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PROGESTERONE AND ITS DERIVATIVE AS ANTICANCER

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ABSTRACT

Human cells grow and multiply to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.[1] Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are the lump of tissue. It occurs when it ignore signals that normally tell cells to stop dividing or to die, trick the immune system into helping cancer cells to stay alive and grow. So, nowadays progesterone and its derivative is used in the cancer treatment (NCI). It was found that Wnt pathway have role in cell growth ad proliferation, here progesterone and its derivatives we use for anticancer activity. Progesterone binds to nuclear and membrane progesterone receptors (PRs) to regulate the expression of genes that control cell growth and apoptosis. Here progesterone derivatives which is presented are Medroxyprogesterone acetate (MPA), Megestrol acetate (MA), Cyproterone acetate (CTA), Chlormadione acetate (CA) and dydrogesterone and review on its activity as anticancer. Further study is proceeding on it, currently this work is review based.

KEYWORDS: These cells may form tumors, which are the lump of tissue.

INTRODUCTION

1.1 CANCER

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer, being the foremost cause of mortality worldwide is a key target for the upcoming researchers. In North America and Europe, cancer has been reported as the second leading cause of death.[1] The pharmaceutical companies and various governmental and non-governmental organizations including National Cancer Institute (NCI) USA, European Organization for Research and Treatment of Cancer (EORTC)and the British Cancer Research Campaign (CRC) have been persistently focusing on the diagnosis, prevention and treatment of cancer. Various etiological factors have been previously described in different reports. One of the most important factors has been identified as the hormonal fluctuation . Breast cancer is one of the leading diseases arisen from the hormonal fluctuation.[2] In 2022, there were 9.7 million cancer-related deaths worldwide According to the American Cancer Society, the estimated number of cancer deaths in the United States in 2023 was 609,820. This estimate was based on data from the National Centre for Health Statistics and central cancer registries. Globally in 2020, there were an estimated 604 127 cervical cancer cases and 341 831 deaths, with a corresponding age-standardised incidence of 13·3 cases per 100 000 women-years (95% CI 13·3–13·3) and mortality rate of 7·2 deaths per 100 000 women-year.[3] WHO estimates that India had over 9.1 lakh cancer deaths in 2022, along with more than 14.1 lakh new cancer cases. In 2024, an estimated 2,001,140 new cases of cancer will be diagnosed in the United States and 611,720 people die from the disease .The most common cancers are breast cancer, prostate cancer, lung and bronchus cancer, colon and rectum cancer. Breast cancer is one of the leading diseases arise from the hormonal fluctuation. (data.gov.in)

1.1.1 Causes: Cancer is caused by a combination of genetic factors and exposure to environmental agents: Genetic factors These include inherited genetic changes, errors that occur when cells divide, and inactivated tumor suppressor genes. Environmental agents: Radiation: Ultraviolet and ionizing radiation can damage DNA and cause mutations. Solar ultraviolet radiation is the primary cause of skin cancer.[4,5] Chemicals: Carcinogenic chemicals in tobacco smoke, asbestos, arsenic, and aflatoxin can damage DNA and cause mutations. Infections: certain viruses, bacteria, or parasites can cause cancer. Other factors: Diet, body weight, and physical activity levels can also influence the risk of developing cancer. Smoking is the most common and preventable cause of cancer. It's estimated that

smoking is responsible for nearly one-third of all cancer deaths.[6]

1.1.2 Clinical symptoms i.e. abnormal vaginal bleeding, Unexplained weight loss or gain Fatigue Pain, Skin changes ,Lumps or swelling, Changes in bowel or bladder habits, Persistent cough or trouble breathing, Difficulty swallowing, Hoarseness, Persistent indigestion or discomfort after eating Persistent, unexplained fevers or night sweats, Unexplained bleeding or bruising.[7]

1.1.3 Type of cancer

Carcinoma: The most common type of cancer, which forms in the epithelial cells that cover the inside and outside of the body. Carcinomas can originate in the skin, lungs, breasts, pancreas, and other organs and glands .Sarcoma: cancer that forms in soft or connective tissues, including bone, muscle, fat, blood vessels, and cartilage. Leukemia: A cancer that starts in the blood-forming tissue of the bone marrow .Lymphoma: A cancer that starts in lymphocytes, the disease-fighting white blood cells that are part of the immune system .Multiple myeloma: A cancer that starts in plasma cells, another type of immune cell. Brain and spinal cord tumors. (NCI)

1.2 Role of immune system react

The immune system responds to cancer cells in a complex way, and cancer cells can evade the immune response in several ways: Innate immunity: The innate immune system detects and processes cancer antigens, and can directly kill cancer cells. For example, NK cells release cytotoxic proteins to kill cancer cells, and macrophages eliminate apoptotic tumor cells.[8] Adaptive immunity: The immune system can trigger adaptive immunity after detecting cancer antigens. Immune cell secretion: secrete molecules that eliminate tumor cells, and recruit more immune cells . At the same time cancer cells can evade the immune response by hiding from immune cells, shutting down immune cells, or overwhelming the immune system.[9]

1.3 Marketed product and therapy (NCI)

Drug NexCAR19, which was approved by the Central Drugs Standard Control Organization (CDSCO) in October 2023.

Drug approved by FDA and WHO are: Pembrolizumab, Imatinib, Lazertinib, Tremelimumab.

Cancer treatments can also include chemotherapy, hormone therapies, immunotherapy drugs,

and bisphosphonates. Targeted therapy: These therapies use small-molecule drugs or monoclonal antibodies to target specific parts of cancer cells. Immunotherapy: These therapies activate the immune system to fight cancer cells. Some examples include immune checkpoint inhibitors like PD1.Liposomes: These spherical vesicles are used to deliver drugs to cancer cells. They are made of phospholipids and can protect drugs from degradation. Doxil and Myocet are examples of liposome- based drugs.[9] Inorganic nanoparticles: These nanoparticles can be used to deliver drugs to cancer cells. They are more stable than organic materials and have unique properties. Iron nanoparticles, gold nanoparticles, carbon nanotubes, and mesoporous silica nanoparticles are some examples of inorganic nanoparticles that are being studied for cancer therapy. Other cancer treatments include surgery, chemotherapy, radiation, hormonal therapy, and laser therapy.[10]

Marketed product for cancer

Fig. 1.1: Tremelimumab.

