Review

New Potential Pharmacological Functions of Chinese Herbal Medicines via Regulation of Autophagy

Betty Yuen Kwan Law †, Simon Wing Fai Mok †, An Guo Wu, Christopher Wai Kei Lam, Margaret Xin Yi Yu and Vincent Kam Wai Wong *

State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau, China; yklaw@must.edu.mo (B.Y.K.L.); smok55@hotmail.com (S.W.F.M.);
wag1114@foxmail.com (A.G.W.); wklam@must.edu.mo (C.W.K.L.); yxyworld@aliyun.com (M.S.Y.Y.)
* Correspondence: kawwong@must.edu.mo; Tel.: +853-8897-2408; Fax: +853-2882-7222
† These authors contributed equally to this work.

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Abstract: Autophagy is a universal catabolic cellular process for quality control of cytoplasm and maintenance of cellular homeostasis upon nutrient deprivation and environmental stimulus. It involves the lysosomal degradation of cellular components such as misfolded proteins or damaged organelles. Defects in autophagy are implicated in the pathogenesis of diseases including cancers, myopathy, neurodegenerations, infections and cardiovascular diseases. In the recent decade, traditional drugs with new clinical applications are not only commonly found in Western medicines, but also highlighted in Chinese herbal medicines (CHM). For instance, pharmacological studies have revealed that active components or fractions from Chaihu (Radix bupleuri), Hu Zhang (Rhizoma polygoni cuspidati), Donglingcao (Rabdosia rubesens), Hou po (Cortex magnoliae officinalis) and Chuan xiong (Rhizoma chuanxiong) modulate cancers, neurodegeneration and cardiovascular disease via autophagy. These findings shed light on the potential new applications and formulation of CHM decoctions via regulation of autophagy. This article reviews the roles of autophagy in the pharmacological actions of CHM and discusses their new potential clinical applications in various human diseases.

Keywords: autophagy; natural products; novel functions; Chinese herbal medicines

1. Introduction

Autophagy is the catabolic process in which eukaryotic cells engulf and lysosomally digest intracellular contents. The process maintains metabolic balance and cellular quality by removing dysfunctional cytoplasmic constituents and recycling basic molecular building blocks. Macroautophagy envelops and delivers the unfavoured intracellular contents to lytic compartment through the doubled-membraned autophagosome [1].

Autophagy-related proteins (Atg) are the main underpinning mechanistic component of macroautophagy. About 30 mammalian homologs of yeast Atg have been discovered. These proteins are responsible for the nucleation and elongation of the isolation membrane through protein complex formation [2,3]. Basal autophagy retains proper physiological functioning of cells through the control of cellular homeostasis, metabolic balance, and protein structural integrity. Additionally, macroautophagy is known as type II programmed cell death with its molecular regulation intricately interconnecting with the apoptotic mechanism [4–7]. Growing evidence also suggests involvement of macroautophagy in innate and adaptive immunity [8,9]. Therefore hampered autophagy is closely associated with proteinopathies, metabolic and immunological disorders. In fact, macroautophagy failure is the molecular culprit of aberrant proteins accumulation in neurodegenerative diseases such as prion, Alzheimer’s and Parkinson’s [10–12]. In metabolic diseases, altered macroautophagy is related to
obesity, hyperglycemia, hypertriglyceridemia, and hypoalphalipoproteinemia [13–16]. A murine model with autophagy related gene (Atg7) conditionally knockout from pancreatic β-cells induced hyperglycemia as a result of reduced insulin synthesis and secretion [17]. In addition, aging is the chronic recession of metabolism and cellular homeostasis, the diminishing macroautophagy over time leads to aged-related physiological and pathological changes, and is reversely related to longevity [18–20]. Also, dampened macroautophagy-induced cellular toxicity promotes tumorigenesis. The progression of prostate, breast and ovarian cancers, and brain tumors including glioblastoma and myeloma are accelerated accompanying dysregulated Atg activities [21–23]. The macroautophagy inducer metformin has demonstrated cytotoxicity against colon cancer cells with mechanism independent of p53 signaling [24]. Saikosaponin-d, (Z)-3,4,5,4'-trans-tetramethoxy-stilbene, liensinine, isoliensinine, dauricine and cepharanthine can be used to treat drug-resistant and apoptosis-resistant cancers by triggering autophagic cell death [25–27]. Macroautophagy also regulates pathogens removal and immunocellular homeostasis maintenance suggesting its critical role in autoimmune and autoinflammatory disorders, for example, ulcerative colitis, Crohn’s disease, chronic obstructive pulmonary disease (COPD), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS) [28–30]. Clinical treatment with small molecules impeding macroautophagy activity, such as CQ (chloroquine), HCQ (hydroxychloroquine), FTY720 (a sphingosine analogue) and P140 peptide (a phosphopeptide), are therapeutically beneficial to lupus patients [31–35]. As such, macroautophagy has become an ideal pharmaceutical target for in-depth investigation. Up-to-date Chinese herbal medicine (CHM) researches have demonstrated that single small-molecules or herbal extracts isolated from herbal medicines such as Bupleurum, curcumin, Polygonum cuspidatum, Rabdosia rubescens, Magnolia hypoleuca, Ligusticum wallichii franchat, and Panax notoginseng can modulate macroautophagy with intervention effects towards tumorigenesis, infectious diseases, as well as neurodegenerative and cardiovascular impairments [36–42]. This review will discuss the context of macroautophagy (hereafter autophagy) regulatory mechanisms and their role in human diseases. Further discussion on specific CHMs will focus on their new therapeutic usage through regulation of autophagy.

2. The Molecular Circuitry Regulating Autophagy

2.1. The Ras-Raf1-MEK1/2-ERK1/2 Cascade

ERK activity is an autophagy inducing signaling cascade in the intestinal-derived cells effecting through the phosphorylation of GTPase-activating protein Gα interacting protein (GAIP) by ERK which is phosphorylated by mitogen-activated protein kinase kinase (MEK1/2) [43]. The activated ERK also abrogates the autophagy inhibitory effects of the trimeric Gi3 protein [44]. Increased level of amino acid negatively regulates autophagy by phosphorylating the Ser259 of Raf1 (mitogen-activated protein kinase), the pivotal gatekeeper of the cascade [45].

2.2. The Beclin 1-Class III PtdIns3K Cascade

Amino acid starvation stimulates beclin 1-class III PtdIns3K interaction for protein complex formation through the assembly of beclin 1 with proteinaceous components like Vps34 (class III PtdIns3K) and p150 facilitating the upregulation of autophagy [46–49]. This process is independent of mTOR and is regulated by anti-apoptotic proteins which are regulated by JNK1- and death-associated protein kinase (DAPK) [50–52]. Nutrient deprivation activated DAPK to phosphorylate Thr119 within the BH3 domain which releases beclin 1 to bind with PtdIns3K for autophagy stimulation [51]. When subjected to starvation, JNK1 phosphorylate T69, S70, and S87 of Bcl-2 to detach beclin 1 from the beclin 1-Bcl-L-2 complex for autophagy activation [50].
2.3. The mTOR-Mediated Cascade

The mammalian TOR performs its function by complexing with other proteins, and appears in two constitutively different forms which are the target of rapamycin complex 1 and 2 (mTORC1 and 2) [53]. Canonically, mTORC1 masters the repression of autophagy responding to growth factor, hormone and amino acid signaling by direct interaction with the Atg machinery and interference of autophagosome formation [54,55]. Compared with mTORC2, mTORC1 is better characterized which together with the TSC1/2 (tuberous sclerosis complex 1/2) complex, an mTORC1 activities suppressor, underpinning the central molecular governance of mTOR cascade.

2.3.1. Class I PtdIns3K-Akt-mTORC1 Pathway

This pathway contributes mainly to the integration of growth factor and insulin signaling. The TSC1/2 complexes collect the signals from cellular sensor such as insulin receptor at the plasma membrane. Class I PtdIns3K is then activated and phosphorylates phosphatidylinositol (4,5)-bisphosphate (PIP$_2$) to phosphatidylinositol (3,4,5)-bisphosphate (PIP$_3$). While class III PtdIns3K product PI3P is critical for autophagy, PIP$_3$ generated by class I PtdIns3K are inhibitory. PIP$_3$ subsequently recruits and activates PKB [56].

2.3.2. 5’ Adenosine Monophosphate-Activated Protein Kinase (AMPK)-Mediated Pathway

During cellular energy stress, the AMP: ATP ratio is increased because of intracellular ATP depletion [57,58] triggering the upstream activator of AMPK, liver kinase B1 (LKB1 kinase) [59]. The activated AMPK can interact directly with the regulatory-associated protein of mTOR (Raptor) subunit of mTORC1 inactivating the protein complex thereby upregulating autophagy [60]. Cytosolic calcium ion (Ca$^{2+}$) concentration is another positive stimulation of AMPK-induced autophagy which is initiated by Ca$^{2+}$/calmodulin-dependent kinase kinase β (CaMKKβ) and endoplasmic reticulum-localized Bcl-2 [61].

3. Role of Manipulating Autophagy in the Pathogenesis of Human Diseases

3.1. Defects Related to Aggregate-Prone Proteins

Accumulation of misfolded proteins is the common feature of the different neurodegenerative diseases [62]. The self-eating property of autophagy is cytoprotective which assists the clearance of the defective β-sheets enriched protein structure [63–67]. Clinically, the beclin 1 level of AD’s brain are found to be significantly depressed [68]. Transgenic mouse overexpressing beclin 1 could improve Parkinson’s disease (PD) progression by reducing α-synuclein aggregation through the enhancement of autophagy [69]. Mutant huntingtin (Htt) forms, the main source of neurotoxic activities of Huntington disease (HD), are sensitive to beclin 1 level as demonstrated by the increased accumulation of Htt upon beclin 1 deficiency [70]. A mouse model of AD and in vitro studies showed that rapamycin effectively induced amyloid-β (Aβ) clearance, and soothed the cognitive deficit [71]. Lithium inhibits inositol monophosphatase (IMPase) which reduces free inositol and IP$_3$ levels promotes the removal of Htt of HD and α-synuclein via autophagy [72,73]. Repressing IP$_3$ synthesis with the sodium salts of carbamazepine and valproate could induce similar therapeutic effects in the experimental models of HD [73–75]. Another mTOR-independent autophagy inducer, trehalose, is also relevant to Htt, α-synuclein and tau aggregations [76,77].

3.2. Metabolic Disorders

3.2.1. Tumorigenesis

Most tumor suppressors and oncogenes are actually cellular metabolism regulators responsible for metabolic pathways including aerobic glycolysis, glutaminolysis and one-carbon metabolism [78]. The major cellular energy monitor AMPK, and hence the downstream autophagy up-regulated
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by the kinase, are closely related to cancer progression in response to metabolic stresses. AMPK activators such as 5-aminoimidazole-4-carboxamide riboside (AICAR) are strongly cytotoxic to the in vitro models of hepatic, gastric and prostate cancers [79–81]. Many other molecular messengers along the autophagy pathways are cancer-related. For example, the induction of the oncogenic mTORC1 attenuates autophagy and support cancer development [81–84]. Clinical trials with cytotoxic drugs rapamycin, temsirolimus and everolimus targeting mTORC1 to induce autophagy have been reported [85]. Therefore, cancer intervention with the use of autophagy inducers can trigger both autophagic cell death and physiological changes, such as cell cycle arrest, on cancer cells. This is of particular interest for most cancers and malignancies in regard to apoptotic resistance towards chemotherapies [86].

3.2.2. Other Metabolic-Related Abnormalities

The systemic balance of glucose and fatty acid is frequently lost in patients enduring metabolic syndromes such as obesity and glucose intolerance. It is evident that the corresponding complex regulatory networks are linked up by autophagy [87]. Chronic consumption of diets with high nutrient abnormally activates mTORC1 [88]. The de novo hepatic lipogenesis can then be stimulated by mTORC1 and its substrate sterol regulatory element-binding protein 1c (SREBP-1c) during the obese state [89,90], which further dampens the expressions of the Atgs LC3, beclin1, Atg5 and Atg7 and thus the autophagic process [91]. While activating autophagy with pharmacological inducers seems to be an ideal method for improving metabolic disorders, caloric restriction appears to be the best strategy for controlling these disorders [92].

3.3. Immune Disorders

3.3.1. Infections Control

Autophagy functions as an immune effector and directly delivers the intracellular microorganism or their components [9] into the lysosome through a specific form of selective autophagy called xenophagy [93,94]. Several medically important bacterial pathogens, such as Mycobacterium tuberculosis (Mtb), group A Streptococcus, Salmonella, Shigella and Listeria can be degraded by xenophagy. The Sindbis virus, herpes simplex virus and the parasite Toxoplasma gondii can also be eliminated by xenophagy [93,95,96].

Beyond the invading microbes, autophagy also targets the innate and adaptive immunity for preventing infections. Autophagy negatively regulates IL-1β and IL-18 expression through maintaining the quality of the intracellular milieu [97]. The overexpression of IL-1β and IL-18 of lipopolysaccharides (LPS)-stimulated macrophages with the loss of Atg16L1 further clarified the role of autophagy in inflammatory immune responses [98]. In vitro studies have verified the potential of some autophagic inducers in infection therapy. The hormonally active form of vitamin D1, 25D3, enhanced macrophage autophagy and prevented human immunodeficiency virus (HIV) replication [99]. Similarly, the small molecule PDK1 inhibitor AR12 cleared Francisella tularensis [100] and Salmonella enterica Serovar Typhimurium [100]. The therapeutic effects of the antibiotics cocktails containing isoniazid and pyrazinamide towards Mtb-infected host cells also corresponded to their autophagy-inducing properties [101].

3.3.2. Autoimmune Diseases and Auto-Inflammation

Autoimmunity is the aberrant activation of immune systems towards self-antigens due to central intolerance [102]. Autophagy is essential for loading the MHC II compartment with intracellular antigens, a process involving the Atg-lysosome interaction [103], implicating the importance of autophagy in the determination of CD4+ T lymphocytes receptor repertoire. Also, the autoreactive thymocytes that have been programed in thymus can be eliminated by autophagy [104]. Besides, the autophagic activity is positively correlated with macrophagic expression of the proinflammatory
cytokines TNF-α and IL-6 which may also contribute to SLE pathogenesis [105]. Glucocorticoids [106], anti-CD20 mAb (Rituximab) [107], bortezomib (Velcade) [108], cyclosporine [109], rapamycin (sirolimus) [110] and vitamin D3 [111] can induce autophagy for ameliorating the symptoms of SLE.

3.4. The Autophagy Regulatory Effects of Herbal Medicine and Their Novel Usage

3.4.1. Herbal Medicine as the Ideal Source of Autophagy Modulators

Since autophagy dysregulation underlies a broad range of pathological conditions, the successful therapeutic outcomes of using autophagy modulators, along with the expanding discoveries regarding the molecular basis of autophagy, suggest the need of intensively investigating the pharmaceutical potential of compounds with autophagy-adjusting ability (Table 1). While a number of synthetic autophagy regulators, such as tamoxifen, sorafenib and the water-soluble synthetic rapamycin temsirolimus, have been reported [112–114], natural autophagic compounds from CHMs are of interested because of their potential new therapeutic applications (Figure 1).

Figure 1. Novel therapeutic applications of CHMs via modulation of autophagy.
Table 1. Comparisons of the autophagic effects and traditional usages of CHMs and their active components.

| Types of CHM | Name of CHM | Traditional Usage [115] | Active Component | Autophagic Effects |
|--------------|-------------|-------------------------|------------------|--------------------|
| Heat-clearing drugs | Radix scutellariae (Huang qin) | Cools heat, drains fire, clears damp-heat, stops bleeding | Baicalin, wogonin | Induction of autophagic cell death in SMMC-7721 cells [116] |
| | Cortex phellodendri (Huang bo) | Clears damp-heat and deficient heat, drains fire, detoxifies | Berberine | Alleviation of ox-LDL induced inflammatory factors by up-regulation of autophagy via AMPK/mTOR signaling pathway [117] |
| | Rhizoma coptidis (Huang lian) | Cools heat, drains fire, clears damp-heat, detoxifies | Berberine | Induction of autophagy and help suppressing the pro-inflammatory phenotype of macrophages [118] |
| | Radix sophorae flavescens (Ku shen) | Cools heat, stops itching, disinfects and detoxifies | Matrine | Induction of autophagic cell death against C6 glioma/SGC-7901/HepG2 cells [119] |
| | Herba rhabdocae (Dong ling cao) | Cools heat, detoxifies and disinfects, moves blood, relieves pain | Oridonin | Induction of autophagic cell death in cancer cells including esophageal, prostate, breast, colorectal, hepatoma carcinoma and cervical carcinoma [120–126] |
| | Radix isatidis (Ban lan gen) | Cools heat, disinfects and detoxifies, clears the throat, cools blood | Fangchinoline, tetrandrine | Fangchinoline activates autophagic cell death through the p53/sestrin2 / AMP pathway of hepatocellular carcinoma [127] |
| | Herba scutellariae barbatae (Ban zhi lian) | Cools heat, detoxifies, breaks up lumps, promotes urination | Pheophorbide | Induction of autophagic effects in cancer cells including HeLa, A549, MCF-7, PC3, HepG2, Hep3B and H 1299 [26] |
| | Rhizoma polygoni cuspidati (Hu zhang) | Moves blood, relieves pain, expels damp-wind, cools heat | Resveratrol | Attenuation of the inflammatory phenotype of vascular endothelium and induction of autophagic cell death in glioma and adeno-carcinoma [128–130] |
| | Herba scutellariae barbatae (Ban zhi lian) | Cools heat, clears damp-heat, breaks up lumps, promotes urination | Pheophorbide | Induction of autophagic cell death in oral squamous carcinoma cells, hormone insensitive prostate cancer and breast adenocarcinoma [131–133] |
| | Nelumbo nucifera (Lian hua) | Drains summerheat, raises the yang, stops bleeding, cools heat | Neferine | Attenuation of mutant huntingtin toxicity in PC-12 cells and inhibition of A549 cell proliferation cells by inducing autophagy [134,135] |
| | Syzygium samarangense (Lian wu) | Clears heat, detoxifies, alleviates itching | Dimethyl cardamonin (DMC) | Induction of autophagic cell death in colorectal carcinoma, pancreas, prostate, myeloid leukemia and multiple myeloma cells [136] |
| | Trichosanthes kirilowii (Huang gua) | Cools heat and promotes urination, detoxifies | Cucurbitacin D, cucurbitacin B, E and I | Induction of autophagy in breast cancer cells by activating the ROS and in melanoma via c-Jun N-terminal kinase (JNK) activation [137,138] |
| | Mallotus philippensis (Cu kang cha) | Cools heat and promotes urination | Rottlerin | Induction of cell death in fibrosarcoma, prostate and pancreatic cancer cells, and prevention of prion protein, amyloid Aβ and α-synuclein through autophagy [139–142] |
| | Rhizoma amarumherneae (Zhi mu) | Cools heat, clears damp-heat, generates fluids, tonifies and supports the yin | Timosaponin AIII | Induction of autophagic cell death in breast cancer and facilitation of the downstream sequestration of aggregation-prone ubiquitinated proteins [143] |
Table 1. Cont.

| Types of CHM | Name of CHM | Traditional Usage | Active Component | Autophagic Effects |
|--------------|-------------|-------------------|------------------|-------------------|
| **Tonifying Drugs** | Radix ophiopogon japonicas (Mai dong) | Tonifies and nourishes the yin, generates fluids, clears the heart and calms the spirit, clears deficient heat | Ophiopogonin B (OP-B) Ophiopogonin D (OP-D) | OP-B induces apoptosis-independent non-small cell lung cancer death and silences through autophagy [144], OP-D inhibits autophagic activity partially accounting for its heart protective effects against DOX-induced toxicity [145] |
| | Radix glycyrrhizae (Gan cao) | Harmonizes and tonifies the qi, spleen and stomach, detoxifies | Licochalcone A, isoliquiritigenin | Induction of autophagic cell death in cervical, breast cancer, androgen-sensitive prostate adenocarcinoma and adenoid cystic carcinoma cancer cells [146] |
| | Radix dipsaci (Xu duan) | Tonifies yang and kidneys, strengthens sinews and bones | Akebia saponin | Induction of autophagic cell death in gastric cancer cell through both the AMPK/mTOR and PI3K/Akt/mTOR signaling pathways [147] |
| | Radix ginseng (Ren shen) | Harmonizes and tonifies the qi, raises the qi, generates fluids | Ginsenosides Rb1, Rg1, Rg3, Rh1, Re, and Rd | Rb1 suppresses neurotoxicity and breast cancer stem cells [148], Re enhances cardiac muscle cell survival through autophagy [149] |
| | Peschiera fuchsiaefolia (Dao zhong sha ma cha) | Harmonizes and tonifies the qi, spleen and stomach, dries damp | Voacamine | Induction of autophagic cell death of multidrug-resistant osteosarcoma, and inhibition of the action of transporter P-gp [150] |
| **Exterior-releasing drugs** | Radix bupleuri (Chai hu) | Releases the exterior, moves and regulates qi, raises qi and yang | Saikosaponins | Cytotoxic to breast and cervical cancers by increasing autophagy-induced ER stress via the CaMKKβ-AMPK-mTOR signaling [25] |
| | Rhizoma zingiberis recens (Sheng jiang) | Releases the exterior, dispels cold, transforms cold phlegm | 6-gingerolis | Induction of autophagic cell death in cervical cancer cell partly via the repression of Akt signaling and in pancreatic cancer through activation of AMPK-mTOR signaling [151] |
| **Wind-dampness dispelling drugs** | Radix tripterigii wilfordii (Lei gong teng) | Cools heat, draws out toxins, reduces swelling and pain | Celastrol | Repression of the proliferation of osteosarcoma cells, preventing neurodegeneration, and ameliorating experimental colitis in IL-10 deficient mice through autophagy [152,153] |
| | Radix stephaniae tetrandrae (Fang ji) | Dispels wind-damp, relieves pain, disperses swelling | Fangchinoline, tetrandrine | Fangchinoline induces autophagic cell death in hepatocellular carcinoma [127]. Tetrandrine induces autophagic cell death in leukemia cells [154] |
| | Radix plumbaginis zeylanicae (Bai hua dan) | Dispels wind-damp, relieves pain, disperses swelling | Plumbagin | Induction of autophagic cell death in breast cancer, lung cancer and tongue squamous carcinoma cells through the mTOR signaling pathway [155] |
| **Dampness draining and transforming drugs** | Rhizoma alismatis (Ze xie) | Promotes urination, drains dampness, clears damp-heat, clears deficient fire | Alisol B, alisol B23-acetate | Induction of autophagic cell death through activation of the CaMKKβ/AMPK/mTOR signaling pathway [156] |
| | Cortex magnoliae officinalis (Hou po) | Transforms dampness, breaks up stagnation, moves and regulates the qi | Magnolol | Induction of autophagic cell death of lung cancer by blocking the PI3K/PTEN/Akt pathway [157] |
### Table 1. Cont.

| Types of CHM                                | Name of CHM                        | Traditional Usage [115] | Active Component | Autophagic Effects                                                                 |
|---------------------------------------------|------------------------------------|-------------------------|------------------|-----------------------------------------------------------------------------------|
| Interior warming and cold expelling drugs   | *Fructus evodiae* (Wu zhu yu)     | Warms cold, disperses cold, relieves pain, directs qi downwards | Evodiamine       | Induction of autophagic cells death in glioblastoma, gastric adenocarcinoma [158], Inhibition of IAV-induced autophagic cell death [159] |
|                                             | *Fructus piperis longi* (Bi bo)   | Warms cold, expels cold, relieves pain | Piperlongumine   | Promotion autophagic cell death of breast, kidney, prostate and lung cancer cells [160,161] |
| Blood regulating drugs                      | *Rhizoma curcumae longae* (Jiang huang) | Regulates blood, moves blood, moves and regulates qi, descends the qi | Curcumin         | Hinders α-synuclein accumulation in neural cells and suppression of the proliferation of glioma cells through induction of autophagy [162,163] |
|                                             | *Radix salviae miltiorrhizae* (Dan shen) | Moves blood, breaks up blood stasis, cools heat, cools blood | Tanshinone IIA   | Induction of autophagic cell death of leukemia via activation of AMPK/mTOR, ERK/mTOR and p70 S6K signaling [164] |
|                                             | *Ligusticum wallichii* (Chuan xiong) | Moves blood, moves and regulates qi, dispels wind | Ligustrazine     | Induction of cytotoxic effects in hepatocellular carcinoma and protection of the kidney from neurotoxicity through autophagy [37,165] |
| External using drugs                        | *Venenum bufonis* (Chan su)       | Opens the orifices, detoxifies, relieves pain | Bufalin          | Induction of cell death in hepatoma cells and suppression of colon cancer cells proliferation through autophagy [166,167] |
|                                             | *Gamboge* (Teng huang)            | Detoxifies, disperses swelling, antiparasitic, alleviates itching | Gambogic acid    | Amelioration of bladder cancer and induction of cytotoxic in leukemia cell through autophagy [168,169] |
|                                             | *Radix poygelae* (Yuan zhi)       | Anchors the yang, dislodges phlegm, opens the orifices | Onjisaponin B    | Acceleration of the degradation of mutant α-synuclein and huntingtin in PC-12 cells through autophagy [170] |
|                                             | *Ganoderma lucidum* (Ling zhi)    | Tonifies the heart and qi, Calms and anchors the spirit | Ganoderic acid C2 | Reduction of accumulation of mutant huntingtins in PC-12 cells, Induction of autophagic cell death in melanoma cells [171] |
|                                             | *Calis polygoni multiflori* (Shou wu teng) | calms and anchors the spirit, anchors the yang | Anthraquinones   | Induction of autophagic cell death in C6 and U251 [172] |
|                                             | *Fructus schisandrae* (Wu wei zi) | Harmonizes and tonifies the yin and qi, securues the essence | Schisandra total lignin | Inhibition of D-galactose-induced brain tissue aging through autophagy [173] |
|                                             | *Semen ziziphi spinosae* (Suan zao ren) | Tonifies yin and blood, astringes and collects, anchors the yang | Jujuboside A, jujuboside B | Jujuboside B induces autophagic cell death in AGS and HCT 116 human cancer cells and suppresses tumor growth [173] |
|                                               | *Succinum* (Ambrum)              | Calms and anchors the spirit, sedates and cools the heart | Vitamin E succinate (VES) | VES-induced autophagy participates in SGC-7901 cell protection by inhibiting mTOR axis phosphorylation [174] |
3.4.2. Heat-Clearing Drugs

Heat-clearing drugs are used to clear damp-heat, fire or heat in the blood and body fluids to maintain regular body temperature and normal hemostatis of body [115,175].

