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REVIEW

Exploiting Nanotechnology for Drug Delivery: Advancing the Anti-Cancer Effects of Autophagy-Modulating Compounds in Traditional Chinese Medicine

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Background: Cancer continues to be a prominent issue in the field of medicine, as demonstrated by recent studies emphasizing the significant role of autophagy in the development of cancer. Traditional Chinese Medicine (TCM) provides a variety of anti-tumor agents capable of regulating autophagy. However, the clinical application of autophagy-modulating compounds derived from TCM is impeded by their restricted water solubility and bioavailability. To overcome this challenge, the utilization of nanotechnology has been suggested as a potential solution. Nonetheless, the current body of literature on nanoparticles delivering TCM-derived autophagy-modulating anti-tumor compounds for cancer treatment is limited, lacking comprehensive summaries and detailed descriptions.

Methods: Up to November 2023, a comprehensive research study was conducted to gather relevant data using a variety of databases, including PubMed, ScienceDirect, Springer Link, Web of Science, and CNKI. The keywords utilized in this investigation included "autophagy", "nanoparticles", "traditional Chinese medicine" and "anticancer".

Results: This review provides a comprehensive analysis of the potential of nanotechnology in overcoming delivery challenges and enhancing the anti-cancer properties of autophagy-modulating compounds in TCM. The evaluation is based on a synthesis of different classes of autophagy-modulating compounds in TCM, their mechanisms of action in cancer treatment, and their potential benefits as reported in various scholarly sources. The findings indicate that nanotechnology shows potential in enhancing the availability of autophagy-modulating agents in TCM, thereby opening up a plethora of potential therapeutic avenues.

Conclusion: Nanotechnology has the potential to enhance the anti-tumor efficacy of autophagy-modulating compounds in traditional TCM, through regulation of autophagy.

Keywords: autophagy, nano-delivery, anti-cancer, traditional Chinese medicine

Introduction

The study of cancer treatment is of paramount importance in the global medical field and faces various challenges.[1] The increasing prevalence of cancer, driven by an aging population and changing lifestyles, puts significant pressure on healthcare providers.[2–4] Traditional treatments such as chemotherapy and radiotherapy have limitations, including harm to healthy tissues, uncertain effectiveness, and the development of drug resistance.[5,6] Consequently, it is crucial for novel technologies and methodologies to be developed to improve the effectiveness of cancer treatment. During recent decades, the advent of emerging technologies, namely nanotechnology, immunotherapy, and gene editing technology, has instilled renewed optimism in the field of cancer treatment.[7–9] Nanotechnology enables the precise delivery of drugs to tumor tissues using nanocarriers, reducing the risk of damage to healthy tissues.[10] Numerous studies have demonstrated the mechanisms and benefits of various nanoformulations in tumor therapy, showing that nanoformulations are more effective than free drugs.[11,12] Furthermore, immunotherapy augments the body's immune system and enhances its response to tumors.[13] The application of gene editing technology has emerged as a prominent area of research, offering

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promising prospects for cancer treatment.[14] In conjunction with the exploration of emerging technologies, there has been a concerted effort to investigate novel pharmaceuticals, particularly Chinese medicines, which are increasingly recognized as valuable assets in the realm of oncological treatment.[15] A burgeoning body of research indicates that Chinese medicines offer promising prospects in the field of oncology.[16–18] The development of these innovative technologies, methodologies, and pharmaceuticals can improve the precision and effectiveness of cancer therapy, thereby contributing to enhanced patient outcomes and quality of life.

Autophagy, a critical process in eukaryotic cells, plays a pivotal role in organelle regeneration, substance recycling, metabolic homeostasis, and adaptation to external stimuli.[19,20] In recent years, there has been a notable increase in research attention towards autophagy in various biological disciplines. Within the field of oncology, autophagy has been acknowledged as a significant mechanism in the regulation of tumor cell survival.[21,22] Additionally, ongoing studies focusing on the modernization of TCM have revealed an increasing number of TCM compounds that exhibit potential in modulating autophagy.[23–25] These compounds present notable advantages compared to traditional chemotherapeutic agents, including platinum-based drugs and anthracyclines, owing to their reduced toxicity, capacity to target multiple sites, and synergistic effects.[26,27] Nevertheless, the widespread presence of indoles and flavonoids in these compounds poses a significant obstacle due to their inadequate water solubility and restricted bioavailability, thereby impeding their potential clinical applicability.[26,28] The incorporation of nano-delivery technology holds promise in overcoming this constraint.

The field of cancer therapy requires novel drugs and technologies for advancement, with the active ingredient components of TCM showing promise as anti-tumor small-molecule drugs. However, limitations in their application for tumor therapy exist. The integration of nano-delivery technology addresses these challenges and enhances the benefits of TCM active ingredients. Autophagy is recognized as a crucial target for modulating the viability and apoptosis of cancer cells. Compounds sourced from TCM can either enhance or impede the autophagy process in tumor cells, thereby facilitating autophagy-induced cell death or hindering protective autophagy to inhibit tumor progression. The utilization of nanotechnology for the delivery of active compounds sourced from TCM allows for the development of a personalized targeted delivery approach designed for specific cancer treatments.[26] This approach enables controlled release, synergistic effects of multiple drugs, and combination therapy, ultimately enhancing the effectiveness of anti-tumor interventions.

Currently, there is a significant gap in academic literature regarding the application of nanoparticles for targeted delivery of autophagy-modulating compounds in TCM for cancer therapy. This lack of comprehensive synthesis and elucidation has motivated us to undertake a thorough investigation utilizing multiple databases. Our study results can be categorized into three main areas: 1. the application of nanoparticles in cancer therapy; 2. the diverse range of autophagy-modulating compounds in TCM, their mechanisms of action against cancer, and their potential significance; 3. the advantages associated with the nanoparticle-mediated administration of autophagy-modulating compounds in TCM, alongside the progress in research and pertinent case studies.

Application of Nanoparticles in Cancer Therapy

In recent years, the field of nanotechnology has made notable advancements, particularly in the area of drug delivery, which has generated optimism for the treatment of cancer.[29–31] Nanoformulations of drugs, characterized by their small dimensions and stable properties, have demonstrated the ability to effectively transport a variety of small molecules including conventional chemotherapeutic drugs, active compounds from TCM, genes, as well as photosensitizers and photothermal agents.[32–34] The nanoformulations mentioned above, which include nanoparticles, nanomicelles, metal-on-framework (MOF) nanoparticles, liposomes, and biomimetic nanoparticles, frequently exhibit advantages such as targeted delivery, controlled release, multidrug synergy, and combined therapy.[35–37] These distinctive characteristics enable nanoformulations to demonstrate superior efficacy compared to free small-molecule drugs. Numerous studies in the literature have shown that nanoformulations exhibit higher anti-tumor toxicity than conventional therapies at equivalent concentrations, as well as a lower IC_{50}.[38–41] The advantages of these nanoformulations are illustrated in Figure 1.