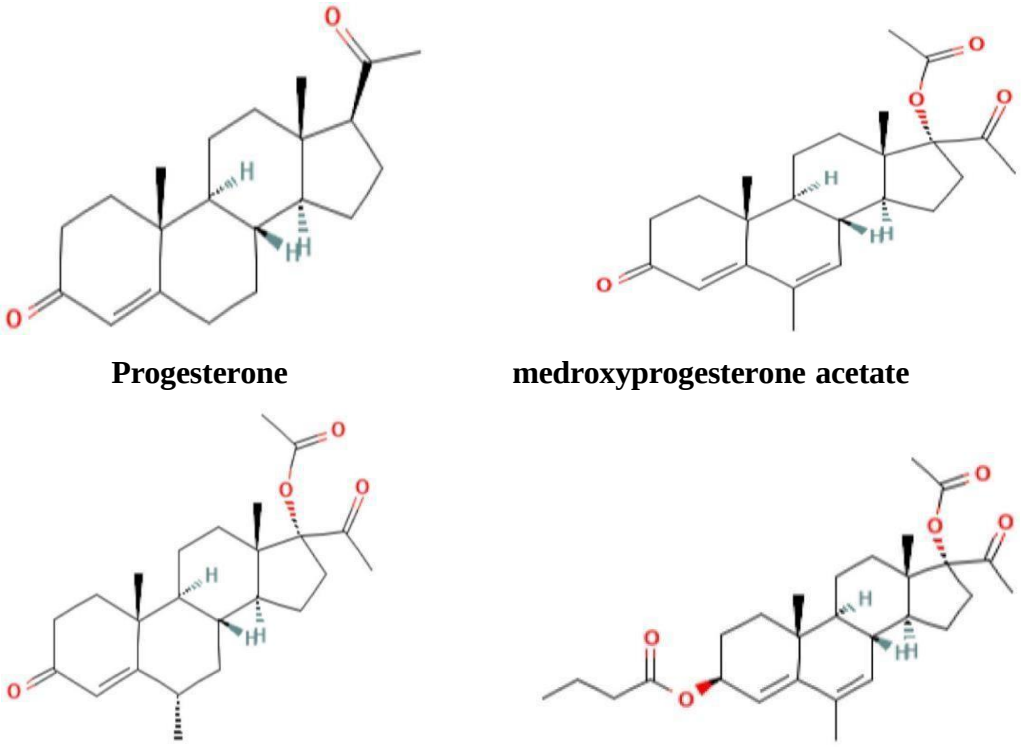
Fig. 1.2: Imatinib tablets.

Fig. 1.3: Pembrolizumab.

1.4 ROLE OF PROGESTERONE IN CANCER

Progesterone and its synthetic analogues, progestins, participate in the regulation of cell differentiation, proliferation and cell cycle progression. Progestins are usually applied for contraception, maintenance of pregnancy, and hormone replacement therapy. Recently, their effectiveness in the treatment of hormone-sensitive tumors was revealed. According to current data, the anticancer activity of progestins is mainly mediated by their cytotoxic and chemo sensitizing influence on different cancer cells. In connection with the detection of previously unknown targets of the progestin action, which include the membrane-associated progesterone receptor (PR), non-specific transporters related to the multidrug resistance (MDR) and mitochondrial permeability transition pore (MPTP), and checkpoints of different signaling pathways, new aspects of their application have emerged. [(11)] It is likely that the favorable influence of progestins is predominantly associated with the modulation of expression and activity of MDR-related proteins, the inhibition of survival signaling pathways, especially TGF-β and Wnt /β-catenin pathways, which activate the proliferation and promote MDR in cancer cells, and the facilitation of mitochondrial-dependent apoptosis. Biological effects of progestins are mediated by the inhibition of these signaling pathways, as well as the direct interaction with the nucleotide-binding domain of ABC-transporters and mitochondrial adenylate translocase as an MPTP component. In these ways, progestins can restore the proliferative balance, the ability for apoptosis, and chemosensitivity to drugs, which is especially important for hormone-dependent tumors associated with estrogen stress, epithelial-to-mesenchymal transition, and drug resistance.[12]

Pregnane progestin which is derived from progesterone have anticancer and chemo sensitizing activity in vivo. These include various substituents at the C3 and C17 carbon atoms of the steroid. The affinity of some of its progesterone and their specific progestogenic activity can even exceed that of progesterone.[13]



Progesterone **medroxyprogesterone acetate**

Megestrol acetate **Gestobutanoyl**

Figure 1.4: Structure of progesterone and its derivatives.

In the course of studies of progesterone and its derivatives as antineoplastic agents, their new important targets associated with the processes of proliferation and apoptosis have been identified.

This review summarized the data on the cytostatic and chemo sensitizing effects of different progesterone and possible mechanisms of their action, It is assumed that the cytostatic and chemo sensitizing effects of progestins is predominantly associated with their own cytotoxic effect on some hormone-dependent tumors (breast cancer, endometrial cancer, cervical cancer); modulation of the expression and activity of multidrug resistance (MDR)–related proteins; and the inhibition of survival signaling pathways that activate the proliferation and MDR protein up-regulation in cancer.[14]

AIM AND OBJECTIVE

Aim: The main aim of this work is to review progesterone and its derivative role in carcino-Prevention.

Objective: To review new pathway and signaling through which cancer can be restricted. Derivatives of progesterone and its activity toward different cancer and effectivity in

combination with other drug as anticancer.

