β 1 (TGF- β 1), snail family transcriptional repressor 1 (SNAI1), glycogen synthase kinase β (GSK- β), N-cadherin, and vimentin, resulting in reduced migratory and invasive capacities of NSCLC cells^[102]. These effects are closely associated with time-dependent ROS accumulation and the coordinated modulation of MAPK, STAT3, and NF- κB signaling pathways, which collectively regulate metastatic progression in lung cancer^[102,111].

Collectively, these findings position 10-HDA as a multifunctional anticancer agent in NSCLC, acting through the activation of ROS-mediated apoptotic pathways, the inhibition of pro-survival and proliferative signaling, and the suppression of metastatic potential *via* EMT blockade. Such convergent mechanisms support the translational potential of 10-HDA as a promising adjunctive therapy for lung cancer.

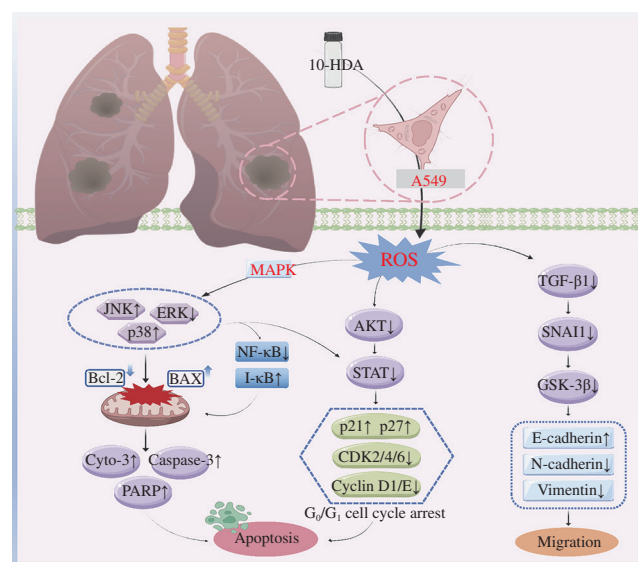


Fig. 2 Molecular signaling pathways regulated by 10-HDA in lung cancer cells. The figure illustrates how 10-HDA modulates key intracellular signaling cascades, including ROS generation, MAPK activation, AKT suppression, TGF- β 1 signaling, STAT3 inhibition, and GSK- β regulation. These molecular events converge to induce G_0/G_1 cell cycle arrest, promote apoptosis, and inhibit the migration of cancer cells.

3.2 Liver cancer

Liver cancer is the sixth most prevalent malignancy worldwide and the fourth leading cause of cancer-related mortality, with a 5-year survival rate of approximately 18%^[112–113]. Hepatocellular carcinoma (HCC) accounts for nearly 90% of liver cancer cases. It arises predominantly in the context of chronic liver disease, most notably chronic hepatitis B virus (HBV) infection, which alone is responsible for approximately 50% of global HCC cases, as well as hepatitis C virus infection, non-alcoholic fatty liver disease, and long-term alcohol consumption^[103,105–106,114]. Despite advances in viral prevention and antiviral therapies, the global burden of HCC continues to rise, underscoring the urgent need for novel therapeutic strategies targeting both tumor growth and metabolic dysregulation^[115].

Within this context, RJFAs, particularly 10-HDA, have demonstrated notable anticancer activity in HCC models^[116-117]. In HepG2 cells, 10-HDA at a concentration of 59.6 $\mu\text{g/mL}$ significantly upregulated the expression of the tumor-suppressive microRNA miR-34a, leading to reduced cell viability and the induction of apoptosis. This effect is mediated through the activation of Caspase-3, upregulation of Bax, modulation of miR-34a, and cleavage of PARP. In addition, another fatty acid in RJ, SA, can downregulate ANGPTL8 expression by reducing HNF4 α protein levels^[108,118]. Consistent pro-apoptotic effects have also been observed in HCCLM3 and Hep3B cells, where 10-HDA inhibits colony formation and migratory capacity while promoting apoptosis *via* modulation of the Bax/Bcl-2/Caspase-8 pathway^[119].

In addition to inducing apoptosis, 10-HDA exhibits pronounced antiproliferative effects by regulating the cell cycle. Treatment of HCCLM3 and Hep3B cells with 10-HDA results in downregulation of cyclin D1 (CCND1), cyclin E1 (CCNE1), and CDK2, accompanied by a reduction in the S-phase cell population, indicating effective suppression of cell cycle progression^[119]. These effects translate into significant tumor growth inhibition *in vivo*, as demonstrated in nude mouse models of HCC, supporting the therapeutic relevance of 10-HDA in liver cancer^[119].

Beyond its effects on apoptosis and proliferation, emerging evidence highlights a critical role for 10-HDA in the metabolic reprogramming of HCC cells. Metabolomic analyses reveal that 10-HDA disrupts hepatic glycolytic metabolism, reduces lactate production, and increases phosphorylated AMP-activated protein kinase (p-AMPK) levels, while downregulating aquaporin-9, thereby altering glycerol metabolism^[120]. Notably, 10-HDA further modulates epigenetic metabolism-gene expression coupling by affecting histone H3 lactylation at the H3K141a and H3K91a sites, thereby suppressing glycolysis-associated transcriptional programs in HCC cells^[119].

Collectively, these findings identify RJFAs, particularly 10-HDA, as multifunctional modulators of liver cancer progression, acting through coordinated regulation of apoptotic signaling, cell cycle control, and metabolic reprogramming. Such integrative mechanisms underscore the translational potential of RJFAs as therapeutic candidates in HCC management, warranting further mechanistic and preclinical exploration, as summarized in Fig. 3.