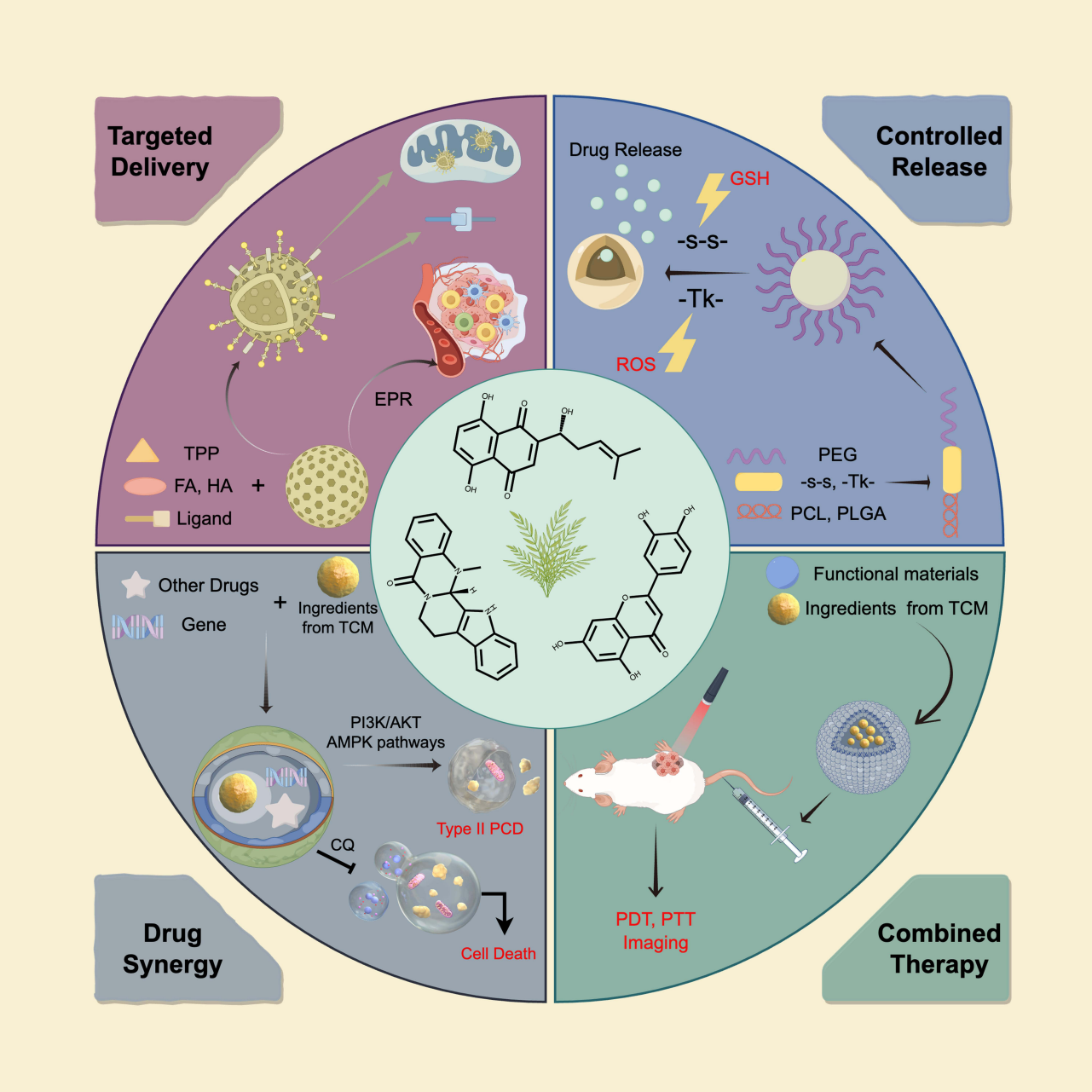

Figure 1 Application of nanoformulations in cancer therapy (diagram by Figdraw ID:USYUWa2b9d). Multifunctional nanoformulations, encompassing nanoparticles, nano micelles, metal-on-framework (MOF) nanoparticles, liposomes, and biomimetic nanoparticles, improve the solubility and biocompatibility of free drug, overcoming delivery barriers, which further provide better anti-cancer effects via targeted delivery, controlled release, drug synergy, and combined therapy.

Targeted Delivery

The successful attainment of targeted delivery of nanoformulations can be achieved through a variety of mechanisms, one of which relies on their inherently small size and the enhanced permeability and retention (EPR) effect observed in the vicinity of tumor sites.[42] Specifically, the rapid growth of tumor cells leads to irregular neovascularization, causing structural abnormalities in the vessel wall and increased microvascular permeability. As a result, nanoparticles with reduced diameters can traverse the vessel wall more easily and penetrate the tumor tissue.[43] This phenomenon facilitates the accumulation and prolonged presence of nanoparticles in the vicinity of the tumor site.

Furthermore, nanoformulations possess the capability to be modified at the surface to enhance targeted delivery. This process entails the integration of antibodies, ligands, or other compounds onto the nanoparticle surface, enabling them to

selectively identify and attach to particular receptors on cancer cell surfaces.[44,45] Through the implementation of this technique, the efficacy of therapeutic targeting can be enhanced, while reducing potential damage to healthy cells. An exemplar of this concept is the utilization of folic acid (FA) as a surface modification on nanoparticles containing resveratrol.[46] This modification allows for an increased drug concentration at the tumor site, thereby enhancing the antitumor toxicity and efficacy.[47]

Controlled Release

An additional advantage of nanoformulations lies in their ability to facilitate the controlled release of co-delivered drugs. This precise release mechanism guarantees timely and targeted delivery of the drug, thereby enhancing its concentration at the specific site of the lesion.[48] As a result, this strategy optimizes the drug's efficacy while minimizing potential harm to healthy cells. Additionally, the controlled release also serves to prolong drug metabolism and excretion, leading to a decreased frequency of administrations and improved patient compliance with the prescribed treatment regimen.[49]

The activation of nanoformulation release can be classified into two distinct methodologies. The first method entails the incorporation of polymers or biodegradable materials with specific chemical groups, such as Tk bonds (thioketal) and s-s bonds (disulfide bond), that are designed to be responsive to stimuli such as pH, GSH, ROS, etc., facilitating controlled drug release based on the environmental conditions within the tumor microenvironment.[50–53] The second approach entails utilizing external stimuli, such as ultrasound and near-infrared (NIR) signals from external sources, to trigger targeted drug release under specific conditions.[54,55] These methods are commonly utilized in combination to develop composite nanomedicine systems, which allow for more precise control over drug release and have gained significant traction in the delivery of active ingredients from TCM.

Multidrug Synergy

Nanoformulations show promise in enhancing treatment effectiveness by enabling the targeted delivery of various therapeutic agents to specific tissues or cells, allowing for the simultaneous exertion of synergistic effects.[56] This strategy often proves successful in overcoming the obstacles associated with single-agent therapy, such as the emergence of drug tolerance and resistance, thus presenting hopeful therapeutic opportunities for multidrug-resistant (MDR) cancer cells.[57] Notably, the combination of autophagy-modulating compounds derived from TCM with autophagy inhibitors such as chloroquine (CQ) can augment the therapeutic impact, while the integration of autophagy inhibition with conventional chemotherapeutic agents can counteract drug resistance in tumor cells.[41,58]

Combined Therapy

Nanoformulations can utilize a variety of materials to transport different drugs, transforming them into nanoplatforms with multiple diagnostic and therapeutic functions.[59] For example, combining photosensitizers and photothermal agents enables the integration of chemotherapy, photothermal therapy (PTT), and photodynamic therapy (PDT).[60] Additionally, the integration of an imaging agent within nanoparticles enables the live observation of a lesion's physiological condition in an in vivo setting. For instance, the inclusion of nanoparticles loaded with a photosensitizer like indocyanine green in tumor tissue enables the utilization of near-infrared (NIR) molecular imaging for precise visualization of the tumor, thereby enhancing treatment accuracy.[61]

Although nanotechnology holds potential for drug delivery, it is important to consider the potential side effects associated with nanoformulations. These formulations may be recognized and rejected by the immune system, leading to allergic reactions or inflammation that can be harmful to the body.[62,63] Additionally, nanomedicines may be rapidly cleared by the liver or kidneys, reducing their effectiveness.[63,64] We are also concerned about the presence of metal nanoparticles with autophagy-regulating properties, particularly those composed of materials such as gold and silver that are challenging to metabolize and eliminate. Localized accumulation of these nanoparticles may contribute to the malignant transformation of healthy cells.[65–68] Besides, nanopreparations have been reported to impact platelet function and coagulation in the blood system, potentially leading to thrombus formation.[63] Therefore, thorough safety evaluation and vigilant monitoring are imperative throughout the development and application of nanomedicine delivery systems to guarantee the safety and effectiveness of nanopreparations.

The aforementioned multifunctional nanoformulations are currently under investigation and have not yet been integrated into clinical practice. Approved nanomedicines for clinical use include Paclitaxel-loaded albumin nanoparticles (Abraxane) and liposomes loading Doxorubicin (Doxil), among others.[69–72] Abraxane has been approved for the treatment of breast cancer, pancreatic cancer, and non-small cell lung cancer, while Doxil is currently approved and utilized in the treatment of multiple cancers, including breast and ovarian cancer.[73,74] Although nanoformulations have shown improved drug solubility and bioavailability, their monofunctionality and limited drug loading capacity may impede their ability to substantially enhance clinical efficacy for tumors. Nonetheless, these successful cases provide strong support for the potential of nano-delivery systems in enhancing drug efficacy, reducing toxicity, and broadening treatment options. As a result, they offer important insights and bolster confidence in the future clinical utilization of multifunctional nanoformulations.

