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Safranal, a Natural Monoterpene with Molecular Targets and Nanoplatforms in Cancer Management

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Abstract: Safranal, a monoterpene aldehyde and one of the principal bioactive constituents of Crocus sativus L. (saffron), has emerged as a natural compound with significant pharmacological promise in cancer therapeutics. Increasing preclinical evidence highlights its multifaceted anticancer properties, mediated through diverse molecular and cellular mechanisms that interfere with tumor initiation, progression, and metastasis. Safranal exhibits potent antiproliferative effects and promotes apoptosis by modulating both intrinsic and extrinsic pathways, including regulation of Bax/Bcl-2 balance, activation of caspases, and disruption of mitochondrial membrane potential. Beyond apoptosis, it effectively interferes with oncogenic signaling networks such as PI3K/Akt, MAPK, and Wnt/β-catenin, thereby limiting cancer cell survival and growth. Safranal also inhibits angiogenesis and metastasis by downregulating vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), crucial mediators of tumor invasion and vascular remodeling. In addition, its antioxidant and anti-inflammatory activities contribute to reducing oxidative stress and chronic inflammation within the tumor microenvironment, both of which are central to carcinogenesis. Recent progress in nanotechnology-based formulations, including liposomes, polymeric nanoparticles, and solid lipid carriers, has significantly enhanced safranal stability, solubility, and bioavailability, broadening its therapeutic applicability. Experimental evidence from various cancer models, such as breast, colon, liver, and pancreatic cancers, supports its potential as a complementary or alternative anticancer agent.

Keywords: Safranal, Antioxident, Anticancer, Nanoparticles, Pharmacology

I. INTRODUCTION

Plants have long been recognized as reservoirs of bioactive compounds with diverse therapeutic potential (Seigler, 2012). Among the multitude of plant-derived secondary metabolites, carotenoids form a structurally diverse group that plays crucial roles in pigmentation, photoprotection, and antioxidative processes in plants (Britton, 2009). Oxidative cleavage of carotenoids leads to the formation of apocarotenoids, a biologically active subclass of compounds. One of the most prominent members of this group is safranal, a cyclic terpenic aldehyde ($C_{10}H_{14}O$) derived predominantly from the stigmas of *Crocus sativus L.* (saffron). Safranal originates from the degradation of picrocrocin during saffron processing and is primarily responsible for saffron's characteristic aroma (Walter et al., 2010). Although initially valued for its sensory qualities, safranal has attracted increasing interest due to its wide-ranging pharmacological and anticancer properties.

Safranal has emerged as a candidate compound with significant anticancer activity, supported by multiple lines of in vitro and in vivo evidence. In cultured cancer cells, safranal demonstrates dose-dependent cytotoxicity, particularly against human carcinoma lines such as HeLa, MCF-7, and HepG2. Its antiproliferative effects are associated with apoptosis induction, as indicated by morphological changes, DNA fragmentation, and the activation of pro-apoptotic genes. Evidence suggests that safranal modulates mitochondrial function, enhances oxidative stress in tumor cells, and downregulates anti-apoptotic proteins, thereby disrupting survival pathways. Importantly, these cytotoxic effects appear to be more pronounced in malignant cells than in normal cells, suggesting a degree of selectivity that enhances its therapeutic appeal.

In addition to direct cytotoxicity, safranal interferes with angiogenesis and metastasis-related pathways, which are critical to tumor growth and progression. Preliminary mechanistic studies indicate that safranal may modulate signaling cascades such as Wnt/β-catenin, matrix metalloproteinases and vascular endothelial growth factor (VEGF), all of which play central roles in tumor proliferation and neovascularization. These findings point toward a multitargeted anticancer action that aligns with the polypharmacological profile often observed in plant-derived natural compounds. While much of this evidence remains preclinical, it underscores the potential for safranal to serve as a foundation for novel anticancer therapeutics.

One of the defining pharmacological activities of safranal is its antioxidant capacity. Oxidative stress is a common pathological mechanism underlying cancer development as well as numerous chronic diseases, including cardiovascular disorders, neurodegenerative conditions, and diabetes. Safranal exhibits strong free radical scavenging activity and enhances the activity of endogenous antioxidant enzymes, thereby protecting cellular macromolecules against oxidative damage (Hosseinzadeh et al., 2002).