*Radix scutellariae* (Huang qin) has been shown to modulate inflammatory diseases like gastroenteritis and hepatitis, and is also effective in controlling tumorigeneses [176]. The two main active components, baicalin and wogonin inhibit the release of proinflammatory mediators from different immunocellular components [177,178]. Baicalin and wogonin might be effective for inducing cytotoxicity or inhibiting proliferation in various human hepatoma [116]. The anti-cancer effects of *Radix scutellariae* such as induction of cell death and cell cycle arrest could be mediated through autophagy [179]. Although the involvement of autophagy in the *Radix scutellariae*-triggered anti-inflammatory property is still elusive, the progression of gastroenteritis and hepatitis are highly autophagic-related [180], suggesting the potential autophagic role of *Radix scutellariae* in such diseases. All these observations suggest that a main part of the clinical functions of *Radix scutellariae* as documented in Chinese traditional medical references are manifested via autophagy.

*Cortex phellodendri* (Huang bo) with berberine as its active ingredient after bark extraction has been traditionally prescribed for the treatment of pneumonia, tuberculosis, meningitis and liver cirrhosis [181,182]. *Cortex phellodendri* is anti-inflammatory in nature, which helps to eliminate invading pathogens, ameliorates acetaldehyde-induced hepatic NF-κB activation during cirrhosis [183,184], and inhibits glial proinflammatory iNOS (nitric oxide synthase) and TNF (tumor necrosis factor)-α activity [185]. Berberine modulates autophagic processes through the AMPK/mTOR signaling pathway [117,186], therefore, the observed anti-inflammatory capability of *Cortex phellodendri* was likely related to berberine-induced autophagy [118,187]. Recently, the dietary supplement Nexrutine® which contains berberine, has been found to have therapeutic potential towards melanoma, multiple myeloma, prostate, pancreatic, breast and non-melanoma skin cancer [188–192]. Since berberine could induce both apoptosis and autophagy during tumorigenesis [193], autophagy may be responsible for the newly discovered anti-cancer properties of *Cortex phellodendri*.

*Rhizoma coptidis* (Huang lian), containing the active component berberine, has been traditionally prescribed for the treatment of pneumonia, tuberculosis, meningitis and liver cirrhosis [181,182]. *Rhizoma coptidis* is anti-inflammatory in nature, which helps to eliminate invading pathogens, ameliorates acetaldehyde-induced hepatic NF-κB activation during cirrhosis [183,184], and inhibits glial proinflammatory iNOS (nitric oxide synthase) and TNF (tumor necrosis factor)-α activity [185]. In response to the anti-diabetic effect of *Rhizoma coptidis*, autophagy was important for regulating the synthesis and secretion of insulin by pancreatic β-cells [17]. Recent studies have also reported the potential of *Rhizoma coptidis* in neurodegeneration therapy [198,199]. With the protective role of autophagy in neurodegenerative and inflammatory diseases, it is notable that the protective effect of *Rhizoma coptidis* may be regulated through autophagy.

*Radix sophorae flavescentis* (Ku shen) was used to alleviate toxicity, killed parasites and induced diuresis according to Chinese medicinal theory [200]. Many traditional formulas contain *Radix sophorae flavescentis*, for example, “Xiaofeng San” was prescribed for treating cutaneous disorders [201], and “Sanwu Huangqin Tang” has long been used for post-partum fevers arising from reproductive organ infections during childbirth [202]. These therapeutic effects suggest the immunomodulatory and anti-inflammatory function of *Radix sophorae flavescentis* may be attributed to the maintenance of systemic homeostasis by clearing off metabolic wastes through autophagy. The active component of *Radix sophorae flavescentis* is matrine, which is pharmacologically related to the suppression of inflammation by inhibiting neutrophil infiltration and oxidative stress, as well as reducing the production of inflammatory mediators [203]. Also, matrine has been reported as T cell anergy inducer through regulating the expression of anergy-associated genes such as Jumonji and CD98 [204]. The autophagic effects of matrine have suggested *Radix sophorae flavescentis* as a promising
anti-cancer herb. For example, matrine was able to induce autophagic cell death against certain cancers [119,205,206], a pharmacological action which has not been reported in Chinese medicinal documents. Although no direct linkage between Radix sophorae flavescentis-induced autophagy and its traditional immunity regulatory effects has been reported, owing to the significant role of autophagy in immunomodulation, the involvement of such a process cannot be neglected.

*Herba rabdosiae* (Dong ling cao) has been extensively used in cancer therapy [207]. This herbal drug was also effective in encountering inflammation, oxidative stress and pathogen invasion [207]. Oridonin, an active component of *Herba rabdosiae*, attenuated neuroinflammation and associated oxidative stress by repressing the microglial production of nitric oxide and pro-inflammatory cytokines like IL-1β and IL-6 [208]. Oridonin inhibited cancer growth by repressing the expression of proinflammatory mediators like IL-33 and bone morphogenetic protein-2 (BMP-2) [209]. Besides, it was able to induce apoptosis and autophagic cell death in various cancer cell types, including esophageal cancer [120], prostate cancer [121], breast cancer [122], multiple myeloma [123], colorectal cancer [124], hepatoma carcinoma [125] and cervical carcinoma [126]. Therefore, the traditional anti-cancer property of *Herba rabdosiae* is highly correlated to autophagy.

*Radix isatidis* (Ban lan gen) is a popular herbal medicine, especially after the severe acute respiratory syndrome (SARS) epidemic, for its clinical applications in upper respiratory tract infections, including the nose, throat, and sinuses [210]. It is also prescribed for other viral infections like measles and hepatitis [211,212], etc. The active components of *Radix isatidis* are bis-benzylisoquinoline alkaloids—fangchinoline and tetrandrine. These active ingredients interact with invading pathogens and modulate the host responses. For example, fangchinoline could stop the replication of human immunodeficiency virus (HIV) Type 1 by disturbing the proteolytic process of viral gp160 [213]; tetrandrine suppressed hepatitis through the repression of NF-κB activation [214]. In addition, fangchinoline activated autophagic cell death through the p53/sestrin2/AMP pathway in hepatocellular carcinoma [127], whereas tetrandrine inhibited leukemia cell proliferation and induced autophagy *in vivo*. To our knowledge, the use of *Radix isatidis* in anti-cancer therapy has not been reported, therefore, these findings shed light to the development of the new usage of *Radix isatidis* in oncology through induction of autophagy. However, the role of autophagy in mediating the traditional anti-inflammatory function of *Radix isatidis* remains to be investigated.

*Stephania japonica* (Qian jin teng) has been traditionally used for relieving fever, diarrhea, dyspepsia and urinary disease [215]. Cepharanthine and dauricune are the active components of the herb that have been commonly used for inflammatory and immunological disorders in Chinese medicine [216,217]. Animal and *in vitro* studies illustrated that cepharanthine suppressed cytokine synthesis, platelet aggregation, plasma membrane lipid peroxidation, and nuclear factor-κB (NF-κB) stimulation [217]. The herb also facilitated the removal of free radicals and alleviated oxidative stress [218,219]. Dauricune exhibited similar anti-inflammatory effects through repressing the expression of inflammatory indicators such as myeloperoxidase, IL-1β and TNF-α [220]. Recently, these two compounds have been postulated as novel anti-cancer drugs. For example, cepharanthine abolished the drug resistance property of cancer cells by modulating the activities of multidrug resistance factor ABCC10 (MRP7) and ATPase [221]. Dauricune had been reported to suppress cancer proliferation and invasion, and promote apoptosis through the NF-κB signaling pathway [216]. Although documentation associating autophagy with the immunomodulatory effects of cepharanthine, dauricune or *Stephania japonica* is scarce, our laboratory discovered that both bioactive components induced autophagic cell death in apoptosis-resistant cancer cells [26]. These findings suggest cepharanthine and dauricune repress cancer growth through autophagy induction, and *Stephania japonica* may be a potential pharmaceutical agent for cancer.

*Rhizoma polygoni cuspidati* (Hu zhang) has been used to relieve inflammation, coughing, fever, and provide diuretic, emmenagogue, emollient and stomachic actions [222,223] and against tumor activity [223]. Resveratrol, the active compound of *Rhizoma polygoni cuspidati*, is a natural antibiotic [224] which inhibits the growth of bacteria and fungi [225,226]. Resveratrol exhibited its
anti-inflammatory effect through inhibiting pro-inflammatory mediator synthesis [227]. Resveratrol also repressed tumorigenesis [228–230]. Increasing evidence has shown the autophagic role of resveratrol. For example, resveratrol attenuated the inflammatory phenotype of vascular endothelium through up-regulation of autophagy [128], and induced autophagic cell death in glioma and adenocarcinoma [129,130]. Recently, resveratrol-induced cardioprotection was found to associate with mTORC2-mediated autophagy and the up-regulation of antioxidant proteins [231,232]. Therefore, autophagy could be the underlying molecular mechanism responsible for the protective effects of *Rhizoma polygoni cuspidati*.

*Herba scutellariae barbatae* (Ban zhi lian) has long been used for cancer therapy [233]. It is also effective in treating inflammatory-related symptoms, for example, furunculosis, pyogenic infections, traumatic injury, edema, venomous snake bite, and jaundice [234]. The active ingredient of the herb, pheophorbide, inhibited cytokines expression and monocyte activities, down-regulated macrophage expression of iNOS, and scavenged reactive oxygen species (ROS) [235]. In addition, pheophorbide was cytotoxic to hepatocellular carcinoma [236] and breast adenocarcinoma [131]. Thus far, literatures correlating pheophorbide and autophagy were mostly about the photodynamic therapy of tumorigenesis involving the induction of autophagy and cancer cell death. In breast adenocarcinoma, pheophorbide induced autophagy through the ERK signaling pathway [131]. It also induced both apoptosis and autophagy via ERK1/2 and p38 in skin cancer [237]. Such autophagy-related therapeutic effect of pheophorbide has also been described in oral squamous carcinoma cells and hormone insensitive prostate cancer [132,133]. Accordingly, the anti-cancer effect of *Herba scutellariae barbatae* could be partly mediated by autophagy.

*Nelumbo nucifera* (Lian hua) has been used for maintaining homeostasis, reducing anxiety, acting against bleeding, and repressing inflammation [238]. Neferine is one of the active components responsible for maintaining glucose and lipid balance during starvation [239]. Anti-inflammatory and anti-oxidative effects of neferine in neurodegenerative disease by suppressing NF-κB activation and lipid peroxidation have also been reported [240]. Protective effects of neferine towards inflammation and oxidative stress were observed in pulmonary fibrosis [241]. Emerging findings suggest that autophagy is one of the pharmaceutical targets of *Nelumbo nucifera*. For example, neferine attenuated mutant huntingtin toxicity by inducing the AMPK-mTOR-dependent autophagic pathway [134]. Such findings correlated the psychopathological regulatory effects of neferine to autophagy. Neferine induced autophagy via the ROS mediated pathway in lung cancer [135], and was found effective in suppressing hepatocellular carcinoma [242]. These findings confirmed the role of the compound in controlling inflammatory progression and its novel usage in tumorigenesis. Therefore, triggering autophagy by *Nelumbo nucifera* could be a new pharmaceutical strategy for encountering inflammatory, neurodegenerative and cancerous diseases.

*Syzygium samarangense* (Lian wu) possessing the anti-free radical ability is indigenously used to manage inflammation-related conditions and removal of oxidative stress [243,244]. Dimethyl cardamonin (DMC) is the active compound isolated from the leaves of *Syzygium samarangense* contributing mainly to the anti-inflammatory and anti-oxidative properties. DMC protected the cells from ROS damage by modulating the glutathione S-transferase and superoxide dismutase (SOD) activities [245,246]. The compound also attenuated NF-κB activation and relieved cellular inflammatory phenotype with decreased serum level of proinflammatory cytokines [247,248]. Recent studies have suggested autophagy induction by DMC was associated with proliferative arrest in colorectal carcinoma by stimulating the p53/JNK-dependent signaling [249,250]. The therapeutic effects of DMC-induced autophagy have also been reported in cancers of the pancreas and prostate, myeloid leukemia and multiple myeloma [136]. Although the autophagic role of *Syzygium samarangense* in anti-inflammation remains to be elucidated, the induction of autophagy is highly correlated to the *Syzygium samarangense*-induced anti-cancer effects.

*Trichosanthes kirilowii* (Cucumber) has been used as folk medicine for the treatment of inflammation and cancer [251]. Pharmacological research further proposed *Trichosanthes kirilowii* as a potential
remedy for suppressing HIV replication [252]. Cucurbitacin D, a major component of the herb, is an anti-inflammatory compound which inhibited pro-inflammatory mediator production via iNOS and NF-κB signaling [253,254] and cyclooxygenase-2 (COX-2) [255]. Cucurbitacin D was effective in the protection against hepatic and cardiovascular damages, the alleviation of diabetic condition, and the removal of invading microbes [256,257]. Cucurbitacin D could be used for repressing tumorigenesis of colorectal carcinoma [258], breast adenocarcinoma [259], and leukemia [260]. Recent findings have demonstrated that structural analogues of cucurbitacin D, for example, cucurbitacins B, E and I, induced autophagy and are potentially beneficial to cancer intervention. Cucurbitacin B triggered autophagy in breast cancer cells by manipulating the ROS activities [137], and in melanoma cells via c-Jun N-terminal kinase (JNK) activation [138]. Cucurbitacin E induced autophagy in cervical and breast cancer cells via activation of AMPK signaling [261]. Similar therapeutic effects have also been reported in cucurbitacin I treatment of glioblastoma [262]. All these observations point towards the likelihood of involvement of cucurbitacin D in autophagy-induced anti-tumor effects.

*Mallotus philippensis* (Cu kang chai) has been used for alleviating inflammatory symptoms caused by bronchitis, rheumatism and infection. The herb is useful in eliminating parasite invasions such as tapeworm [263]. Rottlerin, one of the major active components of the herb, also manifested potent anti-inflammatory properties. Rottlerin regulated inflammatory mediators including COX, protein kinase C δ, lipoxygenase, heme oxygenase and NF-κB [139]. Besides, it also suppressed the progression of malignant cancers by increasing the susceptibility of cancer cells towards apoptosis [264–266]. In addition, the anti-tumor effects of rottlerin were associated with its autophagy activation property in certain cell types [140,267,268]. Rottlerin induced apoptosis and autophagic cell death in prostate [141] and pancreatic cancers via the inhibition of PI3K/Akt/mTOR signaling [142]. Rottlerin also triggered apoptosis and autophagic cell death in fibrosarcoma cells through a PI3K/Akt/mTOR-independent pathway [140]. These findings, together with the protective role of rottlerin in preventing the spreading of misfolded proteins including prion protein, amyloid Aβ, and α-synuclein [139], suggest that *Mallotus philippensis* could be used as a novel therapeutic intervention for cancer-related and neurodegenerative disorders based on its autophagy-inducing ability. Whether autophagy is involved in the traditional anti-inflammatory effects of rottlerin or *Mallotus philippensis* is yet to be determined.

*Rhizoma anemarrhenae* (Zhi mu) has been used for minor symptoms like cough, fever and constipation [269,270]. The herb was also effective in treating diabetes [271]. One of the active components extracted from *Rhizoma anemarrhenae*, timosaponin AIII, relieved inflammation and oxidative damages by regulating the cytosolic Ca^{2+} concentration of endothelial cells [272], and neutrophilic superoxide generation stimulated by arachidonic acid [273]. Recent pharmacological studies demonstrated that the anti-tumor effect of timosaponin AIII was associated with autophagy. Timosaponin AIII elicited autophagy and cytotoxicity in cervical cancer which was independent of apoptosis [274]. It also repressed mTOR activity, triggered ER stress and autophagic cell death in breast cancer [275]. As demonstrated in an insulin resistance rodent model, timosaponin AIII-induced autophagy may be responsible for its diabetes-ameliorating effect through activation of AMPK [271]. In neurodegeneration model, timosaponin AIII activated autophagy and facilitated the downstream sequestration of aggregation-prone ubiquitinated proteins [143]. These findings implied the pharmaceutical potential of applying *Rhizoma anemarrhenae* for the treatment of cancers and neurodegenerative diseases.

3.4.3. Tonifying Drugs

These herbs are used when the zheng qi (normal body condition or upright qi) is weakened, for example, during recovery from illness, during childhood or in old age. The herbs have the ability to tonify (bu), nourish, supplement and strengthen human body [115,276].

*Radix glycyrrhizae* (Liquorice, gan cao) is traditionally used as adjuvant to modify the efficacy of other herbs in a single prescription of around 80% of Chinese herbal formulas [277], which acted against inflammatory symptoms such as relieving cough, sore throat and phlegm production. It is
important for maintaining a proper stomach function and is used for stomach ulcers. Licochalcone A (LA) and isoliquiritigenin (ISL) are compounds extracted from *Radix glycyrrhizae*. LA exhibited anti-inflammatory effects which suppressed pro-inflammatory mediator expression [278,279], and cleared cellular oxidative stress [280]. ISL demonstrated anti-oxidative [281] and immunomodulatory effects [282]. Of note, emerging data suggest that the anti-cancer properties in both compounds are associated with autophagy. LA induced autophagy via PI3K/Akt/mTOR signaling which repressed cervical cancer growth [283]. Androgen-sensitive prostate adenocarcinoma and adenoid cystic carcinoma were sensitive to LA- and ISL-induced autophagic cell death mediated by mTOR inhibition [146,284]. ISL also suppressed breast cancer progression through autophagy induction [285]. Therefore, *Radix glycyrrhizae* has the chemotherapeutic potential to function as an effective cancer therapeutic. Further investigation is needed for clarifying the mediating role of autophagy in the traditional anti-inflammatory effects of the herb.

*Radix dipsaci* (Xu duan) has been used for intervention in osteoporosis, strengthening of tendons and ligaments, and alleviating joint stiffness symptoms by promoting blood circulation in close proximity to the affected areas. The herb exhibits anti-inflammatory properties as reflected by its application in reducing abscesses, swellings, and sores [286]. In addition, *Radix dipsaci* helped to prevent abortion, which implies a regulatory role in the immune system [287]. Akebia saponin PA (AS) is one of the bioactive components found in *Radix dipsaci*, AS induced autophagic and apoptotic cell death of gastric cancer cells through both the AMPK/mTOR and PI3K/Akt/mTOR signaling and the downstream activation of p38/JNK molecular pathway, which facilitated caspase-3-dependent apoptosis [147]. This finding pointed towards the potential therapeutic role of *Radix dipsaci* in cancers. Also, the possibility that autophagy may participate in the immunomodulatory and anti-inflammatory functions of *Radix dipsaci* should not be ignored.

*Radix ginseng* (Ren shen) has been prescribed for maintaining bioenergetics balance as suggested by Chinese herbalists for breathlessness, anorexia, hypodynamia, and diabetes [288]. Since, one of the main functions of autophagy is to retain energy homeostasis, it may be related to the traditional use of *ginseng* as mentioned. Pharmacological studies revealed that the bioactive ginsenosides including Rb1, Rg1, Rg3, Rh1, Re, and Rd [289] ameliorated inflammation, removed oxidative stress, stimulated immune system and regulated apoptosis. Therefore, *Radix ginseng* may cure more diseases than traditionally known. *Radix ginseng* illustrated beneficial effects in neurodegenerations in part due to its anti-oxidative [290] and anti-apoptotic properties [291]. Similar therapeutic uses of *Radix ginseng* have also been reported in cardiovascular disease [292], and cancers [293]. Recent researches have focused on studying the autophagic mechanisms of *Radix ginseng*. Rb1 suppressed neurotoxicity through inhibiting autophagy by beclin-1 downregulation [148]. The compound could also enhance cardiac muscle cell survival through autophagy [149]. The minor Rb1-derived ginsenoside F2 [294] and Rg3 could regulate autophagy leading to the suppression of breast cancer stem cells [295] and hepatocellular carcinoma [296], respectively, suggesting the role of autophagy in the potential new therapeutic action of ginseng.

*Peschiera fuchsiaefolia* (Dao zhong sha ma cha) showed in vitro antimalarial activity against *Plasmodium falciparum* [297]. Voacamine (VOA), a bioactive alkaloid extracted from the herb [298,299], has been reported to induce autophagic cell death of multidrug-resistant osteosarcoma, and inhibit the action of transporter P-glycoprotein (P-gp) [150]. VOA is the ligand of P-gp which expresses in kidney, gastrointestinal tract, brain, etc. [300]. In fact, diabetes mellitus is associated with P-gp dysregulation [301]. Also, the blood brain barrier (BBB) P-gp was associated with abnormal protein aggregation in Alzheimer’s and Parkinson’s diseases, suggesting the potential use of the herb in neurodegenerative disorders [302]. Therefore, the well-known autophagic involvement in diabetes mellitus and neurodegenerations strongly advocated that *Peschiera fuchsiaefolia* may act therapeutically as novel autophagy regulators under such pathological conditions.

*Radix ophiopogonis* (Mai dong) has been used for treating inflammatory symptoms such as cough and phlegm production, and cardiovascular diseases [303]. Ophiopogonin (OP)-B is one
of the bioactive components, and was found to be an inducer of autophagy. In non-small cell lung cancer, OP-B up-regulated autophagy of tumor cells through PI3K/Akt pathways, and induced apoptosis-independent cell death and silences [144]. Another active constituent, OP-D exhibited anti-inflammatory effects through direct inhibition of mitochondrial ROS synthesis [145]. However, such an anti-inflammatory effect was not related to OP-D-induced upregulation of autophagy, as the compound could in fact suppress autophagy per se [145]. Therefore, owing to the close relationship between inflammation progression and autophagy, together with the autophagy modulating role of OP-B and OP-D, it is predicted that the compounds may contribute to the anti-inflammatory activity of the herb by regulating autophagy. Also, the findings of OP-B in inducing autophagic cancer cell death suggest the alternative use of *Radix aphiopogonis* in cancer therapy.

3.4.4. Exterior-Releasing Drugs

These drugs help our body defenses against external stimulus, including invading pathogens, cold, heat, damp-wind or summer heat that may have a noxious effects on the human body, by maintaining a normal and healthy status of organ such as the stomach (wei qi) [115,276].

*Radix bupleuri* (Chai hu) has been used for counteracting different inflammatory conditions including pancreatitis, liver cirrhosis and fever, infections like malaria and common cold, modulating abnormal lipid metabolism and relieving depression [304]. The bioactivities of the main components, the saikosaponins, are responsible for the mentioned clinical indications. For instance, saikosaponins modulated host immunity by manipulating pro-inflammatory mediator release and lymphocyte responses [305]. Saikosaponins also repressed viral replication [306] and fever [307], reduced hepatotoxicity [308] and acted as tranquilizers [306]. Direct evidence for the participation of autophagy in regulating such activities is however lacking. However, contemporary studies verified the anti-tumor effect of saikosaponins, in particular Ssd (saikosaponin-d), through autophagy regulation. Ssd was cytotoxic to different cancers, such as breast and cervical cancers by increasing autophagy-induced ER stress via the CaMKKβ-AMPK-mTOR signaling [25,31]. In fact, formulated decoctions containing *Radix bupleuri* have been prescribed for cancer therapy [309], which supports the idea that *Radix bupleuri* is a novel autophagy enhancer exhibiting therapeutic effects towards cancers.

*Rhizoma zingiberis recens* (Sheng jiang) has been used for centuries for the treatment of colds, arthritis, migraines, nausea and hypertension [310,311]. 6-Gingerolis is the most abundant bioactive ingredient found in *Rhizoma zingiberis recens*. It suppressed oxidative stress by inhibiting iNOS activity of activated macrophage [312]. 6-Gingerol affected the anti-inflammatory properties by regulating Ca$^{2+}$, which may be related to the regulation of autophagy [313]. The anti-mentic qualities of *Rhizoma zingiberis recens* are also related to 6-gingerol through inhibition of the function of serotonin 3 receptor [314]. In addition, *Rhizoma zingiberis recens*-mediated new anti-tumor functions via autophagy induction were further clarified. For instance, 6-gingerol induced cervical cancer cell death by upregulating caspase 3-mediated apoptosis, and autophagy partly via the repression of Akt signaling [315]. In pancreatic cancer, 6-gingerol induced cytotoxicity exclusively through autophagy by activating AMPK-mTOR signaling, which is a process independent of necroptosis and apoptosis [151].

3.4.5. Wind-Dampness Dispelling Drugs

These herbs are responsible for treating painful obstruction (*bi*) syndromes due to wind (wind-*bi* syndrome), cold (cold-*bi* syndrome), dampness (dampness-*bi* syndrome) or heat (heat-*bi* syndrome), which are caused by poor qi or blood circulation [115,276].

*Radix tripterygii wilfordii* (Lei gong teng) has been used for the treatment of inflammation and overactive immune system, including rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis [316]. Celastrol is the bioactive component responsible for exhibiting the anti-inflammatory and anti-oxidative effects for alleviating autoimmune disorders such as chronic inflammation, neurodegenerative disease, and asthma [317]. Recent findings suggested the use of celastrol in cancer therapy as demonstrated by its inhibitory effects in different tumors [318].
Emerging data revealed that autophagy was one of the molecular machineries mediating these celastrol-induced therapeutic functions. By regulating the ROS/JNK signaling pathway, celastrol triggered autophagy and apoptosis which further repressed the proliferation of osteosarcoma cells in both animal and cellular models [152]. Beside, autophagy induction by celastrol through the inhibition of PI3K/Akt/mTOR signaling, have demonstrated therapeutic potential in inflammatory disorders such as Crohn’s disease, which implies that the traditional functions of *Radix tripterigii wilfordii* are mediated through the regulation of autophagy [319]. The compound also prevented neurodegeneration by inducing autophagy in affected neuronal cell death via the targeting JNK and PTEN-Akt/mTOR network [153].

