Project on

Screening of Natural Inhibition of 5-Alpha Reductase type 2 for treatment of Prostate cancer- An Insilico Approach

Submitted By

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I, Surbhi Sharma declare that this project entitled “Screening of Natural Inhibition of 5-Alpha Reductase type 2 for treatment of Prostate cancer- An Insilico Approach” has been prepared by me.

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INTRODUCTION:

1 What is Cancer?

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected.

![Figure 1- Tumor formation](image)

Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). Tumors can grow and interfere with the digestive, nervous, and circulatory systems, and they can release hormones that alter body function. Tumors that stay in one spot and demonstrate limited growth are generally considered to be benign.

More dangerous, or malignant, tumors form when two things occur:

1. A cancerous cell manages to move throughout the body using the blood or lymph systems, destroying healthy tissue in a process called invasion
2. That cell manages to divide and grow, making new blood vessels to feed itself in a process called angiogenesis.

When a tumor successfully spreads to other parts of the body and grows, invading and destroying other healthy tissues, it is said to have metastasized. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat.
In 2007, cancer claimed the lives of about 7.6 million people in the world. Physicians and researchers who specialize in the study, diagnosis, treatment, and prevention of cancer are called oncologists.

1.1 What causes cancer?

Cancer is ultimately the result of cells that uncontrollably grow and do not die. Normal cells in the body follow an orderly path of growth, division, and death. Programmed cell death is called apoptosis, and when this process breaks down, cancer begins to form. Unlike regular cells, cancer cells do not experience programmatic death and instead continue to grow and divide. This leads to a mass of abnormal cells that grows out of control.

1.2 Genes - the DNA type

Cells can experience uncontrolled growth if there are damages or mutations to DNA, and therefore, damage to the genes involved in cell division. Four key types of gene are responsible for the cell division process: oncogenes tell cells when to divide, tumor suppressor genes tell cells when not to divide, suicide genes control apoptosis and tell the cell to kill itself if something goes wrong, and DNA-repair genes instruct a cell to repair damaged DNA.

Cancer occurs when a cell's gene mutations make the cell unable to correct DNA damage and unable to commit suicide. Similarly, cancer is a result of mutations that inhibit oncogene and tumor suppressor gene function, leading to uncontrollable cell growth.

1.3 Carcinogens

Carcinogens are a class of substances that are directly responsible for damaging DNA, promoting or aiding cancer. Tobacco, asbestos, arsenic, radiation such as gamma and x-rays, the sun, and compounds in car exhaust fumes are all examples of carcinogens. When our bodies are exposed to carcinogens, free radicals are formed that try to steal electrons from other molecules in the body. Theses free radicals damage cells and affect their ability to function normally.

1.4 What are the symptoms of cancer?

Cancer symptoms are quite varied and depend on where the cancer is located, where it has spread, and how big the tumor is. Some cancers can be felt or seen through the skin - a lump on the breast or testicle can be an indicator of cancer in those locations. Skin cancer (melanoma) is often noted by a change in a wart or mole
on the skin. Some oral cancers present white patches inside the mouth or white spots on the tongue.

Other cancers have symptoms that are less physically apparent. Some brain tumors tend to present symptoms early in the disease as they affect important cognitive functions. Pancreas cancers are usually too small to cause symptoms until they cause pain by pushing against nearby nerves or interfere with liver function to cause a yellowing of the skin and eyes called jaundice. Symptoms also can be created as a tumor grows and pushes against organs and blood vessels. For example, colon cancers lead to symptoms such as constipation, diarrhea, and changes in stool size. Bladder or prostate cancers cause changes in bladder function such as more frequent or infrequent urination.

As cancer cells use the body's energy and interfere with normal hormone function, it is possible to present symptoms such as fever, fatigue, excessive sweating, anemia, and unexplained weight loss. However, these symptoms are common in several other maladies as well. For example, coughing and hoarseness can point to lung or throat cancer as well as several other conditions.

When cancer spreads, or metastasizes, additional symptoms can present themselves in the newly affected area. Swollen or enlarged lymph nodes are common and likely to be present early. If cancer spreads to the brain, patients may experience vertigo, headaches, or seizures. Spreading to the lungs may cause coughing and shortness of breath. In addition, the liver may become enlarged and cause jaundice and bones can become painful, brittle, and break easily. Symptoms of metastasis ultimately depend on the location to which the cancer has spread.

1.5 How is cancer classified?

There are five broad groups that are used to classify cancer.

1. Carcinomas are characterized by cells that cover internal and external parts of the body such as lung, breast, and colon cancer.
2. Sarcomas are characterized by cells that are located in bone, cartilage, fat, connective tissue, muscle, and other supportive tissues.
3. Lymphomas are cancers that begin in the lymph nodes and immune system tissues.
4. Leukemias are cancers that begin in the bone marrow and often accumulate in the bloodstream.
5. Adenomas are cancers that arise in the thyroid, the pituitary gland, the adrenal gland, and other glandular tissues. Cancers are often referred to by terms that
contain a prefix related to the cell type in which the cancer originated and a suffix such as -sarcoma, -carcinoma, or just -oma. Common prefixes include:

- Adeno- = gland
- Chondro- = cartilage
- Erythro- = red blood cell
- Hemangio- = blood vessels
- Hepato- = liver
- Lipo- = fat
- Lympho- = white blood cell
- Melano- = pigment cell
- Myelo- = bone marrow
- Myo- = muscle
- Osteo- = bone
- Uro- = bladder
- Retino- = eye
- Neuro- = brain

1.6 How is cancer diagnosed and staged?

Early detection of cancer can greatly improve the odds of successful treatment and survival. Physicians use information from symptoms and several other procedures to diagnose cancer. Imaging techniques such as X-rays, CT scans, MRI scans, PET scans, and ultrasound scans are used regularly in order to detect where a tumor is located and what organs may be affected by it. Doctors may also conduct an endoscopy, which is a procedure that uses a thin tube with a camera and light at one end, to look for abnormalities inside the body.

![Figure 2 – Biopsy(cancer cells)](image)

Extracting cancer cells and looking at them under a microscope is the only absolute way to diagnose cancer. This procedure is called a biopsy. Other types of molecular diagnostic tests are frequently employed as well. Physicians will analyze your body's sugars, fats, proteins, and DNA at the molecular level. For example,
cancerous prostate cells release a higher level of a chemical called PSA (prostate-specific antigen) into the bloodstream that can be detected by a blood test. Molecular diagnostics, biopsies, and imaging techniques are all used together to diagnose cancer.

