

Novel Strategies for Tumor Treatment: Harnessing ROS-Inducing Active Ingredients from Traditional Chinese Medicine Through Multifunctional Nanoformulations

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Abstract: Reactive oxygen species (ROS) encompass a diverse group of chemically reactive molecules or ions distinguished by their substantial oxidative potential. Empirical studies have shown that the targeted administration of high toxic concentrations of ROS can effectively induce tumor cell death in various types. Numerous bioactive ingredients derived from traditional Chinese medicine (TCM), recognized for their ROS-inducing properties, have demonstrated significant anti-tumor activity. Nonetheless, their clinical application has been hindered by challenges such as low solubility, limited bioavailability, and poor selectivity. Multifunctional nanoformulations possess the potential to overcome these challenges and enhance the anticancer efficacy of ROS-inducing active compounds. Through extensive searches of various academic databases and a thorough review and screening of relevant literature, this study aims to systematically summarize and generalize multiple active ingredients in TCM that induce ROS generation, along with their multifunctional nanoformulations, from various perspectives. The objective is to provide new insights and references for fundamental cancer research and clinical treatments. Furthermore, we acknowledge that although numerous active ingredients and their nanoformulations in TCM have demonstrated ROS-inducing and anti-tumor potentials, potentially offering novel strategies for tumor therapy, the underlying mechanisms require further comprehensive investigation.

Keywords: traditional Chinese medicine, nanoformulation, reactive oxygen species, cancer

Introduction

Cancer, recognized globally as a life-threatening disease, has long been a central concern of medical research and treatment.¹ Conventional therapeutic modalities, such as surgery, chemotherapy, and radiotherapy, frequently yield suboptimal outcomes and are associated with significant adverse effects, thereby compromising patients' quality of life.² Recently, traditional Chinese medicine (TCM) has emerged as a promising strategy in the management of malignant tumors, with its therapeutic efficacy increasingly substantiated by scientific investigations.^{3,4} Research has indicated that the natural active ingredients found in TCM, which possess various properties that induce ROS generation, exhibit remarkable efficacy in combating malignant tumors.⁵ Compared to chemotherapeutic agents, these natural ROS-inducing ingredients and different formulations are distinguished by their mild action, ease of acquisition, and reduced side effects on the patient's body during treatment, thereby enhancing the patient's well-being.⁶ It is noteworthy that various ROS-inducing active compounds in TCM exhibit multi-targeting capabilities, enabling concurrent modulation of multiple critical signaling pathways in tumor cells.⁷ This multipotency not only mitigates the development of drug resistance in

tumor cells but also substantially enhances therapeutic efficacy, thereby offering promising prospects for cancer treatment.⁸

ROS encompass a broad category of oxygen-containing free radicals and peroxides that are prone to free radical formation, which are intricately linked to oxygen metabolism in living organisms. Empirical research has demonstrated that elevated toxic levels of ROS can effectively inhibit the growth and proliferation of tumor cells, thereby exhibiting significant anticancer efficacy.⁹ The underlying mechanism of this phenomenon is likely attributable to the oxidative damage inflicted by ROS on critical biomolecules, including DNA, proteins, and lipids. This oxidative damage can disrupt the normal physiological functions of tumor cells, consequently inhibiting their growth and proliferation. However, the utilization of ROS is not devoid of risk, as prolonged exposure to elevated concentrations of ROS can also inflict damage on normal cells. Consequently, in practical applications, it is imperative to meticulously regulate the concentration and spatial distribution of ROS to maximize its anticancer efficacy while minimizing adverse effects on healthy tissues.

There remain significant challenges in the effective utilization of ROS-inducing active ingredients derived from TCM for the treatment of malignant tumors. Firstly, these active ingredients exhibit insufficient selectivity towards tumor cells, potentially exerting non-therapeutic effects on normal cells. Secondly, the limited bioavailability and stability of these compounds constrain their anti-tumor efficacy *in vivo*. Furthermore, the complexity of medicinal dosages and the synergistic relationships among these active ingredients necessitate meticulous selection and combination in clinical applications. To overcome these formidable limitations, multifunctional nanoformulations have emerged as a potentially effective solution.^{10,11} In recent years, the advancement of multifunctional nanoformulations has yielded four pivotal advancements in the field of cancer treatment:^{12,13} The first is targeting advantage. By modifying surface functional groups or encapsulating cancer cell membranes, multifunctional nanoformulations can selectively bind to cancer cells, enabling precise targeting therapy and minimizing harm to healthy cells.¹⁴ The second aspect pertains to the efficacy of drug delivery. By leveraging the properties of nanoscale materials, multifunctional nanoformulations can circumvent premature drug release and degradation, thereby enhancing drug stability and bioavailability within the body.¹⁵ The third benefit is the augmentation of therapeutic efficacy. Multifunctional nanoformulations can transport various drugs or therapeutic agents concurrently, enabling multidimensional treatment and enhancing therapeutic outcomes.^{16,17} The final advantage is the mitigation of drug resistance. The formulation of multifunctional nanotechnology can disrupt cellular resistance mechanisms to drugs, effectively combating drug resistance in cancer cells and increasing treatment success rates.¹⁸ Based on these considerations, multifunctional nanoformulations can facilitate the targeted delivery and release of ROS-inducing active ingredients in TCM specifically at the tumor site. These nanoformulations enhance bioavailability and stability, extend the circulation time of the drug within the body, and minimize damage to normal tissues. Consequently, they significantly improve and enhance the durability of the therapeutic effect.

Currently, there is a notable deficiency in the summarization and generalization of active compounds that stimulate the generation of ROS in TCM within both basic and clinical research domains. Consequently, our research team undertook a comprehensive examination of multiple databases. The outcomes of our inquiry and study are organized into four primary sections: 1. The elucidation of ROS concept, generation, classification, and biological functions; 2. The exploration of the interplay between ROS and tumorigenesis, progression, and therapeutic interventions; 3. The compilation and overview of various ROS-inducing compounds and anticancer mechanisms in TCM; 4. The discussion of advancements in the development of nanoformulations of ROS-inducing compounds in TCM.

The Elucidation of ROS Concept, Generation, Classification, and Biological Functions

ROS constitute a heterogeneous group of oxygen-containing free radicals and peroxides that are integral to oxygen metabolism in living organisms, playing a pivotal role in both physiological and pathological processes in humans.^{19–21}

The generation of ROS can be categorized into endogenous and exogenous sources. Endogenous ROS predominantly originate from redox reactions occurring within intracellular mitochondria and the endoplasmic reticulum, as well as from the enzymatic activities of metabolic systems such as the respiratory chain and cytochrome P450.^{22,23} Conversely,

exogenous ROS generation is induced by environmental factors or exposure to chemical substances, including radiation, pharmaceuticals, and heavy metal ions, which can trigger ROS production.²⁴

Various types of intracellular ROS exist, including superoxide anion radicals ($\bullet\text{O}_2^-$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($\bullet\text{OH}$), singlet oxygen ($^1\text{O}_2$), and Ozone (O_3). $\bullet\text{O}_2^-$ is considered the most basic ROS, characterized by an oxygen molecule with an unpaired electron, commonly generated through the mitochondrial respiratory chain and other redox reactions. H_2O_2 is formed through the interaction of $\bullet\text{O}_2^-$ with peroxidase enzymes, while $\bullet\text{OH}$ is generated via the Fenton reaction involving H_2O_2 or $\bullet\text{O}_2^-$ with transition metals such as iron ions. Additionally, $^1\text{O}_2$ represents the excited state of oxygen, typically formed through exposure to light or specific chemical reactions.

ROS possess a broad spectrum of biological functions within organisms.²⁵ Primarily, ROS are instrumental in the eradication of pathogenic microorganisms and are essential to the sterilization process.²⁶ Furthermore, ROS are involved in the modulation of cell growth, proliferation, and various physiological processes through multiple signaling pathways.²⁷ Moreover, optimal levels of ROS can notably enhance apoptosis and aid in the elimination of aberrant cells.²⁸ Additionally, ROS play a crucial role in the regulation of cell differentiation and maturation process.²⁹ As signaling molecules, ROS are pivotal in modulating gene expression, regulating the cellular microenvironment, influencing the cell cycle and apoptotic processes, and promoting cell migration and morphological changes. The synergistic interplay of these roles ensures that cells adhere to a predetermined differentiation program, culminating in the development of mature cells with specialized functions. However, excessive production of ROS can result in oxidative stress, causing damage to intracellular components such as DNA, proteins, and lipids, leading to inflammation, aging, and the onset of various diseases.^{30,31} Thus, maintaining a proper equilibrium of ROS is crucial for sustaining normal physiological functions. Organisms can mitigate excessive ROS levels through the action of antioxidant enzymes, as well as vitamins A, C, and E, among other antioxidants, to safeguard cells from oxidative damage.³²

The Relationship Between ROS and the Genesis, Progression, and Treatment of Malignant Tumors

Initially, scholars held the belief that ROS primarily facilitated tumor progression. Nevertheless, contemporary research has demonstrated that ROS exhibits dual functionality, with its impact contingent upon concentration, duration, and cellular effects.^{33–35} Elevated ROS levels, which remain beneath the toxic threshold, generally activate growth factor receptors and signaling pathways, thus promoting tumor cell proliferation, metastasis, and malignant transformation via the alteration of tumor-associated gene functionality and the initiation of oncogenesis. Conversely, exceeding the toxicity threshold leads to persistent elevated levels of ROS that intensify oxidative stress damage and instigate the initiation of various ROS-mediated death signaling pathways. This ultimately results in multiple forms of tumor cell death, including ferroptosis, autophagic cell death, apoptosis, pyroptosis, and necroptosis. Notably, levels of ROS are typically higher in tumor tissues relative to normal tissues. Consequently, the utilization of ROS-inducing pharmaceuticals that specifically target tumor tissues or multifunctional materials containing these drugs to stimulate ROS production above the toxic threshold is a promising strategy for treating various forms of cancer. Figure 1 illustrates the primary mechanisms of different types of ROS generation and highlights the distribution of ROS concentration levels in normal and tumor cells.