*Radix tripterigii* has bioactive constituents of the herb are fangchinoline and tetrandrine. Both compounds are able to modulate cytokine expression and exhibit anti-inflammatory effects [321]. Fangchinoline reduced blood glucose levels, scavenged free radicals and reduced oxidative stress [322]. Tetrandrine exhibited anti-hypertensive action by disrupting Ca²⁺ movement and NO synthase activity [323]. Although the role of autophagy modulation in such alteration of glucose and Ca²⁺ level remains elusive, both fangchinoline and tetrandrine have been reported to contribute their anti-tumor effect through autophagy. The proliferation and invasion of gastric cancer cells could be suppressed by fangchinoline mediated inhibition of PI3K/AKT signaling [324]. The compound also triggered autophagic cell death by targeting the p53/sestrin2/AMPK signaling in hepatocellular carcinoma [127]. In leukemia cells, autophagy was induced by tetrandrine through the upregulation of Notch1 and ROS signaling [154]. These autophagy-related anti-tumor activity stimulated by fangchinoline and tetrandrine encourage the further development of *Radix tripterigii wilfordii* as an effective drug for cancer therapy.

*Radix stephaniae tetrandrae* (Fang ji) is used for the treatment of edema, anti-hypertension and analgesic, and was usually used as decoction such as “Fang Ji Huang Qi Tang” [320]. The main bioactive constituents of the herb are fangchinoline and tetrandrine. Both compounds are able to modulate cytokine expression and exhibit anti-inflammatory effects [321]. Fangchinoline reduced blood glucose levels, scavenged free radicals and reduced oxidative stress [322]. Tetrandrine exhibited anti-hypertension action by disrupting Ca²⁺ movement and NO synthase activity [323]. Although the role of autophagy modulation in such alteration of glucose and Ca²⁺ level remains elusive, both fangchinoline and tetrandrine have been reported to contribute their anti-tumor effect through autophagy. The proliferation and invasion of gastric cancer cells could be suppressed by fangchinoline mediated inhibition of PI3K/AKT signaling [324]. The compound also triggered autophagic cell death by targeting the p53/sestrin2/AMPK signaling in hepatocellular carcinoma [127]. In leukemia cells, autophagy was induced by tetrandrine through the upregulation of Notch1 and ROS signaling [154]. These autophagy-related anti-tumor activity stimulated by fangchinoline and tetrandrine encourage the further development of *Radix stephaniae tetrandrae* as an effective drug for cancer therapy.

*Radix plumbaginis zeylanicae* (Bai hua dan) has effects in relieving pain, activating blood circulation, and is used for menstrual disorders, detoxification, and elimination of intestinal worms. Plumbagin, the bioactive component of the herb, is well known for its therapeutic safety and effectiveness [325]. Pharmacological studies demonstrated that plumbagin modulates the immune system and resolves inflammation [326,327]. The compound facilitates microbe clearance [328] and modulates lipid metabolism [329]. However, the role of autophagy in mediating these traditional functions of the herb remains to be elucidated. Recently, the anti-tumor activities of plumbagin have been increasingly reported [155,330]. The anti-tumor properties of plumbagin were attributed to the autophagy induction ability of the compound. For instance, plumbagin induced autophagic cell death in breast cancer via the AKT/mTOR signaling pathway [155]. The compound also triggered apoptosis and autophagic cell death in lung cancer and tongue squamous carcinoma cells through the mTOR signaling pathway [331].

### 3.4.6. Dampness Draining and Transforming Drugs

These herbs are prescribed when there is an accumulation of dampness. This kind of disturbance in body fluid (water) metabolism is related to a dysfunction of the lung, spleen, kidney or bladder [115,276].

*Rhizoma alismatis* (Ze xie) is derived from the stem tuber of *Alisma orientale* [332]. The herb reduces the circulatory levels of cholesterol and blood sugar, and promotes urine production and perspiration, which helps to resolve symptoms like chronic nephritis and edema [333]. Alisol B is the active component of *Rhizoma alismatis* which improved lipid metabolism by inhibiting the absorption and synthesis of cholesterol [332]. Alisol B23-acetate, another important constituent of *Rhizoma alismatis*, participates in inhibiting antibody-mediated allergic reactions, and lipopolysaccharide (LPS)-induced iNOS and NO production [334]. Up to now, it is still questionable if autophagy mediates the traditional functions of *Rhizoma alismatis* or its bioactive constituents as mentioned. However, alisol B has been reported as a new autophagy inducer functioning through activation of CaMKII/AMPK/mTOR signaling, induction of apoptosis and triggering of cell death in breast cancer cells [156]. The anti-tumor effects of alisol B23-acetate have also been reported in hepatocellular carcinoma [156]. Therefore,
Rhizoma alismatis has high potential to be developed as an anti-cancer drug through regulation of autophagy.

*Cortex magnoliae officinalis* (Hou Po) helps remove chest stuffiness due to phlegm accumulation, and relieves distension, which suggest its regulatory role in the immune system [335]. In consistence with the clinical indications of *Cortex magnoliae officinalis*, the bioactive component, magnolol, alleviated acute pain and endothelial damage stimulated by inflammation [336]. Other pharmacological effects of the compound included the reduction of anxiety and irritability via the regulation of γ-aminobutyric acid (GABA) receptor expression [337]. Magnolol also possessed anti-fungal properties [338], and was applied for bone repair by regulating the activities of osteoclasts and osteoblasts [157]. Magnolol also interplayed with the autophagic process which was beneficial to cancer therapy, but seemed not to be related to the traditional immunomodulatory effects of the herb. It induced autophagic cell death of lung cancer by blocking the PI3K/PTEN/Akt pathway [339]. Ery5, a compound derived from magnolol, activated autophagy and suppressed angiogenesis, causing apoptosis-independent cytotoxicity in prostate cancer cells [336]. Based on these observations, the effects of *Cortex magnoliae officinalis* on autophagy appear to be a valuable research niche in the search of new cancer treatment modalities.

3.4.7. Interior Warming and Cold Expelling Drugs

These herbs are used to warm the interior organs, expel cold, tonify yang and rescue harmed yang qi and relieve pain. Interior cold of the human body can be caused by exogenous cold, or kidney yang deficiency which finally results in spleen and heart yang deficiency [115,276].

*Fructus evodiae* (Wu zhu yu) was effective for the treatment of gastrointestinal and menstrual disorders, postpartum hemorrhage and headaches [340,341]. Pharmacological studies of the bioactive component, evodiamine, showed that the compound is anti-inflammatory in nature by inhibiting COX-2 expression [342], and inducing blockage of preadipocytes differentiation [343]. Evodiamine also induced apoptosis and suppressed proliferation of cancer cells [158]. Through the modulation of beclin-1 and Bcl-2 expression, evodiamine induced autophagic cell death and apoptosis of gastric adenocarcinoma cells, respectively [344]. In a drug screening test, evodiamine was found to inhibit autophagic cell death of infected cells upon viral inoculation of influenza A through AMPK/TSC2/mTOR signaling [159]. Therefore, evodiamine regulated autophagy through a complex molecular network, further verification of such a circuit would help to discover and standardize the novel usage of evodiamine and *Fructus evodiae*. Further investigations correlating autophagy induced by evodiamine or *Fructus evodiae* to their traditional use should also be undertaken.

*Fructus piperis longi* (Bi bo) represses cough and fever, relieves allergic symptoms like asthma, helps cease pathogen invasions, reduces blood glucose level, induces coronary vasodilation and treats jaundice [345]. The active components, piperlongumine and its derivatives, inhibit pro-inflammatory mediator synthesis [346]. These compounds remove oxidative stress and prevent cardiac damage caused by ROS [347]. They also inhibit platelet aggregation and are used as crude drugs for promoting peripheral blood circulation [348]. Amongst the diverse pharmacological activities, the potential piperlongumine-induced cytotoxic effects towards the different cancer cells have aroused the most attention [349,350]. For example, autophagy induced by piperlongumine mediates the anti-tumor effects of the compound. Piperlongumine attenuates Akt/mTOR signaling and promotes autophagic cell death of cancer cells originated from breast, kidney, prostate and lung [160,161]. Piperlongumine induces autophagy by targeting the p38 signaling in osteosarcoma [351]. Apart from regulating tumorigenesis, the traditionally reported anti-inflammatory effect of the compound partly results from autophagy enhancement [352].
3.4.8. Blood Regulating Drugs

These herbs are used to treat malfunctions in maintaining normal blood hemostasis, such as:
(1) mild forms of blood stagnation caused by slow blood flow which may lead to blood stasis; (2) severe
forms of stagnation due to congealment of phlegm, heat or cold, which lead to formation of solid masses and blood circulation stasis [115,276].

_Rhizoma curcumae longae_ (Jiang huang) is a safe CHM for alleviating intermittent fever and
inflammation of the bronchi, kidney and gall bladder, counteracting infections such as leprosy
and cold, and treating of edema, diarrhea and cancer [353,354]. Curcumin, the main bioactive
component of _Rhizoma curcumae longae_, possesses a unique structure amongst other active constituents
extracted from the herb. Such characteristics conferred curcumin with pharmacological properties
per se correlating with the clinical efficacy of _Rhizoma curcumae longae_. The compound has been
associated with the capability of preventing inflammation [355], tumor progression [356], and oxidative
stress accumulation [357]. Of note, curcumin was pharmacologically beneficial to neurodegenerative
disorders [358,359]. The compound was particularly suitable for neurodegeneration intervention
since the compound could cross the BBB after oral administration, acting as an anti-inflammatory
and antioxidant drug, and amyloid aggregation inhibitor [360,361]. In a Parkinson’s disease model,
curcumin triggered autophagy in neural cells by suppressing the mTOR/p70S6K signaling which
hindered the downstream ε-synuclein accumulation [162]. In addition, curcumin-induced autophagy
was correlated to its anti-cancer properties. By the up-regulation of ERK1/2 and Akt/mTOR/p70S6K
signaling, curcumin induced autophagy and suppressed the proliferation of glioma cells [163],
suggesting the possible autophagic role of curcumin in various disease models.

_Radix salviae miltiorrhizae_ (Dan shen) has been shown to prevent platelet aggregation and facilitate
fibrinolysis [362]. It is a traditional remedy for managing coronary heart disease [363]. The herb
was also used as ingredient in formulations for diabetes such as “tangzhiquing” [364], and was
prescribed for hepatic and renal disorders [365]. Tanshinone IIA is the main bioactive component
abundantly found in _Radix salviae miltiorrhizae_. It modulates inflammation and host immunity by
acting on multiple targets depending on the cell types [366]. For instance, tanshinone IIA inhibited
macrophagic NF-κB activation via the ERK1/2, p38 and JNK pathways [367]. In line with the
clinical indications of _Radix salviae miltiorrhizae_, tanshinone IIA was cardioprotective through its
action upon calcineurin/NFATc3 pathway [368]. Intriguingly, calcineurin regulated AMPK-dependent
autophagy of cardiomyocytes upon oxidative stress [369] implying that the process may underlie the
cardioprotective function of _Radix salviae miltiorrhizae_. In terms of autophagy regulation, tanshinone
IIA has been reported to induce autophagic cell death of leukemia via activation of AMPK/mTOR and
ERK/mTOR, as well as p70 S6K signaling [164]. Such observations suggested new potential uses of
_RADIX salviae miltiorrhizae_ in the treatment of cancer via autophagy.

_Rhizoma chuanxiong_ (Chuan xiong) is well known for its efficacy in improving blood fluidity,
coronary and systemic circulation [370]. Contemporary studies have demonstrated that the herb
modulates the proliferation of vascular smooth muscle cells [371] and prevents endothelial cell
damage [372]. Ligustrazine (tetramethylpyrazine) is the active constituent which increases myocardial
contractility and coronary circulation [373]. In addition, this single molecule acts as an anti-oxidant
to remove superoxide anion, hydroxyl and lipid peroxyl radical which induce oxidative damages in
tissues [374]. However, it is not known if autophagy is modulating the cardioprotective functions of the
herb. Ligustrazine exhibits neuroprotective and anti-inflammatory effects on brain disorders such as
cerebral ischemia, through elevating nuclear factor E2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1)
expression [375]. Recently, ligustrazine has been reported to induce autophagy which was associated
with cytotoxic effects toward hepatocellular carcinoma [37]. The ligustrazine-induced autophagic
effect has also been demonstrated in protecting the kidney from neurotoxicity [165]. Therefore,
the mechanisms underlying the _Rhizoma chuanxiong_ or ligustrazine-induced autophagic process are
intricate. Further investigations are needed to support the usage of the herb in pathological condition
such as cancer and inflammation conditions.
3.4.9. External Use Drugs

These kinds of compounds are applied to eliminate toxins, kill parasites, diminish swelling, relieve pain, expel pus and abscesses, improve wound healing, stop itching or bleeding [115,276].

*Venenum bufonis* (Chan su) is famous for its clinical application in resolving cardiovascular and inflammatory symptoms, including sore throat and tonsillitis, promoting urine production, and acting as an analgesic agent [376–378]. Bufalin is one of the constituents of *Venenum bufonis* exhibiting bioactivities related to the clinical indications described [379]. Recently, bufalin was found to regulate autophagy via cell type-dependent mechanisms to suppress tumorigenesis. In liver cancer, bufalin interacted with the Atg8, JNK, BECN-1 and TNF signaling, and stimulated autophagic cell death of hepatoma cells like Huh7, Hep3B and HA22T [380]. On the other hand, bufalin stopped the proliferation of hepatocellular carcinoma by activating autophagy through the Akt/mTOR and AMPK/mTOR pathways respectively [166]. The bufalin-induced autophagic cell death also effectively suppressed colon cancer cell proliferation via JNK activation [167], and the PTEN/AKT pathways [381]. Through targeting AMPK and the downstream p70S6K, bufalin modulated the apoptotic and autophagic activities of glioma cells [382]. Collectively, these findings support the traditional use of *Venenum bufonis* in the treatment of cancerous diseases via autophagy regulation.

*Garcinia hanburyi* (Teng huang) was used traditionally for treating inflammatory conditions and immunity dysregulation such as ulcerative gingivitis, skin infection, scald and burn, and chronic eczema [383]. The herb was also applied to cease traumatic bleeding, attacking toxin and parasites [383]. Gambogic acid is the major active ingredient of *Garcinia hanburyi* biologically alleviating pain, inflammation, and fever [384]. Recent investigations strongly suggest that gambogic acid is anti-tumor in nature by suppressing the proliferation of cancers of lung [385], liver [385], blood [386] and stomach [387]. Further studies revealed that gambogic acid triggered autophagy and ameliorated bladder cancer by modulating the beclin-1, p62 and NF-κB activities [168]. By up-regulating the beclin-1 expression, gambogic acid induced cytotoxic in leukemia cells through the induction of autophagy and apoptosis [169]. Apparently, *Garcinia hanburyi* and gambogic acid have the potential to be further developed as novel and effective anti-cancer therapeutic strategy. It is also important to verify if autophagy is mechanistically mediating the *Garcinia hanburyi*-induced inflammatory and immunological regulations.

3.4.10. Spirit Calming Drugs

These herbs can be used to treat mental syndromes related to heart (blood and yin) deficiency such as over-activity of the heart, nervousness, fright, restlessness, irritability, insomnia, palpitations or anxiety; or treat syndromes related to liver (yin and yang) deficiency such as dizziness and headaches. This group of drugs is also prescribed to pacify internal wind which can contribute to tremor, spasms, paraesthesias of the limbs, dizziness or difficulties in walking [115,276].

*Radix polygalae* (RP) (Yuan zhi) is commonly prescribed in many classical decoctions such as “Kai Xin San” [388], and “Ding Zhi Wan” [389] for the treatment of forgetfulness [390], anxiety [391], insomnia or depression [392]. Recent pharmacological studies have also reported the sedative-hypnotic [391], memory improving [390], cognitive recognition enhancing [393], antidepressant [392] and neuroprotective effects [170] of RP. RP was reported to inhibit the phosphatidylinositol 3-kinase (PI3K)/Akt or activate the N-methyl-D-aspartate (NMDA) signaling pathways [394,395]. The active ingredients of RP such as onjisaponin B and other identified saponins, were proved to accelerate the clearance of neurodegenerative disease proteins such as huntingtin and α-synuclein, reduce aggregation and toxicity of mutant proteins through the induction of autophagy [170,396]. Therefore, RP may play its traditional sedative effect through degradation of unwanted proteins or organelles by autophagy.

*Ganoderma lucidum* (Ling zhi) is having efficacy in replenishing qi, stabilizing the nervous system and relieving cough and asthma, is commonly prescribed to treat insomnia, palpitation, cough and
phlegm. It exerts tranquilizing effects through tonifying the heart, qi and blood. Triterpenes are the major components of *Ganoderma lucidum*. Pharmacological studies have demonstrated that both *Ganoderma lucidum* extract and ganoderic acid C2 could reduce accumulation of mutant huntingtins in PC-12 cells, alleviate neurotoxicity and behavioral deficits induced by 3-nitropropionic acid, and prevent or reverse memory loss resulting from sleep deprivation [171]. Additionally, it was also reported that *Ganoderma lucidum* triterpene extract (GLT) suppressed the proliferation of human colon cancer cells and inhibited tumor growth in a xenograft model, which were associated with the induction of autophagic cell death [397]. Furthermore, ganoderic acid activated autophagy, which facilitates immune recognition of CD4+ T cells; induced autophagic cell death and apoptosis of melanoma [398] *Ganoderma lucidum* triterpene extract induced autophagy which inhibited the development of colon cancer via p38 MAPK signaling [397]; and suppressed gastric cancer cells through the repression of p62 [399]. All these findings suggest that the traditional therapeutic role of *Ganoderma lucidum* is in part related to autophagy regulation, which may also be responsible for the novel use of the herb in cancer treatment.

*Caulis polygoni multiflori* (Shou wu teng) has been prescribed for nourishing blood, tranquilizing the mind and dispersing wind to treat insomnia, numbness of the skin and rheumatism in traditional Chinese medicine. It was often combined with *Semen ziziphi spinosae* (Suan zao ren) and *Cortex albiziae* (He huan pi) to treat insomnia, distraughtness and dizziness. Modern pharmacological study has suggested an effect of *Caulis polygoni multiflori* extract in protecting rats against CCl4-induced hepatotoxicity through its antioxidant activities [400]. The major active ingredients of Shou Wu Teng, anthraquinones, possessed similar chemical structures but different bioactivities. For example, emodin, the most abundant anthraquinone in rhubarb, inhibits cellular proliferation and prevents metastasis of cancers through apoptosis. Another major anthraquinone in rhubarb, rhein, inhibits the uptake of glucose and leads to cancer cell death caused by changes in membrane-associated functions [401]. Anthraquinone-containing extract of Shou Wu Teng possesses myocardial protective effects by maintaining antioxidant status under oxidative stress conditions [402]. Abnormal aggregation of tau protein is highly correlated with the pathogenesis of Alzheimer’s disease (AD), therefore, with the ability in mitigating aggregation and cytotoxicity of tau [403] anthraquinones possesses high potential in modulating AD. Together with the fact that an anthraquinone were able to induce autophagic cell death in cancer cells [172], Shou Wu Teng may exert its traditional sedative function through the induction of autophagy, which was highly related to the modulation of neurodegenerative disease proteins, as well as cancers [172].

*Fructus schisandrae* (Wu wei zi) has been prescribed to replenish qi, nourish the kidneys and tranquilize the mind to produce a sedative nephroprotective effect. Besides, SC extract was co-administered with other medicine for reducing immunosuppressive drug (cyclosporine A)-induced side effects [404]. Schisandra total lignin (STL), the major active ingredient of *Fructus schisandrae*, delayed mouse brain aging by attenuating apoptosis [405]. In vivo experiments further demonstrated STL inhibited the D-galactose-induced brain tissue aging through regulating autophagy and inhibiting apoptosis in the mice. It has been reported that longevity-promoting regimens such as caloric restriction or inhibition of TOR is associated with induction of autophagy [173]. Therefore, autophagy may be the mechanism responsible for the sedative and anti-ageing effect of *Fructus schisandrae*.

*Semen ziziphi spinosae* (Suan zao ren) is commonly prescribed as “suan zao ren tang” for sedation, nourishing the nerves, insomnia, palpitations, anxiety, dizziness, dry mouth and throat, red tongue, and clinical treatment of neurasthenia, heart neurosis and menopausal syndrome due to deficiencies of the heart and liver [406,407]. The active component of *Semen ziziphi spinosae*, jujuboside B, was reported to inhibit platelet aggregation and target cardiovascular diseases associated with platelet hyperaggregation [408]. Furthermore, the anti-tumor activity of jujuboside B was reported to be associated with the induction of apoptosis and autophagy [409]. Another active neuroprotective component from *Semen ziziphi spinosae*, jujuboside A, could mitigate learning and memory impairment in mice, by reducing the level of Aβ1-42, and inhibiting the activities of acetylcholinesterase (AChE) and
NO in the hippocampus and cerebral cortex of mice [410]. With its traditional effects in tranquilizing the mind and nourishing heart, blood and qi, current pharmacological studies have confirmed the neuroprotective and autophagic role of Semen ziziphi spinosae. As autophagy was highly correlated to the maintenance of cellular homeostasis, which was important for normal function of brain, autophagy may be responsible for the pharmacological action and sedative effects of Semen ziziphi spinosae.

Succinum (Ambrum) has been prescribed for relieving convulsion, tranquilizing the mind, activating blood and removing stasis, inducing diuresis, treating irritability, epilepsy, algomenorrhea and amenorrhea in TCM [411]. It was commonly prescribed with Rhizoma acori graminei (Shi Chang Pu) and Radix polygalae (Yuen Zhi) in “Hu Po Ding Zhi Wan” for treating palpitations, insomnia and forgetfulness [412]. Vitamin E succinate (VES), one of the active components of ambrum, was proved to induce autophagy via the inhibition of mTOR [174]. Besides, VES worked as an anti-neoplastic agent through regulating apoptosis in cancer cells [413]. As autophagy is also highly correlated with modulation of cancers, with the recently identified anti-cancer effect of jujuboside B and VES through induction of autophagy, both Semen ziziphi spinosae and Ambrum may possess new applications in anti-cancer therapy via its traditional tranquilizing effect, which was highly associated with the beneficial effect of autophagy. In addition, the Chinese medicinal herbs including Nelumbo nucifera, Rhizoma acori graminei, Radix salviae miltiorrhizae and Radix ginseng also participate in tranquilization of the mind [414]. Nelumbo nucifera treats palpitations, insomnia and dreamful sleep [415] in TCM. It is commonly prescribed as a formulation with Radix polygalae, Semen ziziphi spinosae and Radix salviae miltiorrhizae. The active component of Nelumbo nucifera, neferine, was identified as a novel autophagic enhancer which facilitates the degradation of mutant neurodegenerative disease proteins in vitro [134]. With the beneficial effect of autophagy in maintaining normal homeostasis in cells, sedative TCMs may play protective role in neurodegenerative diseases, through the removal of disease proteins by autophagy.

4. Current Clinical Application and Limitation in Applying Autophagic Modulators in Therapies

Preclinical or clinical models showed that pharmacological inhibition of autophagy can enhance the sensitivity of tumor cells towards multiple anti-cancer drugs. For example, inhibition of autophagy enhanced apoptosis induced by cetuximab [416] or vorinostat [417]. While CQ enhanced the therapeutic efficacy of saracatinib [418] in prostate cancer xenograft model, inhibition by 3-MA increased fluorouracil (5-FU) [419] induced apoptosis with tumor regression in colon cancer xenografts. Among these autophagy inhibitors, only CQ or HCQ were studied in humans as they cross the blood-brain barrier with HCQ much preferred to human due to the less severe side effects [420].

Based on these preclinical data, phase I or II trials were performed to evaluate the combinational use of autophagy inhibitors (HCQ or CQ) with various anti-cancer cytotoxic agents. However, there are limitations for their use in clinical practice due to the long half-life and high effective concentration of HCQ. A phase I trial was performed to evaluate the combined use of HCQ with temozolomide [421] and radiation in glioblastoma patients. Phase I or II clinical trials evaluating the combination use of bortezomib and CQ [422] are ongoing in patients with recurrent carcinoma. A phase I trial of 2-deoxyglucose [423], an agent that blocks glucose metabolism, showed a reduction in autophagy, suggesting the role of autophagy in cancer therapy.

Similarly, the clinically used mood stabilizers lithium (valproate and carbamazepine) [73], induce mTOR-independent autophagy and enhance the cellular degradation of aggregate-prone mutant huntingtin and α-synuclein. The hypertensive agent rilmenidine [424], a US Food and Drug Administration–approved compound, showed protective effect in Huntington’s disease models and is now under further clinical trials. Protein phosphatase 2A (PP2A) agonists [425] which favor induction of autophagy are currently under clinical trials for Alzheimer’s disease. The clinically used approved antidiabetic drug, metformin [426], attenuates disease development in some neurodegenerative diseases via AMPK activation.
2-Hydroxypropyl-β-cyclodextrin [427], effective in enhancing the clearance of lipids or autophagic substrate burden, can mitigate neurological deficits in an NPC mouse model and is currently under early clinical trials for treating NPC. Another lipofuscinolytic agent, centrophenoxine [428], is an anti-aging antioxidant which possesses potential protective effect for late-stage dementia in small early clinical trials. However, factors such as blood–brain barrier penetration power of the compounds and cellular heterogeneity of brain tissue can also affect the clinical neuroprotective efficacy of autophagy drugs. For example, the different responses of neurons and glia to autophagy or drug must be considered in clinical trial evaluations [429].

