International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Green Poison: A Sustainable Approach to Use Plant Toxin as An Anticancer Agent

Mukund A Gulhane[1], Shailesh G Jawarkar[2], Bhavna S Sharnagat[3]

[1]Undergraduate Student, Vidyabharti College of Pharmacy
[2,3]Vidyabharti College of Pharmacy

Abstract

The rising interest in plant-derived phytochemicals as cancer therapies has revealed numerous bio-active compounds with potent therapeutic potential. Compounds like vinca alkaloids, taxanes, and berberine exhibit diverse biological activities, including anti-tumor, proving effective against various cancer types. Despite the toxicity of some medicinal plants, this feature can be harnessed for drug discovery, offering new treatments for cancer.Plant metabolites target tumor growth by inhibiting tumor-promoting enzymes, repairing DNA, and boosting immune responses. Compounds like vinblastine disrupt micro-tubule dynamics, while curcumin inhibits cancer cell proliferation. Toxic plant-derived metabolites, such as podophyllotoxin and camptothecin, demonstrate unique cancer-fighting mechanisms by targeting topoisomerases and inducing apoptosis.Integrating these phytochemical promise for advancing cancer prevention and treatment, offering more sustainable and effective options.

Keywords: Bioinformatic, oncogenes, Malignant, neuroblastoma, Sanguinaria canadensis.

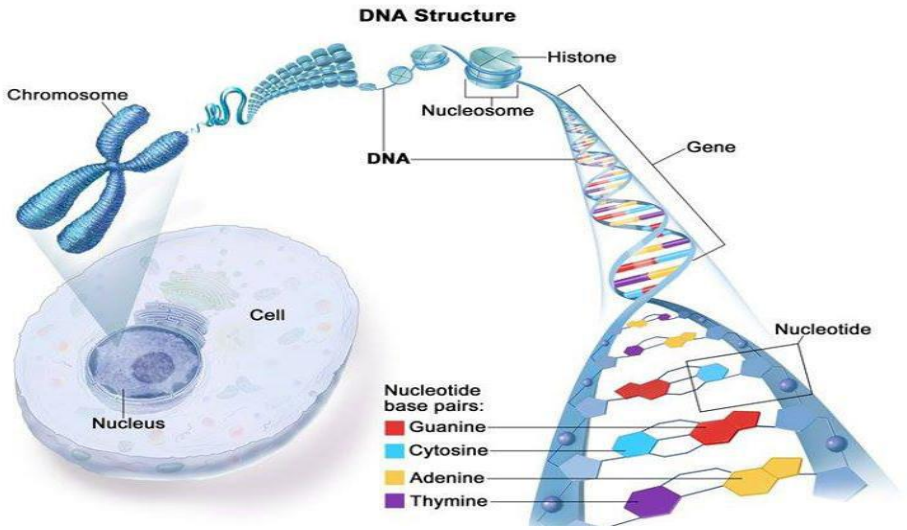
Introduction

Since ancient times, humans have explored various plant species to treat diseases . This exploration has uncovered a wide range of bioactive compounds with therapeutic potential. Among the most studied plant-derived chemicals are flavonoids, carotenoids, alkaloids, and phenolics, known for their diverse medicinal propertie [1], including antitumor activity. Cancer, the second leading cause of death globally, is a genetic disease marked by the uncontrolled growth of abnormal cells and their metastasis to other parts of the body.Cancer is the uncontrolled growth of cells leading to the formation of tumors that can metastasize to various body organs . Despite recent therapeutic advances, cancer remains one of the major causes of death worldwide due to profound therapeutic challenges[2] . According to the GLOBOCAN report, 19.3 million new cancer cases and 10 million cancer-related deaths have been registered in the world in 2020 [3] . The wide application of chemotherapy is still facing problems associated with nonspecific targeting, lack of specificity, drug resistance, and disease recurrence . plant can be helpful in treating cancer via producing various cytotoxic agents, toxins, and prodrug-modifying enzymes . Bioinformatic techniques, including systems pharmacology and cheminformatics, are revolutionizing the development of novel drug compounds derived from medicinal plants[4]. These advanced tools enable researchers to comprehensively analyze the complex interactions between bioactive compounds and biological targets at a molecular level. Systems pharmacology integrates network biology with pharmacology, allowing for a systems-level understanding of drug actions and predicting the efficacy and toxicity of plant-based compounds. Cheminformatics , on the other hand, aids in the virtual screening and optimization of plant-

derived molecules by utilizing vast chemical databases and computational algorithms.
By applying these techniques, scientists can identify key molecular pathways and receptors involved in cancer progression, enabling the design of more targeted therapies. For instance, computational docking studies can predict the binding affinities of plant-derived compounds to cancer-related receptors such as HER2, EGFR, or VEGFR. High-throughput screening and machine learning algorithms further accelerate the identification of lead compounds with cytotoxic or anti-proliferative properties. This integration of bioinformatics with phytomedicine [5]opens new avenues for drug discovery, offering enhanced specificity.

CANCER

Cancer is a disease characterized by the uncontrolled growth and spread of abnormal cells in the body. Normally, cells grow, divide, and replace old or damaged cells in an orderly process. However, in cancer, this regulation breaks down, causing abnormal cells to multiply excessively and form tumors. These tumors can be either benign (non-cancerous) or malignant (cancerous)[6].
Malignant tumors invade nearby tissues and can spread to other parts of the body through metastasis, whereas benign tumors do not invade or spread. While benign tumors generally do not return after removal, cancerous tumors can regrow. Some cancers, such as leukemia, do not form solid tumors but affect the blood and bone marrow.
Cancer cells has several distinct characteristics compared to normal cells: they grow uncontrollably without any external signals, ignore stop signals and mechanism that regulate division and apoptosis, invade surrounding tissues and spread to other areas, recruit blood vessels to nourish the tumor, evade and manipulate the immune system for survival, and often display chromosomal abnormalities such as duplications [7], deletions, and an abnormal number of chromosomes.
The word 'cancer' comes from the Latin for 'crab' – just like the zodiac sign. ...
There are more skin cancer cases due to indoor tanning than lung cancer cases due to smoking Researchers believe that over half of all cancer cases – and up to half of all cancer deaths – are preventable. This means there are between 2.4 million and 3.7 million avoidable deaths per year, 80% of which occur in low- and middle-income countries The left breast is 5 - 10% more likely to develop cancer than the right breast. The left side of the body is also 10% more prone to melanoma (a type of skin cancer). Nobody is exactly sure why this is[7].