After a diagnosis is made, doctors find out how far the cancer has spread and determine the stage of the cancer. The stage determines which choices will be available for treatment and informs prognoses. The most common cancer staging method is called the TNM system. T (1-4) indicates the size and direct extent of the primary tumor, N (0-3) indicates the degree to which the cancer has spread to nearby lymph nodes, and M (0-1) indicates whether the cancer has metastasized to other organs in the body. A small tumor that has not spread to lymph nodes or distant organs may be staged as (T1, N0, M0), for example.

TNM descriptions then lead to a simpler categorization of stages, from 0 to 4, where lower numbers indicate that the cancer has spread less. While most Stage 1 tumors are curable, most Stage 4 tumors are inoperable or untreatable.

1.7 How is cancer treated?

Cancer treatment depends on the type of cancer, the stage of the cancer (how much it has spread), age, health status, and additional personal characteristics. There is no single treatment for cancer, and patients often receive a combination of therapies and palliative care. Treatments usually fall into one of the following categories: surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or gene therapy.

1.8 Surgery

Surgery is the oldest known treatment for cancer. If a cancer has not metastasized, it is possible to completely cure a patient by surgically removing the cancer from the body. This is often seen in the removal of the prostate or a breast or testicle. After the disease has spread, however, it is nearly impossible to remove all of the cancer cells. Surgery may also be instrumental in helping to control symptoms such as bowel obstruction or spinal cord compression.

1.9 Radiation

Radiation treatment, also known as radiotherapy, destroys cancer by focusing high-energy rays on the cancer cells. This causes damage to the molecules that make up the cancer cells and leads them to commit suicide. Radiotherapy utilizes high-energy gamma-rays that are emitted from metals such as radium or high-energy x-
rays that are created in a special machine. Early radiation treatments caused severe side-effects because the energy beams would damage normal, healthy tissue, but technologies have improved so that beams can be more accurately targeted. Radiotherapy is used as a standalone treatment to shrink a tumor or destroy cancer cells (including those associated with leukemia and lymphoma), and it is also used in combination with other cancer treatments.

1.10 Chemotherapy

Chemotherapy utilizes chemicals that interfere with the cell division process - damaging proteins or DNA - so that cancer cells will commit suicide. These treatments target any rapidly dividing cells (not necessarily just cancer cells), but normal cells usually can recover from any chemical-induced damage while cancer cells cannot. Chemotherapy is generally used to treat cancer that has spread or metastasized because the medicines travel throughout the entire body. It is a necessary treatment for some forms of leukemia and lymphoma. Chemotherapy treatment occurs in cycles so the body has time to heal between doses. However, there are still common side effects such as hair loss, nausea, fatigue, and vomiting. Combination therapies often include multiple types of chemotherapy or chemotherapy combined with other treatment options.

1.11 Immunotherapy

Immunotherapy aims to get the body's immune system to fight the tumor. Local immunotherapy injects a treatment into an affected area, for example, to cause inflammation that causes a tumor to shrink. Systemic immunotherapy treats the whole body by administering an agent such as the protein interferon alpha that can shrink tumors. Immunotherapy can also be considered non-specific if it improves cancer-fighting abilities by stimulating the entire immune system, and it can be considered targeted if the treatment specifically tells the immune system to destroy cancer cells. These therapies are relatively young, but researchers have had success with treatments that introduce antibodies to the body that inhibit the growth of breast cancer cells. Bone marrow transplantation (hematopoetic stem cell transplantation) can also be considered immunotherapy because the donor's immune cells will often attack the tumor or cancer cells that are present in the host.

1.12 Hormone therapy

Several cancers have been linked to some types of hormones, most notably breast and prostate cancer. Hormone therapy is designed to alter hormone production in the body so that cancer cells stop growing or are killed completely. Breast cancer
hormone therapies often focus on reducing estrogen levels (a common drug for this is tamoxifen) and prostate cancer hormone therapies often focus on reducing testosterone levels. In addition, some leukemia and lymphoma cases can be treated with the hormone cortisone.

1.13 Gene therapy

The goal of gene therapy is to replace damaged genes with ones that work to address a root cause of cancer: damage to DNA. For example, researchers are trying to replace the damaged gene that signals cells to stop dividing (the p53 gene) with a copy of a working gene. Other gene-based therapies focus on further damaging cancer cell DNA to the point where the cell commits suicide. Gene therapy is a very young field and has not yet resulted in any successful treatments.

1.14 How can cancer be prevented?

Cancers that are closely linked to certain behaviors are the easiest to prevent. For example, choosing not to smoke tobacco or drink alcohol significantly lower the risk of several types of cancer - most notably lung, throat, mouth, and liver cancer. Even if you are a current tobacco user, quitting can still greatly reduce your chances of getting cancer.

Skin cancer can be prevented by staying in the shade, protecting yourself with a hat and shirt when in the sun, and using sunscreen. Diet is also an important part of cancer prevention since what we eat has been linked to the disease. Physicians recommend diets that are low in fat and rich in fresh fruits and vegetables and whole grains.

Certain vaccinations have been associated with the prevention of some cancers. For example, many women receive a vaccination for the human papillomavirus because of the virus's relationship with cervical cancer. Hepatitis B vaccines prevent the hepatitis B virus, which can cause liver cancer.

Some cancer prevention is based on systematic screening in order to detect small irregularities or tumors as early as possible even if there are no clear symptoms present. Breast self-examination, mammograms, testicular self-examination, and Pap smears are common screening methods for various cancers.
What is prostate cancer?

Normally in the prostate, as in the rest of the body, there is a continuous turnover of cells, with new cells replacing old dying ones. In a cancer the balance between the new and old cells is lost, with many more new ones being made and older ones living longer.

Cancer of the prostate can be defined as uncontrolled prostate cell growth.

The malignant growths are known as tumors. They differ from benign tissue enlargements in that the cancerous cells can spread (metastasis) to surrounding tissue, including the rectum and bladder.

However, sometimes the cancer can be detected before it has spread outside the prostate. At this stage the cancer is still treatable with a good rate of success.