It is currently hypothesized that the rational induction of elevated levels of ROS may exhibit superior anticancer effects and broader clinical applicability compared to antioxidant therapies aimed at reducing ROS levels.³⁶ Several ROS inducers and drugs targeting antioxidant enzyme systems, such as cisplatin, oxaliplatin, gemcitabine, ARQ501, and the glutathione inhibitor BSO, have been utilized in clinical settings or are undergoing clinical trials.^{37,38} In clinical practice, healthcare providers frequently opt to induce high levels of ROS generation as a therapeutic approach for tumor treatment. For instance, oxygen radical therapy functions by administering hyperoxidative compounds like oxygen or hydrogen peroxide solution directly into tumor tissues to elevate the levels of ROS, ultimately leading to tumor cell death. It is important to acknowledge that insufficient ROS levels may trigger pro-cancer signaling pathways like PI3K and HIF, potentially aiding in tumor progression. On the contrary, an elevated concentration of ROS surpassing the toxicity threshold can induce heightened oxidative stress in healthy cells, resulting in detrimental effects on normal tissues and organs, including the heart, liver, and kidneys of the individual. Consequently, it is imperative to carefully

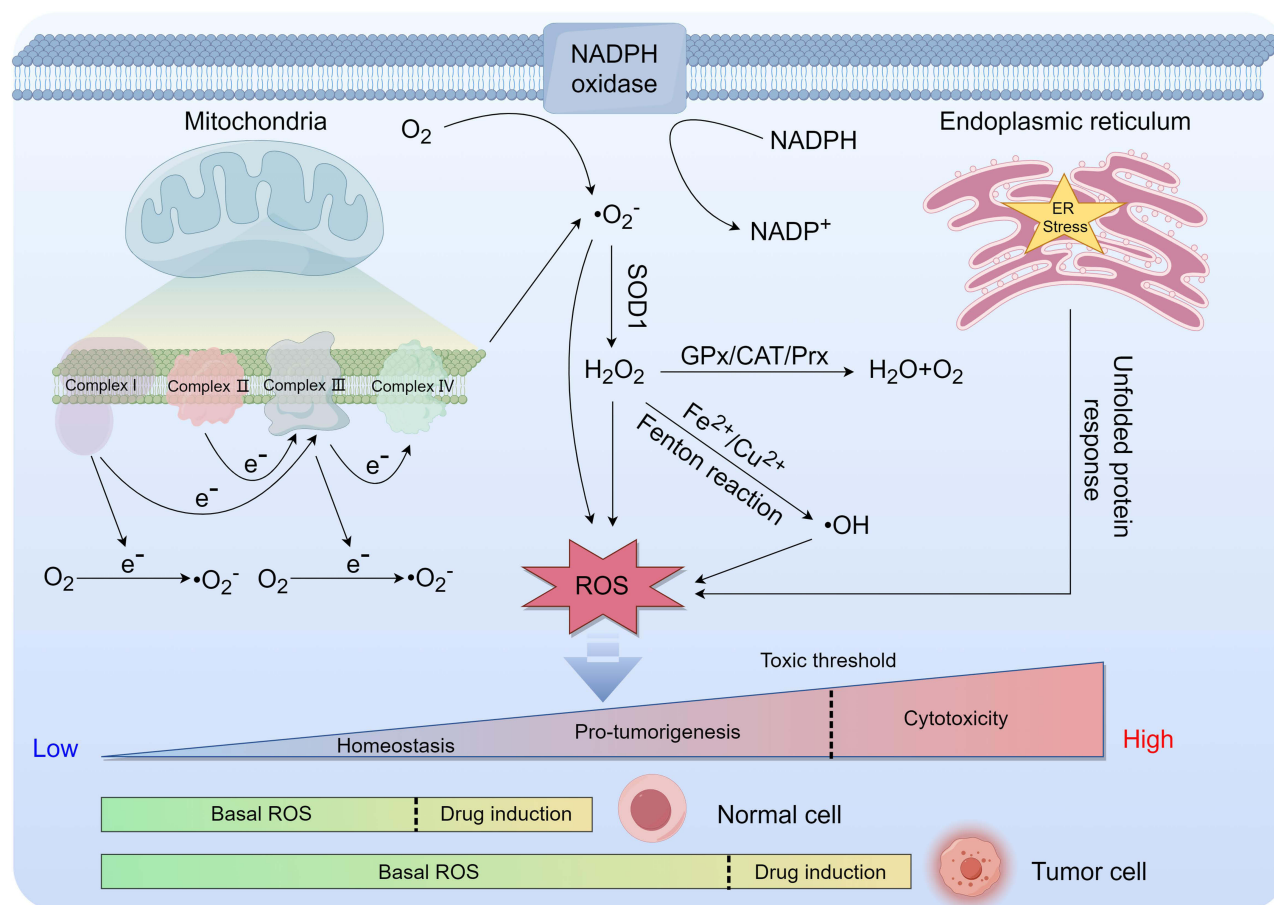


Figure 1 The primary mechanisms of different types of ROS generation and distribution of ROS concentration levels in normal and tumor cells (drawn by Figdraw, ID: ASYIW74747).

manage and maintain ROS levels within the body during cancer therapy to ensure that therapeutic agents selectively target tumor tissues while minimizing harm to healthy tissues.

Summarization of Various ROS-Inducing Active Ingredients in TCM and Their Anti-Cancer Mechanisms

TCM is increasingly recognized as a valuable cultural asset within the field of medicine due to its rich historical background and distinctive therapeutic approaches. In the realm of TCM, a multitude of active ingredients have displayed potential in the treatment of cancer, including various ROS-inducing compounds such as quinones, terpenoids, flavonoids, alkaloids, polyphenols, polysaccharides, sesquiterpene lactones, and others. These ingredients have exhibited inhibitory effects on cell proliferation, as well as the induction of various forms of cell death such as apoptosis, ferroptosis, autophagic cell death, pyroptosis, and necroptosis. We conducted a comprehensive review of representative pieces of literature on various ROS-inducing active ingredients in TCM, elucidated the chemical structural formulae of various types of these compounds (Figure 2), and summarized ROS-induced cell death mechanisms at high concentrations exceeding the toxicity threshold (Figure 3).

Quinones

Quinones, a class of organic compounds containing the structural features of cyclohexadiene dione or cyclohexadiene dimethylene, are commonly found in a variety of TCM plants. This structural characteristic imparts quinones with favorable redox properties. In biological systems, quinones undergo reduction by accepting electrons, leading to the

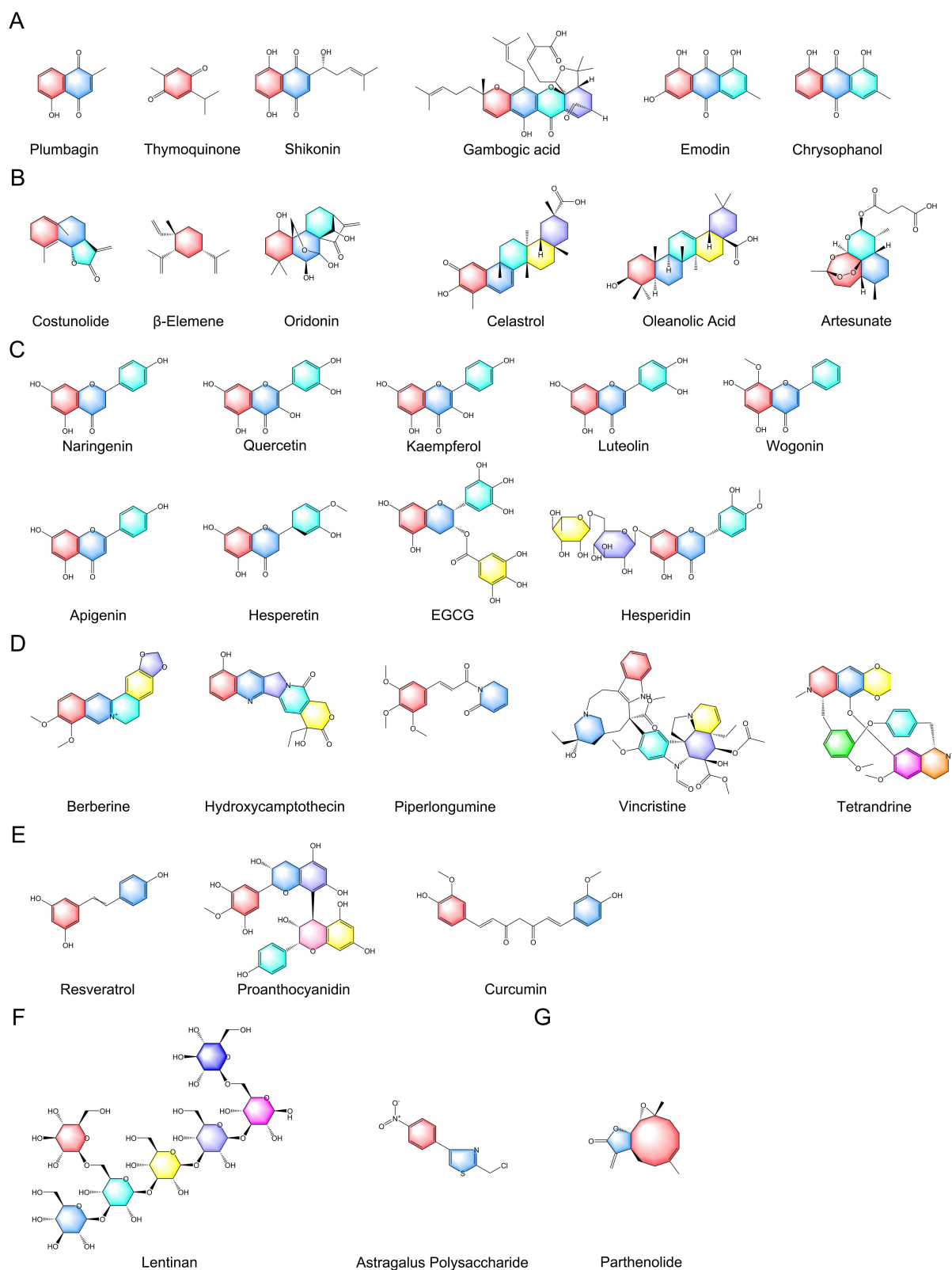


Figure 2 The chemical structural formulae of various types of ROS-inducing ingredients in TCM. (A) Quinones, (B) Terpenoids, (C) Flavonoids, (D) Alkaloids, (E) Polyphenols, (F) Polysaccharides, (G) Sesquiterpene lactones.