TCM Active Ingredients Act as Anti-Tumor Agents by Modulating Autophagy

Autophagy is an evolutionarily conserved cellular process in eukaryotes that aids in the degradation and recycling of intracellular biomolecules and damaged organelles. The initiation of this process is primarily mediated by the ULK1 (UNC-51 Like Kinase 1) complex, which leads to the formation of a phagophore, a flat lipid bilayer structure.[75,76] The VPS34-Beclin1 complex, regulated by ULK1, is essential for elongating the phagophore membrane and establishing a link between autophagy and cancer progression.[77]

The elongation of the phagophore results in the formation of the autophagosome, a double-membrane structure. This crucial process is tightly controlled by two ubiquitin-like pathways, specifically ATG7-ATG3 and ATG7-ATG10.[78,79] It entails the transformation of LC3-I, a cytoplasmic protein, into LC3-II, which aids in the elongation of the autophagosome membrane. Furthermore, the p62 protein plays a significant role in the selective sequestration of degradation by autophagosomes, as it interacts with both LC3-II and the ubiquitin-binding domain of the degraded proteins.[80]

Autophagy plays a crucial role in cancer by exerting varied effects dependent on the specific cancer type, progression, and tumor microenvironment. Recent research has shown that autophagy acts as a protective mechanism, promoting metastasis and drug resistance in cancer cells.[81–83] Conversely, other studies have identified autophagy as a process that facilitates programmed cell death.[84–86] Additionally, autophagy is closely linked with apoptosis, necroptosis, ferroptosis, and immunogenic cell death (ICD).[87–89] A comprehensive examination indicates that Bcl-2 functions as a connection between apoptosis and autophagy, with the potential for mutual activation between autophagy and ferroptosis through the production of reactive oxygen species (ROS) and lipid peroxidation.[90,91] Moreover, necroptosis may be associated with autophagy via RIP3-related pathways.[92,93] Besides, autophagy has been found to induce ICD either directly or indirectly through ferroptosis.[94] Given the capacity of TCM to target multiple components and subsequently stimulate various pathways, a thorough comprehension of the interaction among these pathways becomes essential. The interplay of these cell death pathways is visually represented in Figure 2.

Moreover, autophagy plays a crucial role in the anti-tumor effects of active components found in TCM. Numerous studies have demonstrated that TCM-derived compounds, including alkaloids, flavonoids, coumarins, and lignans, are involved in the regulation of cellular autophagy and show promise as potential cancer therapeutics.[95–99] The effectiveness of TCM active ingredients in inducing changes in intracellular autophagy-related proteins, including LC3, p62, Beclin1, ATG5, etc., has been supported by various signaling pathways, such as the PI3K/AKT/mTOR signaling pathway, AMPK-related signaling pathways, and MAPK-related signaling pathways.[100,101] Additionally, these TCM active ingredients have demonstrated a significant influence on cancer progression. The targets and mechanisms involved in the regulation of autophagy by these TCM-active ingredients are depicted in Figure 3.

This article aims to provide a comprehensive review of various active ingredients derived from TCM that possess the ability to regulate autophagy and induce cell death in tumors. The significance of autophagy in cancer therapy and the distinct advantages offered by these compounds will be thoroughly examined.

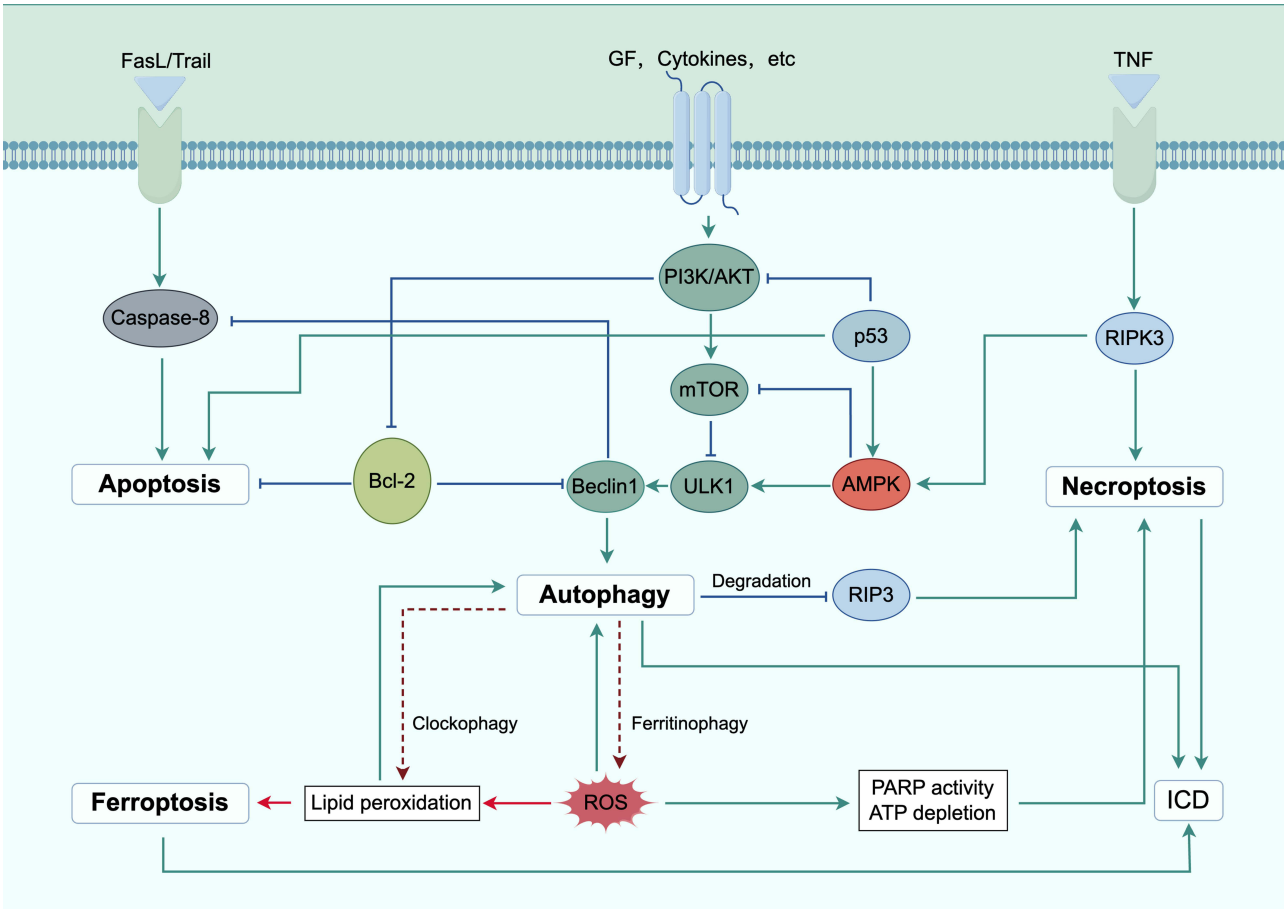

Figure 2 Crosstalk between autophagy and other types of cell death ways (diagram by Figdraw ID: UAIYY17111). There is an intricate interplay of signaling pathways between autophagy and apoptosis, necroptosis, ferroptosis, and ICD, potentially influencing cancer therapy outcomes. Common regulatory molecules are shared between autophagy and other cell death pathways, indicating a complex regulatory relationship between autophagy and multiple cell death pathways.

Evodiamine

Evodiamine (EVO), a compound derived from *Tetradium Ruticarpum*, a traditional Chinese medicinal plant, has been shown to modulate autophagy in tumor cells through multiple signaling pathways.[102] Previous research has highlighted the role of EVO in regulating autophagy via the PI3K/AKT/mTOR, Ras/MEK/ERK, STAT3-related, and Ca^{2+}/JNK pathways. Specifically, EVO has been observed to promote protective autophagy in pancreatic and lung cancers,[103,104] while inhibiting autophagy in glioblastoma.[105] Furthermore, the combination of EVO with 3-methyladenine (3-MA), an autophagy inhibitor has been found to enhance therapeutic efficacy.[103,104,106] Additionally, a compound was synthesized by researchers through the combination of EVO and tetravalent platinum, demonstrating potent anti-cancer properties. In contrast to EVO or Pt monomers, this innovative compound notably increased autophagy levels in MCF-7 cells. However, contrary to previous studies, the introduction of 3-MA did not augment cytotoxicity; instead, it led to a decrease.[107] This occurrence may be attributed to the inadequate autophagy induction caused by EVO alone, which failed to initiate autophagic cell death. Conversely, the novel compound induced substantial levels of autophagy, excessively activating the autophagy pathway beyond the protective threshold, ultimately culminating in autophagic cell death in the cancer cells. This investigation presents potential avenues for the logical and clinical implementation of EVO-derived compounds.