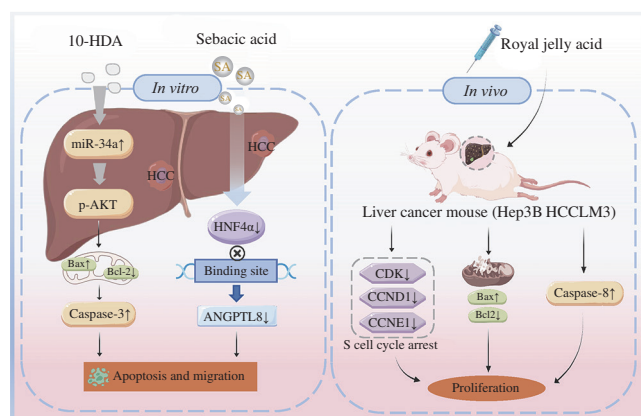


Fig. 3 Molecular signaling pathways of 10-HDA are involved in regulating apoptosis and migration in liver cancer cells. The figure illustrates how 10-HDA modulates multiple signaling cascades, including the activation of miR-34a and Bax, while inhibiting Bcl-2, AKT (p-AKT), and SA-mediated down-regulates of ANGPTL8 expression by reducing the protein level of HNF4 α . These coordinated molecular events lead to cell cycle arrest, induction of apoptosis, and inhibition of cancer cell migration.

3.3 Colorectal cancer

Colorectal cancer is the second leading cause of cancer-related mortality worldwide, with metastatic dissemination representing the principal determinant of poor clinical outcomes^[121]. A central driver of colorectal cancer metastasis is the EMT, a process governed by transcriptional regulators such as SNAIL, which represses epithelial markers, including E-cadherin, while inducing mesenchymal markers, including N-cadherin and vimentin^[122-123]. Accordingly, therapeutic strategies that target EMT-associated signaling networks are of considerable interest in colorectal cancer management.

Within this context, RJFAs, particularly 10-HDA, have demonstrated pronounced anti-metastatic activity in colorectal cancer models. In SW-480 colon cancer cells, treatment with 10-HDA across a concentration range of 10–100 $\mu\text{mol/L}$ results in significant downregulation of SNAIL, accompanied by a marked reduction in the mesenchymal markers N-cadherin and vimentin^[123]. Functionally, these molecular changes result in a substantial inhibition of cell migration and invasion, underscoring the capacity of 10-HDA to suppress EMT-driven metastatic behavior through modulation of SNAIL, a central regulatory node in EMT signaling^[122-123]. Consistently, in HCT116 cells, 10-HDA increases the expression of epithelial markers, including E-cadherin and cytoplasmic β -catenin, thereby stabilizing intercellular adhesion. A similar restoration of epithelial characteristics has been observed in SW-480 cells, where 10-HDA enhances E-cadherin expression at both the transcriptional and protein levels, while suppressing pro-EMT markers^[122].

At the molecular level, the anti-EMT effects of 10-HDA are closely linked to ER β signaling. 10-HDA exhibits high binding affinity for ER β , which is abundantly expressed in colorectal cancer tissues and SW-480 cells^[122]. Upon ligand binding, 10-HDA activates ER β , promoting its nuclear translocation and interaction with estrogen-responsive elements (EREs) within the promoters of downstream target genes^[84]. ER β activation is known to transcriptionally regulate EMT-associated markers, including E-cadherin, N-cadherin, β -catenin, vimentin, and SNAIL, thereby providing a mechanistic basis for the observed suppression of EMT and metastatic potential in colorectal cancer cells^[123-125].

Beyond EMT regulation, RJFAs also exert anti-inflammatory, pro-oxidative, and immunomodulatory effects in colorectal cancer models. In WiDr cells, RJFAs suppress pro-inflammatory mediators, including NF- κ B, interleukin-1 β (IL-1 β), TNF- α , and IL-8, while enhancing the anti-inflammatory cytokine IL-1ra^[126]. In Caco-2 cells, RJFA treatment reduces glutathione (GSH) levels and increases malondialdehyde (MDA) production, indicating oxidative stress-induced apoptosis^[127]. *In vivo*, RJ acids decrease tumor burden, enhance antioxidant enzyme activity, and reduce tumor marker levels in Ehrlich solid tumor-bearing mice^[101]. Additional evidence suggests that RJ may antagonize toll-like receptor 4 (TLR4), further contributing to its immunomodulatory activity within the tumor microenvironment^[101].

The epigenetic relevance of RJFAs in colorectal cancer has also been established, extending beyond hormone-responsive malignancies. In HCT116 cells, treatment with 10-HDA and 10-HDAA at 100 $\mu\text{mol/L}$, either individually or in combination, significantly reduces nuclear HDAC activity and increases chromatin lysine acetylation, consistent with transcriptional depression^[103].

These findings suggest that 10-HDAA, in conjunction with 10-HDA, contributes to HDAC-mediated chromatin remodeling, thereby reinforcing the epigenetic component of RJFA-mediated anticancer activity in colorectal cancer.

Collectively, these findings demonstrate that 10-HDA suppresses EMT and metastatic progression in colorectal cancer through complementary mechanisms involving ER β -mediated transcriptional repression of SNAIL, modulation of inflammatory and oxidative stress pathways, and epigenetic regulation *via* HDAC inhibition. This integrated mode of action highlights 10-HDA as a mechanistically relevant natural compound for targeting EMT-associated metastatic processes in colorectal cancer, as summarized in Fig. 4.