Structure of DNA

Cancer is caused by changes to qualities, which are the essential units of heredity. These qualities are organized in long strands of firmly stuffed DNA known as chromosomes. These hereditary modifications can result from different components. Hereditary changes that cause cancer can happen since of blunders that happen as cells divide.The harm to DNA caused by hurtful substances in the environment, such as the chemicals in tobacco smoke ultraviolet rays[7] . they were inherited from our parents. The body ordinarily dispenses with cells with harmed DNA some time recently they turn cancerous. But the body's capacity to do so goes down as we age. This is portion of the reason why there is a higher hazard of cancer afterward in life.Each person's cancer has a interesting combination of hereditary changes. As the cancer proceeds to develop, extra changes will happen[7].

Types of Genes that Cause Cancer.

The hereditary changes that contribute to cancer tend to influence three primary sorts of genes—proto-oncogenes, tumor silencer qualities, and DNA repair qualities. These changes are now and then called "drivers" of cancer.Proto-oncogenes are included in typical cell development and division. In any case, when these qualities are changed in certain ways or are more dynamic than typical, they may gotten to be cancer-causing qualities (or oncogenes)[8], permitting cells to develop and survive when they ought to not.Tumor silencer qualities are too included in controlling cell development and division. Cells with certain changes in tumor silencer qualities may separate in an uncontrolled manner[9].DNA repair qualities are included in settling DNA. Cells with mutations in these qualities tend to create extra transformations in other qualities and changes in their chromosomes, such as duplications and erasures of chromosome parts. Together, these changes may cause the cells to ended up cancerous[9].

The Role of Oncogenes:

Proto-oncogenes are typical qualities that encode proteins included in directing cell development and division. In their transformed frame, called oncogenes, they contribute to cancer advancement by causing these growth-regulating proteins to ended up excessively dynamic, driving to unchecked cell proliferation[8]. Regularly, proto-oncogenes react to development signals. For occurrence, a development calculate ties to receptors on a cell's surface, activating a signaling cascade that comes to the core and advances cell division.Oncogenes cause these signaling pathways to ended up hyperactive, driving to quick cell division[10]. This can happen through:Overproduction of development components, invigorating both the creating cell and neighboring cells.Mutant receptor proteins that flag development indeed in the nonattendance of development factors.Disruption of intracellular signaling, sending persistent growth-promoting signals to the nucleus[9].

The Role of Tumor Suppressor Genes:

While oncogenes stimulate cell growth, tumor suppressor genes act as the brakes on cell division. These genes send inhibitory messages that counterbalance growth signals.Tumor suppressor genes prevent uncontrolled cell growth by coding for proteins that halt cell division when necessary.When these genes mutate or become inactivated, cells lose this crucial restraint, allowing unchecked proliferation[10]. In some cases, the mutations block inhibitory pathways, or prevent proteins from halting growth-promoting signals, further enabling cancer .

Below are the main categories of cancer based on cell types[10]:

- **Carcinoma**: The most common type of cancer, originating in epithelial cells (which cover body surfaces).
- **Types of carcinomas include:** Adenocarcinoma forms in glands, basal cell carcinoma in skin, squamous cell carcinoma in organ linings, and transitional cell carcinoma in bladder or kidney tissues.
- **Sarcoma**: Forms in bone and soft tissues, including muscles, fat, blood vessels, and tendons. Types include osteosarcoma (bone) and leiomyosarcoma (soft tissue).
- **Leukemia**: A cancer of the blood-forming tissues in the bone marrow. Leukemias do not form solid tumors but result in the accumulation of abnormal white blood cells.
- **Lymphoma**: Begins in lymphocytes, in immune system. Types include:Hodgkin ,Non-Hodgkin Lymphoma
- **Multiple Myeloma**: A cancer that originates in plasma cells, affecting the bone marrow and leading to tumors in bones.
- **Melanoma**: Starts in melanocytes, the cells responsible for producing melanin. It typically occurs on the skin but can also form in other pigmented tissues, like the eyes.
- **Brain and Spinal Cord Tumors**: These tumors arise in the central nervous system and are named based on the type of cell affected, like astrocytes (in astrocytic tumors). They can be benign or malignant[10].

Toxin plant that are more sustainable in cancer cure.

Phytochemicals, bioactive compounds derived from plant sources, have garnered significant attention for their potential as chemotherapeutic agents. These compounds, isolated from various plant extracts, exhibit a broad spectrum of therapeutic effects, including anti-tumor, anti-inflammatory, antioxidant, and antibacterial properties. Notable phytochemicals, such as [vinca alkaloids, taxanes, camptothecin derivatives, cephalotaxus, colchicine, ellipticine, berberine, combretastatins, and triterpenoid acids] [11]have demonstrated potent anticancer activity against various cancer types. In addition to their cancer-fighting capabilities, phytochemicals from plants have shown positive results in managing other health conditions, including diabetes, thyroid dysfunction, infertility, sterility, and other physiological disorders[12]. This multifaceted efficacy highlights the therapeutic promise of plant-derived compounds across a wide range of medical conditions.

Toxicity of Medicinal Plants and Drug Discovery Potential :

Poisons from plants have been discovered through natural observation and experimentation.Many medicinal plants possess varying degrees of toxicity, with about one-third of those used for diabetes treatment being toxic[13].Despite their toxicity, plant-based compounds are crucial for developing effective drugs for critical diseases like cancer.Natural products are increasingly recognized as valuable resources in drug discovery and therapeutic development[13].

