Pharmacological Research - Natural Products 10 (2026) 100518

Contents lists available at ScienceDirect

Pharmacological Research - Natural Products

journal homepage: www.sciencedirect.com/journal/prenap

A review on the ethnopharmacology, anticancer mechanism, toxicity and clinical application of andrographolide isolated from *Andrographis paniculata* (Burm.f.) Nees

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ARTICLE INFO

Keywords:
Andrographis paniculata
Andrographolide
Anticancer
Ethnopharmacology
Toxicity
Clinical trial

ABSTRACT

Andrographis paniculata (Burm. f.) Nees (*A. paniculata*), commonly known as "King of Bitters," has been widely used in traditional medicine in Asia, primarily for its heat-clearing, detoxifying, anti-inflammatory hepatoprotective properties. Andrographolide (AG), a bioactive compound derived from *A. paniculata* has been extensively investigated for its anticancer potential. Numerous studies have demonstrated its efficacy across various cancers, highlighting the potential of AG as a promising drug for cancer therapy. This review aims to systematically summarize the ethnopharmacological uses of *A. paniculata* and its main compound AG, the anticancer mechanisms, preclinical toxicity analysis and clinical therapeutic potential of AG, focusing on its multi-targeted actions across various cancer types and its application in clinical trials. A comprehensive literature survey was conducted using English medium databases from 2015 to 2025. After applied the exclusion and inclusion criteria, 102 articles related to the keywords of "*Andrographis paniculata*", "*Andrographis paniculata* traditional uses", "andrographolide anticancer", "andrographolide toxicity and safety", "andrographolide adverse reactions" and "Andrographolide clinical trial" were compiled for critical review. AG exerts its anticancer effects in animal and different cancer cell lines via various mechanism inducing apoptosis, promoting autophagy, triggering ferroptosis, and arresting the cell cycle, etc. AG is relatively safe compound with less toxicity *in vivo* and *in vitro*. The clinical trials and findings for different disease have been investigated and summarized. Andrographolide has the potential to be a promising drug for cancer treatment. The combination with other drugs and natural compounds can improve therapy. The toxicity and clinical trials need further study.

Abbreviations: A. paniculata,, Andrographis paniculata; AG,, Andrographolide; AKT,, Protein kinase B; AP-1,, Activator protein-1; ATF4,, Activating transcription factor 4; Bax ,, Bax Bcl-2-associated X protein; Bcl-2 ,, Bcl-2 B cell lymphoma 2; BFGF,, Basic fibroblast growth factor; CDK,, Cyclin-dependent kinase; CHOP,, C/EBP homologous protein; C-Myc,, C-myelocytomasis; COX-2 ,, COX-2 Cyclooxygenase-2; CRC,, Colorectal cancer; CTX,, Cetuximab; Cyto C,, cytochrome-c; DDP,, Cisplatin; DKK1,, Dickkopf-1; DR,, Death receptor; EGFR,, Epidermal growth factor receptor.; EMT,, Epithelial to mesenchymal transition; ENOS,, Endothelial nitric oxide synthase; ER,, Estrogen receptor; ERK,, Extracellular signal-regulated kinase; ERS,, endoplasmic reticulum stress; ESCCE,, Esophageal squamous cell carcinoma; FUL,, Fulvestrant; GBM,, Glioblastoma Multiforme; HCC,, Hepatocellular carcinoma; HDAC4,, Histone deacetylase; EGFR,, Epidermal growth factor receptor; HDAC4,, histone deacetylase; HER,, human epidermal receptor; IL-6,, Interleukin-6; INOS,, Inducible Nitric Oxide Synthase; IRE-1,, Inositol-Requiring Enzyme 1; JNK,, c-Jun N-terminal kinases; MiRNA,, MicroRNA; MMP,, Matrix Metalloproteinase; MS,, Multiple Sclerosis; MTOR,, Mammalian target of rapamycin; MyD88,, Myeloid differentiation primary response 88 protein; NF-κB,, Nuclear factor kappa-light-chain-enhancer of activated B; NSCLC,, non-small cell lung cancer; OCSC,, oral cancer stem cells; OSCC,, oral squamous cell carcinoma; PD-1,, Programmed cell death protein 1; PD-L1,, programmed death-ligand 1; PHi,, Intracellular pH; PI3K,, Phosphatidylinositol-3-kinase; PR,, progesterone receptor; ROS,, Reactive oxygen species; STAT3,, Signal transducer and activator of Transcription 3; TCF-1,, T-cell factor 1; TIMP,, Tissue inhibitors of metalloproteinase; TLR4,, Toll-like receptor 4; TNBC,, Triple-negative breast cancer; TNF,, Tumor necrosis factor; TRAIL,, Tumor necrosis factor–related apoptosis-inducing ligand; UPR,, unfolded protein response; VEGF,, Vascular endothelial growth factor; 5-FU,, 5- Fluorouracil.

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https://doi.org/10.1016/j.prenap.2026.100518
Received 18 September 2025; Received in revised form 25 December 2025; Accepted 16 January 2026
Available online 18 January 2026

1. Introduction

Cancer continues to pose a significant challenge to global health. It is a complex disease that results in significant morbidity and mortality worldwide [1]. It is consistently ranked among the leading causes of death worldwide and poses a significant barrier to increasing life expectancy [2]. Cancer is characterized by unregulated, random cell division and invasiveness [3]. Cancer treatments such as chemotherapy, radiotherapy and surgery are harmful to the nervous system and the gastrointestinal tract. They also cause side effects such as ovarian failure and infertility for women [4]. Some natural compounds of plants such as flavonoids, phenolics and lactones have been reported to exhibit remarkable anticancer properties with fewer side effects [5,6]. Evidences showed the feasibility of utilizing plant-derived extracts or compounds for cancer treatment [7]. Plant is well-known as a natural source of bioactive products for thousand years. In particular, medicinal plants have been used for thousands of years as folk medicines in Asian and African populations. They are also widely consumed for health benefits in developed nations [8].

Andrographis paniculata (Burm. f.) Nees (*A. paniculata*) is an herbaceous plant, popularly known as 'the king of bitters' due to its intense bitter taste. *A. paniculata* from the Acanthaceae family has been traditionally used as medicine in China, India, Thailand, Bangladesh, Malaysia and Indonesia [9]. This plant has been widely used in traditional medicine systems due to its pharmacological properties such as clearing heat [10], detoxifying, antiviral [11], antioxidant, anti-inflammatory [12], antimalarial [13], hepatoprotective [14] and reducing swelling and pain [15]. Based on previous review findings, the number of articles reported on pharmacological and therapeutic properties of the plant has increased significantly from seventy-two in 2010–2020 [16] to ninety in 2021 [17]. Many bioactive compounds have been discovered in the leaves of *A. paniculata* including diterpenes, xanthones and flavonoids [18]. Among these, diterpenoids, particularly andrographolide (AG), is recognized as the primary contributors to the plant's pharmacological effects. Recent studies demonstrated that the ability of AG to inhibit the proliferation of various cancer cells including breast, lung, colorectal, gastric, liver, pancreatic, and prostate cancers. It is relatively low toxicity and its multi-targeted nature make AG has the potential to be a promising cancer drug in anticancer therapeutics [19].

This review provides an updated and integrated perspective by combining newly reported molecular mechanisms underlying the anticancer activity of AG across various cancer cell types with its recent findings on toxicity and clinical applications. The potential molecular mechanisms have been systematically organized and illustrated with schematic diagrams to provide a better understanding of interaction mediated through key signaling pathways which collectively contribute to the inhibition of various cancer cell lines.

2. Method

2.1. Data collection

This review was systematically performed by collecting articles from the ScienceDirect, SCOPUS, PubMed, Web of Science, Springer and Wiley online library published between 2015 and 2025 to explore the anticancer potential and mechanism of AG. The key words of the literature search included "*Andrographis paniculata*", "*Andrographis paniculata* traditional uses", "Andrographolide and anticancer", "Andrographolide toxicity and safety" "Andrographolide adverse reactions" and "Andrographolide clinical trial". Papers categorized as randomized controlled trials, case reports, reviews, and research articles published in English only were considered in this review.

2.2. Inclusion and exclusion criteria

The articles were screened to narrow the scope and obtain relevant technical data. Studies focused specifically onethnopharmacological uses of AG and its anticancer mechanism including *in vitro* and *in vivo*, preclinical toxicity studies and clinical treatment effects including adverse reactions or side effects of AG to humans or animals. Publications should be with clear methodology and results. However, studies that are not related to this plant and the above-mentioned keywords, articles without accessible full texts or incomplete information, duplicates or multiple publications of the same data or reviews are not included in this review. The process of data handling and the criteria of data screening are demonstrated in Fig. 1.

3. Result

According to the literature search, a total of 7079 papers was retrieved from all databases. After removing duplicates, 4772 articles remained. By applying the inclusion and exclusion criteria, 104 articles were selected for reviewing. The selected articles primarily focused on the pharmacological activity such as anticancer, anti-inflammatory and hepatoprotective of AG. The papers were further classified into five main categories, namely the pharmacological activities (13.61 %), anticancer mechanism (40.83 %), toxicity (6.51 %), clinical trials (6.51 %) and cancer background (32.54 %) as demonstrated in Fig. 2. There are more than half of the selected articles focusing on the anticancer mechanisms of AG between 2015 and 2025.

4. Ethnopharmacological uses and andrographolide

A. paniculata, as a traditional herb, has been used in folk medicine in China and other regions of East and Southeast Asia for hundreds of years [20]. It is used in ancient Oriental medicine and Ayurvedic medicine. According to the Chinese medical book, *Lingnan Medicinal Collection Record* (嶺南采藥錄, Lǐng nán cǎi yào lù), it is reported that the plant can cure snakebite and manage internal injury cough [21]. Traditional medical systems such as Ayurveda have used this herb to improve liver detoxification function for a long time [18]. *A. paniculata* is also traditionally used to treat fever, dysentery, malaria and gastrointestinal diseases [22,23]. The plant is about 30–110 cm tall, with dark green stems, glabrous leaves, and violet to white flowers as shown in Fig. 3 [24]. The plant contains 32 bioactive substances, including diterpenes, flavonoids, and lactones which can be found in plant roots, leaves, and aerial parts [25].

Andrographolide (AG), the main phytochemical of *A. paniculata*, is a lactone diterpenoid compound with the molecular formula of $C_{20}H_{30}O_5$ (Fig. 4). Its chemical name is 3α, 14, 15, 18-tetrahydroxy-5β, 9βH, 10α-labda-8, 12-dien-16-oic acid γ-lactone [26]. AG has demonstrated to exhibit multiple pharmacological activities, the compound has attracted attention from scientists and researchers, primarily due to its pharmacological properties such as anticancer [27], anti-inflammatory [28], antibacterial [29], immune regulatory [30], neuroprotective [31], hepatoprotective [32] and anti-cardiovascular activities [13]. Recent studies demonstrated that the ability of AG to inhibit the proliferation of various cancer cells including breast, lung, colorectal, gastric, liver, pancreatic, and prostate cancers. Its relatively low toxicity and multi-targeted nature make AG has the potential to be a promising cancer drug in anticancer therapeutics [19].

Although AG exhibits promising anticancer and therapeutic effects, its clinical application is limited, mainly due to its unfavorable pharmacokinetics. It is lipophilic with low aqueous solubility (3.29 ± 0.73 μg/mL at 25 °C) which impairs its dissolution and absorption [33]. Therefore, it has low systemic exposure and bioavailability after oral administration. Nevertheless, strategies such as nano-scaled delivery systems and β-cyclodextrin complexes have been discussing to improve its poor solubility and limited bioavailability [34]. For instances, polymeric andrographolide nanoparticles enhanced its anti-cancer properties three fold by exhibiting reduced IC_{50} in breast cancer cells [35]. Moreover, AG nanoparticles reduced tumor weight by

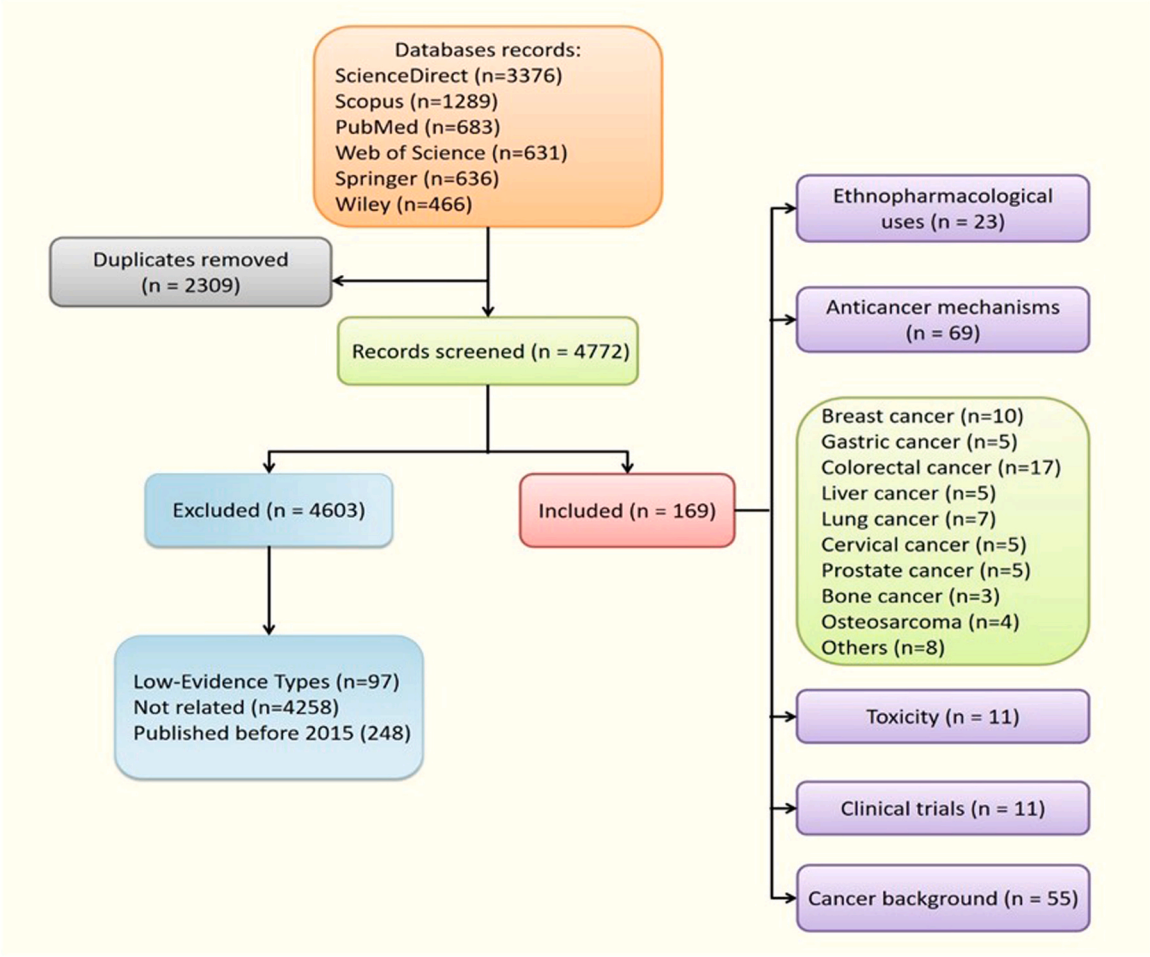

Fig. 1. Systematic literature search methodology for studies on andrographolide and *Andrographis paniculata*.

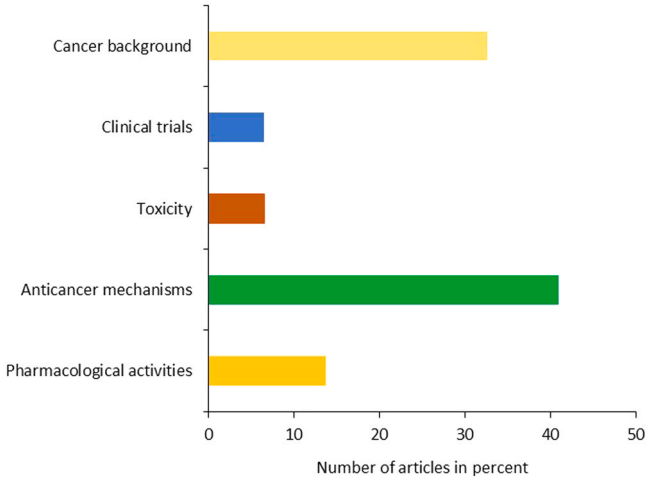

Fig. 2. Percentage of articles reporting on the anticancer mechanisms, toxicity, and clinical trials of andrographolide (2015–2025).

Fig. 3. Plant morphology of *Andrographis paniculata* showing the leaves, stems, flowers and buds.

about 68 % compared with 25 % for free AG in Ehrlich ascites carcinoma model. The improved bioavailability was also proven by the study of Sanati et al. [36] who demonstrated that tumour size of HeLa bearing mice was significantly reduced by 73 % after treated with AG loaded polymeric nanoparticles.

5. Anticancer mechanisms of andrographolide

5.1. Cell cycle arrest

The cell cycle is a series of events to control cell division and replication; dysregulation of the cell cycle mechanism leads to uncontrolled

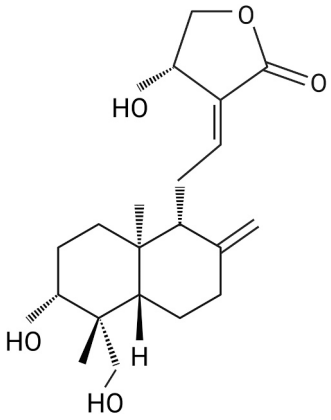

Fig. 4. The chemical structure of andrographolide.

cell growth, which is one of the core characteristics of cancer [37]. It is regulated by cyclins and cyclin-dependent kinases (CDKs) [38]. In another study, AG activated p53 by inducing the DNA damage response, which increased p21 and upregulates p27 by downregulating Skp2 (a ubiquitin ligase that targets p27 for degradation) to induce G_0/G_1 phase arrest in A549 cells [39]. For the G_2/M phase arrest, AG induced ROS and activated p53-dependent G_2/M cell cycle arrest with the upregulation of cyclin B1 and inactivation of CDK in hepatoma cells [40]. In human colorectal carcinoma, AG induces G_2/M arrest by downregulating CDK1 and Cyclin B1 [41]. In addition, AG induced human brain cancer cell cycle arrest at the G_2/M phase by activating extracellular signal-regulated kinase (ERK) 1/2, thereby activating the transcription of C-myelocytomasis (c-Myc) protein and upregulating p53 [42]. Based on previous studies, it is important to highlight that AG could induce cell cycle arrest in various cancer cell lines by modulating key regulatory proteins such as cyclins, CDKs, p21, p27, p16 and p53. Such phenomenon could be observed from its effects on the G_0/G_1, G_1/S, and G_2/M phases. The AG-mediated cell cycle arresting pathway are depicted Fig. 5. (Fig. 6).