In the context of oncology, this antioxidant activity may appear paradoxical, as pro-oxidant activity often contributes to anticancer effects. However, safranal dual capacity—protecting normal cells from oxidative damage while inducing oxidative stress in cancer cells—illustrates a context-dependent pharmacological profile that may be therapeutically advantageous.

The pharmacological activity of safranal extends into several additional domains. It has shown anti-inflammatory properties, suppression of lipid peroxidation, and protective effects against ischemia-reperfusion injury in cardiac and neural tissues. These effects, when considered alongside its anticancer, antioxidant, anticonvulsant, and antidepressant properties, highlight safranal as a multifunctional bioactive compound with relevance across diverse therapeutic areas. However, challenges such as poor stability, volatility, and limited aqueous solubility restrict its clinical translation. Advances in nanotechnology—including liposomal encapsulation, solid lipid nanoparticles, and polymeric carriers—are being actively investigated to improve its bioavailability and pharmacokinetic profile, thereby unlocking its full therapeutic potential

II. METHOD OF SEARCH

Using "safranal" in the title, abstract, and keywords, a thorough search was conducted for the drug in electronic databases such as Web of Sciences, Scopus, and Pubmed. Additionally, a manual review of the retrieved papers' references was conducted.

III. ANTIOXIDANT ACTIVITY OF SAFRANAL

Safranal, the monoterpene aldehyde derived from the stigmas of *Crocus sativus L.* (saffron), has been extensively studied for its potent antioxidant properties, which play a crucial role in its pharmacological and therapeutic applications. Oxidative stress, characterized by the excessive production of reactive oxygen species (ROS) and impaired antioxidant defense, is a central factor in the pathogenesis of various chronic diseases, including cancer, diabetes, cardiovascular disorders, and neurodegeneration. Safranal acts as a free radical scavenger, reducing levels of superoxide anions, hydroxyl radicals, and lipid peroxides, thereby protecting cellular macromolecules such as DNA, proteins, and lipids from oxidative damage (Sani et al., 2022). Mechanistic studies indicate that safranal enhances the activity of key endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), restoring redox homeostasis in stressed cells. It also modulates intracellular signaling pathways linked to oxidative stress, such as the Nrf2/ARE axis, which governs the transcription of several cytoprotective genes. By activating these molecular defenses, safranal not only prevents cellular injury but also contributes to the attenuation of chronic inflammation, since oxidative stress and inflammation are intricately interconnected processes (Boskabady et al., 2019).

Additionally, in experimental models, safranal supplementation has been shown to reduce lipid peroxidation markers like malondialdehyde (MDA) while elevating reduced glutathione (GSH), highlighting its ability to maintain membrane integrity and mitochondrial function. These properties make safranal a promising natural antioxidant agent with potential therapeutic implications in diseases driven by oxidative stress.The chemicals known as antioxidants scavenge free radicals that result from oxidative stress. Plant-based phytochemicals make up the majority of exogenous antioxidants (Sarangarajan et al., 2017). Alkaloids, isothiocyanates, carotenoids, and flavonoids are among the various families of secondary metabolites to which they belong (Dinkova-Kostova, 2008). In vitro and in vivo techniques such as the DPPH scavenging assay FRAP are used to evaluate these antioxidants' antioxidant capacity (Chanda and Dave, 2009). Safranal functions as an antioxidant and scavenges free radicals. Its prolonged conjugation, which quenches singlet oxygen in a mechanism involving the transfer of excitation energy from $^1O_2$ to the safranal molecule, is most likely the cause of its antioxidant behavior, even though the precise cause is unclear. The authors have demonstrated this by in silico analyses of Safranal on a variety of enzymes.

