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Chapter- 1

Exploring the Potent Anticancer Activity of *Andrographis paniculata* (Kalmegh): Mechanisms, Applications and Therapeutic Implications

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Abstract:

Despite advancements in therapeutic approaches, cancer appears to be biggest cause of death globally. Consequently, the primary focus should be on early cancer detection, developing the best possible treatment plan to extend the patient's life, and continuing the hunt for more potent and targeted drugs to treat various cancer types. Stronger anti-cancer drugs have been developed as a result of the current change in natural chemical research towards sophisticated and molecular-level understandings. Infertility, ovarian failure, liver, renal, and heart toxicity, as well as immunosuppressive side effects, are some of the adverse consequences of synthetic medications used in cancer treatment. Consequently, herbal medications may be utilised as an adjuvant therapy in the treatment of cancer. Different plant derived drugs are under research. Among the different medicinal plants, *Andrographis paniculata* (Burm. F) Nees, an herbaceous plant of the Acanthaceae family, is often referred to as the "king of bitters," plays an important role in the treatment of cancer. This plant is commonly used in India, China, Malaysia, and Thailand to treat sore throat, flu, and upper respiratory tract infections. This plant is rich in bioactive compounds. Andrographolide is widely regarded as a vital bioactive component of *A. paniculata*. Andrographolide has a highly bitter taste, is colourless, and is crystalline in appearance. Analgesic, antipyretic, anti-viral, antimalarial, anti-hyperglycemic, hepatoprotective, immunological modulatory, protective against alcohol-induced toxicity, cardiac protective action, and anti-cancer activity are just a few of the many potentials for andrographolide. It is reported that when andrographolide is treated on different cancer cells it possesses anticancer activity.

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Introduction:

Globally, cancer ranks as the second most common cause of death (Das et al., 2022; Kulkarni et al., 2023; Madhu et al., 2023). According to WHO cancer affects one in five individuals globally at a certain point in their lives. Even with the advancements in cancer therapies, such as traditional chemotherapy, surgery, radiation therapy, immunotherapy and hormone therapy, the overall disease-free survival percentage remains low. More difficulties arise from the toxicity that is frequently connected to anti-cancer medication therapy (Chakrovorty et al., 2021; Madhu et al., 2022; Kesavan et al., 2023; Mehta et al., 2023). As a consequence, there is growing enthusiasm for the production of safe, alternative medications, such as using organic compounds obtained from plants to cure and prevent cancer. Because of their accessibility and large safety margin, chemicals extracted from plants have significantly aided in the creation of new drugs and are now being explored to fight against cancer (Tundis et al., 2023). An enormous amount of study on various plant species and their medicinal principles is currently being done to revalue traditional medicine around the world. Reactive oxygen species (ROS) and free radicals (FR) have been linked to a wide range of illnesses, according to experimental data. Plants can be a source of novel molecules with antioxidant activity since they generate a large amount of antioxidants to counteract the oxidative damage brought on by sunlight and oxygen. The world's ancient therapeutic framework, Ayurveda (ayus = life, veda = knowledge, meaning science of life), is being fully restored under the moniker Maharishi Ayurved (Scartezzini and Speroni, 2000). Plants are a natural substance that has been used to cure a variety of illnesses, including cancer (Rami et al., 2023). It is astounding how many and how different kinds of plants there are in the world that have therapeutic qualities. An estimated 70,000 plant species—from lichens to enormous trees—have been utilised medicinally at some point in history (Kuruppu et al. 2019). *Andrographis paniculata* (Burm.f.) Nees are a common plant in tropical regions like Asia that belong to the Acanthaceae family. One of the most significant therapeutic plants in the Ayurvedic and Unani framework —the two oldest known medical systems—is *A. paniculata*. This herb has been utilised in herbal remedies to treat a range of degenerative and infectious disorders (Saxena et al. 2010). It is well recognised that diterpene lactone molecules and *A. paniculata* biological activity are related. The most stable cyclic ester of organic acid is the lactone group, which has five members (gamma lactone). Numerous biological functions, including antibacterial, antifungal, and anticancer properties, have been reported (Suriyo et al., 2021). Andrographolide and its derivatives include neoandrographolide, andrograpanin and 14-deoxy-11,12-didehydro andrographolide. Due to its many medical qualities, andrographolide has been extensively researched. Some of these features include its anti-cancer, antibacterial, antioxidant, anti-inflammatory, antidiabetic, and antiviral effects. In meanwhile, 14-deoxy-11,12-didehydroandrographolide has demonstrated antiviral, antifungal, and anticancer properties (Adiguna et al., 2023). In breast cancer cells, 14-Deoxy-11,12-didehydroandrographolide shows a strong hold on the cell cycle process and cell cycle arrest. Moreover, it induced autophagy in carcinoma cells (Tan et al. 2012). Furthermore, neoandrographolide has been demonstrated to demonstrate anti-inflammatory, anti-viral and hepatoprotective activities (Zhang et al., 2020).