Role of Plant Metabolites in Disease Management :

Primary and secondary metabolites extracted from plants play a vital role in disease management, particularly in cancer treatment.These metabolites exhibit multiple pharmacological properties, including[14]: Plant-derived compounds can target cancer cells and inhibit abnormal processes, making them promising for future drug development.Plant metabolites play a vital role in cancer treatment by

suppressing tumor-promoting enzymes, repairing damaged DNA, stimulating the production of antitumor enzymes, boosting immune function, and inducing antioxidant effects[14].

Specific Metabolites and Their Cancer-Fighting Mechanism:

Certain metabolites from "poisonous plants" have the ability to interact with DNA or RNA through intercalation or alkylation[14].Examples include : Alkaloid, Enzyme inhibitors, ptaquiloside, Phytoestrogen,Terpenes[14].These compounds show significant potential in combating cancer by directly targeting cancer cells. Alongside natural remedies, maintaining a healthy lifestyle—proper diet, exercise, and sleep—can enhance cancer prevention and treatment strategies.

Few examples,

Drug and there mecanism of action [15]

Drug .	**Mechanism of Action.**	**Poisonous Plant**	**Ref**
Vinblastine, Vincristine	Inhibit mitosis by interfering with microtubule formation, arresting cancer cell multiplication	Catharanthus roseus	[15]
Paclitaxel, Docetaxel	Arrest multiplication of cancerous cells by cross-linking the microtubules	Taxus spp.	[15]
Cannabinoid (Sativex®) .	Inhibits cell proliferation in colorectal carcinoma, neuroblastoma, gliomas, lymphomas, thyroid, and breast cancer	Cannabis sativa	[15]
Curcumin .	Inhibits cell growth in many types of cancerous cells .	Curcuma longa	[15]
Podophyllotoxin (Etoposide, Teniposide)	Inhibits topoisomerase II, leading to DNA strand breaks and cancer cell death	Podophyllum peltatum (Mayapple)	[15]
Camptothecin .	Inhibits topoisomerase I, preventing DNA replication and causing cancer cell apoptosis	Camptotheca acuminata	[15]
Thiocolchicine .	Inhibits microtubule polymerization, arresting the cell cycle and inducing apoptosis	Colchicum autumnale (Autumn Crocus)	[15]
Sanguinarine .	Induces apoptosis by targeting NF-κB signaling pathways and disrupting cancer cell growth	Sanguinaria canadensis (Bloodroot)	[15]
Ingenol mebutate .	Causes rapid cell death and induces an immune response against cancer cells	Euphorbia peplus	[15]

Calotropin .	Induces cell cycle arrest and apoptosis, inhibits cancer cell growth	Calotropis gigantea (Latex)	[15]
Uzarigenin .	Disrupts cancer cell membranes, interferes with survival signaling pathways	Calotropis gigantea (Latex)	[15]

There are various plant discovered, observed in nature which are toxic to mankind but with advancement of technology , science of botny,chemistry , receptors , the effective use of this toxin is possible along with the knowledge of pharmaceutical formulation this toxin can be converted into medication.
Some of this plant which has toxin as an anticancer property are describe below few of them are marketed but many of them are under research.
Few Plant are :
Catharanthus roseus (Madagascar Periwinkle) Common Names: Bright eyes, Cape periwinkle, Graveyard plant, Madagascar periwinkle, Old maid, Pink periwinkle. Family: Apocynaceae , Native to: Madagascar (Endemic species) Catharanthus roseus is a perennial flowering plant known for its medicinal properties, particularly as a source of vincristine and vinblastine, which are widely used in the treatment of cancer. Medicinal Uses :Vincristine and vinblastine are plant-derived chemotherapeutic agents used to treat various cancers, including leukemia, lymphoma, and other solid tumors.
Mechanism of Action: The primary antitumor activity of vinblastine is attributed to its inhibition of mitosis. By binding to the microtubular proteins of the mitotic spindle, vinblastine causes crystallization of the microtubules, leading to mitotic arrest and ultimately cell death[16][17].
Key Targets of Catharanthus roseus[15]:

Target	Action	Organism
Tubulin beta-2A chain	Inhibitor	Humans
Tubulin alpha-1A chain	Binder	Humans

Vincristine is a potent anticancer agent primarily known for its ability to inhibit cell division. Its **mechanism of action** involves disrupting mitosis at the metaphase stage by binding to tubulin, for formation of the mitotic spindle. By doing so, vincristine prevents the proper segregation of chromosomes during cell division, leading to cell cycle arrest and eventual death of rapidly proliferating cancer cells. Amino acid metabolism, cyclic AMP and glutathione metabolism, calcium transport via calmodulin, cellular respiration, and the production of nucleic acids and lipids are key biochemical processes in cells.These diverse actions contribute to its effectiveness in treating various cancers, including leukemia and lymphoma[16].
Key Targets of Vincristine[15]:

Target	Actions	Organism
Tubulin beta chain	Inhibitor	Humans
Tubulin alpha-4A chain	Inhibitor	Humans

Taxus.

The **Taxus** species includes several varieties, such as T. baccata (English yew), T. brevifolia (Western yew), T. cuspidata (Japanese yew), T. wallichiana (Himalayan yew), and T. sumatrana (Sumatra yew). All parts of Taxus plants are toxic due to taxane-derived substances (taxol A and B) and glycosides (taxicatine). **Mechanism of Action (MoA)** of Paclitaxel: Paclitaxel hyper-stabilizes microtubule structures, preventing their normal function in cell division.It binds to the β subunit of tubulin, locking microtubules in place, preventing disassembly and disrupting cellular processes like chromosome transport during mitosis.Paclitaxel also induces programmed cell death (apoptosis) by inhibiting the apoptosis regulator Bcl-2 protein[18][19].