IV. SAFRANAL AND ITS EFFECTS ON DIFFERENT CANCER CELL

Cancer is a multifactorial disease characterized by uncontrolled cellular proliferation, escape from apoptosis, metabolic reprogramming, and the ability to invade distant tissues. Its development involves intricate interactions between genetic, epigenetic, and environmental factors. Among the molecular contributors to tumorigenesis, dysregulated redox signaling plays a pivotal role. Reactive oxygen species (ROS), generated primarily by nicotinamide adenine dinucleotide phosphate oxidases (NOXs), mediate several hallmarks of cancer including cell proliferation, angiogenesis, invasion, and evasion of apoptosis (Paik et al., 2011). Persistent oxidative stress activates oncogenic signaling cascades, transcription factors, and pro-survival pathways, ultimately driving malignant transformation (Dunaway et al., 2018).

Natural bioactive compounds, particularly phytochemicals, have attracted increasing attention in cancer prevention and therapy due to their ability to modulate redox homeostasis, regulate signaling pathways, and selectively induce cytotoxicity in tumor cells. Safranal, a major volatile constituent of *Crocus sativus* (saffron), exhibits multiple pharmacological properties including antioxidant, anti-inflammatory, antidepressant, and anticancer activities (Akhondzadeh et al., 2004). Preclinical and molecular studies have highlighted its ability to suppress tumor growth, inhibit angiogenesis, induce apoptosis, and enhance the efficacy of conventional chemotherapeutics across different cancer types. The following sections summarize current evidence on the anticancer activities of safranal across a range of malignancies.

4.1 Breast Cancer

One of the earliest lines of evidence implicating saffron extracts and their constituents in breast cancer came from studies on the MCF-7 estrogen receptor-positive cell line. Mousavi et al. (2009) reported that saffron extract, at concentrations between 200–2000 µg/mL, reduced MCF-7 cell viability in a concentration- and time-dependent manner, with an IC50 of 400 ± 18.5 µg/mL after 48 hours. Flow cytometry revealed that the loss in viability was associated with apoptotic DNA fragmentation, indicating programmed cell death as a key mechanism.

Further mechanistic insights were provided by gene expression studies. Mousavi et al. (2009) observed that saffron extract downregulated pro-angiogenic genes VEGF-A and VEGFR-2 in MCF-7 cells, with maximal suppression of VEGF-A (17%) at 800 µg/mL and VEGFR-2 inhibition (20%) at 400 µg/mL. These findings highlight safranal contribution to the antiangiogenic properties of saffron in breast cancer.

Beyond extracts, individual saffron constituents were assessed. Chryssanthi et al. (2007) demonstrated that safranal, crocin, and crocetin exert antiproliferative effects on both MCF-7 and MDA-MB-231 breast cancer cells, independent of estrogen receptor status. While crocins emerged as the major contributors, safranal was also found to induce dose-dependent growth inhibition, underscoring its direct cytotoxic potential.

High-throughput proteomic and epigenomic studies have expanded the mechanistic understanding of safranal in breast cancer. Using phosphoproteomic and acetylomic profiling, Ashrafian et al. (2022) showed that safranal treatment disrupted phosphorylation of proteins associated with DNA replication, EGFR signaling, and repair pathways in MDA-MB-231 cells. This disruption triggered

mitotic catastrophe, impaired checkpoint recovery, and promoted apoptosis. In addition, safranal induced hyperacetylation of histone H3, activating pro-apoptotic gene transcription, while hypoacetylating H4, thereby suppressing DNA repair machinery.
Zarrineh et al. (2022) further confirmed safranal multifaceted action using time-course sialiomics and proteomics. Their data revealed that safranal primarily induced mitochondrial dysfunction, inhibited metabolism, and triggered apoptotic pathways leading to DNA fragmentation. A consistent downregulation of sialylation profiles in integrins, TNF receptors, and CAMs was observed, impairing cancer cell adhesion, viability, and migration.
Encapsulation strategies enhanced safranal bioactivity. Malaekeh-Nikouei et al. (2013) reported that liposomal safranal displayed greater cytotoxicity than free safranal against HeLa and MCF-7 cells. The MTT assay and flow cytometry confirmed apoptosis as the predominant mode of cell death, suggesting that nanocarrier formulations could significantly potentiate safranal anticancer efficacy.