Botanical and Taxonomic description of Andrographis paniculata:

An annual herbaceous plant, *A. paniculata* is branched, upright, and grows in hedgerows in level areas, hillsides, waste grounds, farms, wet habitats, seashores, and roadsides. It may be grown in gardens as well. For their proper development, wastelands, woods, and moist, shaded areas are preferred. The physiological and morphological information of *A. paniculata* are discussed in Table 1**.** This plant is grown in many places throughout Southeastern and Southern Asia, such as India, Sri Lanka, Indonesia, Java and Pakistan. It is also grown in the West Indies, including Jamaica, Hong Kong and Bahamas Barbados; tropical regions of America; and southwest Nigeria (Hossain et al., 2014). *A. paniculata* is widely used because, in contrast to other species in the genus, it is commonly found throughout much of India, which includes the hilly and plain regions up to 500 m (1,600 ft). The taxonomic description of *A. paniculata* is furnished in Table 2.

Table 1: Botanical description of *A. paniculata* (Dandekar et al., 2024).

Traits	Characteristics/ Values
Plant height	31-102 cm
Stem	Green (Dark)
Length	31-102cm
Diameter	2-6mm
Shape	Oblong, with wings on the younger, angled portions and longitudinal furrows; the nodes are slightly larger.
Leaves	Glabrous
Length	8.0 cm
Width	2.5cm
Arrangement	Pinnate, lanceolate
Flowers	White petals with rose-purple marks
Size	Tiny, loosely spreading terminal and auxiliary racemes or panicles
Seed capsules	Oblong-linear, sharp at both ends
Size	1.90 cm × 0.31 cm

Shape	Sub quadrate, numerous

Table 2: Taxonomic description of *A. paniculata* (Dandekar et al., 2024)

Classification	Common name and Scientific name
Kingdom	Plants, Planate
Subkingdom	Vascular plants, Tracheobionta
Super division	Seed plants, Spermatophyta
Division	Angiosperma
Class	Dicotyledonae
Subclass	Gamopetalae
Series	Bicarpellatae
Order	Personales
Tribe	Justicieae
Family	Acanthaceae
Genus	Andrographis
Species	*A. paniculata* (Burm.f) Nees

Bioactive compounds:

More than 20 diterpenoids and more than 10 flavonoids have been identified as active chemicals from *A. paniculata* that have been extracted using methanol or ethanol from the leaf, stem, and whole plant. Approximately 0.8~1.2%, 0.5~6% and 4% of the stem, leaf, and dried whole plant extracts, respectively, contain andrographolide ($C_{20}H_{30}O_5$), the primary diterpenoid in *A. paniculata* (Chao and Lin, 2010). The remaining primary diterpenoids are isoandrographolide, 14-deoxy-11,12-didehydroandrographolide, deoxyandrographolide and neoandrographolide. The primary flavonoids that were isolated from the methanol or ethanol extract's ethyl acetate (EtOAC)-soluble fraction were 2'-methyl ether, 5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-7,8,2', 3'-tetramethoxyflavone, 5-hydroxy-7,8,2'-trimethoxyflavone,7-O-methylwogonin and 5-hydroxy-7,8,2',5'-tetramethoxyflavone (Sarma, 2016; Chao et al., 2010). The other component consists of macro and trace elements, xanthones and polyphenols (Chauhan et al., 2019).