Curcumin (from Curcuma longa**)**

Family: Zingiberaceae (Ginger family), Key Ingredient Composition:60–70% carbohydrates , 5–10% fat,1–6% curcuminoid(responsible for yellow color)

Mechanism of Action:Curcumin is a potent antioxidant, scavenging harmful radicals such as hydroxyl and superoxide anions.It inhibits lipid peroxidation and prevents peroxide-induced DNA damage.Acts as an anti-inflammatory by suppressing key pathways:Inhibits protein kinases and c-Jun/AP-1 activation.Reduces COX-2 expression, involved in inflammation and cancer[20][21].

Key Targets of Curcumin[44]:

Target	Actions	Organism
Cytochrome P450 3A4	Inhibitor	Humans
DNA (cytosine-5)-methyltransferase 3B	Inhibitor	Humans

Podophyllum peltatum (Mayapple)

Family: Berberidaceae ,

Common Names: Mayapple, American Mandrake, Wild Mandrake, Ground LemonToxicity: All parts of the plant are toxic, especially the unripe fruit, rhizome, foliage, and roots. Ripened fruit is edible in small amounts.Active Compound: Podophyllotoxin, known for its anticancer properties.

Mechanism of Action:The drug interferes with DNA replication by inhibiting topoisomerase II during the late S and early G2 phases.It binds and stabilizes the temporary breaks made by the enzyme, preventing proper DNA unwinding and halting replication.Podophyllotoxin disrupts DNA reparation, leading to cell death in rapidly dividing cancer cells[22][23].

Key Targets of Podophyllotoxin:

Target	Actions	Organism
DNA topoisomerase 2-beta	Modulator	Humans
Tubulin beta chain	Inhibitor	Humans
DNA topoisomerase 2-alpha	Inhibitor	Humans

Camptotheca acuminata

Family: Nyssaceae . Common Names: Happy Tree, Cancer Tree Active Compounds: Camptothecin and its derivatives (Topotecan, Irinotecan) .

Uses: Camptothecin chemicals have shown promise as treatments for cancer and HIV. Modern chemotherapy drugs Topotecan and Irinotecan are derived from Camptothecin.

Mechanism of Action: Camptothecin binds to the topoisomerase I and DNA complex, forming a ternary complex.This complex stabilizes and prevents DNA re-ligation, causing DNA damage that triggers apoptosis (programmed cell death)[24].

Key Targets of Camptothecin:

Target	Actions	Organism
DNA topoisomerase 1	Inhibitor	Humans
Tumor necrosis factor ligand superfamily member 11	Antagonist	Humans

Sanguinaria canadensis (Bloodroot)

Family: Papaveraceae (Poppy family) .

Native Range: Eastern North .

ActiveCompounds: Benzylisoquinoline alkaloids, primarily sanguinarine .

Common Names: Bloodroot. **Uses**: Bloodroot extracts have been promoted for cancer treatments, though the U.S. FDA has cautioned against their use, citing products containing bloodroot as potential "fake cancer cures."

Mechanism of Action: **Sanguinarine**, the primary alkaloid in Bloodroot, induces apoptosis (programmed cell death) by targeting key cellular processes, including the NF-κB signaling pathway, which is critical for cancer cell survival and proliferation. Safety Concerns:Bloodroot products, particularly those ingested orally, are associated with the development of oral leukoplakia, a premalignant lesion that could potentially lead to oral cancer. Products like Viadent, which contained Bloodroot, were withdrawn from the North American[25].

Target	Actions	Organism
NF-κB signaling pathway	Inhibitor	Humans

Euphorbia peplus

Euphorbia peplus (Trivial Spurge, Radium Weed, Cancer Weed) Family: Euphorbiaceae . Common Names: Negligible Spurge, Radium Weed, Cancer Weed, Milkweed . Dynamic Compound: Ingenol mebutate Employments: Customarily as a cure for skin lesions,actinic keratosis (a precancerous skin condition). The plant's sap is harmful to quickly imitating tissue. Component of Action:Ingenol mebutate essentially causes cell rot taken after by neutrophil-mediated irritation and antibody-dependent cell passing of the remaining ailing cells.Early considers recommend it actuates PKC-delta and translocates it into the core and films, whereas downregulating PKC-alpha. This tweak actuates the Ras/Raf/MAPK and p38 pathways and hinders AKT/PKB signaling, which are included in cell survival and proliferation[26][27].

Key Targets of Ingenol mebutate:

Target	Actions	Organism
Protein kinase C delta type	Ligand	Humans

Target	Actions	Organism
Protein kinase C alpha type	Ligand	Humans

Various Mechanisms and Cell Receptors for Anticancer Activity of Plant Toxins

1. **General Mechanism for Receptor-Targeting Immunotoxin:**
   Ligand-Receptor Binding: Facilitates receptor-mediated endocytosis, allowing the toxin to enter cancer cells. Intracellular Action: Toxins like PE38 or diphtheria toxin inhibit critical cellular processes (e.g., protein synthesis), leading to cell death.Example: Targeting various cancers (e.g., leukemia) with plant toxins like vincristine from Catharanthus roseus[28].
2. **CCR9 and CCL25-PE38: Receptor**:
   CCR9 is overexpressed in several cancers, including breast, prostate, ovarian, and lung cancers. Toxin Construct: CCL25-PE38 fuses the ligand CCL25 to the toxin PE38, targeting CCR9-positive cells. Transport Mechanism: CCL25 binds to CCR9, facilitating internalization of the toxin. Effectiveness is limited if some tumor cells do not express CCR9.Example: T-cell acute lymphoblastic leukemia (T-ALL) treatment with CCL25-PE38 targeting CCR9[29].
3. **Eph Receptors: Receptors**: Ephrin receptors (e.g., Ephrin A2 and Ephrin A3) are tyrosine kinase receptors overexpressed in certain cancer. Targeting Strategy: Immunotoxins and antibody-drug conjugates deliver toxic agents specifically to cancer cells.Transport Mechanism: The receptor-ligand interaction promotes endocytosis of the toxin, leading to intracellular action.Example: Colorectal cancer treatment with Eph receptor-targeting immunotoxins, potentially incorporating sanguinarine from Sanguinaria canadensis[29].
4. **MSH Receptors: Targeting Strategy**:
   A fusion of melanocyte-stimulating hormone (MSH) with truncated diphtheria toxin or PE38 targets alpha-MSH receptors on melanoma cells. Transport Mechanism: MSH binding facilitates the internalization of the fusion protein, delivering the toxin into melanoma cells. Example: Melanoma treatment using MSH-PE38KDEL , potentially enhanced with plant toxins like calotropin from Calotropis gigantea.
5. **Additional Targets[30][34]: HER2/neu**: Overexpressed in breast and gastric cancers; targeted by trastuzumab and other therapies, where plant toxins can enhance effect . Example: HER2-positive breast cancer treatment with trastuzumab combined with toxins from Taxus spp. (e.g., paclitaxel) .