Although the molecular mechanisms and functions of many autophagy modulators isolated from CHM were intensively studied, we are still far away from translating these traditional herbs or compounds into clinical applications. Knowledge concerning autophagy research is mainly related to non-selective autophagy describing the molecular responses upon starvation. However, increasing studies are evidencing the significance of selective autophagy which involves specific molecular mediators targeting particular kinds of unwanted intracellular materials [430,431]. Therefore, it is important to clarify the potential discrepancies between selective and non-selective autophagy in terms of their response towards different therapeutic agents. On the other hand, the time of starting the autophagy modulatory treatment should also be considered. For example, early cancer development is likely to be prevented by autophagy induction, as cancer cells exploit nutrients generated by autophagy to survive under the stressful cellular environment at the later stages [432,433]. It is also important to take into account the cells type-specific property of autophagy which may otherwise minimize the efficacy of the applied herbs, and result in unfavourable side effects. The heterogeneous cell types as presented by hepatic lobules can well explain such a scenario. The liver consists mainly of parenchymal cells (hepatocytes) and around 40% of non-parenchymal cells such as hepatic stellate cells (HSCs) [434]. The functional consequences of autophagy induction on these cells vary under different diseased conditions. Autophagy of HSC activated during the end stage of chronic liver disease and hepatic fibrosis could be alleviated by autophagy repression in vitro [435–437]. In contrast, autophagy stimulation is beneficial upon most of the parenchymal cells-related hepatic malignancies. Therefore special caution would need to be taken when applying the autophagic modulators in cancer therapy.

5. Conclusions

An increasing number of Chinese herbal medicines (CHMs) have been discovered as autophagy modulators. Such autophagic-regulatory effects are therapeutically beneficial to a broad range of disorders which are consistent with their traditional usage. Interestingly, many CHM-induced autophagy findings described in this review also demonstrate novel applications in various pathological conditions. These potential therapeutic functions can be summarized into: (1) anti-cancer; (2) neuroprotective; (3) cardiovascular-protective; and (4) antiviral applications. For example, through the activation of autophagic cell death, tumorigeneses can be repressed by Cortex phellodendri, Radix sophorae lavescentis, Radix isatidis, and Stephania japonica which are not associated with cancer therapy according to Chinese herbology. In fact, a plethora of CHMs having similar potential in preventing cancer progression have not been studied before. These herbs include Nelumbo nucifera, Syzygium samarangense, Mallotus philippensis, Rhizoma anemarrhenae, Radix glehniae, Radix ophiopogonis, Radix glycyrrhizae, Radix dipsaci, Radix ginseng, Radix codonopsis, Rhizoma atractylodis macrocephalae, Ganoderma lucidum, Radix bupleuri, Rhizoma zingiberis recens, Radix tripterigii wilfordii, Radix stephaniae tetrandrae, Rhizoma alismatis, Cortex magnoliae officinalis, Fructus piperis longi, Radix salviae miltiorrhizae, Rhizoma chuanxiong, Garcinia hanburyi, Radix plumbaginis zeylanicae, and Fructus evodiae. In contrast, Fructus evodiae can inhibit autophagic cell death of influenza-infected cells which provides insight to the search of CHMs sharing such anti-viral properties. In the case of neurodegenerative disorders, Nelumbo nucifera, Mallotus philippensis, Rhizoma anemarrhenae, Radix ginseng, Radix tripterigii wilfordii, and Rhizoma curcumae longae can trigger previously unidentified autophagy-mediated neuronal
survival. These groups of novel neuroprotective herbs may help remove misfolded protein aggregates via autophagy activation. Also, *Rhizoma polygoni cuspidate* can upregulate the cardiac myocytic autophagy to eliminate damaged proteins uncovering the innovative use of the herb in cardiovascular disorders. It should also be noted that a single CHM usually contain more than one bioactive component. Therefore, the downstream molecular networks modulated by these CHMs are complicated. Precise investigations concerning how CHMs may influence the intricate autophagy machinery is needed, and will be a major challenge for further developing CHM as practical autophagy regulators.

When compared with Western medicines, most of the reviewed autophagy modulators here are bioactive components constituting the CHMs, which have long been prescribed as decoctions or formulations in the Chinese community with well-known pharmacological action, toxicity or side effects. Therefore, clinical trials using these natural herbs may be more safe and reliable. Also, the philosophy of CHM emphasizes the comprehensive and persistent body balance, which tailors them to deal with the autophagy-related diseases, which are pathologically associated with the loss of overall cellular and physiological balance. In addition, the actions of CHM are usually multi-targeting [307,438], making them suitable medications for autophagy-related disorders which are usually polysymptomatic. Therefore, detailed and systematic investigation concerning the interaction between CHMs and autophagy-related disorders in a comprehensive molecular approach is needed. Positive findings in these areas could widen the scope of CHM applications by suggesting novel intervention strategies, which have not been mentioned in the traditional Chinese pharmacopeia.

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**Abbreviations**

The following abbreviations are used in this manuscript:

- **CHM**: Chinese herbal medicine
- **CHMs**: Chinese herbal medicines
- **COPD**: Chronic obstructive pulmonary disease
- **SLE**: Systemic lupus erythematosus
- **RA**: Rheumatoid arthritis
- **MS**: Multiple sclerosis
- **CQ**: Chloroquine
- **HCQ**: Hydroxychloroquine
- **GAIP**: Gα interacting protein
- **MEK1/2**: Mitogen-activated protein kinase kinase
- **Vps34**: Class III PtdIns3K
- **DAPK**: Death-associated protein kinase
- **mTORC1 and 2**: Target of rapamycin complexes 1 and 2
- **PIP<sub>2</sub>**: Phosphorylates phosphatidylinositol (4,5)-bisphosphate
- **PIP<sub>3</sub>**: Phosphatidylinositol (3,4,5)-bisphosphate
- **Liver kinase B1**: LKB1 kinase
- **Htt**: Huntingtin
- **ATG**: Autophagy-related proteins
- **ROS**: Reactive oxygen species
| Abbreviation | Full Form |
|--------------|-----------|
| ERK          | Extracellular signal-regulated kinases |
| TSC          | Tuberous Sclerosis Complex |
| AD           | Alzheimer’s Disease |
| PD           | Parkinson’s Disease |
| HD           | Huntington disease |
| IMPase       | Inositol monophosphatase |
| AICAR        | 5-aminoimidazole-4-carboxamide riboside |
| SREBP-1c     | Sterol regulatory element-binding protein 1c |
| Mtb          | Mycobacterium tuberculosis |
| HIV          | Human immunodeficiency virus |
| JNK          | c-Jun N-terminal kinase |
| NOS          | Nitric oxide synthase |
| TNF          | Tumor necrosis factor |
| AS           | Atherosclerosis |
| NF-κB        | Nuclear factor-κB |
| BMP-2        | Bone morphogenetic protein-2 |
| SARS         | Severe acute respiratory syndrome |
| SOD          | Superoxide dismutase |
| COX-2        | Cyclooxygenase-2 |
| VOA          | Voacamine |
| P-gp         | P-glycoprotein |
| OP           | Ophiopogonin |
| BBB          | Blood brain barrier |
| Ssd          | Saikosaponin-d |
| LPS          | Lipopolysaccharide |
| GABA         | γ-aminobutyric acid |
| Nrf2         | Nuclear factor E2-related factor 2 |
| HO-1         | Heme oxygenase-1 |
| NMDA         | N-methyl-D-aspartate |
| PI3K         | Phosphatidylinositol 3-kinase |
| GLT          | Ganoderma lucidum triterpene extract |
| STL          | Schisandra total lignin |
| AChE         | Acetylcholinesterase |
| VES          | Vitamin E succinate |
| 5-FU         | Fluorouracil |
| PP2A         | Protein phosphatase 2A |
| HSCs         | Hepatic stellate cells |
| LA           | Licochalcone A |
| AMPK         | 5′ adenosine monophosphate-activated protein kinase |
| CaMKKβ       | Ca^{2+}/calmodulin-dependent kinase kinase β |
| mTOR         | mammalian target of rapamycin |
| NPC          | Nasopharyngeal carcinoma |
| RP           | Radix polygalae |
| SNF1         | Sucrose non-fermenting 1 |
| p70 S6K      | p70 ribosomal protein S6 kinase |

References

1. Feng, Y.; He, D.; Yao, Z.; Klionsky, D.J. The machinery of macroautophagy. *Cell Res.* 2014, 24, 24–41. [CrossRef] [PubMed]
2. Itakura, E.; Mizushima, N. Characterization of autophagosome formation site by a hierarchical analysis of mammalian atg proteins. *Autophagy* **2010**, *6*, 764–776. [CrossRef] [PubMed]

3. Mizushima, N.; Yoshimori, T.; Levine, B. Methods in mammalian autophagy research. *Cell* **2010**, *140*, 313–326. [CrossRef] [PubMed]

4. Shen, H.M.; Codogno, P. Autophagic cell death: Loch ness monster or endangered species? *Autophagy* **2011**, *7*, 457–465. [CrossRef] [PubMed]

5. Galluzzi, L.; Vicencio, J.M.; Kepp, O.; Tasdemir, E.; Maiuri, M.C.; Kroemer, G. To die or not to die: That is the autophagic question. *Curr. Mol. Med.* **2008**, *8*, 78–91. [PubMed]

6. Maiuri, M.C.; Zalckvar, E.; Kimchi, A.; Kroemer, G. Self-eating and self-killing: Crosstalk between autophagy and apoptosis. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 741–752. [CrossRef] [PubMed]

7. Kroemer, G.; Levine, B. Autophagic cell death: The story of a misnomer. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 1004–1010. [CrossRef] [PubMed]

8. Kuballa, P.; Nolte, W.M.; Castoreno, A.B.; Xavier, R.J. Autophagy and the immune system. *Annu. Rev. Immunol.* **2012**, *30*, 611–646. [CrossRef] [PubMed]

9. Levine, B.; Deretic, V. Unveiling the roles of autophagy in innate and adaptive immunity. *Nat. Rev. Immunol.* **2007**, *7*, 767–777. [CrossRef] [PubMed]

10. Mok, S.W.; Riemer, C.; Madela, K.; Hsu, D.K.; Liu, F.T.; Gultner, S.; Heise, I.; Baier, M. Role of galectin-3 in prion infections of the cns. *Biochem. Biophys. Res. Commun.* **2007**, *359*, 672–678. [CrossRef] [PubMed]

11. Wolfe, D.M.; Lee, J.H.; Kumar, A.; Lee, S.; Orenstein, S.J.; Nixon, R.A. Autophagy failure in Alzheimer’s disease and the role of defective lysosomal acidification. *Eur. J. Neurosci.* **2013**, *37*, 1949–1961. [CrossRef] [PubMed]

12. Lynch-Day, M.A.; Mao, K.; Wang, K.; Zhao, M.; Klionsky, D.J. The role of autophagy in Parkinson’s disease. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a009357. [CrossRef] [PubMed]

13. Greene, N.P.; Lira, V.A.; Yan, Z. Atg6 deficiency exacerbates glucose intolerance in mice on high-fat diet. *FASEB J.* **2012**, *26*, 869–918.

14. Xiong, X.; Tao, R.; DePinho, R.A.; Dong, X.C. The autophagy-related gene 14 (Atg14) is regulated by forkhead box o transcription factors and circadian rhythms and plays a critical role in hepatic autophagy and lipid metabolism. *J. Biol. Chem.* **2012**, *287*, 39107–39114. [CrossRef] [PubMed]

15. Nunez, C.E.; Rodrigues, V.S.; Gomes, F.S.; Moura, R.F.; Victorio, S.C.; Bombassaro, B.; Chaim, E.A.; Pareja, J.C.; Geloneze, B.; Velloso, L.A.; et al. Defective regulation of adipose tissue autophagy in obesity. *Int. J. Obes.* **2013**, *37*, 1473–1480. [CrossRef] [PubMed]

16. Chatterjee, C.; Sparks, D.L. Extracellular nucleotides inhibit insulin receptor signaling, stimulate autophagy and control lipoprotein secretion. *PLoS ONE* **2012**, *7*, e36916. [CrossRef] [PubMed]

17. Jung, H.S.; Lee, M.S. Macroautophagy in homeostasis of pancreatic β-cell. *Autophagy* **2009**, *5*, 241–243. [CrossRef] [PubMed]

18. Levine, B.; Kroemer, G. Autophagy in the pathogenesis of disease. *Cell* **2008**, *132*, 27–42. [CrossRef] [PubMed]

19. Melendez, A.; Tallozcy, Z.; Seaman, M.; Eskelinen, E.L.; Hall, D.H.; Levine, B. Autophagy genes are essential for dauer development and life-span extension in *C. elegans*. *Science* **2003**, *301*, 1387–1391. [CrossRef] [PubMed]

20. Colman, R.J.; Anderson, R.M.; Johnson, S.C.; Kastman, E.K.; Kosmatka, K.J.; Beasley, T.M.; Allison, D.B.; Cruzen, C.; Simmons, H.A.; Kemnitz, J.W.; et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* **2009**, *325*, 201–204. [CrossRef] [PubMed]

21. Iqbal, J.; Kucuk, C.; Deleeuw, R.J.; Srivastava, G.; Tam, W.; Geng, H.; Klinkebiel, D.; Christman, J.K.; Patel, K.; Cao, K.; et al. Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies. *Leukemia* **2009**, *23*, 1139–1151. [CrossRef] [PubMed]

22. Qu, X.; Yu, J.; Bhagat, G.; Furuya, N.; Hibshoosh, H.; Troxel, A.; Rosen, J.; Eskelinen, E.L.; Mizushima, N.; Ohsumi, Y.; et al. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. *J. Clin. Invest.* **2003**, *112*, 1809–1820. [CrossRef] [PubMed]

23. Huang, X.; Bai, H.M.; Chen, L.; Li, B.; Lu, Y.C. Reduced expression of LC3B-II and beclin 1 in glioblastoma multiforme indicates a down-regulated autophagic capacity that relates to the progression of astrocytic tumors. *J. Clin. Neurosci.* **2010**, *17*, 1515–1519. [CrossRef] [PubMed]
24. Buzzai, M.; Jones, R.G.; Amaravadi, R.K.; Lum, J.J.; DeBerardinis, R.J.; Zhao, F.; Viollet, B.; Thompson, C.B. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. Cancer Res. 2007, 67, 6745–6752. [CrossRef] [PubMed]

25. Wong, V.K.; Li, T.; Law, B.Y.; Ma, E.D.; Yip, N.C.; Michaelangelis, F.; Law, C.K.; Zhang, M.M.; Lam, K.Y.; Chan, P.L.; et al. Saikosaponin-d, a novel SERCA inhibitor, induces autophagic cell death in apoptosis-defective cells. Cell Death Dis. 2013, 4, e720. [CrossRef] [PubMed]

26. Law, B.Y.; Chan, W.K.; Xu, S.W.; Wang, J.R.; Bai, L.P.; Liu, L.; Wong, V.K. Natural small-molecule enhancers of autophagy induce autophagic cell death in apoptosis-defective cells. Sci. Rep. 2014, 4, 5510. [CrossRef] [PubMed]

27. Fan, X.X.; Yao, X.J.; Xu, S.W.; Wong, V.K.; He, J.X.; Ding, J.; Xue, W.W.; Mujtaba, T.; Michaelangelis, F.; Huang, M.; et al. (Z)3,4,5,4′-trans-tetramethoxystilbene, a new analogue of resveratrol, inhibits gefitinib-resistant non-small cell lung cancer via selectively elevating intracellular calcium level. Sci. Rep. 2015, 5, 16348. [CrossRef] [PubMed]

28. Ryter, S.W.; Chen, Z.H.; Kim, H.P.; Choi, A.M. Autophagy in chronic obstructive pulmonary disease: Homeostatic or pathogenic mechanism? Autophagy 2009, 5, 235–237. [CrossRef] [PubMed]

29. Zhou, X.J.; Zhang, H. Autophagy in immunity: Implications in etiology of autoimmune/autoinflammatory diseases. Autophagy 2012, 8, 1286–1299. [CrossRef] [PubMed]

30. Deretic, V. Autophagy in immunity and cell-autonomous defense against intracellular microbes. Immunol. Rev. 2011, 240, 92–104. [CrossRef] [PubMed]

31. Page, N.; Gros, F.; Schall, N.; Decossas, M.; Bagnard, D.; Briand, J.P.; Muller, S. Hsc70 blockade by the therapeutic peptide p140 affects autophagic processes and endogenous mhcii presentation in murine lupus. Ann. Rheum. Dis. 2011, 70, 837–843. [CrossRef] [PubMed]

32. Monneaux, F.; Muller, S. Molecular therapies for systemic lupus erythematosus: Clinical trials and future prospects. Arthritis Res. Ther. 2009, 11, 1–10. [CrossRef] [PubMed]

33. Alinari, L.; Mahoney, E.; Patton, J.; Zhang, X.; Huynh, L.; Earl, C.T.; Mani, R.; Mao, Y.; Yu, B.; Quinion, C.; et al. FTY720 increases CD74 expression and sensitizes mantle cell lymphoma cells to milatuzumab-mediated cell death. Blood 2011, 118, 6893–6903. [CrossRef] [PubMed]

34. Gros, F.; Muller, S. Pharmacological regulators of autophagy and their link with modulators of lupus disease. Br. J. Pharmacol. 2014, 171, 4337–4359. [CrossRef] [PubMed]

35. Okazaki, H.; Hirata, D.; Kamimura, T.; Sato, H.; Iwamoto, M.; Yoshio, T.; Masuyama, J.; Fujimura, A.; Kobayashi, E.; Kano, S.; et al. Effects of FTY720 in MRL-lpr/lpr mice: Therapeutic potential in systemic lupus erythematosus. J. Rheumatol. 2002, 29, 707–716. [PubMed]

36. Law, B.Y.; Mo, J.F.; Wong, V.K. Autophagic effects of Chaihu (dried roots of Bupleurum Chinense DC or Bupleurum scorzoneraefolium WILD). Chin. Med. 2014, 9, 21. [CrossRef] [PubMed]

37. Cao, J.; Miao, Q.; Miao, S.; Li, B.; Zhang, S.; Yang, Q.; Zhou, X.; Zhang, M.; Xie, Y.; Zhang, J.; et al. Tetramethylpyrazine (TMP) exerts antitumor effects by inducing apoptosis and autophagy in hepatocellular carcinoma. Int. Immunopharmac. 2015, 26, 212–220. [CrossRef] [PubMed]

38. Li, X.; Li, X.; Wang, J.; Ye, Z.; Li, J.C. Oridonin up-regulates expression of p21 and induces autophagy and apoptosis in human prostate cancer cells. Int. J. Biol. Sci. 2012, 8, 901–912. [CrossRef] [PubMed]

39. Morselli, E.; Marino, G.; Bennetzen, M.V.; Eisenberg, T.; Megalou, E.; Schroeder, S.; Cabrera, S.; Benit, P.; Rustin, P.; Cirollo, A.; et al. Spermidine and resveratrol induce autophagy by distinct pathways converging on the acetylpotriome. J. Cell Biol. 2011, 192, 615–629. [CrossRef] [PubMed]

40. Huang, Z.; Ye, B.; Dai, Z.; Wu, X.; Lu, Z.; Shan, P.; Huang, W. Curcumin inhibits autophagy and apoptosis in hypoxia/reoxygenation-induced myocytes. Mol. Med. Rep. 2015, 11, 4678–4684. [CrossRef] [PubMed]

41. Chang, K.H.; Yan, M.D.; Yao, C.J.; Lin, P.C.; Lai, G.M. Honokiol-induced apoptosis and autophagy in glioblastoma multiforme cells. Oncol. Lett. 2013, 6, 1435–1438. [PubMed]

42. Meng, X.; Wang, M.; Sun, G.; Ye, J.; Zhou, Y.; Dong, X.; Wang, T.; Lu, S.; Sun, X. Attenuation of Aβ25–35-induced parallel autophagic and apoptotic cell death by gypenoside XVII through the estrogen receptor-dependent activation of Nrf2/are pathways. Toxicol. Appl. Pharmacol. 2014, 279, 63–75. [CrossRef] [PubMed]

43. Ogier-Denis, E.; Pattingre, S.; El Benna, J.; Codogno, P. Erk1/2-dependent phosphorylation of Ga-interacting protein stimulates its GTPase accelerating activity and autophagy in human colon cancer cells. J. Biol. Chem. 2000, 275, 39090–39095. [CrossRef] [PubMed]
44. Ogier-Denis, E.; Couvineau, A.; Maoret, J.J.; Houri, J.J.; Bauvy, C.; De Stefani, D.; Isidoro, C.; Laburthe, M.; Codogno, P. A heterotrimeric G-protein controls autophagic sequestration in the human colon cancer cell line HT-29. *J. Biol. Chem.* 1995, 270, 13–16. [CrossRef] [PubMed]

45. Pattingre, S.; Bauvy, C.; Codogno, P. Amino acids interfere with the Erk1/2-dependent control of macroautophagy by controlling the activation of Raf-1 in human colon cancer HT-29 cells. *J. Biol. Chem.* 2003, 278, 16667–16674. [CrossRef] [PubMed]

46. Vanhaecke, B.; Leevers, S.J.; Ahmadi, K.; Timms, J.; Katso, R.; Driscoll, P.C.; Woscholski, R.; Parker, P.J.; Waterfield, M.D. Synthesis and function of 3-phosphorylated inositol lipids. *Annu. Rev. Biochem.* 2001, 70, 535–602. [CrossRef] [PubMed]

47. Kihara, A.; Kabeya, Y.; Ohsumi, Y.; Yoshimori, T. Beclin-phosphatidylinositol 3-kinase complex functions at the trans-golgi network. *EMBO Rep.* 2001, 2, 330–335. [CrossRef] [PubMed]

48. Lindmo, K.; Stenmark, H. Regulation of membrane traffic by phosphoinositide 3-kinases. *Cell Biol.* 2007, 22, 214–226. [CrossRef] [PubMed]

49. Liang, X.H.; Jackson, S.; Seaman, M.; Brown, K.; Kempkes, B.; Hibshoosh, H.; Levine, B. Induction of autophagy and inhibition of tumorigenesis by beclin 1. *Nature* 1999, 402, 672–676. [PubMed]

50. Wei, Y.; Pattingre, S.; Sinha, S.; Bassik, M.; Levine, B. JNK1-mediated phosphorylation of Bcl-2 regulates AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Mol. Cell* 2010, 32, 218–226. [CrossRef] [PubMed]

51. Zalckvar, E.; Berissi, H.; Mizrachy, L.; Idelchuk, Y.; Koren, I.; Eisenstein, M.; Sabanay, H.; Pinkas-Kramarski, R.; Kimchi, A. DAP kinase-mediated phosphorylation on the BH3 domain of beclin 1 promotes dissociation of beclin 1 from Bcl-XL and induction of autophagy. *EMBO Rep.* 2009, 10, 285–292. [CrossRef] [PubMed]

52. Yang, Z.; Klionsky, D.J. Eaten alive: A history of macroautophagy. *Nat. Cell Biol.* 2010, 12, 814–822. [CrossRef] [PubMed]

53. Sabatini, D.M. MTOR and cancer: Insights into a complex relationship. *Nat. Rev. Cancer* 2006, 6, 729–734. [CrossRef] [PubMed]

54. Pyo, J.O.; Nah, J.; Jung, Y.K. Molecules and their functions in autophagy. *Exp. Mol. Med.* 2012, 44, 73–80. [CrossRef] [PubMed]

55. Yang, Z.; Klionsky, D.J. Mammalian autophagy: Core molecular machinery and signaling regulation. *Curr. Opin. Cell Biol.* 2010, 22, 124–131. [CrossRef] [PubMed]

56. Hardie, D.G.; Hawley, S.A. Amp-activated protein kinase: The energy charge hypothesis revisited. *Bioessays* 2001, 23, 1112–1119. [CrossRef] [PubMed]

57. Hardie, D.G. AMP-activated/SNF1 protein kinases: Conserved guardians of cellular energy. *Nat. Rev. Mol. Cell Biol.* 2007, 8, 774–785. [CrossRef] [PubMed]

58. Liang, J.; Shao, S.H.; Xu, Z.X.; Hennessy, B.; Ding, Z.; Larrea, M.; Kondo, S.; Dumont, D.J.; Gutterman, J.U.; Walker, C.L.; et al. The energy sensing LKB1-AMPK pathway regulates p27kip1 phosphorylation mediating the decision to enter autophagy or apoptosis. *Nat. Cell Biol.* 2007, 9, 218–224. [CrossRef] [PubMed]

59. Gwinn, D.M.; Shackelford, D.B.; Egan, D.F.; Mihaylova, M.M.; Mery, A.; Vasquez, D.S.; Bassik, M.; Levine, B. The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature* 2006, 443, 780–786. [CrossRef] [PubMed]

60. Rubinsztein, D.C. Control of macroautophagy by calcium, calmodulin-dependent kinase-β, and Bcl-2. *Mol. Cell* 2007, 25, 193–205. [CrossRef] [PubMed]

61. Hoyer-Hansen, M.; Bastholm, L.; Sznitarski, P.; Campanela, M.; Szabadkai, G.; Farkas, T.; Bianchi, K.; Feihenbacher, N.; Elling, F.; Rizzuto, R.; et al. Control of macroautophagy by calcium, calmodulin-dependent kinase-β, and Bcl-2. *Mol. Cell* 2007, 25, 193–205. [CrossRef] [PubMed]

62. Rubinsztein, D.C. The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature* 2006, 443, 780–786. [CrossRef] [PubMed]

63. Makin, O.S.; Serpell, L.C. Examining the structure of the mature amyloid fibril. *Biochem. Soc. Trans.* 2002, 30, 521–525. [CrossRef] [PubMed]

64. Nelson, R.; Sawaya, M.R.; Balbirnie, M.; Madsen, A.O.; Riekel, C.; Grothe, R.; Eisenberg, D. Structure of the cross-β spine of amyloid-like fibrils. *Nature* 2005, 435, 773–778. [CrossRef] [PubMed]

