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Natural Inhibitors of Cell Proliferation: Role of Plant Bioactives in Regulating Angiogenesis and Apoptosis

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ABSTRACT

Traditional medicine has been trying to find a cure for cancer for hundreds of years. It is a complicated disease that has affected people all over the world. Genetics, lifestyle choices, and the environment are just a few of the many things that might cause cancer. The Folklore who are affected prefer traditional medicine to chemotherapy and radiotherapy, which have many adverse effects. Medicinal plants, abundant in bioactive compounds, present a viable approach for cancer treatment and prevention. These natural substances have many different anticancer effects, such as killing cancer cells, causing apoptosis, stopping the cell cycle, and stopping angiogenesis and metastasis. Numerous plant-derived substances have demonstrated considerable efficacy in preclinical research and clinical trials. Modern medicine has come a long way, but researchers are still looking at how plant-based remedies could be able to work with or even replace traditional treatments. Traditional herbal or Ayurvedic treatments might mitigate physiological alterations without inducing toxicological consequences. Medicinal plants can improve patient outcomes and complement conventional therapy by targeting various molecular pathways involved in the onset and advancement of cancer. To optimize their therapeutic efficacy, further research is required to elucidate their mechanisms of action, establish optimal doses, and mitigate any potential adverse effects. This review examines the mechanisms of action of many medicinal plants and their bioactive chemicals, emphasizing their potential to target certain cancer pathways. By using the force of nature to find innovative ways to stop and treat cancer.

Keywords: *Cancer, bioactive compounds, medicinal plant, traditional herbal, apoptosis, angiogenesis*

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1. INTRODUCTION

Cancer is the uncontrolled proliferation of a certain type of cell, and it starts with an unwanted mutation that causes genetic defects to build up in several gene classes (Sinauer Associates; 2000). Cancer is a disease that causes cells to grow and spread in an uncontrolled way. It is a serious global health concern. It happens when a cell's DNA changes, which makes it lose its ability to control normal growth. These abnormal cells multiply rapidly to form tumors that can invade adjacent tissues and disseminate through the lymphatic or circulatory systems to remote organs. (Jones et al., 2007). There are numerous things that might cause cancer, such as genetics, lifestyle, and environmental exposures. However, early identification and better treatments have made it possible for many types of cancer to be cured. The Edwin Smith Papyrus, an ancient medical history from Egypt circa 3000 BC, was the first to discuss it. It talked about tumors, especially those that damage the breast, and suggested therapies including cauterization. The Greek doctor Hippocrates came up with the word "cancer" in the 5th century BC to describe tumors that looked like crab claws and didn't cause ulcers (David et.al., 2010). Various civilizations have tried to treat cancer throughout history. For example, ancient Indian Ayurvedic medicine, traditional Chinese medicine, and bloodletting and purging in mediaeval Europe. There were big steps forward in cancer research in the 19th century. For example, Rudolf Virchow found that cancer is a cellular illness and investigated its genetic foundation (David et al., 2010). There is hope for better results now because of surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapeutics (Sonnenblick et al., 2022). Medicinal plants can improve patient outcomes and complement conventional therapy by targeting various molecular pathways involved in the onset and advancement of cancer. To maximize their therapeutic efficacy, further research is.

required to elucidate their mechanisms of action, establish optimal doses, and mitigate any potential adverse effects. This review examines the mechanisms of action of numerous medicinal plants and their bioactive components, emphasizing their potential to target certain cancer pathways. By using the force of nature to find innovative ways to stop and treat cancer.

Cancer is a complicated disease that happens when cells divide and develop in an abnormal way. This is often caused by genetic abnormalities that throw off the delicate balance between cell death and growth. Metastasis is the process by which cancer spreads from its initial cells or tissue to another healthy area of tissues or organs (Sahai et al., 2005). Chemical carcinogens, physical carcinogens, or other biological carcinogens will be the things that effect it. But other groupings of genes are mostly responsible for cell division and the genesis of cancer. Those are genes that can cause cancer and genes that stop cancer from growing. Proto-oncogenes facilitate cellular proliferation via the cell cycle, whereas tumor suppressor genes induce cell cycle disruption, resulting in diminished cellular growth. Numerous genetic and environmental factors influence the onset of cancer (Brown et al., 2021). In addition to these, numerous variables such as transcriptional factors, epigenetic modifications, and immunological activities can either promote or initiate tumor growth through the downregulation or upregulation of specific genes or pathways (Han et al., 2020). The formation of a tumor is marked by abnormal DNA methylation, increased mutability, disrupted intercellular communication, and genetic instability. Cell cycle phases facilitate normal cell proliferation and apoptosis; however, when these processes are disrupted, growth can progress to cancer without apoptosis (Zhang et al., 2020; Conway et al., 2022). The impact of cancer varies significantly based on the affected body parts or organs; however, the effects intensify post-therapy, including chemotherapy, immunotherapy, and oral medications. These effects manifest as hair loss, weight fluctuations, alterations in dietary habits, nausea, fatigue, and a compromised immune system (Han et al., 2020). The psychological toll of cancer is significant. Fear, worry, and depression are frequent feelings that people have when they find out they have cancer. The uncertainty about how therapy will work and how it will affect relationships can be quite hard on your emotions. Cancer can also put a strain on finances, since medical bills and lost wages can eat up resources and make financial problems much worse (Manyazewal et al., 2021; Massague et al., 2021).

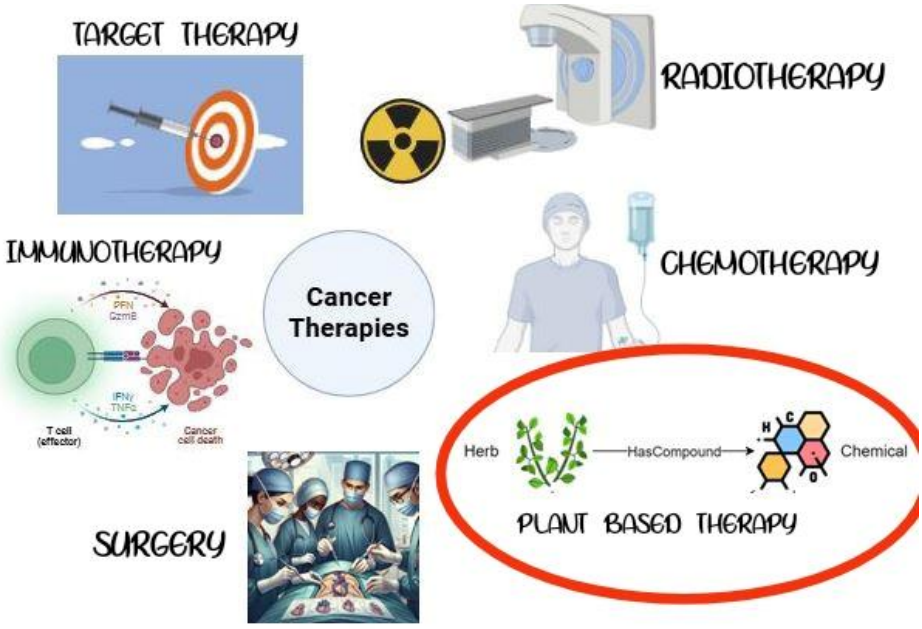


Fig 1- Different types of Cancer therapies, while have various side effects and now looking for plant-based therapies having least side effects with the actual components to be directly used for the treatments.