Icaritin

Icaritin (ICA), an isopentenyl flavonoid derived from *Herba Epimedii*, has been shown in previous research to modulate autophagy through the PI3K/AKT pathway in tumor cells.[108] Its inhibitory effect on autophagy enhances the sensitivity

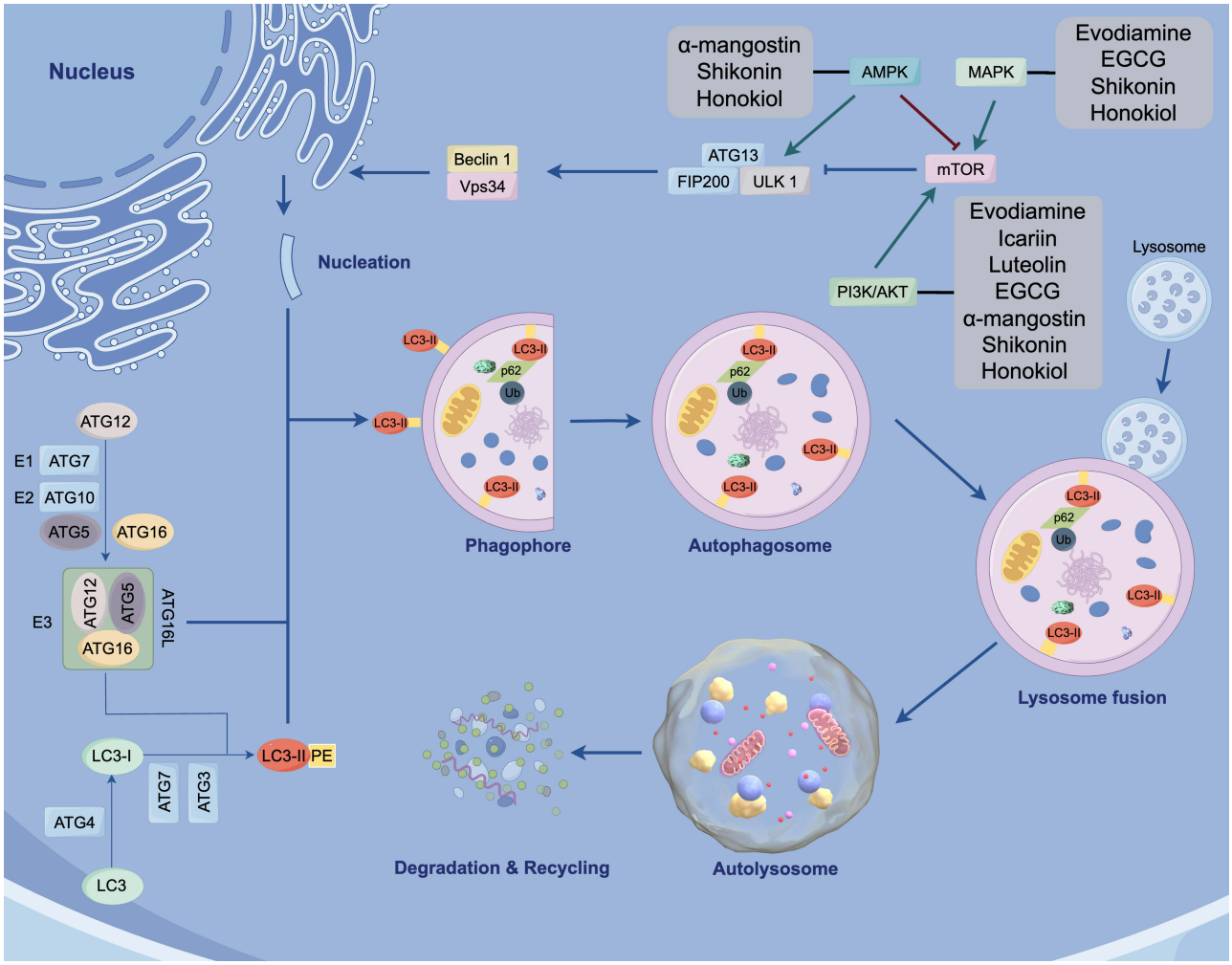

Figure 3 The autophagic process and mechanism (diagram by Figdraw ID:OURUO90494). Autophagy is a highly regulated cellular process involving initiation, nucleation, elongation, fusion, and degradation, which is governed by a sophisticated network of genes and proteins. Key components of autophagy include ATG, LC3, and p62 proteins, with alterations in the levels of LC3 serving as a reliable indicator of autophagic activity.

of breast and ovarian tumor cells to tamoxifen and cisplatin.[108,109] However, a separate study found that when combined with Curcumol, ICA promotes autophagy in prostate cancer cells by inhibiting mTOR downstream.[110] These findings suggest that the regulation of autophagy is a complex process, as ICA can have contrasting effects on autophagy induction or inhibition, potentially varying across different cell lines.

Luteolin

Luteolin (LUT), a naturally occurring flavonoid compound derived from medicinal plants, has shown considerable potential as a therapeutic agent against various types of cancer.[111] The intricate and diverse mechanisms by which LUT modulates tumor cells have been extensively studied.[112] In liver cancer and nasopharyngeal carcinoma cells, LUT has been found to induce autophagic cell death,[113] whereas, in breast and colon cancers, it promotes protective autophagy.[114] Interestingly, in ovarian cancer, LUT inhibits autophagy while simultaneously enhancing cisplatin-induced apoptosis.[115] To identify potential targets for LUT therapy, a recent study utilized advanced techniques such as RNA sequencing and molecular docking programs.[116]

Epigallocatechin Gallate

Extensive research has been conducted on Epigallocatechin gallate (EGCG), a catechin compound, to explore its therapeutic properties in cancer treatment. It has been observed that EGCG can induce cell autophagy and exert toxic

effects by inhibiting the PTEN pathway and suppressing the PI3K/AKT/mTOR signaling pathway.[117] Additionally, EGCG has been found to interfere with the JAK/STAT3 signaling pathway at low concentrations.[118] For instance, a research investigation centered on oral cancer revealed that EGCG not only triggers autophagy via the AKT/STAT pathway but also substantially augments the functionality of apoptosis-related caspases while downregulating the expression of multi-drug resistance gene. This underscores its potential in the treatment of oral cancer from various perspectives.[119] In a separate study concentrating on liver cancer cells, EGCG was observed to stimulate autophagy and diminish AFP levels.[120] Interestingly, in non-small cell lung cancer, EGCG hampers autophagy by suppressing the Ras/MEK/ERK signaling pathway and overcomes Gefitinib resistance in A549 cells.[121]

α-Mangostin

α-mangostin (MGT), derived from *Garcinia sp*., exhibits a diverse array of pharmacological activities. Extensive research has substantiated the ability of MGT and its derivatives to elicit cellular apoptosis and stimulate defensive autophagy in the context of cancer investigations.[122] Intriguingly, the co-administration of autophagy inhibitors notably augments the anti-cancer efficacy of MGT.[123,124] A specific investigation has elucidated that MGT induces autophagy via the PI3K/AKT/mTOR pathway in skin cancer.[125] Furthermore, MGT has been observed to induce autophagic cell death in glioblastoma studies. In contrast to previous findings, this research has unveiled that MGT suppresses mTOR by inhibiting the liver kinase B1/AMPK pathway and directly phosphorylating Raptor, thereby leading to autophagic cell death.[126] Additionally, MGT has been discovered to enhance the susceptibility of gastric cancer cells to cisplatin by inducing autophagy through the inhibition of the STAT3 pathway.[127]

