A REVIEW ON CRUDE DRUGS & THEIR ANTICANCER POTENTIAL

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***Abstract*- Although tremendous advancements has been made in the field of medical sciences cancer still remains the leading cause of death around the world. The etiopathogenesis of cancer is complex besides genetic predisposition other factors are also responsible for the development of cancer such as diet, exposure to ionising radiation, lifestyle, air pollution, excessive amount of free radicals in the body,etc. The treatments mostly being used for cancer are chemotherapy, radiotherapy, cancer surgery, but these treatments can be very painful and can produce severe side effects, so there is a need to find an alternative and certain crude drugs seems to be promising in prevention and treatment of cancer. This review focuses on the anti cancer properties of chemical constituents derived from crude drugs and their action against the carcinogenic cells**

***Keywords*: Tumour, cell cycle arrest, apoptosis, cytotoxicity, chemotherapy, crude drugs, microtubules, angiogenesis**.

INTRODUCTION:

Cancer is tumour formed by uncontrolled growth of cells which has occurred Due to the mutations in the cell's DNA.[1] The mutations in DNA occur due to the Exposure to radiation or interference of free radicals with the structure of DNA. Cancer cells has the ability to reach to the adjacent tissue and even distant organ eventually which can lead to death of the affected patient. There are various types of Cancer based on the site of cancer such as breast cancer, lungs cancer, lymphoid Cancer, skin cancer, cervical cancer, etc. The projected cancer load in India in 2021 Was 26.7Million cases and it is expected to increase 29.8Million in 2025 The Leading cancer sites were lung, breast, oesophagus, mouth, stomach, liver and cervix. The existing cancer therapies like radiotherapy, chemotherapy, cancer surgery are not accessible to all and quite expensive so use of crude drugs in cancer therapy provide safe and economic alternative for cancer treatment in some cases.[2]

1.Artemisinin :

Biological Source: Artemisinin is derived from the sweet wormwood plant *Artemisia annua* belonging to family *Asteraceae.*

Fig.1 Artemisia annua

Artemisinin, a sesquiterpene lactone derived from Sweet Wormwood (Artemisia annua), is a vital component in malaria treatment as well as in cancer therapy. China, the primary global supplier, collaborates extensively with the World Health Organization, contributing up to 70% of annual plant material.The plant, native to China but now cultivated globally, reaches a height of 30 to 100 cm (or up to 200 cm when cultivated) and takes around 8 months to mature. Artemisinin is mainly extracted from leaves, harvested at the beginning of flowering when its content is highest, though generally low at 0.01 to 1.4% of dry weight. Hybrid plants in Switzerland yield up to 2%.[3] China's role extends beyond malaria, with significant research into artemisinin's anticancer effects. Discovered in 1972, artemisinin's isolation led to Youyou Tu's 2015 Nobel Prize. Solvents like hexane extract artemisinin, but various methods, including decoction and supercritical fluid extraction, exist. Semi-synthetic derivatives, developed for malaria and cancer, are five times more effective. Although chemical synthesis and DNA techniques produce these derivatives, isolation from natural sources remains the most economical. Unstable artemisinin supply complicates therapeutics production, driving the development of biological syntheses like using Saccharomyces cerevisiae, though not yet available for industrial use. This highlights artemisinin's significance in global health and ongoing research for sustainable production methods.[4]

Mechanism of action :

Artemisinin and its derivatives, such as dihydroartemisinin’s and artesunate, exhibit diverse anti-cancer effects by influencing cell cycle regulation and proposing ferroptosis as a potential mechanism.[5]

In breast cancer cells, artesunate induces G2/M cell cycle arrest by upregulating Beclin1, an initiator of autophagy. Dihydroartemisinin’s, studied in pancreatic cancer cell lines, causes dose-dependent G0/G1 cell cycle arrest, affecting the expression of cyclin E, CDK2, CDK4, and p27. Additionally, it inhibits NF-κB translocation and DNA-binding activity, suggesting NF-κB as a target for dihydroartemisinin’s growth inhibitory effects.[6]

Exploring the mechanism in head and neck squamous cell carcinoma (HNSCC) cells, dihydroartemisinin’s antimalarial mode of action, involving Fe2+ ions, suggests a link to ferroptosis. HNSCC cells treated with dihydroartemisinin exhibit increased reactive oxygen species (ROS) levels, requiring iron for cell death induction. Mitochondrial morphology changes typical of ferroptosis are observed. The specificity of dihydroartemisinin’s activity on tumor cells could be attributed to targeting higher iron levels crucial for DNA synthesis in rapidly growing tumor cells. Decreased levels of GPx4 and Ras in dihydroartemisinin-treated HNSCC cells further support the hypothesis of ferroptosis, a specific form of programmed cell death.[7]