Andrographolide and Its Derivatives-Pharmacological Importance:

In the present era, various pharmacological aspects have been documented for andrographolide and its derivatives, e.g., anti-cancer, anti-hyperglycemic, hepatoprotective, anti-inflammatory, neuroprotective, anti-viral, anti-fibrosis, anti-atherosclerosis, antioxidant, cardiovascular protective and antimicrobial actions. Andrographolide can scavenge free-radical as well as it can stop inflammation by blocking nitric oxide (NO) induced by lipopolysaccharide synthesis and inducible NO synthase (iNOS) expression, as well as by decreasing IL-2 production and proliferation of T-cell. Depression, neuro-inflammation, Parkinsonism, Alzheimer's disease, and deficiencies in spatial memory can be treated by lactone diterpene (Zhang et al., 2021). Research has revealed that the active components in *A. paniculata* extract have antiviral properties, including defence against ribonucleic acid and DNA viruses. Andrographolide has been demonstrated in silico experiments to inhibit the primary protease of SARS-CoV-2. The HIV, influenza A and HSV-1 viruses may all be effectively inhibited by 14-deoxy-11,12-dehydroandrographolide. However, because of its limited solubility, bitter taste, low stability in the gastrointestinal tract, and low bioavailability, andrographolide and its analogues are currently being studied for their potential benefits. Therefore, while developing therapies, it is important to give careful thought to the dose form of andrographolide and the compounds developed from it (Adiguna et al., 2021).

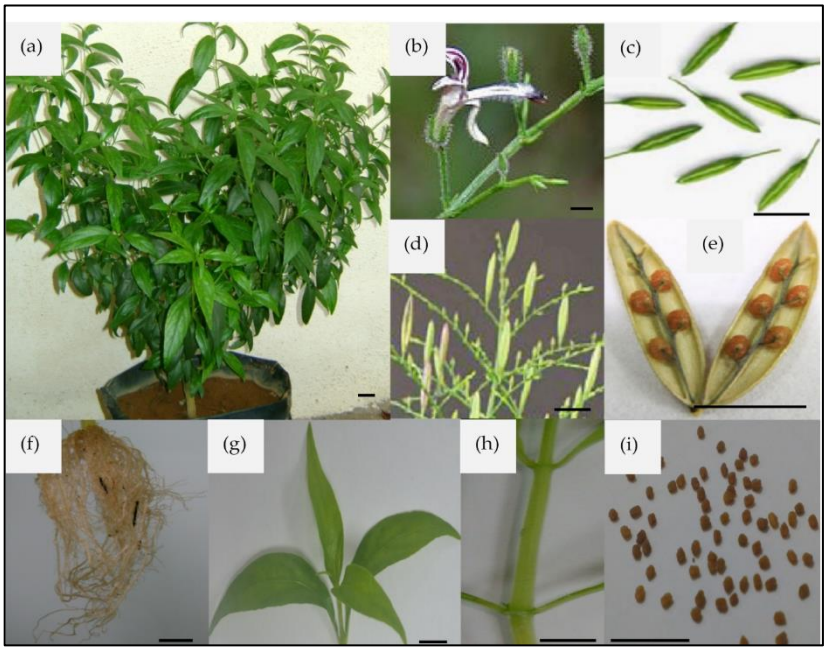

Figure 1. The distinct portions of *Andrographis paniculata*: (a) Aerial segment, (b) flower, (c) panicles on the pod stage: an adult capsule, (d) fruit, (e) capsule after opening, (f) roots, (g) leaves: opposite arrangement, (h) stem, and (i) seed (Hossain et al.)