EGFR (Epidermal Growth Factor Receptor): Overexpressed in many cancers; targeted by immunotoxins like DAB389EGF[30]. Plant toxins, such as vinblastine and vincristine, enhance cytotoxic effects.Example: Breast and lung cancers treated with EGFR-targeting agents combined with vinblastine. CD22: Targeted by immunotoxins for treating hairy cell leukemia, often overexpressed in certain leukemias and lymphomas.Example: Hairy cell leukemia treatments using CD22-targeted immunotoxins with toxins from Euphorbia peplus.

PD-1/PD-L1 and CTLA-4: Immune checkpoint inhibitors that enhance T-cell responses; plant toxins may modify these to improve tumor-targeting. Example: Combination therapies for various cancers using PD-1 inhibitors enhanced with toxins[34] from Curcuma longa (curcumin).

Various method for using toxin as therapy. Various methods for using toxins as therapy focus on enhancing the targeting of cytotoxic drugs to minimize side effects. One approach involves functionalizing

nanoscale drug vehicles, which can achieve moderate targeting effects by taking advantage of enhanced permeability and retention (EPR) in tumors[35]. This reduces the risk of renal toxicity while increasing local drug concentrations. Immunotoxins represent another strategy, combining antibodies with plant toxins to selectively target cancer cells. For example, anti-CD22 [36]antibodies linked to toxins can be effective in treating hairy cell leukemia. Additionally, gene fusion technology enhances specificity by fusing toxins like gelonin with ligands that bind to specific cancer cell receptors, allowing for precise targeting of malignant tissues.

Toxin Based sucidal Gene Therapy :

Gene therapy, a method for delivering genetic material into target cells for therapeutic effects, includes innovative approaches like "suicide gene therapy." This strategy utilizes plasmids expressing toxins such as cytosolic saporin to selectively induce cell death in cancerous cells. Recent studies have tested two toxin-based plasmids, pGEL (gWIZ-gelonin) and pSAP (gWIZ-saporin), on various cancer cell lines (MDA-MB-435, U87MG, 9L, HeLa) using polyethylenimine (PEI) as a transfection agent. These studies demonstrated significant cytotoxic effects at a gene concentration as low as 2 µg/ml. However, a challenge arises from the non-selective delivery of these toxins, which can lead to high cytotoxicity in both cancerous and non-cancerous cells. To address this issue, researchers are exploring more selective delivery systems. For instance, a study by Sama et al. (2018) successfully used a nanoplex approach with peptide-directed delivery for a plasmid carrying the saporin gene, effectively targeting and killing neuroblastoma cells in vitro and in vivo when combined with the transfection agent sapofectosid. Additionally, recent work has shown the antitumoral activity of a plasmid linked to lipid-protamine DNA nanoparticles decorated with a peptide (U11) directed toward human urokinase, highlighting the potential for enhanced specificity in gene therapy[37][38].

Targeting Prostate Cancer :

Prostate cancer (PCA) is a prevalent cancer in men and a leading cause of cancer-related deaths. Prostate-specific antigen (PSA), a kallikrein protease produced by both normal and malignant prostate cells, is commonly used to guide targeted therapies. One innovative approach involves utilizing the PSA promoter to drive the expression of cytotoxic agents. For instance, plant-derived toxins like vinblastine and vincristine, extracted from Catharanthus roseus, can be explored for this purpose.Using adenoviral and lentiviral vectors to carry these plant toxins under the PSA promoter has shown promise in effectively inhibiting prostate tumor growth in mouse xenograft models, specifically targeting PSA-expressing tumors[40].

Nanoparticulate systems, such as those based on the cationic polymer C32, have been developed to deliver suicide genes encoding plant toxins under PSA promoters. This delivery mechanism induces apoptosis in prostate cells while sparing surrounding tissues in preclinical studies.Furthermore, advanced strategies utilizing dual expression control systems have increased the specificity of toxin expression. In these systems, a prostate-specific promoter-driven FLP recombinase triggers the expression of plant toxins, successfully eradicating PSA-expressing prostate cancer cells[41].

Targeting Ovarian Cancer :

Ovarian cancer is a leading cause of death among female reproductive cancers. Strategies to target ovarian tumors often leverage transcriptional regulation specific to ovarian cancer cells. For example, promoters

like those for human chorionic gonadotropin (hCG) and HE4 (WFDC2), which are overexpressed in ovarian cancer, can drive the expression of plant-derived toxins such as sanguinarine or vinblastine.Delivery of these toxin gene constructs via nanoparticulate systems has shown promising results in preclinical models, resulting in significant tumor suppression and prolonged survival compared to traditional chemotherapy.Recent advancements have also utilized the H19 gene promoter, which is highly expressed in ovarian tumors but minimally present in normal tissues, to specifically target these plant toxins to cancer cells. Clinical applications, such as intraperitoneal injections of toxin-linked plasmids, have demonstrated potential in addressing advanced ovarian cancer with minimal adverse effects. Ongoing clinical trials are currently assessing this targeted approach for the treatment of advanced ovarian cancer[41].