5.2. Apoptosis

Apoptosis, also known as programmed cell death, plays a crucial role in cancer biology [43] Extrinsic and intrinsic pathways are the two major apoptosis mechanisms Fig. 7. The former is caused by the binding of death ligands (like FasL) to cell-surface death receptors, whereas the latter is the permeabilization of mitochondrial outer membrane caused by Bcl-2-family pro-apoptotic proteins [44]. The occurrence of either extrinsic or intrinsic pathways depends on the activation of cysteine proteases to cleave caspases at aspartate residues [45].

Loh et al. [46] demonstrated that the concentration of AG > 30 μM decreased the levels of pro-caspase-3, Bcl-2 and PARP (poly--ADP-ribose-polymerase), as well as cleaved caspase-3 in breast cancer cells, thereby activating apoptotic cascade. One year later, Chen et al. [47] reported that AG activated the mitochondrial apoptosis pathway in non-small cell lung cancer cells, as evidenced by the increased expression of pro-apoptotic proteins (Bax and Bak), reduced expression of the anti-apoptotic protein Bcl-2, decreased mitochondrial membrane potential (ΔΨm), promotion of cytochrome-c (cyto C) release from mitochondria into the cytoplasm, and mitochondrial translocation of Bak. Moreover, in the treatment of MDA-MB-231 breast cancer cells, AG increased ROS levels, reduced ΔΨm, upregulated pro-Bax and downregulated Bcl-2 and Bcl-xL, and thus enhancing the activation of caspase-9 and −7 to reduce apoptosis [48].

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of TNF family that induces apoptosis specifically in

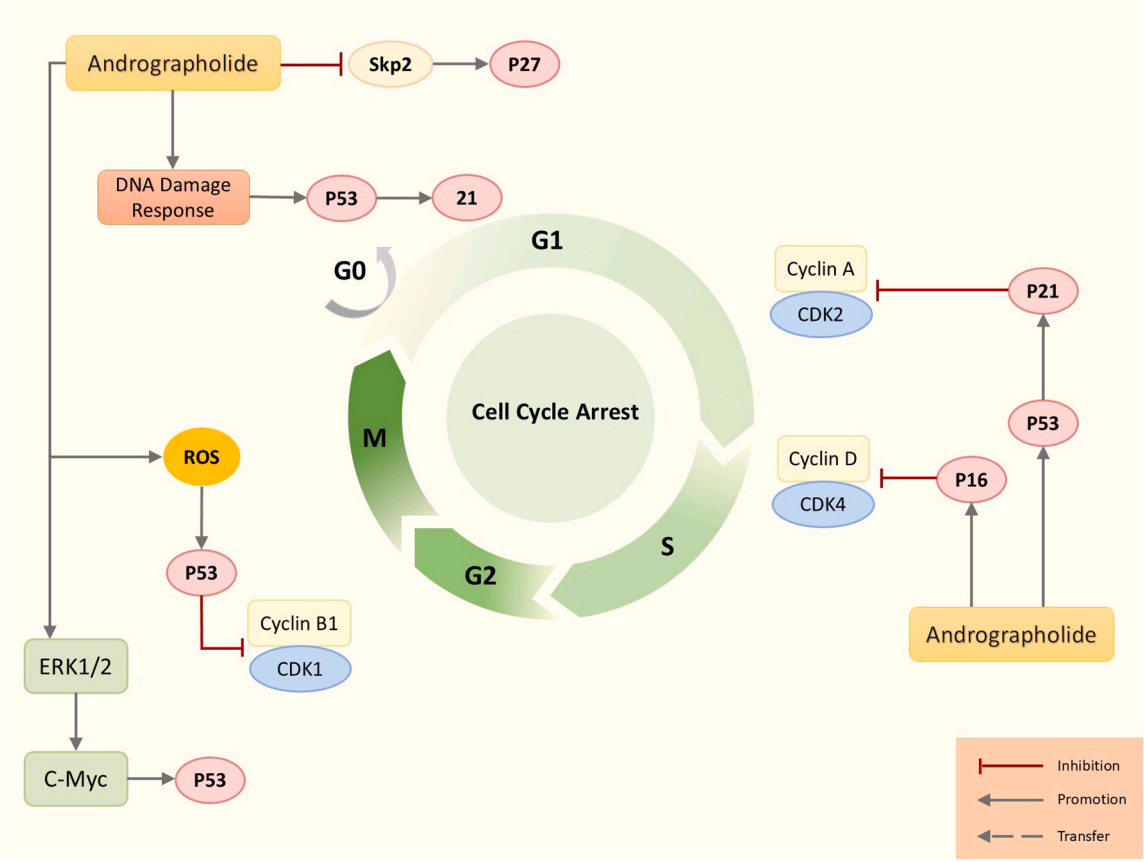

Fig. 5. Mechanism of andrographolide-induced cell cycle arrest in cancer cells.

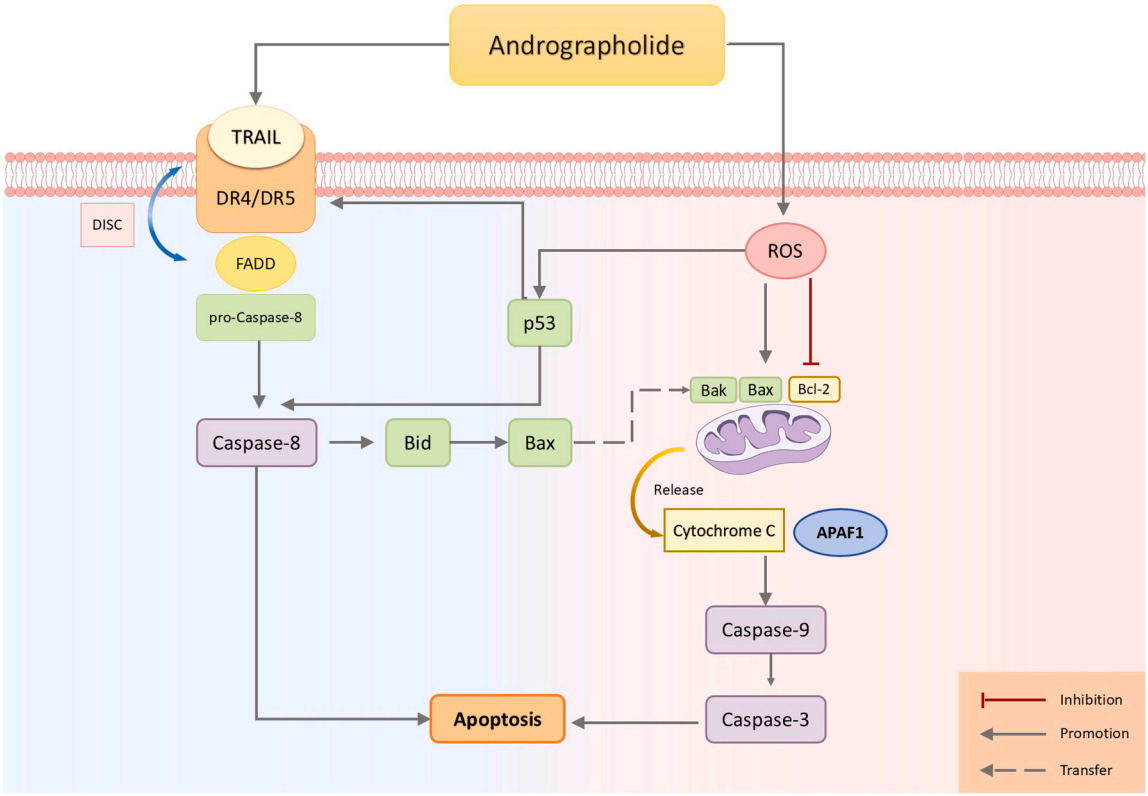

Fig. 6. Extrinsic and internal apoptosis mediated by andrographolide through the activation of key signaling pathways.

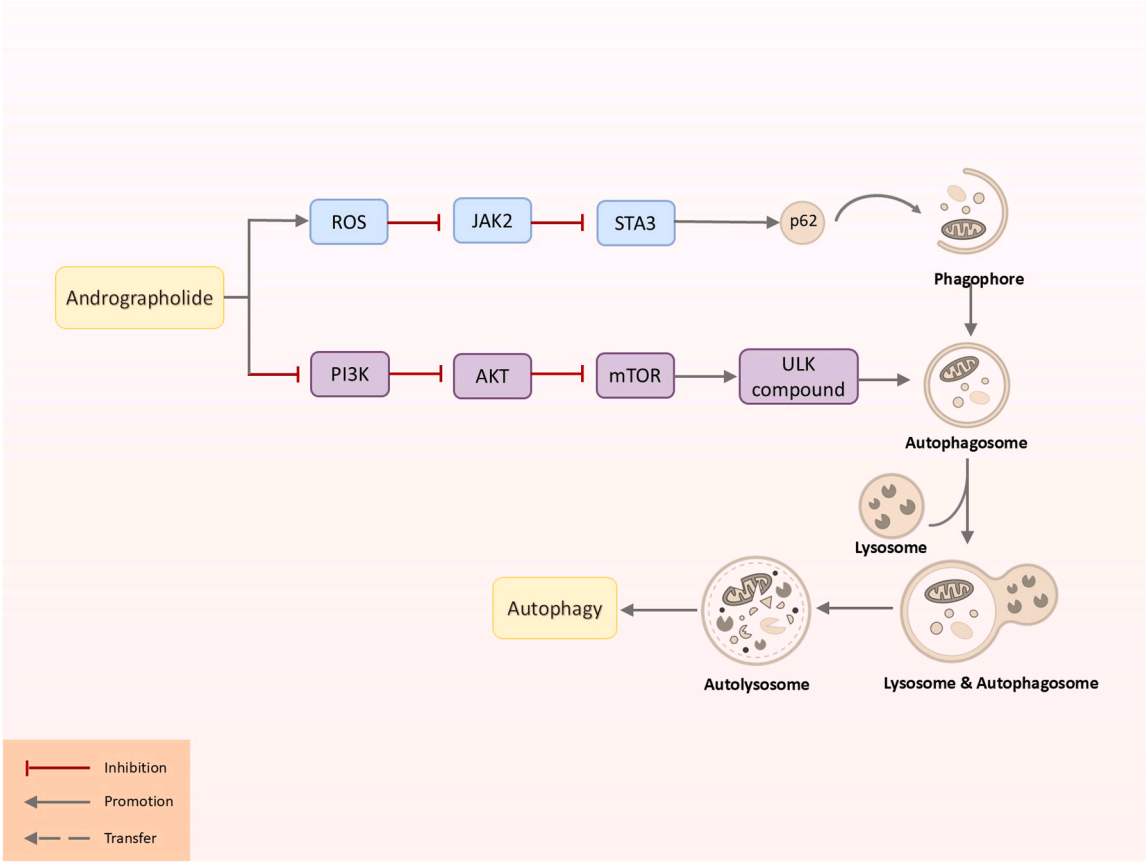

Fig. 7. Possible pathways of andrographolide-mediated autophagy including key signaling components involved in autophagosome formation.

tumor cells. The ligand induces extrinsic apoptosis by binding to specific death receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2) on the surface of cells [49]. AG increased DR4 and DR5 levels in T24 cells in a p53-dependent manner (a tumor suppressor gene), and inactivated NF-κB signaling pathway, enhancing TRAIL-mediated apoptosis [50]. The increase of ROS levels promoted by AG would increase the expression of p53 and DR4 in PCa cells, and consequently promoting the expression of caspase-3 to inducing apoptosis [51]. It is interesting to highlight that AG has the potential to be developed as a chemosensitizer for combined therapy with TRAIL.

Ferroptosis is a form of programmed cell death characterized by the accumulation of lipid ROS. It is a new type of cell death discovered by scientists in recent years [52]. AG downregulated the ferroptosis inhibitor GPX4 and SLC7A11 and promoted ferroptotic events such as ROS production, MDA (a marker of lipid peroxidation) accumulation, GSH (an intracellular antioxidant) depletion, intracellular free iron, and lipid peroxidation in lung cancer cells. Hence, AG might exert its effects in cancer therapy by modulating ferroptosis-related pathways [53]. Furthermore, Li et al. [54] demonstrated that AG inhibited p38 and modulated the Nrf2/HO-1 axis. Indeed, p38 was associated with the regulation of Nrf2, HO-1, GPX4, Fe^{2+}, and lipid peroxidation levels in multiple myeloma cells, ultimately inducing ferroptosis.

5.3. Autophagy

Autophagy is a process that delivers various intracellular proteins and organelles to lysosomes for degradation and recycling, which plays a crucial role in the complex cancer microenvironment [55]. Activation of autophagy can prevent cell damage and promote cell survival when energy or nutrients are insufficient and exposed to cytotoxic insults [56]. AG regulates autophagy in cancer cells through multiple interrelated pathways. PI3K/AKT/mTOR (Phosphoinositide 3-kinase/ Protein kinase B/ mechanistic Target of Rapamycin) pathway is a critical regulator of cell growth and autophagy, in which mTOR is a serine/threonine protein kinase regulating autophagy [57]. AG inhibited Akt and mTOR phosphorylation and increases the expression of class III PI3K to induce autophagic cell death in osteosarcoma cells and decreased the expression of LC3-II, Beclin-1 and Atg5 by enhancing the JNK pathway [58]. In another study, AG inhibited the JAK2/STAT3 pathway in NSCLC and reduced the expression of PD-L1 through the accumulation of P62 or directly inhibited the phosphorylation of STAT3. The reduction of PD-L1 level leads to increased infiltration and activation of $CD8^+$ T cells in the tumor microenvironment, thereby enhancing the anti-tumor immune response [59]. AG inhibited autophagy by interfering with the fusion of autophagosomes and lysosomes. The autophagy induced by AG is shown in Fig. 7

5.4. Inhibition of angiogenesis

Angiogenesis is the physiological process of forming new blood vessels from pre-existing vasculature [60]. Angiogenesis plays a pivotal role in tumor growth and metastasis. Tumors rely on angiogenesis to acquire oxygen and nutrients for their survival and expansion bey [61]. The combination of vascular endothelial growth factor (VEGF) and its receptor VEGF receptor (VEGFR) regulates tumor angiogenesis and metastasis. AG inhibited angiogenesis in hepatocellular carcinoma (HCC) by directly inhibiting VEGFA or inhibiting VEGFR2 and its downstream MAPK pathways including ERK pathway, JNK pathway and p38 MAPK pathway. The expression of VEGFA is mainly regulated by the transcription factor hypoxia-inducible factor-1α (HIF-1α) [62]. AG activated JNK and reduced the expression of metastasis-associated protein 1 (MTA1) and histone deacetylase 1 (HDAC1) in hepatoma cancer cells to degrade HIF-1α protein, decreasing VEGFA expression [63]. Furthermore, AG inhibited HIF-1α expression by inhibiting the PI3K/AKT pathway in breast cancer cells [64]. AG also inhibited the expression of VEGFD by reducing the expression of cFos protein mediated by ubiquitin/proteasome and reducing the transcriptional activity of activator protein-1 (AP-1) [65]. In breast cancer cells, AG inhibited the activation of p300- HAT and then decreased the COX-2 activation. COX-2 is a key enzyme promoting angiogenesis, the inhibition of COX-2 decreased VEGF expressing, thereby inhibiting tumor angiogenesis [66,67]. The main signaling pathways are shown in Fig. 8

5.5. Inhibition of tumor cell invasion and migration

Epithelial–Mesenchymal Transition (EMT) plays a critical role in promoting tumor invasion and migration, and such transition enhances the cell migration [68]. The extracellular matrix (ECM) influences cancer cell adhesion and proliferation. The migration and functions act as a scaffold for the cells in tumor mircroenvironment (TME) [69,70]. Matrix Metalloproteinases (MMPs) can degrade components of ECM, allowing tumor to invade surrounding tissues and entering blood vessels [71]. AG treatment downregulated PI3K/Akt signaling and inactivated of c-Jun/c-Fos (AP-1 heterodimer complex) to reduce the MMP-7 expression and inhibit migration and invasion in NSCLC cells. In another study, AG inhibited the invasion and migration of human glioblastoma multiforme cells by enhancing the phosphorylation of c-Raf/MEK/ERK pathway and inhibiting the expression of CREB, which is the key regulator for the transcriptional inhibition of MMP-2 [72]. In KKU-M213 cells, p-38 MAPK was activated by AG, the EMT pathway protein, claudin-1 was inhibited to express its anti-migration and invasion ability. Nuclear factor-κB (NF-κB) can be considered an effective drug target in cancer treatment [73]. AG decreased MMP-9 expression by inhibiting NF-κB signaling in MDA-MB-231 breast cancer cell [74]. The combination of AG and the inhibitors of Wnt/β-catenin, PI3K/AKT and NF-κB of signaling pathways caused a synergistically inhibitory effect on the migration and invasion of human osteosarcoma cells [75]. The main mechanisms are depicted in Fig. 9.

5.6. The anticancer mechanism of AG against different types of cancer

This section provides a review on the anti-cancer effects of AG against different types of cancer, specifically enhancing the understanding of its mechanisms and action against cancer.

5.7. Breast cancer

Breast cancer has become the most common malignant tumor among women worldwide [76]. Breast cancer is typically classified into luminal A, luminal B, HER2-positive and triple-negative breast cancer (TNBC) according to molecular subtypes [77]. TNBC is the most aggressive [78]. As reported by earlier researchers [44], AG induced apoptosis and G2/M phase of cell cycle arrest in MDA-MB-231 cells through mitochondrial dependent pathway [79]. Another study demonstrated that AG downregulated VEGF pathway by the inhibition of COX-2 and p300 expression in MDA-MB-231 cells [67]. Furthermore, AG is a novel HIF-1 inhibitor. It downregulated HIF-1α-mediated VEGF expression and inhibited the angiogenesis of MDA-MB-231 cells by inhibiting PI3k/Akt/mTOR signaling [64]. NF-κB is an important regulatory signal in breast cancer. Beesetti et al. [80] demonstrated that AG promoted apoptosis in MDA-MB-231 cells by inhibiting NF-κB signaling, while upregulating TIMP1 to inhibit the expression of MMP-7. AG also attenuates the expression of MMP-9 by inhibiting IκBa phosphorylation then suppressing NF-κB signaling. The inhibition of MMP-7/9 reduced the invasion and migration of MDA-MB-231 cells [74]. In addition, AG inhibit the proliferation, metastasis and invasion of MDA-MB-231 cells by suppressing EGFR (epidermal growth factor receptor)-STAT1 (signal transducer and Activator of Transcription 1)-HDAC4 (histone deacetylase) signaling, EGFR, STAT1 and HDAC4 proteins are involved in the EMT progression [81].