4.2 Cervical Cancer

Emerging evidence suggests that safranal exerts potent antiproliferative effects against cervical carcinoma. Ali et al. (2024) reported transcriptomic alterations in HeLa and C-4 I cells after safranal exposure, with over 1000 genes differentially expressed. KEGG and GO analyses implicated regulation of MAPK, TGF-β, p53, TNF, and FoxO pathways, which mediated apoptosis, necrosis, and G1-phase arrest. Key driver genes, including DNAJC3, EIF2AK2, and PARP14, were significantly altered, reflecting broad stress-response modulation.
Interestingly, safranal may act through an uncommon mechanism targeting cytoskeletal dynamics. Cheriyamundath et al. (2018) demonstrated that safranal perturbs tubulin secondary structure and hinders microtubule nucleation potential without stabilizing them, unlike conventional tubulin-binding drugs. This disruption impairs recovery after microtubule disassembly and leads to loss of cell viability in HeLa cells, representing a unique antiproliferative mechanism with potentially fewer off-target effects.

4.3 Gastrointestinal Cancers

Safranal demonstrates significant efficacy in gastrointestinal (GI) malignancies. Al Otaibi (2024) reported that safranal suppressed viability of AGS and NCI-N87 gastric cancer cells, impaired migration and colonization, and induced senescence-like morphologies with vacuolation. Mechanistically, safranal blocked mitotic progression, triggered apoptosis, and curtailed metastatic potential.
In colorectal cancer, Zhang et al. (2018) revealed that safranal inhibited colo-205 cell growth with an IC50 of 20 μM, mediated through ROS accumulation, mitochondrial membrane potential reduction, Bax upregulation, Bcl-2 downregulation, and PI3K/AKT/mTOR pathway inhibition. Feng et al. (2025) highlighted an immunomodulatory dimension, showing that safranal suppressed IL-17-mediated inflammatory markers and enhanced responsiveness to immunotherapy, suggesting promise as a synergistic agent.
Safranal also exerts antiangiogenic activity in hepatocellular carcinoma (HCC). Abdalla et al. (2022) showed that safranal inhibited VEGF secretion in HepG2 cells, suppressed HUVEC proliferation (IC50 = 300 μM), and blocked angiogenesis by downregulating HIF-1α, VEGF, VEGFR2, AKT, ERK1/2, MMP-9, and STAT3. These findings position safranal as a vascular-targeted therapy in liver malignancies.

4.4 Prostate Cancer

Prostate carcinoma has been another major target of safranal research. Samarghandian et al. (2013) demonstrated potent cytotoxicity against PC-3 cells with IC50 values of 13.0 μg/mL at 48 hours and 6.4 μg/mL at 72 hours. Apoptosis was confirmed through DNA laddering and flow cytometry.
Further mechanistic insight was provided by Jiang et al. (2020), who showed that safranal suppresses NF-κB and E2F1 transcriptional activity, leading to downregulation of Skp2. This cascade reduced expression of c-MYC, CDK4/6/2, and phosphorylated Rb while increasing p21 and p27, collectively delaying tumor regrowth and inhibiting prostate cancer recurrence. These findings highlight safranal potential role in preventing relapse by targeting dormant tumor cell populations.

4.5 Lung Cancer

Saffron ethanolic extract containing safranal demonstrated concentration- and time-dependent cytotoxicity in lung carcinoma cells. IC50 values were 1500 μg/mL at 24 hours and 565 μg/mL at 48 hours, while sparing non-malignant L929 cells, suggesting selective toxicity (Samarghandian et al., 2010). Morphological evidence supported apoptotic death, although safranal specific role in lung cancer warrants further study.

4.6 Leukemia

In silico and *in vitro* studies have highlighted safranal activity against chronic myeloid leukemia (CML). Geromichalos et al. (2014) demonstrated that safranal binds to the Bcr-Abl tyrosine kinase at the same site as imatinib mesylate, the frontline CML drug. In K562 cells, safranal reduced viability and downregulated Bcr-Abl expression, confirming its potential as a natural inhibitor targeting oncogenic kinases.