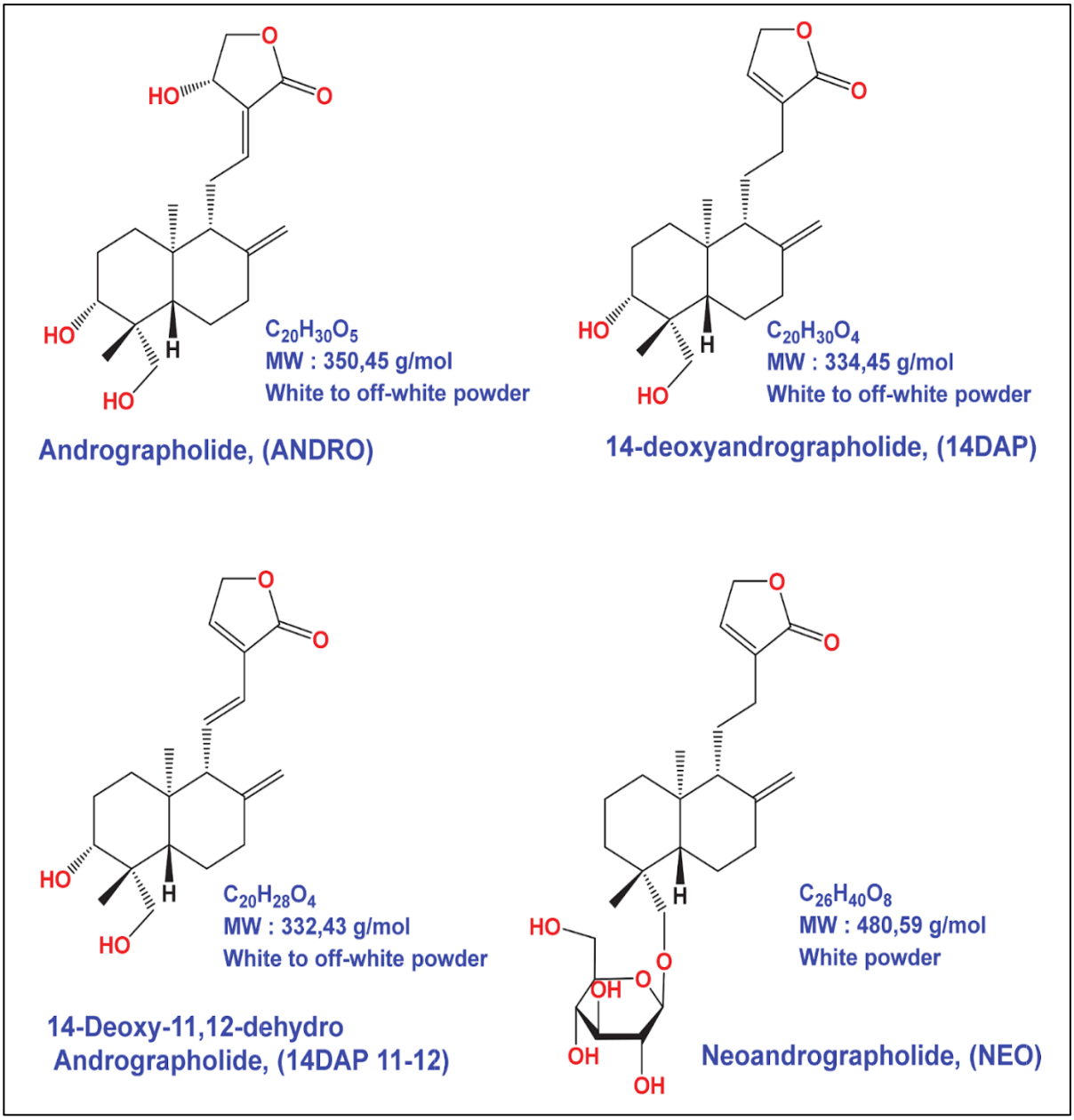

Figure 2. Chemical structure of andrographolide and its derivatives (Mussard et al., 2020)

