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Recent Advances in Anticancer Agents from Natural and Synthetic Sources

Meet Agrawal

Student

UG Scholar, Sigma Institute Of Pharmacy, Bakrol , Ajwa Road, Vadodara, Gujrat, India

Abstract :-

Cancer continues to be one of the top leading causes of death globally, and therefore ongoing work in discovering and developing effective therapeutics is warranted. For many decades, natural and synthetic sources have significantly influenced anticancer drug development. Natural products from plants, marine organisms, and microbes have all greatly aided chemotherapy with different chemical structures and mechanisms of action. Synthetic chemistry and drug design have allowed for the creation of targeted agents and combination therapies with improved efficacy and safety. The aim of the review is to cover recent developments for anticancer agents based on natural products and synthetic agents. We will cover some key plant chemicals (curcumin, paclitaxel, and vinca alkaloids) along with some synthetic agents that include tyrosine kinase inhibitors and monoclonal antibodies. Emerging trends will include hybrid drugs, metal-based complexes, and advanced drug delivery systems such as nanoparticles and liposomes. Also discussed are challenges of multidrug resistance, toxicity, and poor bioavailability as well as future perspectives in the fields of artificial intelligence, nanotechnology, and personalized medicine. Combining knowledge of natural and synthetic medicinal products is an attempt to understand where we are now in anticancer therapeutics and possible future directions as there is a time when the various disciplines of medicinal compounds must come together.

Keywords :- Anticancer agents, natural compounds, synthetic drugs, targeted therapy, drug delivery, chemotherapy, cancer treatment.

1. Introduction : -

Cancer presents a significant public health challenge and is still one of the leading causes of death worldwide. According to the World Health Organization (WHO), cancer represented almost 10 million deaths in 2020. Despite noteworthy advances in diagnosis and treatment, cancer represents an important challenge due to factors such as drug resistance, tumor heterogeneity, toxicities of chemotherapeutic agents, and not responding well to treatment in patients with advanced cancers. The development of anticancer agents remains a dynamic and multidisciplinary field of study, and research groups are in a continuous state of exploration of both natural and synthetic substances to acquire new therapies. Considerable research has demonstrated efficacy of natural sources including medicinal plants, marine organisms and products from microbial-metabolites to provide cancer drugs which have included paclitaxel, camptothecin, and vincristine as some of the more potent anticancer agents. Even if the anticancer drugs are targeted compounds that can demonstrate multiple cellular targets, they also represent valuable leads in the drug discovery process. In parallel, growth of synthetic chemistry, development of structure-activity relationships (SAR), and advances in molecular modelling allows researchers to design and optimize for more selective and high-potency anti-cancer agents. More recently, the field of oncology was still evolving with targeted therapies which include tyrosine kinase inhibitors and

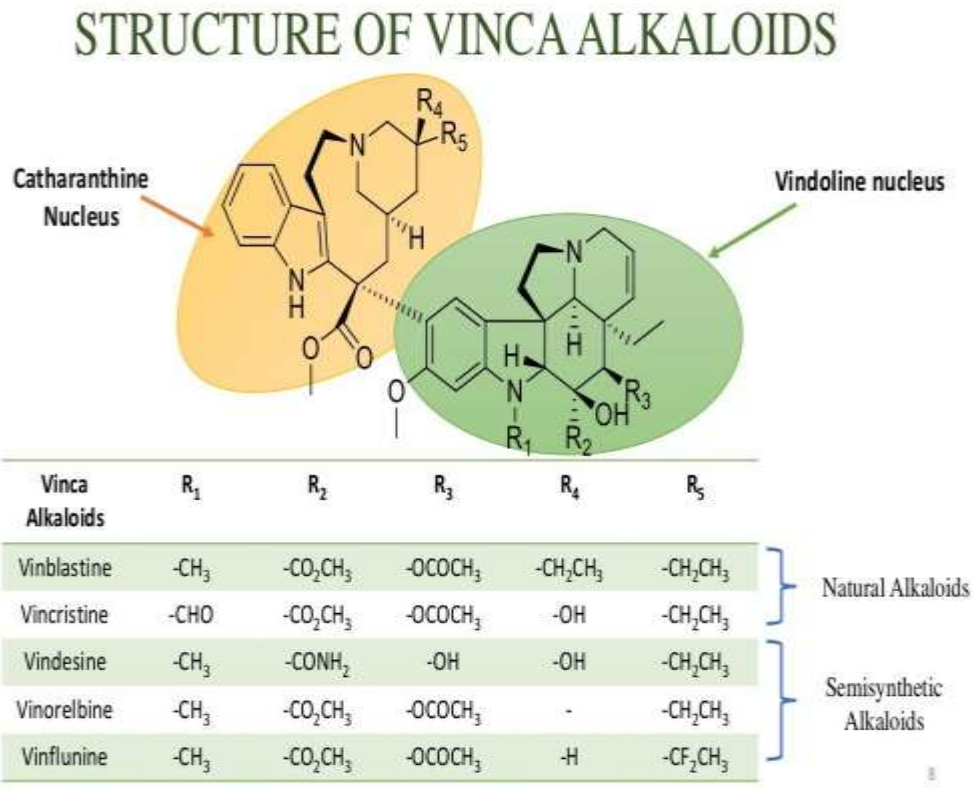
monoclonal antibodies, and aims to attack cancer specific targets while minimizing damage selectively to normal cells. In this review, we provide a detailed survey of recent advances in anticancer agents from natural and synthetic origins, considering their mechanisms of action, structural diversity, and clinical relevance. We also provide commentary on contemporary drug delivery strategies, recent technological advances, and future opportunities that could determine the next generation of anticancer therapeutics.