How does prostate cancer spread?

Cancer cells can spread directly to neighboring parts of the body, such as the seminal vesicles or bladder, by growing outwards through the outer wall or capsule of the prostate. They may occasionally spread through the blood stream and implant in growing bones of the spine.

Finally, cells can also be spread through lymph vessels. These vessels are like a second system of veins except that, instead of blood, they contain a milky fluid that is made up of the cells waste products. Lymph vessels drain via lymph nodes (special bean shaped filters) that eventually empty back in to the blood circulation. During this process the lymph nodes can also be invaded by cancerous cells.

How common is prostate cancer?

Prostate cancer is now the most common cancer in men in the UK with nearly 20,000 men being diagnosed with the disease and 10,000 men dying from it each year. However there have been many recent advances in detecting and treating prostate cancer and patients who are diagnosed early can now have a high chance of cure.

Prostate cancer rarely occurs before 50 years of age and is most commonly seen in men in their 60s and 70s. Indeed, it seems almost inevitable that if one lives long
enough, prostate cancer will develop. However, this does not mean that all men will be aware of the cancer, need any treatment or even die because of the disease.

**Why does prostate cancer occur?**

**The full answer to this question is not known.**

Nevertheless, there are a number of factors that can increase the chance of developing prostate cancer. Relatives of patients with prostate cancer have an increased risk of developing the disease themselves, especially if their father or brother were affected.

The disease is more common in the Afro-American population and rarer in the Chinese. There also appears to be a link with people living in urban areas exposed to pollution and to those consuming large quantities of dietary fat.

**Diet and prostate cancer**

Studies in twins suggest that 45% of prostate cancers are caused by genetics. Migration studies have confirmed the strong influence (55% of prostate cancers) of environmental factors on the risk of developing prostate cancer.

An individual's genetic make-up cannot be altered but environmental influences, the most important of which are dietary, can be modified to reduce this risk.

The following have been shown in medical studies to:

**Reduce the risk of prostate cancer**

- Vitamins A, D & E
- Selenium - found in Brazil nuts
- Carotenoids - especially lycopene, found in (particularly cooked) tomatoes.
- Phytoestrogens - especially soy products, as well as cereals, fruit and vegetables
- Chinese green tea

**Increase the risk of prostate cancer**

- A diet which is heavy in animal fat
- Obesity

**What are the symptoms of prostate cancer?**

There are often no symptoms associated with the early stage prostate cancer. As the disease progresses and the tumour enlarges it may compress and constrict the urethra which runs through the gland, obstructing the flow of urine during urination.
In this situation the patient may notice a weak, interrupted stream of urine that requires straining to urinate. On completion he may still feel that the bladder is not empty.

However these symptoms are not specific to prostate cancer and are most commonly found in benign non-cancerous enlargements of the gland.

Blood in the semen may also be a sign of prostate cancer, although again it is a common finding and not normally related to malignancy.

If a tumour has spread to the bones then it may cause pain. The spine is the most common site for this to occur.

**What does the stage of prostate cancer mean?**

The stage of a prostate cancer refers to how far the cancer has spread. The classification commonly used to stage prostate cancer in the UK is shown here in a simplified form. (The prefix T is used by convention to identify the tumour stage, i.e. T1 or T2). It is very important to remember that although all prostate cancers have the potential to progress; it may take many years to pass from Stage 1 to 4.

**Stage 1**

Earliest stage, where the cancer is so small that it cannot be felt on rectal examination, but is discovered in a prostate biopsy or in prostate tissue that has been surgically removed to ‘unblock’ the flow of urine (as in a transurethral resection of the prostate – TURP).

**Stage 2**

The tumour can now be felt on rectal examination, but is still confined to the prostate gland and has not spread.

**Stage 3**

The tumour has spread outside the gland and may have invaded the seminal vesicles.

**Stage 4**

The tumour has spread to involve surrounding tissues such as the rectum, bladder or muscles of the pelvis.
How is prostate cancer diagnosed?
During a consultation the doctor will initially ask the patient questions to ascertain their general medical health and to see if they are experiencing any symptoms associated with prostate cancer (although, as has been mentioned, such symptoms are not specific to prostate cancer).

Physical examination
Having made a general examination the doctor will then need to perform a rectal examination to feel the gland. A gloved lubricated finger is inserted in to the back passage (rectum) to assess the size and shape of the prostate gland.
Blood test

The prostate can be evaluated by testing for the level of a particular protein in the blood called PSA (prostate specific antigen). Prostate enlargement tends to cause an increase in the level of PSA, with malignant tumors producing a greater increase than benign enlargements. Other, unrelated, conditions can also cause PSA to rise, such as a urinary infection.

The normal range in general for PSA is between 0 and 4 nanograms per millilitre (ng/ml) and as this level rises the chance of a patient having prostate cancer also increases. Clinicians often use an age related PSA range as shown below. The PSA gradually rises with age due to a natural increase in benign prostate tissue, that also makes PSA, which occurs with aging. Patients with widespread cancer may have levels of more than 100 nanograms per mil.

Historical standard options include:

- **Surgery (radical prostatectomy):** An incision is made in the lower abdomen or through the perineum (between the anus and the scrotum), and the prostate is removed. Incomplete surgery, in which the entire tumor cannot be removed, may need to be followed by radiation therapy. Possible side effects of surgery can include incontinence (inability to control urination) and impotence (inability to achieve erection). More recently, several centers are using three small incisions to do robot assisted prostatectomy that results in shorter hospitalization and faster recuperation. This may be preferable for selected patients, but not for all.

- **External beam therapy (EBT):** A method for delivering a beam of high-energy x-rays to the location of the tumor. The beam is generated outside the patient (usually by a linear accelerator) and is targeted at the tumor site. These x-rays can destroy the cancer cells and careful treatment planning allows the surrounding normal tissues to be spared. No radioactive sources are placed inside the patient's body.

- **Watchful waiting:** No treatment, with careful observation and medical monitoring.

Newer, advanced options have been developed in the past 10 to 15 years. These newer options avoid or minimize some of the unpleasant side effects sometimes associated with the standard therapies. These options include:

- **Nerve-sparing radical prostatectomy:** Surgical procedure in which the prostate gland is removed without severing the critical nearby nerves that
send signals between the brain and penis to allow normal sexual functioning. A skilled and experienced surgeon may be able to preserve sexual function in 50 percent to 90 percent of patients by successfully using this procedure.