In ER-positive breast cancer cells, AG induced ROS production, and downregulating the FOXM1-ER-α axis and inhibiting ESR1 transcription

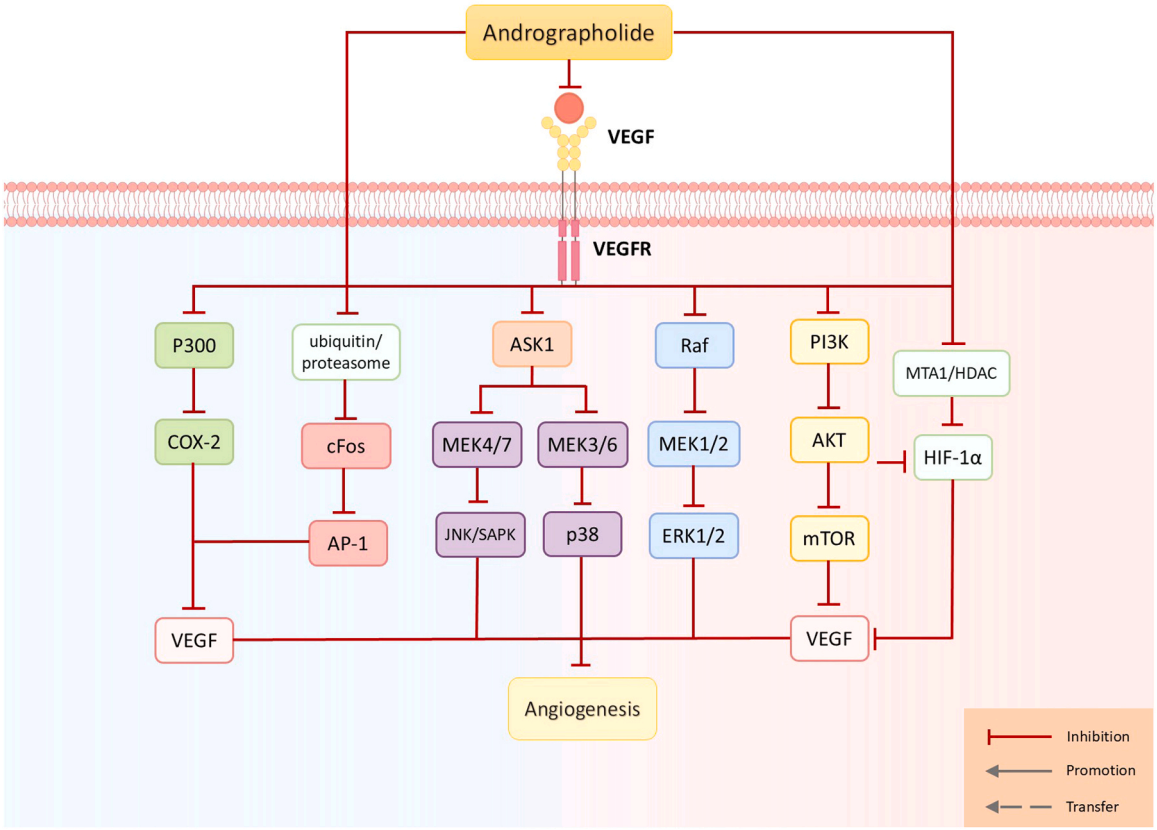

Fig. 8. Andrographolide-mediated anti-angiogenic signaling pathways in cancer cells involving the inhibition of VEGF expression.

to inhibit tumor growth. AG induced apoptosis of MCF-7 cells via a series of mitochondrial-mediated reactions after ROS activation [48]. AG exerted antiproliferative effects in MCF-7 cells by suppressing ERα expression and PI3K/AKT/mTOR signaling [79]. A combined treatment with AG and fulvestrant (FUL) could further inhibit ER-α expression and breast cancer cell growth [82]. Li et al. [83] found that AG could inhibit tumor growth and metastasis in MMTV-PyMT mice, AG reduced the expression of MiR-21–5p in luminal-like breast cancer by inhibiting the expression of NF-κB, promoting the expression of programmed cell death protein PDCD4.

5.8. Gastric Cancer

Gastric cancer is the fifth most common cancer, and its mortality rate ranks third in the world [76]. Based on network pharmacology analysis, AG may exert its therapeutic effect on gastric cancer by regulating targets such as SRC, AKT1, TP53, STAT3, PIK3CA, MAPK1, MAPK3, VEGFA, JUN and HSP90AA1. AG also exerted its pharmacological effects on the signaling pathways such as the HIF-1 signaling pathway and the PI3K-AKT signaling pathway [84]. AG may inhibit the proliferation, invasion and metastasis of SGC7901 cells by inhibiting MMP protein activity and upregulating TIMP protein expression, arresting the cell cycle at the G_2/M phase [85]. In addition, AG increased p53 expression and suppressed oncogene Mdm2 in SGC 7901 cells, thereby promoting mitochondrial intrinsic apoptosis [86]. AG inhibited cell proliferation through extrinsic apoptosis. The combined treatment of AG with recombinant human TRAIL further increased the expression levels of DR4 and DR5 [87]. AG treatment significantly upregulated ferroptosis-related gene expression, including HMOX1, GCLC and GCLM in MKN74 and NUGC4 cells [88].

5.9. Colorectal cancer

Colorectal cancer (CRC) is the second most lethal and third most often diagnosed cancer worldwide [89]. CRC includes colon cancer and rectal cancer which accounts for an estimated 935,173 deaths in 2020, with an age-standardized mortality rate of 9.0 per 100,000 person-years. The presence of epidermal growth factor receptor (EGFR) is correlated with abnormal cell proliferation, excessive differentiation, apoptosis and carcinogenesis [90]. AG inhibited proliferation and induced apoptosis of SW620 cells via TLR4/MyD88/NF-κB/MMP-9 signaling pathway [91]. Moreover, AG reduced the expression of NOTCH 1and JAGGED 1 then inhibited the Notch signaling pathway to exert the anti-proliferation of SW-480 cells [92]. Banerjee et al. [93] first reported that AG could induce endoplasmic reticulum stress (ERS) and promoted cell apoptosis and activated the unfolded protein response (UPR) mediated by inositol-requiring enzyme 1 (IRE-1), leading to C/EBP homologous protein (CHOP) expression and cell apoptosis. AG induced ERS and blocked Akt/mTOR signaling, and thus inhibiting Cyclins B1 and D1 in cell cycle progression [94]. Khan et al. [92] reported that AG significantly induced G2/M cell cycle arrest at a concentration of 16 μM, while higher concentrations (32, 64, 128, and 256 μM) led to G0/G1 arrest in colon cancer HT-29 cells. The PI3K pathway plays an important role in colorectal cancer. AG inhibited the invasion of HCT116 cells by suppressing the PI3K/Akt/mTOR signaling pathway and glycolysis. These mechanisms may enhance the radiosensitivity of HCT116 cells [95].

5-Fluorouracil (5FU) is a commonly used chemotherapy drug for the treatment of CRC [96,97]. AG significantly enhanced the sensitivity of HCT116/5-FUR cells by binding to BAX and inducing cell apoptosis. Combined treatment of AG and 5-FUR significantly inhibited tumor growth in Nude mice [96]. Overexpression of Dickkopf-1 (DKK1) is a key event in 5FU resistance. It is an extracellular inhibitor of Wnt/β-catenin signaling [98]. AG significantly downregulated 5FU-induced DKK1

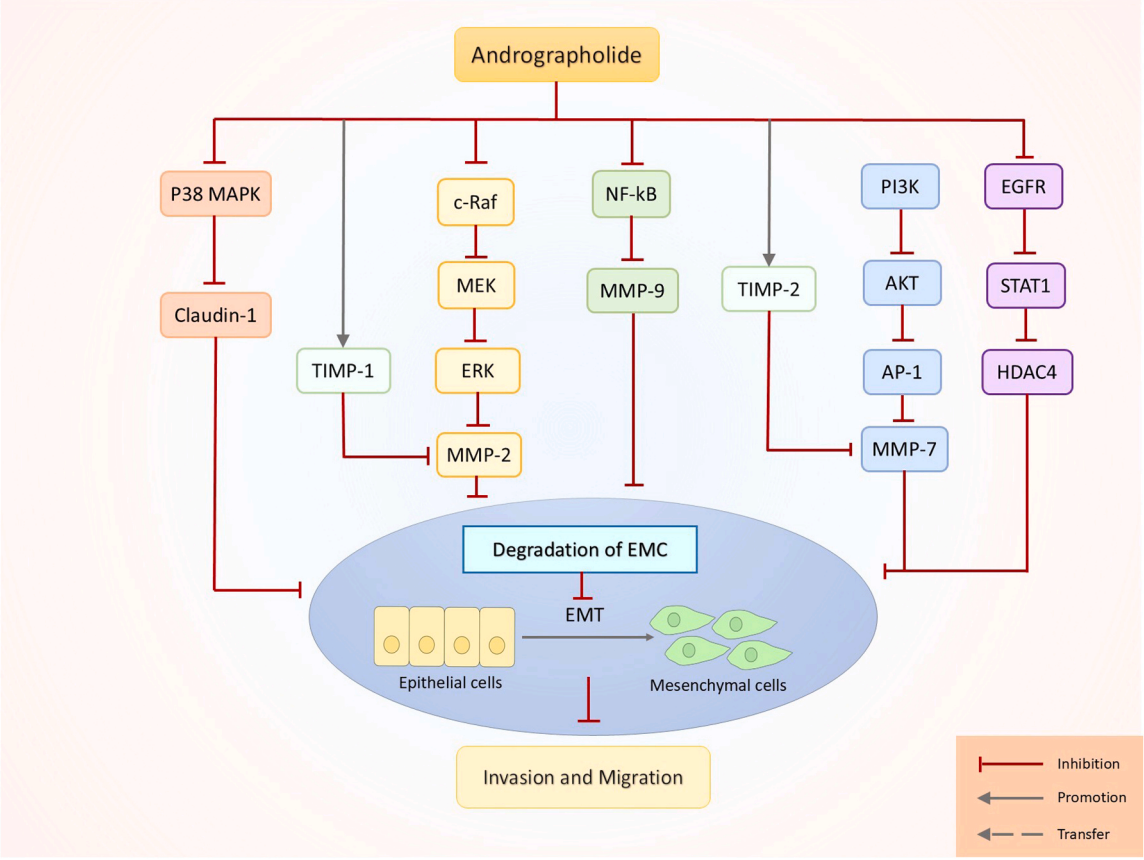

Fig. 9. Mechanisms of andrographolide on cancer cell invasion and migration via the degradation of Epithelial–Mesenchymal Transition (EMT).

overexpression and reversed 5FU-mediated drug resistance in CRC cells by inhibiting downstream Akt [99]. Another study validated AG overcoming 5FU resistance in CRC cells. This inhibitory effect was associated with the activation of ferroptosis and the down-regulation of Wnt16, AXIN2 and TCF7L2 genes to inhibit β-catenin/Wnt signaling, thereby enhancing the sensitivity of CRC to 5FU chemotherapy [100]. In addition, AG downregulated the c-MET pathway both *in vivo* and *in vitro*, synergistically enhancing the anti-tumor efficacy of 5FU against HCT-116 cells, while inhibiting the p-ERK1/2 and p-AKT signaling [101].

In mouse xenograft models, AG enhanced the efficacy of anti-PD-1 (programmed cell death protein 1). Combined treatment with anti-PD-1 antibodies inhibited the expression and activity of COX-2, reduce the synthesis of prostaglandin E2 (PGE2), enhance the function of CD4 + and CD8 + T cells, and significantly inhibit tumor growth [102]. KRAS mutation is one of the causes of resistance of CRC to cetuximab. Liu et al. [103] demonstrated that AG enhanced the sensitivity of KRAS mutant CRC cells to cetuximab (CTX) by reducing the expression of PI3K and AKT by targeting PDGFRβ and EGFR, and inhibited the migration and invasion of CRC cells through the Wnt/β-catenin signaling pathway.

Combination therapy of AG with other natural compounds such as melatonin (MLT) can enhance the anticancer effect [104]. It is demonstrated that the IC_{50} of AG was 15 μM after combined treatment with MLT, significantly reduced compared with the IC_{50} of AG single treatment of 45 μM. The mechanism was associated with ERS-mediated apoptosis by increasing its signaling molecules such as BAX, XBP-1, and CHOP [105]. Combined treatment with AG and MLT significantly inhibited the expression of mitochondrial ribosomal proteins MRPS6, interfered with mitochondrial protein synthesis, led to mitochondrial dysfunction, and inhibited CSC proliferation [106].

5.10. liver cancer

Liver cancer the fourth leading cause of cancer-related mortality worldwide. AG has a promising potential for hepatoma treatment [107]. Hepatocellular carcinoma (HCC) is most common type of primary liver cancer, accounting for approximately 80 % of all liver cancer cases [108]. In p53-WT cells, AG induces G2/M cell cycle arrest, thereby promoting DNA repair and cell survival, while AG induces p62 accumulation and promotes proteasome degradation of DNA repair proteins RAD51 and 53BP1, escaping the protective effect of p53, impairing DNA damage repair, and ultimately leading to cell death [40]. Another study revealed that AG inhibited the expression of HMGB1 and MMP-9 by upregulating MIR22HG and miR-22–3p, thereby suppressing liver cancer cell metastasis and reducing Bcl-2 in promoting mitochondrial apoptosis [109]. In addition, AG suppressed HIF-1α signaling and reduced VEGF, MTA1 and HDAC1 expression in Hep3B and HepG2 cells, thereby inhibiting angiogenesis [63]. AG further downregulated VEGF expression by inducing ubiquitin-dependent proteasomal degradation of cFos [65]. High concentrations of arsenic trioxide (As_2O_3) can be used to treat cancer. Study has found that AG combined with As_2O_3 significantly inhibited the proliferation of HCC cells. The IC_{50} of combined treatment was 2.88 μM, which was much lower than the IC_{50} of As_2O_3 alone (6.23 μM). This anti-tumor effect was associated with EphB4 down-regulation [110].

5.11. Lung cancer

Lung cancer has the highest number of cancer-related deaths and survival rates are low [76]. The main type of lung cancer is non-small-cell lung cancer (NSCLC), which accounts for 85 % of overall cases [111]. NSCLC can be divided into squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Adenocarcinoma is a

common type of lung cancer, characterized by high invasiveness and the fastest lethality [112,113]. p21 and p27 were upregulated in A549 lung adenocarcinoma cells treated with AG by downregulating Skp2 and inducing DNA damage response to activate p53, thereby inducing cell senescence and cell cycle arrests [39]. Furthermore, AG induced apoptosis of human lung adenocarcinoma cells (A549 and H1299) by activating ATF4 and upregulating the pro-apoptotic BH3-only protein Noxa [114].

AG inhibited the growth of NSCLC and induced glucose metabolism reprogramming in H1975 cells [47]. Similarly, Yang et al. [115] found that AG inhibited aerobic glycolysis and pyruvate dehydrogenase kinase 1 (PDK1) in human lung cancer cells. However, PDK1-mediated metabolic changes still need to be further explored. Ferroptosis plays a pro-apoptotic role in NSCLC cancer cells. Jiaqi et al. [53] demonstrated that AG induced ferroptosis and inhibited tumor growth and metastasis in mice. In addition, AG inducing autophagy to enhance anti-tumor immunity in NSCLC cells [59]. The inhibition involved reducing PD-L1 expression by inhibiting the JAK2/STAT3 signaling cascade and p62 accumulation, thereby increasing the infiltration and function of CD8 + T cells, and inhibiting tumor growth.

Paclitaxel (PTX) and AG have a synergistic effect on NSCLC. Study revealed that the IC_{50} value of PTX combined with AG for A549 cells was 0.5–7.4 nM, which was significantly lower than the IC_{50} (15.9 nM) of PTX. The synergistic effect may be the result of ROS accumulation [116]. In drug-resistant NSCLC cells, AG enhanced sensitivity to cisplatin (DDP) treatment by downregulating PTEN expression, promoting the activation of Akt/mTOR signaling, and inhibiting autophagy. DDP combined with AG treatment significantly prevented the growth of the resistant cells *in vivo* [117].

5.12. Cervical cancer

Cervical cancer is the fourth most significant cause of cancer death. Cervical cancer is initiated by infection with high-risk human papillomaviruses (HPVs) and HPV-16 is the predominant high-risk type [118]. In HPV16-positive cervical cancer cells, AG inhibited the proteins associated with ubiquitin-mediated proteolysis pathways including HERC4 and SMURF2 to disturb E6-mediated p53 degradation, restoring the p53 expression and promoting apoptosis [119]. AG also functioned as an inducible nitric oxide synthase (iNOS) inhibitor, suppressing HeLa cell proliferation and inducing G1/S phase arrest in a dose-dependent manner [120]. Pasha et al. [121] demonstrated that AG induced HeLa cell apoptosis by suppressing NF-kB and COX-2 and inhibiting the PI3K/AKT signaling pathway. Furthermore, intracellular pH (pHi) is associated with tumorigenesis, and acidic pHi is suitable for activating apoptotic proteins [122]. A recent study proved that AG reduced pHi by inhibiting membrane transport proteins NHE1/V-ATPase activity in HeLa cells [46].

5.13. Prostate cancer

Prostate cancer (PCa) is one of the most common malignant tumors in men worldwide [123]. It was demonstrated that 10 mg/kg of AG reduced the expression of cell proliferation proteins (pH3, Ki-67) and MMP11 in prostate tumor tissues, and induced DNA damage leading to cell cycle arrest at the G2/M phase, cell apoptosis, and anti-angiogenesis [124]. AG significantly increased the sensitivity of PCa cells to TRAIL-induced apoptosis by promoting p53 and DR4 expression. TRAIL combined treatment with AG significantly increased PCa cell apoptosis [51]. Furthermore, AG activated the caspase cascade and induced apoptosis in PCa cells at an optimal concentration of 13.21 μM [125]. In addition, AG inhibited the expression of chemokine receptors CXCR3 and CXCR7, reduced the response of tumor cells to CXCL11 signals, reduced PCa cell viability and migration ability, and induced cell cycle arrest by regulating cyclin A2, B1, and E [126].

5.14. Bone cancer

Bone cancer can primary or metastatic [127], osteosarcoma (OS) is the most common primary bone tumor, mainly occurring in children and adolescents, and often occurring in the medullary region of long bones [128]. AG activated JNK signaling, leading to apoptosis and cell cycle arrest at G2/M phase in human osteosarcoma cells [129]. In addition, AG can inhibit the proliferation, migration and invasion of human osteosarcoma cells by significantly inhibiting Wnt/β-catenin, PI3K/AKT and NF-κB [75]. AG induced autophagic cell death in osteosarcoma cells, resulting in reduced invasiveness and metastatic potential [58].

Chondrosarcomas account for approximately 20 %-30 % of primary bone tumors [130]. SOX9 is a transcription factor and related to chondrogenesis. It is up-regulated in chondrosarcoma cells [131]. A study demonstrated that AG inhibited SOX9 expression in chondrosarcoma cells by downregulating T-cell factor 1 (TCF-1), leading to G2/M phase arrest via a caspase-3-dependent pathway [132].