65. Komatsu, M.; Waguri, S.; Chiba, T.; Murata, S.; Iwata, J.; Tanida, I.; Ueno, T.; Koike, M.; Uchiyama, Y.; Kominami, E.; et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* 2006, 441, 880–884. [CrossRef] [PubMed]
66. Hara, T.; Nakamura, K.; Matsui, M.; Yamamoto, A.; Nakahara, Y.; Suzuki-Migishima, R.; Yokoyama, M.; Mishima, K.; Saito, I.; Okano, H.; et al. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature* 2006, 441, 885–889. [CrossRef] [PubMed]

67. Tycko, R. Molecular structure of amyloid fibrils: Insights from solid-state NMR. *Q. Rev. Biophys.* 2006, 39, 1–55. [CrossRef] [PubMed]

68. Pickford, F.; Masliah, E.; Britschgi, M.; Lucin, K.; Narasimhan, R.; Jaeger, P.A.; Small, S.; Spencer, B.; Rockenstein, E.; Levine, B.; et al. The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid β accumulation in mice. *J. Clin. Investig.* 2008, 118, 2190–2199. [CrossRef] [PubMed]

69. Spencer, B.; Potkar, R.; Trojo, M.; Rockenstein, E.; Patrick, C.; Gindi, R.; Adame, A.; Wyss-Coray, T.; Masliah, E. Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in α-synuclein models of Parkinson’s and Lewy body diseases. *J. Neurosci.* 2009, 29, 13578–13588. [CrossRef] [PubMed]

70. Shibata, M.; Lu, T.; Furuya, T.; Degterev, A.; Mizushima, N.; Yoshimori, T.; MacDonald, M.; Yankner, B.; Yuan, J. Regulation of intracellular accumulation of mutant huntingtin by beclin 1. *J. Biol. Chem.* 2006, 281, 14474–14485. [CrossRef] [PubMed]

71. Spilman, P.; Podlutskaya, N.; Hart, M.J.; Debnath, J.; Gorostiza, O.; Bredesen, D.; Richardson, A.; Strong, R.; Galvan, V. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-β levels in a mouse model of Alzheimer’s disease. *PLoS ONE* 2010, 5, e9979. [CrossRef] [PubMed]

72. Sarkar, S.; Rubinsztein, D.C. Inositol and IP3 levels regulate autophagy: Biology and therapeutic speculations. *Autophagy* 2006, 2, 132–134. [CrossRef] [PubMed]

73. Sarkar, S.; Floto, R.A.; Berger, Z.; Imarisio, S.; Cordenier, A.; Pasco, M.; Cook, L.J.; Rubinsztein, D.C. Lithium induces autophagy by inhibiting inositol monophosphatase. *J. Cell Biol.* 2005, 170, 1101–1111. [CrossRef] [PubMed]

74. Sarkar, S.; Rubinsztein, D.C. Small molecule enhancers of autophagy for neurodegenerative diseases. *Mol. Biosyst.* 2008, 4, 895–901. [CrossRef] [PubMed]

75. Williams, A.; Sarkar, S.; Cuddon, P.; Tofto, E.K.; Saiki, S.; Siddiqi, F.H.; Jähreiss, L.; Fleming, A.; Pask, D.; Goldsmith, P.; et al. Novel targets for Huntington’s disease in an mTOR-independent autophagy pathway. *Nat. Chem. Biol.* 2008, 4, 295–305. [CrossRef] [PubMed]

76. Schaeffer, V.; Lavenir, I.; Ozcelik, S.; Tolnay, M.; Winkler, D.T.; Goedert, M. Stimulation of autophagy reduces neurodegeneration in a mouse model of human tauopathy. *Brain* 2012, 135, 2169–2177. [CrossRef] [PubMed]

77. Sarkar, S.; Davies, J.E.; Huang, Z.; Tunnaciffe, A.; Rubinsztein, D.C. Trehalose, a novel mTOR-independent autophagy enhancer, accelerates the clearance of mutant huntingtin and α-synuclein. *J. Biol. Chem.* 2007, 282, 5641–5652. [CrossRef] [PubMed]

78. Boroughs, L.K.; DeBerardinis, R.J. Metabolic pathways promoting cancer cell survival and growth. *Nat. Cell Biol.* 2015, 17, 351–359. [CrossRef] [PubMed]

79. Xiang, X.; Saha, A.K.; Wen, R.; Ruderman, N.B.; Luo, Z. AMP-activated protein kinase activators can inhibit the growth of prostate cancer cells by multiple mechanisms. *Biochem. Biophys. Res. Commun.* 2004, 321, 161–167. [CrossRef] [PubMed]

80. Saitoh, M.; Nagai, K.; Nakagawa, K.; Yamamura, T.; Yamamoto, S.; Nishizaki, T. Adenosine induces apoptosis in the human gastric cancer cells via an intrinsic pathway relevant to activation of AMP-activated protein kinase. *Biochem. Pharmacol.* 2004, 67, 2005–2011. [CrossRef] [PubMed]

81. Meisse, D.; Van de Casteele, M.; Beauloye, C.; Hainault, I.; Kefas, B.A.; Rider, M.H.; Foufelle, F.; Hue, L. Sustained activation of AMP-activated protein kinase induces c-Jun N-terminal kinase activation and apoptosis in liver cells. *FEBS Lett.* 2002, 526, 38–42. [CrossRef]

82. Brown, E.J.; Albers, M.W.; Shin, T.B.; Ichikawa, K.; Keith, C.T.; Lane, W.S.; Schreiber, S.L. A mammalian protein targeted by G1-arresting rapamycin-receptor complex. *Nature* 1994, 369, 756–758. [CrossRef] [PubMed]

83. Finger, D.C.; Blenis, J. Target of rapamycin (TOR): An integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. *Oncogene* 2004, 23, 3151–3171. [CrossRef] [PubMed]

84. Easton, J.B.; Houghton, P.J. mTOR and cancer therapy. *Oncogene* 2006, 25, 6436–6446. [CrossRef] [PubMed]

85. Kung, C.P.; Budina, A.; Balaburski, G.; Bergenstock, M.K.; Murphy, M. Autophagy in tumor suppression and cancer therapy. *Crit. Rev. Eukaryot. Gene Expr.* 2011, 21, 71–100. [CrossRef] [PubMed]

86. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell* 2000, 100, 57–70. [CrossRef]
87. Hotamisligil, G.S. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 2010, 140, 900–917. [CrossRef] [PubMed]

88. Newgard, C.B.; An, J.; Bain, J.R.; Muehlbauer, M.J.; Stevens, R.D.; Lien, L.F.; Haqq, A.M.; Shah, S.H.; Arlott, M.; Slentz, C.A.; *et al*. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab.* 2009, 9, 311–326. [CrossRef] [PubMed]

89. Lammert, O.; Grunnet, N.; Faber, P.; Bjornso, K.S.; Dich, J.; Larsen, L.O.; Neese, R.A.; Hellerstein, M.K.; Quistorff, B. Effects of isoenergetic overfeeding of either carbohydrate or fat in young men. *Br. J. Nutr.* 2000, 84, 233–245. [PubMed]

90. Laplante, M.; Sabatini, D.M. mTORC1 activates SREBP-1c and uncouples lipogenesis from gluconeogenesis. *Proc. Natl. Acad. Sci. USA* 2010, 107, 3281–3282. [CrossRef] [PubMed]

91. Yang, L.; Li, P.; Fu, S.; Calay, E.S.; Hotamisligil, G.S. Defective hepatic autophagy in obesity promotes endoplasmic reticulum stress and causes insulin resistance. *Cell Metab.* 2010, 11, 467–478. [CrossRef] [PubMed]

92. Maury, E.; Ramsey, K.M.; Bass, J. Circadian rhythms and metabolic syndrome: From experimental genetics to human disease. *Circ. Res.* 2010, 106, 447–462. [CrossRef] [PubMed]

93. Talloczy, Z.; Virgin, H.W.; Levine, B. PKR-dependent autophagic degradation of herpes simplex virus type 1. *Autophagy* 2006, 2, 24–29. [CrossRef] [PubMed]

94. Mizushima, N.; Levine, B.; Cuervo, A.M.; Klionsky, D.J. Autophagy fights disease through cellular self-digestion. *Nature* 2008, 451, 1069–1075. [CrossRef] [PubMed]

95. Liang, X.H.; Kleeman, L.K.; Jiang, H.H.; Gordon, G.; Goldman, J.E.; Berry, G.; Herman, B.; Levine, B. Protection against fatal sindbis virus encephalitis by beclin, a novel Bcl-2-interacting protein. *J. Virol.* 1998, 72, 8586–8596. [PubMed]

96. Andrade, R.M.; Wessendarp, M.; Gubbels, M.J.; Striepen, B.; Subauste, C.S. CD40 induces macrophage anti-Toxoplasma gondii activity by triggering autophagy-dependent fusion of pathogen-containing vacuoles and lysosomes. *J. Clin. Investig.* 2006, 116, 2366–2377. [CrossRef] [PubMed]

97. Nakahira, K.; Haspel, J.A.; Rathinam, V.A.; Lee, S.J.; Dolinay, T.; Lam, H.C.; Englert, J.A.; Rabinovitch, M.; Cernadas, M.; Kim, H.P.; *et al*. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat. Immunol.* 2011, 12, 222–230. [CrossRef] [PubMed]

98. Saitoh, T.; Fujita, N.; Jang, M.H.; Uematsu, S.; Yang, B.G.; Satoh, T.; Omori, H.; Noda, T.; Yamamoto, N.; Komatsu, M.; *et al*. Loss of the autophagy protein Atg16l1 enhances endotoxin-induced IL-1β production. *Nature* 2008, 456, 264–268. [CrossRef] [PubMed]

99. Campbell, G.R.; Spector, S.A. Vitamin D inhibits human immunodeficiency virus type 1 and mycobacterium tuberculosis infection in macrophages through the induction of autophagy. *PLoS Pathog.* 2012, 8, e1002689. [CrossRef] [PubMed]

100. Chiu, H.C.; Soni, S.; Kulp, S.K.; Curry, H.; Wang, D.; Gunn, J.S.; Schlesinger, L.S.; Chen, C.S. Eradication of intracellular francisella tularensis in THP-1 human macrophages with a novel autophagy inducing agent. *J. Biomed. Sci.* 2009, 16, 110. [CrossRef] [PubMed]

101. Chi, H.C.; Soni, S.; Kulp, S.K.; Curry, H.; Wang, D.; Gunn, J.S.; Schlesinger, L.S.; Chen, C.S. Eradication of intracellular francisella tularensis in THP-1 human macrophages with a novel autophagy inducing agent. *J. Biomed. Sci.* 2009, 16, 110. [CrossRef] [PubMed]

102. Kim, J.J.; Lee, H.M.; Shin, D.M.; Kim, W.; Yuk, J.M.; Jin, H.S.; Lee, S.H.; Cha, G.H.; Kim, J.M.; Lee, Z.W.; *et al*. Host cell autophagy activated by antibiotics is required for their effective antimycobacterial drug action. *Cell Host Microbe* 2012, 11, 457–468. [CrossRef] [PubMed]

103. Levine, B.; Mizushima, N.; Virgin, H.W. Autophagy in immunity and inflammation. *Nature* 2011, 469, 323–335. [PubMed]

104. Kasai, M.; Tanida, I.; Ueno, T.; Kominami, E.; Seki, S.; Ikeda, T.; Mizuochi, T. Autophagic compartments gain access to the MHC class II compartments in thymic epithelium. *J. Immunol.* 2009, 183, 7278–7285. [CrossRef] [PubMed]

105. Aichinger, M.; Wu, C.; Nedjic, J.; Klein, L. Macroautophagy substrates are loaded onto MHC class II of medullary thymic epithelial cells for central tolerance. *J. Exp. Med.* 2013, 210, 287–300. [CrossRef] [PubMed]

106. Li, B.; Yue, Y.; Dong, C.; Shi, Y.; Xiong, S. Blockade of macrophage autophagy ameliorates activated lymphocytes-derived DNA induced murine lupus possibly via inhibition of proinflammatory cytokine production. *Clin. Exp. Rheumatol.* 2014, 32, 705–714. [PubMed]
106. Harr, M.W.; McColl, K.S.; Zhong, F.; Molitoris, J.K.; Distelhorst, C.W. Glucocorticoids downregulate FYN and inhibit IP(3)-mediated calcium signaling to promote autophagy in t lymphocytes. Autophagy 2010, 6, 912–921. [CrossRef] [PubMed]

107. Turzanski, J.; Daniels, I.; Haynes, A.P. Involvement of macroautophagy in the caspase-independent killing of burkitt lymphoma cell lines by rituximab. Br. J. Haematol. 2009, 145, 137–140. [CrossRef] [PubMed]

108. Wu, W.K.; Sakamoto, K.M.; Milani, M.; Aldana-Masankgay, G.; Fan, D.; Wu, K.; Lee, C.W.; Cho, C.H.; Yu, J.; Sung, J.J. Macropathology modulates cellular response to proteasome inhibitors in cancer therapy. Drug Resist Updates 2010, 13, 87–92. [CrossRef] [PubMed]

109. Elmore, S.P.; Qian, T.; Grissom, S.F.; Lemasters, J.J. The mitochondrial permeability transition initiates autophagy in rat hepatocytes. FASEB J. 2001, 15, 2286–2287. [CrossRef] [PubMed]

110. Rubinsztein, D.C.; Gestwicki, J.E.; Murphy, L.O.; Klionsky, D.J. Potential therapeutic applications of autophagy. Nat. Rev. Drug Discov. 2007, 6, 304–312. [CrossRef] [PubMed]

111. Wu, S.; Sun, J. Vitamin D, vitamin d receptor, and macroautophagy in inflammation and infection. Discov. Med. 2011, 11, 325–335. [PubMed]

112. Ma, W.W.; Jimeno, A. Temsirolimus. Drugs Today 2007, 43, 659–669. [CrossRef] [PubMed]

113. Radulovic, S.; Bjelogrlic, S.K. Sunitinib, sorafenib and mTOR inhibitors in renal cancer. Drugs Today 2007, 43, 296–304. [PubMed]

114. Huang, J.; Wu, L.J.; Tashiro, S.; Onodera, S.; Ikejima, T. Reactive oxygen species mediate oridonin-induced apoptosis and autophagy in human cervical carcinoma hela cells. J. Pharmacol. Sci. 2015, 129, 791–799. [CrossRef] [PubMed]

115. Chang, W.H.; Chen, C.H.; Lu, F.J. Different effects of baicalein, baicalin and wogonin on mitochondrial function, glutathione content and cell cycle progression in human hepatoma cell lines. Planta Med. 2002, 68, 128–132. [CrossRef] [PubMed]

116. Fan, X.; Wang, J.; Hou, J.; Lin, C.; Bensoussan, A.; Chang, D.; Liu, J.; Wang, B. Berberine alleviates ox-LDL induced inflammatory factors by up-regulation of autophagy via AMPK/mTOR signaling pathway. J. Transl. Med. 2015, 13, 92. [CrossRef] [PubMed]

117. Jeong, H.W.; Hsu, K.C.; Lee, J.W.; Ham, M.; Huh, J.Y.; Shin, H.J.; Kim, W.S.; Kim, J.B. Berberine suppresses proinflammatory responses through AMPK activation in macrophages. Am. J. Physiol. Endocrinol. Metab. 2009, 296, E955–E964. [CrossRef] [PubMed]

118. Zeng, R.; Chen, Y.; Zhao, S.; Cui, G.H. Autophagy counteracts apoptosis in human multiple myeloma cells exposed to oridonin in vitro via regulating intracellular ROS and SIRT1. Acta Pharmacol. Sin. 2012, 33, 91–100. [CrossRef] [PubMed]

119. Wu, W.K.; Sakamoto, K.M.; Milani, M.; Aldana-Masankgay, G.; Fan, D.; Wu, K.; Lee, C.W.; Cho, C.H.; Yu, J.; Sung, J.J. Macropathology modulates cellular response to proteasome inhibitors in cancer therapy. Drug Resist Updates 2010, 13, 87–92. [CrossRef] [PubMed]

120. Zhang, Y.H.; Wu, Y.L.; Tashiro, S.; Onodera, S.; Ikejima, T. Reactive oxygen species contribute to oridonin-induced apoptosis and autophagy in human cervical carcinoma hela cells. Acta Pharmacol. Sin. 2011, 32, 1266–1275. [CrossRef] [PubMed]
127. Wang, N.; Pan, W.; Zhu, M.; Zhang, M.; Hao, X.; Liang, G.; Feng, Y. Fangchinoline induces autophagic cell death via p53/sestrin2/AMPK signalling in human hepatocellular carcinoma cells. Br. J. Pharmacol. 2011, 164, 731–742. [CrossRef] [PubMed]

128. Chen, M.L.; Yi, L.; Jin, X.; Liang, X.Y.; Zhou, Y.; Zhang, T.; Xie, Q.; Zhou, X.; Chang, H.; Fu, Y.J.; et al. Resveratrol attenuates vascular endothelial inflammation by inducing autophagy through the camp signaling pathway. Autophagy 2013, 9, 2033–2045. [CrossRef] [PubMed]

129. Zhang, J.; Chiu, J.; Zhang, H.; Qi, T.; Tang, Q.; Ma, K.; Lu, H.; Li, G. Autophagic cell death induced by resveratrol depends on the Ca\textsuperscript{2+}/AMPK/mTOR pathway in A549 cells. Biochem Pharmacol. 2013, 86, 317–328. [CrossRef] [PubMed]

130. Li, J.; Qin, Z.; Liang, Z. The prosurvival role of autophagy in resveratrol-induced cytotoxicity in human u251 glioma cells. BMC Cancer 2009, 9, 215. [CrossRef] [PubMed]

131. Bui-Xuan, N.H.; Tang, P.M.; Wong, C.K.; Fung, K.P. Photo-activated pheophorbide-A, an active component of scutellaria barbata, enhances apoptosis via the suppression of ERK-mediated autophagy in the estrogen receptor-negative human breast adenocarcinoma cells MDA-MB-231. J. Ethnopharmacol. 2010, 131, 95–103. [CrossRef] [PubMed]

132. Ahn, M.Y.; Yoon, H.E.; Kwon, S.M.; Lee, J.; Min, S.K.; Kim, Y.C.; Ahn, S.G.; Yoon, J.H. Synthesized pheophorbide a-mediated photodynamic therapy induced apoptosis and autophagy in human oral squamous carcinoma cells. J. Oral Pathol. Med. 2013, 42, 17–25. [CrossRef] [PubMed]

133. Xu, D.D.; Lam, H.M.; Hoeven, R.; Xu, C.B.; Leung, A.W.; Cho, W.C. Photodynamic therapy induced cell death of hormone insensitive prostate cancer PC-3 cells with autophagic characteristics. Photodiagn. Photodyn. Ther. 2013, 10, 278–287. [CrossRef] [PubMed]

134. Wong, V.K.; Wu, A.G.; Wang, J.R.; Liu, L.; Law, B.Y. Neferine attenuates the protein level and toxicity of mutant huntingtin in PC-12 cells via induction of autophagy. Molecules 2015, 20, 3496–3514. [CrossRef] [PubMed]

135. Poornima, P.; Weng, C.F.; Padma, V.V. Neferine from nelumbo nucifera induces autophagy through the inhibition of PI3K/AKT/mTOR pathway and ros hyper generation in a549 cells. Food Chem. 2013, 141, 3598–3605. [CrossRef] [PubMed]

136. Yadav, V.R.; Prasad, S.; Aggarwal, B.B. Cardamonin sensitizes tumour cells to TRAIL through ROS- and CHOP-mediated up-regulation of death receptors and down-regulation of survival proteins. Br. J. Pharmacol. 2012, 165, 741–753. [CrossRef] [PubMed]

137. Ren, G.; Sha, T.; Guo, J.; Li, W.; Lu, J.; Chen, X. Cucurbitacin b induces DNA damage and autophagy mediated by reactive oxygen species (ROS) in MCF-7 breast cancer cells. J. Nat. Med. 2015, 69, 522–530. [CrossRef] [PubMed]

138. Ouyang, D.; Zhang, Y.; Xu, L.; Li, J.; Zha, Q.; He, X. Histone deacetylase inhibitor valproic acid sensitizes B16F10 melanoma cells to cucurbitacin b treatment. Acta Biochim. Biophys. Sin. 2011, 43, 487–495. [CrossRef] [PubMed]

139. Maioli, E.; Torricelli, C.; Valacchi, G. Rottlerin and curcumin: A comparative analysis. Ann. N. Y. Acad. Sci. 2012, 1259, 65–76. [CrossRef] [PubMed]

140. Song, K.S.; Kim, J.S.; Yun, E.J.; Kim, Y.R.; Seo, K.S.; Park, J.H.; Jung, Y.J.; Park, J.I.; Kweon, G.R.; Yoon, W.H.; et al. Rottlerin induces autophagy and apoptotic cell death through a PKC-δ-independent pathway in HT1080 human fibrosarcoma cells—The protective role of autophagy in apoptosis. Autophagy 2008, 4, 650–658. [CrossRef] [PubMed]

141. Kumar, D.; Shankar, S.; Srivastava, R.K. Rottlerin induces autophagy and apoptosis in prostate cancer stem cells via PI3K/Akt/mTOR signaling pathway. Cancer Lett. 2014, 343, 179–189. [CrossRef] [PubMed]

142. Singh, B.N.; Kumar, D.; Shankar, S.; Srivastava, R.K. Rottlerin induces autophagy which leads to apoptotic cell death through inhibition of PI3K/Akt/mTOR pathway in human pancreatic cancer stem cells. Biochem. Pharmacol. 2012, 84, 1154–1163. [CrossRef] [PubMed]

143. Lok, C.N.; Sy, L.K.; Liu, F.; Che, C.M. Activation of autophagy of aggregation-prone ubiquitinated proteins by timosaponin A-III. J. Biol. Chem. 2011, 286, 31684–31696. [CrossRef] [PubMed]

144. Chen, M.; Du, Y.; Qui, M.; Wang, M.; Chen, K.; Huang, Z.; Jiang, M.; Xiong, F.; Chen, J.; Zhou, J.; et al. Ophiopogonin B-induced autophagy in non-small cell lung cancer cells via inhibition of the PI3K/Akt signaling pathway. Oncol. Rep. 2013, 29, 430–436. [PubMed]
145. Zhang, Y.Y.; Meng, C.; Zhang, X.M.; Yuan, C.H.; Wen, M.D.; Chen, Z.; Dong, D.C.; Gao, Y.H.; Liu, C.; Zhang, Z. Ophiopogonin D attenuates doxorubicin-induced autophagic cell death by relieving mitochondrial damage in vitro and in vivo. J. Pharmacol. Exp. Ther. 2015, 352, 166–174. [CrossRef] [PubMed]
146. Chen, G.; Hu, C.; Zhang, W.; Xu, N.; Wang, F.Q.; Jia, J.; Zhang, W.F.; Sun, Z.J.; Zhao, Y.F. Mammalian target of rapamycin regulates isoquiritigenin-induced autophagic and apoptotic cell death in adenoid cystic carcinoma cells. Apoptosis 2012, 17, 90–101. [CrossRef] [PubMed]
147. Xu, M.Y.; Lee, D.H.; Joo, E.J.; Son, K.H.; Kim, Y.S. Akebia saponin PA induces autophagic and apoptotic cell death in Ags human gastric cancer cells. Food Chem. Toxicol. 2013, 59, 703–708. [CrossRef] [PubMed]
148. Chen, Z.; Lu, T.; Yue, X.; Wei, N.; Jiang, Y.; Chan, M.; Ni, G.; Liu, X.; Xu, G. Neuroprotective effect of ginsenoside Rb1 on glutamate-induced neurotoxicity: With emphasis on autophagy. Neurosci. Lett. 2010, 482, 264–268. [CrossRef] [PubMed]
149. Zhang, Z.L.; Fan, Y.; Liu, M.L. Ginsenoside re enhances the survival of H9C2 cardiac muscle cells through regulation of autophagy. Heart 2012, 98, E54–E54. [CrossRef]
150. Meschini, S.; Condello, M.; Calcabrini, A.; Marra, M.; Formisano, G.; Lista, P.; De Millo, A.; Federici, E.; Arancia, G. The plant alkaloid voacamine induces apoptosis-independent autophagic cell death on both sensitive and multidrug resistant human osteosarcoma cells. Autophagy 2008, 4, 1020–1033. [CrossRef] [PubMed]
151. Akimoto, M.; Iizuka, M.; Kanematsu, R.; Yoshida, M.; Takenaga, K. Anticancer effect of ginger extract against pancreatic cancer cells mainly through reactive oxygen species-mediated autol cell death. PLoS ONE 2015, 10, e0126605. [CrossRef] [PubMed]
152. Li, H.Y.; Zhang, J.; Sun, L.L.; Li, B.H.; Gao, H.L.; Xie, T.; Zhang, N.; Ye, Z.M. Celastrol induces apoptosis and autophagy via the ROS/JNK signaling pathway in human osteosarcoma cells: An in vitro and in vivo study. Cell Death Dis. 2015, 6, e1604. [CrossRef] [PubMed]
153. Chen, S.; Gu, C.; Xu, C.; Zhang, J.; Xu, Y.; Ren, Q.; Guo, M.; Huang, S.; Chen, L. Celastrol prevents cadmium-induced neuronal cell death via targeting JNK and PTEN-Akt/mTOR network. J. Neurochem. 2014, 128, 256–266. [CrossRef] [PubMed]
154. Liu, T.; Men, Q.; Wu, G.; Yu, C.; Huang, Z.; Liu, X.; Li, W. Tetrandrine induces autophagy and differentiation by activating ROS and Notch1 signaling in leukemia cells. Oncotarget 2015, 6, 7992–8006. [CrossRef] [PubMed]
155. Kuo, P.L.; Hsu, Y.L.; Cho, C.Y. Plumbagin induces G2-M arrest and autophagy by inhibiting the AKT/mammalian target of rapamycin pathway in breast cancer cells. Mol. Cancer Ther. 2006, 5, 3209–3221. [CrossRef] [PubMed]
156. Law, B.Y.; Wang, M.; Ma, D.L.; Al-Mousa, F.; Michelangeli, F.; Cheng, S.H.; Ng, M.H.; To, K.F.; Mok, A.Y.; Ko, R.Y.; et al. Alisobol B, a novel inhibitor of the sarcoplasmic/endoplasmic reticulum Ca2+ atpase pump, induces autophagy, endoplasmic reticulum stress, and apoptosis. Mol. Cancer Ther. 2010, 9, 718–730. [CrossRef] [PubMed]
157. Kwak, E.J.; Lee, Y.S.; Choi, E.M. Effect of magnolol on the function of osteoblastic MC3T3-E1 cells. Mediat. Inflamm. 2012, 2012, 829650. [CrossRef] [PubMed]
158. Jiang, J.; Hu, C. Evodiamine: A novel anti-cancer alkaloid from evodia rutaecarpa. Molecules 2009, 14, 1852–1859. [CrossRef] [PubMed]
159. Dai, J.P.; Li, W.Z.; Zhao, X.F.; Wang, G.F.; Yang, J.C.; Zhang, L.; Chen, X.X.; Xu, Y.X.; Li, K.S. A drug screening method based on the autophagy pathway and studies of the mechanism of evodiamine against influenza a virus. PLoS ONE 2012, 7, e42706. [CrossRef] [PubMed]
160. Makhov, P.; Golovine, K.; Kuter, E.; Kukitkov, A.; Mehrzad, R.; Corcoran, A.; Tulin, A.; Uzzo, R.G.; Kolenko, V.M. Piperlongumine promotes autophagy via inhibition of Akt/mTOR signalling and mediates cancer cell death. Br. J. Cancer 2011, 104, 899–907. [CrossRef] [PubMed]
161. Wang, F.; Mao, Y.; You, Q.; Hua, D.; Cai, D. Piperlongumine induces apoptosis and autophagy in human lung cancer cells through inhibition of PI3K/Akt/mTOR pathway. Int. J. Immunopathol. Pharmacol. 2015, 28, 362–373. [CrossRef] [PubMed]
162. Jiang, T.F.; Zhang, Y.J.; Zhou, H.Y.; Wang, H.M.; Tian, L.P.; Liu, J.; Ding, J.Q.; Chen, S.D. Curcumin ameliorates the neurodegenerative pathology in A3T3 α-synuclein cell model of Parkinson’s disease through the downregulation of mTOR/p70S6K signaling and the recovery of macroautophagy. J. Neuroimmune Pharmacol. 2013, 8, 356–369. [CrossRef] [PubMed]
163. Hasima, N.; Ozpolat, B. Regulation of autophagy by polyphenolic compounds as a potential therapeutic strategy for cancer. *Cell Death Dis.* 2014, 5, e1509. [CrossRef] [PubMed]

