



REVIEW ARTICLE

Phytochemicals as modulators of autophagy and apoptosis: unveiling synergistic mechanisms in cancer therapy

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Abstract

Naturally occurring bioactive phytochemicals have been used for centuries to treat various pathophysiological disorders. Many studies have revealed that certain phytochemicals exhibit impressive properties that may combat cancer effectively. These natural compounds show promise as valuable therapeutic agents in the fight against various types of cancer, offering hope for innovative treatment strategies. Essentially, phytochemicals can regulate two essential cellular mechanisms, autophagy and apoptosis, which play significant roles in the underlying pathophysiology of carcinogenesis. Combining phytochemicals with conventional chemotherapy can potentially enhance the therapeutic effects while minimizing adverse side effects. Continued advancements in this field are crucial for overcoming the challenges associated with the development of anticancer therapeutics based on phytochemicals. This review aims to shed light on the intricate molecular processes of autophagy and the apoptotic pathway in tumour progression, as well as the potential of phytochemicals in developing anticancer drugs. By harnessing the potential of phytomolecules, it is possible to uncover novel and effective treatments for various types of cancer, thereby paving the way for advancements in anticancer therapy. Taken as a whole, a detailed molecular understanding of the mode of action of phytochemicals in regulating autophagy and apoptosis could lead to the development of strategies for anticancer drugs, advancing towards achieving the United Nations' Sustainable Development Goals (SDG 3: good health and well-being).

Keywords: anticancer therapeutics; apoptosis; autophagy; chemotherapy; phytochemicals; sustainable development goal

Introduction

Cancer remains a prominent global cause of mortality, accounting for a significant number of deaths worldwide. To date, there are minimal treatment options available to combat cancer. Moreover, the high price of advanced anticancer drugs available in the market is not affordable to majority of patients in poor and developing countries (1). Therefore, the discovery of novel, cost-effective anticancer therapeutics is an urgent need. The death toll from cancer has risen dramatically in the twenty-first century, primarily because of unhealthy lifestyles including excessive tobacco use, exposure to physical and chemical carcinogens, alcohol consumption, unhealthy diet and exposure to biological carcinogens. However, growing awareness regarding the significance of making lifestyle modifications, early detection and effective treatment has reduced the prevalence of cancer (2). The number of available cancer treatment options has expanded significantly in recent years, encompassing chemotherapy, immunotherapy, hormone therapy and various forms of radiation-based treatments, such as ionizing radiation therapy (RT) and photodynamic therapy (PDT) (3). The primary objective of cancer therapy is to stop uncontrolled cell growth and also the death of malignant cells, keeping normal cells viable (4). Chemotherapy remains a primary therapeutic approach in the treatment of numerous

cancer types (5). The development of chemotherapy resistance presents a huge challenge in anticancer therapy and resulting in treatment failures and mortality (5). Resistance to chemotherapy can manifest through various mechanisms encompassing multi-drug resistance, alterations in drug metabolism, genetic heterogeneity within tumor cells, changes in target, increased DNA repair activity, amplification of genes involved in drug resistance and stress-induced genetic or epigenetic changes (6). Understanding and addressing the various mechanisms of chemotherapy resistance are essential for developing effective strategies to overcome resistance and improve cancer treatment outcomes.

Attention has increased toward naturally occurring phytochemicals due to their role in tackling chemotherapy resistance and helping to manage the problems caused by standard anticancer treatments. Many chemotherapy drugs yield good results, yet they may fail due to multidrug resistance, often caused by increased P-glycoprotein (P-gp) activity or changes in tumour suppressor genes. Phytochemicals such as curcumin, resveratrol and quercetin have been reported to sensitise resistant cancer cells by inhibiting these efflux pumps and modulating key signalling pathways. For instance, curcumin has been shown to suppress MDR1 gene expression by downregulating the NF- κ B pathway,

thereby enhancing the intracellular accumulation of chemotherapeutics (155). Similarly, resveratrol augments the efficacy of platinum-based drugs by downregulating SIRT1 and inhibiting the PI3K/AKT axis in resistant ovarian cancer cells. Other than helping the body overcome cancer, phytochemicals protect healthy tissues from the toxic side effects of chemotherapy. For example, Epigallocatechin gallate (EGCG) protects the heart against doxorubicin-induced damage through its antioxidant properties (156), while silymarin protects the liver and gingerol the kidneys. These added benefits lead to better treatments at the same time as reducing the adverse effects that may limit treatment. When considering phytotherapy for clinical use, it is crucial to carefully evaluate pharmacokinetics, bioavailability and potential herb-drug interactions.

Understanding how autophagy and apoptosis favour tumour cell chemotherapy resistance is significant in developing innovative approaches to overcome resistance and improve the effectiveness of cancer treatments (7-9). Autophagy, a tightly controlled and evolutionarily conserved cellular process, has attracted significant attention due to its vital function in adapting to metabolic and therapeutic challenges. It functions to maintain or restore metabolic balance by eliminating superfluous proteins and damaged or aged organelles (10-11). Autophagy exhibits paradoxical effects, serving both as a mechanism that promotes cell survival, helping cancer cells counteract the cytotoxic effects of anticancer agents and as a pro-death mechanism, mediating cell death in response to such treatments (12, 13). It acts by removing damaged cellular components, limiting the accumulation of reactive oxygen species (ROS) and maintaining genomic stability. It contributes to the prevention of cancer initiation by eliminating potentially harmful cellular materials. In certain situations, promoting autophagy can be a crucial strategy to impede early tumor development and hinder its progression. However, this cellular process also seen to help tumor cells under therapy-induced stress, contributing to treatment resistance. Furthermore, emerging evidence indicates that if this cellular process gets disrupted it resulted in malignant transformation of cancer stem cells. Autophagy can have both negative and positive role in facilitating cancer stem cells to escape detection by the immune system and develop resistance to anoikis, which is cell death triggered by detachment from the extracellular matrix (14). It was also observed that by suppressing autophagy process, cytotoxic effects of the chemotherapy can be increased, making tumor cells more susceptible to treatment-induced cell death. Hence, autophagy is often referred to as a double-edged sword due to its dual role (15-17). Another cellular pathway which plays important role in inhibiting cancer cell proliferation is apoptosis. Gaining control over the uncontrolled cell proliferation is the key objective of anticancer therapy. Therefore, targeting the apoptotic pathways and promoting apoptosis can be an effective approach in this regard (18). Understanding these pathways and identifying ways to manipulate this interplay may lead to the development of more effective therapeutic approaches. Resistance to chemotherapy in cancer cells often arises from their ability to evade apoptotic mechanisms. This evasion mechanism can encompass the suppression of signals that promote apoptosis,

the enhancement of signals that inhibit apoptosis and abnormalities in the initiation and progression of the apoptotic process. The intricate interplay between autophagy and apoptosis involves a complex functional relationship and recent scientific investigations have unveiled the underlying molecular mechanisms (19). Further research and experimentation are necessary to identify specific targets and strategies for effectively modulating these pathways. Phytochemicals have been found to exhibit diverse biological activities and possess the ability to influence different signalling processes linked to both apoptosis and autophagy (9). A deeper understanding of how autophagy and apoptosis intersect and influence each other is crucial for developing innovative therapeutic strategies for cancer. This review consolidates the existing knowledge and methodologies, fostering advancements in our understanding of the complex interplay between autophagy, apoptosis and carcinoma. We have highlighted the significance of phytochemicals in modulating autophagy and apoptosis, emphasising the need for further research and technological advancements.