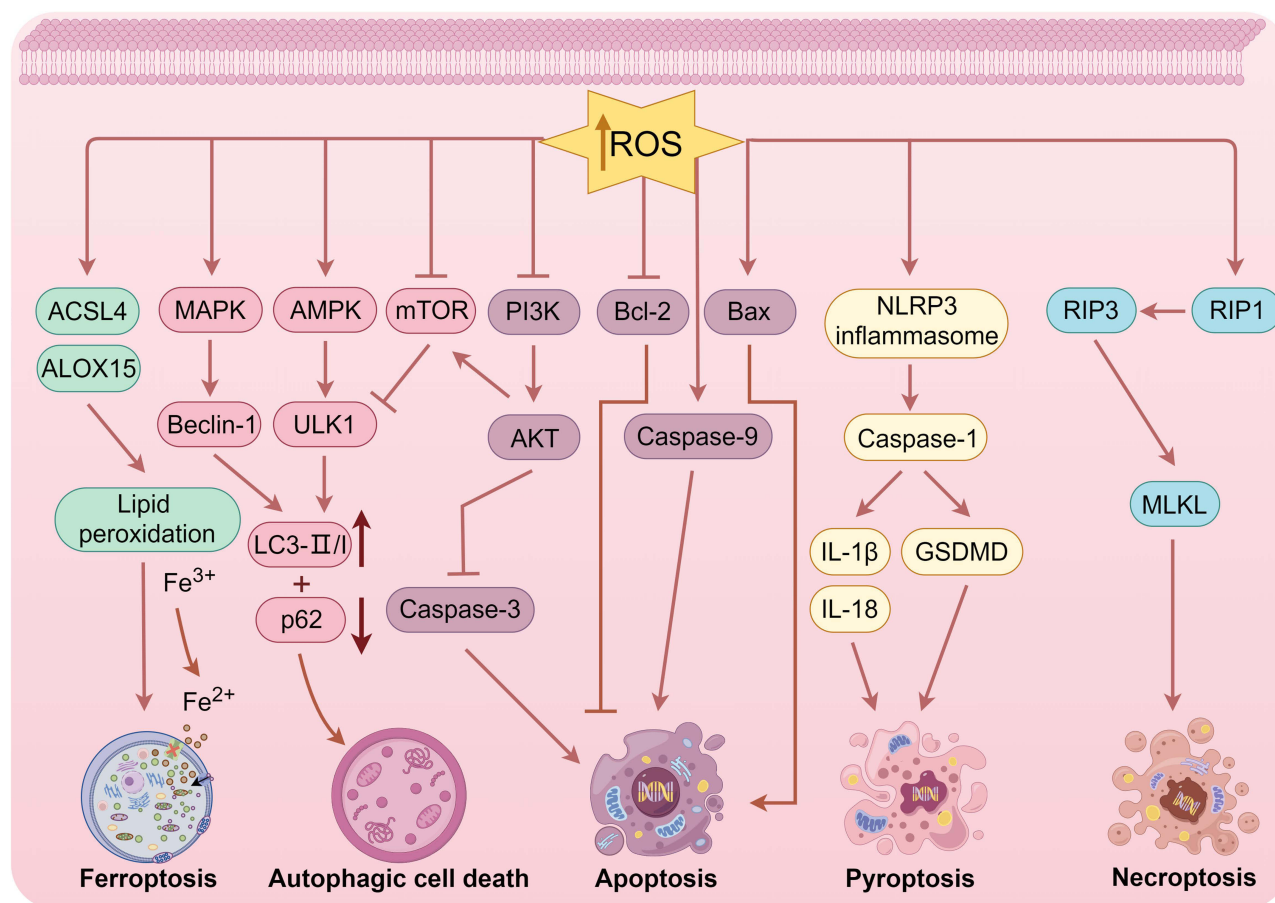


Figure 3 ROS-induced cell death mechanisms at high concentrations exceeding the toxicity threshold (drawn by Figdraw, ID: OPRP196a96).

oxidation of oxygen molecules and the generation of ROS such as H_2O_2 and $\bullet O_2^-$. Prominent quinone components renowned for their capacity to stimulate ROS production encompass plumbagin, thymoquinone, shikonin, gambogic acid, emodin, chrysophanol, and numerous other compounds.

Plumbagin

Plumbagin, an active compound derived from the roots of *Plumbago zeylanica* L., a member of the *Plumbaginaceae* family, has been shown to elicit a G2/M cell cycle arrest through the generation of ROS and activation of the ATM-p53 signaling pathway. This mechanism leads to genotoxicity and subsequent apoptosis in hepatocellular carcinoma cells.³⁹ Within the realm of lung cancer treatment, plumbagin may also induce apoptosis in lung cancer cells by activating caspase-9 and targeting mitochondria-mediated ROS induction.⁴⁰ In addressing the prevalent issue of multidrug resistance in oral cancer, plumbagin could serve as a therapeutic agent to counteract this resistance. It achieves this by synergistically initiating the apoptotic pathway via ROS-mediated endoplasmic reticulum stress and mitochondrial dysfunction.⁴¹

Thymoquinone

Thymoquinone, an active monomer derived from the seeds of *Nigella damascena* L., a plant in the *Ranunculaceae* family, has been shown to inhibit the proliferation, migration, and invasiveness of human bladder cancer cells by modulating ROS, autophagic flux, and miR-877-5p.⁴² Apart from its demonstrated capacity to suppress tumor cell proliferation via ROS-induced apoptosis, thymoquinone has been empirically proven to curtail the stemness of tumor cells and diminish their self-renewal potential.⁴³ Notably, thymoquinone, in exhibiting its independent anti-tumor

properties, has been found to augment the cytotoxicity of the pharmaceutical agent 5-fluorouracil when used in conjunction with metformin. This is achieved through the PI3K/mTOR/HIF1 α pathway and by amplifying oxidative stress within colon cancer cells.⁴⁴

Shikonin

Shikonin, a natural compound derived from the dried roots of *Arnebia euchroma* (Royle) Johnst. and *Lithospermum erythrorhizon* Sieb. et Zucc. or *Arnebia guttata* Bunge. in the *Boraginaceae* family, acts as a potent inhibitor of PKM2. Numerous studies have illustrated the ability of shikonin to impede the proliferation of various cancer cells, including those associated with adult T-cell leukemia/lymphoma, non-small cell lung cancer, colorectal cancer, and osteosarcoma, by inducing forms of cell death linked to ROS, such as apoptosis, ferroptosis, pyroptosis, and autophagy.^{45–50} These effects are mediated through the modulation of key cellular pathways, including mitochondrial dysfunction, endoplasmic reticulum stress, and the regulation of critical gene expression. Furthermore, our team's prior research has demonstrated that shikonin can augment the therapeutic efficacy of oxaliplatin in oxaliplatin-resistant colorectal cancer cells by inducing endogenous apoptosis and endoplasmic reticulum stress through ROS.⁵¹

Gambogic Acid

Gambogic acid, a bioactive compound sourced from the desiccated resin of the *Garcinia hanburyi* Hook. f. in the *Fabaceae* family, has been demonstrated by several researchers to induce endoplasmic reticulum stress via ROS modulation of the JNK pathway, leading to apoptosis and autophagy in prostate cancer cells.⁵² Additionally, Zhao et al have reported that gambogic acid triggers Noxa-mediated apoptosis in colorectal cancer by activating IRE1 α /JNK through ROS signaling.⁵³ In non-small cell lung cancer cells, gambogic acid has been shown to inhibit cell proliferation and induce apoptosis by modulating ROS-mediated endoplasmic reticulum stress.⁵⁴

Emodin

Emodin is primarily sourced from the desiccated roots and rhizomes of *Polygonum palmatum* L., *Rheum tanguticum* Maxim. ex Balf., or *Rheum officinale* Baill. in the *Polygonaceae* family. Studies carried out as early as 2005 have demonstrated that emodin instigates apoptosis in human lung adenocarcinoma cells through the ROS-dependent mitochondrial signaling pathway.⁵⁵ Subsequent research has substantiated emodin's role as a catalyst for iron death in colorectal cancer cells, accomplished via NCOA4-mediated ferritin autophagy, ROS generation, and the deactivation of the NF- κ B pathway.⁵⁶ Further investigations have illuminated that emodin provokes necrosis in renal cancer cells by amplifying ROS-mediated activation of the JNK signaling pathway, concurrently inhibiting glycolysis via the inactivation of the PI3K/AKT signaling pathway and down-regulation of GLUT1, ultimately facilitating cell death.⁵⁷

Chrysophanol

Chrysophanol, a natural anthraquinone closely related to emodin, exhibits a diverse array of pharmacological properties, including antimicrobial, antitussive, intestinal motility, and neuroleptic effects, as well as potent antitumor activity. Studies have demonstrated that chrysophanol can impede the proliferation of human tongue squamous carcinoma SAS cells through modulation of mTOR/PPAR- α signaling and accumulation of ROS.⁵⁸ In oral cancer cell lines, it has been demonstrated that chrysophanol augments the production of ROS while concurrently inhibiting metastasis, invasion, and epithelial-mesenchymal transition.⁵⁹ Interestingly, when chrysophanol was applied to glioma cells, there was an observed translocation of cytochrome C from the mitochondria to the cytoplasm. This translocation was concomitant with a significant accumulation of ROS and the initiation of apoptosis and cell cycle arrest events.⁶⁰

Terpenoids

Terpenoids, characterized by the presence of multiple isoprene structural units, typically possess either a carbon-skeleton cycloalkane structure or a linear structure. The mechanism through which these compounds induce ROS generation in organisms involves their interaction with various intracellular oxidoreductases. Terpenoids have the potential to facilitate ROS generation by reducing oxygen molecules through their interaction with intracellular oxidative enzymes. Notable

terpenoids capable of inducing ROS generation include costunolide, β -elemene, oridonin, celastrol, oleanolic acid, artesunate, and many other compounds.

Costunolide

Costunolide, a sesquiterpene lactone isolated from the dried root of the *Asteraceae* plant, *Acacia lappa Decne.*, possesses a range of pharmacological activities including anti-tumor, anti-inflammatory, anti-allergic, anti-diabetic, and neuroprotective properties. Notably, studies have revealed that costunolide can elicit ROS production in a cell-specific manner, with varying effects observed across different cell lines. For instance, costunolide was found to enhance ROS levels in SK-BR-3 cells while inhibiting ROS elevation in MCF-7 cells.⁶¹ In gastric cancer cells, costunolide demonstrated the capacity to modulate ROS accumulation, promote apoptosis, activate autophagy, and induce cell death through the inhibition of the AKT/GSK3 β signaling pathway.⁶² Notably, costunolide was shown to significantly enhance the ROS-inducing properties of cisplatin and its toxic effects on hypopharyngeal SCC FaDu cells when combined with the clinical drug cisplatin.⁶³

β -Elemene

β -elemene, an active monomer derived from *Curcuma rchenyujin Y.H. Chen et C. Ling* of the *Zingiberaceae* family, is classified as a national class II non-cytotoxic anti-tumor agent. As a pharmacological agent, β -elemene has demonstrated significant ROS-inducing capabilities, and it can stimulate apoptosis and autophagy in colorectal cancer cells through the regulation of the ROS/AMPK/mTOR pathway.⁶⁴ Beyond initiating ROS-dependent death in malignant tumors as a standalone treatment,⁶⁵ β -elemene can also function synergistically with the traditional chemotherapeutic drug, cisplatin, to induce apoptosis in bladder cancer cells via the ROS-AMPK pathway.⁶⁶

Oridonin

Oridonin, a tetracyclic diterpenoid derived from the whole herb of *Rabdosia rubescens* in the *Labiatae* family, has been shown in recent studies to inhibit osteosarcoma cell growth through a dual mechanism involving ferroptosis and apoptosis induction, as well as the promotion of ROS accumulation.⁶⁷ In a similar vein, oridonin enhances RSL3-induced ferroptosis in breast cancer cells through the activation of the JNK/Nrf2/HO-1 oxidative stress pathway, which results in the accumulation of ROS.⁶⁸ It is noteworthy that oridonin, apart from promoting ferroptosis, also facilitates cell death by triggering caspase-dependent apoptosis in colorectal cancer cells through the ROS/JNK/c-Jun signaling axis.⁶⁹

Celastrol

Celastrol, a quinone-methylated triterpenoid compound derived from the dried root of *Tripterygium wilfordii Hook. f.*, a plant in the *Celastraceae* family, exhibits a diverse range of biological activities, such as anti-inflammatory, anti-rheumatoid, and anticancer properties. Studies have shown that celastrol effectively treats non-small cell lung cancer by inhibiting STAT3 signaling and promoting ROS accumulation.⁷⁰ Furthermore, Chen et al illustrated that celastrol can induce ROS-mediated apoptosis in gastric cancer cells by specifically targeting peroxiredoxin-2.⁷¹ In the realm of drug combinations, it was discovered that the co-administration of erastin, a ferroptosis inducer, and celastrol effectively induced cell death in NSCLC cells at nontoxic concentrations, leading to a marked increase in ROS production, disruption of mitochondrial membrane potential, and stimulation of mitochondrial fission.⁷²