Pathways involved in cancer:

Early tumours lack apoptosis, allowing proliferating cells to divide and spread. Excessive cell division leads to cancerous tissue growth and metastasis. Proteins and matrix metalloproteases regulate cell-cell adhesion and metastasis progression (Chaudhry et al., 2022). The identification of genes that suppresses tumour (e.g., BRCA1, TP53 and PTEN) and oncogenes (e.g. BRAF, KIT, MYC and RAS) has led to an enormous amount of information on genetic abnormalities linked to cancer (Campbell et al., 2020; Boga & Bisgin, 2022; Kaur, 2023; Mishra et al., 2023). Signalling pathways and molecular networks are crucial in the regulation of pro-growth and pro-

survival cellular activities, primarily responsible for cancer development and potential treatments (Yip and Papa, 2021). In cancer, the pathways that transduce signals (e.g., Ras/MAPK and PI3K/AKT/mTOR) are often altered or activated. These linked cascades provide upstream signals to intracellular effector proteins and regulators of the cell cycle from receptor tyrosine kinases (RTKs) (Pons-Tostivint et al., 2017). The MAPK and PI3K pathways are closely linked through loop of negative and positive feedback. For example, rapalogs can induce MAPK reactivation, leading to resistance to mTORC1 inhibition. Combining mTOR and MAPK targeting improves therapy sensitivity, as demonstrated by rapalog-induced MAPK reactivation (Janků et al., 2014; Yip and Papa, 2021). According to recent research, pyruvate and lactic acid are strong inducers of intestinal CX3CR1+ phagocytes' GPR31-mediated dendritic processes, which may strengthen the immune response. These results imply that GPR31 may be a good target for antitumor treatment and may have a complicated role in the initiation and spread of cancer (You et al., 2023). GRP91, also known as succinate receptor 1 (SUCNR1), is extensively expressed in a variety of organs. SUCNR1 is a citric acid cycle intermediate molecule that is activated by succinate. Research has demonstrated that SUNCR1 is crucial for tumour metastasis, particularly in those with germline mutations in succinate dehydrogenase (SDH). By combining SUCNR1 in tumour cells and upregulating HIF-1α, extracellular succinate stimulated the PI3K-Akt pathway, boosting cancer cell invasion and causing epithelial-mesenchymal transition (Mak et al., 2010). Studies on the NF-κB signalling pathway in cancer have been going on for many years. Many solid tumours, including gastric cancer and colorectal cancer, commonly exhibit aberrant activation of NF-κB transcription factors. Members of the NF-κB pathway and its regulatory genes regulate the development, proliferation, metastasis, and drug tolerance of cancer cells through blood vessel creation (He et al., 2021). Cancer growth and spread are significantly influenced by p73 and p63, two homologs of the tumour suppressive transcription factor p53. They have excellent structural similarities, allowing most p53-responsive promoters to be bound for transcription with different but overlapping functions (Dötsch et al., 2010). TP53 gene mutations are responsible for 50% of human cancer cases. Wildtype p53 inhibits cell division to prevent cancerous growth, while TP53 mutations disrupt the cell cycle, causing cells to lose control over their own proliferation, leading to the spread of damaged DNA into progenies, resulting in malignant growth (Marei et al., 2021).

The mechanism of action and anti-cancer properties of andrographolide and its derivatives:

Recently, there has been a lot of interest in the ability of fighting against cancer and tumour by andrographolide and its derivatives. In terms of preventing the growth, spread, and migration of different cancerous cells, such as colorectal cancer cell lines, leukemic HL-60 cells, cells of breast cancer, bladder cancer, colon cancer chronic myeloid leukaemia cell lines, murine leukaemia cells, prostate cancer cells, adenocarcinoma PC-3, lymphoma, and many more other cancer cells, these chemicals have shown encouraging anti-cancer properties (Zhang et al., 2021). Recent research confirms the anti-cancer benefits of diterpene found in *A. paniculata* against various cancers, including cervical, renal, breast, lung, colon, and hepatoma cancer. However,

more research is required to find out the primary mode of action (Zeng et al., 2021; Saha and Yadav, 2023). The way in which andrographolide and its derivatives work to prevent cancer are discussed below.