2.Green Tea :

Biological Source: It is obtained from leaves of plant *Camelia sinensis* belonging to family *Theaceae.*

Green tea catechins (GTCs), with epigallocatechin gallate (EGCG) being the most potent, exert significant anti-cancer

Fig.2 Camelia sinensis

effects. The inhibitory potency of catechins follows the order: EGCG > ECG > EGC > EC. Synergistic effects were

observed in catechin mixtures, surpassing the efficacy of pure EGCG. GTCs demonstrate anti-carcinogenic and anti-mutagenic potentials in various human cancers such as breast, esophagus, prostate, stomach, small intestine, colon, liver, and lung.[8]

Animal-based studies, employing xenograft tumor models or carcinogen-induced cancer models, reveal that green tea extracts, catechin mixtures, or pure EGCG influence tumor initiation, promotion, and progression phases. In vivo administration methods include intraperitoneal injection, drinking water, diet, or oral gavage. GTCs induce apoptosis, cell cycle arrest, target receptor tyrosine kinases, inhibit telomerase, and function as both radical scavengers and ROS generators.[9] Their antioxidant ability is ranked as ECG > EGCG > EGC > EC. Moreover, GTCs act as epigenetic modifiers, regulating cellular processes and tumor suppressor genes through DNA methylation inhibition, histone modification, and miRNA expression.[10]

The anti-cancer effects of GTCs involve multiple mechanisms, binding to target proteins such as transmembrane receptors and kinases. EGCG, for instance, exhibits cancer inhibitory activities through the modulation of key signaling and metabolic pathways essential for malignant cell development. The diverse actions and molecular targets of GTCs highlight their potential as effective agents against various cancers.[11]

Mechanism of action :

1.Inhibition of breast cancer :

EGCG, a key green tea catechin, inhibits breast cancer cell proliferation and migration by targeting PI3K/Akt and p53/Bcl-2 pathways, along with telomerase modulation. These catechins affect receptor-mediated pathways, downregulating angiogenesis factors, inhibit STAT-3 and NF-κB, and suppress breast cancer progression via FAK signaling. EGCG's impact on methylation and gene expression, downregulating DNMTs and specific genes like SCUBE2 and TIMP-3, highlights its versatile role. In animal models, EGCG administration inhibits tumor growth, emphasizing its multitargeting potential in breast cancer prevention and treatment.[12]

3. Inhibition of prostate tumorigenesis :

Green tea catechins, particularly EGCG, show promise in inhibiting prostate cancer. Clinical studies reveal reduced progression from intraepithelial neoplasia to cancer with green tea catechin administration. EGCG induces cell cycle arrest and apoptosis, inhibits invasion, and down regulates key molecules. In transgenic mice, EGCG suppresses prostate cancer development and metastases. EGCG emerges as a potential chemo preventive agent for prostate cancer.[12]

2.Inhibition of hepatocellular carcinoma :

Epigallocatechin gallate (EGCG), a tea catechin, exhibits anti-cancer effects against hepatocellular carcinoma (HCC), a deadly liver malignancy. In vitro studies reveal EGCG inhibits HCC cell growth by targeting tyrosine-kinase receptor IGF-1R, inducing apoptosis, and modulating various signaling pathways. Animal models demonstrate that green tea catechins (GTCs), including EGCG, inhibit hepatoma growth, restrict HCC progression, and activate apoptosis. Mechanisms involve suppressing hepatocyte progenitor/stem cells, activating AMPK protein, and modulating self-renewal pathways. EGCG downregulates VEGF/VEGFR and IGF/IGF1R signaling, offering potential efficacy in preventing liver carcinogenesis.[13]

4. Inhibition of tumorigenesis in the gastrointestinal tract :

Green tea catechins, especially EGCG, exhibit anti-cancer effects in the gastrointestinal tract. Epidemiological evidence links green tea consumption to lower esophageal and colorectal cancer incidence. In vitro and in vivo studies demonstrate GTCs' ability to inhibit tumor cell proliferation, induce apoptosis, and suppress angiogenesis. EGCG regulates various signaling pathways and inhibits the expression of key anti-apoptotic proteins. Animal experiments confirm EGCG's inhibitory effects on esophageal and colorectal tumorigenesis. Overall, GTCs show promise in combating gastrointestinal cancer.[14]

5. Inhibition of lung tumorigenesis :

Green tea catechins, notably EGCG, demonstrate preventive and therapeutic effects against lung tumorigenesis, particularly in non-small cell lung cancer (NSCLC). Experimental models show GTCs inhibiting key protein kinases, modulating signaling molecules, and altering gene expressions related to apoptosis, cell cycle, and metastasis. EGCG inhibits phosphorylation of c-Jun and ERK1/2, suppresses EMT, and downregulates growth factor receptors. The compound hampers tumor cell growth, induces apoptosis, and interferes with various growth factors, making catechins promising agents for controlling or reducing lung cancer development.[15]

3.Curcumin :

Biological Source : Curcumin is derived from the rhizomes of *Curcuma longa*, commonly known as turmeric. It belongs to the *Zingiberaceae* family.