Cross Talk between Autophagy and Apoptosis

Autophagy and apoptosis are 2 essential cellular processes that are crucial for maintaining cellular balance. While autophagy refers to a catabolic process that involves the breakdown and recycling of damaged organelles and macromolecules, apoptosis is a type of programmed cell death defined by distinct morphological and biochemical alterations (20). Both mechanisms are highly regulated and frequently triggered in response to cellular stressors, such as nutrient deficiency, oxidative damage, or the presence of chemotherapeutic drugs. The interaction between autophagy and apoptosis is intricate and context-dependent, with the equilibrium between these processes ultimately determining whether a cell survives or undergoes death. This complex interplay is governed by common molecular regulators, signalling pathways and cellular responses to stress, making it an important area of research for comprehending tumour biology, chemotherapy resistance and potential therapeutic strategies (19).

A key point of interaction between autophagy and apoptosis is found in their mutual molecular regulators. Beclin-1, a crucial protein involved in autophagy, serves as a notable example. Beclin-1 is involved in the initiation of the autophagy complex and is essential for the formation of autophagosomes. However, its function is modulated by its interaction with antiapoptotic proteins, such as Bcl-2 and Bcl-xL. When Bcl-2 or Bcl-xL binds to Beclin-1, it hinders its autophagic activity, thereby reducing autophagy (20). In contrast, pro-apoptotic BH3-only proteins such as Bad and Bik can interrupt this interaction, allowing Beclin-1 to facilitate autophagy. This regulatory mechanism highlights the delicate balance between autophagy and apoptosis, as alterations in Beclin-1 activity can tip the outcome toward either cell survival or programmed cell death.

A shared regulator is p53, a tumor suppressor protein that has dual functions in both autophagy and apoptosis. Within the nucleus, p53 activates pro-apoptotic genes such as Bax and Puma, which triggers the intrinsic apoptotic pathway (21). Conversely, cytoplasmic p53 can suppress autophagy by inhibiting AMPK activation or enhancing mTOR activity, which

negatively regulates autophagy. However, under specific circumstances, p53 can also promote autophagy by increasing the expression of genes that are critical for initiating this process. This dual role highlights the intricate relationship between these pathways and the importance of cellular context in shaping their effects. Caspases, the key enzymes in apoptosis, play a vital role in the interaction between autophagy and apoptosis. For example, caspase-8 can cleave Beclin-1, effectively halting autophagy and directing the cellular response towards apoptosis. Similarly, caspase-3 can cleave proteins associated with autophagy, like Atg5 and Atg7, thereby diminishing autophagic processes. These cleavage events ensure that apoptosis occurs without interference from autophagy, especially during significant cellular stress (22). Nonetheless, autophagy can also impact apoptosis by managing mitochondrial health. For instance, autophagy can eliminate damaged mitochondria through a process called mitophagy, preventing the release of pro-apoptotic factors such as cytochrome c and thereby inhibiting apoptosis. This interaction illustrates how autophagy can serve as a survival strategy in certain contexts while also promoting apoptosis in others. The interplay between autophagy and apoptosis is especially important in cancer research. Tumour cells frequently utilise autophagy as a survival strategy to endure the challenging conditions of the tumour microenvironment, including low oxygen levels, nutrient deprivation and oxidative stress. This protective autophagy can also lead to resistance against chemotherapy by allowing tumor cells to survive the stress induced by drugs (19). For example, autophagy has been found to protect cancer cells from the effects of chemotherapeutic drugs such as cisplatin and doxorubicin. In these scenarios, blocking autophagy with pharmacological agents can render tumour cells more sensitive to chemotherapy and improve treatment outcomes.

On the other hand, encouraging apoptosis is a fundamental approach in cancer treatment, as many chemotherapeutic drugs function by prompting programmed cell death in cancer cells. Nevertheless, cancer cells often acquire resistance to apoptosis through various strategies, including the overproduction of antiapoptotic proteins (like Bcl-2 and Bcl-xL) or mutations in genes responsible for promoting apoptosis (such as p53) (23). Gaining an understanding of the relationship between autophagy and apoptosis can offer valuable insights into overcoming these resistance challenges. For instance, combining agents that inhibit autophagy with

those that induce apoptosis has shown promise in preclinical studies as a means to enhance cancer cell death and overcome drug resistance. By deciphering the molecular mechanisms that drive the interplay between autophagy and apoptosis, researchers can develop innovative treatments that modulate these processes to achieve improved clinical outcomes in cancer and other diseases.

Ethnomedicinal Plants Used Against Cancer

Ethnomedicine refers to the use of traditional knowledge in treating various ailments using different naturally occurring substances. Over the last few decades, ethnomedicinal plants have been receiving increasing attention in the development of anticancer therapeutics. Many of the traditionally used plants have been found to possess phytochemicals with anticancer properties (Table 1). Here, we have discussed some of the traditional medicinal plants that have shown anticancer properties. *Allium cepa* L. which is commonly known as onion traditionally used to cure cold, flu, indigestion, pain relief (24). Quercetin rich *Allium cepa* found to possess anticancer property. There is evidence of quercetin interacting with multiple signalling pathways, such as PI3K/AKT, Wnt/ β -catenin and STAT3 (25). Bitter orange, fruits of *Citrus aurantium* L., is used as a traditional medicine in India for treating vomiting, abdominal pain, dysentery, urinary tract infections etc. (26). Bioactive phytochemical hesperetin (HSP), from *Citrus aurantium* L. have shown anticancer properties (27). *Berberis vulgaris*, commonly known as barberry, is a type of shrub traditionally used to treat fever, cough, liver disease, depression and bleeding (28). The phytochemical berberine, present in *Berberis vulgaris*, is found to prevent cancer cell proliferation by inducing apoptosis (29). *Matricaria recutita*, commonly known as chamomile in western culture is traditionally used to treat indigestion, fever, insomnia, muscle cramps, colic pain in children (30). Studies have shown that chamomile shows potential in anticancer properties (31). The roots and rhizomes of hellebore (*Veratrum grandiflorum*) are used in traditional medicine to treat sores, fractures and pain (32). Resveratrol isolated from *Veratrum grandiflorum* O. Loes. roots has shown anticarcinogenic activity (33). *Allium sativum* L., known as garlic is traditionally used to treat cold, asthma, influenza, bronchitis (34). One of the active ingredients of garlic, allicin has shown inhibitory effects on tumour growth (35). Roots of *Scutellaria baicalensis* Georgi used as traditional medicine in china to treat diarrhoea, dysentery, insomnia, inflammation etc. A flavone called baicalin, present in this plant,