Shikonin or Alkannin

Shikonin (SKN), an active naphthoquinone derivative obtained from *Radix Lithospermi*, a traditional Chinese medicine plant, has been extensively investigated for its anti-cancer properties. Previous research has demonstrated that SKN is capable of inducing reactive oxygen species (ROS), regulating autophagy, and initiating apoptosis. Recent studies have further elucidated the mechanisms by which SKN induces autophagy and apoptosis in gastric cancer cells, specifically through the inhibition of the PI3K/AKT/mTOR pathway, thereby reversing their resistance to oxaliplatin.[128,129] In a separate investigation, it was discovered that SKN effectively triggers autophagy in SK-OV-3 ovarian cancer cells by activating the Keap1/Nrf2 signaling pathway, thereby inhibiting both cellular autophagy and invasive properties.[130] Additionally, in the context of liver cancer research, the suppression of the PYCR1 gene further augmented SKN-induced autophagy and apoptosis. These findings imply that a combined therapeutic approach involving drug-gene therapy holds promise as a viable strategy for combating cancer.[131]

Recent investigations have revealed that SKN instigates autophagy and apoptosis by inducing an accumulation of ROS, which is facilitated via MAPK-related pathways.[132–134] Furthermore, SKN has been observed to induce cell necroptosis. In both bladder and lung cancers, SKN regulates autophagy and triggers cellular necrosis through the RIP3/p62/Keap1 pathway. Additionally, the introduction of CQ augments the incidence of necroptosis, implying an antagonistic association between necrosis and autophagy.[93,135,136]

Honokiol

Honokiol (HNK), a biphenolic compound obtained from *Magnolia officinalis*, a medicinal plant belonging to the Magnoliaceae family, has been demonstrated in previous research to possess the ability to induce autophagy in diverse tumor types. LUO et al conducted a study that identified HNK as an autophagy inducer in A549 cells by inhibiting the mTOR pathway.[137] Additionally, HUANG et al discovered that HNK activates autophagy via the ROS/ERK pathway.[138] In a study conducted on glioblastoma, the involvement of HNK in cell autophagy was observed through the activation of both the PI3K/Akt/mTOR and ERS/ROS/ERK signaling pathways, leading to the inhibition of cell migration and the promotion of apoptosis.[139] Furthermore, XU et al synthesized HNK derivatives (1,3,4-thiadiazole/oxadiazole-linked honokiol) through covalent chemical modifications.[140] These derivatives demonstrated a significant tenfold increase in cytotoxicity against various cancer cell types compared to free HNK, while still inducing autophagy via the PI3K/AKT/mTOR pathway.

Other Active Ingredients of TCM

Several other active ingredients of Traditional Chinese Medicine (TCM) have been identified for their potential to regulate autophagy in cancer. It has been confirmed that Echinatin and Tanshinone I possess the ability to induce cell autophagy and promote apoptosis by inhibiting the PI3K/AKT/mTOR pathway.[141,142] Additionally, Triptolide is a potent autophagy inducer and can trigger autophagic cell death in drug-resistant ovarian cancer through the JAK2/STAT3 pathway.[143] Furthermore, Curcumin and Resveratrol, both well-known autophagy-inducers, are capable of mediating autophagy via the PI3K/AKT/mTOR and AMPK pathways.[144,145] These compounds hold promise as anti-cancer agents due to their potential to induce autophagic cell death, inhibit tumor migration, and reverse resistance to Gefitinib. Additionally, numerous other active ingredients derived from TCM possess autophagy-modulating properties; however, the mechanisms underlying their effects remain unknown, necessitating further investigation.

Interestingly, our collective research indicates that the active ingredients of TCM that modulate autophagy appear to utilize common signaling pathways (Figure 3). Specifically, MGT, SKN, and HNK have been shown to influence the AMPK pathways, while EVO, ICA, LUT, and EGCG are involved in regulating autophagy through the PI3K/AKT/mTOR pathway. Additionally, EVO, EGCG, SKN, and HNK have been linked to MAPK-related signaling pathways. This phenomenon could potentially be attributed to the analogous chemical structures of these compounds, necessitating additional research to elucidate the precise underlying mechanisms. Moreover, the potential for certain drugs to interact with multiple targets and pathways, thereby modulating autophagy and other cell death pathways concurrently, raises concerns. Further investigation into these mechanisms may enhance the efficacy of anticancer drugs in inhibiting cancer growth.

The Integration of TCM-Derived Autophagy Compounds with Nanotechnology Offers Great Promise and Advantages

Significant progress has been achieved in the study of nanoparticles containing autophagy-regulating TCM components for cancer treatment. Particularly in the realm of breast cancer, nanoparticles have shown promise in delivering both conventional chemotherapeutic drugs and autophagy-modulating TCM compounds.[146] This strategy enhances drug concentration in tumor sites and induces autophagic cell death, ultimately aiding in the breakdown of solid tumors. In the case of hepatocellular carcinoma (HCC), nanoparticles demonstrate the capacity to increase drug concentration, with specific nanoformulations allowing for targeted therapy through selective binding to surface molecules on HCC cells, thus enabling more precise therapeutic interventions.[46,147,148] Additionally, nanoformulations are instrumental in aiding the permeation of the blood-brain barrier and improving drug bioavailability in the treatment of gliomas.[149,150] Similarly, in the realm of colon cancer,[151,152] nanoformulations containing autophagy-regulating herbal compounds have attracted considerable interest. Moreover, multifunctional nanoformulations that offer targeted delivery, controlled release, combination therapies, and the integration of diagnostic and therapeutic functionalities have shown promising results in combating tumors.

Furthermore, in addition to the aforementioned benefits, there is a notable focus on the safety of the drug. Numerous studies have provided evidence that nanoformulations incorporating active ingredients from TCM demonstrate minimal harm to surrounding tissues, maintain stability in the bloodstream, and do not typically trigger hemolytic reactions.[153,154] Additionally, researchers have evaluated liver and kidney function, as well as blood biochemical markers, in mice following drug administration, with results indicating a favorable safety profile for these nanopreparations.[155]

The efficiency of drug delivery, which is intricately linked to drug effectiveness, is impacted by various factors such as the intrinsic characteristics of the nanopreparation and the physiological environment.[156] The size of the nanoparticle is a key determinant in its biodistribution, with smaller particles displaying improved tissue penetration but also increased susceptibility to clearance in circulation.[157] Furthermore, the zeta potential of the nanoformulation is a critical parameter for assessing drug stability.[158] Unstable nanoformulations are susceptible to premature depolymerization in the circulatory system, hindering their ability to reach the desired target site. Additionally, the body's natural clearance mechanisms, such as the immune system, liver, and kidneys, present obstacles to successful drug delivery.[159] To overcome immunological clearance, researchers have sought to coat the external surface of nanoformulations with biologically-derived

membranes, such as those sourced from red blood cells, white blood cells, platelets, and other sources.[160–163] This strategy aims to evade recognition and phagocytosis by immune cells present in the circulatory system.

The synergistic benefits of integrating autophagy-regulating active components from TCM with nanoformulations have been demonstrated to effectively leverage complementary advantages. As previously elucidated, TCM's active components possess advantages over conventional chemotherapeutic agents, including multi-targeting capabilities, reduced toxicity, and potent synergistic effects. Nevertheless, these active components are hampered by limitations such as poor solubility, low bioavailability, and a short blood circulation cycle, which impede their clinical utility in cancer therapy. Fortunately, the utilization of nano-delivery platforms offers a promising solution to overcome these challenges. The active components of TCM demonstrate multitarget effects by concurrently activating the autophagy-related pathway and inducing apoptosis, ferroptosis, and ICD. Autophagy, in this context, plays a "double-edged sword" role.[164] Numerous studies have shown that autophagy induction impedes apoptosis, diminishing the protective effects of autophagy when autophagy inhibitors are utilized.[165,166] On the contrary, additional research has demonstrated that autophagy facilitates ferroptosis and ICD, resulting in heightened anti-tumor efficacy when autophagy-inducing agents are utilized in combination.[167] Nanoformulations provide a mechanism for implementing multi-drug regimens, enabling the concurrent administration of multiple drugs at the tumor site, thereby facilitating synergistic therapeutic outcomes.

The following Table 1 summarizes the autophagy-modulating ingredients of TCM and their nanoformulations.