2. Natural Anticancer Agents : -

Natural products have provided abundant anticancer agents for many years. Natural products, including plants, marine organisms, and microbes, often have structures and mechanisms of action that are distinctly different than synthetic drugs. Several chemotherapeutic agents in current use were isolated from nature and have led to numerous semi-synthetic and synthetic analogues .

2.1 Plant-Derived Anticancer Agents : -

- **Vinca Alkaloids**



Vinca Alkaloids	R_1	R_2	R_3	R_4	R_5	
Vinblastine	$-CH_3$	$-CO_2CH_3$	$-OCOCH_3$	$-CH_2CH_3$	$-CH_2CH_3$	Natural Alkaloids
Vincristine	-CHO	$-CO_2CH_3$	$-OCOCH_3$	-OH	$-CH_2CH_3$	
Vindesine	$-CH_3$	$-CONH_2$	-OH	-OH	$-CH_2CH_3$	Semisynthetic Alkaloids
Vinorelbine	$-CH_3$	$-CO_2CH_3$	$-OCOCH_3$	-	$-CH_2CH_3$	
Vinflunine	$-CH_3$	$-CO_2CH_3$	$-OCOCH_3$	-H	$-CF_2CH_3$	

Fig 1 : Structure Of Vinca Alkaloids

Vinca alkaloids (vincristine, vinblastine, etc) are from Catharanthus roseus (Madagascan periwinkle) and they interfere with microtubule formation inhibiting mitosis in cancer cells. They are frequently used in leukemias, lymphomas, and breast cancer

- **Taxanes**

Fig 2 : Structure of Taxanes

Paclitaxel was first obtained from the bark of Taxus brevifolia (the pacific yew tree). Paclitaxel stabilizes microtubules inhibiting cell division. It is useful against breast, ovarian, and lung cancers .

- **Camptothecins**

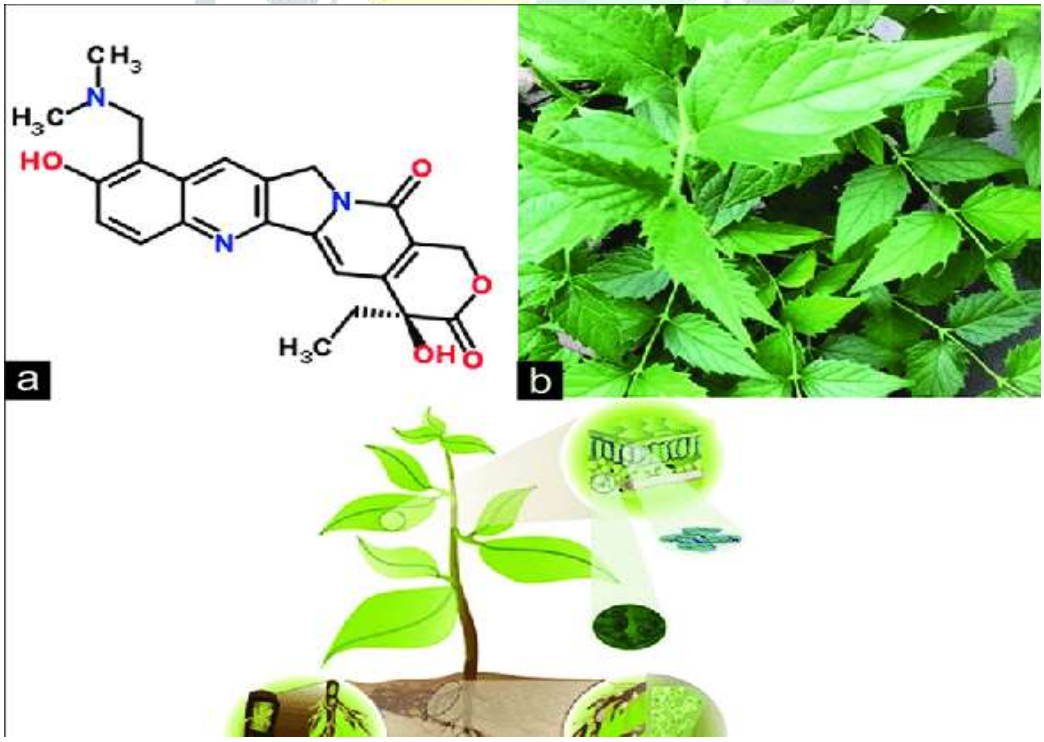


Fig 3 : Structure of Camptothecins

Topotecan and irinotecan are derived from Camptotheca acuminata. Camptothecins inhibit topoisomerase I causing DNA damage or cell death in rapidly dividing cells.

- **Polyphenols and Alkaloids**

Fig 4 : Structure of Polyphenols

Diverse compounds such as curcumin (from turmeric), resveratrol (from grapes), berberine (from species of Berberis) exhibit strong antioxidant and pro-apoptotic activity in preclinical work. These compounds have demonstrated potential for cancer chemoprevention and can be utilized as combinations of existing therapies.

2.2 Marine-Derived Anticancer Agents :-

The marine environment holds a wealth of structurally novel bioactive agents .