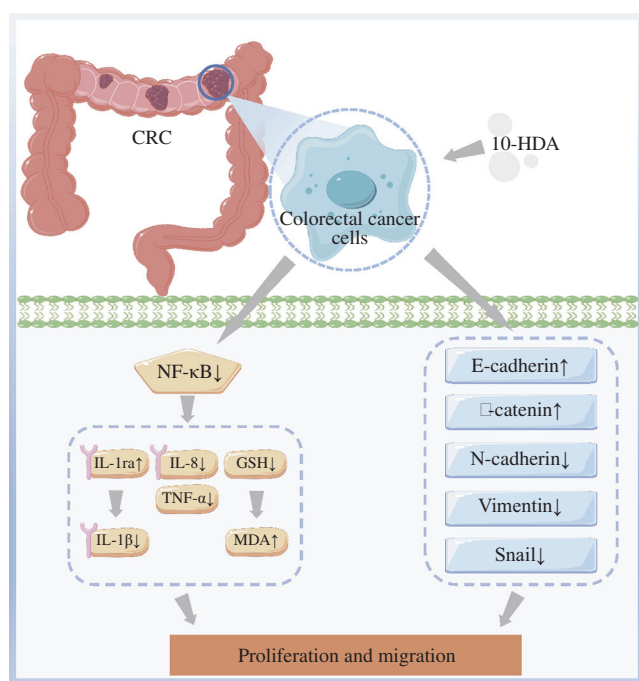


Fig. 4 Molecular signaling pathway of 10-HDA in colorectal cancer cells. The figure illustrates how 10-HDA modulates key molecular pathways in colorectal cancer by inhibiting NF- κ B signaling, resulting in the downregulation of pro-inflammatory cytokines, including TNF- α , IL-8, and IL-1 β . This inhibition is accompanied by decreased levels of the antioxidant GSH and elevated levels of the oxidative stress marker MDA, ultimately contributing to anti-inflammatory and anticancer effects.

3.4 Breast cancer

Breast cancer is the most frequently diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality^[128]. Disease progression, particularly in hormone receptor-positive (HR⁺) subtypes, is closely linked to elevated circulating estrogen levels and dysregulation of ER signaling pathways, which govern tumor initiation, proliferation, and survival^[129-130]. Accordingly, therapeutic strategies targeting ER signaling, including selective ER modulators, ER degraders, and aromatase inhibitors, constitute the cornerstone of contemporary breast cancer management^[131-132]. Within this therapeutic landscape, naturally derived compounds capable of modulating endocrine and epigenetic pathways have attracted growing interest as adjunctive or preventive agents.

Among the bioactive constituents of RJ, unsaturated MCFAs, particularly 10-HDA, have emerged as potential endocrine modulators^[11,25]. Owing to its structural resemblance to endogenous estrogens, 10-HDA can interact with ERs and influence estrogen-responsive gene expression^[25]. Notably, the endocrine activity of RJFAs appears to be highly context-dependent, with both estrogenic and anti-estrogenic effects reported as a function of dose, ER subtype specificity, and the prevailing hormonal milieu.

Preclinical evidence suggests that daily administration of RJFAs at sub-therapeutic doses (< 200 mg/kg) may exert chemopreventive effects through systemic hormonal modulation. Specifically, RJFA treatment has been associated with reduced circulating estrogen levels and increased progesterone levels, changes that correlate with downregulation of ER expression in ER-positive breast cancer cells and inhibition of estrogen-driven proliferation^[25]. These findings support the potential utility of RJFAs as natural endocrine modulators. However, rigorous clinical studies are required to define their safety, optimal dosing regimens, and therapeutic efficacy in breast cancer patients.

Beyond hormonal regulation, RJFAs, including 10-HDA and its saturated analog, 10-HDAA, exert epigenetic effects by inhibiting HDACs, key regulators of chromatin remodeling and gene transcription^[100]. *In vitro* assays using HeLa nuclear extracts demonstrated that both 10-HDA and 10-HDAA significantly inhibit HDAC activity, albeit with lower potency than classical HDAC inhibitors such as trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA)^[103]. In MDA-MB-231 triple-negative breast cancer (TNBC) cells, treatment with either compound resulted in a marked reduction in HDAC3 activity at 12 h, comparable to TSA. However, this inhibitory effect was not sustained at 24 h. Interestingly, combined treatment with both fatty acids led to increased HDAC activity, highlighting the complexity of their epigenetic modulation^[103].

Molecular docking analyses further support these observations, revealing favorable binding affinities of 10-HDA and 10-HDAA for HDACs, comparable to hydroxamic acid-based inhibitors^[133-134]. Despite the transient nature of enzymatic inhibition, both compounds induce prolonged transcriptional responses, including the upregulation of tumor suppressor genes, underscoring their functional relevance as epigenetic modulators with potential chemopreventive utility^[103].

ER subtype-specific effects further complicate the biological actions of RJFAs in breast cancer. In MCF-7 cells, ER β expression is associated with growth inhibition, whereas ER α promotes proliferation. RJFA exposure has been shown to significantly increase ER α expression, which may partially counteract antiproliferative effects in specific cellular contexts^[135]. In addition, RJFAs exhibit estrogen-like activity *via* ER modulation and enhance polyunsaturated fatty acid elongase expression through ER α signaling, as summarized in Fig. 5^[124-125]. These receptor-specific dynamics emphasize the necessity of evaluating RJFAs in distinct ER α - and ER β -dominant breast cancer models.