Table 1 Ingredients of TCM Regulating Autophagy and Its Nano-Delivery Strategy in Cancer Therapy

Ingredients from TCM	Pathways Involved in Autophagy	References	Nano-Delivery Strategies	References
Evodiamine	PI3K/AKT/mTOR Ras/MEK/ERK STAT3 related pathways Ca2+/JNK	[103–105,107,168]	EVO and CQ- loaded liposomes	[169]
			FA-targeted EVO- loaded nano-micelles	[170]
			TPP-targeted Dex-ss-SPCL NPs load DOX and EVO	[171]
			pH-triggered EVO- loaded DUCNPs with in vivo tumour imaging function	[172]
			EGFR-targeted EVO- loaded NCA NPs with in vivo tumour imaging function	[173]
Icariin	PI3K/AKT/mTOR miR-7/mTOR/SREBP1	[108,110]	AEAA-targeted ICA- loaded PLGA-PEG NPs with ICD-induced function	[147]
			ICA and pyropheophorbide-a self- assembled NPs combining ROS-induced, autophagy-induced, and PDT function	[174]
			Thermosensitive liposome loading ICA	[148]
			iRGD-modified ICA- loaded DSPE-PEG NPs encapsulated by RBC membrane	[175]
Luteolin	SGK1/FOXO3a/BNIP3 PI3K/AKT/mTOR	[116,176]	FA-targeted LUT- loaded PEG-PCL NPs	[149]
			ROS-triggered LUT- loaded PPS-PEG NPs	[177]
			ROS-triggered and FA-targeted loaded LUT DSPE-PEG NPs	[178]
Epigallocatechin gallate	PI3K/AKT/mTOR JAK/STAT3 Ras/MEK/ERK HSP90 related pathways	[117,119–121,179,180]	HA-targeted EGCG NPs with ROS-induced and ferroptosis-induced function	[181]
			Manganese carbonyl and dendritic mesoporous silicon NPs loading EGCG with PTT function	[182]
			PD-L1 targeted fluorinated-coordinative-EGCG loaded Zn2+ NPs	[183]
			FA-targeted EGCG- loaded liposomes	[184]
			UV blocker ZnO and the antioxidants lycopene and olive oil copolymer NPs loaded EGCG	[185]
α-mangostin	PI3K/Akt/mTOR LKB/AMPK AMPK/Raptor EBI3/STAT3	[125–127]	PEG-based NPs and liposomes loading MGT	[186–188]
			Cyclodextrin-based NPs loading MGT	[189]
			MGT-loaded PEI based NPs	[190]
Shikonin/Alkannin	PI3K/AKT/mTOR Keap1/Nrf2 galectin-1/JNK RIP/p62/Keap AMPK related pathways p38MAPK ROS related pathways ERS related pathways	[128–130,132–134,136]	SKN and CQ- loaded liposomes combining autophagy-induced and ICD-induced function	[58]
			Fe-Shikonin metal-phenolic networks covering CpG ODN-loaded aluminum hydroxyphosphate nanoparticles loading SKN as in situ nano vaccines inducing ICD, ferroptosis, and necroptosis	[191]
			Transferrin-targeted SKN and JQ1 loaded with ICD-induced function	[192]

(*Continued*)

Table 1 (Continued).

Ingredients from TCM	Pathways Involved in Autophagy	References	Nano-Delivery Strategies	References
Honokiol	PI3K/AKT/mTOR ROS/ERK ERS/ERK AMPK related pathways	[137–140,193]	HA-targeted HNK loaded liposomes HNK loaded Rebaudioside A based self-assembled nano-micelles inducing DNA damage and stimulating ERK signing pathway Chitin and EGCG copolymer NPs loading HNK	[194] [195] [196]

Evodiamine Loaded NPs

As previously stated, EVO can modulate autophagy through its interactions with the PI3K/AKT and MAPK/ERK signaling pathways. Furthermore, it has been documented that the combination of EVO with autophagy inhibitors enhances the induction of apoptosis. In a particular investigation, the combination of EVO and CQ resulted in a substantial accumulation of autophagosomes, leading to a notable decrease in cellular activity.[197] Expanding upon these findings, researchers have developed EVO-CQ-Lips, which exhibit enhanced effectiveness against cancer and reduced toxicity toward normal renal embryonic cells when compared to unencapsulated drugs.[169] Subsequent studies have provided evidence that the aforementioned multifunctional delivery platforms exhibit superior biocompatibility, targeting capabilities, and controlled release in comparison to standard liposomes. For instance, the utilization of a folic acid (FA)-modified EVO-loaded micelle resulted in enhanced antitumor activity by specifically targeting cell membrane folate-binding proteins through FA.[170] Another study[171] involved the development of a nanoparticle co-loaded with EVO and DOX, triphenylphosphine (TPP) was utilized as an agent, while Dextran and star-polycaprolactone were connected through disulfide bonds (-s-s-) to allow micelle depolymerization in response to GSH signals within the tumor microenvironment. Furthermore, the development of EVO-loaded nanoplatforms that enhance imaging capabilities has been achieved. This has been accomplished through the utilization of heterostructures consisting of lanthanide-doped upconversion nanoparticles (DUCNPs) to transport EVO derivatives, thereby enabling in vivo fluorescence imaging using near-infrared (NIR) light.[172] Simultaneously, this approach optimizes solubility and augments the inhibition of tumor growth. In a similar vein, LI et al have undertaken surface modifications with GE11, a fluorescent label, and EGFR-targeting agent, to enhance targeting efficacy and facilitate in vivo tumor imaging.[173]

Icaritin Loaded NPs

As previously mentioned, the induction of autophagy through the mTOR-related pathway by ICA has been observed. To treat HCC, a nano-delivery platform loaded with DOX and ICA, which combines autophagy with ICD, was developed.[147] It has been demonstrated that the activation of autophagy leads to the production of ICD markers, which have been found to have positive effects on ICD. To specifically target HCC, the researchers incorporated AEAA, a functional group that binds to the σ-1 receptor, which is highly expressed on the surface of HCC cells, onto the surface of the nano-delivery platform. Additionally, other researchers have successfully created self-assembled nanoparticles consisting of ICA-pyropheophorbide-a self-assembled nanoparticles (IP NPs),[174] which have shown remarkable stability and uptake capacity. In a separate investigation, the combination of ICA and Coix seed oil was enclosed within heat-sensitive liposomes, resulting in a favorable ability to infiltrate tumor spheroids.[148] Certain scholars employed a cyclic tumor-penetrating peptide (iRGD), which aids in the traversal of nanocarriers through tumor vasculature and their subsequent penetration into tumor parenchyma. This peptide was covalently attached to DSPE-PEG, serving as a carrier for ICA. Additionally, the outer layer of the liposomes was modified with an erythrocyte membrane, thus creating functionalized biomimetic nanoplatforms that enhance the capability of drug delivery.[175]

Luteolin Loaded NPs

Prior research has demonstrated that LUT is involved in the regulation of autophagy and exerts antitumor effects by modulating the PI3K/AKT pathway. Nevertheless, the efficacy of LUT against glioblastoma is hindered by its limited ability to traverse the blood-brain barrier. To tackle this challenge, WU et al have developed FA-modified NPs (FA-PEG-

PCL) that enhance biocompatibility and facilitate the transportation of LUT across the blood-brain barrier, leading to its accumulation at the tumor site.[149] In the context of malignant cancers characterized by elevated levels of ROS, the utilization of ROS-responsive materials for drug delivery presents a promising approach for achieving controlled drug release. FU et al developed ROS-responsive nanoparticles (NPs) utilizing Poly (propylene sulfide)-poly (ethylene glycol) (PPS-PEG) polymers specifically for the treatment of melanoma.[177] The LUT-PPS-PEG NPs exhibited a significant in vivo anti-cancer effect, as expected. Expanding on these findings, WANG et al further modified LUT-loaded NPs with tumor-targeting FA and ROS-responsive Oxi-αCD, resulting in a substantial improvement in the antitumor efficacy of LUTs.[178] However, there is currently a lack of direct evidence demonstrating the ability of LUT-loaded NPs to modulate autophagy in cancer cells. In light of this, further research is needed to examine the potential role of LUT-loaded anti-cancer NPs in regulating autophagy, which provides an intriguing area for future investigation.