In the past few decades, cancer therapy has changed a lot, and there are now many different solutions that are tailored to each patient's needs. Surgery, radiation therapy, and chemotherapy are still important ways to fight cancer (Guedes et.al., 2016). The main purpose of surgery is to cut out cancerous tumors. Chemotherapy employs strong drugs to kill cancer cells across the body, and radiation therapy uses high-energy rays to kill cancer cells (Sudhakar et.al., 2009). Targeted therapies focus on cancer cells and do as little damage as possible to healthy tissues. Immunotherapy, conversely, presents potential for enduring benefits and survival by using the immune system to identify and combat cancer cells (Ferrone et al., 2012). When it comes to natural ways to prevent this condition, medicinal plants with their wide range of bioactive substances have long been known to be able to fight it. The studies into anticancer phytochemicals derived from medicinal plants commenced in 1950 with the identification of alkaloids (vincristine and vinblastine) from Madagascar periwinkle, Catharanthus roseus, and podophyllotoxin from Podophyllum species (Cragg et al., 2005). Other medicinal plants that have been utilized in cancer treatment include Curcuma longa, Withania somnifera, Allium sativum L, Catharanthus roseus,

Hemidesmus indicus, Heliotropium indicum L, among others already mentioned. These botanical gems provide numerous therapeutic opportunities, ranging from cancer prevention to the suppression of tumor growth and metastasis (Sourirajan et al., 2022). As contemporary medicine progresses, the incorporation of plant-based therapeutics offers potential for the development of innovative, efficacious, and less harmful cancer treatments (Ghosh et al., 2020).

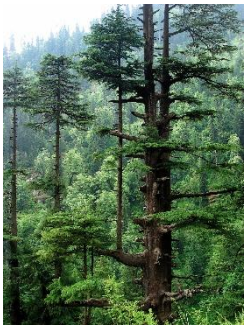
1. Use of medicinal Plants in cancer treatment

The traditional herbal or Ayurvedic medications that combat various health concerns aim to mitigate specific bodily changes while avoiding the toxicological consequences of the medicinal extract (Sourirajan, et al., 2022). Plants containing various bioactive substances target a range of ailments, including cardiovascular diseases, diabetes, thyroid disorders, cancer, asthma, and wound healing (Nebert et al., 2002). Cancer, as a significant causal factor in the general population, ranks second in terms of fatality rate. As previously noted, mutations at the tissue and gene levels occur, which are tough to diagnose promptly; misdiagnosis can lead to changed effects and even fatal outcomes (Futreal et al., 2004). Bioactive compounds, including alkaloids, flavonoids, tannins, and phenols, possess pharmacological properties and can be naturally extracted without altering their structural integrity. When combined with other drugs, they can produce a significant therapeutic effect in certain medications, potentially offering an effective cancer treatment for a wide population (Roy et al., 2022). We all know that India has a lot of natural diversity and gives us a lot of herbal products that have been used for thousands of years. Researchers and scientists are now trying to get the same benefits by using these traditional methods again, while avoiding methods that could have harmful effects or medications that could have a big effect on the body in the future (Nebert, et.al., 2002; Dixit et.al., 2010).

Table1.1: Plants having pharmacological significance for cancer

Plant species	Common Name	Family	Extract	Picture	Reference
Curcuma longa	Curcumin	Zingiberaceae	Rhizome		Kuruppu, et.al (2019).
Withania somnifera	Ashwagandha	Solanaceae	Roots, stems, leaves and whole plant		Sivasankarapillai, et.al (2020).
Allium sativum L	Garlic	Amaryllidaceae	Bulb		Merrouni, et.al (2021)
Catharanthus roseus	Graveyard plant	Apocynaceae	Roots and leaves		Maher, et.al (2021)

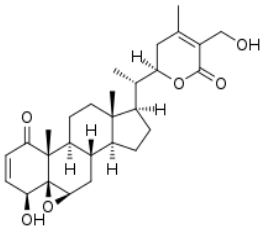
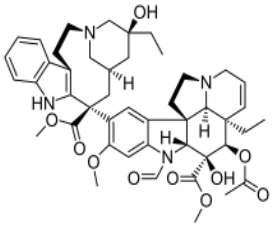
Hemidesmus indicus	Naruneendi	Smilacaceae	Root and leaves		Kuruppu, et.al (2019).
Heliotropium indicum L.	Indian heliotrope	Boraginaceae	Whole plant		Lanchhana, et.al (2023)
Leguminase	Pea or bean family	Fabaceae	Bark		Regassa, et.al (2022).
Gardenia jasminoides J. Ellis	Cape jasmine	Rubiaceae	Stem, bark and fruit		Siddiqui, et.al (2022)
Cannabis sativa	Marijuana	Cannabaceae	Dried buds and leaves		Singh, et.al (2020)

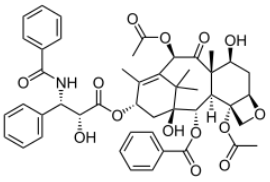
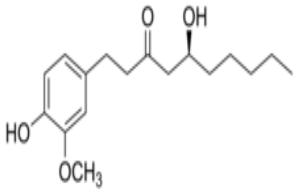
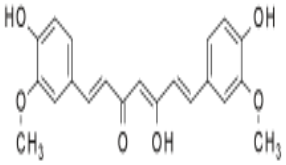
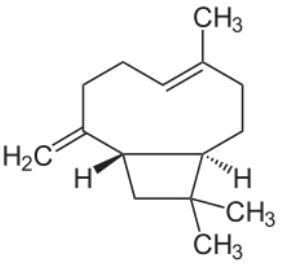
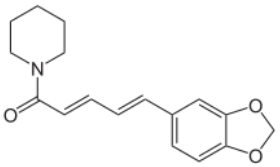
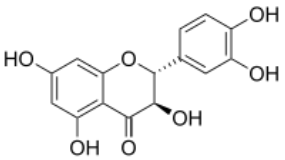
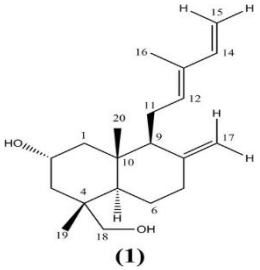
Albizia lebbeck	Indian Siris	Fabaceae	Leaves and pods		Regassa, et.al (2022).
Cedrus deodara	Himalayan cedar	Pinaceae	Bark		Singh, et.al (2020)
Piper longum	Long pepper	Piperaceae	Fruits and seeds		Chandra, et.al (2023)
Zingiber officinale	Ginger	Zingiberaceae	Roots and rhizome		Kuruppu, et.al (2019).

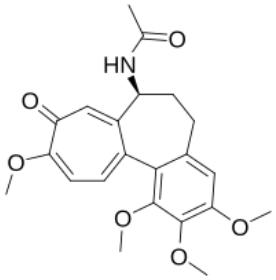
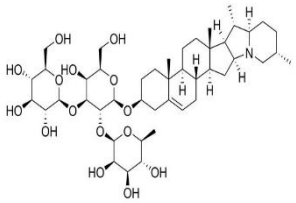
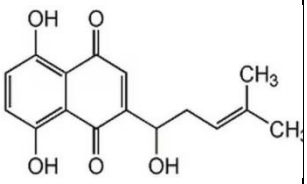
Acorus calamus	Sweet Flag	Acoraceae	Rhizomes and roots		Chandra, et.al (2023)
Raphanus sativus L.	Cultivated raddish	Brassicaceae	Roots,stem and leaf		Siddiqui, et.al (2022)
Moringa oleifera	Drumstick Tree	Moringaceae	Barks		Pal, et.al (2023)
Syzygium cumini	Malabar Plam or jamun	Myrtaceae	Fruits		Regassa, et.al (2022).
Nigella sativa	Black cumin or kalonji	Ranunculaceae	Seeds		Siddiqui, et.al (2022)

Azadirachta indica Meliaceae	Neem	Meliaceae	Leaves		Singh, et.al (2020)
Terminalia arjuna	Arjuna	Combretaceae	Stems		Chandra, et.al (2023)
Boerhavia diffusa	Punarnava	Nyctaginaceae	Leaves		Kuruppu, et.al (2019)
Tithonia diversifolia	Ttree marigold	Asteraceae	Leaves		Maher, et.al (2021)

Table 1.2: Bioactive compounds from plants having anticancer effects.