164. Yun, S.M.; Jung, J.H.; Jeong, S.J.; Sohn, E.J.; Kim, B.; Kim, S.H. Tanshinone IIA induces autophagic cell death via activation of AMPK and ERK and inhibition of mTOR and p70 S6K in KBM-5 leukemia cells. *Phytother. Res.* 2014, 28, 458–464. [CrossRef] [PubMed]

165. Gong, X.; Ivanov, V.N.; Davidson, M.M.; Hei, T.K. Tetramethylpyrazine (TMP) protects against sodium arsenite-induced nephrotoxicity by suppressing ROS production, mitochondrial dysfunction, pro-inflammatory signaling pathways and programmed cell death. *Arch. Toxicol.* 2015, 89, 1057–1070. [CrossRef] [PubMed]

166. Miao, Q.; Bi, L.L.; Li, X.; Miao, S.; Zhang, J.; Zhang, S.; Yang, Q.; Xie, Y.H.; Zhang, J.; Wang, S.W. Anticancer effects of bufalin on human hepatocellular carcinoma HepG2 cells: Roles of apoptosis and autophagy. *Int. J. Mol. Sci.* 2013, 14, 1370–1382. [CrossRef] [PubMed]

167. Xie, C.M.; Chan, W.Y.; Yu, S.; Zhao, J.; Cheng, C.H. Bufalin induces autophagy-mediated cell death in human colon cancer cells through reactive oxygen species generation and JNK activation. *Free Radic. Biol. Med.* 2011, 51, 1365–1375. [CrossRef] [PubMed]

168. Ishaq, M.; Khan, M.A.; Sharma, K.; Sharma, G.; Dutta, R.K.; Majumdar, S. Gambogenic acid induced oxidative stress dependent caspase activation regulates both apoptosis and autophagy by targeting various key molecules (NF-kB, Bcl-2, p62 and NBR1) in human bladder cancer cells. *Biochim. Biophys. Acta* 2014, 1840, 3374–3384. [CrossRef] [PubMed]

169. Chen, J.; Zhou, M.; Zhang, Q.; Xu, J.; Ouyang, J. Gambogenic acid induces death of K562 cells through autophagy and apoptosis mechanisms. *Leuk. Lymphoma* 2015, 56, 2953–2958. [CrossRef] [PubMed]

170. Wu, A.G.; Wong, V.K.; Xu, S.W.; Chan, W.K.; Ng, C.I.; Liu, L.; Law, B.Y. Onjisaponin b derived from radix scutellaria baicalensis extract via suppression of immune modulators and MAP kinase signaling molecules. *Phytochemistry* 1988, 28, 355–362. [CrossRef] [PubMed]

171. Yun, S.M.; Jung, J.H.; Jeong, S.J.; Sohn, E.J.; Kim, B.; Kim, S.H. Tanshinone IIA induces autophagic cell death in cancer cells and pro-inflammatory signaling pathways and programmed cell death. *Chin. J. Pharmacol. Toxicol.* 2008, 22, 151. [CrossRef]

172. Han, J.; Ye, M.; Xu, M.; Sun, J.; Wang, B.; Guo, D. Characterization of flavonoids in the traditional chinese herbal medicine-huangqin by liquid chromatography coupled with electrospray ionization mass spectrometry. *J. Chromatogr. B* 2007, 848, 355–362. [CrossRef] [PubMed]

173. Han, J.; Ye, M.; Xu, M.; Sun, J.; Wang, B.; Guo, D. Characterization of flavonoids in the traditional chinese herbal medicine-huangqin by liquid chromatography coupled with electrospray ionization mass spectrometry. *J. Chromatogr. B* 2007, 848, 355–362. [CrossRef] [PubMed]

174. Lim, B.O. Literature research of chinese medicine recipes for the treatment of psoriasis vulgaris with blood-heat syndrome type. *Chin. J. Integr. Med.* 2011, 17, 150–153. [CrossRef] [PubMed]

175. Tan, Y.Q.; Liu, J.L.; Bai, Y.P.; Zhang, L.X. Literature research of chinese medicine recipes for the treatment of psoriasis vulgaris with blood-heat syndrome type. *Chin. J. Integr. Med.* 2011, 17, 150–153. [CrossRef] [PubMed]

176. Xie, C.M.; Chan, W.Y.; Yu, S.; Zhao, J.; Cheng, C.H. Bufalin induces autophagy-mediated cell death in human colon cancer cells through reactive oxygen species generation and JNK activation. *Free Radic. Biol. Med.* 2011, 51, 1365–1375. [CrossRef] [PubMed]

177. Tan, Y.Q.; Liu, J.L.; Bai, Y.P.; Zhang, L.X. Literature research of chinese medicine recipes for the treatment of psoriasis vulgaris with blood-heat syndrome type. *Chin. J. Integr. Med.* 2011, 17, 150–153. [CrossRef] [PubMed]

178. Hasima, N.; Ozpolat, B. Regulation of autophagy by polyphenolic compounds as a potential therapeutic strategy for cancer. *Cell Death Dis.* 2014, 5, e1509. [CrossRef] [PubMed]

179. Zhang, X.; Tang, X.; Liu, H.; Li, L.; Hou, Q.; Gao, J. Autophagy induced by baicalin involves downregulation of CD147 in SMMC-7721 cells in vitro. *Onco. Rep.* 2012, 27, 1128–1134. [PubMed]

180. Sokollik, C.; Ang, M.; Jones, N. Autophagy: A primer for the gastroenterologist/hepatologist. *Can. J. Gastroenterol.* 2011, 25, 667–674. [CrossRef] [PubMed]

181. Hsu, K.J. *Chinese Traditional Medicine;* Chinese Pharmaceutical Science and Technology Publication Co.: Beijing, China, 1996; p. 802.

182. Gray, A.I.; Bhandari, P.; Waterman, P.G. New protolimonoids from the fruits of phellodendron chinense. *Phytochemistry* 1988, 27, 1805–1808. [CrossRef]
183. Hsiang, C.Y.; Wu, S.L.; Cheng, S.E.; Ho, T.Y. Acetaldehyde-induced interleukin-1β and tumor necrosis factor-α production is inhibited by berberine through nuclear factor-kB signaling pathway in HepG2 cells. *J. Biomed. Sci.* **2005**, *12*, 791–801. [CrossRef] [PubMed]

184. Xu, Y.; Ventura, S. Extracts of bark from the traditional chinese herb phellodendron amurense inhibit contractility of the isolated rat prostate gland. *J. Ethnopharmacol.* **2010**, *127*, 196–199. [CrossRef] [PubMed]

185. Park, Y.K.; Chung, Y.S.; Kim, Y.S.; Kwon, O.Y.; Joh, T.H. Inhibition of gene expression and production of iNOS and TNF-α in LPS-stimulated microglia by methanol extract of phellodendri cortex. *Int. Immunopharmacol.* **2007**, *7*, 955–962. [CrossRef] [PubMed]

186. Deng, Y.; Xu, J.; Zhang, X.; Yang, J.; Zhang, D.; Huang, J.; Lv, P.; Shen, W.; Yang, Y. Berberine attenuates attenuation of gene expression and production of iNOS and TNF-α in LPS-stimulated microglia by methanol extract of phellodendri cortex. *Int. Immunopharmacol.* **2007**, *7*, 955–962. [CrossRef] [PubMed]

187. Fogarty, S.; Hardie, D.G. Development of protein kinase activators: AMPK as a target in metabolic disorders and cancer. *Biochim. Biophys. Acta* **2010**, *1804*, 581–591. [CrossRef] [PubMed]

188. Ghosh, R.; Graham, H.; Rivas, P.; Tan, X.J.; Crosby, K.; Bhaskaran, S.; Schoolfield, J.; Banu, J.; Fernandes, G.; Yeh, I.T.; et al. Phellodendron amurense bark extract prevents progression of prostate tumors in transgenic adenocarcinoma of mouse prostate: Potential for prostate cancer management. *Anticancer Res.* **2010**, *30*, 857–865. [PubMed]

189. Ghosh, R.; Ansari, K.M. Nexrutine® inhibits tumorigenesis in mouse skin and induces apoptotic cell death in human squamous carcinoma A431 and human melanoma A375 cells. *Carcinogenesis* **2012**, *33*, 1909–1918. [CrossRef] [PubMed]

190. Ghosh, R.; Garcia, G.E.; Crosby, K.; Inoue, H.; Thompson, I.M.; Troyer, D.A.; Kumar, A.P. Regulation of Cox-2 by cyclic AMP response element binding protein in prostate cancer: Potential role for nexrutine. *Neoplasia* **2007**, *9*, 893–899. [CrossRef] [PubMed]

191. Gordon, J.; Munoz, A.R.; Chan, D.; Ghosh, R.; Kumar, A.P. STAT3 down regulates LC3 to inhibit autophagy in adipocytes by targeting becn1. *Autophagy* **2014**, *10*, 1776–1786. [CrossRef] [PubMed]

192. Muralimanoharan, S.B.; Kunnumakkara, A.B.; Shylesh, B.; Kulkarni, K.H.; Haiyan, X.; Ming, H.; Aggarwal, B.B.; Rana, R.; et al. Berberine and total base from *Coptis Chinensis* rhizome inhibit brain injury in an aluminum-induced rat model of neurodegenerative disease. *Neurotherapeutics* **2009**, *6*, 893–899. [CrossRef] [PubMed]
218. Kogure, K.; Goto, S.; Abe, K.; Ohiwa, C.; Akasu, M.; Terada, H. Potent antiperoxidation activity of the
219. Kogure, K.; Tsuchiya, K.; Abe, K.; Akasu, M.; Tamaki, T.; Fukuzawa, K.; Terada, H. Direct radical scavenging
220. Yang, X.Y.; Jiang, S.Q.; Zhang, L.; Liu, Q.N.; Gong, P.L. Inhibitory effect of dauricine on inflammatory process
221. Rogosnitzky, M.; Danks, R. Therapeutic potential of the biscoclaurine alkaloid, cepharanthine, for a range of
222. Zhang, Z.Y.; Daniels, R.; Schluesener, H.J. Oridonin ameliorates neuropathological changes and behavioural
223. Nishanthi, M.; Artharthanarieswaran, P.; Devdass, G.; Saravanan, D.; Narendiran, S.; Vijayakumar, B.
224. Feng, D.; Mei, Y.; Wang, Y.; Zhang, B.; Wang, C.; Xu, L. Tetrandrine protects mice from concanavalin
225. Wan, Z.; Lu, Y.; Liao, Q.; Wu, Y.; Chen, X. Fangchinoline inhibits human immunodeficiency virus type 1
226. Jiao, S.D.; Craig, M.
227. Li, Z.T.; Li, L.; Chen, T.T.; Li, C.Y.; Wang, D.Q.; Yang, Z.F.; Zhong, N.S. Efficacy and safety of Ban-Lan-Gen
228. Li, F.; Fan, J.; Wu, Z.; Liu, R.Y.; Guo, L.; Dong, Z.; Wang, Z. Reversal effects of Rabdosia rubescens extract on
229. Zhang, Z.Y.; Daniels, R.; Schlesener, H.J. Oridorin ameliorates neuropathological changes and behavioural
deficits in a mouse model of cerebral amyloidosis. J. Cell Mol. Med. 2013, 17, 1566–1576. [CrossRef] [PubMed]
230. Yue, J.; Shen, W.; Xu, J.; Mou, Y.P.; Zhang, T.; Zhang, B. Study on the inhibitory mechanism of oridonin in
pancreatic cancers BXPC-3 cells by DNA microarray. Zhejiang Zhongyiyao Daxue Xuebao 2013, 37, 606–612.
231. Li, Z.T.; Li, L.; Chen, T.T.; Li, C.Y.; Wang, D.Q.; Yang, Z.F.; Zhong, N.S. Efficacy and safety of Ban-Lan-Gen
granules in the treatment of seasonal influenza: Study protocol for a randomized controlled trial. Trials 2015,
16, 126. [CrossRef] [PubMed]
232. Jiao, S.D.; Craig, M. Ten Lectures on the Use of Medicinals from the Personal Experience of Jiao Shu-De (Jiao Clinical
Chinese Medicine), Bilingual ed.; Paradigm Publication: Brookline, MA, USA, 2001; p. 711.
233. Gary, L. Chinese Medicinal Teas: Simple, Proven, Folk Formulas for Common Diseases & Promoting Health, 1st ed.;
Blue Poppy Press: Boulder, CO, USA, 1996; p. 190.
234. Wan, Z.; Lu, Y.; Liao, Q.; Wu, Y.; Chen, X. Fangchinoline inhibits human immunodeficiency virus type 1
replication by interfering with GP160 proteolytic processing. PLoS ONE 2012, 7, e39225. [CrossRef] [PubMed]
235. Feng, D.; Mei, Y.; Wang, Y.; Zhang, B.; Wang, C.; Xu, L. Tetrandrine protects mice from concanavalin
a-induced hepatitis through inhibiting Nf-κB activation. Immunol. Lett. 2008, 121, 127–133. [CrossRef] [PubMed]
236. Nishanthi, M.; Artharthanarieswaran, P.; Devdass, G.; Saravanan, D.; Narendiran, S.; Vijayakumar, B.
Pharmacognostical studies on leaves of Stephania japonica var. Timoriensis. Int. J. Novel Trends Pharm. Sci.
2011, 2, 39–41.
237. Yang, Z.; Li, C.; Wang, X.; Zhai, C.; Yi, Z.; Wang, L.; Liu, B.; Du, B.; Wu, H.; Guo, X.; et al. Dauricine induces
apoptosis, inhibits proliferation and invasion through inhibiting Nf-κB signaling pathway in colon cancer
cells. J. Cell Physiol. 2010, 225, 266–275. [CrossRef] [PubMed]
238. Rogosnitzky, M.; Danks, R. Therapeutic potential of the bisoclaurine alkaloid, cephæranthine, for a range of
clinical conditions. Pharmacol. Rep. 2011, 63, 337–347. [CrossRef]
239. Kogure, K.; Goto, S.; Abe, K.; Ohiwa, C.; Akasu, M.; Terada, H. Potent antiperoxidation activity of the
bisbenzylisoquinoline alkaloid cephæranthine: The amine moiety is responsible for its PH-dependent radical
scavenging activity. Biochim. Biophys. Acta 1999, 1426, 133–142. [CrossRef]
240. Kogure, K.; Tsuchiya, K.; Abe, K.; Akasu, M.; Tamaki, T.; Fukuzawa, K.; Terada, H. Direct radical scavenging
by the bisbenzylisoquinoline alkaloid cephæranthine. Biochim. Biophys. Acta 2003, 1622, 1–5. [CrossRef]
241. Yang, X.Y.; Jiang, S.Q.; Zhang, L.; Liu, Q.N.; Gong, P.L. Inhibitory effect of dauricine on inflammatory process
following focal cerebral ischemia/reperfusion in rats. Am. J. Chin. Med. 2007, 35, 477–486. [CrossRef] [PubMed]
221. Malofeeva, E.V.; Domanitskaya, N.; Gudima, M.; Hopper-Borge, E.A. Modulation of the ATPase and transport activities of broad-acting multidrug resistance factor ABCC10 (MRP7). *Cancer Res.* **2012**, *72*, 6457–6467. [CrossRef] [PubMed]

222. George, U. *A Dictionary of Plants Used by Man*; Constable: London, UK, 1974; p. 619.

223. Duke, J.A.; Ayensu, E.S. *Medicinal Plants of China*; Reference pubns: Algonac, MI, USA, 1985; p. 705.

224. Delmas, D.; Lancon, A.; Colin, D.; Jannin, B.; Latruffe, N. Resveratrol as a chemopreventive agent: A promising molecule for fighting cancer. *Curr. Drug Targets* **2006**, *7*, 423–442. [CrossRef] [PubMed]

225. Jung, H.J.; Hwang, I.A.; Sung, W.S.; Kang, H.; Kang, B.S.; Seu, Y.B.; Lee, D.G. Fungicidal effect of resveratrol on human infectious fungi. *Arch. Pharm. Res.* **2005**, *28*, 557–560. [CrossRef] [PubMed]

226. Hwang, D.; Lim, Y.H. Resveratrol antibacterial activity against *Escherichia coli* is mediated by Z-ring formation inhibition via suppression of FTSZ expression. *Sci. Rep.* **2015**, *5*. [CrossRef] [PubMed]

227. Das, S.; Das, D.K. Anti-inflammatory responses of resveratrol. *Inflamm. Allergy Drug Targets* **2007**, *6*, 168–173. [CrossRef] [PubMed]

228. Kimura, Y.; Okuda, H. Resveratrol isolated from *Polygonum cuspidatum* root prevents tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma-bearing mice. *J. Nutr.* **2001**, *131*, 1844–1849. [PubMed]

229. Sexton, E.; Van Themsche, C.; LeBlanc, K.; Parent, S.; Lemoine, P.; Asselin, E. Resveratrol interferes with Akt activity and triggers apoptosis in human uterine cancer cells. *Mol Cancer* **2006**, *5*, 45. [CrossRef] [PubMed]

230. Azios, N.G.; Krishnamoorthy, L.; Harris, M.; Cubano, L.A.; Cammer, M.; Dharmawardhane, S.F. Estrogen and resveratrol regulate Rac and Cdc42 signaling to the actin cytoskeleton of metastatic breast cancer cells. *Neoplasia* **2007**, *9*, 147–158. [CrossRef] [PubMed]

231. Petrovski, G.; Gurusamy, N.; Das, D.K. Resveratrol in cardiovascular health and disease. *Ann. N. Y. Acad. Sci.* **2011**, *1215*, 22–33. [CrossRef] [PubMed]

232. Gurusamy, N.; Lekli, I.; Mukherjee, S.; Ray, D.; Ahsan, M.K.; Gherghiceanu, M.; Popescu, L.M.; Das, D.K. Cardioprotection by resveratrol: A novel mechanism via autophagy involving the mTORc2 pathway. *Cardiovasc. Res.* **2010**, *86*, 103–112. [CrossRef] [PubMed]

233. Lin, J.; Chen, Y.; Cai, Q.; Wei, L.; Zhan, Y.; Shen, A.; Sierra, T.J.; Peng, J. *Scutellaria barbata* d don inhibits colorectal cancer growth via suppression of multiple signaling pathways. *Integr. Cancer Ther.* **2013**, *13*, 240–248. [CrossRef] [PubMed]

234. He, F.G.; Zhang, H.S.; Shen, B. Research progress on anticancer effect of *Scutellaria barbata* D.Don and its mechanism. *Bull. Chin. Cancer* **2008**, *17*, 108–112.

235. Islam, M.N.; Ishita, I.; Jin, S.E.; Choi, R.J.; Lee, C.M.; Kim, Y.S.; Jung, H.A.; Choi, J.S. Anti-inflammatory activity of edible brown alga *Saccharina japonica* and its constituents pheophorbide A and pheophytin a in LPS-stimulated RAW 264.7 macrophage cells. *Food Chem. Toxicol.* **2013**, *55*, 541–548. [CrossRef] [PubMed]

236. Pan, Y.; Cai, B.; Wang, K.; Wang, S.; Zhou, S.; Yu, X.; Xu, B.; Chen, L. Neferine enhances insulin sensitivity in insulin resistant rats. *J. Ethnopharmacol.* **2009**, *124*, 98–102. [CrossRef] [PubMed]

237. Yoon, H.E.; Oh, S.H.; Kim, S.A.; Yoon, J.H.; Ahn, S.G. Pheophorbide a-mediated photodynamic therapy induces autophagy and apoptosis via the activation of MAPKS in human skin cancer cells. *Oncol. Rep.* **2014**, *31*, 137–144. [PubMed]

238. Tang, W.C.; Eisenbrand, G. *Chinese Drugs of Plant Origin: Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*, 1st ed.; Springer: Berlin, Germany, 1992; p. 1056.