- **Conformal external beam radiation therapy**: Uses advanced technology to tailor the radiation therapy to an individual's body structures. Relying on computerized three-dimensional images of the prostate, bladder and rectum, the x-ray radiation beam is aimed precisely ("conformed") to affect the diseased area. In this way, less radiation reaches the surrounding normal tissues. Today there are two levels of conformal radiation therapy: 3-D conformal radiation therapy and intensity modulated radiation therapy (IMRT). Both allow for increased doses to the tumor while protecting the normal surrounding organs. IMRT is considered the more conformal of the two but is not necessary or appropriate for all patients.

- **Image-guided radiation therapy**: for either 3-D conformal or IMRT, daily image guidance is increasingly used. Typically three gold fiducial markers, or tiny pieces of metal, are placed in the prostate before the simulation and treatment. X-rays are taken either with the same beam as that of the treatment or an add-on low energy x-ray beam aligned to the linear accelerator. The metallic markers will be visible on the x-rays. This is done to check the position of the prostate on a daily basis just before the treatment and appropriate adjustment and alignment of prostate to high-dose external beam radiation therapy.

- **Proton beam therapy**: a type of conformal therapy that bombards the diseased tissue with protons instead of x-rays.

- **Cryotherapy**: A procedure that uses extremely low temperatures (-190°C) to freeze and destroy cancer cells. Some experienced physicians have had good results with low complication rates using cryotherapy; however, others have not. This should be considered experimental at this time as upfront treatment for prostate cancer, until there is longer follow-up for patients treated with this modality. This technique was developed as an alternative to surgery for patients who have recurrent cancer in the prostate after radiation treatments.

- **Brachytherapy**: the temporary placement of radioactive materials within the body, usually employed to give an extra dose—or boost—of radiation to the area of the excision site.

With seed implant treatment, radiation hits the prostate first, and only then it strikes normal tissues. While the implant technique has been around for decades, recent advances in imaging technology have made it more effective. Using ultrasound to see the prostate gland better, physicians can place each seed in the
prostate more carefully and better control the effect on surrounding tissues. Long-term results are available for up to 10—12 years at some institutions. These results show that ultrasound-guided radioactive implantation is highly effective in controlling prostate cancer and has essentially the same result as surgery or external radiation for appropriately selected low-risk prostate cancer patients.

- **High Dose Rate (HDR) Brachytherapy:** This technique was developed to supplement the dose of radiation given as external beam therapy for patients with high risk prostate cancer. In skilled hands, this is an effective regimen to treat such cancers. Patients receive several weeks of standard external beam radiation therapy, followed by one to three HDR sessions. These sessions require anesthesia and placement of several needles into the prostate. The patient is then hooked up to the HDR machine, where a radioactive source moves up and down each needle, delivering radiation. This type of brachytherapy leaves no permanent radiation in the patient.

Use of this technique by itself (i.e., without the external beam treatments) for low-risk patients is still in the experimental stages.

**Biochemical pathway of prostrate cancer:**

Prostate cancer constitutes a major health problem in Western countries. It is the most frequently diagnosed cancer among men and the second leading cause of male cancer deaths. Early detection through serum testing for prostate specific antigen (PSA) and improved procedures for surgical intervention and radiation therapy have significantly reduced the number of fatalities; however, there is still no effective cure for men with advanced disease. The identification of key molecular alterations in prostate-cancer cells implicates carcinogen defenses (GSTP1), growth-factor-signaling pathways (NKX3.1, PTEN, and p27), and androgens (AR) as critical determinants of the phenotype of prostate-cancer cells and defines specific targets for the detection, diagnosis, and treatment of prostate cancer. Although the drugs that are currently in use for the treatment of prostate cancer disrupt androgen action, in the future, new drugs that interfere with other growth-signaling pathways will be pursued.

The identification of key molecular alterations in prostate-cancer cells implicates carcinogen defenses (GSTP1), growth-factor-signaling pathways (NKX3.1, PTEN, and p27), and androgens (AR) as critical determinants of the phenotype of prostate-cancer cells. Glutathione S-transferases (GSTP1) are detoxifying enzymes that catalyze conjunction of glutathione with harmful, electrophilic molecules, thereby
protecting cells from carcinogenic factors. Cells of prostatic intraepithelial neoplasia, devoid of GSTP1, undergo genomic damage mediated by such carcinogens. NKX3.1, PTEN, and p27 regulate the growth and survival of prostate cells in the normal prostate. Inadequate levels of PTEN and NKX3.1 lead to a reduction in p27 levels and to increased proliferation and decreased apoptosis. After therapeutic reduction in the levels of testosterone and dihydrotestosterone, the emergence of androgen-independent prostate cancer has been associated with mutations in the androgen receptor (AR) that permit receptor activation by other ligands, increased expression of androgen receptors accompanying AR amplification, and ligand-independent androgen-receptor activation.
Fig No 5: Biochemical pathway of prostate cancer
Drug target for prostate cancer:

Finasteride:
Androgens are involved in the development of prostate cancer. Finasteride, an inhibitor of 5alpha-reductase, inhibits the conversion of testosterone to dihydrotestosterone, the primary androgen in the prostate, and may reduce the risk of prostate cancer.

Finasteride is used for the treatment of benign prostatic hyperplasia (BPH) (also known as enlarged prostate) at a dose of 5 mg once a day. It may take six months or more to see the full effects of finasteride. If the drug is discontinued, any therapeutic benefits will be reversed. Finasteride may improve the symptoms associated with BPH such as difficulty urinating, getting up during the night to urinate, hesitation at the start of urination, and decreased urinary flow.

Fig no: 6 Structure of finasteride

Finasteride is used alone or in combination with another medication (doxazosin [Cardura]) to treat benign prostatic hypertrophy (BPH, enlargement of the prostate gland). Finasteride improves symptoms of BPH such as frequent and difficult urination and may reduce the chance of acute urinary retention (suddenly being unable to pass urine). It also may decrease the chance of needing prostate surgery. Finasteride is also used to treat male pattern hair loss (a common condition in which men have gradual thinning of the hair on the scalp, leading to a receding hairline or balding on the top of the head.) Finasteride has not been shown to treat thinning hair at the temples and is not used to treat hair loss in women or children. Finasteride is in a class of medications called 5-alpha reductase inhibitors. Finasteride treats BPH by blocking the body's production of a male hormone that causes the prostate to enlarge. Finasteride treats male pattern hair loss by blocking the body's production of a male hormone in the scalp that stops hair growth.