LITERATURE REVIEW

3.1 Steroid

A group of lipids (fats) that have a certain chemical structure .Examples of steroids include sex hormones, cholesterol, bile acids, and some drugs (NCI) Steroids have an **excellent ability to penetrate** cell membranes and bind to the nuclear and membrane receptors. Even a small change in steroid moiety can elicit an extensive biological response. All these facts have attracted Medicinal Chemists and Biochemists. . This review is a concise report on steroid based anticancer molecules for the treatment of various types of cancer .example of hormone: progesterone.[15]

3.2 Wnt/Beta- catenin pathway

The Wnt/β-catenin signaling pathway, also called the canonical Wnt signaling pathway, is a participating in diverse physiological processes such as proliferation, differentiation, apoptosis, migration, and tissue homeostasis. Increasing evidence indicates that dysregulation of the Wnt/β- catenin cascade contributed to the development and progression of some tumors.[16]

In the Wnt/β-catenin pathway, abnormal regulation of the transcription factor β-catenin, which is the pivotal component of the Wnt signalling pathway, leads to early events in carcinogenesis Within the degradation complex, glycogen synthase kinase 3β (GSK3β) and casein kinase 1α (CK1α) mediate the phosphorylation of β-catenin, promoting its ubiquitination and subsequent proteasomal degradation . β-catenin-dependent signalling pathway is triggered by the binding of secreted cysteine-rich glycoprotein ligands Wnt to the LRP-5/6 receptors and FZD receptors. In the presence of Wnt ligand, the binding of Wnt ligand and receptors on the cell surface induces disheveled (DVL), causing the aggregation of the complex (AXIN, GSK3β, CK1, APC) to the receptor . Subsequently, the phosphorylation and inhibition of GSK3β ensure an elevation of cytosolic β-catenin concentration. Un-phosphorylated β-catenin in the cytosol migrates to the nucleus and accumulates, interacting with T cell-specific factor (TCF)/lymphoid enhancer-binding factor (LEF) and coactivators, such as Pygopus and Bcl-9, to trigger the Wnt target genes like c-Myc, cyclin D1 and CDKN1A, resulting in the upregulation of TCF/LEF target gene.[17]

The inner layer of the human uterus, the endometrium is a dynamic tissue that undergoes

hundreds of cycles of proliferation, differentiation and shedding during a woman's reproductive years. It is the fine balance between the activities of the two female sex hormones, estradiol and progesterone. l Wnt/β- catenin signalling pathway may underlie this finely tuned hormonal equilibrium in endometrial homeostasis and, upon its constitutive activation, lead to neoplastic transformation of the endometrium. During the menstrual cycle, estradiol will enhance Wnt/β-catenin signaling in the proliferative phase, while progesterone inhibits Wnt/β-catenin signaling, thus restraining estrogen' proliferative actions, during the secretory phase. In case of enhanced or unopposed estrogen signaling, constitutive activation of Wnt/β-catenin signaling will trigger endometrial hyperplasia, which may develop further into endometrial cancer.[18]

- **Wnt/Beta–catenin signaling pathway**

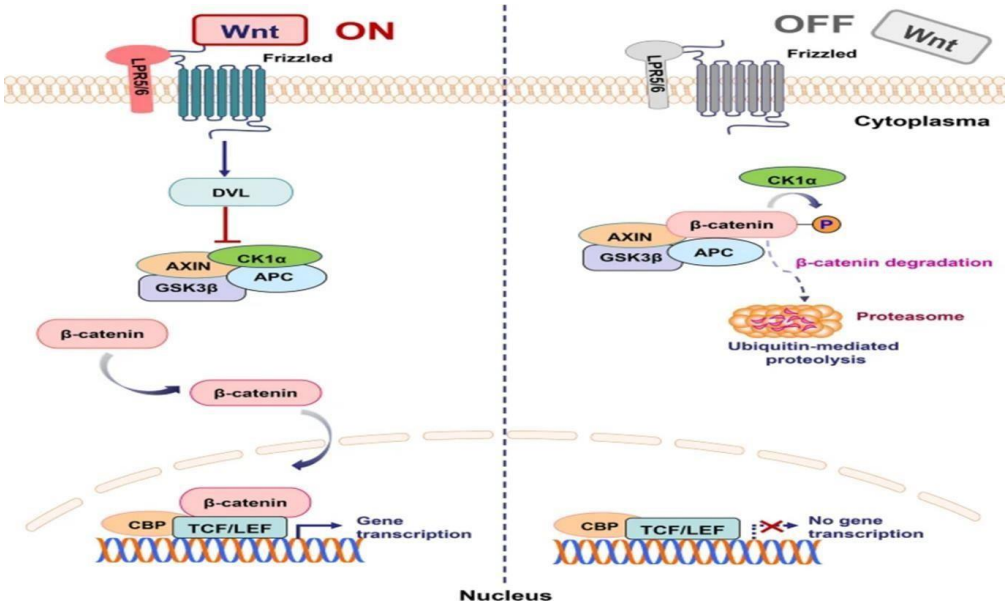


Figure 3.1: Wnt pathway.

3.3 Progesterone activity in Wnt pathway

Progesterone induction of **DKK1** and **FOXO1** results in inhibition of Wnt signaling in the human endometrium. This Wnt inhibitory effect of progesterone is likely to play a rate-limiting role in the maintenance of endometrial homeostasis and, on its loss, in tumor onset and progression toward malignancy. Inhibits β-catenin expression:FOXO1 causes the degradation of β-catenin and prevents it from accumulating in the nucleus.[19] Compete with TCF for β-catenin: FOXO1 competes with T cell factor (TCF) for interaction with β-catenin, which prevents β-catenin-mediated gene transcription. FOXO1 may act as a tumor suppressor in various malignancies . DKK1: A gene that encodes a WNT signaling pathway inhibitor. The

DKK1-involved signaling pathways. (A) DKK1-mediated inhibition of canonical Wnt signaling. DKK1 inhibits β-catenin-dependent Wnt signaling by binding to the LRP5/6 co-receptor and blocking Wnt binding, which results in β-catenin degradation.[20]