5.15. Oral cancer

Oral cancer is a common cancer, oral squamous cell carcinoma (OSCC) is the predominant histological subtype [133]. AG ($\geq$ 30 μM) caused cell contraction and migration inhibition, inducing apoptosis in OEC-M1 cells [134]. Yang et al. [135] first time reported that AG could inhibit oncogenic properties of oral cancer stem cells (OCSC) through activation of miR-218-targeting Bmi1 and enhanced radiosensitivity, which inhibited OSCC tumor aggressiveness. Furthermore, AG acted as an effective sensitizer to DDP, exerting synergistic anti-tumor effects in oral squamous cell carcinoma (OSCC). This synergistic effect has been verified in both *in vitro* and *in vivo* experiments. It upregulated p-p53 expression *in vitro* and downregulated Ki-67 expression *in vivo* [136].

5.16. Other cancer

In recent years, there have been few studies on AG for some cancers, mainly the following studies: AG combined with radiotherapy could increase the expression of Bax and cleave-caspase3 and inhibited esophageal cancer cell apoptosis. This radiosensitivity effect was mediated by inducing cell cycle arrest at the G0/G1 phase [137]. AG inhibited bladder cancer cell proliferation and migration by suppressing PI3K/AKT/NF-κB signaling [138]. In cholangiocarcinoma (CCA), AG activated p38 MAPK signaling pathway, leading to enhanced Snail expression and claudin-1 inhibition, which effectively inhibits cancer cell migration and EMT [139]. In pancreatic cancer (PC), AG induced oxidative stress associated cell death and promoted autophagy [140]. Another study has also demonstrated the inhibitory effect of AG on pancreatic cancer (PC). Zhuang et al. [141] indicated that AG inhibited DNMT3B to reduce DNA methylation and activated the expression of tumor suppressor gene ZNF382. These finding reveals the potential of AG to be a drug for PC. In addition, AG enhanced the sensitivity of renal cell carcinoma to TRAIL-mediated proliferation inhibition [142]. These findings highlight the multifaceted anticancer potential of AG, which can not only enhance the effect of radiotherapy, but also target key oncogenic pathways, induce apoptosis, and inhibit metastasis.

6. Toxicity of andrographolide

AG has been widely recognized for its remarkable anticancer, anti-inflammatory, and antioxidant properties. Since it is the herbal compound of *A. paniculata*, AG is generally considered safe for consumption. Nevertheless, the toxicity of AG still needs to be carefully evaluated to ensure its safe dosage for applications [143]. Table 2 arranges findings from the limited toxicological assessments of AG conducted between 2015 and 2025, including both *in vitro* and *in vivo* studies using different animal models.

Table 1
The mechanism of andrographolide on various cancers.

Cancer type	Cell line/Animal model	Dose	Inference	Reference
Breast cancer	MDA-MB-231 MCF-7	AG: 0–10 μg/mL	Suppressing the expression and activity of EGFR, STAT1 and HDAC4	[81]
	MCF-7, MDA-MB-231	AG: 7.5–120 μM	Inhibiting the expression of Erα and the PI3K/AKT/mTOR signaling pathway.	[79]
	MDA-MB-231 MCF-7, T-47D, MCF-10A	AG: 5–100 μM	Inducing ROS accumulation reducing MMP, Bcl-2 and Bcl-xL, increasing Bax and Apaf-1	[48]
	Female BALB/c mice	50 mg/kg	Activating caspase-3 and caspase-3	
	MDA-MB-231, MDA-MB-468, 4T1	AG: 10–30 μM	Inhibiting of the NF-κB-THOC1 axis	[144]
	Female BALB/c and C57BL/6 mice	AG: 10 mg/kg		
	MCF7, T47D	AG: 80 μM FUL: 25 μM	Downregulate FOXM1-ER-α axis by inducing ROS	[82]
	Female BALB/c mice	AG: 150 mg/kg/d FUL: 5 mg		
	MDA-MB-231, T47D	AG: 100 mg	Inhibiting HIF-1 and its upstream PI3K/AKT signaling	[64]
	Female BALB/c mice	AG: 25–100 mg/kg		
	MDA-MB-231, MCF-7, T47D, MDA-MB-361, and BT549	AG: 5–50 μM	In vitro: suppressed COX-2 expression and mediated acetylation of NF-κB	[67]
	xenograft nude mice model	AG: 5–10 mg/kg		
	MDA-MB-231, SKOV-3, A431	AG: 10–50 μM	Inhibiting NF-κB, downregulating MMP-7	[80]
	MCF-7	AG: 0–160 μM	Inhibiting NF NF-κB, the expression of miR-21–5p and PDCD4.	[83]
	MMTV-PyMT mice	AG: 5 μg/g		
	MDA-MB-231	AG: 7, 5–120 μM	Decreasing MMP-9, suppressing NF-κB signaling	[74]
	BALB/c nu/nu mice	AG: 50 mg/kg		
Gastric cancer	SGC7901	0–40 μg/mL	Upregulating expression of Timp-1/2, cyclin B1, p-Cdc2, Bax, and Bik Downregulating expression of MMP-2/9 and Bcl-2	[85]
	SGC7901, AGS	AG: 5–50 μg/mL	Inducing caspase-3and PARP activating p53, reducing Mdm-2	[86]
	SNU601, SNU638 AGS	AG: 10–50 μM TRAIL: 5–20 ng/mL	Increasing ROS, P21, inducing DR4 and DR5, decreasing Bcl-xL	[87]
	MKN74, NUGC4	AG: 10–100 μg/mL	Upregulating GCLC, GCLM, HMOX-1 expression	[88]
Colorectal cancer	HT290, IEC6	AG: 1–1024 μM	Increasing ROS, activating caspase-3, reducing MMP	[145]
	SW620	AG: 5–25 μM	Activating caspase-3/9 Inhibiting TLR4, MyD88, NF-κB-p65 and MMP-9	[91]
	HCT116, SW480	AG: 10–40 ng/μL 5FU: 10–40 μM	Activating caspase 9 and ferroptosis, inhibiting β-catenin/Wnt signaling pathways	[100]
	Male athymic nude mice	AG: 125 mg/kg 5FU: 30 mg/kg		
	HCT116, SW480	AG: 30 ng/μL 5FU:10 μM	Downregulating the expression of DKK1, attenuating Akt-phosphorylation.	[99]
	7-week-old male athymic nude mice	AG: 125 mg/kg 5FU:30 mg/kg		
	Male BALB/c nude mice (HCT116, LoVo)	CTX: 2 mg/kg AG: 20 mg/kg	Inhibiting PI3K/AKT and PDGFR/AKT signaling pathways.	[103]
	COLO 205, T84, FHC, CCD-18Co	AG: 0–150 μM	Increasing ROS, reducing$\Delta\Psi$m, inducing ERS	[94]
	T84, HCT116	AG: 0–150 μM	Inducing ERS, activating GRP-78/IRE-1/XBP-1/CHOP signaling pathway	[93]
	C57BL/6 mice	AG: 5–60 μM		
	HCT116	AG: 5–80 μM	Inhibiting PI3K/Akt/mTOR signaling pathway	[95]
	HCT116	AG: 10 μM 5-FU: 0.5–2 μM	Increasing BAX	[96]
	Nude mice	AG: 25 mg/kg 5-FU: 25 mg/kg		
	HCT116	AG: 10 μM 5-FU: 0–40 μM	Inhibiting c-MET pathway, p-ERK1/2 and p-AKT.	[101]
	BALB/c nude mice	AG: 5 mg/kg 5-FU: 5 mg/kg		
	COLO 205, T84	AG: 0–150 μM	Activating ERS, TRE-1, decreasing Prx, Trx, increasing CHOP, XBP-1	[105]
	HT29, HCT15, HCT116, FHC	AG: 9.3 μM MCT: 0.18 μM	Inhibiting MRPS6, OPA1, MFNI	[106]
	NSG mice	AG: 9.3 μM MCT: 0.18 μM		
Liver cancer	HepG2, Huh7, Hep3B, HL-7702, HCC-M, HCT116	AG: 0–90 μM	Inducing p62 accumulation, DNA damage	[40]
	Male athymic Balb/c nude mice	AG: 15, 30 mg/kg		
	HepG2, SK-Hep-1, SK-Hep-1	AG: 12.5–100 μM	Increasing MIR22HG, miR-22–3p expression, reducing BCL-2 and Pro-Caspase 9/7/3, HMGB1, MMP-9 expression	[109]
	Male Balb/c nude mice	AG: 50, 100 mg/kg		
	Hep3B, HepG2	AG: 0–50 μM	Decreasing VEGFA, MTA1, HDAC1 expression, inducing JNK activation	[63]
	Specific pathogen-free nude male mice	AG: 10 mg/kg		
	HepG2, Huh7, SNU-449	AG: 0–1600 nM As_2O_3: 0–16 μM	Downregulating EphB4, activating of cleaved caspase-3	[110]
	Male BALB/c nude mcie	AG: 20 mg/kg As_2O_3:5 mg/kg		
	Hep3B, HepG2	AG: 25, 50 μM	Decreasing VEGFD, cFos expression	[65]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Cell line/Animal model	Dose	Inference	Reference
	Specific pathogen-free nude male mice	AG: 5, 10 mg/kg		
Lung cancer	A549, H1299, SK-MES-1, Lewis, BEAS-2B	AG: 0.78–100 μM	Upregulating ATF4 and Noxa,	[114]
	H1975, H1299, H1650, H460, BEAS-2B	AG: 2.5–10 μM	Inhibiting JAK2/STAT3 and PD-L1, increasing p62 accumulation, enhancing CD8 + T cell infiltration and function	[59]
	C57bl/6 J mice	AG: 2.5–10 mg/kg		
	H1975	AG: 2.5–20 μM	Activating the mitochondrial apoptosis pathway, restraining glycolysis	[47]
	A549, NCI-H292, NCI-H522	AG: 20–75 μM	Inhibiting PDK1 expression and aerobic glycolysis, inducing mitochondrial apoptosis	[115]
	A549, A549/DDP Female NCR-nu/nu mice	AG: 2.5–20 μM DDP: 8–32 μg/mL AG: 5 mg/kg DDP: 0.75 mg/mL	Downregulating PTEN expression, promoting the activation of the Akt/mTOR signaling	[117]
	H460, H1650 Lewis	AG: 10–30 μM	Inhibiting ferroptosis-related protein GPX4 and SLC7A11, enhancing mitochondrial dysfunction	[53]
	C57BL/6 mice	AG: 5, 10 mg/kg		
	A549, NCI-H1795 Female BALB/c mice	AG: 10–20 μM AG: 50, 100, 150 mg/kg	Upregulating p21 and p27	[39]
Cervical cancer	SiHa, CaSki, C33A	AG: 0–160 μM	Inhibiting HERC4, SMURF2, restoring p53 expression	[119]
	HeLa, SiHa	AG: 2–10 μM	Inhhibiting NF-kB, COX-2 expression, increasing PTEN	[121]
	Female C57BL/6 mice	AG: 15, 30 mg/kg		
	HeLa, HEK	AG: 0–80 μM	Inhibiting the iNOS expression	[120]
	HeLa, End1, Ect1	AG: 3–1000 μM	Inhibiting NHE1, PARP, pro-Caspase-3, and Bcl-2 expression	[46]
Prostate cancer	PC3,22PVI, LNCaP, PWPEI	AG: 10–25 μM	Downregulating Ph3, Ki-67, MMP11, inducing DNA damage and activating p53	[124]
	SCID mice	AG: 10 mg/kg		
	PC3, DUI45, JCA-1, TsuPr1, LNCaP, 293 T, PS30	AG: 10–30 μmol/L TRAIL: 20 ng/mL	Promoting ROS, upregulating p53 and DR4	[51]
	BALB/C mice	AG: 10 mg/kg TRAIL: 100 μg		
	PC3, Hs27	AG: 0–200 μM	Increasing caspase-3/8/9	[125]
	PC3, LNCaP, PrEC	AG: 5–100 μM	Increasing cyclin A2 and B1, reducing cyclin E2, inhibiting CXCR3, CXCR7	[126]
Bone cancer	HOS, U2OS, SAOS-2	AG: 20–80 μM	Increasing levels of ROS production and the expression of JNK, activating caspase-3/8/9	[129]
	Female BALB /c-nu mice	AG: 15, 30 mg/kg		
	143B, MG63, U2OS, SaoS2, HS-5, MIHA, HEB, HK2	AG: 10–20 μM	Suppressing the activity of Wnt/β-catenin, PI3K/AKT and NF-κB signaling pathways	[75]
	U-2OS、MG-63, SaOS-2	AG: 3–60 μM	Suppressing PI3K/Akt/mTOR signaling pathways	[58]
Oral cancer	OCSC	AG: 6.25–50 μM	Downregulating ALDH1, Oct-4, Nang, Sox2 and miR-218 expression	[135]
	CAL-27	AG: 2–32 μM DDP: 500–800 μM	Increasing P-AKT, activating P-p53, inhibiting Ki-67	[136]
Pancreatic cancer	PANC-1, MIA PaCa-2	AG: 1–30 μM	Inhibiting DNMT3B expression, inducing ZNF382 expression	[141]
	Male nude mice	AG: 10 mg/kg		
	PANC-1, BxPC3, PaTu8988, PC	AG: 10–40 μM	Inhibiting DJ-1, upregulating ROS, LC3-II, reducing p62	[140]
	BALB/c mice	AG: 5–20 mg/kg		
Esophageal cancer	5637, T24	AG: 7.5–480 μg/mL	Increasing Bax and Cleaved-Caspase3, decreasing Bcl-2 and NF-κB	[137]
Renal cell carcinoma	786-O, OS-RC-2, ACHN	AG: 5, 10 μM TRAIL: 50 ng/mL	Downregulating caspase-8/9, DR4, increasing Bax	[142]
Bladder cancer cell	T24, 5637	AG: 0–80 μM	Suppressing p65, p-AKT	[138]
	Male BALB/c nude	AG: 10 mg/kg		
Cholangiocarcinoma	HuCCA-1, KKU-100, KKU-M213, RMCCA-1	AG: 0–200 μM	Suppressing claudin-1, activating p-38 MAPK signaling pathway	[139]

Table 2
Toxicological evaluation of andrographolide and related formulations in animal models.

Animal Model	Drug	Dosage	Toxicity	Main Findings	reference
Sprague-Dawley rats	AP-Bio® (standardized *A. paniculata* extract)	Acute: 5000 mg/kg BW; Subacute: 300, 600, 900 mg/kg/day	No observed toxicity	LD_{50} > 5000 mg/kg; NOAEL = 900 mg/kg/day; safe under tested conditions	[146]
Sprague-Dawley rats	Andrographolide-2-hydroxypropyl-β-cyclodextrin complex	Acute: Oral: 2000 mg/kg Inhalation: 5 mg/L/4 h Subacute: Oral: 200, 400, 666 mg/kg for 28 days Inhalation: 0.5, 1, 1.66 mg/L/4 h for 28 days	Mild to moderate liver and lung lesions at high inhalation dose	Oral LD_{50} > 2000 mg/kg; Inhalation MTD > 5 mg/L/4 h; NOAEL: 0.5 mg/L/4 h/day; LOAEL: 1 mg/L/4 h/day	[147]
Swiss albino mice	Standardized ethanolic extract of first true leaf of *A. paniculata*	300, 2000, 5000 mg/kg BW	No observed toxicity	A single oral administration was greater than 5000 mg/kg BW	[148]
SPF-grade male C57BL/6 J mice	PSDS	250, 500 mg/kg BW	Kidney injury and senescence	PSDS dose-dependently suppressed the mRNA expression of SIRT3	[149]

6.1. Cytotoxicity of andrographolide

From the above studies, it is demonstrated that AG shows strong cytotoxicity to various cancer cell lines including breast cancer, lung cancer, colon cancer, liver cancer, etc., mainly through the mechanism of inhibiting cancer cell proliferation and inducing cancer cell apoptosis. However, this cellular selectivity is not absolute, and potential cytotoxicity risks to normal cells should also be considered. In addition, AG induced inflammation of human renal tubular epithelial cells by increasing the expression of human kidney injury factor (KIM-1). This effect could be mediated through oxidative stress and endoplasmic reticulum stress, and thus suggesting potential nephrotoxicity [150]. Another study showed that AG induced NRK-52E cell senescence, fibrosis and inflammation by inhibiting SIRT3 [149]. The two studies revealed that AG induced nephrotoxicity and kidney injury. AG exhibited reproductive toxicity, which was demonstrated by the increase in ROS levels mitochondrial membrane potential, and induction of caspase-3 in inhuman embryonic stem cells (hESCs) and apoptosis of cells [151]. The ctotoxicity caused by AG is mostly dose-dependent and time-related, so further research on the dosage and duration of use is needed to avoid toxic damage to cells or normal tissues.

6.2. In vivo toxicity

Multiple preclinical studies investigated the acute and subchronic toxicity of AG using different animal models (Table 2). A standardized extract of *A. paniculata* (AP-Bio®) was used and the median lethal dose (LD_{50}) was found to exceed 5000 mg/kg in rats [146]. The observed adverse effect level (NOAEL) in a subchronic toxicity study was 900 mg/kg. These findings indicated a wide safety margin for oral administration. Further research on both oral and inhalational routes of administration revealed that the LD_{50} of AG and its inclusion complex (andrographolide-2-hydroxypropyl-β-cyclodextrin) was greater than 2000 mg/kg, and no adverse effects on body weight, hematological parameters, or hepatic and renal functions were observed [147]. However, some studies reported adverse effects under specific conditions. In a murine model of carbon tetrachloride (CCl_4)-induced liver fibrosis, AG reduced inflammation and fibrosis. Nevertheless, a dose of 50 mg/kg

Table 3
Clinical trials of andrographolide.