Finasteride may cause side effects:

- inability to have or maintain an erection
- decreased sexual desire
- decreased volume of ejaculate (amount of semen)
• pain in the testicles

2 Dutasteride:

Dutasteride is used to treat an enlarged prostate (benign prostatic hyperplasia, or BPH). Dutasteride is in a class of medications called 5-alpha reductase inhibitors. It works by blocking the production of a natural substance that enlarges the prostate. This shrinks the prostate, relieves symptoms of BPH, such as frequent and difficult urination, and decreases the chance that surgery will be needed to treat this condition.

![Structure of dutasteride](image)

**Fig No: 7** Structure of dutasteride

Dutasteride belongs to a class of drugs called 5-alpha-reductase inhibitors, which block the action of the 5-alpha-reductase enzymes that convert testosterone into dihydrotestosterone (DHT). Finasteride, which is also approved for BPH, but also the treatment of hair loss, belongs to this group of drugs. Dutasteride inhibits both isoforms of 5-alpha reductase, Type I and Type II, while finasteride only inhibits Type II. A clinical study done by GlaxoSmithKline, the EPICS trial, did not find dutasteride to be more effective than finasteride in treating BPH.

It works by lowering amounts of the hormone responsible for prostate growth (dihydrotestosterone). Dutasteride reduces urinary blockage and improves urine flow.

3 Dutasteride may cause side effect:

• inability to have or maintain an erection
- decrease in sex drive
- difficulty ejaculating
- breast tenderness or enlargement

The teratogenic effect from Dutasteride is harmful to male children. Women who are pregnant should not handle the capsules, as inadvertent consumption will cause birth defects of the male fetus. The effect would be similar to 5-alpha-reductase deficiency, where a developing male child is naturally deficient in 5-alpha reductase Type II, and thus unable to synthesize it. As dutasteride blocks the same process, developing males would have a DHT deficiency with its adverse effects as a result of the drug.

**Cancer chemoprevention:**

Prostate cancer (CaP) is second only to lung cancer as the cause of cancer-related deaths in American men and is responsible for over 29,000 deaths per year. One promising approach to reduce the incidence of CaP is through chemoprevention, which has been recognized as a plausible and cost-effective approach to reduce cancer morbidity and mortality by inhibiting precancerous events before the occurrence of clinical disease. Indeed, CaP is an ideal candidate disease for chemoprevention because it is typically diagnosed in the elderly population with a relatively slower rate of growth and progression, and therefore, even a modest delay in the development of cancer, achieved through pharmacologic or nutritional intervention, could result in substantial reduction in the incidence of clinically detectable disease. In this review, we have summarized the recent investigations and mechanistic studies on CaP chemoprevention using dietary agents, such as selenium, vitamins D and E, lycopene, phytoestrogens, flavonoids, and green tea polyphenols. Well-designed trials are required to delineate the potential clinical usefulness of these agents through issues, such as determining the optimal period and route of administration, systemic bioavailability, optimal dosing and toxicity of the agent, and single or combinatorial approach. It is hoped that, combining the knowledge based on agents with targets, effective approaches for CaP chemoprevention can be established.

### 3.1 Principles of Chemoprevention

The multistage process of cancer development leading to clinically visible and metastasized cancers in humans is a long process, generally taking many years through well-defined stages, known as initiation, promotion, and progression.
Chemoprevention is defined as the use of specific agents to block or delay the process of carcinogenesis, thereby preventing the development of invasive cancer. The basic difference between cancer chemoprevention and cancer treatment lies in that the goal of the former approach is to lower the rate of cancer incidence by delaying or suppressing the process of cancer development. It is now recognized that cancer chemoprevention can be achieved by targeting various cell processes. Blocking the formation of the ultimate carcinogen by inhibiting its uptake by the body and/or inhibiting the formation of carcinogenic compounds or preventing metabolic activation of procarcinogens might well be one of the mechanisms to accomplish this goal. Secondarily, deactivation and detoxification through phase I and phase II metabolic enzymes, prevention of carcinogen binding to DNA with inhibition of DNA-carcinogen adduct formation, enhanced DNA repair, and modulation of enzymes like poly(ADP-ribosyl)transferase are other target processes of chemoprevention.

Compounds may exert their chemopreventive effect by scavenging oxygen radicals or inhibiting polyamine metabolism, thereby preventing mutagenesis and uncontrolled cell proliferation. Others may exert their antiproliferative effect through regulation of signal transduction pathways or modulation of hormones, growth factors, or target receptors present in the cells. Induction of apoptosis, inhibition of angiogenesis, preventing basement membrane degradation, and activation of antimetastasis genes are other mechanisms through which chemopreventive agents may act to retard the growth of tumor cells. The importance and usefulness of antibodies to oncogene products or oncoproteins cannot be ignored. Restoration of immune response with compounds acting as immunostimulants may result in augmentation of cell-mediated and natural killer cell cytotoxicity.

Numerous phytochemicals derived from edible plants have been reported to interfere with a specific stage of the carcinogenic process. Many mechanisms have been shown to account for the anticarcinogenic actions of dietary constituents, but attention has recently been focused on intracellular-signalling cascades as common molecular targets for various chemopreventive phytochemicals.
**Biochemical Pathway of Cancer Chemoprevention:**