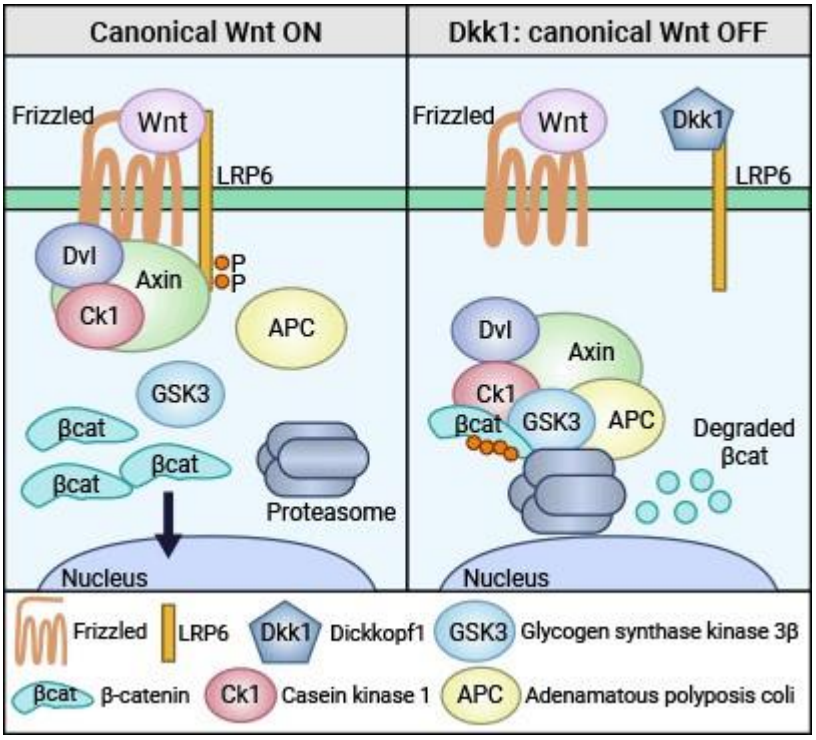


Figure 3.2: DKK1 effect on Wnt pathway.

3.4 Progesterone Derivative structure

Progesterone and its derivatives have pregnane ring which is further differentiate into acetylated and no acetylated ,which are as follows:

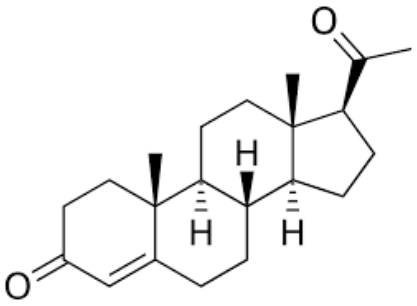


Figure 3.3: Progesterone.

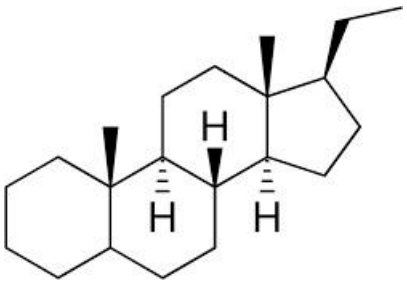
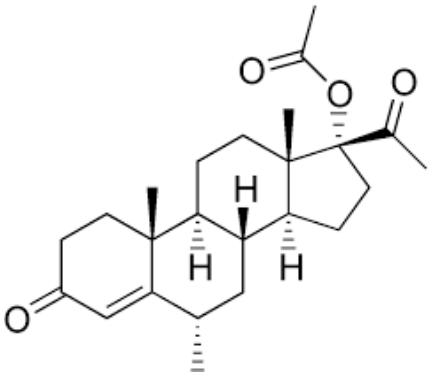
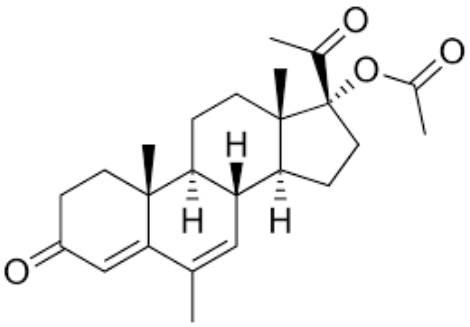


Figure 3.4: Pregnane ring.

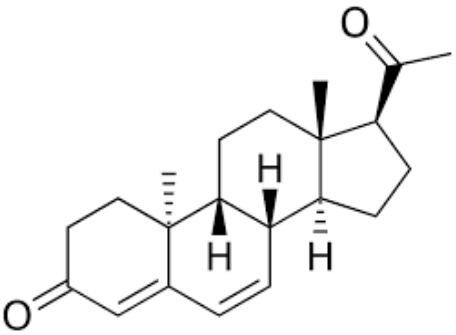


Medroxyprogesterone acetate cyproterone acetate

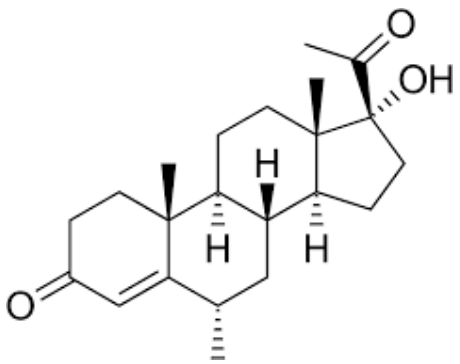


Megestrol acetate

Figure 3.5: Acetylated.



Dydrogesterone



Medrogestone

Figure 3.6: Non acetylated pregnane ring.

3.5 Medroxyprogesterone acetate

Natsuko Murata *et. At* reported that Tumour growth is often accompanied by angiogenesis, the resulting blood vessels supplying nutrients necessary to tumour cells. The development of new blood vessels is also a crucial step in the invasion and metastases of cancer cells of breast cancer, melanoma, lung cancer, prostate cancer and other cancers. Thus, discovery of drugs which suppress angiogenesis has become one of the major focuses in cancer research. So, 9a-fluoromedroxyprogesterone acetate (FMPA, 17a-acetoxy-9a-fluoro-6amethylprogesterone) is a fluorinated analogue of medroxyprogesterone acetate (MPA) which is used as a therapeutic agent for breast and endometrium cancer and possesses anti-angiogenic activity.[21]

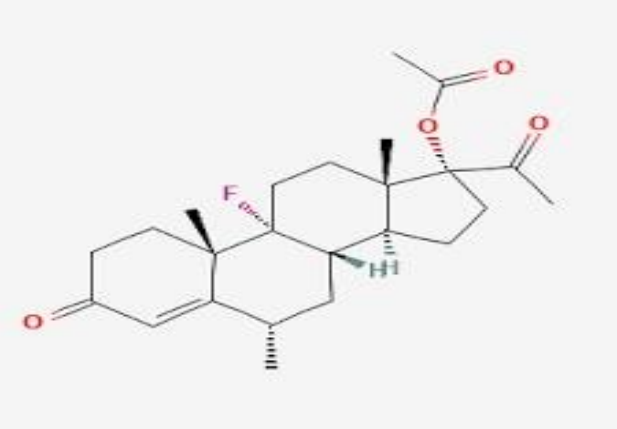


Figure 3.7: 9a-fluoromedroxyprogesterone acetate.