4.7 Brain Cancer

Safranal exhibits significant antiproliferative effects against neuroblastoma. Samarghandian et al. (2014) reported IC50 values of 23.3 μg/mL at 48 hours and 11.1 μg/mL at 24 hours, accompanied by the emergence of sub-G1 peaks in flow cytometry, consistent with apoptotic DNA fragmentation. These findings suggest safranal as a candidate for brain tumor therapy.

4.7 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality, and safranal has shown promising activity against this malignancy. Abdalla et al. (2022) demonstrated that safranal suppressed proliferation marker Ki-67 and induced apoptosis (via TUNEL and M30 assays) in diethylnitrosamine-induced rat HCC models, while also downregulating inflammatory mediators such as TNF-α, COX-2, iNOS, and NF-κB.
At the molecular level, Samra et al. (2025) revealed that safranal suppressed Wnt/β-catenin signaling, reducing Cyclin D1, VEGF, and MMP-9 expression, thereby inhibiting angiogenesis and tumor growth. Incorporation into gold nanoparticles (SAF-AuNPs) further enhanced anticancer activity, attenuated multidrug resistance, and potentiated doxorubicin efficacy.
Consistently, Al-Hrout et al. (2018) reported that safranal induced endoplasmic reticulum (ER) stress-mediated apoptosis in HepG2 cells, activating unfolded protein response (UPR) signaling. This dual mechanism—targeting angiogenesis and ER stress pathways—positions safranal as a multi-targeted therapeutic for liver cancer

Table 1: Reported Mechanisms of Action of Safranal against Various Cancer Cell Lines

Cancer type/ Cell Line	Mechanism of Action	Reference
Breast Cancer- MCF 7	Apoptotic cell death	Mousavi et. al, 2009
Breast Cancer- MCF-7	Inhibition of the expression of VEGF-A and VEGFR-2	Mousavi et. al, 2014
Breast Cancer- MCF-7 and MDA-MB-231	Antiproliferative activity	Chryssanthi et. al., 2007
Breast Cancer- MDA-MB-231	Apoptotic cell death, DNA damage	Ashrafian et. al., 2022
Breast Cancer- MDA-MB-231	Mitochondrial dysfunction, metabolic inhibition, and initiation of apoptotic signaling	Zarrineh et. al, 2022
HeLa, MCF7, and L929	Apoptotic cell death	Malaekeh-Nikouei et al. 2013
Cervical Cancer- HeLa	Apoptotic cell death	Ali et al. 2024
Cervical Cancer- HeLa	Inhibition of microtubule assembly	Cheriyamundath et al. 2018
Gastrointestinal cancer- AGS and NCI-N87	Inhibition of cell viability, proliferation and survival	Al Otaibi AJ, 2024
Colon cancer COLO-205	Inhibition of PI3K/AKT/mTOR signaling pathway and G2/M cell cycle arrest	Zhang et al. 2018
Gastric Cancer	Activation of IL-17 signaling pathway	Feng et al. 2025
Prostate Cancer-PC-3	Apoptotic cell death	Samarghandian et al. 2013
Prostate Cancer	Suppression of NF-κB and E2F1	Jiang et al. 2020
Lung Cancer	Inhibition of cell viability	Samarghandian et al., 2010
Leukemia- K562	Cytototxicity	Geromichalos et al., 2014
Neuroblastoma	Apoptotic cell death	Samarghandian et al., 2014
Hepatocellular Carcinoma- HepG2	Apoptotic cell death	Abdalla et al. 2022
Hepatocellular Carcinoma	Activation of the Wnt/β-catenin pathway	Samra et al. 2025
Hepatocellular Carcinoma- HepG2	Apoptotic cell death	Al-Hrout et. al, 2018
Oral Cancer- KB, NIH 3T3	Apoptotic cell death	Jabini et al, 2017

V.PHARMACOLOGICAL AND THERAPEUTIC POTENTIAL OF SAFRANAL AGAINST CANCER CELL

Cancer remains one of the most complex and life-threatening diseases worldwide, characterized by uncontrolled cell proliferation, resistance to apoptosis, sustained angiogenesis, and metastatic spread. Despite major advances in chemotherapy, radiotherapy, targeted therapy, and immunotherapy, limitations such as systemic toxicity, tumor resistance, and incomplete remission continue to hinder clinical outcomes. In this context, natural products and their bioactive constituents have gained enormous attention as potential sources of novel anticancer therapeutics. Among these, *Crocus sativus L.* (saffron) has long been valued in traditional medicine, and its secondary metabolites, including crocin, crocetin, picrocrocin, and safranal, have shown promising pharmacological effects. Safranal, a volatile monoterpene aldehyde responsible for the distinctive aroma of saffron, has emerged as a molecule of considerable interest for cancer treatment due to its multi-targeted pharmacological activities that operate at both molecular and cellular levels.