Species name	Bioactive compound	Chemical structure	Cancer	References
Withania somnifera	Withanolide		Various forms, including melanoma, B cell lymphoma, breast, pancreatic, and colon level	Sivasankarapillaet. al (2020).
Catharanthus roseus	Vinca alkaloids		Leukemia	Maher, et.al (2021)

Taxus brevifolia	Paclitaxel (Taxol)		Various forms, including cancers of the breast, ovaries, lungs, head and neck, oesophagus, prostate, and bladder.	Kuruppu, et.al (2019)
Zingiber officinale	Gingerols		Gastrointestinal, liver and oesophageal cancers	Kuruppu, et.al (2019)
Cucurma longa	Curcumin		Various forms include T cell leukemia, B cell lymphoma, breast, prostate, hepatocellular, colon, and renal cancers.	Kuruppu, et.al (2019)
Hemidesmus indicus	Caryophyllene		Different tyes: liver, uterine and breast cancers and leukaemia.	Kuruppu, et.al (2019)
Piper longum	Piperine		Lung Carcinoma	Chandra, et.al (2023)
Cedrus deodara Pinaceae	Taxifolin		Human epidermoid carcinoma of nasopharynx	Singh, et.al (2020)
Curcuma mutabilis	Labdane diterpenoid	 (1)	Human cancer cell lines, K562 and HCT1161	Soumya, et.al (2021)

Colchicum autumnale L.	Colchicine		Solid tumor, leukemia	Siddiqui, et.al (2022)
Albizia lebbeck	Saponin		Different types: cervix, larynx, hepatocarcinoma, breast, and colon carcinoma	Regassa, et.al (2022)
Arnebia euchroma	Shikonin		Prevents malfunctioning and cancer-causing compounds	Regassa, et.al (2022)

2. BIOACTIVE COMPOUNDS FROM MEDICINAL PLANTS INHIBITING CELL CYCLE

Internal and external forces together changed the normal cell cycle and signaling, which led to genetic changes in an organism. Changes in the rate of the cell cycle, overexpression of specific enzymes, or any gene can readily cause malignant mass growth. The genetic changes turn on oncogenes and turn down tumor suppressor genes (Campos et.al., 2019). Downregulation of CDK leads to growth cessation, resulting in either overexpression of cells or improper growth patterns, which cause unclear DNA methylation, chromatin modification, histone packing, and, to some extent, DNA fragmentation. Consequently, it has been depicted that thousands of genes deregulate cancer cells (Parsa et al., 2012).

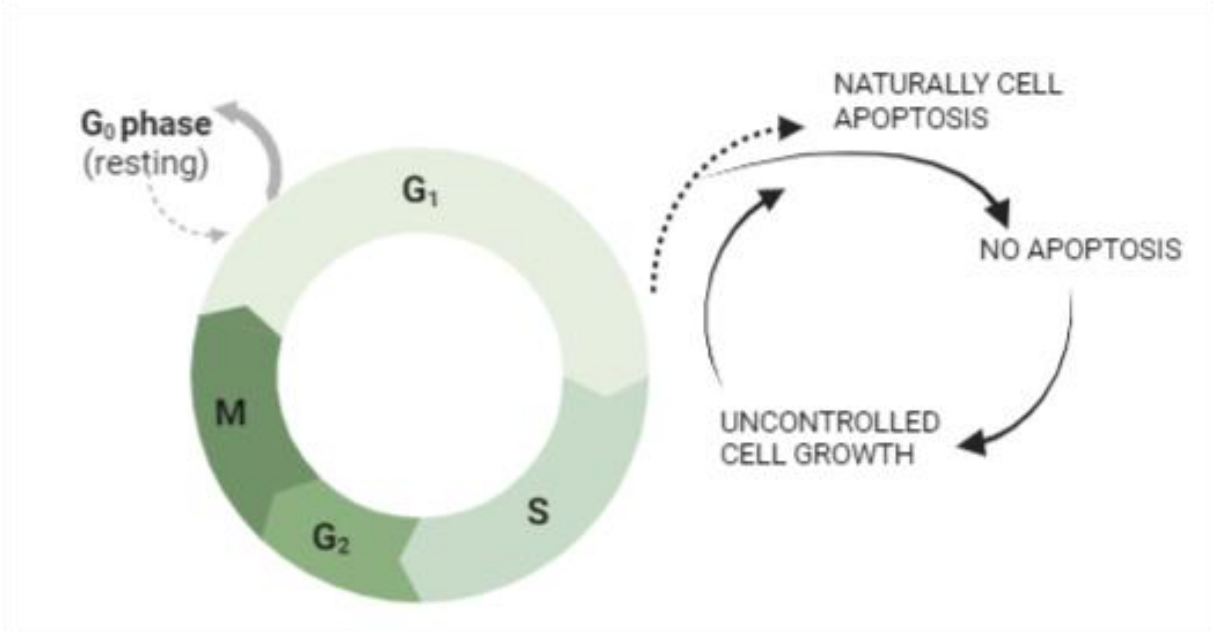


Fig 2: Interconnection between cell cycle and cancer formation

Changes in lifestyle impact individuals significantly, as exposure to a carcinogenic environment compels the body's

mechanisms to adapt, resulting in certain imbalances that may lead to irregular cell synthesis, hyper-toxicity, and altered angiogenesis (Campos et al., 2019). Studies indicate that individuals with a substantial hereditary predisposition to cancer are inherently susceptible to the disease from birth, attributable to inherited germline mutations in genes associated with cancer development (Elebiyo, et al., 2022). Cancer is characterized as a genetic disease that impacts somatic cells, which exhibit abnormalities in both amount and structure. The initial evidence emerged from the modified tumor-specific translocation in leukemia and lymphoma, highlighting the significance of oncogenes and transcriptional factors in disease control alongside environmental influences. To prevent such diseases, individuals should adopt lifestyle modifications

and facilitate the early detection of malignant lesions (Parsa, N. 2012).

Everyone knows that herbal extracts and products have been around from ancient times or the early 1950s. At this moment, there is too much use of native plants to make the novel molecule that fights cancer and other ailments. To treat cancer, more than 60–70% of active chemicals come from plants, which are also known as secondary metabolites. Unlike major metabolic components, secondary metabolites function to safeguard the body against microbial invasions and animal predation, rather than participating in general metabolism. Some secondary metabolites present in plants are flavonoids, phenols, terpenoids, alkaloids, and compounds that contain Sulphur (Kuruppu et.al, 2019).

2.1 CDK INHIBITION:

Cyclin-dependent kinases (CDKs) are a group of enzymes that are very important for controlling the cell cycle because they make sure that cells divide in an orderly way. On the other hand, CDK dysregulation is a sign of cancer and can cause cells to grow out of control. CDK inhibitors are drugs that halt the action of certain CDKs. This interrupts the cell cycle and stops cancer cells from growing. These inhibitors have emerged as a viable strategy for cancer treatment (Zhang et al., 2021).

2.1.1 Curcurma longa - Traditionally recognized for its extensive effects on many ailments, the phenolic compounds recovered from the plant species mostly include curcumin, desmethoxycurcumin, and bisdemethoxycurcumin derived from the rhizomes of the plant (Aggarwal et al., 2012). Curcumin is alone effective in countering the dysregulation of CDK inhibition. Curcumin has been demonstrated to enhance the expression of CDK inhibitors such as p21 and p27. There are two kinds of CDK inhibitors: INK-4 and Cip/Kip. INK4 inhibitors stop Cyclin D from binding to CDKs and CDK 6, while Cip/Kip stops cyclin/CDK complexes from forming (Kwok et.al., 2023). Curcumin enhances the expression of Cip/Kip CDK inhibitors, hence obstructing the interaction of cyclin D1 with CDK4 and CDK6. Curcumin also lowers the phosphorylation of Rb and stops E2F-regulated gene transcription, which stops tumors from forming (Srivatsan et al., 2011; Gull et al., 2023).

2.1.2 Cannabis sativa - It is also a well-known plant from India, although it is not a very common one. The main phenolic chemicals that are extracted from it include cannabinoids (CBD) and terpenes from the leaves (Andre et al., 2016). CBD also increases the activity of caspase-3/7 in a dose-dependent way and stops the cell cycle by lowering the levels of cyclins and cyclin-dependent kinases. Cannabinoids stop cancer cells from growing and make the cell cycle stop. During the G0/G1 phase, the synthetic cannabinoid WIN 55.212-2 induces cell cycle arrest and inhibits cellular proliferation. Anandamide induces cell cycle arrest in the S phase of human breast cancer cells by upregulating p21 and p27 levels while downregulating CDK2 and Cdc25A. CBD decreases the levels of the p21 protein and increases the levels of the p53 protein (Cardoso et.al., 2023; Zhong, 2020).