FMPA exhibited an in vitro anti-angiogenic activity 100 times as strong as MPA in a chorioallantois membrane (CAM) and exhibited a 7-fold stronger anti-angiogenic effect than MPA in a rabbit corneal. In addition, FMPA, complexed with g-cyclodextrin (g-CyD), has shown anti-tumour effect on rat mammary carcinomas induced by 7, 12-dimethylbenzanthracene (DMBA) which is greater than the effect of the parent compound,

MPA. Here he developed another synthesis route to develop FMPA which yield 12% yield.

FMPA showed significant inhibitory effects on the growth of DMBA-induced rat mammary carcinomas at doses of 30 and 120 mg/kg as compared with a control group during the treatment and withdrawal periods. The number of tumours which appeared after treatment was also significantly inhibited by FMPA (1) doses of 30 and 120 mg/kg as compared with the control group. It has been reported that FMPA complexed with g-CyD showed antitumor effect on DMBA-induced rat mammary carcinomas, and its effect is greater than that of the parent compound, MPA.[22] The bioavailability of FMPA complexed with g-CyD was found to be about 6 times higher than that of FMPA. This study also indicates that FMPA (1) has strong antitumor activity, so that FMPA may well be a useful oral drug for the treatment of human breast and endometrium cancer.

Table 3.1: Substitution and synthesis of FMPA.

Compound name	Yield
17a-Acetoxy-9a-fluoro-6a-methylprogesterone	8 mg
17a-Acetoxy-11b-hydroxy-6a-methyl-4-pregnene-3,20-dione	285 mg
17a-Acetoxy-9a-fluoro-6a-methylprogesterone	37.9 mg

Anti tumour effect on rat mammary carcinoma: DMBA was administered orally at a single dose of 20 mg/body to female Sprague-Dawley rats about 50 days old. When the diameter of the first developed mammary tumour became 0.5—1.5 cm 8—12 weeks after DMBA administration, the animal was incorporated into the study. FMPA, complexed with DM-b-CyD, was administered to the animals orally once a day at doses of 30 and 120 mg a day for 3 weeks. Distilled water and DM-b- CyD (498 mg/ml) were ministered to the animals orally once a day at a volume of 6 ml/kg/day for 3 weeks. The two largest perpendicular diameters of each tumour were measured on the first day of treatment and thereafter once a week for 6 weeks. The multiplied product of these diameters was expressed as tumour size , is reduced.so, FMPA is more effective as antitumour cell.[23]

L. KANGA *et. At* reported that It is of clinical significance that the response of breast cancer patients to hormonal treatments can be predicted by determining the hormone receptor levels of the tumours. Toremifene. a new antiestrogenic antitumor compound, increases the progesterone receptor levels in the target tissue as a result of which the tumours might

become more sensitive to progestins. The combination of antioestrogen + progestin is therefore theoretically interesting. Clinically, however the combination of tamoxifen and MPA has not given better results than either drug alone. Therefore the effect of toremifene and MPA was evaluated both invitro and in vivo. Several dose levels were used in in vivo studies. RPM1 1640 was used in the actual cell cultures.[24]

Table 3.2: Comparing effect of Control and combination of TOR and MPA.

Group	Number of tumour in beginning	Number of disappear tumour per animal	Change of tumour number per animal	Statistical significance
Control	63	0	4.4 +/- 3.3	0
TOR (3 mg/kg)	61	0.54	0.5 +/- 1.1	<0.05
MPA (50 mg/ kg)	10	0	0.5 +/-0.7	<0.05
TOR + MPA (3 + 10 mg/ kg)	19	3.3	-2.5 +/- 1.3	<0.001
TOR + MPA (3 + 30 mg/kg)	22	2.0	-1.8+/- 1.5	<0.001
TOR + MPA (1O + 100 mg/kg)	34	8.0	-5.3 +/- 3.1	<0.001

The combination was, especially at high doses, very effective and eradicated all tumour in several animals.

HANS CHRISTIAN BLOSSEY, MD *et. At* stated that MPA is a effective drug in the hormonal therapy of breast cancer. One of the characteristic features of this drug is that its antitumor activity shows two levels of therapeutic efficiency: the response rates with low or moderate dosages and high dosages response rates of 40% and more were observed. we have demonstrated the pharmacokinetic and endocrine background of high-dose and lower dose MPA therapy, and we have generated hypotheses for the mechanisms of action of the drug in metastatic breast cancer. Postmenopausal patients with metastatic breast cancer were treated with medroxyprogesterone acetate (MPA) in dosages between 500 mg and 1500 mg orally per day. The relation of MPA plasma concentrations and endocrine effects were studied in a longitudinal fashion. MPA inhibits tumour cell growth through the progesterone receptor. A dual mechanism for the antitumor activity of high dose is postulated MPAc.

3.6 MAGESTROL ACETATE

Renzo Canetta *et .At* stated that Since 1968, megestrol acetate has been used in clinical oncology and this report reviews available data on megestrol acetate therapy in cancer. Unlike progesterone, megestrol acetate is effective when given orally. Megestrol acetate (17 a-acetoxy-6- methylpregna-4-, 6-diene-3, 20- dione) is a synthetic derivative of the naturally

occurring steroid hormone, progesterone. Since 1896 when Beatson reported positive responses to endocrine manipulation in certain advanced breast cancer patients a variety of hormone-related approaches have been used in this indication. He finally reported that megestrol with it substitution give a better effect as anticancer.[26]

YAN XIA *et .At* reported that Liver cancer, one of the most common primary malignancies with a high fatality rate, often responds poorly to current therapies. Normal human liver was modulated by sex hormones in morphology and function.

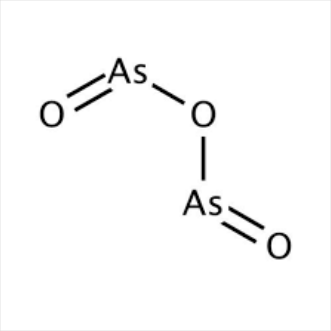


Figure 3.8: Arsenic trioxide.

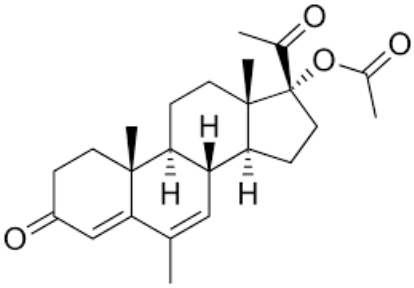


Figure 3.9: Megestrol acetate.