239. Zhao, L.; Wang, X.; Chang, Q.; Xu, J.; Huang, Y.; Guo, Q.; Zhang, S.; Wang, W.; Chen, X.; Wang, J. Neferine, a bisbenzylisoquinoline alkaloid attenuates bleomycin-induced pulmonary fibrosis. *Eur. J. Pharmacol.* **2010**, *627*, 304–312. [CrossRef] [PubMed]
242. Yoon, J.S.; Kim, H.M.; Yadunandam, A.K.; Kim, N.H.; Jung, H.A.; Choi, J.S.; Kim, C.Y.; Kim, G.D. Neferine isolated from nelumbo nucifera enhances anti-cancer activities in Hep3b cells: Molecular mechanisms of cell cycle arrest, ER stress induced apoptosis and anti-angiogenic response. *Phytotherapy Research* **2013**, *20*, 1013–1022. [CrossRef] [PubMed]

243. Reynertson, K.A.; Yang, H.; Jiang, B.; Basile, M.J.; Kennelly, E.J. Quantitative analysis of antiradical phenolic constituents from fourteen edible myrtaceae fruits. *Food Chem.* **2008**, *109*, 883–890. [CrossRef] [PubMed]

244. Soubir, T. Antioxidant activities of some local bangladeshi fruits (*Artocarpus heterophyllus*, *Annona squamosa*, *Terminalia bellirica*, *Syzygium samarangense*, *Averrhoa carambola* and *Olea europea*). *Sheng Wu Gong Cheng Xue Bao* **2007**, *23*, 257–261. [PubMed]

245. Su, M.Y.; Huang, H.Y.; Li, L.; Lu, Y.H. Protective effects of 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone to pc12 cells against cytotoxicity induced by hydrogen peroxide. *J. Agric. Food Chem.* **2011**, *59*, 521–527. [CrossRef] [PubMed]

246. Yu, W.G.; Qian, J.; Lu, Y.H. Hepatoprotective effects of 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone on CCl4-induced acute liver injury in mice. *J. Agric. Food Chem.* **2011**, *59*, 12821–12829. [CrossRef] [PubMed]

247. Kim, Y.J.; Ko, H.; Park, J.S.; Han, I.H.; Amor, E.C.; Lee, J.W.; Yang, H.O. Dimethyl cardamonin inhibits lipopolysaccharide-induced inflammatory factors through blocking NF-kB p65 activation. *Int. Immunopharmacol.* **2010**, *10*, 1127–1134. [CrossRef] [PubMed]

248. Lee, J.H.; Jung, H.S.; Giang, P.M.; Jin, X.; Lee, S.; Son, P.T.; Lee, D.; Hong, Y.S.; Lee, K.; Lee, J.J. Blockade of nuclear factor-kB signaling pathway and anti-inflammatory activity of cardamomin, a chalcone analog from alpinia conchigera. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 271–278. [CrossRef] [PubMed]

249. Kim, Y.J.; Kang, K.S.; Choi, K.C.; Ko, H. Cardamonin induces autophagy and an antiproliferative effect through JNK activation in human colorectal carcinoma HCT116 cells. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2559–2564. [CrossRef] [PubMed]

250. Ko, H.; Kim, Y.J.; Amor, E.C.; Lee, J.W.; Kim, H.J.; Yang, H.O. Induction of autophagy by dimethyl cardamonin is associated with proliferative arrest in human colorectal carcinoma HCT116 and lovo cells. *J. Cell Biochem.* **2011**, *112*, 2471–2479. [CrossRef] [PubMed]

251. Alghasham, A.A. Cucurbitacins—a promising target for cancer therapy. *Int. J. Health Sci.* **2013**, *7*, 77–89. [CrossRef]

252. Zhao, J.; Ben, L.-H.; Wu, Y.-L.; Hu, W.; Ling, K.; Xin, S.-M.; Nie, H.-L.; Ma, L.; Pei, G. Anti-HIV agent trichosanthis enhances the capabilities of chemokines to stimulate chemotaxis and g protein activation, and this is mediated through interaction of trichosanthis and chemokine receptors. *J. Exp. Med.* **1999**, *190*, 101–111. [CrossRef] [PubMed]

253. Park, C.S.; Lim, H.; Han, K.J.; Baek, S.H.; Sohn, H.O.; Lee, D.W.; Kim, Y.G.; Yun, H.Y.; Baek, K.J.; Kwon, N.S. Inhibition of nitric oxide generation by 23,24-dihydrocucurbitacin d in mouse peritoneal macrophages. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 705–710. [CrossRef] [PubMed]

254. Recio, M.C.; Prieto, M.; Bonuccelli, M.; Orsi, C.; Manez, S.; Giner, R.M.; Cerda-Nicolás, M.; Rios, J.L. Anti-inflammatory activity of two cucurbitacins isolated from *Cayaponia tayuya* roots. *Planta Med.* **2004**, *70*, 414–420. [PubMed]

255. Jayaprakasham, B.; Seeram, N.P.; Nair, M.G. Anticancer and antiinflammatory activities of cucurbitacins from *Cucurbita andreana*. *Cancer Lett.* **2003**, *189*, 11–16. [CrossRef]

256. Escandell, J.M.; Recio, M.C.; Manez, S.; Giner, R.M.; Cerda-Nicolás, M.; Gil-Benso, R.; Rios, J.L. Dihydrocucurbitacin B inhibits delayed type hypersensitivity reactions by suppressing lymphocyte proliferation. *J. Pharmacol. Exp. Ther.* **2007**, *322*, 1261–1268. [CrossRef] [PubMed]

257. Clericuzio, M.; Mella, M.; Vita-Finzi, P.; Zema, M.; Vidari, G. Cucurbitane triterpenoids from *Leucopaxillus gentianaeus*. *J. Nat. Prod.* **2004**, *67*, 1823–1828. [CrossRef] [PubMed]

258. Escandell, J.M.; Kaler, P.; Recio, M.C.; Sasazuki, T.; Shirasawa, S.; Augenlicht, L.; Rios, J.L.; Klampfer, L. Activated KRAS protects colon cancer cells from cucurbitacin-induced apoptosis: The role of p53 and p21. *Biochem. Pharmacol.* **2008**, *76*, 198–207. [CrossRef] [PubMed]

259. Kim, S.R.; Seo, H.S.; Choi, H.S.; Cho, S.G.; Kim, Y.K.; Hong, E.H.; Shin, Y.C.; Ko, S.G. *Trichosanthes kirilowii* ethanol extract and cucurbitacin d inhibit cell growth and induce apoptosis through inhibition of STAT3 activity in breast cancer cells. *Evid. Based Complement. Altern. Med.* **2013**, *2013*. [CrossRef] [PubMed]
260. Ding, N.; Yamashita, U.; Matsuoka, H.; Sugiura, T.; Tsukada, J.; Noguchi, J.; Yoshida, Y. Apoptosis induction through proteasome inhibitory activity of cucurbitacin d in human T-cell leukemia. Cancer 2011, 117, 2735–2746. [CrossRef] [PubMed]

261. Zha, Q.B.; Zhang, X.Y.; Lin, Q.R.; Xu, L.H.; Zhao, G.X.; Pan, H.; Zhou, D.; Ouyang, D.Y.; Liu, Z.H.; He, X.H. Cucurbitacin E induces autophagy via downregulating mTORc1 signaling and upregulating ampk activity. PLoS ONE 2015, 10, e0124355. [CrossRef] [PubMed]

262. Yuan, G.; Yan, S.F.; Xue, H.; Zhang, P.; Sun, J.T.; Li, G. Cucurbitacin I induces protective autophagy in glioblastoma in vitro and in vivo. J. Biol. Chem. 2014, 289, 10607–10619. [CrossRef] [PubMed]

263. Asif, H.M.; Akram, M. A helicobacter pylori treatment strategies and options: A review. Int. J. Pharm. Biomed. Res. 2014, 5, 69–73.

264. Tillman, D.M.; Izeraadjene, K.; Szucs, K.S.; Douglas, L.; Houghton, J.A. Rottlerin sensitizes colon carcinoma cells to tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis via uncoupling of the mitochondria independent of protein kinase C. Cancer Res. 2003, 63, 5118–5125. [PubMed]

265. Lim, J.H.; Park, J.W.; Choi, K.S.; Park, Y.B.; Kwon, T.K. Rottlerin induces apoptosis via death receptor 5 (DR5) upregulation through chop-dependent and PKC δ-independent mechanism in human malignant tumor cells. Carcinogenesis 2009, 30, 729–736. [CrossRef] [PubMed]

266. Zhang, J.; Liu, N.; Zhang, J.; Liu, S.; Liu, Y.; Zheng, D. PKCδ protects human breast tumor MCF-7 cells against tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis. J. Cell Biochem. 2005, 96, 522–532. [CrossRef] [PubMed]

267. Akar, U.; Ozpolat, B.; Mehta, K.; Fok, J.; Kondo, Y.; Lopez-Berestein, G. Tissue transglutaminase inhibits autophagy in pancreatic cancer cells. Mol. Cancer Res. 2007, 5, 241–249. [CrossRef] [PubMed]

268. Balgi, A.D.; Fonseca, B.D.; Donohue, E.; Tsang, T.C.; Lajoie, P.; Proud, C.G.; Nabi, I.R.; Roberge, M. Screen for chemical modulators of autophagy reveals novel therapeutic inhibitors of mTORc1 signaling. PLoS ONE 2009, 4, e7124. [CrossRef] [PubMed]

269. Song, S.J.; Chi, D.Q.; Xia, M.Y.; Li, L.Z.; Xu, L.; Yin, Y. Application of Timosaponin AIII in Anemarrhena to Preparation of Antitumor Drugs. CN 103599122 A, 26 February 2014.

270. Wang, Y.; Dan, Y.; Yang, D.; Hu, Y.; Zhang, L.; Zhang, C.; Zhu, H.; Cui, Z.; Li, M.; Liu, Y. The genus anemarrhena bunge: A review on ethnopharmacology, phytochemistry and pharmacology. J. Ethnopharmacol. 2013, 153, 42–60. [CrossRef] [PubMed]

271. Han, J.; Yang, N.; Zhang, F.; Zhang, C.; Liang, F.; Xie, W.; Chen, W. Rhizoma anemarrheneae extract ameliorates hyperglycemia and insulin resistance via activation of AMP-activated protein kinase in diabetic rodents. J. Ethnopharmacol. 2015, 172, 368–376. [CrossRef] [PubMed]

272. Wang, G.J.; Lin, L.C.; Chen, C.F.; Cheng, J.S.; Lo, Y.K.; Chou, K.J.; Lee, K.C.; Liu, C.P.; Wu, Y.Y.; Su, W.; et al. Effect of timosaponin A-III, from anemarrheneae Asphodeloides bunge (Liliaceae), on calcium mobilization in vascular endothelial and smooth muscle cells and on vascular tension. Life Sci. 2002, 71, 1081–1090. [CrossRef] [PubMed]

273. Zhang, J.; Zhang, M.; Sugahara, K.; Sagara, Y.; Meng, Z.; Xu, S.; Kodama, H. Effect of steroidal saponins of Anemarrhenae rhizoma on superoxide generation in human neutrophils. Biochem. Biophys. Res. Commun. 1999, 259, 636–639. [CrossRef] [PubMed]

274. Sy, L.K.; Yan, S.C.; Lok, C.N.; Man, R.Y.; Che, C.M. Timosaponin A-III induces autophagy preceding mitochondria-mediated apoptosis in hela cancer cells. Cancer Res. 2008, 68, 10229–10237. [CrossRef] [PubMed]

275. King, F.W.; Fong, S.; Griffin, C.; Shoemaker, M.; Staub, R.; Zhang, Y.L.; Cohen, I.; Shtivelman, E. Timosaponin AIII is preferentially cytotoxic to tumor cells through inhibition of mTOR and induction of er stress. PLoS ONE 2009, 4, e7283. [CrossRef] [PubMed]

276. Matkowskina, A.; Jamilowkowsa-Kozlowska, W.; Nawrot, I. Chinese medicinal herbs as source of antioxidant compounds—Where tradition meets the future. Curr. Med. Chem. 2013, 20, 984–1004. [CrossRef] [PubMed]

277. Wang, X.Y.; Zhang, H.; Chen, L.L.; Shan, L.H.; Fan, G.W.; Gao, X.M. Liquorice, a unique “guide drug” of traditional chinese medicine: A review of its role in drug interactions. J. Ethnopharmacol. 2013, 150, 781–790. [CrossRef] [PubMed]

278. Furuhashi, I.; Ivata, S.; Sato, T.; Inoue, H.; Shibata, S. Inhibition by licochalcone a, a novel flavonoid isolated from liquorice root, of IL-1β-induced PGE2 production in human skin fibroblasts. J. Pharm. Pharmacol. 2005, 57, 1661–1666. [CrossRef] [PubMed]
279. Kwon, H.S.; Park, J.H.; Kim, D.H.; Kim, Y.H.; Park, J.H.; Shin, H.K.; Kim, J.K. Licochalcone a isolated from licorice suppresses lipopolysaccharide-stimulated inflammatory reactions in RAW264.7 cells and endotoxin shock in mice. *J. Mol. Med.* **2008**, *86*, 1287–1295. [CrossRef] [PubMed]

280. Kühnl, J.; Roggenkamp, D.; Gehrke, S.A.; Stäb, F.; Wenck, H.; Kolbe, L.; Neufang, G. Licochalcone a activates Nrf2 *in vitro* and contributes to licorice extract-induced lowered cutaneous oxidative stress *in vivo*. *Exp. Dermatol.* **2015**, *24*, 42–47. [CrossRef] [PubMed]

281. Vaya, J.; Belinsky, P.A.; Aviram, M. Antioxidant constituents from licorice roots: Isolation, structure elucidation and antioxidative capacity toward LDL oxidation. *Free Radic. Biol. Med.* **1997**, *23*, 302–313. [CrossRef]

282. Kakegawa, H.; Matsumoto, H.; Satoh, T. Inhibitory effects of some natural products on the activation of hyaluronidase and their antiallergic actions. *Chem. Pharm. Bull.* **1992**, *40*, 1439–1442. [CrossRef] [PubMed]

283. Tsai, J.P.; Lee, C.H.; Ying, T.H.; Lin, C.L.; Lin, C.L.; Hsueh, J.T.; Hsieh, Y.H. Licochalcone a induces autophagy through PI3K/Akt/mTOR inactivation and autophagy suppression enhances licochalcone a-induced apoptosis of human cervical cancer cells. *Oncotarget* **2015**, *6*, 28851–28866. [PubMed]

284. Yo, Y.T.; Shieh, G.S.; Hsu, K.F.; Wu, C.L.; Shiau, A.L. Licorice and licochalcone-a induce autophagy in lncap prostate cancer cells by suppression of Bcl-2 expression and the mTOR pathway. *J. Agric. Food Chem.* **2009**, *57*, 8266–8273. [CrossRef] [PubMed]

285. Wang, Z.; Wang, N.; Liu, P.; Chen, Q.; Situ, H.; Xie, T.; Zhang, J.; Peng, C.; Lin, Y.; Chen, J. Microrna-25 regulates chemoresistance-associated autophagy in breast cancer cells, a process modulated by the natural autophagy inducer isoliquiritigenin. *Oncotarget* **2014**, *5*, 7013–7026. [CrossRef] [PubMed]

286. Xu, L.; Wang, W. *Chinese Materia Medica: Combinations and Applications*, 1st ed.; Elsevier Health Sciences: Amsterdam, The Netherlands, 2002; p. 866.

287. Wu, J.N. *An Illustrated Chinese Materia Medica*, 1st ed.; Oxford University Press: Oxford, UK, 2002; p. 712.

288. Xiang, Y.Z.; Shang, H.C.; Zhang, B.L. A comparison of the ancient use of ginseng in traditional chinese medicine with modern pharmacological experiments and clinical trials. *Phytother. Res.* **2008**, *22*, 851–858. [CrossRef] [PubMed]

289. Chen, C.F.; Chiou, W.F.; Zhang, J.T. Comparison of the pharmacological effects of panax ginseng and panax quinquefolium. *Acta Pharmacol. Sin.* **2008**, *29*, 1103–1108. [CrossRef] [PubMed]

290. Chen, X.C.; Zhu, Y.G.; Zhu, L.A.; Huang, C.; Chen, Y.; Chen, L.M.; Fang, F.; Zhou, Y.C.; Zhao, C.H. Ginsenoside F2 attenuates dopamine-induced apoptosis in PC12 cells by suppressing oxidative stress. *Eur. J. Pharmacol.* **2003**, *473*, 1–7. [CrossRef]

291. Xu, B.B.; Liu, C.Q.; Gao, X.; Zhang, W.Q.; Wang, S.W.; Cao, Y.L. Possible mechanisms of the protection of ginsenoside Re against MPTP-induced apoptosis in substantia nigra neurons of Parkinson’s disease mouse model. *J. Asian Nat. Prod. Res.* **2005**, *7*, 215–224. [CrossRef] [PubMed]

292. Kim, J.H. Cardiovascular diseases and panax ginseng: A review on molecular mechanisms and medical applications. *J. Ginseng Res.* **2012**, *36*, 16–26. [CrossRef] [PubMed]

293. Saw, C.L.; Wu, Q.; Kong, A.N. Anti-cancer and potential chemopreventive actions of ginseng by activating Nrf2 (Nfe2l2) anti-oxidative stress/anti-inflammatory pathways. *Chin. Med.* **2010**, *5*, 37. [CrossRef] [PubMed]

294. Hong, H.; Cui, C.H.; Kim, J.K.; Jin, F.X.; Kim, S.C.; Im, W.T. Enzymatic biotransformation of ginsenoside Rp1 and gypenoside XVII into ginsenosides Rd and F2 by recombinant β-glucosidase from flavobacterium johnsoniae. *J. Ginseng Res.* **2012**, *36*, 418–424. [CrossRef] [PubMed]

295. Mai, T.T.; Moon, J.; Song, Y.; Viet, P.Q.; Phuc, P.V.; Lee, J.M.; Yi, T.H.; Cho, M.; Cho, S.K. Ginsenoside F2 induces apoptosis accompanied by protective autophagy in breast cancer stem cells. *Cancer Lett.* **2012**, *321*, 144–153. [CrossRef] [PubMed]

296. Kim, D.G.; Jung, K.H.; Lee, D.G.; Yoon, J.H.; Choi, K.S.; Kwon, S.W.; Shen, H.M.; Morgan, M.J.; Hong, S.S.; Kim, Y.S. 20(S)-ginsenoside RG3 is a novel inhibitor of autophagy and sensitizes hepatocellular carcinoma to doxorubicin. *Oncotarget* **2014**, *5*, 4438–4451. [CrossRef] [PubMed]

297. Federici, E.; Palazzino, G.; Nicoletti, M.; Galeffi, C. Antiplasmodial activity of the alkaloids of Peschiera fuchsiaefolia. *Planta Med.* **2000**, *66*, 93–95. [CrossRef] [PubMed]

298. Wang, N.; Feng, Y. Elaborating the role of natural products-induced autophagy in cancer treatment: Achievements and artifacts in the state of the art. *Biomed. Res. Int.* **2015**, *2015*. [CrossRef] [PubMed]

299. Meschini, S.; Condello, M.; Marra, M.; Formisano, G.; Federici, E.; Arancia, G. Autophagy-mediated chemosensitizing effect of the plant alkaloid voacamine on multidrug resistant cells. *Toxicol. In Vitro* **2007**, *21*, 197–203. [CrossRef] [PubMed]
300. Brady, J.M.; Cherrington, N.J.; Hartley, D.P.; Buist, S.C.; Li, N.; Klaassen, C.D. Tissue distribution and chemical induction of multiple drug resistance genes in rats. Drug Metab. Dispos. 2002, 30, 838–844. [CrossRef] [PubMed]

301. Liu, H.; Zhang, D.; Xu, X.; Liu, X.; Wang, G.; Xie, L.; Pang, X.; Liu, L. Attenuated function and expression of p-glycoprotein at blood-brain barrier and increased brain distribution of phenobarbital in streptozotocin-induced diabetic mice. Eur. J. Pharmacol. 2007, 561, 226–232. [CrossRef] [PubMed]

302. Bartels, A.L. Blood-brain barrier P-glycoprotein function in neurodegenerative disease. Curr. Pharm. Des. 2011, 17, 2771–2777. [CrossRef] [PubMed]

303. Zhao, K.J.; Dong, T.T.; Cui, X.M.; Tu, P.F.; Tsim, K.W. Genetic distinction of Radix adenophorae from its adulterants by the DNA sequence of 5S-rRNA spacer domains. Am. J. Chin. Med. 2003, 31, 919–926. [CrossRef] [PubMed]

304. Zhao, Z.Z.; Xiao, P.G. Encyclopedia of Medicinal Plants; World Publishing Corporation: Shanghai, China, 2009; p. 2000.

305. Bermejo Benito, P.; Abad Martinez, M.J.; Silvan Sen, A.M.; Sanz Gomez, A.; Fernandez Matellano, L.; Sanchez Contreras, S.; Diaz Lanza, A.M. In vivo and in vitro antiinflammatory activity of saikosaponins. Life Sci. 1998, 63, 1147–1156. [CrossRef]

306. Cheng, P.W.; Ng, L.T.; Chiang, L.C.; Lin, C.C. Antiviral effects of saikosaponins on human coronavirus 229e in vitro. Clin. Exp. Pharmacol. Physiol. 2006, 33, 612–616. [CrossRef] [PubMed]

307. Idris-Usman, M.S.; John-Africa, L.; Akuodor, G.C.; Ugwu, T.C.; Osunkwo, U.A. Antinociceptive and antipyretic properties of the pharmaceutical herbal preparation, radix bupleuri in rats. J. Med. Plants Res. 2010, 4, 659–663.

308. Cao, J.X.; Guo, B.M.; Zhang, H.F. Discussion on the adverse drug reaction monitoring by community pharmacies. Chin. J. Pharmacovigil. 2011, 8, 38–40.

309. Yang, J.K. Xian Dai Zhong Yi Zhong Liu Xue (Modern Oncology Study-Chinese Medicine); Shanghai University of Traditional Chinese Medicine Press: Shanghai, China, 2004.

310. Reginster, J.Y.; Gillot, V.; Bruyere, O.; Henrotin, Y. Evidence of nutriceutical effectiveness in the treatment of osteoarthritis. Curr. Rheumatol. Rep. 2000, 2, 472–477. [CrossRef] [PubMed]

311. Chrubasik, S.; Pittler, M.H.; Roufogalis, B.D. Zingiberis rhizoma: A comprehensive review on the ginger effect and efficacy profiles. Phytomedicine 2005, 12, 684–701. [CrossRef] [PubMed]

312. Ippoushi, K.; Azuma, K.; Ito, H.; Horie, H.; Higashio, H. [6]-gingerol inhibits nitric oxide synthesis in activated J774.1 mouse macrophages and prevents peroxynitrite-induced oxidation and nitrination reactions. Life Sci. 2003, 73, 3427–3437. [CrossRef] [PubMed]

313. Dedov, V.N.; Tran, V.H.; Duke, C.C.; Connor, M.; Christie, M.J.; Mandadi, S.; Roufogalis, B.D. Gingerol: A novel class of vanilloid receptor (VR1) agonists. Br. J. Pharmacol. 2002, 137, 793–798. [CrossRef] [PubMed]

314. Huang, Q.R.; Iwamoto, M.; Aoki, S.; Tanaka, N.; Tajima, K.; Yamahara, J.; Takaishi, Y.; Yoshida, M.; Tomimatsu, T.; Tamai, Y. Anti-5-hydroxytryptamine3 effect of galanolactone, diterpenoid isolated from ginger. Chem. Pharm. Bull. 1998, 46, 2000–2004. [CrossRef] [PubMed]

315. Chakraborty, D.; Bishayee, K.; Ghosh, S.; Biswas, R.; Mandal, S.K.; Khuda-Bukhsh, A.R. [6]-gingerol induces caspase 3 dependent apoptosis and autophagy in cancer cells: Drug-DNA interaction and expression of certain signal genes in hela cells. Eur. J. Pharmacol. 2012, 694, 20–29. [CrossRef] [PubMed]

316. Tang, W.; Zuo, J.P. Immunosuppressant discovery from Tripterygium wilfordii hook F: The novel triptolide analog (5R)-5-hydroxytriptolide (LLDT-8). Acta Pharmacol. Sin. 2012, 33, 1112–1118. [CrossRef] [PubMed]

317. Zakeri-Milani, P.; Valizadeh, H.; Islambulchilar, Z. Comparative bioavailability study of two cefixime formulations administered orally in healthy male volunteers. Arzneimittel-Forsch. 2007, 57, 97–100. [CrossRef] [PubMed]

318. Kannaiyan, R.; Manu, K.A.; Chen, L.; Li, F.; Rajendran, P.; Subramaniam, A.; Lam, P.; Kumar, A.P.; Sethi, G. Celastrol inhibits tumor cell proliferation and promotes apoptosis through the activation of c-Jun N-terminal kinase and suppression of PI3K/Akt signaling pathways. Apoptosis 2011, 16, 1028–1041. [CrossRef] [PubMed]

319. Zhao, J.; Sun, Y.; Shi, P.; Dong, J.N.; Zuo, L.G.; Wang, H.G.; Gong, J.F.; Li, Y.; Gu, L.L.; Li, N.; et al. Celastrol ameliorates experimental colitis in IL-10 deficient mice via the up-regulation of autophagy. Int. Immunopharmacol. 2015, 26, 221–228. [CrossRef] [PubMed]
320. Shen, Y.C.; Chou, C.J.; Chiou, W.F.; Chen, C.F. Anti-inflammatory effects of the partially purified extract of radix Stephaniae tetrandrae: Comparative studies of its active principles tetrandrine and fangchinoline on human polymorphonuclear leukocyte functions. *Mol. Pharmacol.* 2001, 60, 1083–1090. [PubMed]

321. Choi, H.S.; Kim, H.S.; Min, K.R.; Kim, Y.; Lim, H.K.; Chang, Y.K.; Chung, M.W. Anti-inflammatory effects of fangchinoline and tetrandrine. *J. Ethnopharmacol.* 2000, 69, 173–179. [CrossRef]

322. Tsutsumi, T.; Kobayashi, S.; Liu, Y.Y.; Kontani, H. Anti-hyperglycemic effect of fangchinoline isolated from *Stephania tetrandra* radix in streptozotocin-diabetic mice. *Biol. Pharm. Bull.* 2003, 26, 313–317. [CrossRef] [PubMed]

323. Huang, Y.T.; Cheng, Y.R.; Lin, H.C.; Chen, S.M.; Hong, C.Y. Haemodynamic effects of chronic octreotide and tetrandrine administration in portal hypertensive rats. *J. Gastroenterol. Hepatol.* 1998, 13, 266–272. [CrossRef] [PubMed]

324. Tian, F.; Ding, D.; Li, D. Fangchinoline targets PI3K and suppresses PI3K/Akt signaling pathway in SGC7901 cells. *Int. J. Oncol.* 2015, 46, 2355–2363. [CrossRef] [PubMed]

325. Padhye, S.; Dandawate, P.; Yusufi, M.; Ahmad, A.; Sarkar, F.H. Perspectives on medicinal properties of plumbagin and its analogs. *Med. Res. Rev.* 2012, 32, 1131–1158. [CrossRef] [PubMed]

326. Checker, R.; Patwardhan, R.S.; Sharma, D.; Menon, J.; Thoh, M.; Sandur, S.K.; Sainis, K.B.; Poduval, T.B. Plumbagin, a vitamin K3 analogue, abrogates lipopolysaccharide-induced oxidative stress, inflammation and endotoxic shock via NF-κB suppression. *Inflammation* 2014, 37, 542–554. [CrossRef] [PubMed]

327. Zhang, K.; Ge, Z.; Da, Y.; Wang, D.; Liu, Y.; Xue, Z.; Li, Y.; Li, W.; Zhang, L.; Wang, H.; et al. Plumbagin suppresses dendritic cell functions and alleviates experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* 2014, 273, 42–52. [CrossRef] [PubMed]

328. Kuete, V.; Alihert-Franco, S.; Eyong, K.O.; Ngameni, B.; Foleyec, G.N.; Nguemeving, J.R.; Tangmouo, J.G.; Fotso, G.W.; Komguem, J.; Ouahouo, B.M.; et al. Antibacterial activity of some natural products against bacteria expressing a multidrug-resistant phenotype. *Int. J. Antimicrob. Agents* 2011, 37, 156–161. [CrossRef] [PubMed]

329. Li, J.; Shen, L.; Lu, F.R.; Qin, Y.; Chen, R.; Li, J.; Li, Y.; Zhan, H.Z.; He, Y.Q. Plumbagin inhibits cell growth and potentiates apoptosis in human gastric cancer cells in vitro through the NF-κB signaling pathway. *Acta Pharmacol. Sin.* 2012, 33, 242–249. [CrossRef] [PubMed]

330. Sandur, S.K.; Ichikawa, H.; Sethi, G.; Ahn, K.S.; Aggarwal, B.B. Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) suppresses NF-κB activation and NF-κB-regulated gene products through modulation of p65 and IκBα kinase activation, leading to potentiation of apoptosis induced by cytokine and chemotherapeutic agents. *J. Biol. Chem.* 2006, 281, 17023–17033. [CrossRef] [PubMed]

331. Li, Y.C.; He, S.M.; He, Z.X.; Li, M.; Yang, Y.; Pang, J.X.; Zhang, X.; Chow, K.; Zhou, Q.; Duan, W.; et al. Plumbagin induces apoptotic and autophagic cell death through inhibition of the PI3K/Akt/mTOR pathway in human non-small cell lung cancer cells. *Cancer Lett.* 2014, 344, 239–259. [CrossRef] [PubMed]

332. Li, C.W.; Wu, S.S. Ze xie diao xue zhi de yan jiu jin zhan. *Asia Pac. Tradit. Med.* 2009, 5, 152–153.

333. Wagner, H.; Bauer, R.; Melchart, D.; Xiao, P.G.; Staudinger, A. *Chromatographic Fingerprint Analysis of Herbal Medicines*; Springer: Berlin, Germany; 2011; pp. 903–921.