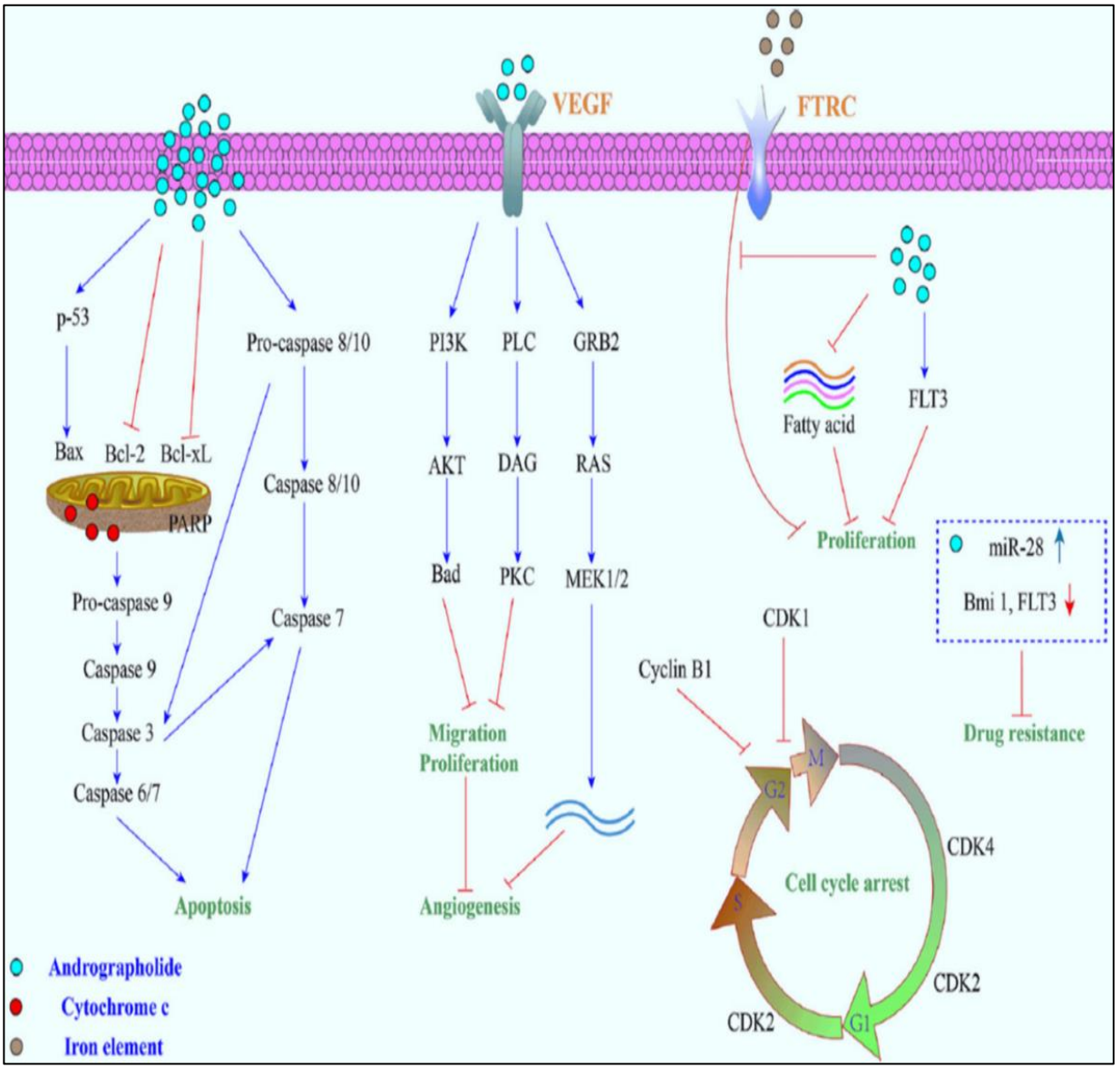

Figure 3. An illustration of andrographolide's anti-cancer mode of action (Tundis et al., 2023)