Notably, high-dose administration of RJFA extracts has been linked to increased proliferation of breast cancer cells *in vitro*, indicating a dose-dependent biphasic response^[135]. Such findings warrant caution, particularly in estrogen-dependent malignancies, and underscore the potential risks associated with uncontrolled exposure to estrogenic compounds^[136].

In summary, RJFA acts through dual pharmacological mechanisms, including hormonal modulation and HDAC-mediated

epigenetic regulation, to influence the behavior of breast cancer cells. Their structurally defined interactions with ERs and chromatin-modifying enzymes position them as mechanistically relevant candidates for integrative breast cancer prevention and therapy. However, the pronounced context- and dose-dependent effects of RJFAs necessitate further mechanistic investigation and well-controlled clinical validation to establish their therapeutic index and applicability across diverse breast cancer subtypes.

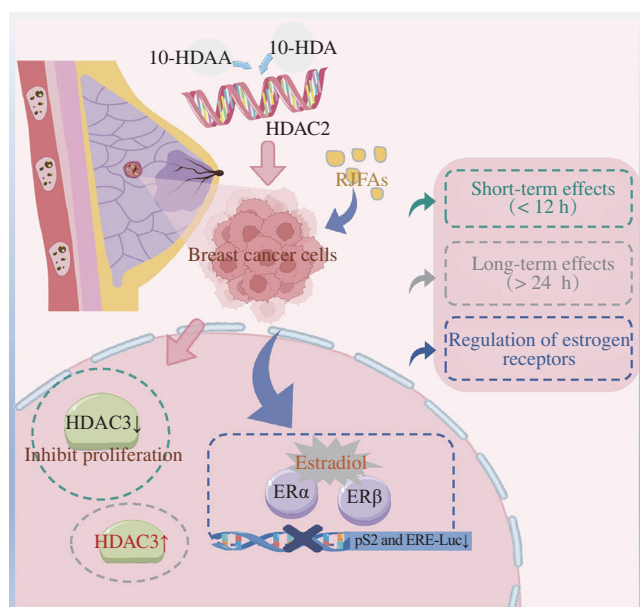


Fig. 5 Molecular signaling pathways regulated by 10-HDA and 10-HDAA in breast cancer cells. The figure illustrates how 10-HDA modulates key signaling cascades, including the activation of ER α and ER β signaling pathways, which promote the altered transcription of estrogen-responsive genes and inhibit HDAC3. These effects highlight the complex role of 10-HDA in regulating apoptosis and proliferation in breast cancer cells.

3.5 Skin cancer

Skin cancer is the most common malignancy worldwide and arises primarily from uncontrolled proliferation of epidermal cells induced by ultraviolet radiation and environmental carcinogens^[137]. Clinically, skin cancers are broadly classified into non-melanoma skin cancers (NMSCs) and melanoma. NMSCs account for the majority of cases, with basal cell carcinoma representing approximately 70% and squamous cell carcinoma around 25% of diagnoses in Caucasian populations^[138-139]. Although less prevalent, melanoma is a highly aggressive malignancy responsible for a disproportionate share of skin cancer-related mortality due to its strong metastatic potential^[140-141].

Melanoma originates from melanocytes, whose physiological function is governed by melanogenesis, a tightly regulated process under the transcriptional control of microphthalmia-associated transcription factor (MITF). MITF regulates the expression of key melanogenic enzymes, including tyrosinase (TYR) and TYR-related proteins TRP-1 and TRP-2, which collectively determine melanin biosynthesis and melanocyte survival^[142].

At the molecular level, melanoma pathogenesis involves a complex interplay of genetic and signaling alterations, including oncogenic mutations in B-Raf proto-oncogene (BRAF) and

neuroblastoma RAS viral oncogene homolog (NRAS), which are particularly prevalent in melanomas associated with chronic sun exposure, mucosal surfaces, and acral regions^[143]. Additional contributing events include the deletion of cyclin-dependent kinase inhibitor 2A (CDKN2A)^[144], the amplification or overexpression of MITF^[144], and aberrant signaling through KIT proto-oncogene, receptor tyrosine kinase (KIT) and metabotropic glutamate receptor 1 (mGluR1), all of which promote melanoma initiation and progression^[145-146].

Within this context, RJFAs, particularly 10-HDA, have demonstrated inhibitory activity against melanoma-associated melanogenic signaling. In B16F10 melanoma cells, treatment with 10-HDA at concentrations ranging from 0.1 to 1.0 mmol/L significantly suppresses MITF expression, leading to downregulation of its downstream targets TRP-1, TRP-2, and TYR, and resulting in a marked reduction in melanin production^[147]. These findings suggest that 10-HDA directly interferes with the transcriptional machinery that governs melanocyte differentiation and pigment synthesis^[12,147-148].

Collectively, these findings demonstrate that 10-HDA modulates melanoma-associated molecular pathways primarily by suppressing MITF-driven melanogenic signaling, resulting in reduced expression of key melanogenic enzymes and inhibition of melanin synthesis. This mechanistic profile highlights 10-HDA as a biologically relevant RJFA with translational potential in melanoma-related dermatological and oncological applications, as summarized in Fig. 6.