Table 1. Examples of traditional medicinal plants used in different types of cancer

Sl. No	Name of the traditional medicinal plant	Target cancer	References
1	<i>Allium cepa</i>	Lukemia, breast cancer	(114)
2	<i>Galenia africana</i>	Breast cancer	(115)
3	<i>Centaurea castriferrei</i>	Prostate cancer, lung cancer and glioblastoma	(116)
4	<i>Phyllanthus emblica</i>	Lung, ovary, colon	(117)
5	<i>Scutellaria baicalensis</i> and <i>Oroxylum indicum</i>	Breast cancer, tongue cancer	(118, 131)
6	<i>Chrysanthemum morifolium</i>	Colon cancer, Prostate cancer, lung cancer	(119)
7	<i>Aristolelia chilensis</i>	Endometrial cancer	(120)
8	<i>Rosmarinus officinalis</i> L.	Breast cancer, colon cancer, prostate	(121, 122)
9	<i>Pinus massoniana</i>	Liver cancer, cervical cancer	(123)
10	<i>Lessertia frutescens</i>	Skin cancer, lung cancer	(124)
11	<i>Toona sinensis</i>	Prostate cancer	(125)
12	<i>Curcuma longa</i>	Cancers of prostate, breast, lung, esophagus, liver, stomach	(126)
13	<i>Emblica officinalis</i>	Cancers of pancreas, stomach, uterus	(127)
14	<i>Zingiber officinale</i>	Ovary cancer	(128)
15	<i>Withania somnifera</i>	Malignant melanoma, cancers of larynx, colon, cervix, prostate, breast	(129, 130)

has shown anticancer properties (36). In traditional Chinese medicine (TCM), there are mentions of using *Ginkgo biloba* to treat mental health conditions (37). Many studies have shown that extract of this plant has anti tumor properties (38). In TCM, the extract of the fruit of *Evodia rutaecarpa* is traditionally used to treat skin inflammation (39). One of the major bioactive compounds of *Evodia rutaecarpa*, *evodiamine* has shown to inhibit cancer cell proliferation by inducing apoptosis (40). In South Africa, *Aspalathus linearis* is traditionally used to treat various diseases, including allergies, asthma, dermatological conditions and colic pain in children. Extracts of this plant have shown anticancer and tumour-inhibitory effects (41). Since ancient times, traditional natural medicines have played a crucial role in managing diseases and ancient medicine practitioners were skilled in this area, regardless of their understanding of bioactive compounds (42-44). Today, researchers are increasingly concentrating on bioactive molecules derived from plants to combat serious illnesses, as these substances typically have minimal side effects for humans.

Phytochemical Regulation of the PI3K/Akt/mTOR Pathway

Phytochemicals, which are naturally occurring bioactive compounds found in plants, can modulate the PI3K/Akt/mTOR signalling pathway to regulate autophagy and apoptosis, thereby influencing cellular survival and death, particularly in cancer and stress-related diseases. Many phytochemicals act as inhibitors of the PI3K/Akt/mTOR axis, leading to mTORC1 inhibition and induction of autophagy (150). For example, compounds such as curcumin, resveratrol, quercetin and epigallocatechin gallate (EGCG) have been shown to suppress PI3K activation or inhibit Akt phosphorylation, which in turn reduces mTORC1 activity. This downregulation removes the inhibitory phosphorylation on ULK1, allowing the initiation of autophagy and the formation of autophagosomes. Concurrently, these phytochemicals promote apoptosis by diminishing Akt-mediated phosphorylation of pro-apoptotic proteins. This includes the reactivation of BAD and caspase-9, as well as the enhanced nuclear translocation of FOXO transcription factors, which upregulate apoptotic genes such as BIM, PUMA and Fas ligand. Furthermore, phytochemicals often reduce the levels of antiapoptotic proteins, such as Bcl-2 and Mcl-1, thereby sensitising cells to programmed cell death. Through these combined effects, phytochemicals target the PI3K/Akt/mTOR pathway to simultaneously induce autophagy and apoptosis, making them promising agents for therapeutic intervention in cancer and other diseases characterized by dysregulated cell survival pathways.

Autophagy and its Role in Cancer

Autophagy is a process by which cells use to clean up damaged organelles, faulty proteins and pathogen invaders that threaten the stability of cells. There are three main types of autophagy based on the mode of cargo delivery to lysosomes: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). Scientists have primarily examined macroautophagy, a process in which a double-membrane structure, known as an autophagosome, seizes items from within the cell to be destroyed. When there is stress or nutrient shortage, ULK1/2 complex gets activated, however mTOR regulate this negatively and AMPK regulate this positively. As a result, the Beclin-1-VPS34 complex leads to the nucleation of

the membrane and PI3P production to bring other ATG proteins into action. The formation of an autolysosome occurs when an autophagosome fuses with a lysosome after ATG5–ATG12–ATG16L1 and LC3-II play their roles in membrane elongation and closure. Direct folding of the lysosomal membrane, which is what microautophagy means, helps clear misplaced materials from inside the cell, mainly when there is an abundance of nutrients. However, CMA differentially targets proteins inside cells that have a KFERQ-like motif which are then transferred to the lysosome by the pairing of Hsc70 and LAMP-2A. Cellular signaling pathways such as PI3K/AKT/mTOR control the process of autophagy. Autophagy shows dual role in cancer, helping tumors to survive under stress, while also stopping the development of new tumors by removing damaged harmful molecules. It has been shown that curcumin, resveratrol and EGCG, along with other phytochemicals, can affect autophagy and thus suggest that autophagy might make a suitable target for therapies that fight cancer.

Autophagy acts to maintain cellular homeostasis, functions as a regulatory process in tumor progression. The formation of preautophagosomal structures, called phagophore assembly sites (PAS), indicates the initiation of the Autophagy process (45). Endoplasmic reticulum of multicellular eukaryotes is the place where ATG proteins are recruited to facilitate the formation of autophagosomes (46). PI(3)P plays a critical role in initiating the formation of phagophore assembly sites (PAS). Several proteins, such as ULK1 (Unc-51-like kinase), 5' adenosine monophosphate-activated protein kinase (AMPK) and mechanistic target of rapamycin complex 1 (mTOR), are involved in this cellular process. These proteins contribute to the formation of phagophores during the initiation of autophagy, with Beclin-1, Vps34 and Vps15 serving as recruiters of effectors for phagophore formation in this process (47, 48). After the formation of phagophores, phagocytosis takes place, followed by the expansion and closure of the membrane, leading to the elongation and development of a structure called an autophagosome. This autophagosome then merges with lysosomes and forms a structure known as an autolysosome (Fig. 1) (49). The formation of autolysosomes ensures the efficient enzymatic degradation, elimination and recycling of cargo, allowing the cell to maintain homeostasis. Many studies have shown that the role of the autophagy process in cancer is very complex. Its role can vary depending upon type and stage of cancer. Autophagy can exhibit distinct functions at various stages of tumour development, having both positive and negative effects on the fate of cancer cells. Understanding the interplay between autophagy and cancer is crucial for developing effective therapeutic strategies, including targeting autophagy to sensitise cancer cells to treatment or modulating autophagy to enhance tumour cell death (50). Certain anticancer drugs have the ability to modulate autophagy, thereby implicating autophagy-regulated chemotherapy in cancer cells (51, 52). Additionally, the regulation of autophagy has a significant impact on the expression of tumor suppressor proteins and oncogenes. By regulating the expression of mTOR and AMPK autophagy can be induced and prevent uncontrolled cell proliferations (53). Conversely, the phosphoinositide 3-kinase/Akt/mTOR pathway, an intracellular signalling pathway, has the ability to activate oncogenes, leading to autophagy inhibition and promoting tumour growth