- **Trabectedin**

Trabectedin is found in Ecteinascidia turbinata, a marine tunicate. This newly-derived agent binds to DNA in the minor groove and disrupts transcription. Trabectedin is approved for use in soft tissue sarcoma and ovarian cancer.

- **Plitidepsin**

Plitidepsin is derived from Aplidium albicans, a marine organism. Plitidepsin is able to target eEF1A2 (a protein required for tumor survival) and has been shown to be active in multiple myeloma.

- **Salinosporamide A**

Salinosporamide A comes from a marine actinomycete called Salinispora tropica. This proteosome inhibitor in biology is highly potent as an anticancer agent and is currently in clinical trials for a multitude of cancers.

2.3 Metabolites from Microorganisms :-

Microorganisms, especially actinomycetes, have been shown to generate a variety of anticancer antibiotics .

- **Actinomycins**

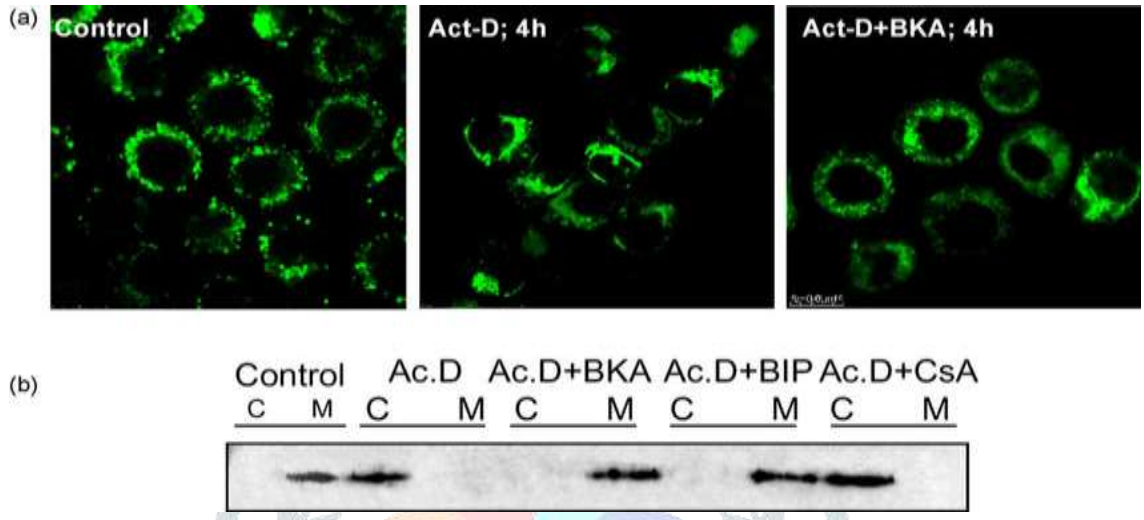


Fig 5 : Structure of Actinomycin - D

Actinomycin D intercalates one base pair of DNA and inhibits RNA synthesis. This drug has been utilized primarily in pediatric malignancies such as Wilms' tumor.

- **Anthracyclines**

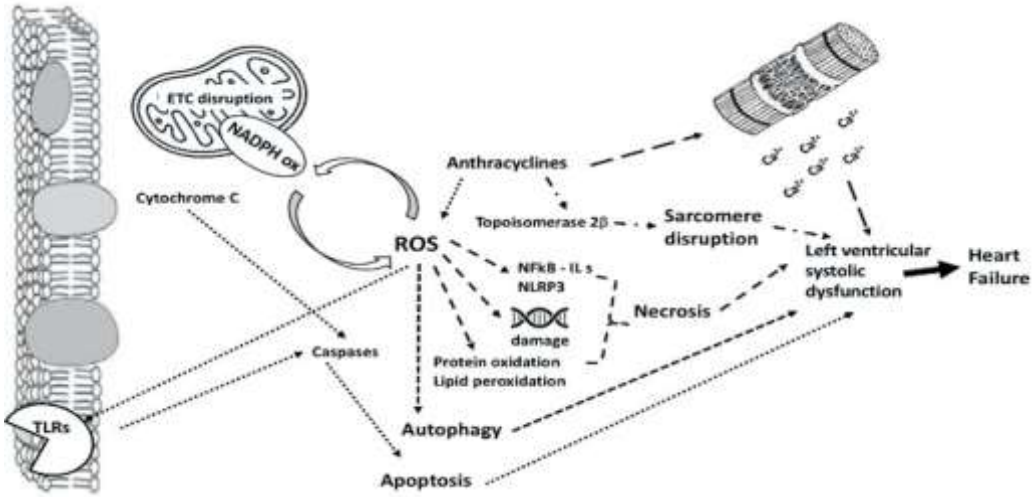


Fig 6 : Induced Cardiac Dysfunction

Doxorubicin and daunorubicin are agents isolated from Streptomyces and are powerful drugs that intercalate DNA and generate free radicals to induce apoptosis.

- **Mitomycins**
- Mitomycin C is a bioreductive alkylating agent obtained from Streptomyces caespitosus that cross-links DNA and is utilized in the treatment of gastrointestinal malignancies and bladder cancer.

3. Synthetic Anti Cancer Agents :-

Synthetic anticancer drugs have dramatically changed cancer therapy by providing custom compounds with enhanced potency, selectivity, and reduced toxicity profile. The agents can be traditional cytotoxic drugs or advanced targeted therapy and new molecular constructs.