Induction of Growth Inhibitory Activity and Apoptosis:

In several human cancer cell types, andrographolide causes apoptotic cell death by activating the extrinsic death receptor pathway, which includes caspase-8 and caspase-3. Bax, Bcl-2 family member and bid, having ability of pro-apoptosis are essential in relaying the andrographolide-induced signal of cell death. Cytochrome c discharge and apoptotic cell death are the ultimate outcomes of this signal, which is initially sent to mitochondria from caspase-8 and subsequently

to downstream effector caspase 3. A recent study found that in several cell lines of human carcinoma, treatment of andrographolide significantly enhanced the level of TRAIL, which stands for TNF-α-related apoptosis inducing ligand, an essential part of the extrinsic apoptosis pathway (Varma et al., 2011). Bhat and Murthy (2021) have reported that apoptotic cell death was induced in human ovarian teratocarcinoma (PA-1) cells. In comparison with the cells without treatment, there was a reported rise in the cell number having caspase 3 activation and a decreased Bcl-2 following therapy with andrographolide. Shi et al. (2008) revealed the andrographolide's pharmacophore action and how cells are halted in the G1/S stage of the cell cycle by using the CKI–cyclin–Cdk network. Also, it induced a G0/G1 stage halting in MCF-7 cells. Furthermore, in rheumatoid arthritis, andrographolide at dosages of 10–30 μM demonstrated pro-apoptotic and growth inhibitory effects through decreased levels of CDK-4 protein, a decreased Bcl2/Bax ratio, and G0/G1 stage halting in the cell cycle by suppression of p27 and p21. Andrographolide and its derivatives, 3,19-(3-chloro-4fluorobenzylidene) and 3,19-(2-bromobenzylidene), have shown potent growth-inhibition and cytotoxicity in various cell lines. Andrographolide suppresses the progress of cell-cycle at the G2/M checkpoint in PC3, C4-2b and LNCaP cells, as well as at the G1/S checkpoint in DU-145 cells, according to a recent study. Furthermore, it has been demonstrated that andrographolide stops osteosarcoma cell growth by halting the cell cycle in the G2/M stage and it promotes caspase-mediated death. Andrographolide showed a strong anti-tumor effect in vivo with little toxicity (Wang et al., 2020).

Inhibition of Tumor Angiogenesis:

When C57BL/6 mice were injected with melanoma cells (B16F-10), andrographolide was demonstrated to suppress angiogenesis, which is specific to tumour, by decreasing the production of pro- and anti-angiogenic molecules like interleukin-2, vascular endothelial growth factor, TNF-α and NO. Additionally, it suppressed the activities of metalloproteinase 9 and angiogenesis-critical matrix metalloproteinase 2 (MMP-2) in colon cancer cells. In addition, andrographolide increased the expression of prolyl hydroxylase and hydroxyl-HIF-1 while decreasing the vascular endothelial growth factor (VEGF), suggesting that it may be used as an anti-angiogenesis or chemotherapeutic medication to treat non-small-cell lung cancer (NSCLC). In rat and hamster buccal cells, 17-hydro-9-dehydro-andrographolide suppressed angiogenesis and vascular endothelial cell growth. Furthermore, it was shown that it can be docked to the pocket of the angiogenesis-related vascular endothelial growth-factor receptor (VEGFR2) where ATP binds (Dai et al., 2017; Tundis et al., 2023). Andrographolide's mechanism of action involves inhibiting NF-κB, PI3K/AKT, STAT3 and v-Src activities, down-regulating cell cycle progression mediators, and inhibiting angiogenesis and metastasis. A new andrographolide derivative (AGS-30) has been found to exhibit anti-angiogenic properties by inhibiting endothelial cell proliferation, incursion, relocation, and tube formation. Andrographolide inhibits STAT3, PI3K/AKT, v-Src, and NF-κB activities, downregulating cell cycle progression, angiogenesis, and metastasis. A new derivative of andrographolide (AGS-30) displays anti-angiogenic properties by inhibiting endothelial-cell incursion, proliferation, tube formation,