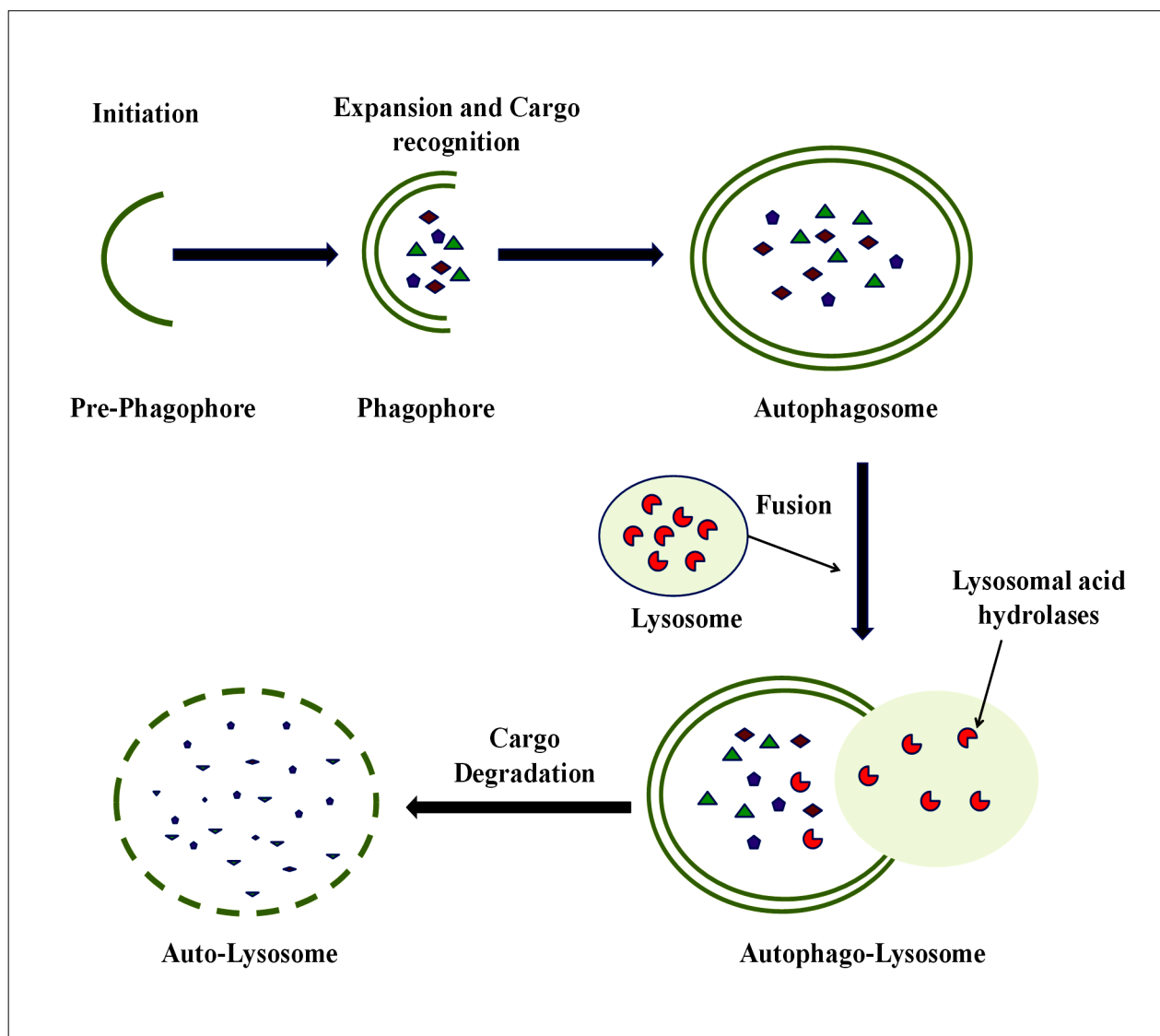


Fig. 1. Key events during the autophagic pathway: formation of pre-autophagosomal structure. Next, the phagophore formation is mediated by protein factors. Ultimately, the association of a mature autophagosome and lysosome leads to the formation of an autolysosome and the degradation of cargo.

(54). Inhibition of autophagy can regulate cancer progression with its impact determining whether it functions as a protective mechanism in cancer cells or causes cell death (55). Malignant cells undergo intense metabolic alterations to support their proliferation and survival in adverse microenvironments. The maintenance of metabolic adaptations in cancer cells heavily relies on autophagy (56). Despite the recognition of autophagy as a mechanism for sustaining the metabolism of tumour cells under stressful conditions, the precise interplay between metabolism in cancer cells and autophagy signalling remains unclear. Key signalling components, such as mTOR and AMPK, regulate autophagy by modulating glucose levels and amino acid availability (47). Autophagy initiation and the formation of autophagosomes are regulated by various factors, including specific metabolites, growth factors, palmitate, reactive oxygen species (ROS), oxygen concentration, amino acid levels, the ATP-to-ADP ratio and oncogenes. These factors play important roles in governing the process of autophagy by influencing its initiation and the subsequent formation of autophagosomes (57). Notably, this intracellular process, autophagy, has been found to exhibit a "dual role" in cancer, with the ability to either inhibit or promote the initiation and progression of cancer.