2.1.3 Azadirachta indica - Indian species recognized for their multifaceted applications in disease eradication and wound healing. It is possible to get phenolic compounds from plants like azadirachtin and nimbolide (Biswas et.al., 2021). A group of proteins called transcription factors, CDKs, cyclins, cell cycle checkpoint proteins, and CDK inhibitors work together to govern the cell cycle. Azadirachta indica from Meliaceae has many bioactive compounds, including azadirachtin, which reduces the levels of cyclin B and cyclin D1, especially in HeLa cells. This causes the formation of CKI p21, which stops the G0/G1 cell cycle. Nimbolide, an active compound in neem, influences cyclins, CDKs, and CKIs. It makes colon cancer cells stop in both G0/G1 and G2/M phases (Chandra et al., 2014). It also targets the G2/M cell cycle checkpoint proteins Rad17 and CHK2. Scientists have shown that these chemicals can interrupt the cell cycle at distinct stages, like G1 and G2/M. They believe this happens because cyclins and CDKs are turned down, which stops cells from expanding (Kumar et al., 2021) Other neem compounds, such as gedunin, also stop cancer cells from growing and multiplying. The combination of gedumin and cisplatin can significantly inhibit the proliferation of ovarian cancer cells, suggesting a potential therapeutic avenue (Chandra et al., 2014; Sistla et al., 2014).

2.1.4 Allium sativum L - The Indian species that is used to heal illness and is eaten as a vegetable (Ansary et.al., 2020). Garlic is helpful for your health since it has organosulfur compounds in it, such as ajoene, allicin, alliinase, diallyl sulphide (DAS), diallyl trisulfide (DATS), S-allyl cysteine (SAC), and methylallyltrisuphide (Shang et al., 2019). Garlic extract has been demonstrated to stop the cell cycle in many types of cancer cells, such as those in the bladder, stomach, and epithelial ovarian tumors. SAC's ability to boost the levels of natural CDK inhibitors like p21 and p27 can make cell cycle arrest even stronger. DATS, on the other hand, can stop CDK1 activity, which stops the cell cycle at the G2/M phase. Bioactive

chemicals like DATS and SAC can even interrupt the G2/M-phase cell cycle and stop cancer cells from growing. S-propargyl-l-cysteine (SPRC) stops the cell cycle and slows the growth of pancreatic ductal adenocarcinoma cells. S-allylmercaptocysteine (SAMC) inhibits the proliferation of hepatocellular carcinoma cells and negatively impacts the cell cycle.

2.1.5 Withania somnifera

Ashwagandha contains specific bioactive compounds, such as Withaferin A, that can stop the cell cycle at different points, like G1, S, and G2/M. This arrest is primarily due to its ability to inhibit the activity of CDKs. It can downregulate the expression of cyclins (proteins that activate CDKs) and CDKs themselves, thereby disrupting the cell cycle

progression. Additionally, it can upregulate the expression of cell cycle inhibitors, such as p21 and p27, which further contribute to cell cycle arrest (Mathew et al., 2023; Almeida, et al., 2022).

2.2 Apoptosis

Apoptosis is necessary to maintain cellular homeostasis. At this point, cells go through each morphological and biochemical changes. These changes include the breakdown of the cytoskeleton and the shrinkage of the cell, the condensation of chromatin, the activation of caspases and the fragmentation of DNA, the budding of membranes, and the appearance of apoptotic bodies that are bound to the membranes (Ravindran and Aggarwal, 2009).

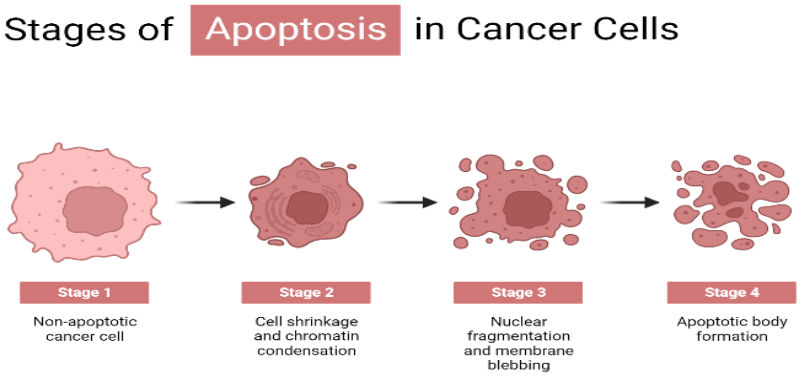


Fig 3: Stages of apoptosis

2.2.1 Curcurma Longa - It demonstrates both intrinsic and extrinsic mechanisms by which curcumin can trigger apoptosis, or programmed cell death (Ravindran et al., 2009). Activating the extrinsic pathway through Fas and death receptors (DR4/DR5), which leads to the activation of caspase-8. Activating the intrinsic pathway by damaging DNA and affecting different signaling molecules (like p53, AMPK, Akt/PI3K, JNK, and p38), which ultimately changes the mitochondria (releasing cytochrome C) and activates caspase-9. Overcoming anti-apoptotic mechanisms by down-regulating inhibitors of apoptosis (like proteins from the Bcl-2 family and IAPs) and cFLIP. Both routes converge on the activation of caspase-3, a pivotal executioner caspase that ultimately induces apoptosis (Goel and Aggarwal, 2008).

2.2.2 Cannabis sativa – It has two separate parts: CBD and THC (delta-9-tetrahydrocannabinol), a psychotropic cannabinoid, has been shown to induce apoptosis in various cancer cell types, including glioblastoma (brain cancer). It frequently operates via both CB1 and CB2 receptors on cancer cells, resulting in the synthesis of ceramide, a pro-apoptotic chemical, and the induction of endoplasmic reticulum stress (Danenberg et al., 2015). Cannabidiol can function in both receptor-dependent and receptor-independent manners. In receptor-dependent interactions, CBD can bind to cannabinoid receptors (CB1 and CB2), typically exhibiting lower affinity compared to THC. When these receptors are turned on, they can send signals that cause cells to die. CBD can also bind to other receptors, such as TRPV1 and TRPV2, which are part of the processes that lead to cell death. In receptor-independent conditions, an increase in reactive oxygen species (ROS) leads to cell death and oxidative stress. Interfering with mitochondrial function affects apoptosis and energy production, which puts stress on the endoplasmic reticulum (ER) and starts the processes that lead to cell death. This inhibits survival signaling pathways that are often very active in cancer cells, such as Akt/mTOR, which lowers levels of anti-apoptotic proteins like Bcl-2 and raises levels of pro-apoptotic proteins like Bax This activates the caspases family of proteases, which starts the process of apoptosis. promoting the autophagy process, which is when cells digest themselves and can sometimes lead to cell death (Seltzer and Zhang, 2020).

2.2.3 Azadirachta indica

Research indicates that phytochemicals such as azadirachtin and nimbolide greatly contribute to the apoptotic effects reported in Neem extracts (Kumar, 2024).These two compounds function in both intrinsic and extrinsic pathways; more specifically, in the intrinsic (mitochondrial) pathway (Srivastava and Chandra, 2012). When the mitochondrial membrane potential is disturbed, pro-apoptotic proteins penetrate the cytoplasm from the gap between the membranes. Once in the cytoplasm, cytochrome C binds to pro-caspase-9 and Apaf-1 (apoptotic protease activating factor 1) to create the apoptosome complex (Srivastava and Chandraet, 2012). Caspase Activation Caspase-9 is turned on by the apoptosome, which then triggers on other effector caspases, mostly caspase-3. After then, active caspase-3 cuts up multiple cellular substrates to start the apoptotic program, which leads to DNA breakage, cytoskeletal breakdown, and cell death. Regulation of Bcl-2 Family Proteins. Neem can change how the Bcl-2 protein family works and how much of it is made, which influences how permeable the outer membrane of the mitochondria is (Chaube and Pandey, 2014). Research on the Extrinsic Pathway up controlling of Death Receptors (Tripathi and Chaube, et.al., 2012) suggests that neem components may boost the production of death receptors on the surface of cancer cells, such as Fas (CD95) and TRAIL receptors (DR4 and DR5). Ligand Binding and DISC Formation When the ligands (TRAIL or Fas ligand) attach to these receptors, they make the Death-Inducing Signaling Complex (DISC). Caspase-8 Pro-caspase-8 and FADD (Fas-associated death domain) are two examples of adaptor proteins present in the DISC. The DISC turns pro-caspase-8 into caspase-8. Caspase-8 can directly activate caspase-3, which can lead to apoptosis. Caspase-8 can also cut Bid (a BH3-mediated domain death agonist) into truncated Bid (t-Bid), which causes crosstalk with the intrinsic pathway. After moving to the mitochondria, t-Bid helps cytochrome C get out of the cell, linking the intrinsic and extrinsic routes (Chaube and Pandey, 2014).