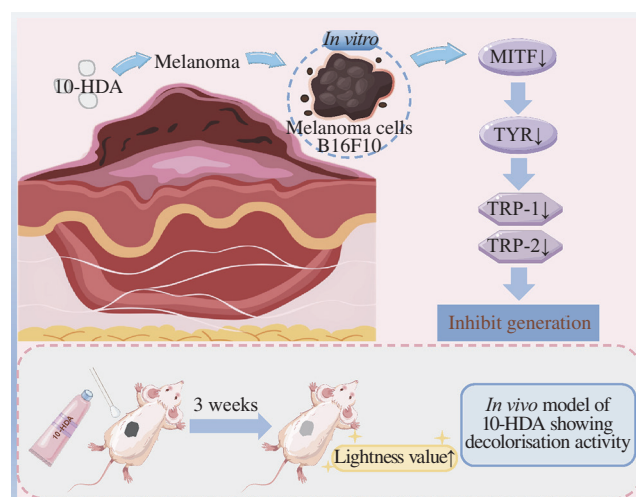


Fig. 6 Molecular pathway of 10-HDA in melanoma cells. The diagram illustrates how 10-HDA suppresses melanin synthesis in B16F10 melanoma cells by downregulating MITF, a central regulator of melanogenesis. This downregulation leads to a decrease in the expression of downstream melanogenic enzymes, including TYR, TRP-1, and TRP-2, ultimately resulting in reduced melanin production.

3.6 Kidney cancer

Kidney cancer, most commonly represented by renal cell carcinoma (RCC), is among the most prevalent malignancies of the urinary tract and ranks as the seventh most common cancer worldwide. Over the past 2 decades, its incidence has increased at an annual rate of approximately 2%^[149]. Clear cell RCC (ccRCC) is the predominant histological subtype, accounting for nearly 80% of cases and characterized by an unfavorable prognosis, as approximately 40%

of patients develop metastatic disease and exhibit a 5-year survival rate of only about 10%^[150]. These clinical challenges underscore the need for therapeutic strategies that not only target tumor progression but also mitigate renal injury and treatment-related toxicity.

Within this context, RJFAs, particularly 10-HDA, have demonstrated protective and therapeutic effects in experimental models of nephrotoxicity and renal pathology^[43]. Oral administration of RJ at doses of approximately 100 mg/(kg·day) in streptozotocin-induced diabetic rats and isoproterenol-treated mice resulted in pronounced 10-HDA-associated biological activity, characterized by reduced ROS levels, restoration of renal morphology, and enhancement of endogenous antioxidant enzyme activity^[18,51,151]. Similarly, RJFAs administered at oral doses ranging from 50 to 100 mg/(kg·day) significantly attenuated cisplatin-induced nephrotoxicity, as evidenced by reduced histopathological renal damage and suppression of TNF- α expression^[34,152].

At the molecular and immunological levels, RJFAs modulate key inflammatory signaling pathways relevant to renal injury and tumor-associated inflammation. 10-HDA has been shown to inhibit NF- κ B activation and nitric oxide production in lipopolysaccharide (LPS)-stimulated macrophages, indicating suppression of pro-inflammatory signaling cascades^[153]. In parallel, 10-HDA modulates inducible nitric oxide synthase (iNOS), IL-10, and p53-related inflammatory responses in neuro-renal models, further supporting the immunoregulatory capacity of RJFAs^[61,154].

Collectively, these findings suggest that RJFAs exert multifaceted protective effects in renal disease models by coordinating the suppression of oxidative stress, inflammation, and immune dysregulation. While direct anticancer effects in RCC remain to be fully elucidated, the ability of RJFAs to mitigate nephrotoxicity and modulate tumor-associated inflammatory pathways supports their potential utility as adjunctive agents in kidney cancer management.

4. Synergistic effects, adjuvant potential, and bioavailability of RJFA

4.1 Synergistic effects of RJFA with cancer drugs

Cancer remains a critical global health challenge due to its rising incidence and high mortality rate. Over 19 million new cancer cases were reported globally, with projections estimating nearly 33 million by 2040^[113,155]. These complex disease trajectories necessitate multimodal treatment strategies, including the repurposing of drugs and combination therapies^[156]. Integrating natural bioactive compounds such as RJ with conventional chemotherapeutics has emerged as a promising approach to enhance therapeutic efficacy and reduce adverse effects^[157-159].

Several studies have demonstrated the synergistic effects of RJ and its major fatty acid components when combined with established chemotherapeutic agents. In MDA-MB-231 breast cancer cells, co-administration of RJ with thymoquinone (RJ-TQ) significantly increased Caspase-3-mediated apoptosis, without cytotoxicity to normal small intestinal cells^[160]. Similarly, RJ enhanced the efficacy of temozolomide in U87MG glioblastoma cells^[161]. In colorectal cancer, RJ and its fatty acid (10-HDA) potentiated the effects of HuIFN- α N3 in Caco-2 cells by inducing lipid peroxidation, depleting GSH, and inhibiting cell proliferation^[127]. Additionally,

the nutraceutical formulation GE132 Plus, which combines RJ with antioxidants, has demonstrated antiproliferative effects in MCF-7, PC3, and SW48 cells with minimal toxicity to normal endothelial cells at therapeutic doses^[162-163].

Cisplatin, a widely used chemotherapeutic agent, is effective against various malignancies but is limited by its nephrotoxicity and hepatotoxicity^[164-165]. RJ co-administration significantly reduced oxidative stress, apoptosis, and fibrogenic markers in renal tissues, while enhancing the activity of antioxidant enzymes^[166-167]. Clinically, RJ has been shown to stabilize serum creatinine and urea levels during cisplatin therapy^[168], prevent oral mucositis in patients with head and neck cancer^[169], and alleviate fatigue in those treated with a honey-RJ mixture^[170]. Additionally, RJ mitigated cyclophosphamide-induced genotoxicity and ovarian damage *via* DNA protection mechanisms^[159]. Moreover, RJ enhanced the cytotoxic efficacy of 5-FU in HCT-116 colorectal cancer cells, reducing the IC₅₀ by 45%^[33].