Role of Apoptosis in Cancer

Targeting apoptosis is an effective strategy for developing anticancer therapy regardless of the specific cancer type (18). Apoptosis is indeed a central pathway involved in regulating programmed cell death and is connected to both intrinsic and extrinsic pathways. These pathways provide different means of initiating apoptosis and converge at the same central machinery responsible for executing cell death (Fig. 2) (58). To induce apoptotic pathway in target cells, the extrinsic pathway relies on signals originating from outside the cell that trigger the binding of specific ligands such as Fas ligand (a member of the TNF family) and TNF-related apoptosis-inducing ligand (TRAIL). These ligands interact with death receptors (DRs), which are transmembrane proteins present on the cell surface and signals originating from outside the cell that trigger the binding of specific ligands, such as Fas ligand (a member of the TNF family) and TNF-related apoptosis-inducing ligand (TRAIL) (59). These ligands interact with death receptors (DRs), which are transmembrane proteins present on the cell surface (59). Caspases, categorized as initiator, effector or executioner which plays key roles in extrinsic apoptotic signaling pathway. One of the key regulators involved in intrinsic apoptotic pathway is bcl-2 family proteins. Based on their functions Bcl-2

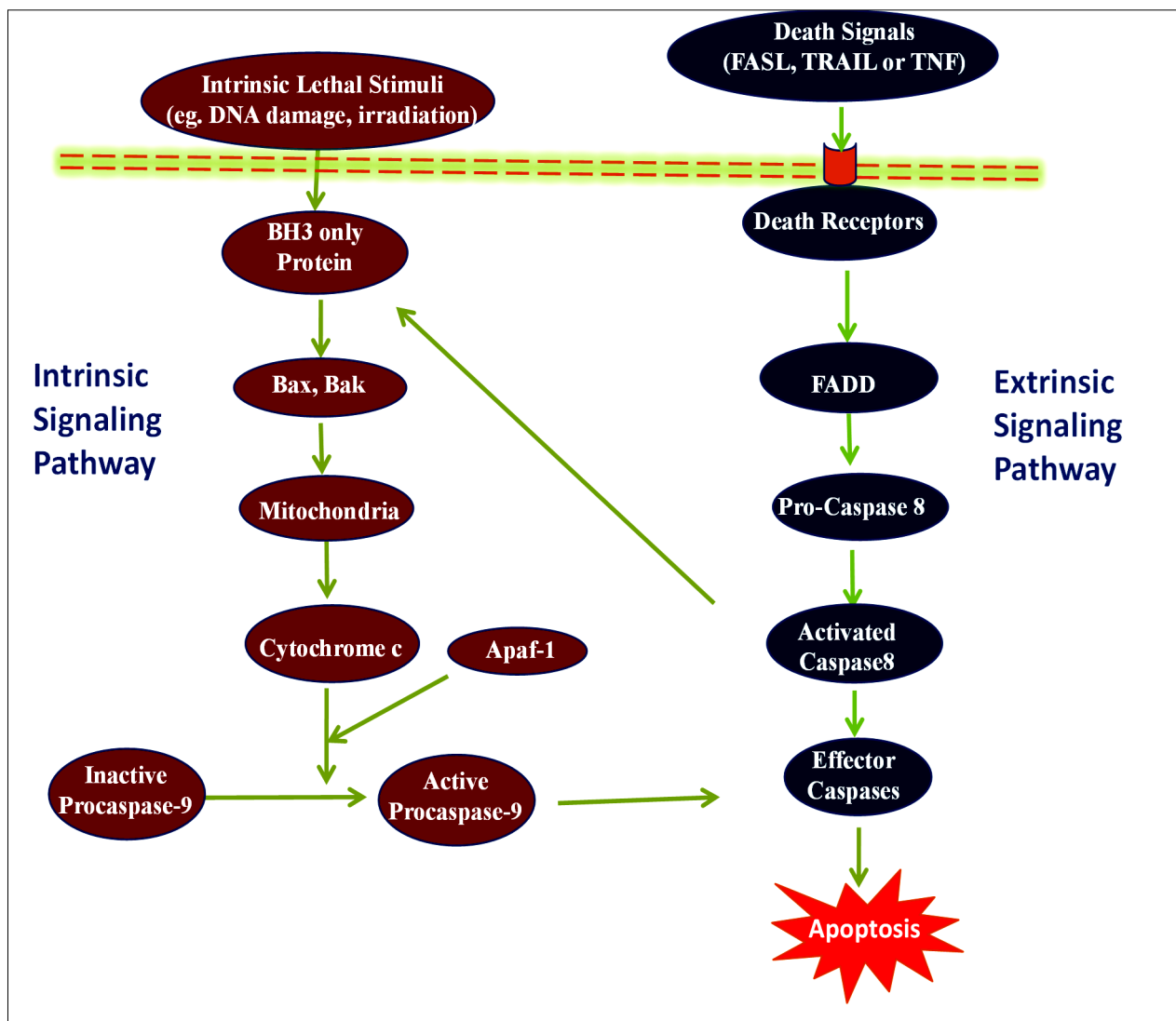


Fig. 2. The apoptotic pathway: intrinsic and extrinsic pathways are extremely vital in executing the apoptotic pathway in cancer. In the extrinsic pathway, binding of Fas ligand (FasL) to Fas initiates the recruitment of Fas-associated death domain (FADD), which connects death receptor signalling to the caspase cascade. The BH3-only protein, Bid, is activated by Caspase-8 and it cross-links between the extrinsic and intrinsic pathways. The intrinsic pathway involves cytochrome c, Apaf-1 and caspase-9.

family proteins are grouped into proapoptotic and antiapoptotic. Proteins such as Bid, Bax, Bcl-2 related ovarian killer (Bok), Bak, active caspase-3, Bad are part of proapoptotic group and proteins such as Bcl-2, Bcl-XL, Bcl-W, Bfl-1 and Mcl-1 are part of antiapoptotic group (60). The intrinsic apoptotic pathway can be activated by various cellular signals, such as the overexpression of oncogenes and DNA damage (61). Various factors, such as growth factor deprivation, excessive calcium levels, oxidants, DNA-damaging molecules and microtubule-targeting drugs, can serve as additional triggers for the intrinsic apoptotic pathway (62). The BCL-2 family of proteins acts as an important regulator of the apoptotic signalling pathway. In response to different apoptotic signals, the expression of BH3-only proteins can be upregulated, which in turn activates both BAX and BAK (63). Tumor suppressor protein p53 can controlled the activity of BAX. Activated BAX and BAK undergo oligomerisation at the mitochondrial outer membrane (MOM) and cause its permeabilisation (64). This is a crucial event in the intrinsic pathway because MOM permeabilisation allows different apoptotic factors to exit the mitochondria and initiate the activation of downstream caspases, causing cell death. Binding of Cytochrome C to apoptotic protease activating factor (Apaf-1) and activating

procaspase9 are essential for apoptosome formation. Within the apoptosome, the inactive procaspase-9 undergoes a conformational change, converting it into its active form, caspase-9. Activated caspase-9 then act as a key initiator caspase in the apoptotic pathway. It cleaves and activates the executioner caspases 3 and 7, which are responsible for the rapid breakdown of cellular proteins, leading to the dismantling of essential cellular components and ultimately resulting in cell death (65).