relocation, and expression of VEGF in colon carcinoma cells (HT-29). It also suppresses angiogenesis and growth of tumor in nude mice (Yadav et al., 2022).

Inhibition of Proliferation:

It has been discovered that andrographolide inhibits the proliferation of certain cancer cell lines. Research has indicated that it diminishes the viability of SiHa cells, human monocytic leukaemia and NCI-H929 cells, as well as MCF-7 and MDAMB-231, which are breast cancer cells. Additionally, it has encouraged anti-proliferative action against the human malignant melanoma cell lines C8161 and A375. Utilising the 3-(4,5-dimethylthiazole-2-yl)-2,5-biphenyl tetrazolium bromide (MTT) test, andrographolide's cytotoxic potential was evaluated. The findings imply that andrographolide may be used as a possible cancer and other cancer therapy. With an IC_{50} value of 3.7 µg/mL, andrographolide has been investigated for its anti-proliferation characteristics on colon carcinoma cells HT-29. The cytotoxicity of a group of 3,19-O-acetal derivatives was caused by the 3,19-hydroxyl groups' protection with the suitable ethylidene/benzylidene moiety, which resulted in significant anti-cancer effects (Devendar et al., 2015).

Autophagy Induction:

In numerous diseases, including cancer, autophagy—which breaks down and repairs damaged macromolecules and organelles—is an essential mechanism. It can cause death or promote survival depending on the kind and stage of the cancer. It is crucial to do research on signalling pathways connected to autophagy. It has been demonstrated that the diterpene andrographolide inhibits osteosarcoma cell invasion and metastasis by upregulation of the JNK pathway and inhibiting the PI3K/Akt and mTOR signalling pathways. It could be an effective targeted medication for fighting against cancer (Tundis et al., 2023).

Immunostimulant Characteristics:

It has been discovered that the plant *Andrographis paniculata*, which is well-known for its immunomodulatory properties, stimulates mice's “antigen specific” as well as "antigen nonspecific" immune responses, effectively defending against several infectious and carcinogens. Andrographolide acts indirectly on cancer cells by controlling the synthesis of molecules such as natural killer (NK) cells, TNF-α, IFN-γ and IL-2. Increased TNF-α production and CD expression marker result in the increase of lymphocyte cytotoxic action against cancer cells. Andrographolide inhibits the development of tumours by inducing proliferation that is induced by mitogen of bone marrow cells and increasing the generation of cytotoxic T lymphocytes, as demonstrated by in vivo tests. Andrographolide improves medical outcomes for persons having late-stage malignancies by enhancing the activity of TNF-α and NK cells when taken with other nutraceuticals (Varma et al., 2011).

Conclusion and Future Aspects:

Naturally occurring andrographolide has demonstrated encouraging anti-cancer efficacy, mostly via inducing apoptosis. It has been researched as a therapy for malignant cancer in conjunction with radiation and other medications. Presently underway initiatives concentrate on primary progressive multiple sclerosis, esophageal carcinoma, and colorectal cancer. Derivatives of andrographolide have been suggested as having higher medicinal effectiveness and less toxicity. Large-scale experiments are yet required to confirm pharmacokinetic and efficacious parameters. A number of chemical changes and nanoparticle developments have enhanced the pharmacokinetics of andrographolide.

Authors' contribution

The original concept and design of the book chapter has been done by JB and SHM. SHM and AC did article drafting. SD did review and editing.

Conflict of interest

The authors declare that they have no conflict of interest.

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