Recent advances in drug delivery have expanded the therapeutic applications of fatty acid components in RJ^[54,103]. In a DMBA-induced skin cancer model, 10-HDA was incorporated into fatty acid vesicles and co-formulated with magnolol (Mag), a phytochemical with anticancer properties. These 10-HDA-based vesicles outperformed conventional oleic acid (OA)-based ufasomes, demonstrating reduced Ki67 expression, decreased MDA levels, increased GSH activity, decreased tumor multiplicity, and improved histopathological outcomes^[138]. These results validate the enhanced efficacy of 10-HDA-based vesicular systems in topical skin cancer therapy and chemoprevention.

In TNBC, a subtype known for its limited treatment options, the combination of RJ-TQ produced significant cytotoxic synergy. In MDA-MB-231 cells, combination therapy at sub-IC₅₀ concentrations significantly reduced cell viability and induced apoptosis 3- to 5-fold compared to either treatment alone^[160]. Flow cytometry analysis revealed a 6-fold increase in apoptotic cells, with Caspase-3 cleavage confirming enhanced apoptosis^[171].

These findings collectively underscore the adjuvant potential of RJ in cancer therapy, demonstrating its ability to potentiate chemotherapeutic efficacy, reduce off-target toxicity, and enhance apoptosis through immunomodulatory and redox-mediated pathways. Furthermore, the low toxicity profile of RJ highlights its translational value as a nutraceutical adjunct in integrative cancer therapy.

4.2 Nanoparticle-based delivery of RJFA

Despite the diverse pharmacological properties of RJ, including antioxidant, anti-inflammatory, antibacterial, and antitumor effects, its clinical use is hindered by poor physicochemical stability and sensitivity to air, heat, light, and moisture^[172-173]. To overcome these limitations, nanotechnology-based delivery systems have been developed to enhance the bioavailability of RJ, shelf stability, and therapeutic consistency^[174].

Chitosan-based nanoparticles (NPs) encapsulating RJ were prepared using ionic gelation, a mild and solvent-free encapsulation method, achieving an encapsulation efficiency of 48.68% and a loading capacity of 31.90%^[174]. Compared with free RJ, the chitosan NP formulation exhibited improved thermal stability, enhanced antioxidant and antibacterial activities, greater storage stability, and a controlled-release profile that protected gastrointestinal conditions^[175-176].

In breast cancer models, layered double hydroxide (LDH)-based RJ nanocarriers (RJ-LDH) significantly outperformed free RJ in suppressing tumor volume. RJ-LDH-50 notably increased serum interferon- γ (IFN- γ) levels while decreasing TGF- β and forkhead box P3 (FoxP3), indicating inhibition of regulatory T cells and enhancement of Th1 immune responses. RT-PCR analysis confirmed T-bet upregulation and FoxP3 suppression, suggesting potent immunomodulation^[177-179].

In green nanotechnology applications, RJ-mediated silver NPs (RJ-AgNPs) have demonstrated potent anticancer effects by modulating the vascular endothelial growth factor (VEGF)/PI3K/Akt/MMP-2 signaling pathway in HeLa and A549 cells. RJ-AgNPs reduced nitric oxide, VEGF, and cyclooxygenase-2 (COX-2) levels, and induced apoptosis through the regulation of oxidative stress and inflammation^[180].

Co-delivery systems have further enhanced the efficacy of RJFA, as demonstrated in lead acetate-induced toxicity models. The co-administration of 10-HDA with zinc oxide NPs (ZnO-NPs) restored antioxidant enzyme levels, suppressed inflammatory cytokines, and regulated apoptotic signaling, offering superior protection compared to either agent alone^[181].

Overall, NP-based delivery platforms, including CSNPs, LDH, AgNPs, and ZnO-NPs, significantly enhance the stability, bioavailability, and therapeutic efficacy of RJFA. These innovations enable targeted delivery, immune enhancement, and integration of RJ-derived compounds into nanomedicine for cancer therapy.

4.3 Bioavailability and metabolic barriers of RJFA

Although RJFA exhibits promising pharmacological activities, its clinical utility is hindered by poor bioavailability and metabolic instability^[12,90]. Rapid degradation in the gastrointestinal tract and hepatic first-pass metabolism diminishes systemic concentrations, thereby limiting therapeutic efficacy^[182-183]. Xenobiotic metabolism, including *N*-acetylation via *N*-acetyltransferase (NAT), influences the clearance of RJ compounds and is implicated in the pathogenesis of colorectal, bladder, and breast cancers^[184].

Gastrointestinal enzymatic degradation and extensive hepatic transformation present key pharmacokinetic (PK) challenges. Strategies such as nanoencapsulation and lipid-based carriers have been proposed to protect RJ constituents from degradation and enhance intestinal absorption^[45]. These formulation approaches aim to optimize the PK profile of 10-HDA and other RJFAs for systemic therapeutic use^[33].

PK studies in humans provide additional insights. In a clinical trial, 12 healthy volunteers received RJ or enzyme-treated RJ (ETRJ) in capsule or tablet form (800–1 600 mg). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of plasma and urine samples revealed increased levels of 2-decenedioic acid (2-DA), SA, and 3-hydroxysebacic acid (3-HSA) after RJ intake^[185]. The absence of intact 10-HDA and 10-HDAA in plasma indicated that they undergo metabolism via ω -oxidation, likely due to the terminal hydroxyl groups undergoing hepatic phase I transformation.