Targeting breast cancer :

Focusing on breast cancer : Podophyllotoxin is a plant subsidiary that has illustrated an antitumor impact on triple-negative breast cancer cells by restraining cell movement and intrusion and actuating apoptosis. The Quality Set Improvement Examination appeared that the expression of a few qualities frequently related with a destitute forecast in breast cancer (i.e., PLK1, CDC20, CDK1) in the cell cycle is repressed by directing P53 by podophyllotoxin in triple-negative breast cancer cells[42]

Cell Cycle Target Inhibition and Anti-Cancer Drug Discovery

Up until the early 1990s, the discovery of novel anti-tumor agents from natural sources primarily relied on testing for cytotoxic activity against cancer cell lines grown in vitro or in vivo. Many naturally derived anti-cancer agents discovered through such assays exert their cytotoxic effects by interacting with tubulin, thereby inhibiting various stages of the cell cycle. Notable agents include vinblastine, vincristine, colchicine, combretastatin, and maytansine, all of which target microtubule formation and interfere with cell division.

Mechanism of Action: These agents work by binding to tubulin, a crucial component of the microtubule network necessary for successful mitosis. Microtubules are essential for the separation of chromosomes during the metaphase-to-anaphase transition. When agents like vinblastine or vincristine bind to tubulin, they prevent the polymerization of microtubules, effectively arresting the cell in the M-phase of the cell cycle. This interruption in mitosis leads to cell death, particularly in rapidly dividing cancer cells.

Vinblastine and Vincristine: Derived from Catharanthus roseus (Madagascar periwinkle), these agents disrupt microtubule assembly, halting cancer cell proliferation[16]. They are widely used in treating Hodgkin's lymphoma, non-Hodgkin's lymphoma, and testicular cancer[43].

Colchicine: Traditionally used for gout, colchicine has been repurposed in cancer treatment due to its ability to bind to tubulin and inhibit microtubule polymerization. This mechanism is effective against some forms of breast cancer and lung cancer[43].

Combretastatin: Derived from the African willow tree, this agent depolymerizes microtubules, leading to the destruction of tumor vasculature, and is particularly effective in treating thyroid cancer and colorectal cancer[43].

Maytansine: Isolated from certain Ethiopian plants, maytansine inhibits microtubule dynamics, causing mitotic arrest and apoptosis. It has been used as a basis for antibody-drug conjugates (e.g., trastuzumab emtansine), which specifically target HER2-positive breast cancer[43].

Cell Cycle Process Inhibition :

The primary cell cycle process inhibited by these drugs is the M-phase, particularly during mitosis. During this phase, chromosomes align and separate to form two daughter cells. Disruption of the spindle apparatus, which is crucial for chromosome segregation, leads to cell arrest in the mitotic phase. This inability to complete mitosis ultimately results in apoptotic cell death, as the cell cannot properly divide and maintain its function. Drugs like vinblastine and vincristine prevent microtubule formation, thereby disrupting the spindle apparatus[43]. This interference halts cell progression through mitosis, ensuring that rapidly dividing cancer cells are effectively targeted and eliminated. As a result, these agents play a vital role in cancer therapy by exploiting the unique characteristics of cancer cell division.

Toxin Entry: Retrograde Transport through the Secretory Pathway :

The synthesis, transport, and secretion of proteins in eukaryotic cells follow a well-characterized pathway that various plant toxins exploit to exert their effects. Protein synthesis begins on free ribosomes in the cytosol and continues as ribosomes attach to the endoplasmic reticulum (ER). Newly formed polypeptides enter the ER lumen through cotranslational translocation. Within the ER, proteins undergo modifications and proper folding with the assistance of resident chaperones, ensuring they achieve biological functionality before progressing further.

These proteins are then transported from the ER to the Golgi apparatus and subsequently to the trans-Golgi network (TGN), which sorts them for export via secretory vesicles. These vesicles transport proteins to the plasma membrane for secretion. This entire secretory process, elucidated by George Palade and colleagues, involves vesicular budding and fusion at each transport stage. Interestingly, plant toxins like ricin exploit this secretory pathway in reverse. Ricin is internalized by cells through endocytosis and traffics back to the ER from the cell surface, following a retrograde transport route. Once in the ER, ricin evades normal secretory mechanisms and crosses the ER membrane into the cytosol, where it inhibits ribosome function, leading to cell death. Ricin's ability to hijack the cell's transport systems is facilitated by a sequence similar to the KDEL retrieval signal, which allows it to move from the Golgi back to the ER. This pathway, typically responsible for rescuing mislocalized ER proteins, becomes the route for ricin's entry into the cytosol. In this manner, plant toxins like ricin exploit eukaryotic protein transport systems to reach their cytosolic targets and disrupt cellular functions[44][45][46].

Cell surface

Plant toxins, such as ricin, employ sophisticated methods to enter cells and induce cytotoxic effects by leveraging cellular endocytosis pathways. Unlike some bacterial toxins that rely solely on clathrin-mediated endocytosis, plant toxins can utilize multiple endocytic pathways for cell entry. Ricin, for example, can enter cells through both clathrin-dependent and clathrin-independent mechanisms, allowing it to evade cellular defenses effectively. While dynamin mutations can block clathrin-mediated endocytosis and protect against toxins like diphtheria toxin (DT), ricin remains effective due to its ability to bypass this pathway and exploit alternative routes[47].