Fig.3 Curcuma longa

Curcumin, derived from Curcuma longa (turmeric), exhibits significant anticancer potential, supported by 50 years of research. Its efficacy lies in suppressing tumor cell proliferation, down-regulating key transcription factors (NF-κB, AP-1, Egr-1), and modulating various molecular targets involved in inflammation and cancer progression. Curcumin acts as an antioxidant and anti-inflammatory agent, inhibiting tumour initiation, promotion, and metastasis.[16] Clinical trials confirm its safety up to 10 g/day. The comprehensive review underscores curcumin's substantial promise for cancer prevention and therapy, emphasizing its multifaceted molecular actions.[17]

Mechanism of action :

NF-κB, a pivotal transcription factor, modulates genes involved in growth, inflammation, and apoptosis. Constitutive NF-κB activation impedes chemotherapy-induced apoptosis in various cancers. Signal transducer and activator of transcription 3 (STAT3), activated by factors like EGF and IL-6, contributes to cancer resistance by influencing apoptosis, proliferation, and angiogenesis. Active STAT3 is implicated in diverse cancers.[18] Curcumin hampers both STAT3 and NF-κB signaling pathways crucial for cancer progression, demonstrated in prostate cancer cell lines and clinical samples. The persistent activation of these pathways underscores their significance in cancer development.[19]

4. **Taxol :**

Biological Source : Taxol, also known as paclitaxel, is derived from the bark of the Pacific yew tree, *Taxus brevifolia*. It belongs to the *Taxaceae* family.

Fig.4 Taxus brevifolia

Paclitaxel, known as Taxol, is an FDA-approved microtubule-stabilizing drug for treating ovarian, breast, lung, and Kaposi's sarcoma, with off-label use for various cancers. Traditionally, it induces mitotic arrest, causing cell death. However, recent evidence reveals low intratumoral concentrations, leading to multipolar divisions. This newfound insight holds promise for developing a biomarker to identify the 50% of patients benefiting from paclitaxel therapy, discussed alongside the drug's history and evolving understanding of its mechanism.[20]

Mechanism of action :

Taxol, derived from the yew tree bark, is an antimitotic drug used in cancer therapy by blocking the cell cycle in G1 or M phase, stabilizing microtubules. In vitro, Taxol decreases critical tubulin assembly concentration, increases polymerization rate, and enhances microtubule stability against various factors.[21] Widely applied in microtubule chemistry and biophysical experiments, it aids in understanding kinesin-like molecular motors. Electron cryomicroscopy has been employed to investigate the fine structure of in vitro assembled microtubules with and without Taxol, contributing to insights for designing improved drugs and understanding microtubule stabilization across diverse conditions.[22]

5.Vinca Alkaloids :

Biological Source : Vinca alkaloids, including vincristine, vinblastine, vindesine, and vindoline, are derived from the Madagascar periwinkle *(Catharanthus roseus).* The biological family of Madagascar periwinkle is *Apocynaceae*.[23]