2.2.4 Allium sativum L - Allium is an organo-sulfur chemical that works against cancer by causing apoptosis. Diallyl trisulfide (DATS), present in garlic, enhances hydrogen peroxide (H_2O_2) levels, hence activating JNK1/2. Phosphorylation and inhibition of Bcl-2 occur when JNK1/2 is activated. DATS directly inhibits Bcl-2 (Herman and Singh, 2004). Lower levels of Bcl-2 let Bax into the mitochondria, where it starts the release of pro-apoptotic proteins, turns on caspase-9 and caspase-3, and finally causes apoptosis. DATS appears to impede this process by activating ERK1/2, as its inhibitor (PD98059) increases JNK1/2 phosphorylation and possibly apoptosis. It can combat malignant cells by metastasis, cell cycle arrest, and cellular malfunction (Herman and Singh, 2004).

2.2.5 Withania somnifera - It was explained in a short study that it is at the center of the plant and spreads out from there to show its most important biological activity. Ashwagandha has been proven to cause apoptosis via changing proteins such caspases, p53, MAPKs, survivin, Bcl2, and PARP (Bhat et al., 2022. Its bioactive elements change essential apoptotic pathways, notably by increasing the levels of pro-apoptotic proteins like Bax and decreasing the levels of anti-apoptotic proteins like Bcl-2. This causes the potential of mitochondrial membranes to break down and cytochrome C to be released. Ashwagandha also activates caspases, which are the proteins that cause apoptosis, and it can damage DNA, which can cause cell death through p53 pathway. Moreover, it can augment the internal apoptotic pathway by regulating death receptors. Withania somnifera effectively induces programmed cell death in malignant cells by targeting several stages of the apoptotic machinery, underscoring its therapeutic potential in combating cancer (Shami et al., 2024).

2.3 Role in angiogenesis and metastasis

Angiogenesis, the growth of new blood vessels, is necessary for cancer to expand beyond a few millimeters (Liu et.al., 2023). Tumors secrete pro-angiogenic substances such as Vascular Endothelial Growth Factor (VEGF), which promote the proliferation and migration of endothelial cells to create new blood vessels that provide oxygen and nutrients. This tumor vasculature is frequently aberrant and permeable, facilitating metastasis, the dissemination of carcinoma cells to remote locations (Carmeliet et al., 2000). Metastasis is a complicated process that happens in many steps. It starts with local invasion, where carcinoma cells break down the extracellular matrix and enter nearby tissues (Valastyan etal., 2011). Next comes intravasation cancer cells enters blood or lymphatic vessels. Cells live in the circulatory system when they are in circulation. Where extravasation cells leave the arteries at places far away. Lastly, colonization cells multiply to create secondary tumors (Fidler et al., 1998).

2.3.1 Curcurma longa - Curcumin is the most essential part of Curcuma longa. It stops angiogenesis by lowering the production and activity of major pro-angiogenic factors like interleukin-8 (IL-8), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor. It achieves this by messing up a multitude of signaling pathways that are necessary for these factors to be overexpressed, include the PI3K/Akt/mTOR, NF-κB, and MAPK pathways. (Srivatsan et al., 2011; Gull et al., 2023). Curcumin can also reduce the expression of angiogenic receptors on endothelial cells, which makes it harder for them to respond to pro-angiogenic signals. This stops the creation of new blood vessels, which is needed for tumors to grow and spread (Bachmeier et.al., 2010). Curcumin fights metastasis by getting in the way of several processes in the metastatic cascade. It stops the extracellular matrix (ECM) from breaking down by stopping the activity and expression of matrix metalloproteinases (MMPs), which are enzymes that cancer cells need to invade (Davoodvandi et al., 2021). Curcumin also stops cancer cells from moving and invading by changing adhesion molecules (including integrins and E-cadherin) and blocking signaling pathways that make cells move, like the Rho GTPases and NF-κB. It can also stop the epithelial-mesenchymal transition (EMT), which is when cancer cells become more mobile and aggressive. Curcumin can stop cancer cells from spreading to other parts of the body by focusing on these important phases (Mogharrabi et al.,

2020).

2.3.2 Cannabis sativa - Cannabis sativa and its cannabinoids, particularly delta-9-tetrahydrocannabinol and cannabidiol, have shown potential anti-cancer effects by affecting angiogenesis and metastasis. However, the research is still developing and sometimes gives different results depending on the type of cancer, the cannabinoid, and the experimental conditions. One-way cannabinoids may stop the growth of tumors is by stopping Vascular Endothelial Growth Factor (VEGF), which is a critical factor in the production of new blood vessels that tumors need to grow (Blazquez et al., 2004). Some studies indicate that certain cannabinoids directly inhibit the proliferation and migration of endothelial cells, with the deactivation of the CB1 receptor providing additional evidence (Kogan et al., 2006). Nonetheless, conflicting evidence suggests that cannabis may not consistently directly suppress the angiogenic characteristics of endothelial cells. Cannabinoids may also indirectly establish an anti-angiogenic milieu by influencing several pro- and anti-angiogenic variables (Pisanti, et al., 2011).

Cannabinoids exhibit anti-metastatic properties by obstructing critical processes involved in cancer dissemination. Research indicates that they impede the migration and invasion of many cancer cells, frequently via modifying cell adhesion molecules and the extracellular matrix (Davoodvandi et al., 2021). This is partially accomplished by downregulating MMPs, enzymes essential for ECM (extra cellular matrix) disintegration and invasion (Blázquez et al., 2008). Moreover, certain evidence suggests that cannabis can inhibit epithelial-mesenchymal transition, a mechanism that increases the motility of cancer cells. These effects are often facilitated by cannabinoid receptors and consequent alterations in intracellular signaling pathways that regulate cellular motility and invasiveness (Zhang et al., 2018).

2.3.3 Azadirachta indica - Neem and its components, including azadirachtin and nimbolide, demonstrate anti-angiogenic properties by inhibiting VEGF, an essential factor in the creation of tumour blood vessels. (Arumugam et al., 2014). The synthesis of these growth signals is diminished due to their interference with pro-angiogenic signaling pathways, including PI3K/Akt/mTOR and NF-κB. Neem extracts can directly stop endothelial cells from moving, growing, and forming tubes, which are all important steps in the growth of new blood vessels (Batra et al., 2022).

Neem and its constituents demonstrate anti-metastatic properties by obstructing the invasion and migration of cancer cells, which are essential processes in metastasis. Research shows that Neem does this by changing cell adhesion molecules and how they interact with the extracellular matrix (ECM). Additionally, Neem inhibits matrix metalloproteinases (MMPs), enzymes that break down the ECM and make it easier for cells to invade (Islam and Lee, 2024)). Emerging data indicates that Neem may also disrupt the epithelial-mesenchymal transition (EMT), a process that increases the motility of cancer cells. These effects are frequently mediated by the modulation of critical signalling pathways such as NF-κB and MAPK, which are integral to the motility and invasiveness of cancer cells, hence constraining cancer dissemination (Rajendran et al. 2024; Chavhan et al. 2023).