Once inside the cell, ricin follows a retrograde transport route, progressing from early endosomes to the trans-Golgi network (TGN) and eventually reaching the endoplasmic reticulum (ER). Unlike diphtheria toxin, which translocates directly into the cytosol from the endosome, ricin takes a more complex journey to the ER, where it exploits the protein retrotranslocation machinery. This mechanism allows the ricin A chain to enter the cytosol, where it irreversibly inactivates ribosomes by depurinating a specific adenine

residue in the 28S rRNA. This action inhibits protein synthesis, ultimately leading to cell death.Importantly, plant toxins like ricin do not rely on the acidic environment of endosomes for cytosolic entry, which differentiates them from bacterial toxins sensitive to pH changes. This characteristic enhances their potency, as they can bypass mechanisms that typically protect cells from such toxins. Ricin's ability to evade multiple cellular defense mechanisms underscores the sophisticated strategies plant toxins employ to achieve their lethal effects[47].

Intracellular Transport of Plant Toxins Beyond Endosomes

Ricin, a potent plant toxin, follows a complex intracellular trafficking route after endocytosis, moving beyond the endosomal compartment. Early electron microscopy studies revealed that ricin, besides entering lysosomes or being recycled to the cell surface, accumulates in the trans-Golgi network (TGN). This suggested that ricin A chain translocates into the cytosol from the TGN. However, subsequent studies showed that the critical step for ricin's cytotoxicity occurs when the toxin is transported further to the endoplasmic reticulum (ER). The extreme potency of ricin means that even small amounts entering the cytosol can be lethal to the cell, making it challenging to track the full route of this translocation[48].

Studies using brefeldin A (BFA), which disrupts the Golgi apparatus, provided key insights into ricin trafficking. BFA treatment protects cells from toxins like ricin and Pseudomonas exotoxin (PE) by disrupting their retrograde transport to the ER, without affecting the transport of diphtheria toxin (DT), which translocates directly from endosomes. Importantly, ricin's transport to the TGN is unaffected by BFA, but BFA-induced Golgi disassembly blocks its further transport, preventing the toxin from reaching the ER, where it would normally translocate into the cytosol. Retrograde transport from the TGN to the ER is crucial for toxins like ricin, and is typically facilitated by interaction with recycling cellular components. Ricin's B chain contains galactose-binding sites that allow it to bind to galactosylated surface components and potentially exploit recycling glycoproteins for transport. Additionally, ricin's glycosylation allows it to bind to mannose receptors, such as those on macrophages, further facilitating its retrograde transport. If the B chain's sugar-binding sites are inactivated, ricin loses its cytotoxicity, emphasizing the importance of these interactions for intracellular trafficking.Unlike bacterial toxins that rely on KDEL sequences to interact with the KDEL receptor and facilitate retrograde transport to the ER, ricin lacks this sequence. However, ricin's B chain galactose-binding properties likely enable it to hitchhike on other recycling components that carry KDEL or similar signals, allowing it to reach the ER. Once in the ER, ricin's A chain is retrotranslocated into the cytosol, where it inhibits protein synthesis by depurinating the 28S rRNA, leading to cell death[48].

Conclusion:

The convergence of advancements in computational technology, biological sciences, and chemistry heralds a transformative era in drug discovery, particularly in the realm of cancer therapeutics. With the intricate understanding of genomic and proteomic landscapes, researchers are now poised to design in silico drug candidates utilizing plant-derived toxins. For instance, the utilization of vinblastine and vincristine, isolated from Catharanthus roseus, exemplifies how computational models can predict and enhance the cytotoxic efficacy of these alkaloids against a myriad of malignancies, from leukemias to solid tumors. Moreover, the application of machine learning algorithms to predict the interactions of phytochemicals, such as curcumin from Curcuma longa, with key molecular targets opens new avenues for tailored therapies. This digital approach allows for the screening of vast chemical libraries against spe-

cific cancer pathways, significantly expediting the identification of potent candidates.
Innovations in drug delivery systems, guided by insights into cellular transport mechanisms, further augment the therapeutic potential of these compounds. By employing nanoparticles or liposomes to encapsulate and deliver plant toxins like podophyllotoxin from Podophyllum peltatum, researchers can enhance bioavailability while minimizing off-target effects.As we harness the power of in silico methodologies alongside traditional pharmacognosy .

Reference:

1. S. Singh, R. Jarial, S.S. Kanwar Therapeutic effect of herbal medicines on obesity: herbal pancreatic lipase inhibitors , Wudpecker J Med Plants, 2 (2013), pp. 53-65
2. D. Schottenfeld, J.F. Fraumeni Jr. Cancer Epidemiology and Prevention Oxford University Press (2006)
3. https://www.uicc.org/news/globocan-2020-global-cancer-data.
4. Sharma V., Sarkar I.N. Bioinformatics opportunities for identification and study of medicinal plants. Brief. Bioinform. 2013;14:238–250. [PMC free article].
5. Cui Z.J., Gao M., Quan Y., Lv B.M., Tong X.Y., Dai T.F., Zhou X.H., Zhang H.Y. Systems Pharmacology-Based Precision Therapy and Drug Combination Discovery for Breast Cancer. Cancers. 2021;. [PMC free article] [PubMed].
6. World Health Organization . 12 sep 2018 . retrived 19 dec 2018.
7. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. (September 2008). "Cancer is a preventable disease that requires major lifestyle changes".
8. "Oncogenes." Kimball's Biology Pages, archived on 31 Dec. 2017, Wayback Machine. Accessed 4 Oct. 2024, World Cancer Report 2014. World Health Organization. 2014.
9. World Cancer Report 2014. World Health Organization. 2014.
10. National Cancer Institute. 17 September 2007. Retrieved 10 June 2014.
11. S. Singh, R. Jarial, S.S. Kanwar.
12. Therapeutic effect of herbal medicines on obesity: herbal pancreatic lipase inhibitors , Wudpecker J Med Plants, 2 (2013), pp. 53-65.
13. B.A. Weaver , How taxol/paclitaxel kills cancer cells Mol Biol Cell, 25 (18) (2014), pp. 2677-2681.
14. Reference : T.N. Aung, Z. Qu, R.D. Kortschak, D.L. Adelson Understanding the effectiveness of natural compound mixtures in cancer through their molecular mode of action Int J Mol Sci, 18 (3) (2017), p. 656.
15. www.drugbank.com
16. P. Thakore, R.K. Mani, S.J. Kavitha , A brief review of plants having anti-cancer property , Int J Pharm Res Dev, 3 (2012), pp. 129-136.
17. Germplasm Resources Information Network. Agricultural Research Service, United States Department of Agriculture. Retrieved 4 August 2019.
18. Plants of the World Online. Royal Botanic Gardens, Kew. 2023. Retrieved 29 August 2023.
19. M.S. Darshan, M.S. Loftu, M. Thadani Mulero, B.P. Levy, D. Escuin, X.K. Zhou, et al. Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer . Cancer Res, 71 (2011), pp. 6019-6029.
20. Wang CY, Mayo MW, Baldwin AS Jr. : TNF- and cancer therapy-induced apoptosis: potentiation by inhibition of NF-kappaB.