3.1 Traditional Chemotherapeutic Agents :-

- **Alkylating Agents**

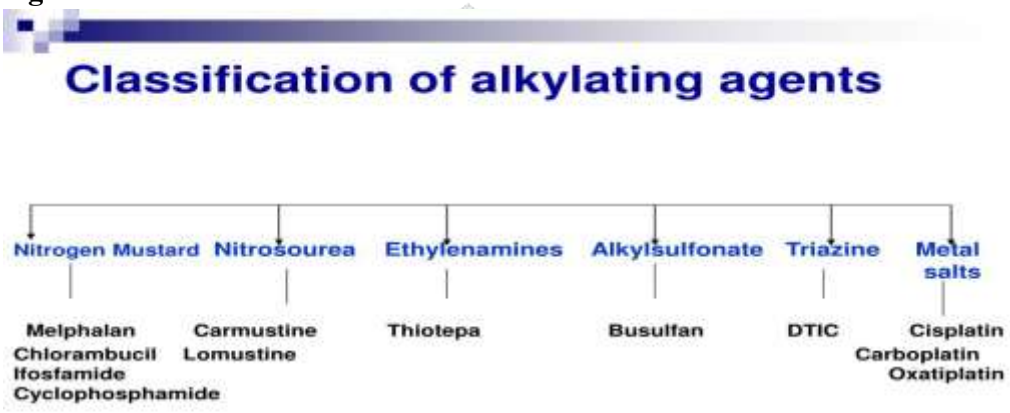


Fig 6 : Classification of alkylating agents

These materials bind covalently with DNA causing cross-linking as well as disrupting replication and transcription. Some common alkylating agents include:

- Cyclophosphamide

- Ifosfamide

-

Chlorambucil

Fig 7 : Effective against

- Antimetabolites

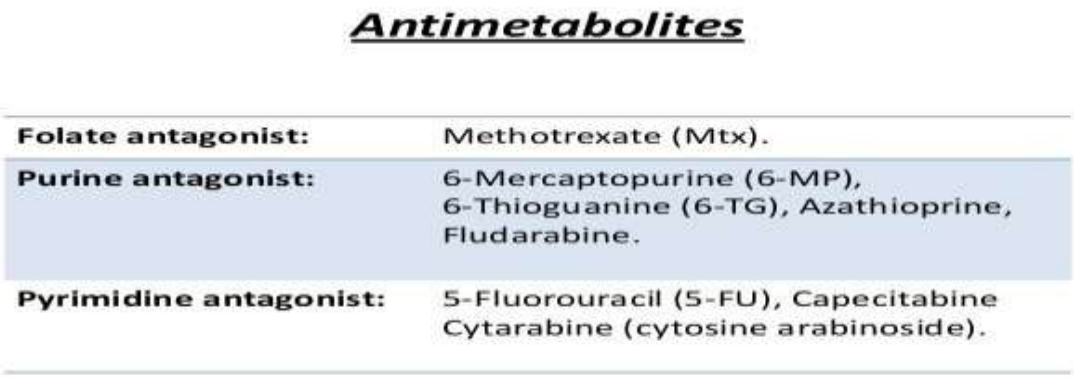


Fig 8 : Antimetabolites antagonist

These agents are structurally similar to natural metabolites and inhibit nucleotide synthesis and block DNA/RNA synthesis. Common antimetabolite drugs include:

- 5-Fluorouracil (5-FU)

- Methotrexate

- Cytarabine

- **Topoisomerase inhibitors**

Compound	Target	Company	State	Condition
BNP-1350	Top I	Biomunerik	Phase III	ovarian cancer, non-small cell lung cancer, brain cancer, melanoma
Gepotidacin	Top II	GlaxoSmithKline	Phase III	urinary tract infection, gonorrhea, bacterial infection, respiratory infection
Aldoxorubicin	Top II	Bristol-Myers Squibb	Phase III	sarcoma, pancreatic cancer, colorectal cancer, triple negative breast tumors
TNP-2092	Top I, Top II	Tennor Therapeutics	Phase II	hepatic encephalopathy, hyperammonemia, gastric cancer, gastric ulcer, gastritis
PEN-866	Top I	Madrigal Pharmaceuticals	Phase II	squamous cell carcinoma, esophageal cancer, adenocarcinoma, small cell lung cancer, astrocytoma, pancreatic cancer, endometrial cancer
EP-0057	Top I	Ellipses Pharma	Phase II	ovarian cancer
U3-1402	Top I	Daiichi Sankyo	Phase II	non-small cell lung cancer, colorectal cancer, breast cancer

Fig 9 : Table of topoisomerase inhibitors

Interfere with DNA unwinding during replication:

- Etoposide (Topoisomerase II inhibitor)

- Topotecan (Topoisomerase I inhibitor)

3.2 Targeted therapies :-

These therapies act directly on specific molecular targets that are involved in the progression of the cancer, and they minimize harm to normal cells.