2.3.4 Allium sativum - Various bioactive substances, especially organosulfur compounds such as allicin, diallyl disulphide (DADS), and S-allyl cysteine (SAC), have shown potential anti-cancer properties via affecting angiogenesis and metastasis through several routes. Garlic's anti-angiogenic properties impede the development of new blood vessels essential for tumor growth. Research indicates that garlic components can diminish the synthesis and secretion of VEGF, an essential signal for this process (Sanie-Jahromi et al., 2023). Garlic also disrupts in significant signaling pathways such as PI3K/Akt/mTOR and NF-κB, which normally increase the production of these growth signals in cancer. Garlic can also directly stop the growth, movement, and organization of endothelial cells, which are the cells that make these new blood vessels. These synergistic effects indicate that garlic can efficiently restrict tumor sustenance and proliferation by inhibiting its vascular supply (Sanie-Jahromi et al., 2023).

Garlic exhibits anti-metastatic properties by obstructing the migration of cancer cells. Studies show that garlic extracts and its components stop several types of cancer cells from invading and moving, which are important steps in metastasis (Kim et.al., 2013). This is frequently associated with garlic's capacity to modify cell adhesion molecules and their engagement with the extracellular matrix. Garlic also lowers the levels of MMPs, which are enzymes that break down the ECM and make it easier for bacteria to invade. New data also suggests that garlic can stop EMT, which is a process that makes cancer cells more mobile and aggressive. These effects are often achieved by the modulation of signaling pathways such as NF-κB and MAPK, which regulate cancer cell motility and invasion (Sasaki et al., 2024).

2.3.5 Withania somnifera - Withaferin A, a principal component of Ashwagandha, obstructs angiogenesis by diminishing VEGF expression and signaling, hence selectively decreasing endothelial cell proliferation. Ashwagandha extracts exhibit anti-angiogenic properties in CAM tests by diminishing the growth of blood vessels and inhibiting pro-angiogenic proteins such as VEGF and angiogenin (Atteeq et al., 2022). Moreover, Withaferin A can inhibit NF-κB, a transcription element that facilitates angiogenesis. These results indicate that Ashwagandha components may impede the blood flow essential for tumor proliferation (Wicinski et al., 2024).

Ashwagandha root extract and its compounds, notably withaferin A and withanone, exhibit potential in impeding cancer spread. They interfere with EMT by altering vimentin, a protein that facilitates cancer dissemination (Yang et al., 2013). In laboratory experiments, these chemicals also stop cancer cells from moving and invading. They also suppress the levels

of proteins that help cells move, such as hnRNP-K, VEGF, and metalloproteases. In experiments on animals, Ashwagandha has slowed the growth of tumors and the growth of secondary tumors in the lungs. Withaferin A targets numerous components that induce metastasis in drug-resistant breast cancer cells, demonstrating its promise against aggressive cancer spreads (Gao et.al., 2014; Szarc vel Szic et.al., 2014).

3. PREDOMINANT ANTICANCER COMPOUNDS FROM MEDICINAL PLANTS

The ongoing quest for potent anticancer drugs has resulted in the identification of numerous sources, including the vast diversity within the plant kingdom. Plants and plant products have served as medicinal sources since antiquity, and various established medical systems are founded on this traditional knowledge. Presently, these traditional medicinal plants are recognized as sources for isolating natural compounds with potential health-promoting properties (Kumar et al., 2015). Additionally, modern medicine can evaluate and ascertain the pharmacological values that traditional systems assert and propose (Khan et al., 2022). Several plant-derived drugs are now recognized as fundamental components in cancer therapy, significantly impacting patient outcomes. This opening will talk about two of the best-known anticancer drugs that come from plants: vincristine from the Madagascar periwinkle (Catharanthus roseus) and paclitaxel, which was first taken from the bark of the Pacific yew tree (Taxus brevifolia) (Mize et al. 2023). These molecules, with their unique ways of affecting important cellular processes, show how essential natural products are in the fight against cancer (WHO. 2023). Terpenes, podophyllotoxin and its semi-synthetic derivatives, camptothecin and its analogues, and vinca alkaloids and their analogues are some of the plant-based anticancer medications that are commonly used. Others are mostly used to prevent cancer (Asma et al., 2022).

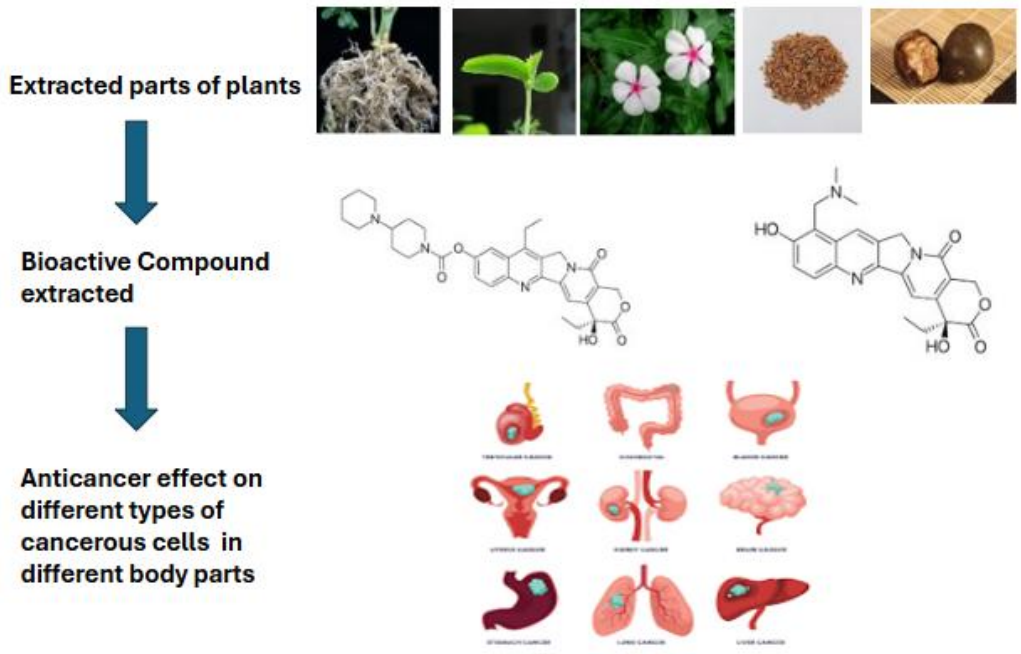


Fig 4: Medicinal plants and their bioactive compounds having potential anticancer properties.

3.1 Vinca Alkaloids and its Derivatives

Vinca alkaloids are a group of natural compounds that stop mitosis and microtubules. These are indole and dihydro-indole alkaloids that come from the Catharanthus roseus. They are well-known medications used in the treatment for cancer because they stop cells from dividing (Banyal et al., 2023). Vinca alkaloids work on the mitotic phase of cell growth and stop cells from dividing. It disrupts tubulins in spindle fibers and halts the synthesis of microtubules, causing the cell cycle to stop at metaphase. Vinca alkaloids break down microtubules, which stop the mitotic spindles from working properly, leading to cell death or apoptosis. There are two main groups of microtubule-targeting antimitotic drugs: microtubule-destabilizing agents and microtubule-stabilizing agents. Vinca alkaloids are agents that only work on certain phases of the cell cycle, mostly M (mitotic) and to a lesser extent S (synthesis) phase (Kumar et al. 2022). Many anticancer drugs are natural alkaloids that come from plants. Some of these are berbamine, veratridine, vincristine, vinblastine, vinorelbine, and vinflunine.