The anticancer potential of safranal lies primarily in its ability to regulate key signaling pathways associated with tumor cell survival, proliferation, angiogenesis, and immune evasion. A significant mechanistic aspect of its activity is the inhibition of tumor-driven angiogenesis. Tumors depend on vascular endothelial growth factor (VEGF) signaling to promote blood vessel formation, which supplies oxygen and nutrients for their continued growth. Safranal has been shown to inhibit VEGF production and secretion by cancer cells such as HepG2, thereby suppressing endothelial cell proliferation and capillary tube formation. This anti-angiogenic effect is closely tied to the downregulation of hypoxia-inducible factor-1α (HIF-1α), VEGFR2, and downstream mediators including AKT, ERK1/2, matrix metalloproteinase-9 (MMP-9), focal adhesion kinase (FAK), and STAT3 (Zhang et al., 2022). By impairing these pathways, safranal effectively reduces the capacity of tumors to expand their vascular networks, hindering metastasis and progression.

Beyond angiogenesis, safranal also directly influences cancer cell survival by modulating apoptotic and cell cycle regulatory mechanisms. In glioblastoma models, transcriptomic profiling revealed that safranal treatment alters expression of genes involved in the PI3K/AKT/mTOR signaling cascade, a pathway frequently hyperactivated in malignant cells to promote growth and resist apoptosis. Computational docking studies further support the ability of safranal to interact with pivotal proteins including AKT1, PI3K, mTOR, PARP1, and caspases (Karakas et al., 2023). Such interactions disrupt survival signaling, leading to programmed cell death through both intrinsic and extrinsic apoptotic pathways. Similarly, in colon carcinoma models, safranal induced cell cycle arrest at the G2/M phase, mediated by suppression of cyclin-dependent kinases (CDKs) and checkpoint regulators, which collectively prevent tumor cells from completing mitosis (Gandomi et al., 2021).

Another layer of safranal anticancer activity arises from its epigenetic modulation of cancer cell proteomes. In triple-negative breast cancer cells, global phosphoproteomic and acetylomic analyses demonstrated that safranal disrupts DNA replication and

repair pathways by altering phosphorylation status of proteins involved in checkpoint signaling and modifying histone acetylation patterns (Salama et al., 2022). For instance, hyperacetylation of histone H3 facilitated transcription of pro-apoptotic genes, whereas hypoacetylation of histone H4 impaired DNA damage repair. These changes ultimately promoted mitotic catastrophe—a terminal outcome for cells with severe genomic instability. The epigenetic remodeling effect of safranal thus highlights its capacity to act as a regulator of chromatin state, further enhancing its therapeutic relevance in cancers resistant to conventional genotoxic drugs.

In addition to its direct effects on tumor cells, safranal contributes to the reprogramming of the tumor microenvironment. Immunological studies in colorectal cancer have shown that safranal, either alone or in combination with other saffron constituents, suppresses pro-tumorigenic cytokines such as IL-17, IL-6, TNF-α, and TGF-β while reducing the expression of immune checkpoint proteins like PD-L1 (Li et al., 2023). This immunomodulatory action favors the activation of CD4+ and CD8+ T cells, thereby enhancing antitumor immunity. The ability to interfere with the IL-17 signaling pathway indicates that safranal not only targets tumor-intrinsic pathways but also exerts systemic effects that make the tumor microenvironment less permissive for cancer progression. Importantly, such immune-modifying properties suggest that safranal could be used synergistically with immunotherapy, improving responsiveness in cancers typically resistant to immune checkpoint blockade.