Tyrosine Kinase Inhibitors (TKIs): These block signal transduction pathways that mediate cell proliferation. Examples include :

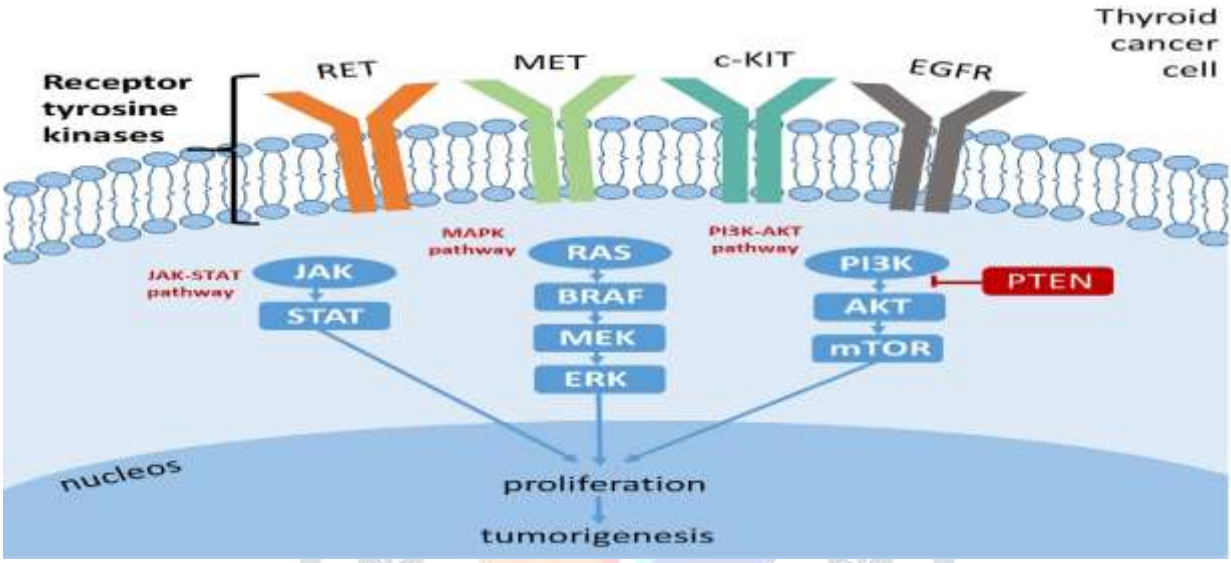


Fig 10 : Tyrosine Kinase Inhibitors

- Imatinib (used in chronic myeloid leukemia);
- Gefitinib or Erlotinib (both of which target the EGFR in lung cancer).

Monoclonal antibodies (mAbs): These agents are designed to bind specific antigens on cancer cells. Some well-known examples are:

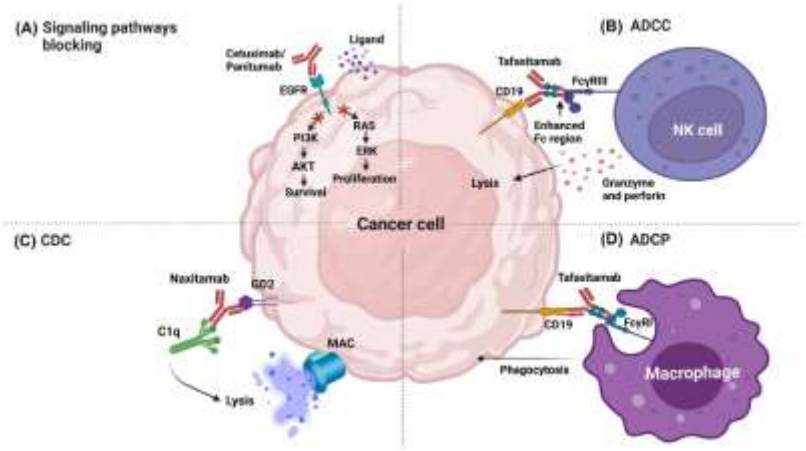


Fig 11 : mAbs

- Trastuzumab (used in HER2-positive breast cancer);
- Rituximab (used in CD20-positive B-cell lymphoma);
- Bevacizumab (this agent targets VEGF for anti-angiogenesis);

Hormonal therapies : These are primarily used in breast and prostate cancers. Some examples of hormonal therapies include:

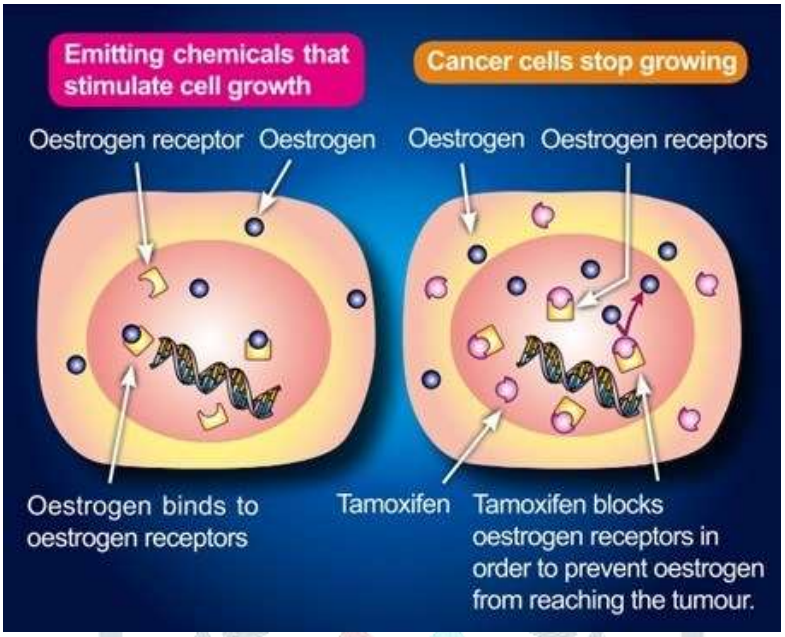


Fig 12 : Hormonal Therapies

- Tamoxifen (a selective estrogen receptor modulator).
- Flutamide (an androgen receptor antagonist).