Vincristine disrupts microtubules and functions mostly during the M-phase of the cell cycle. It forms a complex with the β-tubulin subunit on the vinca-binding domain. It influences acute lymphocytic leukemia, Hodgkin lymphoma, non-

Hodgkin lymphoma, neuroblastoma, Wilms tumor, and other lymphomas (Cahlíkova et al., 2025). Vinblastine, another derivative, induces M-phase-specific cell cycle arrest by interfering with the synthesis of microtubules and the proper formation of the mitotic spindle and kinetochore. It can also affect the synthesis of proteins and nucleic acids at larger levels. It is clinically utilized for breast cancer, testicular cancer, lymphocytic lymphoma, and Kaposi's sarcoma (Cho et al., 2022; Das et al., 2023). Vinorelbine, a semi-synthetic derivative that kills cells and stops mitosis, also messes with the dynamics of microtubules by stopping tubulin polymerization. It promotes microtubule depolymerization at elevated doses and can inhibit mitotic progression at reduced levels. It attaches to β-tubulin subunits at the Vinca-binding domain (Kumar et.al., 2023). In therapeutic settings, it is used to treat breast cancer and non-small cell lung cancer (NSCLC). Vindesine is a synthetic version of vinblastine that stabilizes and binds to tubulin, halting polymerization and mitotic spindle formation. This stops the cell cycle at metaphase. It also stops the production of macromolecules. Some in vitro studies indicate that it is more efficient than vinblastine in inducing mitotic arrest. It affects breast, esophageal, colorectal, and acute lymphocytic leukemia, as well as malignant melanoma (Cho et al. 2022). Vinflunine (VFL), a third-generation synthetic vinca alkaloid, binds to tubulin at or near the vinca binding sites to stop microtubules. A G2/M arrest occurs, microtubule polymerization is suppressed, and apoptosis is promoted. Vinflunine not only slows down the formation of microtubules, but it also messes up the way they move. The unique structure of this vinca alkaloid may help it get around some of the resistance mechanisms seen with other vinca alkaloids (Cho et al., 2022). It is utilized in clinical environments for the treatment of advanced or metastatic urothelial tract transitional cell carcinoma (Capasso et al., 2022).

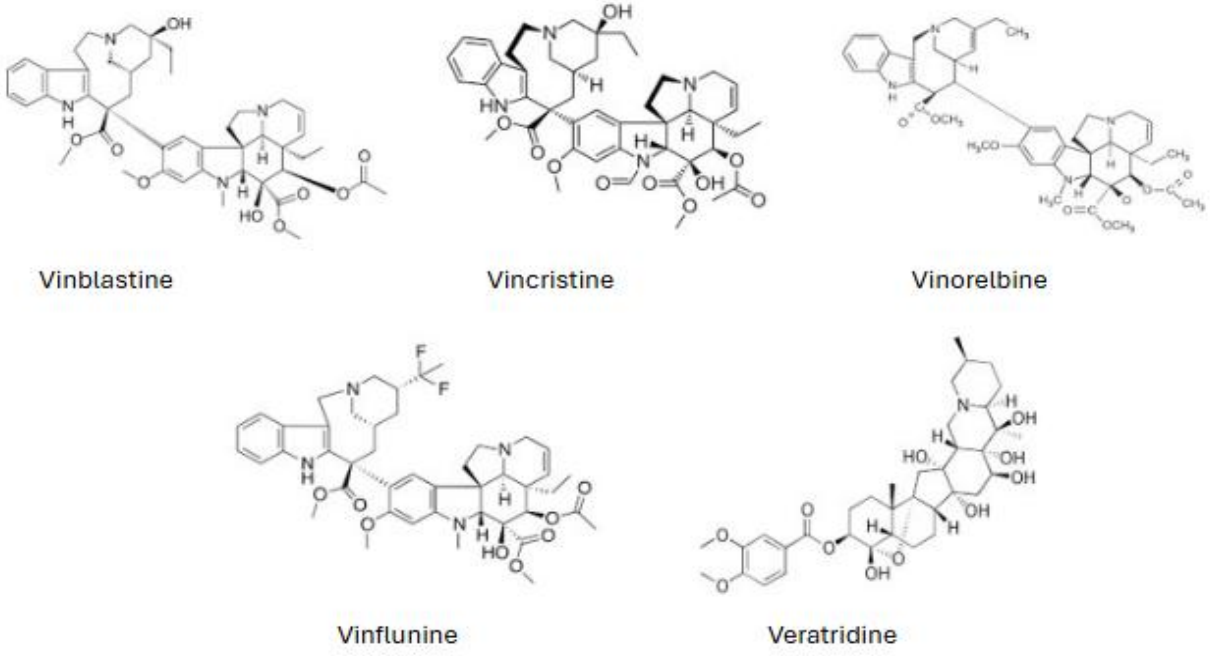


Fig 5: Chemical structures of vinblastine, vincristine, vinorelbine, vinflunine, and veratridine.

3.2 Podophyllotoxin

Podophyllotoxin (PTOX) is a natural chemical derived largely from the roots and rhizomes of Podophyllum plants, namely Podophyllum peltatum and Podophyllum hexandrum. A lot of recent cancer research has focused on it since it is quite cytotoxic. Despite PTOX being too toxic for systemic use in cancer treatment (Fan et.al 2021), several clinically approved anticancer drugs have been created using it as a crucial lead chemical. Podophyllotoxin primarily inhibits cancer by obstructing tubulin polymerization. Microtubules are important for the mitotic spindle throughout cell division; thus, they are broken. When the malignant cells are stopped in the G2/M phase of the cell cycle, they undergo apoptosis, or programmed cell death (Shah et al., 2021). Podophyllotoxin directly targets tubulin, while its clinically used derivatives, such teniposide and etoposide, act by blocking DNA topoisomerase II, which is an enzyme that DNA needs to copy and fix itself. DNA is ultimately being compromised, resulting in cellular demise (Nitiss et al., 2009).

Natural PTOX's direct systemic use in cancer treatment is limited by its high toxicity and low absorption. However, its structure has been altered to create derivatives with improved pharmacological characteristics, including reduced toxicity and enhanced efficacy. Etoposide and Teniposide are two important analogues that work on different types of cancer cells, including small cell lung cancer, testicular cancer, lymphomas, and some acute leukemias. Their strong ability to change

the structure of cells makes them semi-synthetically stronger against cancer (Asma et.al., 2022).

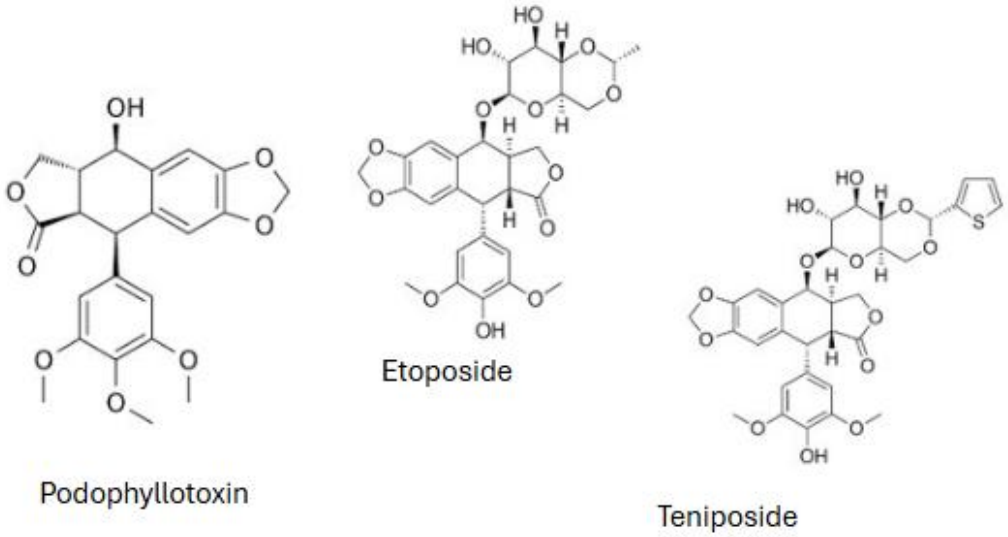


Fig 6: Chemical structures of podophyllotoxin, etoposide, and teniposide

3.3 Taxanes

Taxane diterpenoids are a group of natural compounds that have changed cancer chemotherapy. Most of them come from plants in the Taxus genus, which are taken from yew trees. These are widely employed in the treatment of many solid tumors, including malignancies of the breast, ovaries, lungs, prostate, and head and neck (Asma et al., 2022). Microtubules, which are key parts of the cytoskeleton that help cells keep their shape, move things around inside cells, and most crucially, divide (mitosis), are the principal target of taxanes anticancer effect. Taxanes, a type of mitotic inhibitor, stabilise microtubules by binding to the β-tubulin subunit and stopping it from breaking down. Vinca alkaloids and other inhibitors, on the other hand, stop the synthesis of microtubules. Taxanes disturb the natural dynamic instability of microtubules, which is necessary for proper mitotic spindle activity during cell division, by hyper-stabilizing them (Xu et al., 2025). Docetaxel was the first drug to be used in clinical settings that showed significant activity against different types of cancer. Researchers want to make modified derivatives that will get rid of the bad side effects of docetaxel and paclitaxel, two approved taxane drugs that are still limited in how they can be used. Due to structural modifications, new compounds exhibiting enhanced solubility, optimized cytotoxicity, and reduced toxicity have been identified (Xu et al., 2025).