Oleanolic Acid

Oleanolic acid, a triterpenoid compound, is derived from the dried mature fruits of *Ligustrum lucidum*, a plant in the family *Oleaceae Hoffmanns. & Link*, and the root bark and stem bark of *Aralia chinensis*, a plant in the family *Araliaceae*. Recent studies have shown that oleanolic acid exhibits potential anti-cancer properties by inhibiting the proliferation of cervical cancer Hela cells through the regulation of the ACSL4-related ferroptosis signaling pathway and the promotion of Fe²⁺ and ROS accumulation.⁷³ Furthermore, oleanolic acid has been shown to trigger autophagic cell death in hepatocellular carcinoma cells via the PI3K/Akt/mTOR and ROS-dependent signaling pathways.⁷⁴ It is worth noting that the co-administration of oleanolic acid with the FDA-approved drug sorafenib, at sublethal concentrations,

presents a promising strategy for enhancing oxidative stress and elevating ROS levels to induce cell death in hepatocellular carcinoma.⁷⁵

Artesunate

Artesunate, a derivative of *Artemisia annua* Linn. from the *Asteraceae* family, is a proven antimalarial drug with additional anti-tumor properties. Recent studies have demonstrated its ability to induce endoplasmic reticulum stress-driven ROS-mediated cell death in hepatocellular carcinoma cells by disrupting unstable iron pools and iron redistribution.⁷⁶ Moreover, it has been suggested that artesunate instigates ferroptosis in myeloma cells through the inhibition of SREBP2 nuclear translocation and the upregulation of ROS, Fe²⁺, and lipid peroxidation.⁷⁷ Additionally, Zhou et al discovered that artesunate induces autophagy-mediated apoptosis in human bladder cancer cells by increasing ROS levels and activating the AMPK-mTOR-ULK1 signaling pathway.⁷⁸

Flavonoids

Flavonoids, a group of natural compounds characterized by benzene and furan ring structures, have been the subject of recent research indicating their potential dual function as antioxidants and inducers of ROS in various tumor cells and cancer types. This dual role can be attributed to the chemical structure of flavonoids, which feature multiple electrophilic groups and aromatic ring structures, contributing to their antioxidant properties by scavenging free radicals and stabilizing intracellular oxidative conditions. Conversely, flavonoids can interact with cell membrane receptors, leading to the production of ROS and subsequent activation of various cellular signaling pathways, influencing cellular physiological processes. Notable flavonoid components known to induce ROS generation include naringenin,^{79–81} quercetin,^{82–84} kaempferol,^{85–87} luteolin,^{88–90} wogonin,^{91,92} apigenin,^{93–95} hesperetin,^{96,97} epigallocatechin gallate (EGCG),^{98–100} hesperidin,^{101–103} and others. These compounds are commonly present in a variety of fruits, vegetables, teas, and TCM, sharing a common or similar parent core structure that results in significant similarities in physicochemical properties. Research has shown that flavonoids possess the ability to impede tumor growth and metastasis, induce cell cycle arrest, and trigger various forms of cell death by influencing multiple ROS-related signaling pathways, including AMPK, p38, AKT/mTOR, and ASK1/JNK.

Alkaloids

Alkaloids, characterized by the presence of nitrogen atoms and exhibiting base-like properties, are a class of compounds with significant medicinal value. These compounds possess structural features such as nitrogen-containing heterocycles and aromatic rings, which contribute to their diverse biological activities. Among the alkaloid components capable of inducing the generation of ROS are berberine, hydroxycamptothecin, piperlongumine, tetrandrine, vincristine, and numerous other compounds.

Berberine

Berberine, an isoquinoline alkaloid sourced from the medicinal plant *Coptis chinensis* Franch. in *Ranunculaceae* family, exhibits a range of pharmacological effects, such as antibacterial, antiviral, hypoglycemic, hypolipidemic, anti-gastric ulcer, and treatment of cardiovascular and cerebral vascular diseases. In recent years, there has been an increasing focus on the potential antitumor effects of berberine. Chen et al have illustrated that berberine can trigger apoptosis in NSCLC cells through the ROS-mediated activation of the ASK1/JNK pathway and the mitochondrial pathway.¹⁰⁴ Furthermore, berberine has been shown to impede the progression of renal cancer cells by regulating ROS production and promoting DNA damage.¹⁰⁵ In glioblastoma multiforme U87MG cells, berberine has been found to elevate levels of ROS, thiobarbituric acid reactive substances, and protein carbonylation through the induction of oxidative stress.¹⁰⁶

7-Ethyl-10-Hydroxycamptothecin

7-ethyl-10-hydroxycamptothecin, also known as SN-38, is an indole alkaloid derived from the seeds or root bark of *Camptotheca acuminata* Decne. in the *Davidia involucrata* Baill. This compound is commonly utilized in clinical oncology due to its close association with DNA topoisomerase I, a key enzyme involved in DNA replication and transcription regulation. Research has demonstrated that SN-38 effectively enhances ROS production in LOVO and

HCT116 cells, and in combination with chloroquine, it synergistically induces a heightened ROS level. This effect may be attributed to the p53-ROS crosstalk, as well as the activation of lysosomal and mitochondrial apoptotic pathways.¹⁰⁷

Piperlongumine

Piperlongumine, a naturally occurring alkaloid present in the fruit or root of the *Piperaceae* Giseke plant in the *Piper longum* L. family, exhibits anti-inflammatory, anti-bacterial, anti-tumor, and anti-angiogenic properties. Mitra et al have demonstrated the remarkable therapeutic potential of piperlongumine in combating various types of cancers, particularly breast cancer.¹⁰⁸ When combined with piperlongumine, clinical drugs such as doxorubicin and docetaxel have shown synergistic effects that surpass the efficacy of individual agents.¹⁰⁹ Moreover, studies have demonstrated that piperlongumine enhances ROS production and diminishes stem cell and epithelial cell mesenchymal transition phenotypes in SOX9-deficient human lung cancer cells, exhibiting heightened anti-metastatic properties.¹¹⁰ Intriguingly, piperlongumine has the potential to act as a potent ROS inducer and, in conjunction with the therapeutic agent bortezomib, it can synergistically instigate cholangiocarcinoma cell death via oxidative stress pathways.¹¹¹

Tetrandrine

Tetrandrine, a bisbenzylisoquinoline alkaloid derived from the tuberous roots of *Stephania tetrandra* S. Moore, a plant belonging to the *Menispermaceae* family, exhibits anti-inflammatory, anti-allergic, platelet aggregation inhibiting, and anticancer properties. Research has indicated that tetrandrine induces ROS production in human lung cancer A549 cells. The inhibition of mitochondrial ATP production using oligomycin and the uncoupling agent FCCP not only amplifies tetrandrine-induced ROS generation but also enhances the cytotoxic effects of tetrandrine.¹¹² Furthermore, certain researchers have shown that tetrandrine-induced ROS also triggers non-liganded Fas-mediated apoptosis through the activation of procaspase-8 and bid cleavage in prostate cancer cells.¹¹³ Additionally, Liu et al discovered that tetrandrine suppresses tumor stem cell properties and the epithelial-mesenchymal transition process in triple-negative breast cancer by modulating the SOD1/ROS signaling pathway.¹¹⁴ SOD1, a pivotal antioxidant enzyme prevalent in eukaryotic cells, serves a primary function in catalyzing the dismutation reaction of $\bullet\text{O}_2^-$, yielding H_2O_2 and O_2 . This process is of paramount importance for maintaining intracellular redox homeostasis, since ROS, when present in moderation, act as signaling molecules involved in physiological processes such as cell proliferation and differentiation. Conversely, an overabundance of ROS can lead to oxidative stress, compromising cellular structures and functions, and potentially triggering apoptosis.

Vincristine

Vincristine, an alkaloid derived from *Catharanthus roseus* (L). G. Don of the *Apocynaceae* family, is a widely utilized antitumor medication in clinical settings for the management of various cancer types, particularly childhood acute lymphoblastic leukemia. Its primary mode of action involves the inhibition of microtubule protein polymerization and disruption of spindle formation during cell division, thereby impeding the proliferation of cancer cells. Furthermore, vincristine exhibits immunomodulatory and anti-inflammatory properties that have the potential to augment immune function within the body. Research indicates that vincristine initiates a series of axonal pathological events, ultimately leading to mitochondrial dysfunction, increased levels of axonal ROS, and SARM1-mediated axonal degeneration.¹¹⁵ Early studies from 2002 identified the regulatory role of ROS in the initial stages of the mitochondrial signaling pathway responsible for vincristine-induced apoptosis in acute lymphoblastic leukemia cells.¹¹⁶

Polyphenols

Polyphenols are a group of compounds with multiple phenolic hydroxyl groups, distinguished by the presence of multiple hydroxyl groups on various aromatic rings. It is important to note that hydroxyl groups possess the ability to provide hydrogen atoms and engage in antioxidant reactions by directly capturing free radicals, while polyphenolic compounds induce intracellular ROS generation through binding to metal ions or interacting with receptors on cell membranes to modulate redox reactions. Examples of polyphenols capable of inducing ROS generation include curcumin, resveratrol, proanthocyanidin, and various other compounds.

Curcumin

Curcumin, a yellow pigment extracted from the rhizomes of the *Zingiberaceae* plant *Curcuma longa* L., is an acidic polyphenol with varied pharmacological properties. A recent scholarly investigation has corroborated that curcumin possesses a distinctive capacity for mitochondrial targeting, which results in mitochondrial dysfunction and fatal mitochondrial phagocytosis. This is accompanied by an increase in SDH activity and an overproduction of ROS, which collectively augment the effectiveness of radioactive iodine in eliminating thyroid cancer cells.¹¹⁷ The ROS-mediated KEAP1/NRF2/miR-34a/b/c cascade signaling pathway is instrumental in curcumin's anticancer process, demonstrating the potential to impede the metastasis of colorectal cancer cells via a p53-independent mechanism.¹¹⁸ In a similar vein, curcumin has been observed to stimulate cellular pyroptosis and apoptosis, while concurrently inhibiting the proliferation of HepG2 cells through the activation of ROS signaling.¹¹⁹

Resveratrol

Resveratrol, a non-flavonoid polyphenolic organic compound, is commonly present in various fruits and TCM and is recognized for its potent antioxidant properties that safeguard cells against oxidative harm. Interestingly, multiple studies have demonstrated that resveratrol can trigger various cell death pathways reliant on ROS and impede tumor progression. Liu et al discovered that resveratrol can induce ferroptosis in acute myeloid leukemia cells through a ROS-dependent mechanism involving the Hsa-miR-335-5p/NFS1/GPX4 pathway.¹²⁰ In glioma cells, treatment with resveratrol at a concentration of 15 μ M for 48 hours resulted in increased production of ROS, activation of autophagy, induction of endoplasmic reticulum stress and apoptosis, and decreased survival of both 2D and 3D clones.¹²¹ Notably, a study conducted by several researchers demonstrated that pairwise combinations of resveratrol, EGCG, and diallyl trisulfide led to enhanced ROS production through the mitochondrial caspase-dependent pathway, ultimately resulting in cell death in the A431 skin cancer cell line.⁹⁸

Proanthocyanidin

Proanthocyanidin, a polyphenolic polymer, is commonly found in various natural sources such as apples, hawthorns, grapes, strawberries, peanuts, and other plants. It is also recognized as one of the polyphenolic constituents in TCM. Research conducted as early as 2009 demonstrated that proanthocyanidin present in beer can trigger apoptosis, protein carbonylation, and cytoskeleton disorganization in human colorectal adenocarcinoma cells through the generation of ROS.¹²² Subsequent studies have further revealed that proanthocyanidin derived from cranberry exhibits anti-angiogenic properties and cytotoxic effects on ovarian cancer cells, inducing apoptosis, G2/M phase cell cycle arrest, and ROS generation in chemotherapy-resistant SKOV-3 cells through both endogenous and exogenous pathways.¹²³

Polysaccharides

Polysaccharides, a group of compounds composed of multiple glycosyl units, are prevalent in various organisms such as plants, fungi, and marine species, exhibiting a wide range of biological functions. Several polysaccharide constituents, including lentinan and astragalus polysaccharide, have been identified as capable of inducing the generation of ROS.