3.3 Recent Developments and Synthetic Innovations : -

- **Hybrid Compounds**

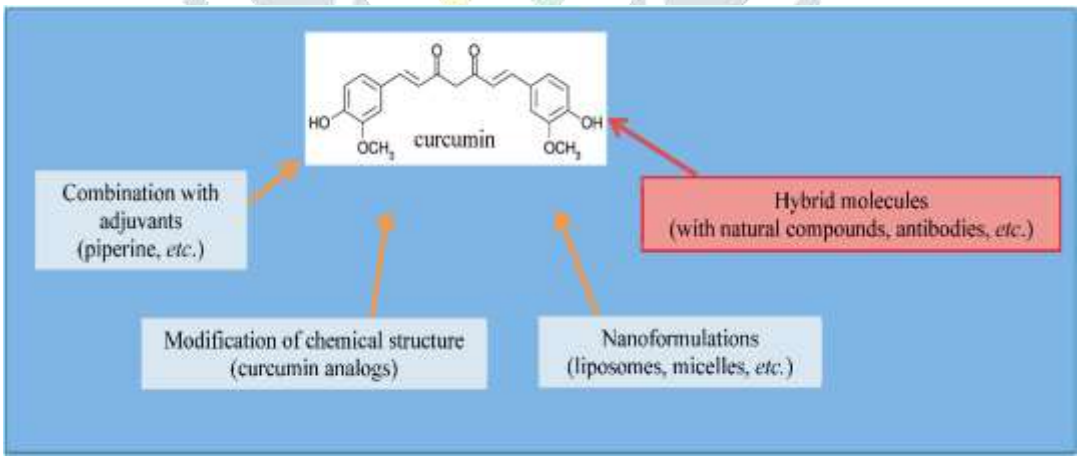


Fig 13 : Hybrid molecules used

Hybrid molecules were constructed by linking together natural and synthetic pharmacophores in a way that enhances bioavailability and reduces toxicity. One example of a hybrid would include hybrid analogs of curcumin which had better anticancer activity.

- **Metal Complexes**

Transition metal complexes were developed and show some potential, including cisplatin, carboplatin, and other new agents that are based on ruthenium or gallium that have activity in resistant tumors.

- **PROTACs (Proteolysis Targeting Chimeras)**

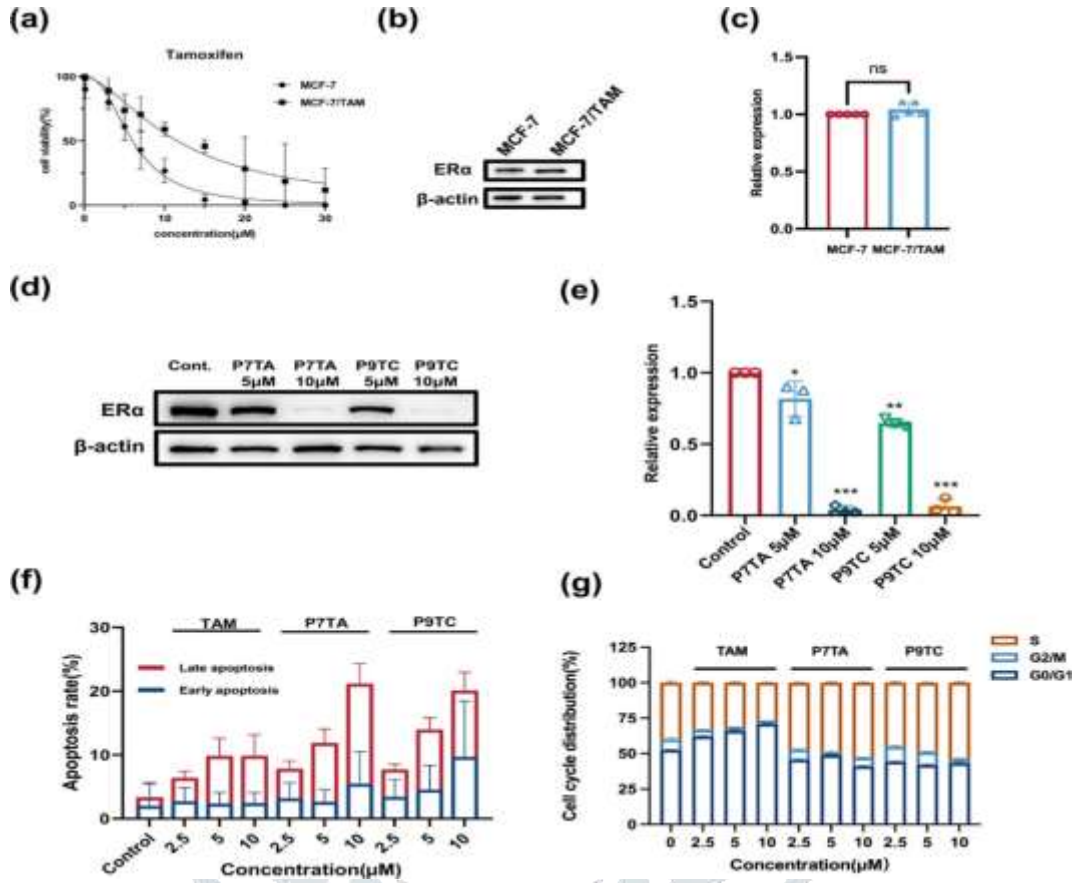


Fig 14 : Proteolysis Aptamer

PROTACs are bifunctional molecules that promote selective degradation of proteins implicated in cancer. PROTACs are emerging technologies with great possibility for personalized cancer therapy.