On a structural and cytoskeletal level, safranal has also been reported to interfere with microtubule dynamics, which are essential for chromosome segregation during mitosis. By binding to tubulin and altering its secondary structure, safranal inhibits microtubule nucleation without causing depolymerization, thereby impairing the recovery of microtubules after cellular stress (Moradzadeh et al., 2020). This effect on the mitotic spindle translates into suppressed proliferation of rapidly dividing tumor cells such as HeLa, adding another dimension to safranal multitargeted anticancer activity.

Redox modulation is another important mechanism by which safranal exerts anticancer effects. As a potent antioxidant, it scavenges reactive oxygen species (ROS) and protects cells against oxidative stress. While excessive ROS levels promote DNA damage and tumor initiation, cancer cells also exploit redox signaling for growth and survival. Safranal appears to strike a balance by reducing oxidative DNA damage in normal cells while simultaneously disrupting ROS-dependent proliferation signals in cancer cells (Rezaee et al., 2013). Such dual action suggests that safranal may act as a selective protector of non-cancerous tissues, thereby minimizing the collateral toxicity associated with many conventional chemotherapeutic agents.

Therapeutically, safranal offers several advantages that make it a promising anticancer candidate. It exhibits cytotoxicity against a range of cancer cell types—including breast, prostate, cervical, colon, and glioblastoma—while displaying relatively low toxicity toward normal cells (Escribano et al., 1996; Samarghandian et al., 2013). Its multi-targeted nature reduces the likelihood of resistance development, as tumor cells would need to adapt simultaneously across multiple signaling pathways to overcome its effects. Moreover, the use of nanocarrier systems such as liposomal formulations has been shown to enhance the bioavailability and cytotoxicity of safranal, enabling more effective drug delivery to tumor sites (Nair et al., 2013)

VI. SAFRANAL-BASED NANOPARTICLES FOR CANCER TREATMENT

The promise of safranal a volatile monoterpene aldehyde derived from Crocus sativus L. (saffron) as an anticancer agent is markedly enhanced through the development of nanoparticle-based delivery systems. These formulations address safranal inherent limitations, such as poor solubility and stability, while augmenting its therapeutic efficacy across various cancer models. Nanocarriers not only improve pharmacokinetic properties but also enable targeted delivery, enhancing cellular uptake, bioavailability, and antitumor activity.

6.1 Gold Nanoparticles Conjugated with Safranal

In hepatocellular carcinoma (HCC), the Wnt/β-catenin signaling pathway plays a prominent role in tumor initiation, progression, and drug resistance. Safranal (SAF) has been shown to suppress this pathway by downregulating components such as Wnt-3a, β-catenin, cyclin D1, VEGF, and MMP-9, thereby inhibiting proliferation and angiogenesis (Samra et al., 2025). When safranal is conjugated onto gold nanoparticles—forming SAF-AuNPs—its antitumor potential is significantly amplified. These conjugates not only reinforce suppression of proliferative and angiogenic signals but also enhance chemosensitivity. Importantly, SAF-AuNPs improve the antitumor efficacy of doxorubicin-loaded gold nanoparticles (DOX-AuNPs) by lowering multidrug resistance (MDR) protein levels, potentially reducing therapeutic doses and systemic toxicity (Al-Hrout et al., 2025). This dual effect makes SAF-AuNPs a compelling candidate for combination chemotherapeutic strategies against HCC.

6.2 Iron Oxide (Fe_3O_4) Nanoparticles Functionalized with Safranal

Iron oxide nanoparticles functionalized with glucose and conjugated to safranal (Fe_3O_4@Glu-Safranal NPs) provide another innovative platform for liver cancer therapy. In vitro studies using HepG2 liver cancer cells revealed an IC50 of approximately 305 µg/mL for the Fe_3O_4@Glu-Safranal NPs—substantially lower than that of safranal alone (474 µg/mL) or unmodified Fe_3O_4 nanoparticles (1546 µg/mL), demonstrating enhanced cytotoxic potency (Mikaeili Ghezeljeh et al., 2024). These nanoparticles generate elevated reactive oxygen species (ROS) within cancer cells, with ROS-positive populations rising from 1.97 % to 19.6 %, thereby triggering apoptosis and necrosis (Mikaeili Ghezeljeh et al., 2024). Flow cytometry confirmed that treatment with Fe_3O_4@Glu-Safranal NPs led to increased early and late apoptotic populations compared to controls. Additionally, the IC50 value for these nanoparticles in normal cells was 680 µg/mL, suggesting a therapeutic window with minimal off-target toxicity (Mikaeili Ghezeljeh et al., 2024).