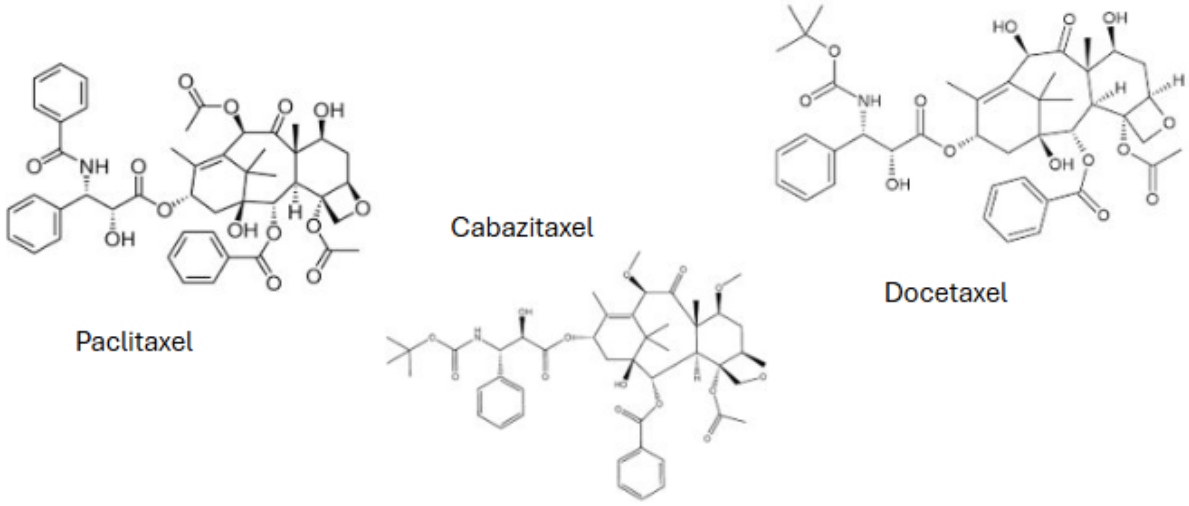


Fig 7: Chemical structures of paclitaxel, cabazitaxel and docetaxel.

3.4 Camptothecin and Its Derivatives

Camptothecin (CPT), a cytotoxic quinoline alkaloid, was initially discovered in the bark and stem of the Chinese tree

Camptotheca acuminata. The discovery of this novel way for chemotherapy drugs to work in the 1960s was a major turning point in cancer research. The parent compound's poor solubility and adverse effects hampered its clinical use, but its semi-synthetic derivatives have emerged as key agents in several cancer treatments (Venditto et.al., 2010). Camptothecin (CPT) is an anticancer medication that comes from the plant Camptotheca acuminata. It acts by stopping topoisomerase-I from completing its job, which breaks DNA and eventually kills cells (Hsiang et.al., 1985). Clinical trials were halted because of its high toxicity and low solubility in water. To get around these limits, several CPT derivatives have been made and approved for use in clinical settings. Irinotecan, belotecan, and topotecan are three CPT drugs that actively block DNA topoisomerase–I, which is an enzyme that helps with transcription and DNA replication. These medicines work against solid tumors, ovarian cancer, small cell lung cancer, and cervical cancer (Oberlies et.al., 2004). Another CPT semi-synthetic derivative, 9-aminocamptothecin (9-AC), has not yet shown clinically significant anticancer action, but it has exhibited pronounced efficacy in preclinical studies (Asma et al., 2022).

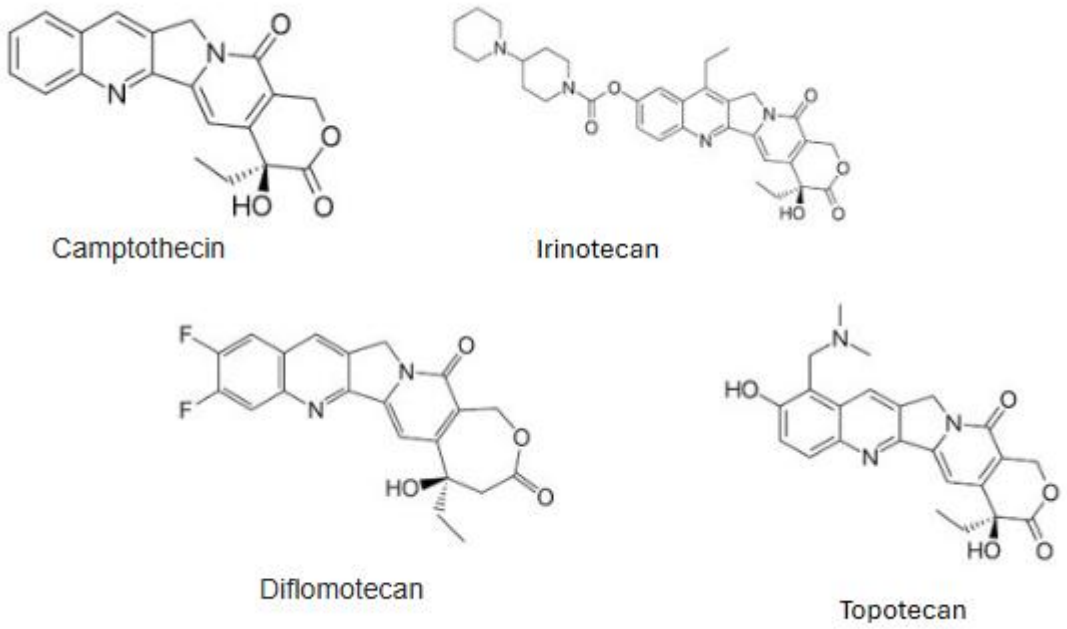


Fig 8: Chemical structures of camptothecin, irinotecan, diflomotecan, and topotecan

4. CONCLUSION

Medicinal plants, with their extensive history in traditional medicine, have become a significant source of anticancer drugs, as well as possessing antioxidant, anti-inflammatory, antifungal, and antibacterial characteristics. These plants have a wide range of bioactive chemicals, such as alkaloids, flavonoids, phenols, and terpenoids, that are very good in fighting cancer. One of the most important ways that medicinal herbs fight cancer is by stopping or slowing down the cell cycle. These chemicals can stop the cell cycle at certain points by targeting cyclin-dependent kinases (CDKs), which can lead to cell death or apoptosis. Furthermore, the bioactive constituents can provoke metastasis or undesirable angiogenesis by altering several signaling pathways. Nonetheless, although medicinal plants provide significant therapeutic potential, numerous difficulties persist. One big problem is that many compounds that come from plants are not very bioavailable, which means they cannot be easily absorbed by the body. Even if they have benefits, they can also interact with other drugs and cause adverse effects like allergies. To address this issue, researchers are investigating diverse drug delivery methods, including liposomal formulations and nanoparticles, to improve the absorption and effectiveness of these drugs. Phytochemical awareness propels phytomedicine research owing to the adverse effects of synthetic drugs and the accessibility of plants. This study emphasizes plant-derived chemicals that demonstrate efficacy against cancer in laboratory and animal trials. It is important to study plant phytochemicals more to find effective and cheap cancer treatments. Moreover, the intricate characteristics of cancer need a multi-targeted strategy, and the integration of chemicals produced from medicinal plants with conventional medicines may yield synergistic effects and enhance patient outcomes. Researching phytochemicals that fight cancer can help make cancer medications safer. Researching well-known anticancer plants in relation to various cancers may provide essential information for present and future cancer therapies. In conclusion, medicinal plants are a useful source for making new cancer treatments. We can employ the power of nature to fight this terrible disease by learning

about the molecular pathways that make them work against cancer and finding ways to make them easier to use.

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