Protease-treated RJ enhanced fatty acid absorption, suggesting that RJ protein binding may reduce the availability of free fatty acids in the gut^[182]. Fatty acids are known to bind albumin^[186], potentially impeding passive uptake. Quantitative metabolite profiling confirmed

dose-dependent increases in urinary excretion of dicarboxylic acid metabolites within 12 h post-ingestion, supporting their use as biomarkers for RJ absorption and metabolism^[185].

These findings highlight key metabolic and absorption barriers facing RJFAs, including rapid hepatic oxidation and gastrointestinal protein binding, which may limit their effectiveness. Strategies such as enzyme pre-treatment and NP formulation hold promise for improving bioavailability and advancing the clinical utility of RJ-derived therapeutics.

5. Limitations and future perspectives

5.1 Limitations

Despite growing evidence supporting the pharmacological potential of RJ and its primary fatty acid, 10-HDA, several limitations must be addressed for clinical translation to be feasible. A major concern is the safety profile of RJ, particularly its potential to trigger allergic reactions. Although RJ is widely used in foods, supplements, and cosmetics and generally regarded as non-toxic, adverse effects, including contact dermatitis, rhinitis, conjunctivitis, bronchospasm, anaphylactic shock, and, rarely, death, have been reported. These reactions are often more severe than those elicited by other bee products^[187]. Individuals with known allergies to hive products or with atopic histories (e.g., asthma and eczema) are at high risk and should avoid RJ. Special caution is also warranted in children, pregnant or lactating women, and immunocompromised individuals. Moreover, first-time reactions may arise from cross-reactivity with unrelated allergens, underscoring the need for allergy testing and comprehensive toxicological evaluation^[187].

In addition to safety concerns, the application of RJFAs is hindered by inefficiencies in current extraction and standardization methods. Traditional techniques, such as solvent extraction and the Soxhlet method, are hindered by low efficiency, lengthy processing times, and the use of toxic solvents. While newer approaches, such as h-LLE, offer improvements, challenges related to solvent compatibility persist. Advanced detection techniques such as liquid chromatography-high-resolution mass spectrometry (LC-HRMS) have facilitated the identification of 15 long-chain fatty acids, including regioisomers of hydroxymyristic, hydroxypalmitic, and hydroxystearic acids^[188]. However, pure solvents may also extract non-lipid contaminants such as sugars and proteins, reducing product specificity. To address this, sequential solvent extraction and chromatographic purification are often implemented^[189].

UAE offers significant advantages, including shorter processing time, lower energy consumption, and high extraction efficiency, making it suitable for industrial-scale RJFA isolation^[190]. However, inappropriate ultrasound parameters can induce the generation of free radicals, potentially leading to degradation of bioactive lipids^[191-192]. Advanced techniques, such as microwave-assisted extraction, supercritical fluid extraction, and pulsed electric field-assisted extraction, have demonstrated superior efficiency, reduced environmental impact, and minimal thermal degradation^[193], underscoring the need for continuous optimization of UAE parameters to maintain product quality.

Despite its efficacy, solvent extraction remains constrained by environmental and health risks, especially when using volatile organic

solvents. Ethanol, a greener alternative, has demonstrated effective RJFA recovery with 99% ethanol yielding 10-HDA-rich fractions exceeding 10% concentration^[82]. Nevertheless, solvent volume requirements, energy input, and prolonged extraction times present challenges for industrial scalability.

Green technologies, including ultrasound-assisted, microwave-assisted, and pulsed electric field-assisted methods, demonstrate promise in enhancing yield and reducing solvent usage. However, they require further optimization for scalability and routine use^[194]. Establishing standardized protocols for extraction, purification, and quality control is essential for ensuring product consistency, safety, and reproducibility^[23].

Another barrier is the compositional variability of RJ, which is influenced by factors such as bee species, botanical source, geography, and seasonality^[195-196]. For example, significant differences in 10-HDA content have been reported across RJ samples from Brazil, Japan, India, Turkey, and Switzerland^[197], which complicates cross-study comparisons and undermines reproducibility. The route of administration also significantly affects outcomes. In murine models of mammary carcinoma, intravenous RJ administration inhibited metastasis, while intraperitoneal and subcutaneous routes were ineffective^[198]. Although oral delivery is most practical for humans, the optimal route for anticancer efficacy remains undefined and requires PK and pharmacodynamic (PD) evaluation.

Moreover, while RJFAs such as 10-HDA, and 10-HDAA exhibit antioxidant, anti-inflammatory, and anticancer effects, their structure-activity relationships (SARs) are poorly understood^[199-200]. Elucidating SARs is critical for rational design and optimization of bioactivity^[108]. These compounds also exhibit favorable physicochemical properties, making them suitable for formulation into functional foods and nutraceuticals, thereby enhancing stability and consumer appeal. However, their therapeutic potential in real-world settings remains insufficiently explored^[90].

Finally, despite compelling preclinical evidence, human clinical data are limited. Large-scale nutritional, epidemiological, and interventional studies are crucial for validating the safety, efficacy, and long-term effects of RJFA in cancer prevention and therapy^[90]. Addressing these multifaceted limitations, spanning safety, extraction, standardization, variability, SAR elucidation, and translational gaps, will be key to unlocking the full therapeutic potential of RJFA for clinical and commercial integration^[103].