4. Novel Drug Delivery Systems :-

Fig 15 : NDDS in cancer

One of the exceptions being the wide range and distribution of drugs, especially in non-cancerous cells, causing systemic toxicity and a limited therapeutic index. Novel drug delivery systems (NDDS) will enhance therapeutic targeting, reduce adverse effects, and improve drug stability and bioavailability. It may also enhance the delivery of non-water soluble natural products and sophisticated synthetic agents.

4.1 Liposomes :-

Liposomes are spherical vesicles made from lipid bilayers, and can encapsulate hydrophilic and lipophilic drugs.

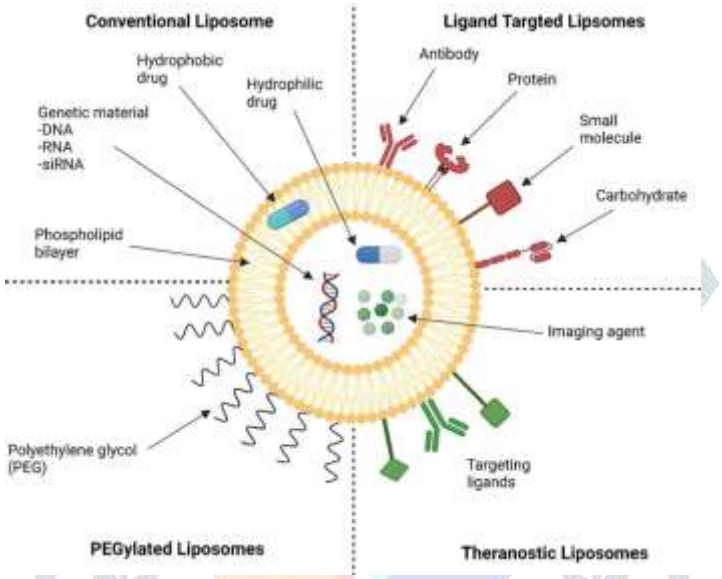


Fig 16 : Liposomes

- Example: Doxil (liposomal doxorubicin) - increases circulation time and reduces cardiotoxicity.
- Indicated for breast cancer, Kaposi's sarcoma and ovarian cancer.

4.2 Nanoparticles :-

Nanoparticles (NPs) provide targeted and controlled release of anticancer drugs by utilizing the enhanced permeability and retention (EPR) effect observed in Tumors.

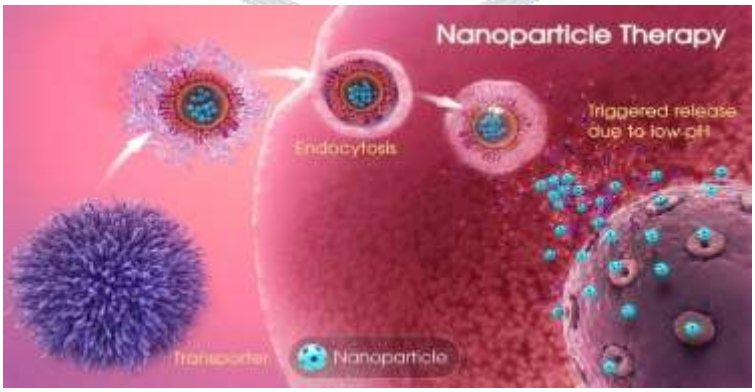


Fig 17 : Nanoparticles

- Types: Polymeric NPs, solid lipid NPs, metallic NPs (e.g., gold, silver).
- Applications: delivery of paclitaxel, curcumin and other poorly water-soluble drugs.

Through functionalization with receptors, nanoparticles can facilitate active targeting of Tumor receptors.

4.3 Antibody-Drug Conjugates (ADCs) :-

ADCs are molecules made up of a monoclonal antibody connected to a cytotoxic agent.

- For example: Brentuximab vedotin -- targets CD30 in Hodgkin’s lymphoma.

ADCs provide the targeting specificity of antibodies combined with the potent effect of chemotherapeutics.