Megestrol acetate (MA), a synthetic progestin with multiple drug actions, was widely used in management of endometrial carcinoma and breast carcinoma. Besides, arsenic trioxide (ATO), which have a remarkable therapeutic effect on treatment of APL (acute promyelocytic leukemia) could induce apoptosis in solid tumour cell lines, such as cervical cancer cells, human sarcoma cells. The co- treatment of MA/ATO could enhance antitumor efficacy in liver cancer cell lines (Hep G2).

In the present study, we investigated the antitumor activity and underlying mechanisms of MA/ATO combination in liver cancer cell lines (Hep G2 and BEL 7402 cells). It was showed that treatment of combined MA/ATO enhanced the inhibition of cell viability and apoptosis.

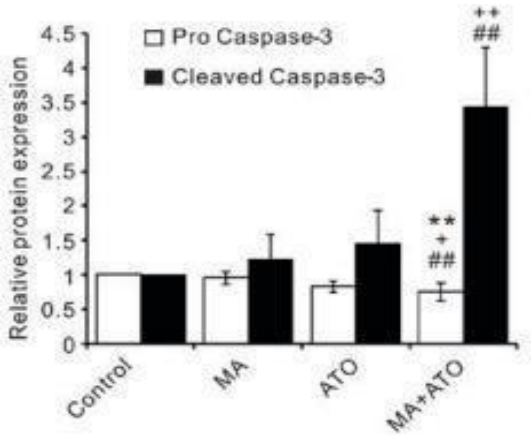


Figure 3.10: Comparing effect of Control and combination of MA+ATO.

Cells were seed in 6-well cell culture plates (1x106 cells/well) and incubated overnight. Then, culture media were removed and replaced with fresh media containing with or without drugs at 37˚C for 24 h. The cells were harvested, washed, and resuspended in phosphate-buffered saline (PBS). The apoptotic cell death rate was examined and result showed better effect.[27]

A. LICCHETTA *et .At* reported that Breast cancer is a major health problem with more than 1,000,000 new cases and 370,000 deaths yearly worldwide, and 25% of patients who relapse in spite of early diagnosis, and appropriate and specific treatment. metronomic chemotherapy is an anticancer strategy which uses conventional cytotoxic drugs administered at very low dose in close intervals. We have designed a phase ii trial to investigate the safety and antitumor activity of the newest metronomic chemo-hormonal-therapy with daily cyclophosphamide and twice daily megestrol acetate in patients with metastatic pretreated breast cancer. This study was designed as an open label mono-institutional two-step .phase ii trial to investigate the toxicity and activity of a new schedule of oral chemo- hormonal-therapy combining daily CTX and twice-daily MA in metastatic breast cancer patients. The results of the studies demonstrated the efficacy of either CTx and MA alone ,is low. The antitumor activity and toxicity of the newest metronomic chemo-hormonal regimen (mCM) combining oral daily CTx and oral twice-daily MA in heavily pretreated metastatic breast cancer patients.[28]

Wei Wen *et. At* reported that Combination treatment of pterostilbene and megestrol acetate suppresses cell survival and cell cycle pathways in endometrial cancer cells. Endometrial cancer is the most common gynaecologic cancer in the United States, and unlike most other cancers, its incidence and mortality has been rising over the past decade. One frequently used

drug in endometrial cancer patients, especially those with metastatic lung lesions or who are medically unfit for surgical management, is the progestin, megestrol acetate, which is associated with a 20-30% response rate in patients with advanced and recurring endometrial cancer. To potentially enhance the activity of megestrol acetate in endometrial cancer patients, we have explored non-toxic natural supplements. Recently, pterostilbene, a naturally occurring phenolic compound primarily found in blueberries, has been shown to possess antitumor activity.

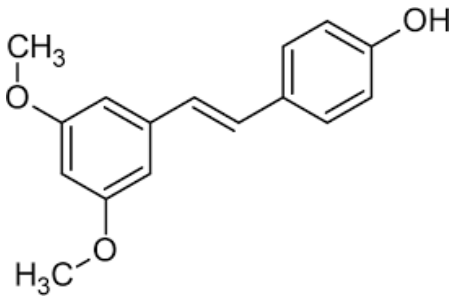


Figure 3.11: Pterostilbene.

Pterostilbene (PTE) has superior bioavailability as compared to resveratrol, with a favourable safety profile, and appears to act via apoptotic and anti-proliferative mechanisms in multiple solid cancer cells.

Table 3.3: Evaluation of synergistic interaction between PTE and Megestrol on cells.

Cells	PTE: Megestrol	Combination index (CI)			Fold reduction (IC_{50})	
		ED50	ED75	ED90	PTE	Megestrol
HEC-1A	1:1	0.36	0.47	0.61	2.75	>1000
ECC-1	1:1	0.34	0.47	0.64	2.91	>1000

This combination enhance the antitumor activity of megestrol acetate in endometrial cancer. They tested the antiproliferative effect of pterostilbene with and without megestrol acetate in multiple endometrial cancer cells, and their anti-tumour effect in an endometrial cancer xenograft mouse model. Its results introduce pterostilbene as a potential therapeutic adjunct which effectively synergizes the antineoplastic effect of megestrol acetate in endometrial cancer, likely by reducing estrogen receptor expression, inhibiting signalling and subsequently suppressing cancer cell growth and survival.[29]

3.7 CYPROTERONE ACETATE

P.H.B. WILLEMSE *et .At* reported that Cyproterone acetate (CPA) is a progestin which

has been used mostly for its anti-androgenic properties, e.g. patients with prostatic cancer. Recently, it was found to have substantial activity in male breast cancer. Twenty-three patients, mean age 64 years, range 52-75 years, were entered and treated with CPA 400 mg daily. The serum levels of CPA, cortisol, androstenedione, DHAS, LH, FSH and prolactin were measured during CPA treatment. The levels of cortisol and androstenedione did not change, while LH, FSH and DHAS were suppressed. The DHAS showed an inverse relation to serum CPA concentrations. The prolactin levels rose uniformly. The therapeutic effect of CPA in postmenopausal patients with advanced breast cancer is not satisfying, and inferior to that of other progestins. Side-effects are frequent, possible as a result of the high dosage.[30]

Massimo Lopez, M.D. *et .At* reported that . Male breast cancer (MBC) is considered an androgen- dependent tumour, and as in prostatic cancer, responses have been reported with use of antiandrogens or gonadotropin-releasing hormone analogues. Thus, it is reasonable to postulate that better results could be achieved by combining these two agents.