Participants	Disease	Products	Does	Side Effects	Findings	Identifier	Reference
34 patients with advanced or metastatic squamous cell carcinoma of esophagus	ESCCE	Andrographolide concentrated granules	130 mg/kg	Epigastric pain, Acid reflux, Dizziness et al.	Improving dysphagia symptoms and reversing gut microbiota dysbiosis; extended survival	NCT04196075	[154]
52 patients with advanced or recurrent andmetastatic CRC older than or equal to 65	CRC	Xeloda with Andrographolide	Xeloda: 1250 mg/m^2, po bid, d1–14, q3w AG: 500 mg, ivd qd, d1–14, q3w	No mention	Combination therapy enhanced anticancer effects	NCT01993472	[155]
44 subjects with not active PPMS or SPMS	Multiple sclerosis	AG	140 mg, b.i.d. for 24 months	Rash, dysgeusia	Reduced brain atrophy and slowed disability progression	NCT02273635	[156]
38 people who were healthy and 35 people who had prediabetes	Type 2 diabetes mellitus	Sambiloto extract capsules	No mention	Hand tremors, red spots on faces, itchiness, lethargy, weakness, diarrhea, and palpitation	Increased GLP-1, decreased DPP-4 activity, improved insulin sensitivity	NCT03455049	[157]
13 patients	Migraine	A supplement contains magnesium 281.25 mg, vitamin B 24.8 mg, feverfew150 mg, coenzyme Q10 20 mg, and *Andropraphis paniculata* 100 mg	one or two tablets/day	Mid diarrhea	Reduced migraine frequency, intensity, and duration	NCT04463875	[158]
Sixty-three adults aged 18–60 years, without co-morbidity, with laboratory24 confirmed mild COVID-19	COVID-19	*A. paniculata* extract capsules	3 capsules (60 mg. andrographolide) t. i.d. for 5 days	Mid diarrhea	Faster reduction in COVID-19 symptoms, protective effects against worsening	TCTR20210708001	[159]
86 patients with laboratory-confirmed COVID-19 and mild symptoms	COVID-19	Kan Jang®/Nergecov®	Six Kan Jang® (daily dose of 90 mg AG)	Mild pruritus	Faster recovery and Reduced symptom duration (sore throat, fatigue)	NCT04847518	[160]
103 male and female patients with I-II osteoarthritis of the knee	knee osteoarthritis	ParActin®	300 and 600 mg/day	Acidity, constipation, oral ulcers	Slower brain atrophy And trend toward reduced disability progression	NCT03262792	[156]
179 patients with uncomplicated URTIs	URTI	Extracts of the leaves of *A. paniculata* (Kan Jang)	60 mg /day	Well-tolerated	Faster reduction in URTI symptoms And earlier full recovery	No	[161]

aggravated liver injury and caused weight loss in mice [152]. Moreover, PSDS (a disuccinate salt of AG used in injection form) was found to induce kidney injury and cellular senescence in mice via SIRT3 inhibition [149]. Additionally, Gu et al. [150] revealed the potential nephrotoxicity of AG from 0 to 250 μmol/L could inhibit the proliferation of human renal tubular epithelial (HK-2) cells and induce apoptosis through endoplasmic reticulum (ER) stress and inflammatory pathways. Despite AG and its related products demonstrated a high level of safety in most animal models, special caution is warranted at higher doses, via injectable routes, or in specific disease contexts. To support the therapeutic use of AG in humans, further clinical studies are needed to elucidate its long-term safety and toxicity profile under various physiological and pathological conditions.

7. Clinical application

Although AG have significant potential in many clinical areas, it also exhibits certain level of biological toxicity and adverse events [28]. A systematic review and meta-analysis revealed that AG predominantly involved gastrointestinal issues such as diarrhea, nausea, and vomiting, as well as skin disorders including rashes and pruritus [153]. Table 3 lists the clinical trials of AG against diseases such as colorectal cancer, esophageal cancer, knee osteoarthritis, and others. The trials focusing on cancer treatment are relatively limited. Further research is strongly needed, especially in evaluating the toxicity and drug interactions of AG. Clinical data will provide insights into these risks, with specific demographic associations reported in adverse drug reaction cases. A larger-scale of clinical trials will also provide more conclusive evidence for the application of AG in cancer treatment.

A phase II clinical trial was conducted to investigate the impact of *A. paniculata* water extract in the palliative management of metastatic esophageal squamous cell carcinoma (ESCC) in cancer treatment. The study was designed as a randomized and placebo-controlled clinical trial. The extract was found to reduce dysphagia and other symptoms associated with the disease. The outcomes were assessed with the symptom of relief and quality of life, overall survival and treatment tolerability as endpoints. It has the potential to reverse gut microbiota dysbiosis in ESCC patients. Patients completed the treatment and achieved longer overall survival periods with no severe treatment-related adverse effects reported. Hence, AG could be a valuable adjunct in the palliative care of esophageal cancer patients [154]. In an open-label, randomized, controlled trial, AG was combined with capecitabine in patients with unresectable, advanced, recurrent, and metastatic colorectal cancer. The study population consisted of patients with diagnosed colorectal cancer undergoing systemic treatment. Clinical outcomes focused on tumor response and disease control, while treatment tolerability and safety were also assessed. The results indicated that the combination therapy was more effective in enhancing the anticancer effects of capecitabine, without a significant increase in treatment-related adverse effects. [155]. Overall, the findings suggest that AG may enhance the efficacy of capecitabine and represent a potential adjuvant strategy for colorectal cancer treatment

AG exhibits anti-inflammatory activity, making it a promising anti-inflammatory drug [162]. It can be applied to some inflammatory associated diseases, including upper respiratory tract infections (URTI), osteoarthritis, and viral infections such as COVID-19. A double-blind, randomized, placebo-controlled trial assessed the efficacy of a standardized extract of *A. paniculata* (ParActin®) for reducing pain in 103 adult patients with mild to moderate knee osteoarthritis. The patients took 300 mg/day or 600 mg/day ParActin® for 12 weeks. The treatment improved stiffness, physical function, and fatigue scores from day 28 onward and its benefits sustained through day 84 [163]. The adverse events were mainly mild gastrointestinal symptoms, with no significant differences between groups in liver or renal safety markers.

A clinical study showed that patients with COVID-19 treated with the extract of *A. paniculata* could recover faster from the symptoms of fever, cough and sore throat. Patients with mild COVID-19 received 60 mg of AG three times daily for 5 days. No serious adverse effects were reported, and only mild gastrointestinal discomfort was observed in a few cases [164]. The AG treated group showed no pneumonia cases (vs. 10.7 % in placebo). Furthermore, a faster viral clearance (34.5 % vs. 57.1 %) and significantly fewer patients with elevated inflammatory response (vs. 17.9 % in placebo). No significant hematologic, hepatic, or renal adverse effects were observed. These results suggest a favorable efficacy and safety profile of *A. paniculata* extract in mild COVID-19. Anyhow, the findings were based on small sample size with twenty-nine patients treated with the plant extract and twenty-eight patients as the placebo control group. Another study employed a quadruple-blind and placebo-controlled design to evaluate a standardized herbal formulation containing *A. paniculata* (Kan Jang®) or a fixed combination of *A. paniculata* and *Eleutherococcus senticosus* extracts, for patients with mild COVID-19. Patients were randomized to receive Kan Jang® tablets (90 mg AG daily) or placebo daily for 14 days. The results indicated that the Kan Jang® group experienced a significantly shorter median time to symptom recovery. Kan Jang® significantly reduced the total duration of symptoms and improved common complaints such as fatigue and sore throat [160]. Adverse events such as mild pruritus observed in four patients in the Kan Jang® group and six in the placebo group were mild and comparable between groups. Recent pharmacokinetic studies revealed that AG showed low and non-linear bioavailability. The maximum plasma concentration (Cmax) did not exhibit a dose dependent manner. The Cmax achieved 11.62 and 15.03 μg/L for 60 mg/day and 120 mg/day, respectively for 7 days [165]. Another studies reported that the incorporation of solubilizers (β-cyclodextrin and sodium dodecyl sulfate) and bioenhancer (piperine) improved oral bioavailability and pharmacokinetics of AG in beagle dogs [166]. Clinical studies integrated AG with its pharmacokinetics and pharmacometabolomics responses to understand the dose-response relationship of orally administered AG capsules. It was found that the Cmax was 10.15 ng mL-1, 7.02 ng mL-1 and 58.45 ng mL-1 for three biomarkers such as AG, 14-deoxyandrographolide and neoandrographolide, respectively after 1.5 h of oral administration. Most probably, the metabolism of the biomarkers converted them into conjugated forms as no free biomarkers were detected in urine.

It is also noteworthy that AG also shows good therapeutic effects. A pilot clinical trial tested the oral consumption of 140 mg AG for 24 months by patients and they showed non-active progressive multiple sclerosis. The side effects were mild rash and dysgeusia. AG was well tolerated and showed potential to reduce brain atrophy and disability progression. It needs to be further evaluated in a larger clinical trial [156]. Most clinical trials involve small to moderate sample sizes as presented in Table 3, which limits statistical power and the ability to detect rare or delayed adverse effects. Furthermore, the administered doses ranged from 60 to 600 mg/day and intervention periods spanned 5 days to 24 months. The substantial heterogeneity in AG dosage, formulation, and treatment duration across the previous studies also complicate comparisons and dose–response interpretation. More importantly, the batch-to-batch variability in phytochemical composition and product formulation may influence pharmacokinetics, therapeutic efficacy, and safety outcomes.

An open-label prospective trial assessed a fixed multi-ingredient supplement containing *A. paniculata* for episodic migraine prevention. The supplement containing magnesium 281.25 mg, vitamin B 24.8 mg, feverfew 150 mg, coenzyme Q10 20 mg, and *A. paniculata* 100 mg was evaluated for episodic migraine prophylaxis. The patients took one or two tablets daily. The supplement reduced migraine frequency, duration and intensity [158]. A significant reduction in monthly migraine days and severity was achieved and the treatment was well-tolerated with only mild and transient gastrointestinal adverse events. In a crossover study, the effects of *A. paniculata* (Sambiloto) were assessed on GLP-1 and DPP-4 levels in both normal and prediabetic individuals. Among the 73 participants who completed the study, five individuals (2 healthy,

3 prediabetic) reported mild to moderate adverse events, including hand tremors, facial flushing, itching, drowsiness, fatigue, diarrhea, and palpitations. The adverse effects were generally mild to moderate, mostly on the gastrointestinal symptoms and dermatological reactions. Somehow, the incidence of the adverse events was typically below 10 % and serious adverse effects were not reported till to date [167]. Supplementation significantly increased GLP-1 and reduced DPP-4 activity, particularly in prediabetic subjects, indicating enhanced incretin response and improved insulin sensitivity [157].

These clinical trials have provided substantial evidence for the therapeutic potential of AG in treating cancer and inflammation related diseases. The results of the trials have triggered the development and research of AG-related drugs in the future studies [168]. Even though AG demonstrated good safety in clinical studies, the allergic reactions still need to be carefully monitored. A distinct toxicity profile was observed with injectable AG derivatives (e.g., Xiyanping, Chuanhuning). The formulations exhibited an adverse drug reaction incidence rate between 3.69 % and 5.48 % [143]. Therefore, it is important to well design randomized controlled trials by employing standardized formulations, robust pharmacokinetic evaluation, clinical endpoints and systematic monitoring of drug–drug interactions and long-term toxicity to more conclusively establish the clinical efficacy and safety profile of AG, particularly in cancer therapy.

8. Conclusion

Cancer remains a significant global health challenge and one of the leading causes of death worldwide. Current therapeutic approaches such as surgery, chemotherapy, radiation, and targeted therapies often face significant limitations, including severe side effects, drug resistance, and limited efficacy for advanced or metastatic cancers. Therefore, it is essential to find innovative anticancer drugs that are safe and effective with minimal side effects.

AG is a diterpenoid lactone isolated from the leaves and stems of *A. paniculata*, a traditional medicinal herb widely used in Asia. However, a standardized extraction process for achieving high recovery and consistent purity of andrographolide has not been established till to date. Most studies used the plant extract or crude extract which varies in composition and complicates the data interpretation of scientific findings. Hundreds of years ago, it was used to treat many diseases in folk medicine such as fever, cough, mosquito bites. AG has a broad range of pharmacological effects including anti-cancer, anti-inflammatory, antioxidant, and immune-modulatory properties and so on. Recent studies have highlighted the promising anticancer potential of AG, which demonstrated activity against various types of cancer, including breast, lung, liver, colorectal and gastric cancer. AG exerts its anticancer effects through mechanisms such as inducing apoptosis, inhibiting proliferation, anti-angiogenesis, and regulating oxidative stress. In addition, AG combined with chemical drugs such as DDP, 5-UF, and CTX can improve tumor radiosensitivity and reverse drug resistance. The synergistic effects of AG with drugs have been further proven by its chemosensitizing potential in P-glycoprotein overexpressing multidrug-resistant cancer cell lines [169]. At present, no conclusive evidence suggests the antagonistic interactions between AG and chemotherapeutic agents in the published literature.

Although AG has significant potential in cancer treatment with high biological safety, it still has some toxic effects at a high dose such as cause kidney toxicity or liver toxicity. Most of the current studies on AG are based on animals or cells, and even if multiple targets of action are identified, it is still unknown whether the same anticancer results be achieved in humans. A major gap is the limited pharmacokinetic–-pharmacodynamic data for AG, likely due to the challenges in predicting effective plasma levels and therapeutic responses resulted from its low solubility and poor bioavailability. The other methodological limitation includes small sample size, and thus limiting the statistical power and reproducibility of the findings. A substantial proportion of the evidence is derived from *in vitro* experiments without corresponding *in vivo* validation. The limitation directly restricts the translational relevance of the reported mechanisms. There are relatively few clinical studies, especially on cancer patients always show slight or mild adverse reactions such as headaches, gastrointestinal discomfort, and fever. Therefore, further research is still needed on the large scale clinical trials in order to confirm the safe dose and its anticancer efficacy.

The ultimate goal of this view is to explore the mechanism of action of AG on cancer, provide a theoretical basis for its clinical transformation, and lay a theoretical foundation for subsequent clinical trials. The future studies may focus on the combination formulations or delivery systems to improve systemic exposure of AG in habiting cancer cells.

CRediT authorship contribution statement

Xiaohan Wu: Conceptualization, Investigation, Writing – original draft, Data curation. **Lee Suan Chua:** Supervision, Writing – review & editing, Funding acquisition, Resource, Project administration. **Khairunadwa Binti Jemon:** Supervision.

Funding

This research received financial support from Universiti Teknologi Malaysia, Q.J130000.3846.23H03.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Data availability

No data was used for the research described in the article.

References

[1] H. Bhardwaj, A. Noumani, J.K. Himanshu, S. Chakravorty, P.R. Solanki, Recent advancement in the detection of potential cancer biomarkers using the nanomaterial integrated electrochemical sensing technique: a detailed review, Mater. Adv. 5 (2) (2024) 475–503, https://doi.org/10.1039/D3MA00621B.
[2] F. Bray, M. Laversanne, E. Weiderpass, I. Soerjomataram, The ever-increasing importance of cancer as a leading cause of premature death worldwide, Cancer 127 (16) (2021) 3029–3030, https://doi.org/10.1002/cncr.33587.
[3] D. Choudhary, A. Kaur, P. Singh, G. Chaudhary, R. Kaur, M.F. Bayan, B. Chandrasekaran, S.M. Marji, R. Ayman, Target protein degradation by protacs: a budding cancer treatment strategy, Pharm. Ther. 250 (2023) 108525, https://doi.org/10.1016/j.pharmthera.2023.108525.
[4] D. Meirow, D. Nugent, The effects of radiotherapy and chemotherapy on female reproduction, 43, Hum. Reprod. Update 7 (6) (2001) 535, https://doi.org/10.1093/humupd/7.6.535.
[5] M. Wang, Y. Li, T. Pan, N. Jia, Plant natural compounds in the cancer treatment: a systematic bibliometric analysis, Heliyon 10 (14) (2024) e34462, https://doi.org/10.1016/j.heliyon.2024.e34462.
[6] Z. Malik, R. Parveen, B. Parveen, S. Zahiruddin, M. Aasif Khan, A. Khan, S. Massey, S. Ahmad, S.A. Husain, Anticancer potential of andrographolide from *Andrographis paniculata* (burm.f.) nees and its mechanisms of action, J. Ethnopharmacol. 272 (2021) 113936, https://doi.org/10.1016/j.jep.2021.113936.
[7] L.-j Yang, T. Han, R.-n Liu, S.-m Shi, S.-y Luan, S.-n Meng, Plant-derived natural compounds: a new frontier in inducing immunogenic cell death for cancer treatment, Biomed. Pharm. 177 (2024) 117099, https://doi.org/10.1016/j.biopha.2024.117099.
[8] P. Bajpai, S. Usmani, R. Kumar, O. Prakash, Recent advances in anticancer approach of traditional medicinal plants: a novel strategy for cancer chemotherapy, Intell. Pharm. 2 (3) (2024) 291–304, https://doi.org/10.1016/j.ipha.2024.02.001.