4.4 Polymeric Micelles and Hydrogels :-

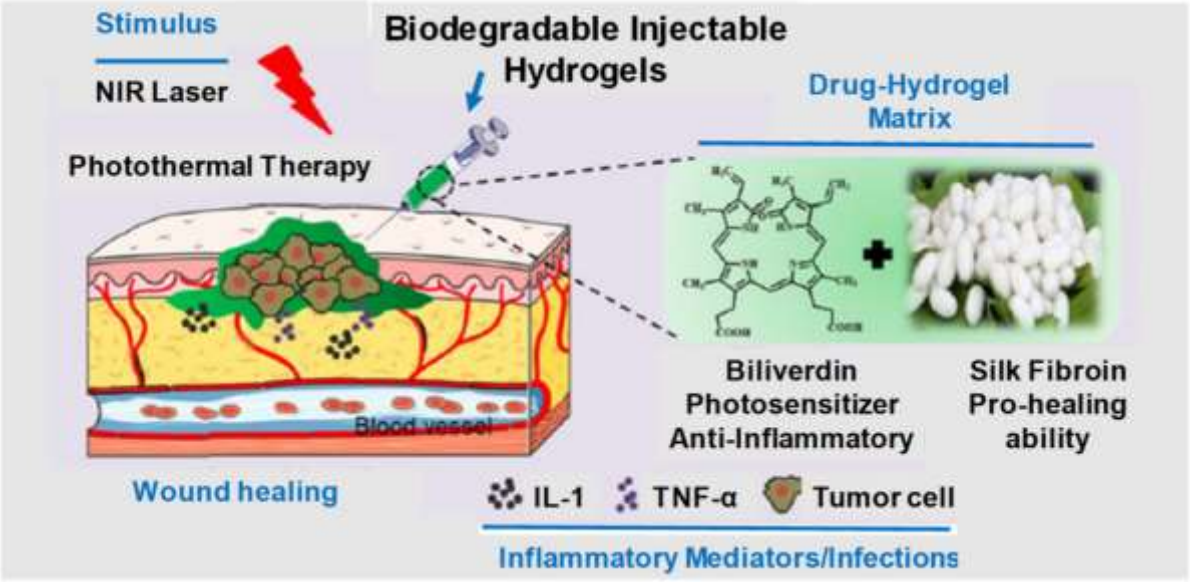


Fig 18 : Injectable hydrogels

- **Micelles:** Used for solubilizing hydrophobic drugs like docetaxel.
- **Hydrogels:** Enable localized delivery and sustained drug release at Tumor sites.

4.5 Natural Product-Loaded Delivery Systems :-

Formulating natural agents such as **curcumin**, **resveratrol**, and **berberine** into nanoparticles, liposomes, or micelles enhances their stability, bioavailability, and anticancer efficacy.

4.6 Intelligent Delivery Systems :-

Stimulation-responsive systems (smart delivery systems) , (pH, temperature, and enzyme-activated) can control drug release through the tumor microenvironment. The use of magnetic nanoparticles and ultrasound responsive systems also offer interesting potential for targeting therapy.

5. Challenges and Future Prospects :-

Despite the significant advancements in the development of anticancer agents, several critical challenges remain. Addressing these challenges is essential to enhance the clinical success of both natural and synthetic therapeutics.

5.1 Major Concerns :-

• Multidrug Resistance (MDR)

Cancer cells often cause resistance through the action of efflux pumps (such as P-glycoprotein) causing the target of the drug to change in a way that the drug may no longer bind or be effective or the more extreme cases where cancer cells develop mechanisms to repair DNA that has been damaged by the drug causing it to become ineffective.

• Toxicity and Side effects

Many of the cytotoxic agents lacks specificity, when taken it affects both neoplastic and non-neoplastic cells. This affects not just the response to the neoplastic cells but causes side effects such as immunosuppression, cardiotoxicity or neurotoxicity to the normal cells.

• Poor Bioavailability of Natural Products

Many of the phytochemicals with high promise (curcumin, resveratrol) have poor solubility, high metabolism rates, and low absorption rates.

• Tumor Heterogeneity

There is genetic heterogeneity and cellular heterogeneity observed in cancers, with heterogeneity even within the histological sections of the same tumor, which can make treatment very difficult. This causes variability response in cancer patients.

• Cost and Availability

Novel therapies, such as monoclonal antibodies, while being a very effective therapies, are costly treatments and can makes them less accessible to patients especially in low-and middle-income countries.

5.2 Future Prospects :-

Personalized and Precision Medicine. Implementation of genomic, proteomic, and metabolomics information will allow a patient to have a treatment plan that is tailored to the personalized cancer profile of the individual. CRISPR and Gene Editing. CRISPR interventive technology may afford both direct correction of mutations responsible for the cancer and include therapies that sensitize Tumors to drugs already in use. Artificial Intelligence and Machine Learning. There are a number of AI tools developed to interpret drug responses and characteristics of a novel target and molecular modelling has ramped up the pace of fundamental drug development. Combination Therapies. If it is possible to combine things that are either naturally occurring or synthetic, or potentially target a number of different pathways simultaneously, a mixture of drugs may circumvent the issue of resistance and improve efficacy. Immunotherapy Expansion. Immune checkpoint inhibitors (e.g., PD-1/PD-L1, CTLA-4 blockers) and forms of CAR-T cell therapy are emerging as promising treatment options for previously untreatable cancers. Green Chemistry and Sustainable Synthesis. Synthesis of anticancer agents in a more environmentally conscious way and employing biotech can become a preferred method to manufacture scalable and ethically- sourced drug therapies.

6. Conclusion :-

The fight against cancer has continued to advance the search and development of new anticancer agents from both natural and synthetic sources. Historically, Nature has populated the shelf of bioactive compounds with agents that have formed the basis of modern chemotherapy, while, the expanding world of synthetic chemistry, molecular biology, and computational design have fostered the design of more sophisticated and efficacious agents with improved safety profiles. This review emphasizes the opportunities we can explore when integrating the strengths of both paradigms to facilitate the new discovery of innovative and effective anticancer therapeutics. However, we still face formidable challenges including multidrug resistance, bioavailability, toxicity and tumor heterogeneity that dampened clinical success. Future success in the discovery and development of novel anticancer agents will likely employ a multidisciplinary paradigm involving nanotechnology, bioinformatics, artificial intelligence, and personalized medicine. We must embrace these technologies and strategies to facilitate the development of the next generation of anticancer agents which will ultimately improve patient outcomes and help reduce the global burden of cancer.

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