Lentinan

Lentinan, a polysaccharide compound derived from shiitake mushrooms, is characterized by polysaccharide chains composed of β -(1 \rightarrow 3)-D-glucan and β -(1 \rightarrow 6)-D-glucan arranged in alternating patterns. Treatment of lung cancer A549 cells with lentinan resulted in elevated levels of ROS and decreased activity of GPX4. The heightened ROS levels triggered the activation of caspase-3, leading to DNA double-strand breaks and inhibition of cell proliferation.¹²⁴ Further investigations have revealed that the concurrent administration of paclitaxel and lentinan exhibits a synergistic apoptotic impact on A549 cells by promoting ROS production, triggering the activation of the NLRP3 inflammasome, and stimulating the ASK1/p38 MAPK signaling pathway.¹²⁵

Astragalus Polysaccharide

Astragalus polysaccharide, a polysaccharide compound derived from the roots of the *Leguminosae* plant *Astragalus membranaceus* var. *mongholicus* (Bunge) P.K.Hsiao, primarily consists of polysaccharide chains made up of α -glucose and galactose chains. Recent scholarly investigations have elucidated that an innovative cold-water-soluble polysaccharide, derived from *Astragalus membranaceus*, possesses the capability to trigger mitochondria-dependent apoptosis in gastric cancer MGC-803 cells. This induction leads to the accumulation of intracellular ROS, the disruption of mitochondrial membrane potential, an augmentation in the Bax/Bcl-2 ratio, and the subsequent activation of caspase-9/-3 expression.¹²⁶

Sesquiterpene Lactones

Sesquiterpene lactones, a diverse class of secondary metabolites primarily sourced from plants within the *Compositae* family, exhibit a broad spectrum of biological properties, such as anti-tumorigenic, anti-inflammatory, and antibacterial effects.

Parthenolide

Parthenolide, a naturally occurring compound extracted from the flower buds of the *Compositae* plant *Tanacetum Parthenium*, is characterized by its structural composition, which includes an α -methyl- γ -lactone ring and a terpene framework. Recent research has demonstrated the potential of parthenolide to inhibit the progression of various malignant tumors, including lymphoid malignancies, osteosarcoma, breast cancer, and multiple myeloma, through the induction of ROS-mediated apoptosis and autophagic cell death.^{127–130}

Development of Nanoformulations of ROS-Inducing Active Ingredients Derived from TCM

As previously noted, active ingredients sourced from TCM offer distinct advantages over traditional clinical chemotherapeutic agents, including mild effects, multi-targeting capabilities, synergistic properties, and ease of accessibility. However, these active ingredients also present limitations such as poor water solubility, low bioavailability, complex dosage requirements, short circulation periods in the bloodstream, and limited accumulation at tumor sites.

To address these challenges, the utilization of multifunctional nanoformulations emerges as a promising solution. Through the application of advanced nanotechnology, the precise delivery of active compounds capable of inducing ROS generation from TCM can be realized, leading to targeted release of nanomedicines, improved bioavailability, decreased toxicity, and optimal synergistic effects of various drug types. Utilizing nanocarriers facilitates the more precise accumulation of drugs at the tumor site, thereby minimizing harm to normal tissues and greatly enhancing therapeutic efficacy. Furthermore, nanoformulations can extend drug circulation, increase stability, prevent rapid metabolism, and enhance the sustained therapeutic impact.

Through a comprehensive analysis of existing literature, we have compiled a summary of prevalent nanoformulations containing ROS-inducing active compounds in TCM and their potential multifunctional efficacy benefits, as depicted in Figure 4.

Plumbagin-Loaded Nanoformulations

A novel lipid-polymer hybrid nanoparticle formulation loaded with plumbagin and transferrin, developed by Sakpakdeejaroen et al, effectively targets tumors by harnessing the high expression of transferrin receptors on cancer cells.¹³¹ Further research has delved into the potential of plumbagin-loaded silver nanoparticles in targeting tumor angiogenesis, inducing ROS generation, and eliciting tumor cell apoptosis.^{132,133} The immunosuppressive tumor micro-environment (TME) poses a significant challenge in the treatment of hepatocellular carcinoma. To address this, Han et al have formulated a biomimetic nanostructure containing low-dose plumbagin and dihydrotanshinone I, encapsulated within an erythrocyte membrane, which successfully reverses the chemo-immunotherapeutic constraints imposed by the immunosuppressive TME.¹³⁴

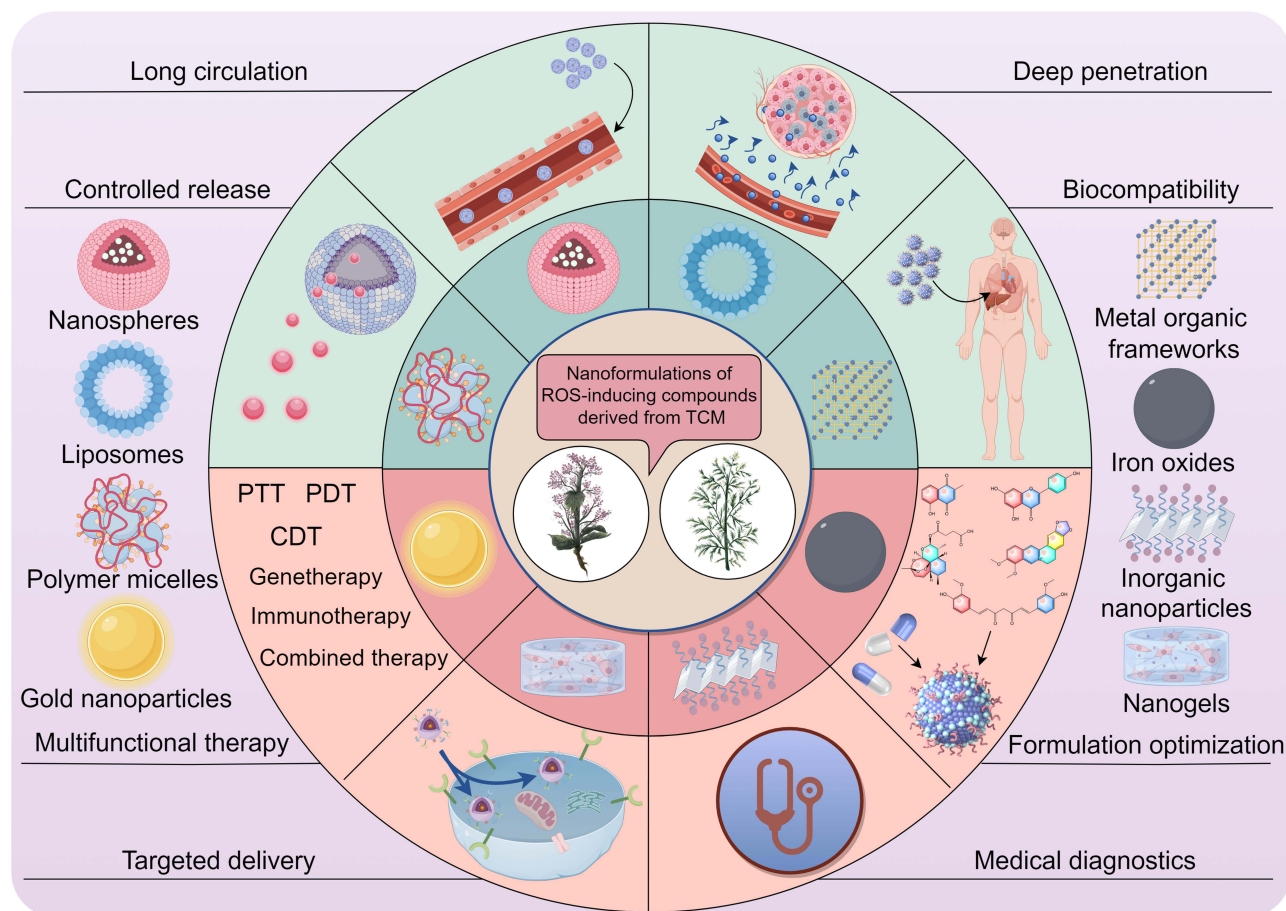


Figure 4 An overview of prevalent nanoformulations containing ROS-inducing active ingredients in TCM and their potential multifunctional efficacy benefits (drawn by Figdraw, ID:TRPWO2c2ee).