The NF-κB signalling pathway converges on the multiprotein complex called the IκB kinase (IKK) signalsome, leading to IκB phosphorylation (P), ubiquitylation (Ub) and subsequent degradation by the 26S proteasome. NF-κB is then released and translocated to the nucleus, where it binds to specific promoter regions of various genes. The IKK signalsome is activated by the NF-κB-inducing kinase (NIK). Pathways that regulate NIK are likely to involve signalling through a family of mitogen-activated protein kinases (MAPKs), such as MAPK kinase kinase-1 (MEKK1) — a kinase that lies upstream of extracellular signal-regulated kinase (ERK) — MAPK/ERK kinase (MEK1/2) and p38 MAPK. Recent reports showed...
that NF-κB activation is also regulated by the AKT signalling pathway. Phosphatidylinositol 3-kinase (PI3K) activates AKT/protein kinase B via phosphorylation by 3-phosphoinositide-dependent protein kinase-1 (PDK1). Genistein specifically inhibits AKT activity and AKT-mediated NF-κB activation. Epigallocatechin gallate (EGCG) can block the activities of PI3K and AKT. There is crosstalk between the AKT and NF-κB signalling pathways — AKT phosphorylation leads to activation of NF-κB by stimulating IκB kinase (IKK) activity. IKK is also a target for chemopreventive phytochemicals, including curcumin, resveratrol and EGCG. The MAPK family proteins also regulate expression of AP1 — a heterogenous set of dimeric proteins made up of members of the c-JUN, c-FOS and ATF families. In this pathway, activation of ERK1/2 phosphorylates ELK1, c-JUN NH2-terminal kinase (JNK) phosphorylates c-JUN, and p38 phosphorylates both ELK1 and ATF2. This leads to transcriptional activation of target genes. External stimuli — including phorbol ester and ultraviolet radiation — activate specific isoforms of protein kinase C (PKC), which, in turn, leads to stimulation of the p21 RAS-ERK signalling pathway via RAF and MEK1/2. Activation of p38 and JNK is mediated by MAPK kinase-4 (MKK4), which is under control of the upstream kinase MEKK.
Nuclear Receptor Superfamilies:

Nuclear receptors play many important roles in eukaryotic development, differentiation, reproduction and metabolic homeostasis (Ribeiro et al., 1995; Bain et al., 2006). Proteins of the nuclear receptor super-family are single polypeptide chains with three major domains: a variable amino-terminal domain, a highly conserved DNA-binding domain (DBD), and a less conserved carboxyl-terminal ligand binding domain (LBD). The superfamily is sub-divided into three classes. Class 1 is the steroid receptor family, and includes the progesterone receptor (PR), the estrogen receptor (ER) (Figure 1), the glucocorticoid receptor (GR), the androgen receptor (AR) and the mineralocorticoid receptor. Class 2, or the thyroid/retinoid family, includes the thyroid receptor (TR), vitamin D receptor (VDR), the retinoic acid receptor (RAR) and the peroxisome proliferator-activated receptor (PPAR). The third class of nuclear receptors is known as the orphan receptor family. This class of nuclear receptor comprises a set of proteins sharing significant sequence homology to known nuclear receptors, but for which the ligands have not yet been identified. Orphan nuclear receptor offer a unique system for the discovery of novel signaling pathways that could provide new drug targets for the treatment of a variety of human diseases.

Subfamily 1: Thyroid Hormone Receptor-like
- Group A: Thyroid hormone receptor (Thyroid hormone)
  - 1: Thyroid hormone receptor-α (TRα; NR1A1, THRA)
  - 2: Thyroid hormone receptor-β (TRβ; NR1A2, THRβ)

- Group B: Retinoic acid receptor (Vitamin A and related compounds)
  - 1: Retinoic acid receptor-α (RARα; NR1B1, RARA)
  - 2: Retinoic acid receptor-β (RARβ; NR1B2, RARB)
  - 3: Retinoic acid receptor-γ (RARγ; NR1B3, RARG)

- Group C: Peroxisome proliferator-activated receptor (fatty acids, prostaglandins)
  - 1: Peroxisome proliferator-activated receptor-α (PPARα; NR1C1, PPARA)
  - 2: Peroxisome proliferator-activated receptor-β/δ (PPARβ/δ; NR1C2, PPARD)
  - 3: Peroxisome proliferator-activated receptor-γ (PPARγ; NR1C3, PPARG)

- Group D: Rev-ErbA (heme)
  - 1: Rev-ErbAα (Rev-ErbAα; NR1D1)
  - 2: Rev-ErbAβ (Rev-ErbAβ; NR1D2)
• Group F: RAR-related orphan receptor (cholesterol, ATRA)
  o 1: RAR-related orphan receptor-α (RORα; NR1F1, RORA)
  o 2: RAR-related orphan receptor-β (RORβ; NR1F2, RORB)
  o 3: RAR-related orphan receptor-γ (RORγ; NR1F3, RORC)

• Group H: Liver X receptor-like (oxysterol)
  o 1: Liver X receptor-α (LXRα; NR1H3)
  o 2: Liver X receptor-β (LXRβ; NR1H2)
  o 3: Farnesoid X receptor (FXR; NR1H4)

• Group I: Vitamin D receptor-like
  o 1: Vitamin D receptor (VDR; NR1I1, VDR) (vitamin D)
  o 2: Pregnane X receptor (PXR; NR1I2) (xenobiotics)
  o 3: Constitutive androstane receptor (CAR; NR1I3) (androstane)

Subfamily 2: Retinoid X Receptor-like
• Group A: Hepatocyte nuclear factor-4 (HNF4) (fatty acids)
  o 1: Hepatocyte nuclear factor-4-α (HNF4α; NR2A1, HNF4A)
  o 2: Hepatocyte nuclear factor-4-γ (HNF4γ; NR2A2, HNF4G)

• Group B: Retinoid X receptor (RXRα) (retinoids)
  o 1: Retinoid X receptor-α (RXRα; NR2B1, RXRA)
  o 2: Retinoid X receptor-β (RXRβ; NR2B2, RXRB)
  o 3: Retinoid X receptor-γ (RXRγ; NR2B3, RXRG)

• Group C: Testicular receptor
  o 1: Testicular receptor 2 (TR2; NR2C1)
  o 2: Testicular receptor 4 (TR4; NR2C2)
• Group E: TLX/PNR
  o 1: Human homologue of the Drosophila tailless gene (TLX; NR2E1)
  o 3: Photoreceptor cell-specific nuclear receptor (PNR; NR2E3)

• Group F: COUP/EAR
  o 1: Chicken ovalbumin upstream promoter-transcription factor I (COUP-TFI; NR2F1)
  o 2: Chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII; NR2F2)
  o 6: V-erbA-related gene | V-erbA-related (EAR-2; NR2F6)

Subfamily 3: Estrogen Receptor-like
• Group A: Estrogen receptor (Sex hormones: Estrogen)
  o 1: Estrogen receptor-α (ERα; NR3A1, ESR1)
  o 2: Estrogen receptor-β (ERβ; NR3A2, ESR2)