[9] S. Hossain, Z. Urbi, H. Karuniawati, R.B. Mohiuddin, A.M. Qrimida, A.M. M. Allzrag, L.C. Ming, E. Pagano, R. Capasso, *Andrographis paniculata* (burm. f.) wall. ex nees: an updated review of phytochemistry, antimicrobial pharmacology, and clinical safety and efficacy, Life 11 (4) (2021), https://doi.org/10.3390/life11040348.
[10] R.A. Muluye, Y. Bian, P.N. Alemu, Anti-inflammatory and antimicrobial effects of heat-clearing chinese herbs: A current review, 8, J. Tradit. Complement. Med. 4 (2) (2014) 93, https://doi.org/10.4103/2225-4110.126635.
[11] M. Jiang, F. Sheng, Z. Zhang, X. Ma, T. Gao, C. Fu, P. Li, *Andrographis paniculata* (burm.f.) nees and its major constituent andrographolide as potential antiviral agents, J. Ethnopharmacol. 272 (2021) 113954, https://doi.org/10.1016/j.jep.2021.113954.
[12] S.P. Adiguna, J.A. Panggabean, R.T. Swasono, S.I. Rahmawati, F. Izzati, A. Bayu, M.Y. Putra, C. Formisano, C. Giuseppina, Evaluations of andrographolide-rich fractions of *Andrographis paniculata* with enhanced potential antioxidant, anticancer, antihypertensive, and anti-inflammatory activities, Plants 12 (6) (2023) 1220, https://doi.org/10.3390/plants12061220.
[13] P.I.B. Apsari, I.K. Suryana, B.K. Satriyasa, D.A.A.S. Laksmi, D.K. Wati, I.M.A. G. Wirasuta, Towards andrographolide as antimalarial: a systematic review, Biomed. Pharm. J. 18 (1) (2025) 499–515, https://doi.org/10.13005/bpj/3103.
[14] A. Balap, B. Atre, S. Lohidasan, A. Sinnathambi, K. Mahadik, Pharmacokinetic and pharmacodynamic herb-drug interaction of *Andrographis paniculata* (nees) extract and andrographolide with etoricoxib after oral administration in rats, J. Ethnopharmacol. 183 (2016) 9–17, https://doi.org/10.1016/j.jep.2015.11.011.
[15] A.K. Thakur, S.S. Chatterjee, V. Kumar, Adaptogenic potential of andrographolide: an active principle of the king of bitters (*Andrographis paniculata*), J. Tradit. Complement. Med. 5 (1) (2015) 42–50, https://doi.org/10.1016/j.jtcme.2014.10.002.
[16] S. Mehta, A.K. Sharma, R.K. Singh, Ethnobotany, pharmacological activities and bioavailability studies on "King of Bitters" (Kalmegh): a review (2010-2020), Comb. Chem. High. Throughput Screen 25 (5) (2022) 788–807, https://doi.org/10.2174/1386207324666210310140611.
[17] S. Mehta, A.K. Sharma, R.K. Singh, Pharmacological activities and molecular mechanisms of pure and crude extract of Andrographis paniculata: an update, Phytomed 1 (4) (2021) 100085, https://doi.org/10.1016/j.phyplu.2021.100085.
[18] S. Kumar, K.K. Ratha, S. Jaiswal, M.M. Rao, R. Acharya, Exploring the potential of Andrographis paniculata and its bioactive compounds in the management of liver diseases: a comprehensive food chemistry perspective, Food Chem. Adv. 4 (2024) 100674, https://doi.org/10.1016/j.focha.2024.100674.
[19] J. Hu, Y. Li, X. Xie, Y. Song, W. Yan, Y. Luo, Y. Jiang, The therapeutic potential of andrographolide in cancer treatment, Biomed. Pharm. 180 (2024) 117438, https://doi.org/10.1016/j.biopha.2024.117438.
[20] T.P. Chau, S. Devanesan, R. Ayub, K. Perumal, Identification and characterization of major bioactive compounds from Andrographis paniculata (Burm. f.) extracts showed multi-biomedical applications, Environ. Res. 242 (2024) 117763, https://doi.org/10.1016/j.envres.2023.117763.
[21] X. Chen, J. Ren, J. Yang, Z. Zhu, R. Chen, L. Zhang, A critical review of *Andrographis paniculata*, Med. Plant Biol. 2 (1) (2023), https://doi.org/10.48130/MPB-2023-0015.
[22] S. Netrphan, C.T. Darwell, P. Wanichananan, C. Theerawitaya, K. Tongmark, S. Cha-um, S. Janta, S. Chakhonkaen, N. Sangarwut, J. Yamjabok, K. Sikaewtung, K. Kaewmungkun, P. Summat, A. Muangprom, Morphological diversity among *Andrographis paniculata* genotypes based on traits determined mainly by high-throughput phenotyping platform, Genet. Resour. Crop Evol. (2024), https://doi.org/10.1007/s10722-024-02301-y.
[23] S. Raman, V. Murugaiyah, T. Parumasivam, *Andrographis paniculata* dosage forms and advances in nanoparticulate delivery systems: an overview, Molecules 27 (19) (2022) 6164, https://doi.org/10.3390/molecules27196164.
[24] P.M. Ruengthanoo, A. Changthong, P. Sriraj, J. Prathumtet, N. Laikaew, R. Aukkanimart, Anti-inflammatory effects of *Andrographis paniculata* (Fah Talai Jone) via TNFα-JNK pathway and bioactive compound identification, Phytomed 5 (1) (2025) 100720, https://doi.org/10.1016/j.phyplu.2024.100720.
[25] B.C. Adedayo, O.M. Ajiboye, I.S. Oyeleye, R.O. Ojo, G. Oboh, Effect of alkaloid extract from *Andrographis paniculata* (burm. f.) nees and *Phyllanthus amarus* schumach. & Thonn. on cognitive related biochemicals in the brain of streptozotocin-induced diabetic rats, Pharmacol. Res. Mod. Chin. Med. 9 (2023) 100314, https://doi.org/10.1016/j.prmcm.2023.100314.
[26] R. Patil, V. Jain, Andrographolide: a review of analytical methods, J. Chromatogr. Sci. 59 (2) (2021) 191–203, https://doi.org/10.1093/chromsci/bmaa091.
[27] S. Abdullah, P. Chatterjee, A review on the molecular mechanisms and pharmacology of andrographolide from *Andrographis paniculata* (burm. f.) nees in the management of the interplay between type 2 diabetes and breast cancer, Phytomed 5 (2) (2025) 100772, https://doi.org/10.1016/j.phyplu.2025.100772.
[28] X. Li, W. Yuan, J. Wu, J. Zhen, Q. Sun, M. Yu, Andrographolide, a natural anti-inflammatory agent: an update, Front. Pharm. 13 (2022) 920435, https://doi.org/10.3389/fphar.2022.920435.
[29] M. Li, T. Zhang, L. Zhu, R. Wang, Y. Jin, Liposomal andrographolide dry powder inhalers for treatment of bacterial pneumonia via anti-inflammatory pathway, Int. J. Pharm. 528 (1-2) (2017) 163–171, https://doi.org/10.1016/j.ijpharm.2017.06.005.
[30] X. Yin, X. Zhuang, W. Luo, M. Liao, L. Huang, Q. Cui, J. Huang, C. Yan, Z. Jiang, Y. Liu, W. Wang, Andrographolide promote the growth and immunity of Litopenaeus vannamei, and protects shrimps against Vibrio alginolyticus by regulating inflammation and apoptosis via a ROS-JNK dependent pathway, Front. Immunol. 13 (2022) 990297, https://doi.org/10.3389/fimmu.2022.990297.
[31] J. Lu, Y. Ma, J. Wu, H. Huang, X. Wang, Z. Chen, J. Chen, H. He, C. Huang, A review for the neuroprotective effects of andrographolide in the central nervous system, Biomed. Pharm. 117 (2019) 109078, https://doi.org/10.1016/j.biopha.2019.109078.
[32] E. Toppo, S.S. Darvin, S. Esakkimuthu, M.K. Nayak, K. Balakrishna, K. Sivasankaran, P. Pandikumar, S. Ignacimuthu, N.A. Al-Dhabi, Effect of two andrographolide derivatives on cellular and rodent models of non-alcoholic fatty liver disease, Biomed. Pharm. 95 (2017) 402–411, https://doi.org/10.1016/j.biopha.2017.08.071.
[33] P. Tipduangta, S. Chansakaow, P. Tansakul, R. Meungjai, P. Dilokthornsakul, Polymer matrix and manufacturing methods in solid dispersion system for enhancing andrographolide solubility and absorption: A systematic review, Pharmaceutics 16 (5) (2024) 688, https://doi.org/10.3390/pharmaceutics16050688.
[34] S. Mehta, A.K. Sharma, R.K. Singh, Therapeutic journey of *Andrographis paniculata* (Burm. f.) nees from natural to synthetic and nanoformulations, Mini Rev. Med. Chem. 21 (12) (2021) 1556–1577, https://doi.org/10.2174/1389557521666210315162354.
[35] B.A. Oseni, C.P. Azubuike, O.O. Okubanjo, C.I. Igwilo, J. Panyam, Encapsulation of andrographolide in poly(lactide-co-glycolide) nanoparticles: Formulation optimization and *in vitro* efficacy studies, Front Bioeng. Biotechnol. 9 (2021) 639409, https://doi.org/10.3389/fbioe.2021.639409.
[36] P. Sanati, L.S. Chua, R. Nasiri, S.-S. Hashemi, Nanoencapsulation of andrographolide rich extract for the inhibition of cervical and neuroblastoma cancer cells, J. Biomed. Nanotechnol. 16 (9) (2020) 1370–1380, https://doi.org/10.1166/jbn.2020.2973.
[37] S. Cavalu, A.M. Abdelhamid, S. Saber, E.A. Elmorsy, R.S. Hamad, M.A. Abdel-Reheim, G. Yahya, M.M. Salama, Cell cycle machinery in oncology: A comprehensive review of therapeutic targets, FASEB J. 38 (11) (2024) e23734, https://doi.org/10.1096/fj.202400769R.
[38] W. Chen, X. Zhuang, Y. Chen, H. Yang, L. Shen, S. Feng, W. Min, K. Yuan, P. Yang, Recent advances in regulating the cell cycle through inhibiting CDKs for cancer treatment, Chin. J. Nat. Med. 23 (3) (2025) 286–298, https://doi.org/10.1016/S1875-5364(25)60846-6.
[39] J. Zhang, C. Li, L. Zhang, Y. Heng, S. Wang, Y. Pan, L. Cai, Y. Zhang, T. Xu, X. Chen, R.M. Hoffman, L. Jia, Andrographolide, a diterpene lactone from the traditional chinese medicine *Andrographis paniculata*, induces senescence in human lung adenocarcinoma via p53/p21 and Skp2/p27, Phytomedicine 98 (2022) 153933, https://doi.org/10.1016/j.phymed.2022.153933.
[40] X.Y. Li, X. Cui, C.Q. Xie, Y. Wu, T. Song, J.D. He, J. Feng, Q.R. Cui, J.L. Bin, Q. Y. Li, C. Xiao, J.H. Deng, G.D. Lu, J. Zhou, Andrographolide causes p53-independent HCC cell death through p62 accumulation and impaired DNA damage repair, Phytomedicine 121 (2023) 155089, https://doi.org/10.1016/j.phymed.2023.155089.
[41] I. Khan, S. Mahfooz, M. Faisal, A.A. Alatar, I.A. Ansari, Andrographolide induces apoptosis and cell cycle arrest through inhibition of aberrant hedgehog signaling pathway in colon cancer cells, Nutr. Cancer 73 (11-12) (2021) 2428–2446, https://doi.org/10.1080/01635581.2020.1828942.
[42] N.S. Othman, D.K. Mohd Azman, Andrographolide induces G2/M cell cycle arrest and apoptosis in human glioblastoma DBTRG-05MG cell line via ERK1/2 /c-Myc/p53 signaling pathway, Molecules 27 (19) (2022), https://doi.org/10.3390/molecules27196686.
[43] C.H. Ho, C.K. Fan, Y.C. Chu, S.P. Liu, P.C. Cheng, Effects of pterostilbene on inducing apoptosis in normal bladder and bladder cancer cells, Tissue Cell 94 (2025) 102794, https://doi.org/10.1016/j.tice.2025.102794.
[44] L. Lossi, The concept of intrinsic versus extrinsic apoptosis, Biochem. J. 479 (3) (2022) 357–384, https://doi.org/10.1042/BCJ20210854.
[45] T. Kuwana, L. Bouchier-Hayes, J.E. Chipuk, C. Bonzon, B.A. Sullivan, D.R. Green, D.D. Newmeyer, BH3 domains of BH3-only proteins differentially regulate Bax-mediated mitochondrial membrane permeabilization both directly and indirectly, 35, Mol. Cell 17 (4) (2005) 525, https://doi.org/10.1016/j.molcel.2005.02.003.
[46] S.H. Loh, Y.T. Tsai, S.F. Huang, T.C. Yu, P.C. Kuo, S.C. Chao, M.F. Chou, C.S. Tsai, S.P. Lee, Effects of andrographolide on intracellular pH regulation, cellular migration, and apoptosis in Human cervical cancer cells, Cancers 12 (2) (2020) 387, https://doi.org/10.3390/cancers12020387.
[47] Z. Chen, W.J. Tang, Y.H. Zhou, Z.M. Chen, K. Liu, Andrographolide inhibits non-small cell lung cancer cell proliferation through the activation of the mitochondrial apoptosis pathway and by reprogramming host glucose metabolism, Ann. Transl. Med. 9 (22) (2021) 1701, https://doi.org/10.21037/atm-21-5975.
[48] M. Banerjee, S. Chattopadhyay, T. Choudhuri, R. Bera, S. Kumar, B. Chakraborty, S.K. Mukherjee, Cytotoxicity and cell cycle arrest induced by andrographolide lead to programmed cell death of MDA-MB-231 breast cancer cell line, J. Biomed. Sci. 23 (2016) 40, https://doi.org/10.1186/s12929-016-0257-0.
[49] M. Kundu, Y.E. Greer, A. Lobanov, L. Ridnour, R.N. Donahue, Y. Ng, S. Ratnayake, K. White, D. Voeller, S. Weltz, Q. Chen, S.J. Lockett, M. Cam, D. Meerzaman, D.A. Wink, R. Weigert, S. Lipkowitz, TRAIL induces cytokine production via the NFkB2 pathway promoting neutrophil chemotaxis and neutrophil-mediated immune-suppression in triple negative breast cancer cells, Cancer Lett. 620 (2025) 217692, https://doi.org/10.1016/j.canlet.2025.217692.
[50] Y. Deng, R. Bi, H. Guo, J. Yang, Y. Du, C. Wang, W. Wei, Andrographolide enhances TRAIL-induced apoptosis via p53-mediated death receptors up-regulation and suppression of the NF-small ka, cyrillic B pathway in bladder cancer cells, Int. J. Biol. Sci. 15 (3) (2019) 688–700, https://doi.org/10.7150/ijbs.30847.