Epigallocatechin Gallate-Loaded NPs

Despite extensive studies on the upregulation of intracellular ATG5, Beclin1, and LC3-II induced by EGCG through various pathways, additional research is required to ascertain the comparative effectiveness of nano-delivered EGCG in inducing autophagy. To facilitate more comprehensive investigations, we present a summary of several potential strategies for delivering EGCG. Notably, FAN et al have recently developed nanoparticles by conjugating EGCG with hyaluronic acid, which specifically targets CD44, a protein that exhibits high expression in GBM cell lines. These nanoparticles facilitate the accumulation of EGCG at the tumor site and stimulate the generation of ROS, thereby inducing ferroptosis.[181] In a separate investigation, YANG et al employed manganese carbonyl and dendritic mesoporous silicon as carriers for delivering EGCG. The study provided evidence that EGCG functions as an inhibitor of HSP90, thereby enhancing PTT.[182] Considering the established correlation between HSP90 and autophagy, it would be intriguing to investigate whether autophagy plays a more direct role in tumor treatment when utilizing these nanodrugs.[179] Furthermore, extensive research has been conducted on a nano-delivery system employing inorganic zinc as a carrier for loading EGCG.[183] Similarly, the development of EGCG-loaded liposomes incorporating FA has been pursued for the targeted treatment of colon cancer.[184]

α-Mangostin Loaded NPs

As previously stated, MGT exhibits significant antitumor efficacy, prompting the development of diverse PEG-based nano-delivery systems for its administration. Notably, MGT-loaded MPEG-PCL nanoparticles have been employed for melanoma therapy,[186] while MGT-loaded PEG-PLA nanoparticles have been explored for pancreatic cancer treatment.[187] In a breast cancer study, liposomes were utilized as carriers for MGT, leading to the dissolution of breast cancer tumors at lower concentrations compared to free MGT, thereby underscoring the enhanced effectiveness of the nanoparticle formulation.[188] In addition, both cyclodextrins and PEI have been employed as carriers for the delivery of MGT. The encapsulation of MGT in nanoparticles has demonstrated enhancements in drug biocompatibility and penetration, reductions in hematotoxicity, and improvements in its anti-cancer proliferative effects.[189,190] It is important to highlight that autophagy induction by MGT has been extensively established through various pathways, including PI3K/AKT/mTOR, AMPK, and STAT3. Therefore, the utilization of MGT-containing nanoparticles presents a promising strategy for inducing autophagy in cancer cells.

Shikonin/Alkannin Loaded NPs

In a study conducted by LI et al, it was found that SKN, a potent inducer of autophagy, possesses various anti-cancer activities.[58] To enhance the anti-cancer effect, liposomes were developed to deliver SKN and CQ. SKN not only induces ICD and autophagy but also initiates the autophagy-mediated degradation of tumor antigens, potentially attenuating the ICD response. Fortunately, the autophagy inhibitor CQ can rescue this effect. In a recent study by SHI et al, cytosine guanine dinucleotide (CpG) oligodeoxynucleotide (ODN) was designed and constructed. These nanoparticles were loaded with CpG ODN and capped by a Fe-Shikonin metal-phenol network (Alum-CpG@Fe-Shikonin NPs, MPNs).[191] Upon internalization by tumor cells, these nanoparticles undergo decomposition, resulting in the formation of Fe^{2+} and SKN. This process subsequently triggers ICD through the induction of ferroptosis and necroptosis.

Concurrently, CpG ODN initiates a cascade of anti-cancer immune responses. The combined action of both components exhibits significant anti-cancer efficacy, leading to the elimination of tumor cells and suppression of distant tumors. In a separate investigation involving the use of SKN-NPs to induce ICD, lactoferrin was employed as a carrier to encapsulate JQ1, a BET bromodomain inhibitor, along with SKN. This formulation facilitated the promotion of ICD in cancer cells.[192]

Honokiol Loaded NPs

HNK has been verified to induce autophagy, and this review aims to analyze current nano-delivery approaches as a basis for further comprehensive inquiries. In a study conducted by WANG et al, HNK was enclosed within hyaluronic acid (HA)-modified liposomes to achieve active targeting.[194] Furthermore, in addition to liposomes, natural small molecules have been employed to generate nanocellular micelles for drug delivery. Rebaudioside A (RA), a small molecule derived from stevia, exhibits the ability to self-assemble into micelles that serve as carriers for HNK. Notably, EGCG, an autophagy inducer previously mentioned, has also been recognized as a suitable material for the creation of nanocarriers.[195] In a separate investigation, a polymer composed of Chitin and EGCG was developed to load HNK.[196]

NPs Loaded with Other Active Ingredients of TCM

The encapsulation of paclitaxel NPs (Nab-PTX) with albumin enhanced the intracellular uptake of lung and colorectal cancer cells and has already been used in clinical practice.[198] In recent research, it was observed that Nab-PTX induces autophagosome formation and upregulates LC3-II levels via the selective autophagy receptor SQSTM1/p62 (Figure 4A).[199] Furthermore, there exist diverse strategies presently accessible for the delivery of curcumin via nanoparticles.[200,201] Notably, in a study of chitosan liposomes co-loaded with nicotinic and curcumin, nicotinic-induced autophagy and curcumin increased the number of autophagosomes, achieving synergy at the level of autophagy induction (Figure 4B).[202] In a separate investigation, scientists devised a versatile nanoplatform employing ROS-responsive Tk bonds (thioketal) for the transportation of triptolide and photosensitizers.[203]

Discussions and Prospects

The field of oncology therapeutics has witnessed substantial advancement over the last decade in the realm of nano-delivery platforms. Approved nanomedicines for clinical application encompass Paclitaxel-loaded albumin nanoparticles (Abraxane), liposomes loading Doxorubicin (Doxil), and other formulations.[70,71] Nevertheless, these nanocarriers demonstrate limited functionality, low drug delivery efficacy, and susceptibility to the emergence of drug resistance. Consequently, the adoption of multifunctional nano-delivery platforms presents a promising strategy to overcome these obstacles. The inclusion of targeting agents, such as FA and TPP, in various compounds has been demonstrated to improve the accumulation of drugs specifically at the tumor site.[204–206] Controlled release mechanisms can be attained by utilizing materials that are sensitive to GSH and ROS. Additionally, the incorporation of photosensitizers and photo-thermal agents allows for the integration of PDT and PTT with traditional chemotherapy.[60] As highlighted in this review, these versatile nanoplatforms have exhibited significant anti-cancer efficacy in both in vitro and in vivo experiments. Although multifunctional nanoplatforms show great promise, their high cost of preparation, complex production methods, and differences between human and animal environments pose significant obstacles to their clinical application.[207–209] Additionally, recent research has shown that the enhanced EPR effect, a key targeting mechanism for nanomedicines, may not be effective for all types of tumors, highlighting the need for new targeting approaches.[210]

The incorporation of autophagy-modulating herbal compounds into nanoparticles represents a promising pursuit. Nanodelivery technology facilitates the circumvention of delivery obstacles to the tumor site, allowing for controlled release to reduce toxicity. Furthermore, this method complements other chemotherapeutic agents or PDT and PTT for a more holistic treatment approach. Research indicates that the modulation of cellular autophagy is more pronounced following drug delivery through nano-formulations as opposed to free drugs, possibly due to the concentration of drug accumulation at the tumor site. It is important to highlight that, despite the considerable research efforts directed toward integrating autophagy-regulating TCM compounds into nanopreparations, there is a lack of literature specifically