• Group B: Estrogen related receptor
  o 1: Estrogen-related receptor-α (ERRα; NR3B1, ESRRRA)
  o 2: Estrogen-related receptor-β (ERRβ; NR3B2, ESRRRB)
  o 3: Estrogen-related receptor-γ (ERRγ; NR3B3, ESRRG)

• Group C: 3-Ketosteroid receptors
  o 1: Glucocorticoid receptor (GR; NR3C1) (Cortisol)
  o 2: Mineralocorticoid receptor (MR; NR3C2) (Aldosterone)
  o 3: Progesterone receptor (PR; NR3C3, PGR) (Sex hormones: Progesterone)
  o 4: Androgen receptor (AR; NR3C4, AR) (Sex hormones: Testosterone)

Subfamily 4: Nerve Growth Factor IB-like
• Group A: NGFIB/NURR1/NOR1
  o 1: Nerve Growth factor IB (NGFIB; NR4A1)
  o 2: Nuclear receptor related 1 (NURR1; NR4A2)
  o 3: Neuron-derived orphan receptor 1 (NOR1; NR4A3)

Subfamily 5: Steroidogenic Factor-like
• Group A: SF1/LRH1
  o 1: Steroidogenic factor 1 (SF1; NR5A1) (phospholipids)
  o 2: Liver receptor homolog-1 (LRH-1; NR5A2)

Subfamily 6: Germ Cell Nuclear Factor-like
• Group A: GCNF
  o 1: Germ cell nuclear factor (GCNF; NR6A1)

Subfamily 0: Miscellaneous
• Group B: DAX/SHP
  o 1: Dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (DAX1, NR0B1)
  o 2: Small heterodimer partner (SHP; NR0B2)

• Group C: Nuclear receptors with two DNA binding domains (2DBD-NR)
Nuclear receptors and mechanisms of signaling: All nuclear receptors modulate gene transcription, although amongst the three classes there are differences in the mechanisms through which this is achieved (Ribeiro, 1995; Aranda and Pascual, 2001; Bain et al., 2006). Ligands for nuclear receptors circulate in the body bound to plasma proteins. Following dissociation from these proteins the ligands enter cells and bind to their receptors. Steroids and vitamin D probably enter cells through passive diffusion, whereas thyroid hormone and retinoic acid might gain cellular entrance via specific transport processes.

Steroid receptors are bound to Hsps, such as Hsp90 and Hsp70, in the cytoplasm. Upon binding ligand, the free receptors then translocate to the nucleus and bind as homodimers to imperfect palindromic response elements at upstream promoter sites. DNA binding is coupled to the recruitment of transcriptional co-activators such as the p160 family (Xu and Li, 2003). Nuclear receptors can in some instances repress gene expression in a ligand-dependent manner, and in some cases promote gene transcription.

The class 2 nuclear receptors typically function as heterodimers. TR, VDR, RAR and PPAR associate with the retinoid X receptor (RXR) and bind as a dimeric complex to direct repeat response elements (Ribeiro, 1995; Aranda and Pascual, 2001; Eckey et al., 2003; Bain et al., 2006). The heterodimers are bound to their response element regardless of whether ligands are present and in the absence of heat shock proteins. Gene activation is suppressed by co-repressors such as silencing mediator for retinoic acid and thyroid hormone receptors (SMRT) and nuclear co-repressor (NCoR). Co-repressors are displaced by ligand binding allowing transcriptional activation to take place (Collingwood et al., 1999).

Nuclear receptor structure:

A typical nuclear receptor consists of a variable NH2 terminal region (the A/B domain) and a highly conserved DNA-binding domain (DBD or C domain) (Tata, 2002; Robinson-Rechavi et al., 2003; Bain et al., 2006). The DBD contains a P-box, which is a short motif responsible for DNA-binding specificity and is involved in dimerization of nuclear receptors including the formation of both heterodimers and homodimers. The elucidiation of the 3D structure of the DBD reveals the presence of two zinc fingers.

A linker region known as domain D is situated between the DBD and the ligand binding domain. This region functions as a flexible hinge and contains the nuclear localization signal. Phosphorylation of the hinge region is coupled with increased transcriptional activation. The ligand binding domain (LBD or E domain) is
responsible for the binding of cognate ligand or hormone. This domain also contains a ligand-regulated transcriptional activation function (AF-2) necessary for recruiting transcriptional co-activators, which interact with chromatin remodeling proteins and the general transcriptional activation machinery. Most nuclear receptors contain an amino acid sequence N-terminal to the DBD in the variable A/B domain, which contains a transcriptional activation function known as AF-1. In contrast to the moderately conserved AF-2, the AF-1 shows weak conservation across the nuclear receptor super-family and may mediate differential promoter regulation in vivo. The AF-1 sequence functions as a ligand-independent transcriptional activator, but can also functionally synergize with AF-2.

**Figure 9: Nuclear receptor structure**

Proteins of the nuclear receptor super-family are single polypeptide chains consisting of three major domains: a variable amino-terminal domain, a highly conserved DNA-binding domain (DBD), and a less conserved carboxyl-terminal ligand binding domain (LBD). AF: activation function (domain 1 and 2). H: hinge. Mutations in the nuclear hormone receptors lead to a variety of inherited disorders. Mutations in X-linked ARs result in testicular feminization syndrome with androgen unresponsiveness or hypo-responsiveness. Glucorticoid resistance and hereditary vitamin D resistant rickets are rare autosomal recessive disorders linked to mutations in the LBD or the DBD of the GR or the VDR respectively (Ribeiro et al., 1995).
5-alpha reductase:

5-alpha reductase is an enzyme that was first discovered in the male prostate. Here it catalyzes the conversion of testosterone to dihydrotestosterone, which in turn binds to the androgen receptor and initiates development of the external genitalia and prostate. The gene for 5-alpha reductase has been mapped to chromosome 5.