5.2 Future perspectives

While preliminary studies underscore the anticancer potential of RJFA, particularly 10-HDA, critical challenges must be addressed to enable its clinical translation. Advancing these bioactive compounds as therapeutic agents requires a cohesive, multidisciplinary strategy integrating pharmacology, immunology, biotechnology, and clinical medicine. The following priority areas outline essential directions to bridge the gap between preclinical promise and clinical applicability.

5.2.1 Standardization and safety validation

Robust standardization is essential to ensure therapeutic reproducibility and regulatory compliance. Comprehensive studies should characterize seasonal and geographic variations in RJFA

profiles, define optimal storage conditions, and establish safe dosing parameters. Advanced analytical platforms (e.g., LC-MS/MS, nuclear magnetic resonance (NMR)) should be applied to rigorously profile RJ-derived extracellular vesicles (RJEVs) and lipid fractions. To ensure safety, particularly for vulnerable populations, pre-administration allergy screening and toxicological assessments should be integrated into the development pipeline.

5.2.2 PKs and population-specific studies

Detailed PK and PD studies are required to evaluate absorption, distribution, metabolism, and excretion (ADME) profiles. Population-specific assessments, including adolescents, the elderly, and pregnant individuals, will inform personalized dosing strategies and therapeutic windows. Moreover, investigating interactions with conventional chemotherapeutics and their potential to modulate multidrug resistance mechanisms is vital for safe co-administration.

5.2.3 Mechanistic insights via omics technologies

Although RJFA exerts antioxidant, anti-inflammatory, and lipid-modulating effects, its underlying molecular mechanisms remain incompletely defined. Integrative omics approaches, such as single-cell transcriptomics, spatial genomics, and microbiome profiling, can identify precise cellular targets and pathways. These tools also provide avenues for discovering predictive biomarkers and supporting the design of personalized therapies.

5.2.4 Formulation optimization and derivative development

Limited bioavailability remains a barrier to clinical efficacy. Novel delivery systems, such as NP formulations and liposomal carriers, should be explored to enhance stability, solubility, and tissue targeting. Structural analogs (e.g., diHDA-glycerol) and semisynthetic derivatives may offer improved pharmacological profiles and should undergo systematic functional and safety evaluation. Additionally, the development of RJ-based nutraceuticals and functional foods demands strict quality control and regulatory oversight.

5.2.5 Overcoming technological and structural barriers

Green and scalable extraction methods, including ultrasound-, microwave-, and pulsed-electric field-assisted technologies, should be optimized for industrial applications. Parallel efforts should clarify SAR to guide the rational design of potent analogs. High-throughput screening platforms can accelerate the identification of novel bioactives and enable effective combinations with existing therapies.

5.2.6 Clinical validation and synergistic combination therapies

Large-scale, randomized clinical trials targeting specific conditions (e.g., HCC, hyperlipidemia, and inflammatory disorders) are crucial for validating efficacy and safety. Investigating RJFA as an adjuvant in synergistic combination therapies, particularly with chemotherapeutics and immunotherapies, may enhance therapeutic outcomes, reduce toxicity, and address drug resistance. Mechanistic preclinical models should be prioritized to support synergistic efficacy and guide trial design.

By addressing these research priorities, RJFA may be effectively translated into novel adjunctive or standalone therapies within the field of integrative oncology. Their success will depend on sustained interdisciplinary collaboration and rigorous validation at both preclinical and clinical levels, ultimately bridging the gap between natural product research and real-world therapeutic innovation.

6. Conclusion

RJ, a bioactive secretion from the hypopharyngeal glands of honeybees, is a multifunctional natural product with diverse therapeutic properties, including anticancer activity. This review synthesizes preclinical and limited clinical evidence on RJ and its primary bioactive fatty acid, 10-HDA, as emerging anticancer agents. Preclinical studies demonstrate that RJ and 10-HDA suppress tumor growth, invasion, and metastasis *via* modulating apoptosis, inflammation, oxidative stress, and angiogenesis in multiple cancer models. Notably, RJ improves survival outcomes in animal studies and mitigates chemotherapy-induced toxicities, such as mucositis, fibrosis, nephrotoxicity, and hepatotoxicity, through its regulatory effects on molecular pathways, including NF- κ B, nuclear factor erythroid 2-related factor 2 (Nrf2), and PI3K/Akt. While clinical data remain sparse, preliminary findings suggest that RJ is safe and tolerable in cancer patients, supporting its potential as an adjuvant therapy to enhance treatment efficacy and quality of life.

Beyond oncology, the rich composition of proteins, peptides, fatty acids, and polyphenols in RJ confers a broad spectrum of pharmacological effects, including antimicrobial, immunomodulatory, neuroprotective, and hepatoprotective activities. These properties extend to metabolic disorders, reproductive health, and gastrointestinal protection, particularly in oxidative stress-related conditions. However, the translation of RJ-derived agents into clinical practice requires addressing critical limitations, including standardization of formulations, optimization of dosing regimens, and validation through robust randomized controlled trials.

The integration of RJ into personalized and preventive medicine frameworks is further bolstered by advances in drug delivery technologies, such as nanoscale formulations, which may enhance bioavailability and target specificity. Therefore, given the escalating global cancer burden and the urgent need for innovative therapies, prioritizing research on the anticancer potential of RJ is imperative. Future studies should focus on elucidating molecular mechanisms, refining preclinical models, and conducting large-scale clinical trials to establish RJ and 10-HDA as evidence-based adjuvants in cancer therapy. Collectively, RJ emerges as a promising natural product with translational potential across multifaceted therapeutic applications.

Conflicts of interest

The authors declare no conflicts of interest.

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