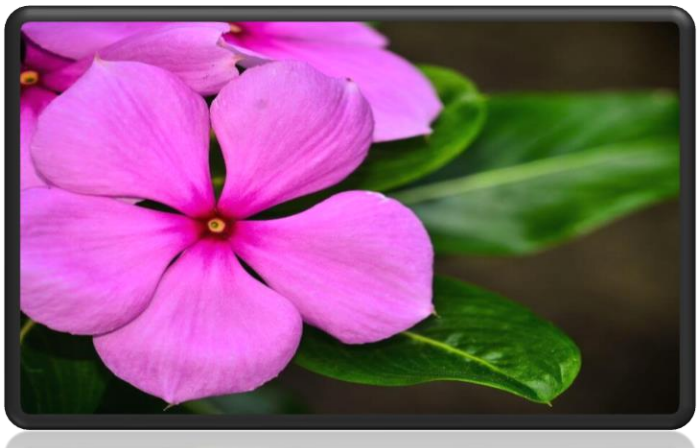

Fig.5 Catharanthus roseus

These are extracted from whole plant of Catharanthus roseus belonging to the family Apocynaceae. The major vinca alkaloids having anticancer properties are: Vincristine, Vinblastine, Vindeline, Vindesine. Vinca alkaloids interacts with tubulin and causes disruption of microtubules function which leads to metaphase [24] These compounds connects to binding sites on tubulin reversibly and interrupts microtubule congregation and blocks the polymerization which results in mitotic block and apoptosis. [25] They are effective on both malignant and non-malignant cells. Vinca alkaloids have been found to be effective against acute leukemia, neuroblastoma, Wilm's tumour, Hodgkin's disease,etc.

Mechanism of Action :

Vinca alkaloids, like vinblastine (VBL) and vincristine (VCR), exhibit diverse biochemical activities beyond microtubule interruption. They bind to distinct tubulin sites, separate from taxanes and other agents, with evidence supporting the existence of two binding sites per tubulin dimer. This binding rapidly occurs and can reverse. VBL disrupts microtubule congregation, leading to a "kinetic cap" at low concentrations, reducing growth and shortening rates. This disturbance, particularly at mitotic spindle ends, induces metaphase arrest.[26] Notably, even clinically irrelevant doses impact both malignant and non-malignant cells in non-mitotic cycles. VBL and related agents demonstrate anti-angiogenic effects in vitro, inhibiting endothelial processes crucial for angiogenesis. In combination with anti-vascular endothelial growth factor antibodies, VBL enhances antitumor responses, especially in resistant tumours. Overall, vinca alkaloids inhibit cell proliferation through microtubule binding, causing mitotic block and apoptosis, with potential therapeutic implications in cancer treatment.[27]

6.Ginseng :

Biological Source : Ginseng is obtained from the roots of plants belonging to the *Panax* genus. The biological family of Ginseng is *Araliaceae*.

Fig.6 Panax roots

Ginseng is rich in active components, such as ginsenosides and polysaccharides, contributing to its diverse pharmacological effects. Notably, ginsenosides and ginseng polysaccharides are key players in its anticancer properties.[28] Ginsenosides, the primary active ingredients, exert vasorelaxation, antioxidation, anti-inflammatory, and anticancer effects. These amphipathic steroidal saponins are classified into protopanaxadiol (PPD), protopanaxatriol (PPT), and oleanane groups, each with distinct chemical structures. Red ginseng, produced through steaming, exhibits higher activity due to unique ginsenosides. The relative amounts of ginsenosides also aid in distinguishing Panax species, with American ginseng differing in Rf levels and Panax ginseng showing variations in Rg1/Rb1 ratios. Ginsenosides serve as markers for quality control, with specific compounds like Rb1, Rb2, Rc, Rd, Re, and Rg1 being quantitatively significant. Each ginsenoside's pharmacology and mechanisms vary based on its unique chemical structure.[29]

Mechanism of action :

The anticancer activities of ginsenosides, the primary bioactive components of ginseng has activities on various cancer types, including breast, brain, liver, gastric, and lung cancers. Ginsenosides, particularly Rg3, Rh2, and CK, demonstrate diverse mechanisms in inhibiting cancer progression. They impact cell proliferation, viability, invasion, migration, apoptosis, and autophagy through modulation of key signaling pathways such as PI3K/Akt, Wnt/β-catenin, and AMPK-mTOR.[30] Ginsenosides also posses synergistic effects with existing cancer therapies. Ginsenosides exhibit pharmacological activities beyond anticancer effects, including immune response boosting and anti-inflammatory properties.[31]

CONCLUSION :

This review highlights the diverse potential of natural compounds derived from crude drugs in combating cancer. Artemisinin, found in Sweet Wormwood, demonstrates promise in breast cancer through cell cycle regulation and ferroptosis induction. Green tea catechins, particularly EGCG, exhibit significant anti-cancer effects across various types of cancer, impacting crucial pathways and molecular targets. Curcumin, derived from turmeric, showcases multifaceted actions, targeting NF-κB and STAT3 signaling pathways. Additionally, Taxol and Vinca alkaloids, with their microtubule-stabilizing properties, prove effective in treating various cancers. Ginseng, rich in ginsenosides, presents diverse pharmacological effects, including anticancer activities through modulation of key signaling pathways. The exploration of these natural compounds provides a foundation for further research into alternative and potentially safer cancer treatments. The review underscores the importance of investigating these compounds both individually and in combination with existing therapies, paving the way for a more comprehensive and effective approach to cancer prevention and treatment.

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