[51] R.J. Wei, X.S. Zhang, D.L. He, Andrographolide sensitizes prostate cancer cells to TRAIL-induced apoptosis, Asian J. Androl. 20 (2) (2018) 200–204, https://doi.org/10.4103/aja.aja_30_17.
[52] J. Li, F. Cao, H.L. Yin, Z.J. Huang, Z.T. Lin, N. Mao, B. Sun, G. Wang, Ferroptosis: past, present and future, Cell Death Dis. 11 (2) (2020) 88, https://doi.org/10.1038/s41419-020-2298-2.
[53] L. Jiaqi, H. Siqing, W. Qin, Z. di, Z. Bei, Y. Jialin, Andrographolide promoted ferroptosis to repress the development of non-small cell lung cancer through activation of the mitochondrial dysfunction, Phytomedicine 109 (2023) 154601, https://doi.org/10.1016/j.phymed.2022.154601.
[54] W. Li, H. Fu, L. Fang, H. Chai, B. Ding, S. Qian, Andrographolide induced ferroptosis in multiple myeloma cells by regulating the P38/Nrf2/HO-1 pathway, Arch. Biochem. Biophys. 742 (2023) 109622, https://doi.org/10.1016/j.abb.2023.109622.
[55] J. Debnath, N. Gammoh, K.M. Ryan, Autophagy and autophagy-related pathways in cancer, Nat. Rev. Mol. Cell Biol. 24 (8) (2023) 560–575, https://doi.org/10.1038/s41580-023-00585-z.
[56] D. Kumar, B. Das, R. Sen, P. Kundu, A. Manna, A. Sarkar, C. Chowdhury, M. Chatterjee, P. Das, Andrographolide analogue induces apoptosis and autophagy mediated cell death in U937 cells by inhibition of PI3K/Akt/mTOR pathway, PLoS One 10 (10) (2015) e0139657, https://doi.org/10.1371/journal.pone.0139657.
[57] E. Wen, G. Xin, W. Su, S. Li, Y. Zhang, Y. Dong, X. Yang, C. Wan, Z. Chen, X. Yu, K. Zhang, H. Niu, W. Huang, Activation of TLR4 induces severe acute pancreatitis-associated spleen injury via ROS-disrupted mitophagy pathway, Mol. Immunol. 142 (2022) 63–75, https://doi.org/10.1016/j.molimm.2021.12.012.
[58] Y. Liu, Y. Zhang, J. Zou, L. Yan, X. Yu, P. Lu, X. Wu, Q. Li, R. Gu, D. Zhu, Andrographolide induces autophagic cell death and inhibits invasion and metastasis of human osteosarcoma cells in an autophagy-dependent manner, Cell Physiol. Biochem 44 (4) (2017) 1396–1410, https://doi.org/10.1159/000485536.
[59] X.R. Wang, Z.B. Jiang, C. Xu, W.Y. Meng, P. Liu, Y.Z. Zhang, C. Xie, J.Y. Xu, Y. J. Xie, T.L. Liang, H.X. Yan, X.X. Fan, X.J. Yao, Q.B. Wu, E.L. Leung, Andrographolide suppresses non-small-cell lung cancer progression through induction of autophagy and antitumor immune response, Pharmacol. Res. 179 (2022) 106198, https://doi.org/10.1016/j.phrs.2022.106198.
[60] M. Rajabi, S.A. Mousa, The role of angiogenesis in cancer treatment, Biomedicines 5 (2) (2017) 34, https://doi.org/10.3390/biomedicines5020034.
[61] R.I. Teleanu, C. Chircov, A.M. Grumezescu, D.M. Teleanu, Tumor angiogenesis and anti-angiogenic strategies for cancer treatment, J. Clin. Med. 9 (1) (2019) 84, https://doi.org/10.3390/jcm9010084.
[62] Y. Yang, T. Rao, Y. Jiang, Y. Zhan, J. Cheng, Z. Yin, K. Ma, X. Zhong, X. Guo, S. Yang, Electroacupuncture ameliorates cognitive impairment and white matter injury in vascular dementia rats via activating HIF-1alpha/VEGF/VEGFR2 pathway, Neurosci 573 (2025) 364–380, https://doi.org/10.1016/j.neuroscience.2025.03.063.
[63] L. Shi, G. Zhang, Z. Zheng, B. Lu, L. Ji, Andrographolide reduced VEGFA expression in hepatoma cancer cells by inactivating HIF-1alpha: The involvement of JNK and MTA1/HDCA, Chem. Biol. Inter. 273 (2017) 228–236, https://doi.org/10.1016/j.cbi.2017.06.024.
[64] J. Li, C. Zhang, H. Jiang, J. Cheng, Andrographolide inhibits hypoxia-inducible factor-1 through phosphatidylinositol 3-kinase/AKT pathway and suppresses breast cancer growth, Onco Targets Ther. 8 (2015) 427–435, https://doi.org/10.2147/OTT.S76116.
[65] L. Ji, Z. Zheng, L. Shi, Y. Huang, B. Lu, Z. Wang, Andrographolide decreased VEGFD expression in hepatoma cancer cells by inducing ubiquitin/proteasome-mediated cFos protein degradation, Biochim. Biophys. Acta Rev. Cancer 1850 (4) (2015) 750–758, https://doi.org/10.1016/j.bbagen.2015.01.005.
[66] T. Pan, D. Zhou, Z. Shi, Y. Qiu, G. Zhou, J. Liu, Q. Yang, L. Cao, J. Zhang, Centromere protein U (CENPU) enhances angiogenesis in triple-negative breast cancer by inhibiting ubiquitin-proteasomal degradation of COX-2, Cancer Lett. 482 (2020) 102–111, https://doi.org/10.1016/j.canlet.2019.11.003.
[67] Y. Peng, Y. Wang, N. Tang, D. Sun, Y. Lan, Z. Yu, X. Zhao, L. Feng, B. Zhang, L. Jin, F. Yu, X. Ma, C. Lv, Andrographolide inhibits breast cancer through suppressing COX-2 expression and angiogenesis via inactivation of p300 signaling and VEGF pathway, J. Exp. Clin. Cancer Res. 37 (1) (2018) 248, https://doi.org/10.1186/s13046-018-0926-9.
[68] J. Yuan, L. Yang, H. Zhang, N.M. Beeraka, D. Zhang, Q. Wang, M. Wang, H.V. Pr, G. Sethi, G. Wang, Decoding tumor microenvironment: EMT modulation in breast cancer metastasis and therapeutic resistance, and implications of novel immune checkpoint blockers, Biomed. Pharm. 181 (2024) 117714, https://doi.org/10.1016/j.biopha.2024.117714.
[69] B. Arneth, Tumor microenvironment, Medicina 56 (1) (2019) 15, https://doi.org/10.3390/medicina56010015.
[70] S. Guo, C.-X. Deng, Effect of stromal cells in tumor microenvironment on metastasis initiation, Int. J. Biol. Sci. 14 (14) (2018) 2083, https://doi.org/10.7150/ijbs.25720.
[71] J. Li, J. Liu, W. Yue, K. Xu, W. Cai, F. Cui, Z. Li, W. Wang, J. He, Andrographolide attenuates epithelial-mesenchymal transition induced by TGF-β1 in alveolar epithelial cells, J. Cell. Mol. Med. 24 (18) (2020) 10501–10511, https://doi.org/10.1111/jcmm.15665.
[72] S.L. Yang, F.H. Kuo, P.N. Chen, Y.H. Hsieh, N.Y. Yu, W.E. Yang, M.J. Hsieh, S. F. Yang, Andrographolide suppresses the migratory ability of human glioblastoma multiforme cells by targeting ERK1/2-mediated matrix metalloproteinase-2 expression, Oncotarget 8 (62) (2017) 105860–105872, https://doi.org/10.18632/oncotarget.22407.
[73] R. Eskandani, M. Kazempour, R. Farahzadi, Z. Sanaat, M. Eskandani, K. Adibkia, S. Vandghanooni, A. Mokhtarzadeh, Engineered nanoparticles as emerging gene/drug delivery systems targeting the nuclear factor-κB protein and related signaling pathways in cancer, Biomed. Pharm. 156 (2022) 113932, https://doi.org/10.1016/j.biopha.2022.113932.
[74] Z. Zhai, X. Qu, H. Li, Z. Ouyang, W. Yan, G. Liu, X. Liu, Q. Fan, T. Tang, K. Dai, A. Qin, Inhibition of MDA-MB-231 breast cancer cell migration and invasion activity by andrographolide via suppression of nuclear factor-κB-dependent matrix metalloproteinase-9 expression, Mol. Med. Rep. 19 (3) (2019) 1979, https://doi.org/10.3892/mmr.2019.9833.
[75] H. Huang, Q. Lu, X. Yuan, P. Zhang, C. Ye, M. Wei, C. Yang, L. Zhang, Y. Huang, X. Luo, J. Luo, Andrographolide inhibits the growth of human osteosarcoma cells by suppressing Wnt/beta-catenin, PI3K/AKT and NF-kappaB signaling pathways, Chem. Biol. Inter. 365 (2022) 110068, https://doi.org/10.1016/j.cbi.2022.110068.
[76] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (3) (2021) 209–249, https://doi.org/10.3322/caac.21660.
[77] N. Dasari, G.S. Guntuku, S. Pindiprolu, Targeting triple negative breast cancer stem cells using nanocarriers, Discov. Nano 19 (1) (2024) 41, https://doi.org/10.1186/s11671-024-03985-y.
[78] J. Mao, K. Wang, J. Tong, W. Zhang, G. Shen, D. Wang, Z. Liao, Z. Zhang, Q. Miao, S. Jiang, K. Zhang, Discovery of dual PARP/NAMPT inhibitors for the treatment of BRCA wild-type triple-negative breast cancer, Bioorg. Med. Chem. Lett. 120 (2025) 130117, https://doi.org/10.1016/j.bmcl.2025.130117.
[79] R. Tohkayomatee, S. Reabroi, D. Tungmunnithum, W. Parichatikanond, D. Pinthong, Andrographolide exhibits anticancer activity against breast cancer cells (MCF-7 and MDA-MB-231 cells) through suppressing cell proliferation and inducing cell apoptosis via inactivation of ER-alpha receptor and PI3K/AKT/mTOR signaling, Molecules 27 (11) (2022), https://doi.org/10.3390/molecules27113544.
[80] S.L. Beesetti, M. Jayadev, G.V. Subhashini, L. Mansour, S. Alwasel, A.H. Harrath, Andrographolide as a therapeutic agent against breast and ovarian cancers, Open Life Sci. 14 (2019) 462–469, https://doi.org/10.1515/biol-2019-0052.
[81] C. Kaewpiboon, N. Boonnak, A.W. Salae, S. Pakdeepromma, N. Yawut, Y. H. Chung, Andrographolide targets EGFR to impede epithelial-mesenchymal transition in human breast cancer cells, J. Pharm. Biomed. Anal. 248 (2024) 116267, https://doi.org/10.1016/j.jpba.2024.116267.
[82] T. Xu, Y. Jiang, S. Yuan, L. Zhang, X. Chen, W. Zhao, L. Cai, B. Xiao, L. Jia, Andrographolide inhibits ER-positive breast cancer growth and enhances fulvestrant efficacy via ROS-FOXM1-ER-alpha axis, Front. Oncol. 12 (2022) 899402, https://doi.org/10.3389/fonc.2022.899402.
[83] J. Li, L. Huang, Z. He, M. Chen, Y. Ding, Y. Yao, Y. Duan, L. Zixuan, C. Qi, L. Zheng, J. Li, R. Zhang, X. Li, J. Dai, L. Wang, Q.Q. Zhang, Andrographolide suppresses the growth and metastasis of luminal-like breast cancer by inhibiting the NF-kappaB/miR-21-5p/PDCD4 signaling pathway, Front. Cell Dev. Biol. 9 (2021) 643525, https://doi.org/10.3389/fcell.2021.643525.
[84] R.P. Yadav, S. Sadhukhan, M.L. Saha, S. Ghosh, M. Das, Exploring the mechanism of andrographolide in the treatment of gastric cancer through network pharmacology and molecular docking, Sci. Rep. 12 (1) (2022) 18413, https://doi.org/10.1038/s41598-022-18319-0.
[85] L. Dai, G. Wang, W. Pan, Andrographolide inhibits proliferation and metastasis of SGC7901 gastric cancer cells, BioMed. Res. Int. 2017 (2017) 6242103, https://doi.org/10.1155/2017/6242103.
[86] H. Gao, H. Li, W. Liu, S.K. Mishra, C. Li, Andrographolide induces apoptosis in gastric cancer cells through reactivation of p53 and inhibition of mdm-2, Dokl. Biochem. Biophys. 500 (1) (2021) 393–401, https://doi.org/10.1134/S1607672921050070.
[87] S.C. Lim, H.J. Jeon, K.H. Kee, M.J. Lee, R. Hong, S.I. Han, Andrographolide induces apoptotic and non-apoptotic death and enhances tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in gastric cancer cells, Oncol. Lett. 13 (5) (2017) 3837–3844, https://doi.org/10.3892/ol.2017.5923.
[88] R. Ma, T. Shimura, C. Yin, Y. Okugawa, T. Kitajima, Y. Koike, Y. Okita, M. Ohi, K. Uchida, A. Goel, L. Yao, X. Zhang, Y. Toiyama, Antitumor effects of andrographis via ferroptosis-associated genes in gastric cancer, Oncol. Lett. 22 (1) (2021) 523, https://doi.org/10.3892/ol.2021.12784.
[89] B. Mi, Y. Jin, M. Zheng, H. Cheng, J. Zhang, Stigma, colorectal cancer knowledge and self-efficacy among colorectal cancer survivors: a cross-sectional study based on random forest analysis, Eur. J. Oncol. Nurs. 76 (2025) 102858, https://doi.org/10.1016/j.ejon.2025.102858.
[90] Y. Chen, J. Yang, Y. Zuo, C. Zhang, Y. Pu, Q. Ren, X. Li, Y. Huang, H. Huang, H. Yang, O. You, X. Xia, A. Lu, S. Shi, Y. Deng, J. Lu, Voacamine is a novel inhibitor of EGFR exerting oncogenic activity against colorectal cancer through the mitochondrial pathway, Pharmacol. Res. 184 (2022) 106415, https://doi.org/10.1016/j.phrs.2022.106415.
[91] R. Zhang, J. Zhao, J. Xu, D.X. Jiao, J. Wang, Z.Q. Gong, J.H. Jia, Andrographolide suppresses proliferation of human colon cancer SW620 cells through the TLR4/NF-kappaB/MMP-9 signaling pathway, Oncol. Lett. 14 (4) (2017) 4305–4310, https://doi.org/10.3892/ol.2017.6669.
[92] I. Khan, S. Mahfooz, M. Saeed, I. Ahmad, I.A. Ansari, Andrographolide inhibits proliferation of colon cancer SW-480 cells via downregulating notch signaling pathway, Anticancer Agents Med. Chem. 21 (4) (2021) 487–497, https://doi.org/10.2174/1871520620666200717143109.
[93] A. Banerjee, H. Ahmed, P. Yang, S.J. Czinn, T.G. Blanchard, Endoplasmic reticulum stress and IRE-1 signaling cause apoptosis in colon cancer cells in

response to andrographolide treatment, Oncotarget 7 (27) (2016) 41432–41444, https://doi.org/10.18632/oncotarget.9180.
[94] A. Banerjee, V. Banerjee, S. Czinn, T. Blanchard, Increased reactive oxygen species levels cause ER stress and cytotoxicity in andrographolide treated colon cancer cells, Oncotarget 8 (16) (2017) 26142–26153, https://doi.org/10.18632/oncotarget.15393.
[95] X. Li, R. Tian, L. Liu, L. Wang, D. He, K. Cao, J.K. Ma, C. Huang, Andrographolide enhanced radiosensitivity by downregulating glycolysis via the inhibition of the PI3K-Akt-mTOR signaling pathway in HCT116 colorectal cancer cells, J. Int Med Res. 48 (8) (2020) 0300060520946169, https://doi.org/10.1177/0300060520946169.
[96] W. Wang, W. Guo, L. Li, Z. Fu, W. Liu, J. Gao, Y. Shu, Q. Xu, Y. Sun, Y. Gu, Andrographolide reversed 5-FU resistance in human colorectal cancer by elevating BAX expression, Biochem. Pharm. 121 (2016) 8–17, https://doi.org/10.1016/j.bcp.2016.09.024.
[97] Y. Abe, N. Sakuyama, T. Sato, K. Kishine, K. Nagayasu, A. Nakatani, M. Kitajima, T. Watanabe, K. Nishimura, T. Ochiai, I. Nagaoka, Evaluation of the 5-fluorouracil plasma level in patients with colorectal cancer undergoing continuous infusion chemotherapy, Mol. Clin. Oncol. 11 (2019) 289–295.
[98] O. Aguilera, J.M. Gonzalez-Sancho, S. Zazo, R. Rincon, A.F. Fernandez, O. Tapia, F. Canals, B. Morte, V. Calvanese, J.L. Orgaz, N. Niell, S. Aguilar, J.M. Freije, O. Grana, D.G. Pisano, A. Borrero, J. Martinez-Useros, B. Jimenez, M.F. Fraga, J. Garcia-Foncillas, C. Lopez-Otin, M. Lafarga, F. Rojo, A. Munoz, Nuclear DICKKOPF-1 as a biomarker of chemoresistance and poor clinical outcome in colorectal cancer, Oncotarget 6 (8) (2015) 5903–5917, https://doi.org/10.18632/oncotarget.3464.
[99] Y. Zhao, C. Wang, A. Goel, Andrographis overcomes 5-fluorouracil-associated chemoresistance through inhibition of DKK1 in colorectal cancer, Carcinogenesis 42 (6) (2021) 814–825, https://doi.org/10.1093/carcin/bgab027.
[100] P. Sharma, T. Shimura, J.K. Banwait, A. Goel, Andrographis-mediated chemosensitization through activation of ferroptosis and suppression of beta-catenin/Wnt-signaling pathways in colorectal cancer, Carcinogenesis 41 (10) (2020) 1385–1394, https://doi.org/10.1093/carcin/bgaa090.
[101] M. Su, B. Qin, F. Liu, Y. Chen, R. Zhang, Andrographolide enhanced 5-fluoro-uracil-induced antitumor effect in colorectal cancer via inhibition of c-MET pathway, Drug Des. Devel. Ther. 11 (2017) 3333–3341, https://doi.org/10.2147/DDDT.S140354.
[102] W. Liu, T. Fan, M. Li, G. Zhang, W. Guo, X. Yang, C. Jiang, X. Li, X. Xu, A. Tang, K. Liu, L. Liu, L. Kong, Q. Xu, Y. Sun, Andrographolide potentiates PD-1 blockade immunotherapy by inhibiting COX2-mediated PGE2 release, Int. Immunopharmacol. 81 (2020) 106206, https://doi.org/10.1016/j.intimp.2020.106206.
[103] Y.F. Liu, Z.Q. Feng, T.H. Chu, B. Yi, J. Liu, H.Y. Yu, J. Xue, Y.J. Wang, C.Z. Zhang, Andrographolide sensitizes KRAS-mutant colorectal cancer cells to cetuximab by inhibiting the EGFR/AKT and PDGFRβ/AKT signaling pathways, Phytomed 126 (2024), https://doi.org/10.1016/j.phymed.2024.155462.
[104] V. Banerjee, N. Sharda, J. Huse, D. Singh, D. Sokolov, S.J. Czinn, T.G. Blanchard, A. Banerjee, Synergistic potential of dual andrographolide and melatonin targeting of metastatic colon cancer cells: using the chou-talalay combination index method, Eur. J. Pharm. 897 (2021) 173919, https://doi.org/10.1016/j.ejphar.2021.173919.
[105] N. Sharda, T. Ikuse, E. Hill, S. Garcia, S.J. Czinn, A. Bafford, T.G. Blanchard, A. Banerjee, Impact of andrographolide and melatonin combinatorial drug therapy on metastatic colon cancer cells and organoids, Clin. Med. Insights Oncol. 15 (2021) 11795549211012672, https://doi.org/10.1177/11795549211012672.
[106] A. Midde, N. Arri, T. Kristian, S. Mukherjee, P.S. Sen Gupta, Y. Zhang, M. Karbowski, J. Waddell, N. Maharajan, M.S. Hassan, H.M. O'Hagan, M. Zalzman, A. Banerjee, Targeting mitochondrial ribosomal protein expression by andrographolide and melatonin for colon cancer treatment, Cancer Lett. 619 (2025) 217647, https://doi.org/10.1016/j.canlet.2025.217647.
[107] S. Gao, H. Tan, J. Gang, Inhibition of hepatocellular carcinoma cell proliferation through regulation of the cell cycle, AGE-RAGE, and leptin signaling pathways by a compound formulation comprised of andrographolide, wogonin, and oroxylin a derived from *Andrographis paniculata* (Burm.f.) nees, J. Ethnopharmacol. 329 (2024) 118001, https://doi.org/10.1016/j.jep.2024.118001.
[108] A. Arnett, D.A. Siegel, S. Dai, T.D. Thompson, J. Foster, E.J. di Pierro, B. Momin, P.J. Lupo, A. Heczey, Incidence and survival of pediatric and adult hepatocellular carcinoma, United States, 2001–2020, Cancer Epidemiol. 92 (2024) 102610, https://doi.org/10.1016/j.canep.2024.102610.
[109] Y. Luo, J. Hu, Y. Jiao, L. Liu, D. Miao, Y. Song, W. Yan, Y. Li, Y. Jiang, Andrographolide anti-proliferation and metastasis of hepatocellular carcinoma through LncRNA MIR22HG regulation, J. Nat. Med. 78 (1) (2024) 123–145, https://doi.org/10.1007/s11418-023-01752-4.
[110] X. Duan, T. Li, X. Han, J. Ren, P. Chen, H. Li, S. Gong, The antitumor effect of arsenic trioxide on hepatocellular carcinoma is enhanced by andrographolide, Oncotarget 8 (53) (2017) 90905–90915, https://doi.org/10.18632/oncotarget.18677.
[111] L. Wang, J. Zhou, S. Jing, B. Liu, J. Fang, T. Xue, Sublobar or lobar resection in early-stage peripheral non-small cell lung cancer less than 2cm: A meta-analysis for randomized controlled trials, Am. J. Surg. 241 (2025) 116069, https://doi.org/10.1016/j.amjsurg.2024.116069.
[112] T. Denisenko, I. Budkevich, B. Zhivotovsky, Cell death-based treatment of lung adenocarcinoma, Cell Death Dis. 9 (2) (2018) 117, https://doi.org/10.1038/s41419-017-0063-y.
[113] C. Zappa, S.A. Mousa, Non-small cell lung cancer: current treatment and future advances, Transl. Lung Cancer Res. 5 (3) (2016) 288–300, https://doi.org/10.21037/tlcr.2016.06.07.
[114] J.Q. Zhang, C.J. Li, L. Zhang, Y.Q. Heng, T. Xu, Y.J. Zhang, X.H. Chen, R. M. Hoffman, L.J. Jia, Andrographolide induces noxa-dependent apoptosis by transactivating ATF4 in human lung adenocarcinoma cells, Front. Pharm. 12 (2021), https://doi.org/10.3389/fphar.2021.680589.
[115] E.S. Yang, Y. Do, S.Y. Cheon, B. Kim, J. Ling, M.K. Cho, T. Kim, S.J. Bae, K.T. Ha, Andrographolide suppresses aerobic glycolysis and induces apoptotic cell death by inhibiting pyruvate dehydrogenase kinase 1 expression, Oncol. Rep. 49 (4) (2023), https://doi.org/10.3892/or.2023.8509.
[116] H. Yuan, B. Sun, F. Gao, M. Lan, Synergistic anticancer effects of andrographolide and paclitaxel against A549 NSCLC cells, Pharm. Biol. 54 (11) (2016) 2629–2635, https://doi.org/10.1080/13880209.2016.1176056.
[117] S. Mi, G. Xiang, D. Yuwen, J. Gao, W. Guo, X. Wu, X. Wu, Y. Sun, Y. Su, Y. Shen, Q. Xu, Inhibition of autophagy by andrographolide resensitizes cisplatin-resistant non-small cell lung carcinoma cells via activation of the Akt/mTOR pathway, Toxicol. Appl. Pharm. 310 (2016) 78–86, https://doi.org/10.1016/j.taap.2016.09.009.
[118] B. Sudha, N.S. Kumar, S. Sumathi, Women's ignorance and misperception of cervical cancer: Evidence-based analysis from low-and middle-income countries, Curr. Probl. Cancer 54 (2025) 101157.
[119] P. Udomwan, C. Pientong, P. Tongchai, A. Burassakarn, N. Sunthamala, S. Roytrakul, S. Suebsasana, T. Ekalaksananan, Proteomics analysis of andrographolide-induced apoptosis via the regulation of tumor suppressor p53 proteolysis in cervical cancer-derived human papillomavirus 16-positive cell lines, Int. J. Mol. Sci. 22 (13) (2021), https://doi.org/10.3390/ijms22136806.
[120] A. Pasha, D.V. Kumbhakar, R. Doneti, K. Kumar, G. Dharmapuri, P.K. Poleboyina, H.S. K, P. Basavaraju, D. Pasumarthi, A.S. D, P. Soujanya, I.Arnold Emeson, V. Bodiga, S.C. Pawar, Inhibition of inducible nitric oxide synthase (iNOS) by andrographolide and *in vitro* evaluation of its antiproliferative and proapoptotic effects on cervical cancer, Oxid. Med. Cell. Longev. 2021 (1) (2021) 6692628, https://doi.org/10.1155/2021/6692628.
[121] A. Pasha, K. Kumar, S.K. Heena, I. Arnold Emerson, S.C. Pawar, Inhibition of NF-kB and COX-2 by andrographolide regulates the progression of cervical cancer by promoting PTEN expression and suppressing PI3K/AKT signalling pathway, Sci. Rep. 14 (1) (2024) 12020, https://doi.org/10.1038/s41598-024-57304-7.
[122] C. Ward, J. Meehan, M.E. Gray, A.F. Murray, D.J. Argyle, I.H. Kunkler, S. P. Langdon, The impact of tumour pH on cancer progression: strategies for clinical intervention, Explor. Target. Antitumor Ther. 1 (2) (2020) 71–100, https://doi.org/10.37349/etat.2020.00005.
[123] Y. Tang, X. Yi, J. Ai, mRNA vaccines for prostate cancer: a novel promising immunotherapy, Biochim. Biophys. Acta Rev. Cancer 1880 (3) (2025) 189333, https://doi.org/10.1016/j.bbcan.2025.189333.
[124] I.S. Forestier-Roman, A. Lopez-Rivas, M.M. Sanchez-Vazquez, K. Rohena-Rivera, G. Nieves-Burgos, H. Ortiz-Zuazaga, C.A. Torres-Ramos, M. Martinez-Ferrer, Andrographolide induces DNA damage in prostate cancer cells, Oncotarget 10 (10) (2019) 1085–1101, https://doi.org/10.18632/oncotarget.26628.
[125] J. Manimaran, D.K.M. Azman, The effects of andrographolide on apoptosis in PC-3 cell line via the involvement of caspases 3, 8 and 9, Pharmacogn. J. 15 (4) (2023) 612–621, https://doi.org/10.5530/pj.2023.15.128.
[126] H. Mir, N. Kapur, R. Singh, G. Sonpavde, J.W. Lillard, Jr, S. Singh, Andrographolide inhibits prostate cancer by targeting cell cycle regulators, CXCR3 and CXCR7 chemokine receptors, Cell Cycle 15 (6) (2016) 819–826, https://doi.org/10.1080/15384101.2016.1148836.
[127] X.-L. Wen, X.-Y. Chen, Y.-l Jin, Z.-G. Sun, A.-G. Zhang, K. Wang, Multimodal probes for the detection of bone cancer-related disease in biological systems: recent advances and future prospects, TrAC Trends Anal. Chem. 181 (2024) 118030, https://doi.org/10.1016/j.trac.2024.118030.
[128] R.K. Yip, J.S. Rimes, B.D. Capaldo, F. Vaillant, K.A. Mouchemore, B. Pal, Y. Chen, E. Surgenor, A.J. Murphy, R.L. Anderson, Mammary tumour cells remodel the bone marrow vascular microenvironment to support metastasis, Nat. Comm. 12 (1) (2021) 6920, https://doi.org/10.1038/s41467-021-26556-6.
[129] S. Wang, H. Li, S. Chen, Z. Wang, Y. Yao, T. Chen, Z. Ye, P. Lin, Andrographolide induces apoptosis in human osteosarcoma cells via the ROS/JNK pathway, Int. J. Oncol. 56 (6) (2020) 1417–1428, https://doi.org/10.3892/ijo.2020.5032.
[130] F. Kouhen, M. Chahid, R.E. Mjabber, O. Bensalah, M. Naciri, H.E. Gouach, O. Kaanouch, N. Benslima, R. Karmi, Y. Mahdi, B.E. Khannoussi, M. Afif, Maxillary aggressive chondrosarcoma: a rare and challenging case, Radiol. Case. Rep. 20 (5) (2025) 2521–2526, https://doi.org/10.1016/j.radcr.2025.02.003.
[131] H. Song, K.-H. Park, Regulation and function of SOX9 during cartilage development and regeneration, Semin. Cancer Biol. 67 (2020) 12–23, https://doi.org/10.1016/j.semcancer.2020.04.008.
[132] H.T. Zhang, J. Yang, G.H. Liang, X.J. Gao, Y. Sang, T. Gui, Z.J. Liang, M.S. Tam, Z. G. Zha, Andrographolide induces cell cycle arrest and apoptosis of chondrosarcoma by targeting TCF-1/SOX9 Axis, J. Cell. Biochem 118 (12) (2017) 4575–4586, https://doi.org/10.1002/jcb.26122.
[133] H. Wang, Q. Luo, X. Feng, R. Zhang, J. Li, F. Chen, NLRP3 promotes tumor growth and metastasis in human oral squamous cell carcinoma, BMC Cancer 18 (2018) 1–10, https://doi.org/10.1186/s12885-018-4403-9.
[134] H.Y. Liao, C.C. Huang, S.C. Chao, C.P. Chiang, B.H. Tang, S.P. Lee, J.K. Wang, Real-time monitoring the cCytotoxic effect of andrographolide on human oral epidermoid carcinoma cells, Biosens. (Basel) 12 (5) (2022) 304, https://doi.org/10.3390/bios12050304.
[135] P.Y. Yang, P.L. Hsieh, T.H. Wang, C.C. Yu, M.Y. Lu, Y.W. Liao, T.H. Lee, C.Y. Peng, Andrographolide impedes cancer stemness and enhances radio-sensitivity in oral