Phytochemicals: Potential Fine-Tuners of Autophagy-Apoptotic Pathway

Both autophagy and apoptotic pathways play significant role in cancer treatment process, mainly during chemotherapy. The autophagy process is responsible for the selective removal and degradation of unwanted intracellular components through lysosomes. This self-digestion process is crucial in enhancing cellular defence mechanisms, enabling cells to resist various intracellular and extracellular stresses and maintaining cellular homeostasis. There are many evidences that show the dual nature of the autophagy process in cancers, where it can have both promoting and inhibitory effects on the development of tumours. Indeed, the process of autophagy initiation holds

promise as a potential strategy for cancer treatment, particularly due to its ability to induce type 2 cell death. At the initiating stage of tumorigenesis, tumour-suppressing factors can negatively regulate autophagy regulators, thereby promoting autophagy activation (53). By regulating reactive oxygen species levels (ROS) autophagy can suppress the carcinogenesis process. Excessive ROS production can lead to oxidative stress, DNA damage and genomic instability, all of which are closely linked to carcinogenesis (Fig. 3) (66). On the contrary, negative regulators of autophagy are known to be activated by several oncogenes, resulting in the inhibition of autophagy and promotion of tumorigenesis (54). Interestingly, in certain instances, metabolic by-products and synthetic derivatives derived from natural sources have exhibited enhanced chemopreventive activity compared to the original natural compounds (67). Phytochemicals have shown promise in the treatment of many cancers due to their multifaceted therapeutic activities (Table 2) (68). Recent research highlights the potential of phytochemicals as promising agents for cancer treatment, particularly in modulating the autophagic-apoptotic pathways, regardless of whether these pathways act independently or interactively within cancer cells. By harnessing the synergistic effects of these agents, there is a potential to improve patient outcomes and reduce the likelihood of treatment resistance in various cancer types.

Phytochemicals in autophagy signalling

Several studies have been conducted to investigate the influence of plant-derived phytochemicals on the autophagy pathway. Phytochemicals have demonstrated the ability to regulate autophagy signalling through various mechanisms. Some phytochemicals can induce autophagy by activating key regulators of the autophagy pathway such as AMPK and (mTOR). Activation of 5' adenosine monophosphate activated protein kinase and inhibition of mTOR can stimulate autophagy initiation (69). Apigenin, a flavonoid derivative has been reported to exhibit inhibitory effects on cell growth and induce autophagy in HepG2 cells (70). Apigenin induce autophagy by inhibiting the phosphatidylinositol 3-kinases/Akt/mTOR pathway (71). Allicin, a phytochemical, act as anticancer compound by modulating autophagy processes. Allicin exhibits its ability to inhibit the PI3K/mTOR signal pathway, downregulates p53 and Bcl-2 expression, while enhance the AMPK/TSC2 pathway and Beclin-1 signaling pathways (69, 72). Naturally occurring pigments, such as anthocyanins, have been shown to induce autophagy, although the specific mechanism involved has not been fully elucidated (73). Berberine, an alkaloid compound belonging to the isoquinoline family, demonstrates anticancer properties by promoting autophagy through the inhibition of the MAPK/mTOR/ULK1 pathway (74). A flavonoid, Aspalathin, have shown the ability to reduce cardiotoxicity caused by cancer drug Doxorubicin. It triggers autophagy-related genes, decreases p62 expression and activates the AMP-activated protein kinase and

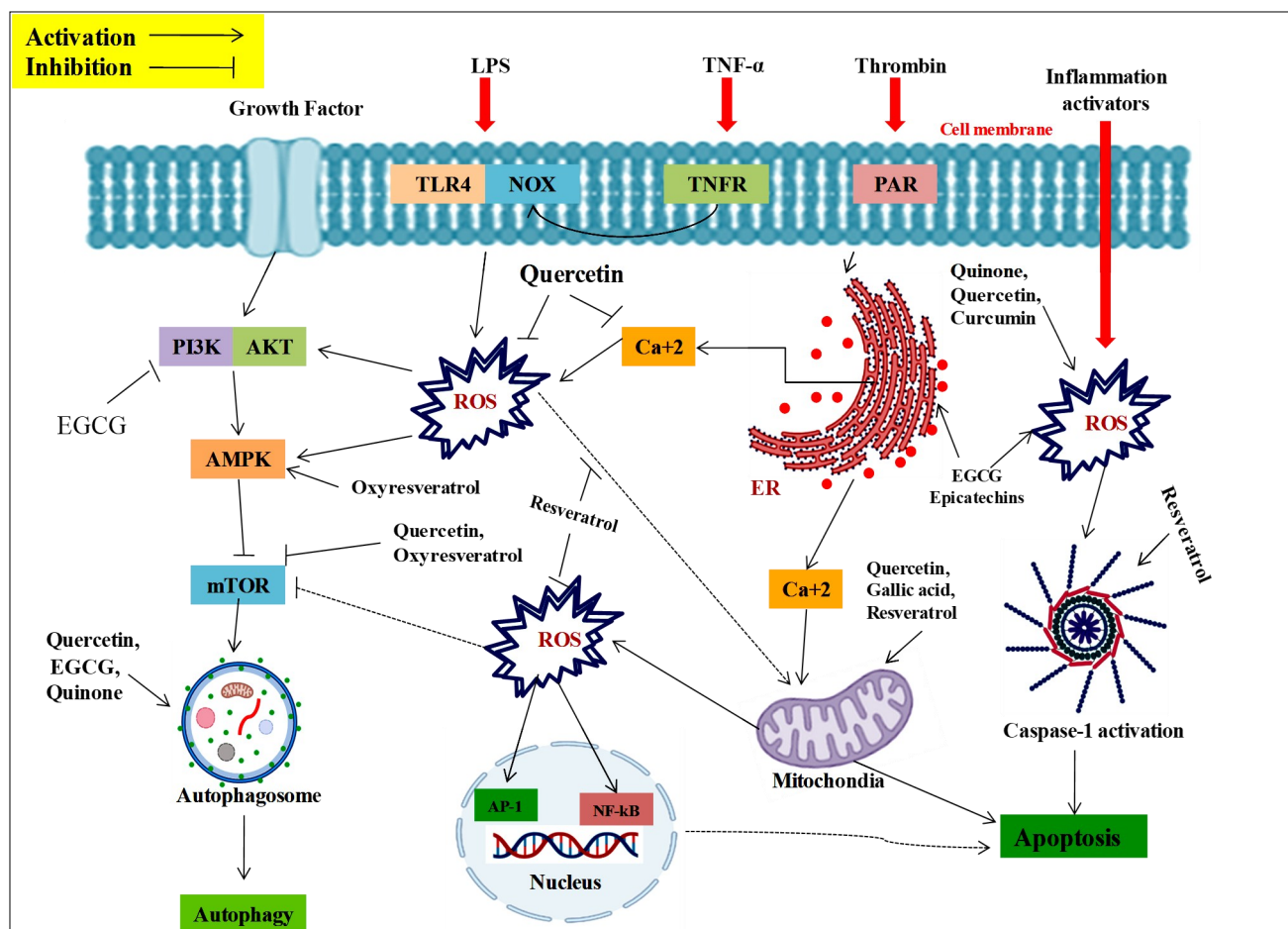


Fig. 3. Mode of action of phytochemicals: Various internal and external stimuli causes generation of reactive oxygen species (ROS). Phytochemicals, the plant-derived molecules, primarily inhibit phosphoinositide 3-kinase (PI3K) or mammalian target of rapamycin (mTOR), thus inducing autophagy and also leading to a reduction in ROS production. The phytochemicals activate mitochondrial ROS generation, while others scavenge ROS and ultimately protect the DNA from potential damage. Thus, the autophagy-apoptosis pathway is modulated by phytochemicals, resulting in a reduction of ROS production.