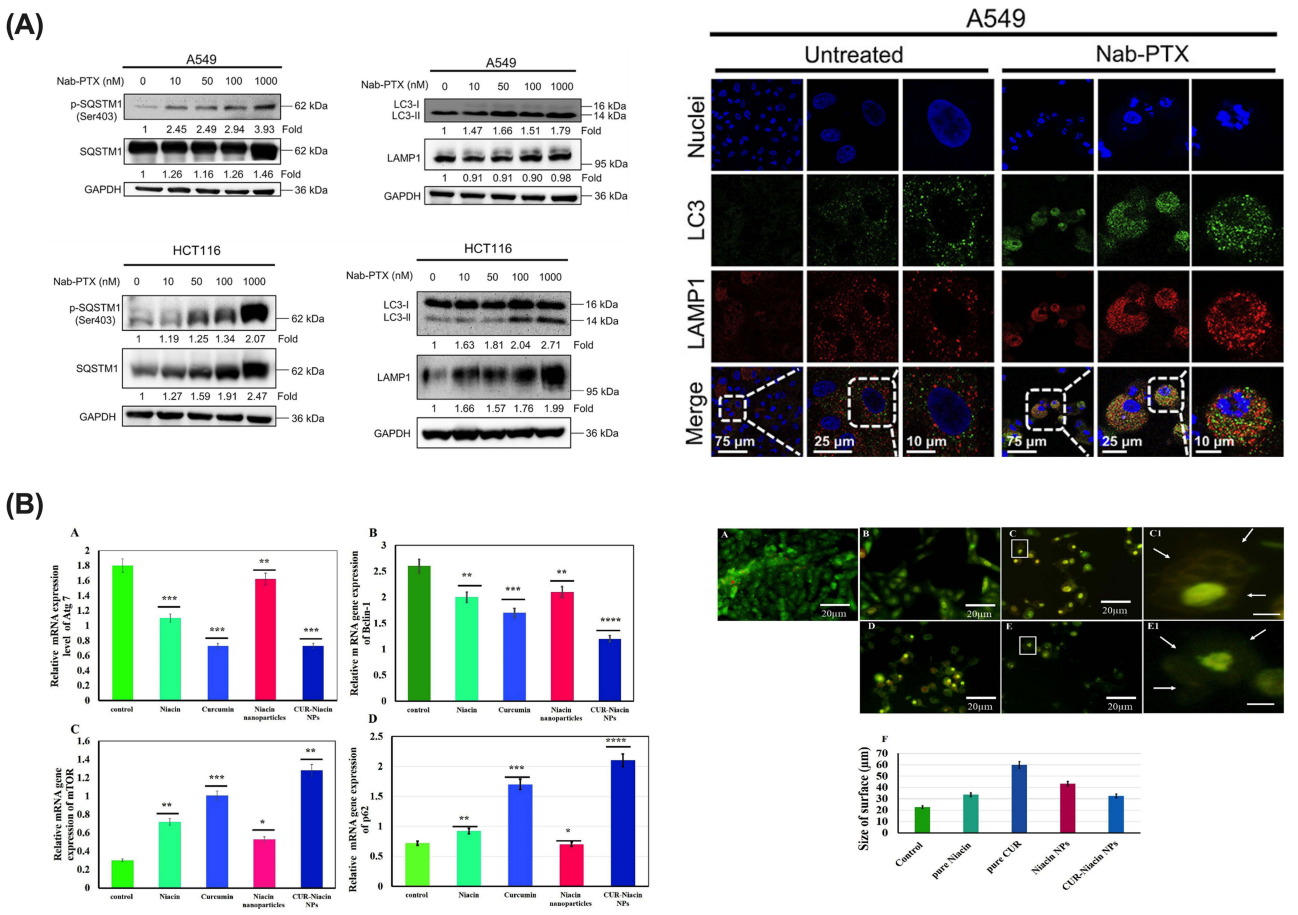

Figure 4 Autophagic activity depicted by compounds from TCM-loaded NPs in cancer. (**A**) Enhanced expression of autophagic proteins LC3-II and SQSTM1/p62 was observed in lung and colorectal cancer cells after treatment with Nab-PTX in Western blots and immunofluorescence. Reprinted from Lin YW, Lin TT, Chen CH, et al. Enhancing Efficacy of Albumin-Bound Paclitaxel for Human Lung and Colorectal Cancers through Autophagy Receptor Sequestosome 1 (SQSTM1)/p62-Mediated Nanodrug Delivery and Cancer therapy. *ACS Nano*. Oct 10 2023;17 (19):19,033–1905. Copyright 2023 American Chemical Society.[199] (**B**) Nicotinic, curcumin, and their nanoparticles regulate expressions of autophagy-related genes (ATG7, Beclin1, mTOR, and p62) and promote autophagosomes formation. The data are shown as the means ± SD (n = 3). * p ≤ 0.05, **p ≤ 0.01, *** p ≤ 0.001 and **** p ≤ 0.0001. Reprinted from *Int J Biol Macromol*. Volume: 245. Hanafy NAN, Sheashaa RF, Moussa EA, Mahfouz ME. Potential of curcumin and niacin-loaded targeted chitosan-coated liposomes to activate autophagy in hepatocellular carcinoma cells: An in vitro evaluation in HePG2 cell line. 125,572. Copyright 2023, with permission from Elsevier.[202]

examining the mechanisms by which these nanopreparations modulate autophagy in tumor cells. Therefore, a deeper comprehension of these mechanisms would significantly enhance the progress of precision tumor therapy.

Interestingly, autophagy, a cellular process of self-degradation, plays a crucial role in tumor development, progression, and treatment. Its complex involvement results in a dualistic nature, with some aspects promoting tumor cell death and others providing protection. While TCM has been found to contain active components that modulate autophagy and exhibit strong anticancer effects, the exact mechanisms remain poorly understood, necessitating further comprehensive research. Furthermore, autophagy possesses the capacity to augment the susceptibility of cancer cells to radiotherapy and chemotherapy, as well as reverse drug resistance.

In prospective studies, it is theorized that the integration of artificial intelligence (AI) may improve the effectiveness of the nanoformulation preparation process and tackle existing obstacles.[211] Specifically, machine learning (ML) can be applied throughout various stages of creating versatile nano-delivery systems that transport active ingredients from TCM. ML can assist in identifying and refining new small molecule drugs, as well as forecasting potential targets for investigating novel autophagy signaling pathways.[212,213] Moreover, ML is instrumental in predicting and prioritizing characterization parameters and optimizing delivery strategies in the design of nanomedicines.[214] When designing nanomedicines, ML plays a crucial role in predicting and prioritizing characterization parameters, as well as optimizing delivery strategies.[215] Additionally, ML can be utilized to assess and predict treatment efficacy.[216] This review

emphasizes the importance of autophagic flux levels and different autophagic pathways in the treatment of tumors, as well as the interplay between autophagy and other mechanisms of cell death. Therefore, ML can be employed to gather past data, develop models, and examine the relationship between autophagy and patient outcomes, as well as the crosstalk between autophagy and other forms of cell death.

Conclusions

This comprehensive review provides a summary of autophagy-regulating compounds in TCM, detailing their anticancer mechanisms and potential therapeutic value. Additionally, we synthesize multiple sources of literature to assess the potential of nanotechnology in addressing delivery challenges and augmenting the anticancer properties of these compounds. However, it is imperative to acknowledge limitations in our study, particularly the lack of in-depth exploration into the mechanisms of autophagy regulation by active compounds in TCM. Nevertheless, it is imperative to recognize specific constraints within our research. Firstly, our examination of the autophagy regulation mechanism by active compounds of TCM lacks thoroughness. Secondly, our comprehension of the interplay between autophagic death induced by autophagy-regulating active compounds of TCM and other cell death pathways is inadequate, warranting additional comprehensive investigation.

In summary, our research indicates that the incorporation of nanotechnology for the precise delivery of active TCM compounds, in conjunction with autophagy modulation as a therapeutic strategy for cancer, holds significant potential. The integration of nanotechnology, TCM components, and autophagy in cancer therapy offers a synergistic approach that overcomes the limitations of individual strategies and provides avenues for personalized and precise treatment. It is imperative to prioritize the development of affordable and safe nano-delivery systems for delivering autophagy-modulating compounds derived from TCM to advance both fundamental and clinical research in this field.

Abbreviation

AKT, Protein kinase B; AMPK, AMP-activated protein kinase; ATG, Autophagy-associated protein; Beclin1, Recombinant Beclin 1; EPR, Enhanced permeability and retention; ERK, Extracellular regulated protein kinases; ICD, Immunogenic cell death; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH- associated protein l; LC3, Microtubule-Associated Protein 1 Light Chain 3; MAPK, Mitogen-activated protein kinase; MEK, Mitogen activation inhibitor; ML, Machine learning; mTOR, Mammalian target of rapamycin; Nrf2, Nuclear Factor erythroid 2-Related Factor 2; PI3K, Phosphatidylinositol 3 kinase; PTEN, Phosphatase and tensin homolog deleted on chromosome ten; RIP, Receptor interacting protein; SQSTM1, Recombinant Sequestosome 1; TCM, Traditional Chinese Medicine; TPP, Triphenylphosphine; ULK1, UNC-51 Like Kinase 1; VPS34, Vacuolar Protein Sorting 3.

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 all these areas; took part in drafting and writing, substantially revised or critically reviewed the article; have agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication; 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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