Thymoquinone-Loaded Nanoformulations

The study conducted by Gulbay et al introduced a thymoquinone-loaded nanoparticle that exhibited enhanced cellular uptake and stability of thymoquinone, ultimately resulting in improved therapeutic outcomes for endometrial cancer cells.¹³⁵ In the context of breast cancer treatment, thymoquinone loaded cubic phase nanoparticles, prepared using the emulsification homogenization method, exhibited favorable subcellular localization and pro-apoptotic effects.¹³⁶ Furthermore, thymoquinone loaded mesoporous silica nanoparticles were found to inhibit cell invasion and enhance in vitro cytotoxicity through ROS-mediated apoptosis.¹³⁷ Additionally, Ibrahim et al developed thymoquinone-loaded PLGA nanoparticles for the treatment of melanoma by leveraging sustained release and tailored size to enhance permeability and retention effects.¹³⁸

Shikonin-Loaded Nanoformulations

Recent research indicates that the utilization of shikonin-loaded nanomedicines has shown promise as an effective approach to cancer treatment. Various nanodrug delivery platforms, including liposomes, polymeric micelles, nanoparticles, nanogels, and nanoemulsions, have been employed to facilitate the targeted delivery of shikonin, thereby enhancing its anti-tumor efficacy.¹³⁹ For instance, the use of functional liposomes encapsulating shikonin has demonstrated potential for cancer therapy through the induction of ROS-boosting necroptosis.¹⁴⁰ Furthermore, Chen et al have devised a delivery nanosystem incorporating shikonin and hyaluronic acid-modified hollow Fe-MOF, serving as an effective glycolysis-mediated agent to enhance the effectiveness of microwave thermotherapy.¹⁴¹ In terms of immunomodulation, Long et al have developed shikonin-loaded and hyaluronic acid-modified MPDA nanoparticles for

immunotherapy purposes, which can induce immune-metabolic reprogramming and regulate glycolysis, EMT, and anticancer immunity by inhibiting PKM2. This targeted drug delivery approach shows great promise for the treatment of colorectal cancer.¹⁴²

Gambogic Acid-Loaded Nanoformulations

In contemporary research, the utilization of gambogic acid nano-delivery has emerged as a promising strategy for tumor therapy.¹⁴³ A gambogic acid nanoparticle with low toxicity and high tumor-targeting capabilities has been adeptly fabricated through a two-step emulsification process by Huang et al. His nanoparticles, coated with CT26 colon cancer cell membrane on a poly (lactic-co-glycolic acid)/GA foundation, demonstrate the ability to stimulate dendritic cells and effectively immunize against cancer.¹⁴⁴ Furthermore, a thermosensitive injectable hydrogel with a rapid gelation time and excellent biocompatibility has been successfully formulated by Zhang et al. This hydrogel has shown notable enhancement in therapeutic efficacy against gastric cancer when encapsulating gambogic acid nanoparticles and the tumor-penetrating peptide iRGD.¹⁴⁵

Emodin-Loaded Nanoformulations

A method for emodin-conjugated PEGylation of Fe₃O₄ nanoparticles has been developed by Ren et al, facilitating the application of these nanoparticles in FI/MRI dual-modal imaging as well as targeted therapy in mice with pancreatic tumor xenografts.¹⁴⁶ Additionally, other researchers synthesized ROS/pH dual-sensitive polymer micelles for the simultaneous delivery of emodin and chlorambucil. This approach enhances oxidative stress levels by inducing ROS production and GSH depletion, while also reducing chlorambucil exocytosis. These effects collectively enhance drug chemotoxicity and improve the efficacy of tumor therapy.¹⁴⁷

Chrysophanol-Loaded Nanoformulations

A gold-chrysophanol-loaded poly (DL-lactide-co-glycolide) nanoparticle, synthesized by Lu et al, has demonstrated their capability to modulate the p53/ROS crosstalk. These nanoparticles suppress histone deacetylase and AKT signaling pathways by regulating cell cycle proteins, ultimately leading to cell cycle arrest at the sub-G phase. This arrest consequently inhibits prostate cancer cell proliferation and triggers apoptosis. Furthermore, these nanoparticles improve the bioavailability of chrysophanol to a certain extent.¹⁴⁸

Terpenoid-Loaded Nanoformulations

Costunolide-Loaded Nanoformulations

Several academics have developed optimized bilosome-based nanoparticles incorporating costunolide, which have demonstrated efficacy in inhibiting colorectal cancer LS174T cells in the sub-G1 phase, inducing apoptosis through up-regulation of caspase-3, TP53, and BAX, and down-regulation of BCL2 mRNA levels, as well as compromising cell membrane integrity. These nanoparticles also enhance cytochrome c release and ROS generation to further promote apoptosis and reduce cell membrane integrity, thereby exerting potent anti-tumor effects. Importantly, these nanoparticles exhibited no cytotoxic effects on normal human colonic epithelial cells, indicating a favorable safety profile and relative selectivity.¹⁴⁹

β-Elemene-Loaded Nanoformulations

A novel nanodelivery system, incorporating two-dimensional stanene-based nanosheets and β-elemene, has been developed by Chen et al to counteract the immunosuppressive effects caused by tumor-associated macrophages in solid tumors. This formulation effectively mitigates TAM-induced immunosuppression, thereby augmenting the effectiveness of chemo-immunotherapy.¹⁵⁰ Additionally, other researchers utilized a liquid-phase exfoliation method to produce the stanene-based nanosheets essential for creating the β-elemene delivery system. This nanoformulation boasts a remarkable photothermal conversion efficiency and can harness ultrasound for ROS generation, positioning it as a viable option for near-infrared-mediated photothermal therapy and precise delivery of anticancer drugs.¹⁵¹

Oridonin-Loaded Nanoformulations

Recently, a multifunctional therapeutic nanoplatform has been developed for the precise diagnosis and efficient treatment of pancreatic cancer. This nanoformulation utilizes gold nanocages that have been modified with hyaluronic acid and conjugated with anti-glypican-1 antibody, oridonin, gadolinium, and Cy7 dye. The nanoplatform exhibits long-term stability, as well as fluorescent and MRI properties, enabling multimodal imaging and targeted therapy in pancreatic tumor xenografted mice.¹⁵² Additionally, Cai et al synthesized a cell-penetrating peptide-modified metal-organic framework nanoplatform for targeted co-delivery of oridonin and survivin siRNA in vivo.¹⁵³ Furthermore, lipid-layered cisplatin has been co-encapsulated with oridonin in nanoparticles utilizing drug conjugation techniques for the combined treatment of lung cancer.¹⁵⁴ Moreover, GE11 peptide-conjugated selenium nanoparticles have been synthesized, designed to specifically target cancer cells overexpressing EGFR. This approach aims to enhance anticancer efficacy while minimizing toxicity to normal cells.¹⁵⁵

Celastrol-Loaded Nanoformulations

Niu et al successfully synthesized two nanoconjugates by conjugating celastrol onto PEGylated EpCAM aptamer or antibody dendrimers. Their study demonstrated, for the first time, that these nanoformulations can enhance the specificity of tumor accumulation and penetration in cancer animal models. Additionally, the nanoconjugates were found to effectively deliver celastrol with a favorable biosafety profile.¹⁵⁶ Furthermore, Niu et al developed a tumor-targeted, ROS-responsive celastrol-loaded smart nanoparticle that increased endogenous ROS levels through celastrol delivery, thereby inducing tumor cell apoptosis.¹⁵⁷ Moreover, other researchers created novel polymeric nanomicelles loaded with celastrol to enhance the inhibition of retinoblastoma growth and angiogenesis by addressing the low water solubility of celastrol.¹⁵⁸

Oleanolic Acid-Loaded Nanoformulations

Several researchers have successfully developed a novel EGFR-targeted, oleanolic acid-loaded albumin nanoparticle with promising haemocompatibility and lung safety profiles, demonstrating the potential for targeted delivery of oleanolic acid in lung cancer treatment.¹⁵⁹ Furthermore, Kumbham et al utilized oleanolic acid-coupled human serum albumin nanoparticles encapsulated with adriamycin to achieve synergistic chemotherapy effects, effectively inhibiting oropharyngeal carcinoma and melanoma progression.¹⁶⁰ Notably, Zhang et al have determined that the co-delivery of cisplatin and oleanolic acid through silicon nanoparticles resulted in a significant enhancement of apoptosis and reversal of multidrug resistance in lung cancer cells.¹⁶¹ Similarly, Bao et al have shown that paclitaxel-loaded oleanolic acid nanoparticles offer the advantage of synergistic chemotherapy and hold promise for the treatment of breast cancer and brain metastasis originating from breast cancer.¹⁶²

Artesunate-Loaded Nanoformulations

To address the challenges posed by the water solubility and bioavailability of artesunate, Xia et al developed solid lipid nanoparticles loaded with artesunate. This nanoformulation was found to increase Fe^{2+} levels, inhibit AKT/mTOR signaling, downregulate GPX4 expression, and induce ferroptosis in esophageal squamous cell carcinoma cells.¹⁶³ Other researchers have employed a nano-chemotherapeutic strategy utilizing PEGylated graphene oxide loaded with superparamagnetic iron oxide nanoparticles and artesunate. This approach effectively induces oxidative stress through the activation of the Fenton effect, leading to the release of Fe^{2+} and subsequent destruction of cancer cells.¹⁶⁴ Recent literature has also highlighted the efficacy of multifunctional artesunate-loaded nanoformulations derived from various materials in the treatment of tumors through chemo-photothermal, chemo-catalytic, and chemo-dynamic mechanisms, all of which have demonstrated significant effectiveness.^{165–167}

Flavonoid-Loaded Nanoformulations

Naringenin-Loaded Nanoformulations

Several researchers' group developed a chitosan-coated naringenin nanoparticle utilizing chitosan as a base material, demonstrating its ability to impede the proliferation of breast cancer cells and induce apoptosis through the efficient

elevation of oxidative stress, facilitation of ROS release, and activation of caspase-3 activity.¹⁶⁸ To enhance the therapeutic potential of naringenin's anticancer properties, researchers have utilized macrophage-encapsulated bionic proteolipid vesicles to deliver the compound. This approach has demonstrated improved biocompatibility of the nanoformulation and has effectively suppressed the proliferation and metastasis of lung cancer cells by modulating the apoptosis signaling pathway.¹⁶⁹ Furthermore, naringenin-loaded liquid crystalline nanoparticles have exhibited promising anti-inflammatory and anticancer effects in human airway epithelial-derived basal cells and human lung epithelial cancer cells, respectively.¹⁷⁰

Quercetin-Loaded Nanoformulations

Various nanoformulations of quercetin have been studied for their preclinical anticancer activity and mechanisms.^{171,172} A recent study by Das et al demonstrated the efficacy of a quercetin-encapsulated chitosan nanoparticle in inducing mitochondrial dysfunction, enhancing ROS production, inducing apoptosis, inhibiting colony formation and migration, promoting chromatin condensation in oral cancer CAL33 cells, and inhibiting tumor progression.¹⁷³ It is worth noting that solid lipid nanoparticles co-coated with a clinically targeted drug erlotinib and quercetin, can achieve synergistic effects by inhibiting the expression of nuclear EGFR and targeting lung cancer through the PI3K/AKT signaling pathway.¹⁷⁴

Kaempferol-Loaded Nanoformulations

In 2012, researchers developed kaempferol-containing nonionic polymeric nanoparticles that exhibit potent anti-tumor activity while demonstrating minimal toxicity toward healthy cells.¹⁷⁵ Subsequent investigations have revealed that kaempferol, a promising anticancer agent, can be integrated into gold nanoclusters to form nanoparticles. These composite nanoclusters exhibit low cytotoxicity towards normal human cells and high cytotoxicity towards lung cancer A549 cells, enabling targeted delivery of anticancer drugs and facilitating bioimaging through the destruction of cancer cell nuclei.¹⁷⁶ Furthermore, Mollaei et al developed a novel nanoformulation of kaempferol, utilizing human serum albumin as an adjuvant and folic acid-linked chitosan polymer to enhance cellular uptake, water solubility, and anti-tumor efficacy of kaempferol.¹⁷⁷

Luteolin-Loaded Nanoformulations

To improve the specificity of luteolin in targeting tumor cells, researchers developed a novel luteolin-coated gold nanoparticle capable of inducing cytotoxic effects on HeLa cells by arresting the cell cycle at the subG1 phase and triggering apoptosis in tumor cells via the activation of caspase-3, caspase-8, and caspase-9.¹⁷⁸ Furthermore, Fu et al conducted a study in which they developed highly efficient luteolin-loaded nanoformulations utilizing poly(ethylene glycol). Their findings demonstrated that these nanoformulations effectively suppressed the proliferation, migration, and invasion of tumor cells, and exhibited superior efficacy in tumor tissues compared to free luteolin.¹⁷⁹ To enhance the treatment of gliomas, Wu et al developed folic acid-modified poly(ethylene glycol)-poly(ϵ -caprolactone) nano-micelles containing luteolin, which demonstrated inhibition of tumor cell growth, increased cell invasion compared to free luteolin, and induced greater apoptosis. Additionally, no significant adverse effects were observed in mice following treatment.¹⁸⁰