Table 2. Potential phytomolecules modulating autophagy and apoptosis in cancer models

Sl. No	Phytochemical	Cancer type / Model	Range of effective dosage / IC ₅₀	Mechanism targeted	Outcome	Reference
1	Allicin	A549 and NCI-H460 non-small cell lung cancer cells	15-30 µg/mL (<i>in vitro</i>)	ROS accumulation	Autophagy and apoptosis induction	132
2	Apigenin	Prostate (LNCaP)	40 -80 µM	Inhibits PI3K/AKT, p53 activation	Apoptosis induction	133
3	Baicalein	Glioblastoma (U87)	200 µM	Inhibits mTOR, induces LC3-II	Autophagy-dependent apoptosis	134
4	Berberine	SW480 cells	50 µM (<i>in vitro</i>) IC ₅₀ of 3.436 µM	Regulation of Notch1/PTEN/PI3K/AKT/mTOR pathway	Apoptosis induction	135
5	Convallatoxin	A549 lung, HeLa cervical and breast cancer cells	2–10 nM (<i>in vitro</i>)	mTOR inhibition; caspase-3 and PARP cleavage	Induces autophagy and apoptosis	136
6	Curcumin	U87-MG, U373-MG glioma cells (<i>in vitro</i>); mouse models (<i>in vivo</i>)	50µM	NF-κB, AKT, STAT3, PI3K/Akt/mTOR	Autophagic cell death	137, 138
7	EGCG	HepG2 (<i>in vitro</i>)	30 µM	ER stress, caspase activation	Induces both autophagy and apoptosis	139
8	Emodin	Lung (A549)	IC ₅₀ = 16.85 µg/ml (~60 µM)	Disrupts mitochondrial potential	Apoptosis and cell cycle arrest	140
9	Genistein	Breast (T47D)	60µM	Blocks ERK1/2, upregulates Bax	Apoptosis via intrinsic pathway	141
10	Honokiol	PANC-1 cell line	20-40 mg/kg, intraperitoneally, every other day for 5 weeks	miR-101 expression regulation Mcl-	Apoptotic cell death	142
11	Luteolin	BxPC-3 pancreatic cancer in nude mice	84 mg/kg, intraperitoneally, 7 times/week (week 1), then 5 times/week (weeks 2-6)	K-ras, GSK-3β, NF-κB inhibition	Apoptosis induction	143
12	PHY34 (Phyllanthusmin derivative)	HGSOC cell lines	IC ₅₀ of 4 nM	inhibit the ATP6V0A2 subunit of V (vacuolar)-ATPase	Late-stage autophagy inhibition followed by apoptotic cell death	144, 145
13	Quercetin	MG-63 osteosarcoma cells; mice	500 µM (<i>in vitro</i>)	Disruption of the mitochondria membrane	Caspase-dependent apoptosis	146
14	Resveratrol	Breast (MCF-7)	50-100 µM	Activates p53, AMPK; inhibits Bcl-2	Induces apoptosis	147
15	Silibinin	HT1080 fibrosarcoma cells	40 µM (<i>in vitro</i>)	Via reactive oxygen species-p38 and c-Jun N-terminal kinase pathways	Autophagy induction	148
16	α-mangostin	T47D breast cancer cells	(IC ₅₀) of 7.5 µM	PI3K/AKT, AMPK, MAPK and ROS signaling.	Apoptosis induction	149

Forkhead box O pathways (75). Cordycepin induces autophagy by generating ROS, enhancing the expression of p53 and LC3I/II (76). Curcumin, a phyto-polyphenol have shown to increase the level of reactive oxygen species (ROS) in many types of cancer cells which in turn cause DNA damage in those cells, also induces autophagy, can influence many other signaling pathways like Akt, Jun N terminal-kinase (JNK)-P54, ERK1/2 and P38 MAP kinase in NSCLC A549 cells (77). Evodiamine found in the *Tetradium ruticarpum* plant, have demonstrated that it can activate autophagy by upregulating the expression of Bax and Beclin-1, while decreasing the expression of Bcl-2 (78). The phytochemical Fisetin has been reported to exhibit anticancer effects in prostate cancer cells by inducing autophagy, which is mediated by the inhibition of the mTOR signalling pathway (79). Fisetins' ability to downregulate the mTOR pathway is attributed to its inhibitory effect on Akt, a protein kinase that plays a role in mTOR activation. In tumor cells, Genistein has been observed to exhibit both chemopreventive and chemotherapeutic effects. Treatment of ovarian cancer cells with Genistein has shown its ability to induce the autophagy process by reducing Akt phosphorylation (80). A bioactive metabolite, Ginsenoside F2 has demonstrated its anticancer properties by inducing autophagy in breast cancer cells (81). A natural polyphenol compound, Hispolon, induces autophagy and exhibits anticancer effects in

cervical cancer cell lines (82, 83). Falcariindiol (FAD), a naturally occurring compound, has been shown to enhance the autophagy process in response to endoplasmic reticulum stress (84, 85). It activates autophagy as a cellular response to ER stress, which helps in maintaining cellular homeostasis and mitigating the stress-induced damage. Toxicarioside O, a bioactive compound found in the seeds of *Antira toxicaria*, exhibits anticancer activity by inducing autophagy via Akt/mTOR signaling (86). Mangostin, a compound derived from the mangosteen fruit has shown its anticancer properties by inducing autophagy in human glioblastoma (87). Quercetin, a natural compound, has been observed to interact with key pathways involved in cancer, including the PI3K/Akt, Wnt/beta-catenin and STAT3 pathways (25). Rottlerin enhances autophagy via activation of AMPK and increase LC3 expression (88). Stem cells. Silibinin, derived from the herb *Silybum marianum*, has shown anticancer activity by modulating the autophagy process in cancer cells. Silibinin increases LC3-II expression, which is a marker of autophagosome formation, indicating the induction of autophagy (89). Sulforaphane (SFN), an isothiocyanate phytochemical, induces autophagy-dependent death of pancreatic carcinoma cells that are highly resistant to conventional treatments (90). A bioactive phytocompound, Ursolic acid (UA) has shown anti-proliferative effects in various

cancer types. Numerous studies have shown that UA can increase beclin-1 expression, thereby inducing autophagy in cancer cells (91). Tripterygium is a plant known for its medicinal properties and one of its active components is tripchlorolide. Studies have shown that treatment with tripchlorolide can inhibit the PI3K/Akt/mTOR signaling pathway (92). A calcium channel blocker Tetrandrine derived from *Stephania tetrandra* S. Moore suppresses hepatocellular carcinoma in human by inhibiting the Wnt/ β -catenin pathway and reducing MTA1 expression, leading to autophagy (93). Quinacrine can activate p53 and p21 and inhibit topoisomerase activity, collectively contributing to its anticancer properties in breast cancer cells (94). Tangeritin, a flavonoid compound has shown its anticancer activity by inducing activity of CYP1 enzyme and regulating the expression of CYP1A1/CYP1B1 proteins in breast cancer cells (95). Treatment with Licochalcone A, a chalconoid has shown to inhibit phosphoinositide-3-kinase/Akt/mTOR signal pathway and induce autophagy in breast cancer cell lines MCF-7 cells (96). Juglanin, a natural product, has shown promising anticancer activity by regulating the autophagy process through a ROS-dependent JNK signal pathway in breast carcinoma cells (97). A bioactive phytocompound, Cucurbitacin B (CucB), has demonstrated its anticancer activity by inducing autophagy and cell death through increased ROS levels in breast cancer cells (98).