carcinomas via miR-218 activation, Oncotarget 8 (3) (2017) 4196–4207, https://doi.org/10.18632/oncotarget.13755.
[136] S. Chen, H. Hu, S. Miao, J. Zheng, Z. Xie, H. Zhao, Anti-tumor effect of cisplatin in human oral squamous cell carcinoma was enhanced by andrographolide via upregulation of phospho-p53 *in vitro* and *in vivo*, Tumour Biol. 39 (5) (2017) 1010428317705330, https://doi.org/10.1177/1010428317705330.
[137] Z.M. Wang, Y.H. Kang, X. Yang, J.F. Wang, Q. Zhang, B.X. Yang, K.L. Zhao, L. P. Xu, L.P. Yang, J.X. Ma, G.H. Huang, J. Cai, X.C. Sun, Andrographolide radiosensitizes human esophageal cancer cell line ECA109 to radiation *in vitro*, Dis. Esophagus 29 (1) (2016) 54–61, https://doi.org/10.1111/dote.12255.
[138] L. Xuan, J.-h Hu, R. Bi, S.-q Liu, C.-x Wang, Andrographolide inhibits proliferation and promotes apoptosis in bladder cancer cells by interfering with NF-κ B and PI3K/AKT signaling *in vitro* and *in vivo*, Chin. J. Integr. Med. 28 (4) (2022) 349–356, https://doi.org/10.1007/s11655-022-3464-4.
[139] P. Pearngam, S. Kumkate, S. Okada, T. Janvilisri, Andrographolide Inhibits cholangiocarcinoma cell migration by down-regulation of claudin-1 via the p-38 signaling pathway, Front. Pharm. 10 (2019) 827, https://doi.org/10.3389/fphar.2019.00827.
[140] Z. Wang, H. Chen, X. Cai, H. Bu, S. Lin, Andrographolide induces protective autophagy and targeting DJ-1 triggers reactive oxygen species-induced cell death in pancreatic cancer, PeerJ 12 (2024) e17619, https://doi.org/10.7717/peerj.17619.
[141] K.R. Zhuang, C.F. Chen, H.Y. Chan, S.E. Wang, D.H. Lee, S.C. Chen, B.U. Shyr, Y. J. Chou, C.C. Chen, S.H. Yuan, Y.I. Chang, H.T. Lee, S.L. Fu, Andrographolide suppresses the malignancy of pancreatic cancer via alleviating DNMT3B-dependent repression of tumor suppressor gene ZNF382, Phytomed 132 (2024) 155860, https://doi.org/10.1016/j.phymed.2024.155860.
[142] R. Bi, Y. Deng, C. Tang, L. Xuan, B. Xu, Y. Du, C. Wang, W. Wei, Andrographolide sensitizes human renal carcinoma cells to TRAIL-induced apoptosis through upregulation of death receptor 4, Oncol. Rep. 44 (5) (2020) 1939–1948, https://doi.org/10.3892/or.2020.7737.
[143] Y.X. Shang, C. Shen, T. Stub, S.J. Zhu, S.Y. Qiao, Y.Q. Li, R.T. Wang, J. Li, J.P. Liu, Adverse effects of andrographolide derivative medications compared to the safe use of herbal preparations of Andrographis paniculata: results of a systematic review and meta-analysis of clinical studies, Front. Pharm. 13 (2022) 773282, https://doi.org/10.3389/fphar.2022.773282.
[144] Y.J. Chou, C.C. Lin, Y.C. Hsu, J.L. Syu, L.M. Tseng, J.H. Chiu, J.F. Lo, C.H. Lin, S. L. Fu, Andrographolide suppresses the malignancy of triple-negative breast cancer by reducing THOC1-promoted cancer stem cell characteristics, Biochem. Pharm. 206 (2022) 115327, https://doi.org/10.1016/j.bcp.2022.115327.
[145] I. Khan, F. Khan, A. Farooqui, I.A. Ansari, Andrographolide exhibits anticancer potential against human colon cancer cells by inducing cell cycle arrest and programmed cell death via augmentation of intracellular reactive oxygen species level, Nutr. Cancer 70 (5) (2018) 787–803, https://doi.org/10.1080/01635581.2018.1470649.
[146] S.K. Murugan, B. Bethapudi, A.N. Rao, J.J. Allan, D. Mundkinajeddu, P. D'Souza, Toxicological safety assessment of AP-Bio(R), a standardized extract of Andrographis paniculata in sprague dawley rats, J. Appl. Toxicol. 43 (11) (2023) 1630–1644, https://doi.org/10.1002/jat.4501.
[147] S. Chandrama Singh, M. Choudhary, A. Mourya, D.K. Khatri, P.K. Singh, J. Madan, H. Singh, Acute and subacute toxicity assessment of andrographolide-2-hydroxypropyl-beta-cyclodextrin aomplex via oral and inhalation route of administration in sprague-dawley rats, Sci. World J. 2022 (1) (2022) 6224107, https://doi.org/10.1155/2022/6224107.
[148] L. Worasuttayangkurn, W. Nakareangrit, J. Kwangjai, P. Sritangos, N. Pholphana, P. Watcharasit, N. Rangkadilok, A. Thiantanawat, J. Satayavivad, Acute oral toxicity evaluation of Andrographis paniculata-standardized first true leaf ethanolic extract, Toxicol. Rep. 6 (2019) 426–430, https://doi.org/10.1016/j.toxrep.2019.05.003.
[149] Y. Cai, L. Huang, Y. Hou, P. Pang, Y. Zhou, X. Zhang, Y. Long, H. Li, H. Muhetaer, M. Zhang, B. Wu, Molecular mechanisms of andrographolide-induced kidney injury and senescence via SIRT3 inhibition, Toxicol. Appl. Pharm. 498 (2025) 117306, https://doi.org/10.1016/j.taap.2025.117306.
[150] L.L. Gu, X.Y. Zhang, W.M. Xing, J.D. Xu, H. Lu, Andrographolide-induced apoptosis in human renal tubular epithelial cells: Roles of endoplasmic reticulum stress and inflammatory response, Environ. Toxicol. Pharm. 45 (2016) 257–264, https://doi.org/10.1016/j.etap.2016.02.004.
[151] H. Huang, H. Cao, C. Xing, Y. Hua, M. Zhang, L. Jin, Andrographolide induce human embryonic stem cell apoptosis by oxidative stress response, Mol. Cell. Toxicol. 15 (2019) 209–219, https://doi.org/10.1007/s13273-019-0024-x.
[152] L. Lin, R. Li, M. Cai, J. Huang, W. Huang, Y. Guo, L. Yang, G. Yang, T. Lan, K. Zhu, Andrographolide ameliorates liver fibrosis in mice: involvement of TLR4/NF-kappaB and TGF-beta1/Smad2 signaling pathways, Oxid. Med. Cell. Longev. 2018 (1) (2018) 7808656, https://doi.org/10.1155/2018/7808656.
[153] A. Widyawaruyanti, A. Jonosewojo, H. Ilmi, L. Tumewu, A. Imandiri, E. Widiastuti, L. Dachliyati, M.F. Budiman, D. Setyawan, A.F. Hafid, I.S. Tantular, Safety evaluation of an antimalarial herbal product from *Andrographis paniculata* (AS201-01) in healthy volunteers, J. Basic Clin. Physiol. Pharm. 34 (5) (2023) 639–645, https://doi.org/10.1515/jbcpp-2020-0381.
[154] P.W. Chiu, G.G. Yue, M.K. Cheung, H.C. Yip, S.K. Chu, M.Y. Yung, J.C. Wu, S. M. Chan, A.Y. Teoh, E.K. Ng, H. Norimoto, C.B. Lau, The effect of Andrographis paniculata water extract on palliative management of metastatic esophageal squamous cell carcinoma-a phase II clinical trial, Phytother. Res. 37 (8) (2023) 3438–3452, https://doi.org/10.1002/ptr.7815.
[155] Y. Shu, J. Sun, P. Cai, W. Wang, X. Han, Y. Gu, An open-label, randomized, controlled clinical trial to explore the curative effects between the treatment of capecitabine and andrographolide and the single capecitabine in the patients with pathological and/or histologic diagnosed unresectable, advanced, recurrent, and metastatic colorectal cancer, TPS819, J. Clin. Oncol. 35 (2017) TPS819, https://doi.org/10.1200/JCO.2017.35.4_suppl.TPS819.
[156] E. Ciampi, R. Uribe-San-Martin, C. Cárcamo, J.P. Cruz, A. Reyes, D. Reyes, C. Pinto, M. Vásquez, R.A. Burgos, J. Hancke, Efficacy of andrographolide in not active progressive multiple sclerosis: a prospective exploratory double-blind, parallel-group, randomized, placebo-controlled trial, BMC Neurol. 20 (2020) 1–10, https://doi.org/10.1186/s12883-020-01745-w.
[157] T.J.E. Tarigan, E.H. Purwaningsih, M. Yusra, Abdullah, J. Nafrialdi, M. R. Prihartono, I. Saraswati, Subekti, Effects of sambiloto (*Andrographis paniculata*) on GLP-1 and DPP-4 concentrations between normal and prediabetic subjects: A crossover study, Evid. Based Complement. Altern. Med. 2022 (1) (2022) 1535703, https://doi.org/10.1155/2022/1535703.
[158] M. Vikelis, E.V. Dermitzakis, G.S. Vlachos, P. Soldatos, K.C. Spingos, P. Litsardopoulos, E. Kararizou, A.A. Argyriou, Open label prospective experience of supplementation with a fixed combination of magnesium, vitamin B2, feverfew, *Andrographis paniculata* and coenzyme Q10 for episodicmigraine prophylaxis, J. Clin. Med. 10 (1) (2020) 67, https://doi.org/10.3390/jcm10010067.
[159] P. Kanokkangsadal, C. Mingmalairak, N. Mukkasombat, P. Kuropakornpong, P. Worawattananutai, T. Khawcharoenporn, I. Sakpakdeejaroen, N.M. Davies, A. Itharat, Andrographis paniculata extract versus placebo in the treatment of COVID-19: a double-blinded randomized control trial, Res. Pharm. Sci. 18 (6) (2023) 592–603, https://doi.org/10.4103/1735-5362.389947.
[160] L. Ratiani, E. Pachkoria, N. Mamageishvili, R. Shengelia, A. Hovhannisyan, A. Panossian, Efficacy of Kan Jang® in patients with mild COVID-19: Interim analysis of a randomized, quadruple-blind, placebo-controlled trial, Pharmaceuticals 15 (8) (2022) 1013, https://doi.org/10.3390/ph15081013.
[161] J. Melchior, A.A. Spasov, O.V. Ostrovskij, A.E. Bulanov, G. Wikman, Double-blind, placebo-controlled pilot and phase III study of activity of standardized Andrographis paniculata herba nees extract fixed combination (kan jang) in the treatment of uncomplicated upper-respiratory tract infection, 50, Phytomedicine 7 (5) (2000) 341, https://doi.org/10.1016/S0944-7113(00)80053-7.
[162] M. Low, C.S. Khoo, G. Munch, S. Govindaraghavan, N.J. Sucher, An in vitro study of anti-inflammatory activity of standardised *Andrographis paniculata* extracts and pure andrographolide, BMC Complement. Altern. Med. 15 (2015) 18, https://doi.org/10.1186/s12906-015-0525-7.
[163] J.L. Hancke, S. Srivastav, D.D. Caceres, R.A. Burgos, A double-blind, randomized, placebo-controlled study to assess the efficacy of *Andrographis paniculata* standardized extract (ParActin®) on pain reduction in subjects with knee osteoarthritis, Phytother. Res. 33 (5) (2019) 1469–1479, https://doi.org/10.1002/ptr.6339.
[164] K. Wanaratna, P. Leethong, N. Inchai, W. Chueawiang, P. Sriraksa, A. Tabmee, S. Sirinavin, Efficacy and safety of *Andrographis paniculata* extract in patients with mild COVID-19: a randomized controlled trial, Arch. Intern. Med. Res. 5 (2021) 423–427, https://doi.org/10.26502/aimr.0125.
[165] P. Songvut, J. Akanimanee, T. Suriyo, N. Pholphana, N. Rangkadilok, D. Panomvana, P. Puranajoti, J. Satayavivad, Non-linear oral bioavailability and clinical pharmacokinetics of high-dose *Andrographis paniculata* ethanolic extract: relevant dosage implications for COVID-19 treatment, Pharm. Biol. 63 (1) (2025) 42–52, https://doi.org/10.1080/13880209.2024.2444446.
[166] P. Songvut, T. Boonyarattanasoonthorn, N. Nuengchamnong, T. Junsai, T. Kongratanapasert, K. Supannapan, P. Khemawoot, Enhancing oral bioavailability of andrographolide using solubilizing agents and bioenhancer: comparative pharmacokinetics of *Andrographis paniculata* formulations in beagle dogs, Pharm. Biol. 62 (1) (2024) 183–194, https://doi.org/10.1080/13880209.2024.2311201.
[167] W. Worakunphanich, M. Thavorncharoensap, S. Youngkong, K. Thadanipon, A. Thakkinstian, Safety of *Andrographis paniculata*: a systematic review and meta-analysis, Pharmacoepidemiol. Drug Saf. 30 (6) (2021) 727–739.
[168] B. Zeng, A. Wei, Q. Zhou, M. Yuan, K. Lei, Y. Liu, J. Song, L. Guo, Q. Ye, Andrographolide: a review of its pharmacology, pharmacokinetics, toxicity and clinical trials and pharmaceutical researches, Phytother. Res. 36 (1) (2022) 336–364, https://doi.org/10.1002/ptr.7324.
[169] D.S. Lakra, P. B, D. N, D. T, K. G, R.P. N, Chemosensitizing potential of andrographolide in P-glycoprotein overexpressing multidrug-resistant cancer cell lines, Nat. Prod. Res 38 (6) (2024) 941–946, https://doi.org/10.1080/14786419.2023.2208261.