Wogonin-Loaded Nanoformulations

Sabra et al utilized self-assembly techniques to create a nanomicellar formulation containing amphiphilic zeaxolysin-lactoferrin encapsulated with rapamycin and wogonin. This nanoformulation demonstrated enhanced cytotoxicity against MCF-7 breast cancer cells and ascites tumor animal models, as well as improved tumor targeting, resulting in increased anti-tumor efficacy and reduced side effects.¹⁸¹ Furthermore, Huang et al developed a nanoformulation consisting of cadmium-telluride quantum dots with wogonin. This formulation was found to effectively address multidrug resistance in cells and induce apoptosis by facilitating the interaction between wogonin and leukemia KA cells.¹⁸² To regulate the release rate of wogonin, researchers encapsulated the compound in solid lipids within the nanoformulation, resulting in a sustained and controlled release of the drug over a period of 72 hours, leading to increased cytotoxicity.¹⁸³

Apigenin-Loaded Nanoformulations

Recently, researchers have incorporated apigenin into chitosan to enhance its hydrophobicity and subsequently coated it with albumin-folic acid to improve stability and bioavailability, resulting in successful targeting of HepG2 cancer cells.¹⁸⁴ Additionally, other researchers have developed lactose-tailored PLGA nanoformulations loaded with apigenin, demonstrating increased cytotoxicity and apoptotic potential compared to free apigenin.¹⁸⁵

Hesperetin-Loaded Nanoformulations

To address the challenge of poor water solubility in hesperetin, researchers have developed a chitosan folate hesperetin nanoformulation through the covalent conjugation of folic acid with chitosan molecules. This nanoformulation leverages the targeting capabilities of folic acid and the permeability of nanoparticles to enhance the delivery of hesperetin in colorectal cancer and elicit anti-tumor effects.¹⁸⁶ Furthermore, it is worth mentioning that additional researchers have developed chitosan nanoparticles incorporating DCLK1-functionalized folic acid conjugated hesperetin, with a specific focus on targeting colon cancer stem cells, using a similar approach.¹⁸⁷ Moreover, Wang et al have devised a targeted drug delivery system utilizing hyaluronic acid-modified liposomes loaded with cisplatin and hesperetin to enhance the synergistic anticancer effects of clinical drugs, thereby reducing systemic toxicity and improving the efficacy against triple-negative breast cancer.¹⁸⁸

EGCG-Loaded Nanoformulations

Recent research has demonstrated the development of EGCG-loaded flower-shaped Au nanoclusters, gold nanoparticles, and PLGA-encapsulated nanoformulations for enhanced delivery of EGCG to cancer cells.^{189–191} Han et al employed microfluidics technology to create a fluorinated assembly of EGCG-ligands-siTOX nanoparticles for immunotherapy, with the goal of synergistically modulating tumor cells and exhausted T cells to improve the therapeutic response rate in cold tumors.¹⁹² In the realm of liver cancer treatment, He et al developed thermosensitive nanospheres containing fluorinated-modified EGCG, which effectively induce immunogenic cell death and damage-associated molecular patterns.¹⁹³

Hesperidin-Loaded Nanoformulations

Research has demonstrated that gold nanoparticles loaded with hesperidin exhibit high biocompatibility and serve as effective drug delivery systems, showing promise as novel agents for combating cancer and inflammation, as well as inducing phagocytosis.¹⁹⁴ Furthermore, several studies have validated the use of magnetic casein-CaFe₂O₄ nanohybrid carrier conjugated with progesterone to enhance the cytotoxicity of hesperidin against breast and ovarian cancer.¹⁹⁵ Additionally, the nanoformulation of imatinib and hesperidin has been demonstrated to target MDR-1 gene expression, Bax/Bcl-2, caspase-3, and Ki-67 associated with drug resistance and apoptosis, thereby significantly improving the effectiveness of the anticancer treatment compared to using either agent alone.¹⁹⁶

Alkaloid-Loaded Nanoformulations

Berberine-Loaded Nanoformulations

Singh et al developed a hydrophilic nanogel comprising chitosan and sodium alginate through the ion gelation technique to deliver berberine hydrochloride, enhancing its uptake and promoting apoptotic cell death mediated by oxidative stress in HepG2 cells.¹⁹⁷ Furthermore, researchers have utilized CD44-labelled hyaluronic acid-chitosan liposome carriers to encapsulate berberine and doxorubicin, allowing for sustained release of both compounds in diverse physiological conditions characterized by high permeability and increased cytotoxicity. This approach has shown promising outcomes in the treatment of lung cancer.¹⁹⁸ Additionally, berberine-loaded Janus gold mesoporous silica nanocarriers and glucose-coated berberine nanodrugs have been developed for multidimensional tumor therapy.¹⁹⁹

SN38-Loaded Nanoformulations

Recent advancements in nanodrug delivery systems for SN38 in the field of antitumor research have shown rapid development.^{200,201} Liu et al have developed a polymeric, ROS-responsive nanoformulation for in vivo drug delivery, which has shown promising results in enhancing DNA damage and inducing DC cell maturation for cancer immunotherapy through ultrasound-triggered sonodynamic therapy.²⁰² Wu et al developed a biocompatible superparamagnetic chitosan-based nanopatform for targeted delivery of SN38 in a mouse xenograft colorectal cancer model, resulting in a tumor inhibition rate of 81%.²⁰³ Furthermore, various formulations such as SN38-conjugated gold nanoparticles, CD133-targeted self-assembled PEGylated carboxymethylcellulose-SN38 nanoparticles, and novel polymer micelles containing SN38 have shown promising results in preclinical studies across multiple cancer types.^{204–206}

Piperlongumine-Loaded Nanoformulations

A PLGA-based nanomedicine containing piperlongumine was developed by Singh et al, which demonstrated the ability to disrupt glycolytic metabolism in triple-negative breast cancer stem cells through the regulation of GAPDH and FBPI.²⁰⁷ Additionally, this nanomedicine was found to inhibit cancer stem-like cells by modulating STAT3 in a triple-negative breast cancer mammosphere model.²⁰⁸ In the realm of drug conjugation for clinical applications, Liu et al employed PLGA and D- α -tocopheryl polyethylene glycol succinate as carriers for the simultaneous delivery of paclitaxel and piperlongumine. Their nanoformulations exhibited significant antitumor efficacy and minimal toxicity towards non-target tissues in a HepG2 xenograft tumor model when compared to the free drug.²⁰⁹

Tetrandrine-Loaded Nanoformulations

A new bionic platelet membrane-encapsulated delivery system for tetrandrine has been developed using polycaprolactone-b-poly-b-polycaprolactone nanoparticles by Jiang et al. This system demonstrated enhanced evasion of macrophage phagocytosis and improved antitumor efficacy against non-small cell lung cancer.²¹⁰ Additionally, several research groups have synthesized self-assembled reduction-sensitive paclitaxel dimer prodrug and tetrandrine nanoformulations to enhance the synergistic therapeutic effects and drug release.²¹¹ Notably, Li et al developed a novel supramolecular synergistic drug delivery nanoformulation utilizing advanced “carrier-free” self-assembled nanofibers for the simultaneous delivery of paclitaxel and tetrandrine. This formulation was found to enhance the clinical efficacy of paclitaxel in gastric cancer by promoting apoptosis in mitochondria, while also reducing associated side effects.²¹²

Vincristine-Loaded Nanoformulations

Numerous studies have investigated the use of vincristine-based nanoformulations in both preclinical and clinical settings.²¹³ Researchers have utilized smart polymer magnetic nanocarriers with dextran shells, superparamagnetic iron oxide cores, and folic acid to deliver vincristine to testicular tumor cells, resulting in a significant increase in apoptosis levels.²¹⁴ Wang et al developed an anti-CD133 antibody-targeted therapeutic immunomagnetic albumin microbeads loaded with vincristine, which demonstrated efficacy in suppressing tumor cell migration, invasion, and brain-targeted diagnosis and therapy from an immunotherapeutic standpoint.²¹⁵ Furthermore, a variety of smart nanoparticles containing vincristine have been engineered for the effective management of diverse tumor types.^{216,217}

Polyphenol-Loaded Nanoformulations

Curcumin-Loaded Nanoformulations

Recent research has demonstrated the widespread utilization of curcumin-loaded nanoformulations for combination therapy involving drug-drug interactions and gene disruption-drug interactions. Vahedi et al developed a dual drug delivery system utilizing a polyamide-amine dendrimer to encapsulate curcumin and form a complex with linc-RoR siRNA at an optimal N/P ratio. This nanoformulation was effectively internalized in MCF-7 breast cancer cells, leading to synergistic cytotoxic effects through the dual delivery of linc-RoR siRNA and curcumin. This resulted in cell cycle arrest in the G1 phase and induction of apoptosis.²¹⁸ In the realm of breast cancer treatment, other researchers have co-encapsulated gemcitabine with curcumin in folate-modified PLGA nanoparticles, resulting in significant accumulation in

MDA-MB-231 cells. This nanoformulation demonstrated enhanced efficacy in inducing cytotoxicity, apoptosis, and cell cycle arrest, as well as overcoming drug resistance in breast cancer compared to individual agent formulations.²¹⁹ Furthermore, Amandi et al pioneered the construction of artemisinin- and curcumin-loaded liposomal nanoparticles for the co-delivery of these active ingredients in TCM, resulting in the promotion of apoptosis, induction of cell cycle blockade, and significant anti-cancer effects on human colorectal cancer cells.²²⁰

Resveratrol-Loaded Nanoformulations

The issue of low bioavailability of resveratrol has been addressed by Wang et al, who developed D- α -Tocopheryl polyethylene glycol 1000 succinate-resveratrol-solid lipid nanoparticles to enhance its therapeutic effectiveness, particularly in combating multidrug resistance in breast cancer.²²¹ Additionally, Liu et al developed gold nanoparticles functionalized with Au-Se-bonded peptides for triple-negative breast cancer therapy. These nanoparticles, loaded with resveratrol, functioned as gatekeepers to prevent glutathione interference in the bloodstream, resulting in prolonged release of resveratrol at the tumor site and enhanced therapeutic efficacy.²²² Notably, significant progress has been made by several researchers who have successfully developed biocompatible resveratrol-conjugated gold nanoparticles using an innovative green nanotechnology method. These nanoformulations have exhibited remarkable in vitro stability in various biological environments and have proven effective in human breast (MDAMB-231), pancreatic (PANC-1), and prostate (PC-3) cancer cell lines.²²³