Eleven men with recurrent or progressive carcinoma of the breast have been treated with buserelin 1500 µg subcutaneously daily in the first week and 600 µg daily subsequently and cyproterone acetate (CPA) 100 mg twice a day orally starting 24 hours before the first dose of buserelin.

Table 3.4: Serum level of CPA,FSH,LH,DHAS at 200mg and 400mg CPA daily.

	Baseline	200 mg	400mg
CPAµG/L	------	0.8	1.74*
DHASµG/L	1.79	2.12	1.26*
Cortisol nM/L	450	--	4158
FSH	44.2	--	16.8*
LH	65.2	--	22.3*
Prolactin	204	--	312*

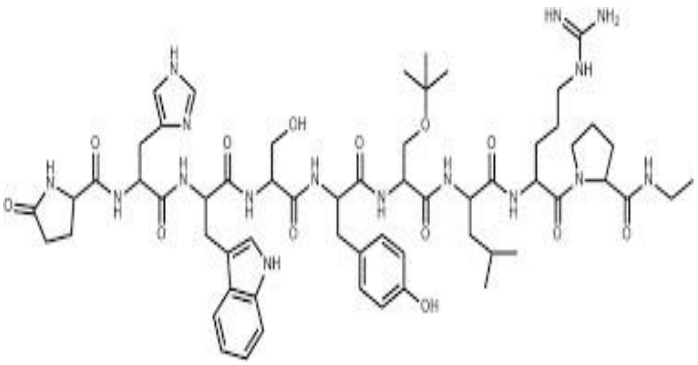


Figure 3.12: Busereline.

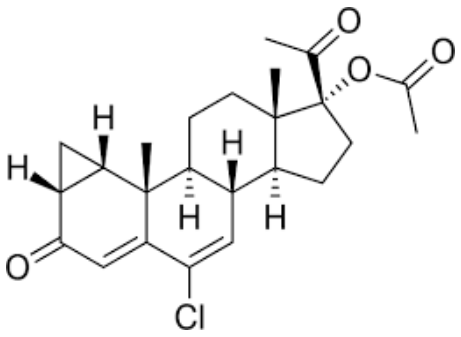


Figure 3.13: Cyproterone acetate.

Objective response was evaluated according to the criteria of the World Health 0rganiation. Duration response was dated from the first day of treatment to date of progression. As a result total androgen blockade with buserelin and CPA seems effective in the treatment of patients with advanced cancer of male breast, but its superiority over standard androgen suppression remains to be demonstrated.[31]

3.8 CHLORMADIONE ACETATE

Mikio Sugimoto *et. At* reported that they conducted and evaluate the effect of low-dose chlormadinone acetate, an antiandrogen agent, on the persistence rate of active surveillance in patients with low-risk prostate cancer. The study was a multi centre, placebo-controlled, double-blind, randomized controlled trial conducted at 38 sites in Japan. Low-risk prostate cancer patients were randomly assigned to the chlormadinone group or the placebo group and the persistence rate of active surveillance was evaluated for 3 years. PSA levels were significantly lower in the chlormadinone group from 3 to 36 months and the difference between the two groups was ~4.0–5.5 μg/mL throughout the study period. Testosterone levels and prostate volume were significantly lower in the chlormadinone group at 12, 24 and 36 months compared with the placebo group. The most common adverse event in the chlormadinone group was constipation in 22.5% people. In conclusion, in low-risk PC patients, low-dose chlormadinone reduced prostate volume, the number of positive cores and prolonged the persistence rate of AS while maintaining QOL. Results showed that low-dose chlormadinone contributes to prolonged as anticancer. However, the effects of chlormadinone on the long-term prognosis need further investigation.[32]

KOICHIRO AKAKURA, M.D.*et* . *At* reported that In 1993 Kelly and Scherl first reported 9 cases of flutamide withdrawal syndrome in patients with prostate cancer, who manifested disease progression after combined therapy with medical.

CMA is useful in prostate cancer till the time we use. Withdrawal of CMA, a fall in PSA levels and remarkable clinical improvement were observed in both cases. One patient revealed a decrease and the other an increase in serum prostate acid phosphatase after the discontinuation of CMA. Serum levels of testosterone, prolactin, dehydroepiandrosterone, dehydroepiandrosterone sulphate, and androstenedione were not significantly elevated after CMA withdrawal. Withdrawal of the steroidal antiandrogen CMA resulted in a decline in PSA levels and clinical improvement in prostate cancer patients with disease progresssion. Changes in testosterone, prolactin, or adrenal androgens were not a cause of the antiandrogen withdrawal syndrome.[33]

3.9 DYDROGESTETRONE

Karam A. El-Sharkawy et. At reported K novel dydrogesterone derivatives of thiophene, pyrimidine, pyrazole, pyridine, coumarin and isoxazole. In which Benzoyl thienopyrimidine derivative, Phenyl thienopyrimidine derivative and Thienopyridine derivative was found as heights effective against all the three different tumour cell lines. That synthesised compound data reported in following table.