Phytochemicals in apoptotic signaling

Angelicin, a bioactive phytocompound, has been found to exhibit cytotoxic effects and induce apoptosis in the cloned subline SH-SY5Y of the human neuroblastoma cell line SK-N-SH, which is mediated through an intrinsic caspase-dependent pathway (99). Falcariindiol works in conjunction with approved cancer drugs to enhance their effectiveness in eliminating cancer cells through caspase-dependent cell death. Alisol B 23-acetate, a natural triterpenoid, has shown anticancer activity in non-small cell lung cancer (NSCLC) cells and suppresses their viability. It induces apoptosis in these cells via the phosphatidylinositol 3-kinase/Akt/mTOR signalling pathway (100). Luteolin, a bioactive phytocompound possesses potent anticancer properties against various cancer types including lung cancers (101). It was observed that the key mechanism through which luteolin acts is by inducing G0/G1 phase cell cycle arrest. Luteolin reduces Bcl2 expression at transcript level. Bcl-2 is an antiapoptotic protein that inhibits the activation of caspases and promotes cell survival. By decreasing Bcl-2 expression, luteolin helps in inducing apoptosis. Collectively, these effects of luteolin, including caspase-8 activation, Bcl-2 downregulation and stimulation of autophagy, contribute to the decreased cell survival in the human hepatocarcinoma cell line SMMC-7721 (102). All the above-mentioned findings indicate that luteolin holds promise to be a potential therapeutic compound against hepatocellular carcinoma. Kaempferol, a natural flavonol, exhibits ROS mediated apoptosis in human colorectal carcinoma cells (103). Many studies on the phytocompound Oridonin have shown its anticancer properties, including its efficacy against gastric cancer (104). Oridonin promotes apoptosis in human cancer cells by stimulating caspase-3 activity and regulating the expression levels of Bcl-2 and Bax (105). Triptolide, a natural compound derived from an herb, exhibits effects on the Akt/mTOR/p70S6K pathway, which is involved in cell growth, survival and protein synthesis (106). Galangin, a type of flavonoid compound found in many plants, exhibits its anticancer

properties by promoting apoptosis in renal cancer cells through multiple mechanisms. Studies have demonstrated that galangin treatment increases the expression of Bax, a pro-apoptotic protein, in renal cancer cells. Bax plays a crucial role to induce permeabilization in the membrane of mitochondria and releasing of cytochrome c (Cyt-c). Cyt-c release then triggers the activation of caspases, leading to apoptosis (107). Myricetin, a flavonol compound, has shown its ability to induce apoptosis in human papillary thyroid cancer (HPTC) cells (108). Hesperetin is a promising natural compound due to its anticancer effects against many cancer types. By upregulating the level of Fas, FADD and Caspase-8 hesperetin promotes apoptosis in H522 cells (109). A natural pigment compound, Cyanidin-3-glucoside (C3G) has shown to possess potential anticancer effects, particularly in breast cancer. The regulation of miR-124 and the subsequent downregulation of STAT3 by C3G provide a potential mechanism for its anticancer effects in breast malignancy (110). Naturally occurring phenethyl isothiocyanates (PEITC) has been shown to decrease the expression of HER2, EGFR and STAT3. Additionally, they enhance apoptosis by promoting caspase 3 activation and PARP cleavage (111). In addition to apoptosis, it has been observed that phytochemicals possess the capability to induce necroptosis in tumor cells (112, 113).

Challenges in Interpreting Phytochemical Actions Across Cancer Models

While curcumin, resveratrol and quercetin are known to influence autophagy and apoptosis, the results seen in cancer depend on the type and the method of research. For example, curcumin has been shown to activate autophagy in breast cancer cells by inhibiting the PI3K/AKT/mTOR pathway, whereas it primarily induces apoptosis in liver cancer cells through the p53 pathway and affects mitochondrial function. It appears that how cells are set up, with particular mutations in p53 and differences in metabolism, might control which response takes precedence. The activation of AMPK-mediated autophagy by resveratrol was observed in colon cancer HCT116 cells, though it induced apoptosis in lung cancer A549 cells with little autophagy participation. For this reason, we should carefully compare the type of tumour, the method used to study them and the dosage of the phytochemicals before deciding on their anticancer effects. For this reason, drawing general conclusions from these studies may limit their practical usefulness. Researchers should focus on making comparisons and identifying mechanisms to better explain why these effects occur in different contexts.

Challenges in Clinical Translation of Phytochemicals

Although many preclinical tests indicate that phytochemicals can influence autophagy and apoptosis, they still encounter problems for use in human cancer treatment (151-153). One issue is that most studies rely on cell line studies or animal models, none of which simulate all the factors present in real human tumours, such as variations among cells, immune system interactions, or how the body processes drugs. In addition, the way natural compounds affect people and the ease with which they can be delivered often limit their use in medical treatment (154). Curcumin and resveratrol are examples of compounds with low bioavailability and rapid metabolism, resulting in reduced performance when tested in living organisms. Third, there are few proper clinical studies

testing phytochemicals alone or in conjunction with chemotherapy, making it challenging to make strong recommendations for clinical practice. There is no agreement yet on the most effective methods, doses and combinations to deliver drugs so that they work effectively and safely. To close the gap between research and patient treatments, learning from clinical studies and better phytochemical formulations, as well as testing them in patient models, is important.

Conclusion and Future Perspectives

The rising incidence of cancer underscores an urgent need for innovative therapeutic strategies, yet the intricate nature of cancer biology poses significant challenges in the development of targeted treatments. Recent advancements in our understanding of autophagy, the process by which cells remove damaged components and apoptosis, or programmed cell death, are becoming increasingly vital, as the interplay between these two mechanisms holds substantial implications for cancer therapy. Phytochemicals represent a diverse and promising category of natural compounds that have shown potential in modulating essential biological processes, such as autophagy and apoptosis, particularly in cancer cells. Phytochemicals can influence these processes through various mechanisms, including the activation or inhibition of signalling pathways, modulation of gene expression and induction of oxidative stress. A comprehensive research approach combining *in vitro* and *in vivo* studies of phytochemicals on autophagy and apoptosis is crucial for developing drugs that target both mechanisms. Combining phytochemical compounds with conventional therapies also has the potential to enhance the potency in treating cancer and preventing tumour recurrence in cancer patients.

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Authors' contributions

SM was responsible for data curation and writing the initial draft. GKP conceptualized and conceived the idea for the manuscript. Both authors made substantial contributions to the manuscript and approved the final version before submission.

Compliance with ethical standards

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