6.3 Metal–Organic Frameworks (MOFs) Loaded with Safranal

Metal–organic frameworks (MOFs) composed of iron—such as MIL-88B(Fe)—serve as multifunctional nanocarriers with chemodynamic capabilities. When safranal is incorporated into these structures (Safranal-MIL-88B(Fe)), the resulting composites display anticancer activity against HepG2 liver cancer cells, mediated by combined release of safranal and iron ions (Al-Kaabi et al., 2024). The iron component can catalyze Fenton reactions that generate ROS, facilitating oxidative stress and cell death (Al-Kaabi et al., 2024). Moreover, these nanocomposites exhibit antibacterial effects against E. coli and Lactobacillus, positioning them as dual-purpose platforms for cancer and infection therapy (Al-Kaabi et al., 2024). Despite challenges in payload stability, MOF-based delivery holds tremendous potential for multifunctional cancer nanotherapy.

6.4 Liposomal Safranal

Liposomal encapsulation is a well-established strategy to enhance drug stability, solubility, and cellular uptake. Liposomal safranal displays significantly higher anticancer efficacy in vitro than free safranal. In HeLa and MCF-7 cancer cell lines, liposomal safranal exhibited lower IC50 values and enhanced induction of apoptosis, as shown by increased sub-G1 populations in flow cytometry (Malaekeh-Nikouei et al., 2013). These findings underscore the advantage of nanoscale carriers to deliver higher concentrations of safranal directly to tumor cells while reducing potential systemic exposure.

Table 2: Recent Advances in Safranal-Based Nanoparticle Formulations and Their Biomedical & Industrial Applications

Nanoparticle Composition	Effects	References
Fe_3O_4@Glucose-Safranal NPs	Liver Cancer Treatment	Mikaeili Ghezeljeh et al, 2024
SAF-AuNPs	Against hepatocellular carcinoma by argeting the Wnt/β-catenin pathway.	Samra et al, 2025
Safranal-loaded solid lipid nanoparticles	skin protection from solar UV radiation	Khameneh et al, 2015
Safranal-PLGA-NPs	Cytotoxicity to pancreatic cancer	Aminaltojjari et al, 2024
Safranal-loaded solid lipid nanoparticles	Protection from UV irradiation	Sanju et al, 2022
Safranal-MIL-88B(Fe) nanostructure	Dual-purpose therapeutic use for cancer and microbial infections	Alkaabi et al, 2024
Nanostructured Lipid Vehicle-Safranal	Therapy for generalized epilepsy	Bo-Qiang et al, 2018
Arabic gum-Safranal Microcapsules	Food Industry application	Yousefi Javan et al, 2024
Liposomal Safranal	Cytotoxicity against HeLa and MCF7	Malaekeh-Nikouei et al, 2013

VII.CONCLUSION

Safranal represents a promising natural compound with broad-spectrum anticancer potential, acting through multiple complementary mechanisms that target fundamental hallmarks of cancer. By inducing apoptosis, suppressing proliferation, and modulating oncogenic signaling cascades, safranal effectively disrupts tumor growth and progression. Its ability to inhibit angiogenesis and metastasis through regulation of VEGF and MMPs further underscores its therapeutic relevance, while antioxidant and anti-inflammatory actions provide additional protection against tumor-promoting microenvironmental factors. Advances in nanotechnology-based delivery systems have addressed critical limitations of solubility and stability, enhancing its pharmacological efficacy and paving the way for potential clinical applications. Preclinical evidence across diverse cancer models strongly supports its therapeutic utility, though translational and clinical validation remain essential to define its safety, optimal dosage, and therapeutic window in humans. Overall, safranal holds considerable potential as a complementary or alternative anticancer agent, meriting further in-depth mechanistic and clinical investigations.

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