21. Goel A, Kunnumakkara AB, Aggarwal BB : Curcumin as "Curecumin": From kitchen to clinic. Biochem Pharmacol 75: 787-809, 2008.
22. Hartwell J.L., Schrecker A.W. Components of Podophyllin. V. The Constitution of Podophyllotoxin. J. Am. Chem. Soc. 1951;73:2909–2916. doi: 10.1021/ja01150a143.
23. Ardalani H., Avan A., Ghayour-Mobarhan M. Podophyllotoxin: A novel potential natural anticancer agent. Avicenna J. Phytomed. 2017;7:285–294.
24. S.H. Kim, J.A. Kaplan, Y. Sun, A. Shieh, H.L. Sun, C.M. Croce, et al.
25. The self-assembly of anticancer camptothecin–dipeptide nanotubes: a minimalistic and high drug loading approach to increased efficacy.
26. Don't Use Corrosive Cancer Salves (Escharotics) Stephen Barrett, M.D .
27. Hazel Dempster; Bronwen Keighery; Greg Keighery; Rod Randall; Bob Dixon; Bill Betts; Margo O'Byrne; Diane Matthews. "Euphorbia terracina Workshop Proceedings 2000" (PDF). Archived from the original (PDF) on 2009-10-25.
28. Braun, S.A.; Homey, B.; Gerber, P.A. (October 2014). "Erfolgreiche Behandlung eines Morbus Bowen mit Ingenolmebutat". Der Hautarzt (in German).
29. Valdivia-Silva JE, Franco-Barraza J, Silva AL, Pont GD, Soldevila G, Meza I, et al. Effect of pro-inflammatory cytokine stimulation on human breast cancer: implications of chemokine receptor expression in cancer metastasis.
30. Kwon A., John M., Ruan Z., Kannan N. Coupled regulation by the juxtamembrane and sterile α motif (SAM) linker is a hallmark of ephrin tyrosine kinase evolution. J. Biol. Chem. 2018;293:5102–5116.
31. Capone E., Giansanti F., Ponziani S., Lamolinara A., Iezzi M., Cimini A., Angelucci F., Sorda R., Laurenzi V., Natali P.G., et al. EV20-Sap, a novel anti-HER-3 antibody-drug conjugate, displays promising antitumor activity in melanoma.
32. Natural Products Structural Diversity-II Secondary Metabolites: Sources, Structures and Chemical Biology.
33. Bioactive compounds of Calotropis gigantea for cancer treatment Author links open overlay panelJayalekshmi C, Nishanth Mohan Das, Rajiv Periakaruppan.**Tatro J.B., Wen Z., Entwistle M.L., Atkins M.B., Smith T.J., Reichlin S., Murphy J.R. Interaction of an alpha-melanocyte-stimulating hormone-diphtheria toxin fusion protein with melanotropin receptors in human melanoma metastases.**
34. Targeting Receptors on Cancer Cells with Protein Toxins Antonella Antignani,* Eric Chun Hei Ho, Maria Teresa Bilotta, Rong Qiu, Robert Sarnvosky, and David J. FitzGerald
35. Menestrina G., Schiavo G., Montecucco C. Molecular mechanisms of action of bacterial protein toxins. Mol. Aspect. Med. 1994.
36. Moolten F.L. Drug sensitivity ("suicide") genes for selective cancer chemotherapy.
37. Toxin-Based Therapeutic Approaches Assaf Shapira and Itai Benhar.
38. Cho K.R., Shih Ie M. Ovarian cancer. Annu Rev Pathol.
39. Lilja H. A kallikrein-like serine protease in prostatic fluid cleaves the predominant seminal vesicle protein. J. Clin. Invest.
40. Peng W., Chen J., Huang Y.H., Sawicki J.A. Tightly-regulated suicide gene expression kills PSA-expressing prostate tumor cells. Gene Ther. 2005;12:1573–1580.
41. Munagala R, Aqil F, Gupta RC. Promising molecular targeted therapies in breast cancer.
42. www.drugbank.com.

43. Simpson, J.C., D.C. Smith, L.M. Roberts, and J.M. Lord. 1998. Expression of mutant dynamin protects cells against diphtheria toxin but not against ricin.
44. Toxin Entry: Retrograde Transport through the Secretory Pathway J. Michael Lord and Lynne M. Roberts.
45. Pelham HRB. Control of protein exit from the endoplasmic reticulum. Annu Rev Cell Biol. 1989;5:1–23.
46. Wishart D.S. Current Protocol Bio-informatics. Introduction to Chem-informatics. Volume 14. John Wiley & Sons; Edmonton, AB, Canada: 2007. pp. 1–9.
47. Argent RH, Roberts LM, Wales R, Robertus JD, Lord JM. Introduction of a disulfide bond into ricin A chain decreases the cytotoxicity of the ricin holotoxin. J Biol Chem.
48. Yoshida T, Chen C, Zhang M, Wu HC. Disruption of the Golgi apparatus by brefeldin A inhibits the cytotoxicity of ricin, modeccin, and Pseudomonastoxin. Exp Cell Res. 1991;192:389–395.