Proanthocyanidin-Loaded Nanoformulations

Research has progressed in the development of deformable nanoparticles responsive to the TME, with Qian et al introducing a novel nanoformulation. This nanoformulation incorporated a tumor acid-responsive peptide checkpoint inhibitor polymer (PEG-DMA-DPA-1), combined with a mixture of proanthocyanidin and mitoxantrone, aimed at enhancing immunogenic cell death. These nanoparticles exhibited self-assembly within the acidic microenvironment of tumors, ultimately leading to local reprogramming of the TME in CT26 tumor-bearing mice. This innovative approach demonstrated improved efficacy in immunotherapy for colorectal cancer while mitigating associated toxicity.²²⁴ Furthermore, ZhuGe et al synthesized silk fibroin nanoparticles containing indocyanine green, followed by the creation of a durable nanoformulation through cross-linking with proanthocyanidin. This formulation effectively targets and eliminates residual glioma cells in the surgical cavity when exposed to near-infrared irradiation.²²⁵

Polysaccharides-Loaded Nanoformulations

Lentinan-Loaded Nanoformulations

In response to the issue of selenium nanoparticles aggregating into non-bioactive forms, lentinan-selenium nanoparticles were developed utilizing lentinan as a template, as exemplified by Gao et al. This nanoformulation demonstrates high stability at 4°C for a minimum of 8 weeks, induces cell cycle arrest at the G0/G1 phase in HCT-116 cells, stimulates apoptosis through activation of the mitochondria-mediated apoptotic pathway, and exhibits negligible toxicity towards normal cells.²²⁶ Furthermore, certain researchers have engineered selenium nanoparticles functionalized with lentinan. These nanoparticles are capable of targeting the mitochondria of tumor cells through the TLR4/TRAFF3/MFN1 signaling pathway, leading to alterations in mitochondrial membrane potential and the generation of ROS, thereby promoting apoptosis in the tumor cells.²²⁷

Astragalus Polysaccharide-Loaded Nanoformulations

To overcome the limitations of anti-tumor immunity, focused ultrasound has been utilized to construct a multifunctional nanoformulation, as exemplified by Xiong et al. This nanoformulation consists of poly(ethylene glycol) platinum nanoparticles encapsulating astragalus polysaccharide and gold nanorods, synthesized via the double emulsion method. This novel approach enhances the efficacy of focused ultrasound-induced immunity for sustained and systemic anti-tumor effects, as well as providing imaging and thermal enhancement.²²⁸ In the context of hepatocellular carcinoma treatment, a study conducted by Jiao et al prepared nanocomposites by modifying selenium nanoparticles with astragalus

polysaccharide, serving as a stabilizer and dispersant. This intervention significantly impeded the proliferation of HepG2 cells in a dose-dependent manner, leading to alterations in cell morphology, cell cycle arrest in the S-phase, and ultimately inducing apoptosis of HepG2 cells via the mitochondria.²²⁹ Similarly, selenium nanoparticles combined with astragalus polysaccharides, synthesized by Duan et al, exhibited cytotoxic effects on MCF-7 cells through the inhibition of cellular autophagy and apoptosis mediated by the mitochondrial pathway.²³⁰ Furthermore, Wang et al developed a self-assembled delivery system targeting ER α -positive breast tumors using a double-targeted approach involving quercetin-3'3-dithiodipropionic acid, astragalus polysaccharides, and folic acid, demonstrating effective suppression of multidrug resistance.²³¹

Sesquiterpene Lactone-Loaded Nanoformulations

Parthenolide-Loaded Nanoformulations

Researchers have developed a novel polydopamine-coated PLGA nanoformulation containing parthenolide, which demonstrates selective cytotoxicity and induces apoptosis in gastric cancer cells.²³² Additionally, Gao et al have created nano-magnetic liposomes encapsulating parthenolide and glucose oxidase. This nanoformulated anticancer strategy combines chemotherapy, chemodynamic therapy, starvation therapy, and magnetically targeted therapy, exhibiting significant synergistic anticancer efficacy in vivo and in vitro with minimal biological toxicity.²³³ To enhance the treatment of advanced hepatocellular carcinoma, several scholars developed a novel parthenolide nanocrystal drug delivery system aimed at addressing the limited water solubility of parthenolide and enhancing its therapeutic synergy with sorafenib. The nanoformulation demonstrated superior therapeutic efficacy compared to individual administration of parthenolide and sorafenib, as evidenced by increased intracellular uptake, inhibition of cell proliferation and migration, and significant tumor suppression in animal models, all while exhibiting minimal toxicity.²³⁴

Discussion

As scientific research advances, experts and scholars in the field of medicine have progressively recognized that ROS play a pivotal role in the occurrence, progression, and treatment of malignant tumors.²⁰ Initially, ROS were predominantly considered detrimental, promoting tumor development, as evidenced by their significantly elevated concentrations in tumor cells compared to normal cells. However, in recent years, mounting evidence suggests that the role of ROS in the development of malignant tumors is dynamic, exhibiting dichotomous effects contingent upon their concentration and duration of exposure.²¹ Specifically, low-toxic high concentrations of ROS can activate a series of growth factor receptors and signaling pathways, thereby promoting the proliferation, metastasis, and malignant transformation of tumor cells through the modulation of tumor-related genes and the induction of oncogenic mutations, among other mechanisms. Conversely, when the concentration of ROS surpasses the toxicity threshold, it can exacerbate oxidative stress damage and activate multiple ROS-mediated cell death signaling pathways, leading to various forms of cell death in tumor cells and thereby significantly inhibiting tumor growth. Given the elevated levels of ROS in tumor cells, the development of pharmacological agents that induce ROS generation and specifically target tumor tissues to elevate ROS concentrations beyond the toxicity threshold within the tumor has emerged as a promising therapeutic strategy for cancer treatment.

In recent years, a diverse array of active ingredients derived from TCM that induce ROS generation have exhibited distinct advantages as a novel approach to cancer therapy, attributable to their pronounced anti-tumor effects.⁵ Primarily, these active ingredients are sourced from natural plants or animals, which are abundant and exhibit high biocompatibility with the human body, resulting in relatively low toxicity. This characteristic renders them frequently perceived as safer and more reliable alternatives in the realm of cancer treatment. Secondly, these active constituents in TCM frequently exhibit multi-targeted properties, facilitating synergistic anti-tumor effects among various components, thereby mitigating the risk of drug resistance in tumor cells. Furthermore, guided by the holistic principles inherent in Chinese medicine, these active constituents emphasize the balance of yin and yang as well as the harmonization of qi and blood. These characteristics are instrumental in enhancing overall patient health and bolstering the body's anti-tumor capabilities. Nonetheless, the ROS-inducing active ingredients derived from TCM encounter several challenges, including poor water solubility and bioavailability, non-specific distribution, and rapid metabolic degradation. To address these limitations, the

development of multifunctional nanoformulations represents a promising strategy, potentially enhancing the anticancer efficacy of these ROS-inducing TCM compounds.

The present review systematically examined and analyzed ROS-inducing ingredients derived from TCM. It was found that these active compounds encompass a diverse array of chemical types, including quinones, terpenoids, flavonoids, alkaloids, polyphenols, polysaccharides, and sesquiterpene lactones. Furthermore, the review investigated the diversity of these compounds concerning their anticancer mechanisms, revealing their extensive involvement in the inhibition of cell proliferation, promotion of apoptosis, ferroptosis, autophagic cell death, pyroptosis, and necroptosis, among other processes. Moreover, this paper provides a comprehensive summary of nanoformulations incorporating ROS-inducing compounds, highlighting two principal strategies for their preparation. The first strategy involves the direct nanoformulation and processing of these compounds into nanoparticles. The second strategy employs nano-carrier systems to prepare these compounds, either in isolation or in combination with other drugs, into a diverse array of nanodrugs, including but not limited to liposomes, polymer micelles, gold nanoparticles, metal-organic frameworks, iron oxides, inorganic nanoparticles, and hydrogels. Through the application of advanced nanotechnology and the integration of active ingredients in TCM capable of inducing ROS generation, the development of effective nanosized drug preparations can be realized. This approach not only enhances targeted drug release, increases bioavailability, and reduces toxicity, but also optimizes the efficacy of drug combinations. Nanocarriers facilitate the targeted aggregation of pharmaceuticals within tumor tissues, thereby minimizing collateral damage to healthy tissues, significantly enhancing therapeutic efficacy, and reducing adverse side effects. Besides, nanomedicines can extend the systemic circulation time of drugs, improve their stability, and prevent rapid metabolism, thereby sustaining the therapeutic effect over a prolonged period.

In this manuscript, we present the inaugural systematic induction and comprehensive summary of TCM-derived ROS-inducing components and their nanoformulations, to provide a significant reference for the clinical application of TCM drugs in tumor treatment. This study holds substantial implications for the future exploration of TCM within the realm of modern medicine and is anticipated to introduce novel concepts and methodologies to the field of clinical oncology. Nevertheless, despite our rigorous efforts to systematically organize and synthesize the available data, certain limitations persist in this review. Firstly, considering the extensive range of ROS-inducing compounds present in TCM, our study is limited to examining only some of the more prevalent compounds, thereby not providing a comprehensive analysis of all ROS-inducing compounds and their nanoformulations pertinent to tumor therapy. Secondly, regarding the investigation of the pharmacological mechanisms of action and the clinical efficacy evaluation of these compounds and nanoformulations, our content requires further refinement and in-depth exploration. Lastly, constrained by the scope and depth of the current study, we were unable to comprehensively address the potential side effects and interactions of these compositions. These areas represent critical directions for future research and warrant further detailed examination.

Currently, the development of multifunctional nanomedicine formulations is progressively advancing. Through innovative strategies, multiple research teams have successfully formulated a variety of nanoformulations with broad application prospects. These formulations exhibit significant potential not only in the field of anti-tumor therapy but also in other therapeutic domains, such as the treatment of anaerobic bacterial infections.^{235–237} Notably, recent advancements in nanomedical research underscore the importance of constructing supramolecular hosts with specific recognition sites and drug-loaded guest molecules based on the host-guest molecular recognition mechanism, employing techniques like self-assembly. This approach aims to achieve precise targeting and controlled release of drugs within the TME. Such supramolecular systems, endowed with specific functions and properties, demonstrate extensive application value in various forms of malignant tumor therapy. For instance, they can enhance the efficacy of chemotherapy and phototherapy,²³⁸ facilitate mRNA vaccine delivery,²³⁹ modulate the TME to synergize with tumor immunotherapy,²⁴⁰ and enable in situ self-enhanced cancer photochemotherapy.²⁴¹ These regulatory strategies offer novel insights and methodologies for tumor treatment. It is reasonable to believe that with the continuous advancements in supramolecular chemistry, nanotechnology, and biotechnology, the active ingredients in TCM, particularly those with ROS-inducing properties, will also be able to effectively combine with various supramolecular materials (such as cyclodextrins and pillararenes) based on their inherent attributes. This will facilitate the development of supramolecular nanomedicine formulations derived from TCM. This research domain is anticipated to yield further breakthrough achievements, bringing enhanced hope and well-being to personalized treatment for cancer patients.

Conclusions

Overall, although our study provides new perspectives on the ROS-inducing components of TCM and its nano-formulations for the treatment of tumors, more basic and clinical experiments are needed to verify whether they can widely serve clinical oncology patients in the future.

Data Sharing Statement

The current study does not have any datasets generated or analyzed for data sharing.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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