Table 3.5 Doxorubicin and Dydrogesteron substitution activity

COMPOUND	SF-268 CNS cancer GI_{50} (µmol L−1)	MCF-7 Breast adenocarcinoma GI_{50} (µmol L−1)	NCI-H460 Non-small cell lung cancer GI_{50} (µmol L−1)	WI-38 GI_{50} (µmol L−1)	Substitution name
2d	0.05 ± 0.02	0.03 ± 0.02	0.06 ± 0.03	>100	Benzoyl thienopyrimidine derivative
2C	1.12 ± 2.1	0.09 ± 0.03	1.6 ± 3.7	>100	Phenyl thienopyrimidine derivative
10a	1.7 ± 0.06	1.4 ± 0.9	1.4 ± 0.9	>100	Thienopyridine derivative
Doxorubicin	0.05 ± 0.007	0.07 ± 0.007	0.07 ± 0.008	>100	-

The highest inhibitory effect of the newly synthesized compounds 2d (Benzoyl thienopyrimidine derivative), 2C (Phenyl thienopyrimidine derivative) and 10a (Thienopyridine derivative) was evaluated on the in vitro growth of the three human tumour cell lines representing different tumour types, namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460), and CNS cancer (SF-268).[34]

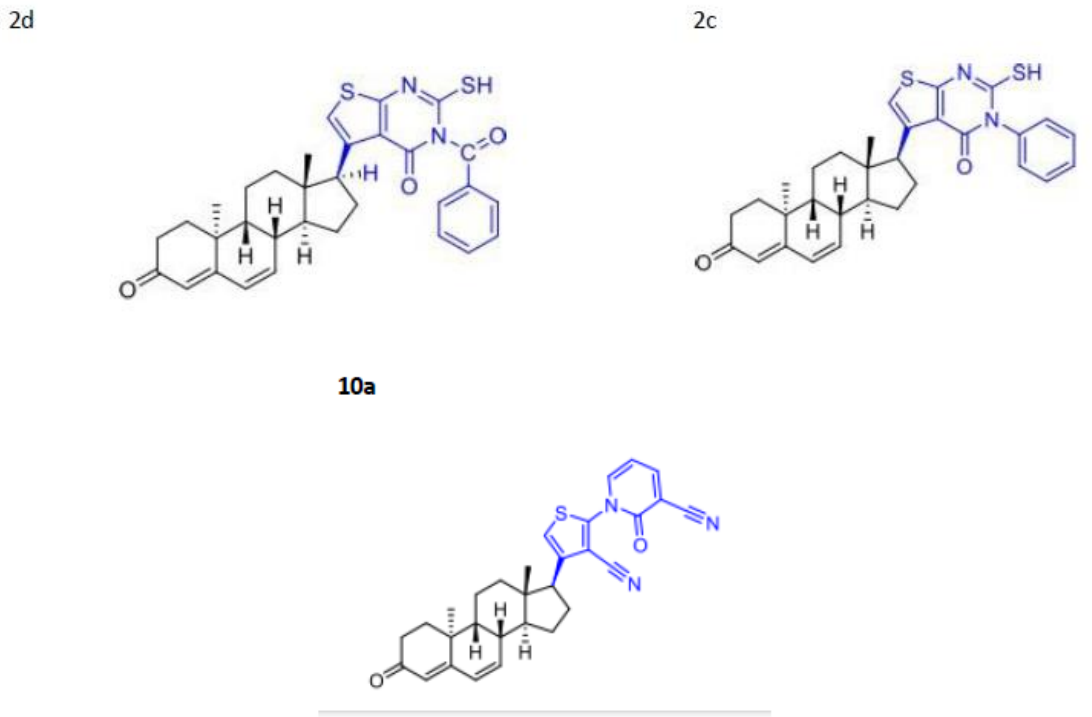


Figure 3.14: Structure of Dydrogesteron substitution.

Marisa Cabeza et .At reported that Dydrogesterone is a progestin produced by Abbott Laboratories and distributed in over 100 countries worldwide. This compound is used for the treatment of a variety of gynaecological conditions related to progesterone deficiency. This steroid is orally active at low doses and binds to PR with an RBA .The pharmaceutical effect of dydrogesterone has been described as a neuroendocrine modulator of ovarian and endometrial functions. On the other hand, dydrogesterone inhibited the activity of the enzymes 5a-reductase (5a-R2) as well as 17-b- hydroxysteroid dehydrogenase (17-b-HSD) . These data are important since the growth of estrogen/progesterone-insensitive breast cancer tumour is due to the presence of a high concentration of 5a-progesterone (5aP) metabolite. As a result of this, dydrogesterone could be an alternative for the treatment of breast cancer.[35]

GÉRARD SAMUEL CHETRITE et. At reported that estradiol is one of the main factors which control the growth and evolution of breast cancer. Consequently, to block the formation of E2 inside cancer cells has been an important target in recent years. There is substantial information that mammary cancer tissue contains all the enzymes responsible for the local implicated in the last steps of E2 formation in breast cancer tissues: the ‘aromatase pathway', which transforms androgens into estrogens and the ‘sulfatase pathway' which converts estrone sulphate into estrone by estrone-sulfatase.

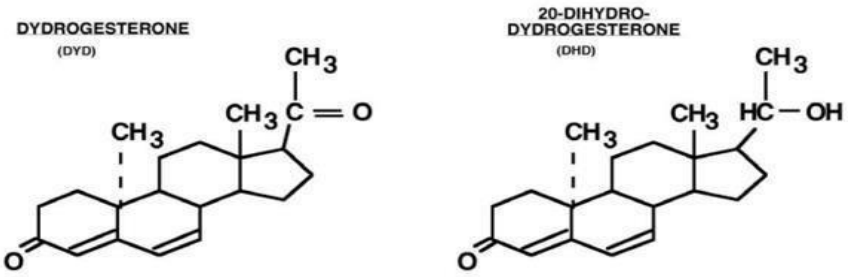


Figure 3.15: Structure of Dydrogesteron and 20 Dihydrogesterone.

The progestogen dydrogesterone interfered significantly with the estrone sulfatase activity only at the concentration of 5x10-5 M (-63% and -48%) of inhibition in MCF-7 and T-47D cells, respectively. The 20-dihydro-metabolite strongly decreased the production of E2 from E1S in a dose-dependent manner in the two cell lines. This inhibitory effect was high at 5x10-5 M.

In the present study, they explored the effects of dydrogesterone and its 20-dihydro-derivative on estrone sulfatase in the MCF-7 and T-47D breast cancer cell lines and on reductive 17,-hydroxysteroid dehydrogenase.[36]

CONCLUSION

Cancer, being the foremost cause of mortality worldwide is a key target for the upcoming researchers, its a concern worldwide. At present certain medicines and therapy is present in market than also a new ad novel idea of using steroidal hormone to cure cancer is in process. This review was carried out to see how progesterone and its derivatives show its activity as anticancer. Its derivatives: Medroxyprogesterone ,Megestrol acetate and Dydrogesterone is currently studied and certain experiment is carried out to observe its activity as anticancer , its data and research is collected in this review.

At the end I conclude that progesterone derivatives can be effectively use in the treatment of cancer. It was a brief review and it still need deep research.

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