334. Huang, Y.T.; Huang, D.M.; Chueh, S.C.; Teng, C.M.; Goh, J.H. Alisol b acetate, a triterpene from *Magnolia officinalis*, exerts anti-inflammatory and suppressive effects on human polymorphonuclear functions. *Biochem. Pharmacol.* 2014, 92, 73–89. [CrossRef] [PubMed]

335. Kumar, S.; Guru, S.K.; Pathania, A.S.; Kumar, A.; Bhushan, S.; Malik, F. Autophagy triggered by magnolol derivative negatively regulates angiogenesis. *Cell Death Dis.* 2013, 4, e889. [CrossRef] [PubMed]

336. Chen, C.R.; Tan, R.; Qu, W.M.; Wu, Z.; Wang, Y.; Urade, Y.; Huang, Z.L. Magnolol, a major bioactive constituent of the bark of *Magnolia officinalis*, exerts anti-inflammatory effects via the gaba/benzodiazepine receptor complex in mice. *Br. J. Pharmacol.* 2011, 164, 1534–1546. [CrossRef] [PubMed]

337. Bang, K.H.; Kim, Y.K.; Min, B.S.; Na, M.K.; Rhee, Y.H.; Lee, J.P.; Bae, K.H. Antifungal activity of magnolol and honokiol. *Arch. Pharm. Res.* 2000, 23, 46–49. [CrossRef] [PubMed]

338. Li, H.B.; Yi, X.; Gao, J.M.; Ying, X.X.; Guan, H.Q.; Li, J.C. Magnolol-induced h460 cells death via autophagy but not apoptosis. *Arch. Pharm. Res.* 2007, 30, 1566–1574. [CrossRef] [PubMed]
340. Yu, X.; Wu, D.Z.; Yuan, J.Y.; Zhang, R.R.; Hu, Z.B. Gastroprotective effect of fructus evodiae water extract on ethanol-induced gastric lesions in rats. *Am. J. Chin. Med.* **2006**, *34*, 1027–1035. [CrossRef] [PubMed]

341. Wang, L.; Hu, C.P.; Deng, P.Y.; Shen, S.S.; Zhu, H.Q.; Ding, J.S.; Tan, G.S.; Li, Y.J. The protective effects of rutacearpine on gastric mucosa injury in rats. *Planta Med.* **2005**, *71*, 416–419. [CrossRef] [PubMed]

342. Takada, Y.; Kobayashi, Y.; Aggarwal, B.B. Evodiamine abolishes constitutive and inducible Nf-κB activation by inhibiting IκBα kinase activation, thereby suppressing Nf-κB-regulated antiapoptotic and metastatic gene expression, up-regulating apoptosis, and inhibiting invasion. *J. Biol. Chem.* **2005**, *280*, 17203–17212. [CrossRef] [PubMed]

343. Wang, T.; Wang, Y.; Yamashita, H. Evodiamine inhibits adipogenesis via the EGFR-PKC pathway. *FEBS Lett.* **2009**, *583*, 3655–3659. [CrossRef] [PubMed]

344. Rasul, A.; Yu, B.; Zhong, L.; Khan, M.; Yang, H.; Ma, T. Cytotoxic effect of evodiamine in SGC-7901 human gastric adenocarcinoma cells via simultaneous induction of apoptosis and autophagy. *Oncol. Rep.* **2012**, *27*, 1481–1487. [PubMed]

345. Christina, A.J.M.; Saraswathy, G.R.; Robert, S.J.H.; Kothai, R.; Chidambaranathan, N.; Nalini, G.; Therasal, R.L. Inhibition of CCL4-induced liver fibrosis by piper longum linn.? *Phytomedicine* **2006**, *13*, 196–198. [CrossRef] [PubMed]

346. Bang, J.S.; Oh da, H.; Choi, H.M.; Sur, B.J.; Lim, S.J.; Kim, J.Y.; Yang, H.I.; Yoo, M.C.; Hahn, D.H.; Kim, K.S. Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1β-stimulated fibroblast-like synoviocytes and in rat arthritis models. *Arthritis Res. Ther.* **2009**, *11*, R49. [CrossRef] [PubMed]

347. Wakade, A.S.; Shah, A.S.; Kulkarni, M.P.; Juvekar, A.R. Protective effect of piper longum l. On oxidative stress induced injury and cellular abnormality in adriamycin induced cardiotoxicity in rats. *Indian J. Exp. Biol.* **2008**, *46*, 528–533. [PubMed]

348. Iwashita, M.; Oka, N.; Ohkubo, S.; Saito, M.; Nakahata, N. Piperlongumine, a constituent of piper longum linn., inhibits rabbit platelet aggregation as a thromboxane A2 receptor antagonist. *Eur. J. Pharmacol.* **2007**, *570*, 38–42. [CrossRef] [PubMed]

349. Liu, J.M.; Pan, F.; Li, L.; Liu, Q.R.; Chen, Y.; Xiong, X.X.; Cheng, K.; Yu, S.B.; Shi, Z.; Yu, A.C.; et al. Piperlongumine selectively kills glioblastoma multiforme cells via reactive oxygen species accumulation dependent JNK and p38 activation. *Biochem. Biophys. Res. Commun.* **2013**, *437*, 87–93. [CrossRef] [PubMed]

350. Bezerra, D.P.; Pessoa, C.; de Moraes, M.O.; Silveira, E.R.; Lima, M.A.; Elmiro, F.J.; Costa-Lotufo, L.V. Antiproliferative effects of two amides, piperine and piplartine, from piper species. *Z. Naturforsch. C* **2005**, *60*, 539–543. [CrossRef] [PubMed]

351. Wang, Y.; Wang, J.W.; Xiao, X.; Shan, Y.; Xue, B.; Jiang, G.; He, Q.; Chen, J.; Xu, H.G.; Zhao, R.X.; et al. Piperlongumine induces autophagy by targeting p38 signaling. *Cell Death Dis.* **2013**, *4*, e824. [CrossRef] [PubMed]

352. Sun, L.D.; Wang, F.; Dai, F.; Wang, Y.H.; Lin, D.; Zhou, B. Development and mechanism investigation of a new piperlongumine derivative as a potent anti-inflammatory agent. *Biochem. Pharmacol.* **2015**, *95*, 156–169. [CrossRef] [PubMed]

353. Aggarwal, B.B.; Kumar, A.; Bharti, A.C. Anticancer potential of curcumin: Preclinical and clinical studies. *Anticancer Res.* **2003**, *23*, 363–398. [PubMed]

354. Anand, P.; Sundaram, C.; Jhurani, S.; Kunnumakkara, A.B.; Aggarwal, B.B. Curcumin and cancer: An “old-age” disease with an “age-old” solution. *Cancer Lett.* **2008**, *267*, 133–164. [CrossRef] [PubMed]

355. Aggarwal, B.B.; Harikumar, K.B. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int. J. Biochem. Cell Biol.* **2009**, *41*, 40–59. [CrossRef] [PubMed]

356. Ravindran, J.; Prasad, S.; Aggarwal, B.B. Curcumin and cancer cells: How many ways can curry kill tumor cells selectively? *AAPS J.* **2009**, *11*, 495–510. [CrossRef] [PubMed]

357. Ruby, A.J.; Kuttan, G.; Babu, K.D.; Rajasekharan, K.N.; Kuttan, R. Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Lett.* **1995**, *94*, 79–83. [CrossRef]

358. Bandopadhyay, U.; Kaushik, S.; Varticovski, L.; Cuervo, A.M. The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. *Mol. Cell Biol.* **2008**, *28*, 5747–5763. [CrossRef] [PubMed]
Sharma, S.; Zhuang, Y.; Ying, Z.; Wu, A.; Gomez-Pinilla, F. Dietary curcumin supplementation counteracts reduction in levels of molecules involved in energy homeostasis after brain trauma. Neuroscience 2009, 161, 1037–1044. [CrossRef] [PubMed]

Yang, F.; Lim, G.P.; Begum, A.N.; Ubeda, O.J.; Simmons, M.R.; Ambegaokar, S.S.; Chen, P.P.; Kayed, R.; Glade, C.G.; Frautschy, S.A.; et al. Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J. Biol. Chem. 2005, 280, 5892–5901. [CrossRef] [PubMed]

Garcia-Alloza, M.; Borrelli, L.A.; Rozkalne, A.; Hyman, B.T.; Bacskai, B.J. Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model. J. Neurochem. 2007, 102, 1095–1104. [CrossRef] [PubMed]

Zhou, L.M.; Zuo, Z.; Chow, M.S.S. Danshen: An overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. J. Clin. Pharmacol. 2005, 45, 1345–1359. [CrossRef] [PubMed]

Chiou, G.C.; Yan, H.Y.; Lei, X.L.; Li, B.H.; Shen, Z.F. Ocular and cardiovascular pharmacology of Salviae miltiorrhizae. Molecules 2016, 21, 359. [CrossRef] [PubMed]

Jang, S.I.; Kim, H.J.; Kim, Y.J.; Jeong, S.I.; You, Y.O. Tanshinone IIA inhibits LPS-induced Nf-κB activation in RAW 264.7 cells: Possible involvement of the NIK-IKK, ERK1/2, p38 and JNK pathways. Eur. J. Pharmacol. 2006, 542, 1–7. [CrossRef] [PubMed]

Tan, X.; Li, J.; Wang, X.; Chen, N.; Cai, B.; Wang, G.; Shan, H.; Dong, D.; Liu, Y.; Li, X.; et al. Tanshinone IIA protects against cardiac hypertrophy via inhibiting calcineurin/NFATC3 pathway. Int. J. Biol. Sci. 2011, 7, 383–389. [CrossRef] [PubMed]

He, H.; Liu, X.; Lv, L.; Liang, H.; Leng, B.; Zhao, D.; Zhang, Y.; Du, Z.; Chen, X.; Li, S.; et al. Calcineurin suppresses AMPK-dependent cytoprotective autophagy in cardiomyocytes under oxidative stress. Cell Death Dis. 2014, 5, e977. [CrossRef] [PubMed]

Liu, J.Y. Advances of ligusticum chuanxiong. Tianjin Pharm. 1991, 3, 29–31.

Hou, Y.Z.; Zhao, G.R.; Yuan, Y.J.; Zhu, G.G.; Hiltunen, R. Inhibition of rat vascular smooth muscle cell proliferation by extract of Ligusticum chuanxiong and Angelica sinensis. J. Ethnopharmacol. 2005, 100, 140–144. [CrossRef] [PubMed]

Hou, Y.Z.; Zhao, G.R.; Yang, J.; Yuan, Y.J.; Zhu, G.G.; Hiltunen, R. Protective effect of Ligusticum chuanxiong and Angelica sinensis on endothelial cell damage induced by hydrogen peroxide. Life Sci. 2004, 75, 1775–1786. [CrossRef] [PubMed]

Chiou, G.C.; Yan, H.Y.; Lei, X.L.; Li, B.H.; Shen, Z.F. Ocular and cardiovascular pharmacology of tetramethylpyrazine isolated from Ligusticum wallichii Franch. Zhongguo Yao Li Xue Bao 1991, 12, 99–104. [PubMed]

Zhang, Z.H.; Yu, S.Z.; Wang, Z.T.; Zhao, B.L.; Hou, J.W.; Yang, F.J.; Xin, W.J. Scavenging effects of tetramethylpyrazine on active oxygen free radicals. Zhongguo Yao Li Xue Bao 1994, 15, 229–231. [PubMed]

Kao, T.K.; Chang, C.Y.; Ou, Y.C.; Chen, W.Y.; Kuan, Y.H.; Pan, H.C.; Liao, S.L.; Li, G.Z.; Chen, C.J. Tetramethylpyrazine reduces cellular inflammatory response following permanent focal cerebral ischemia in rats. Exp. Neurol. 2013, 247, 188–201. [CrossRef] [PubMed]

Shimada, K.; Fujii, Y.; Yamashita, E.; Nizakari, Y.; Sato, Y. Studies on cardiotoxic steroids from the skin of Japanese toad. Chem. Pharm. Bull. 1977, 25, 714–730. [CrossRef] [PubMed]

Chen, K.K.; Kovarikova, A. Pharmacology and toxicology of toad venom. J. Pharm. Sci. 1967, 56, 1535–1541. [CrossRef] [PubMed]

Zhang, D.M.; Liu, J.S.; Tang, M.K.; Yi, A.; Cao, H.H.; Jiang, L.; Chan, J.Y.; Tian, H.Y.; Fung, K.P.; Ye, W.C. Bufotalin from venenum bufonis inhibits growth of multidrug resistant HepG2 cells through G2/M cell cycle arrest and apoptosis. Eur. J. Pharmacol. 2012, 692, 19–28. [CrossRef] [PubMed]
387. Yu, J.; Guo, Q.L.; You, Q.D.; Zhao, L.; Gu, H.Y.; Yang, Y.; Zhang, H.W.; Tan, Z.; Wang, X. Gambogic acid-induced G2/M phase cell-cycle arrest via disturbing CDK7-mediated phosphorylation of CDC2/p34 in human gastric carcinoma BGC-823 cells. Carcinogenesis 2007, 28, 632–638. [CrossRef] [PubMed]

388. Zhang, H.; Han, T.; Zhang, L.; Yu, C.H.; Wan, D.G.; Rahman, K.; Qin, L.P.; Peng, C. Effects of tenuifolin extracted from Radix Polygalae on learning and memory: A behavioral and biochemical study on aged and amnesic mice. Phytomedicine 2015, 22, 587–594. [CrossRef] [PubMed]

389. Yao, Y.; Jia, M.; Wu, J.G.; Zhang, H.; Sun, L.N.; Chen, W.S.; Rahman, K. Anxiolytic and sedative-hypnotic activities of polygalasaponins from polygala tenuifolia in mice. Pharm. Biol. 2010, 48, 801–807. [CrossRef] [PubMed]

390. Shin, I.J.; Son, S.U.; Park, H.; Kim, Y.; Park, S.H.; Swanberg, K.; Shin, J.Y.; Ha, S.K.; Cho, Y.; Bang, S.Y.; et al. Preclinical evidence of rapid-onset antidepressant-like effect in chronic mild stress-induced depressive rats. J. Ethnopharmacol. 2013, 150, 1053–1061. [CrossRef] [PubMed]

391. Le, T.K.; Jeong, J.J.; Kim, D.H. Cionosterol and ethyl cholestan-22-enol isolated from the rhizome of polygala tenuifolia inhibit phosphatidylinositol 3-kinase/AKT pathway. Biol. Pharm. Bull. 2012, 35, 1379–1383. [CrossRef] [PubMed]

392. Wu, A.G.; Wong, V.K.W.; Zeng, W.; Liu, L.; Law, B.Y.K. Identification of novel autophagic radix polygala fraction by cell membrane chromatography and UHPLC-(Q)TOF-Ms for degradation of neurodegenerative disease proteins. Sci. Rep. 2015, 5. [CrossRef] [PubMed]

393. Thyagarajan, A.; Jednak, A.; Nguyen, H.; Terry, C.; Baldridge, L.A.; Jiang, J.; Sliva, D. Triterpenes from ganoderma lucidum induce autophagy in colon cancer through the inhibition of p38 mitogen-activated kinase (p38 MAPK). Nutr. Cancer 2010, 62, 630–640. [CrossRef] [PubMed]
398. Hossain, A.; Radwan, F.F.; Doonan, B.P.; God, J.M.; Zhang, L.; Bell, P.D.; Haque, A. A possible cross-talk between autophagy and apoptosis in generating an immune response in melanoma. *Apoptosis* 2012, 17, 1066–1078. [CrossRef] [PubMed]

399. Reis, F.S.; Lima, R.T.; Morales, P.; Ferreira, I.C.; Vasconcelos, M.H. Methanolic extract of ganoderma lucidum induces autophagy of ags human gastric tumor cells. *Molecules* 2015, 20, 17872–17882. [CrossRef] [PubMed]

400. Ip, S.P.; Tse, A.S.M.; Poon, M.K.T.; Ko, K.M.; Ma, C.Y. Antioxidant activities of polygonum multiflorum thunb., in *vivo* and in *vitro*. *Phytother. Res.* 1997, 11, 42–44. [CrossRef]

401. Huang, Q.; Lu, G.; Shen, H.M.; Chung, M.C.; Ong, C.N. Anti-cancer properties of anthraquinones from rhubarb. *Med. Res. Rev.* 2007, 27, 609–630. [CrossRef] [PubMed]

402. Yim, T.K.; Wu, W.K.; Mak, D.H.; Ko, K.M. Myocardial protective effect of an anthraquinone-containing extract of polygonum multiflorum *ex vivo*. *Planta Med.* 1998, 64, 607–611. [CrossRef] [PubMed]

403. Pickhardt, M.; Gazova, Z.; von Bergen, M.; Khlistunova, I.; Wang, Y.; Hascher, A.; Mandelkow, E.M.; Biernat, J.; Mandelkow, E. Anthraquinones inhibit TAU aggregation and dissolve Alzheimer’s paired helical filaments in *vivo* and in cells. *J. Biol. Chem.* 2005, 280, 3628–3635. [CrossRef] [PubMed]

404. Lai, Q.; Wei, J.; Mahmoodurrahman, M.; Zhang, C.; Quan, S.; Li, T.; Yu, Y. Pharmacokinetic and nephroprotective benefits of using *Schisandra Chinensis* extracts in a cyclosporine a-based immune-suppressive regime. *Drug Des. Dev. Ther.* 2015, 9, 4997–5018.

405. Yu, C.Y.; Yu, C.R.; Li, H.; Ju, W.B.; Jiang, E.P.; Chen, J.G. Schisandra total lignin attenuates apoptosis of the endoplasmic reticulum pathway to delay mouse brain aging. *Chin. J. Pathophysiol.* 2014, 30, 1967–1973.

406. Chan, Y.Y.; Chen, Y.H.; Yang, S.N.; Lo, W.Y.; Lin, J.G. Clinical efficacy of traditional chinese medicine, suan zao ren tang, for sleep disturbance during methadone maintenance: A randomized, double-blind, placebo-controlled trial. *Evid. Based Complement. Altern. Med.* 2015, 2015, 2015. [CrossRef] [PubMed]

407. Yeh, C.-H.; Arnold, C.K.; Chen, Y.-H.; Lai, J.-N. Suan zao ren tang as an original treatment for sleep difficulty in climacteric women: A prospective clinical observation. *Evid. Based Complement. Altern. Med.* 2011, 2011, 673813. [CrossRef] [PubMed]

408. Reis, F.S.; Lima, R.T.; Morales, P.; Ferreira, I.C.; Vasconcelos, M.H. Methanolic extract of ganoderma lucidum *ex vivo*. *Phytother. Res.* 2016, 30, 859–868. [CrossRef] [PubMed]

409. Xu, M.Y.; Lee, S.Y.; Kang, S.S.; Jung, Y.S. *Zizyphus jujuba* and its active component jujuboside B inhibit platelet aggregation. *Phytother. Res.* 2012, 27, 829–834. [CrossRef] [PubMed]

410. He, G.P.; Bao, Z.X.; Chen, B.J.; Li, L. Analysis on characteristic of kaixin powder and its similar prescriptions. *Chin. Arch. Tradit. Chin. Med.* 2012, 3, 583–584.

411. Weber, T.; Lu, M.; Andera, L.; Lahm, H.; Gellert, N.; Fariss, M.W.; Sattler, W.; Ucker, D.S.; Terman, A.; et al. Vitamin E succinate is a potent novel antineoplastic agent with high selectivity and cooperative activity with tumor necrosis factor-related apoptosis-inducing ligand (APO2 ligand) in *vivo*. *Clin. Cancer Res.* 2002, 8, 863–869. [PubMed]

412. Jia, Y.M.; Zhang, X. Analysis of rule and clinance of mind-calming medicine purgative. *China J. Chin. Med.* 2011, 26, 1078–1082.

413. Ming, R.; VanBuren, R.; Liu, Y.; Yang, M.; Han, Y.; Li, L.T.; Zhang, Q.; Kim, M.J.; Schatz, M.C.; Campbell, M.; et al. Genome of the long-living sacred lotus (*Nelumbo nucifera* Gaertn.). *Genome Biol.* 2013, 14, R41. [CrossRef] [PubMed]

414. Li, Q.X.; Fan, Z. The epidermal growth factor receptor antibody cetuximab induces autophagy in cancer cells by downregulating HIF-1α and Bcl-2 and activating the beclin 1/hVps34 complex. *Cancer Res.* 2010, 70, 5942–5952. [CrossRef] [PubMed]

415. Carew, J.S.; Medina, E.C.; Esquivel, J.A., 2nd; Mahalingam, D.; Swords, R.; Kelly, K.; Zhang, H.; Huang, P.; Mita, A.C.; Mita, M.M.; et al. Autophagy inhibition enhances vorinostat-induced apoptosis via ubiquitinated protein accumulation. *J. Cell Mol. Med.* 2010, 14, 2448–2459. [CrossRef] [PubMed]

416. Wu, Z.; Chang, P.C.; Yang, J.C.; Chu, C.Y.; Wang, L.Y.; Chen, N.T.; Ma, A.H.; Desai, S.J.; Lo, S.H.; Evans, C.P.; et al. Autophagy blockade sensitizes prostate cancer cells towards SRC family kinase inhibitors. *Genes Cancer* 2010, 1, 40–49. [CrossRef] [PubMed]
421. Rosenfeld, M.R.; Grossman, S.A.; Brem, S.; Dobrenis, K.; O'Dwyer, P.; Wang, D.; Piao, S.; Davis, L.E.; Mikkalsen, T.; Yang, Z.J.; Chee, C.E.; Huang, S.; Sinicrope, F.A. The role of autophagy in cancer: Therapeutic implications. *Nat. Rev. Drug Discov.* 2003, 2, 373–385. [CrossRef] [PubMed]

422. Stein, M.; Lin, H.X.; Jeyamohan, C.; Dvorzhinski, D.; Gouder, M.; Bray, K.; Eddy, S.; Goodin, S.; White, E.; DiPaola, R.S. Targeting tumor metabolism with 2-deoxyglucose in patients with castrate-resistant prostate cancer and advanced malignancies. *Prostate* 2010, 70, 1388–1394. [CrossRef] [PubMed]

423. Salminen, A.; Kaarniranta, K.; Hiltunen, M.; Soininen, H. AMP-activated protein kinase: A potential player in Alzheimer’s disease. *J. Neurochem.* 2011, 118, 640–651. [CrossRef] [PubMed]

424. Morgan, D.O.; Menon, M.; Cardoso, J.; Cheng, L.; Liao, J.; Zhuang, X.; Xu, J.; Xie, H.; Wängström, R.; Li, Q.; Feng, Q.; Quan, H.; Jin, J.; Wang, Y.; Zhan, J.; Zhang, D.; Li, Z.; Li, Y.; Zeng, Z.; Deng, Y.; Chang, E.; Zhang, H.; Liang, S.; Xie, A.; Li, J.; Ma, Y.; Shi, Y.; Zhou, L.; Li, L.; Zou, Y. Targeting autophagy in cancer. *Nat. Rev.* 2012, 12, 34–47. [CrossRef] [PubMed]

425. Rubinsztein, D.C.; Codogno, P.; Levine, B. Autophagy modulation as a potential therapeutic target for diverse diseases. *Nat. Rev. Drug Discov.* 2012, 11, U709–U784. [CrossRef] [PubMed]

426. Magnaudeix, A.; Wilson, C.M.; Page, G.; Bailleul, C.; Codogno, P.; Leveque, P.; Labrousse, F.; Corre-Delage, M.; Yardin, C.; Terro, F. PP2A blockade inhibits autophagy and causes intraneuronal accumulation of ubiquitinated proteins. *Neurobiol. Aging* 2013, 34, 770–790. [CrossRef] [PubMed]

427. Pék, G.; Fülöp, T.; Zs-Nagy, I. Gerontopsychological studies using nai (“nürnberger alters-inventar”) on patients with organic psychosyndrome (DSM III, category 3) treated with centetophenine in a double blind, comparative, randomized clinical trial. *Arch. Gerontol. Geriatr.* 1989, 9, 17–30. [CrossRef]

428. White, E. Deconvoluting the context-dependent role for autophagy in cancer. *Nat. Rev. Cancer* 2012, 12, 401–410. [CrossRef] [PubMed]

429. Janku, F.; McConkey, D.J.; Hong, D.S.; Kurzrock, R. Autophagy as a target for anticancer therapy. *Nat. Rev. Clin. Oncol.* 2011, 8, 528–539. [CrossRef] [PubMed]

430. Kmiec, Z. Cooperation of liver cells in health and disease. *Adv. Anat. Embryol. Cell Biol.* 2001, 161, 1–151.

431. Battaller, R.; Brenner, D.A. Liver fibrosis. *J. Clin. Invest.* 2005, 115, 209–218. [CrossRef] [PubMed]

432. Toghi, T.; Kikuchi, S.; Wakatsuki, S.; Uemura, T.; Takahashi, T.; Ueno, K. A role for autophagy during hepatic stellate cell activation. *J. Cell Biol.* 2011, 194, 729–744. [CrossRef] [PubMed]

433. Yang, E.R.; Wang, B.Z.; Lee, Y.J.; Kim, B.M.; Kim, Y.J.; Hong, H.D.; Jeon, H.K.; Chung, H.W. Effect of *Bupleuri radix* extracts on the toxicity of 5-fluorouracil in HepG2 hepatoma cells and normal human lymphocytes. *Basic Clin. Pharmacol. Toxicol.* 2008, 103, 305–313. [CrossRef] [PubMed]

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