Androgens are the crucial factors to stimulate the initial interactions between the epithelium and mesenchyme. One of the key events in androgen metabolism is the transformation of circulating testosterone to 5α-dihydrotestosterone (DHT) by tissue-linked 5α-reductase. Both, the formation of a male phenotype and the androgen-mediated growth of the prostate are mediated by DHT. To date the function of 5α-reductase 1 (5αR1) still remains unclear whereas 5α-reductase 2 (5αR2) is supposed to be the predominant isoenzyme in human accessory sex tissue. Only little data are New studies confirm that both isoenzymes are present throughout fetal development. The function of 5-alpha-reductase 1 (5αR1) regarding its effects on urogenital sinus development still remains unclear while 5-alpha-reductase 2 (5αR2) is considered predominant in human accessory sex tissue and is responsible for prostate and male external genitalia development. The same is true for downstream products of DHT-action, namely 17β-hydroxysteroid-dehydrogenase 2 (17βHSD 2), 3 (17 βHSD 3), and 7 (17 βHSD 7). They act as steroidogenic enzymes regulating hormone homeostasis in target organs.

Meanwhile it has been proven that abnormalities in androgen metabolism, reductase activity and the androgen receptor can result in a broad spectrum of disturbances in sex development.

Realizing the physiological role of 5αR1 and 5αR2 it is necessary to expose their experssional time itinerary and allocation within the developing prostate. Therefore investigating the involvement of both isoforms in branching and budding processes in the fetal prostate is mandatory. Research focusing on the basics of prostate cancer and benign prostatic disorders already emphasized the pathophysiological importance of both enzymes. As a final point, the central role of 5αR1 in human genital development should be revisited.
5-alpha reductase deficiency:

5-alpha-reductase is an enzyme that converts testosterone to dihydrotestosterone (DHT) in peripheral tissues. 5-alpha-reductase deficiency-2 is biochemically characterized by low to low normal levels of testosterone and decreased levels of 5α-DHT, creating a higher testosterone/DHT ratio.

Figure 10 - Biochemical effects of 5-alpha-reductase type 2 deficiency in testosterone biosynthesis. Typically levels of testosterone are elevated, whereas levels of dihydrotestosterone (DHT) are significantly decreased, leading to male undervirilization.

A deficiency of the type 2 isozyme 5-alpha-reductase, which transforms testosterone to DHT, is the root cause of this disorder. The conversion involves hydroxylation at the 5 carbon position of the A ring of the steroid molecule. This steric change flattens the configuration of DHT, allowing it to fit into the androgen receptor in a way testosterone cannot. Thus, DHT, the most potent androgen, is bound selectively to the androgen receptors in genital skin and fibroblasts, making its action necessary for the development of normal male genital anatomy in the fetus. As with most
single enzyme disorders, 5-alpha-reductase type 2 deficiency is autosomal recessive and sex limited because it only affects genetic males.

The major issue for individuals with 5-alpha-reductase type 2 deficiency (5-ARD) is gender assignment. Almost all children with 5-alpha-reductase type 2 deficiency are assigned a female gender at birth.

Some males with 5-alpha-reductase type 2 deficiency respond with an increase in penile size when 2% dihydrotestosterone (DHT) cream is applied to the lower abdomen.

Two genes coding for 5-alpha-reductase have been identified, each for a slightly different isoenzyme. The gene for 5-alpha-reductase type 1 has been determined to be on chromosome 5. Its product is expressed only in nongenital skin and liver at low levels from the time the individual is aged 3 years to puberty, at which time enzyme expression is measurable in sebaceous glands and scalp. Linkage analysis has demonstrated that the type 1 enzyme is unrelated to the clinical syndrome of 5-alpha-reductase type 2 deficiency. The other isoenzyme, 5-alpha reductase type 2, determined on chromosome 2, correlates with clinical symptoms. It is expressed in high levels in the prostate and other androgen-sensitive tissues. Interestingly, partial virilization of males with 5-alpha-reductase type 2 deficiency occurs at puberty and may be attributable to the rise in type 1 enzyme activity at that time.

More recently, 5-alpha reductase was found in human scalp and elsewhere in the skin, where it carries out the same reaction as in the prostate. It is thought that disturbances in 5-alpha reductase activity in skin cells might contribute to male pattern baldness, acne, or hirsutism. The discovery of a plant homolog of human 5-alpha reductase may lead to new drugs, and the race is now on to find inhibitors of 5-alpha reductase.

**Classification of the two isoforms:**

**Type 1:**
- **Number of amino acids** = 259
- **Tissue expressed** = in skin and scalp of newborns and permanently expressed in skin from the time of puberty, also expressed in liver.
- **Function** = androgen regulation of sebaceous glands and sebum production
Type 2:
- **Number of amino acid** = 254
- **Tissue expressed** = The type 2 isozyme is transiently expressed in skin and scalp of newborns. Type 2 is the predominant isozyme detectable in fetal genital skin, male accessory sex glands, and in the prostate, including benign prostatic hyperplasia and prostate adenocarcinoma tissues.
- **Function** = while 5-alpha-reductase 2 (5αR2) is considered predominant in human accessory sex tissue and is responsible for prostate and male external genitalia development.

**Role of 5 Alpha Reductase type 2 inhibitors in Prostate Cancer**

5α-reductase inhibitors (or 5-alpha-reductase inhibitors) are a group of drugs with antiandrogenic activity, used in the treatment of benign prostatic hyperplasia and androgenic (or androgenetic) alopecia. These drugs decrease the levels of available 5α-reductase prior to testosterone binding with the enzyme, thus reducing levels of dihydrotestosterone that derives from such a bond.

The enzyme 5α-reductase is involved in the conversion of testosterone to the active form dihydrotestosterone by reducing the Δ4,5 double-bond. In benign prostatic hyperplasia, dihydrotestosterone acts as a potent cellular androgen and promotes prostate growth - inhibiting the enzyme reduces the excessive prostate growth. In alopecia, male-pattern baldness is one of the effects of androgenic receptor activation. Reducing the levels of dihydrotestosterone thus reduces alopecia.

**5 Alpha Reductase Inhibitors and BPH:**

By inhibiting the production of dihydrotestosterone (DHT) locally within the prostate gland, 5alpha-reductase inhibitors have the effect of reducing prostate volume, improving lower urinary tract symptoms, increasing peak urinary flow, and decreasing the risk of acute urinary retention and need for surgical intervention. The combination of a 5alpha-reductase inhibitor and a alpha1-adrenergic antagonist significantly reduces the clinical progression of BPH over either drug class alone.
3.1.1 Purpose of 5-alpha Reductase Inhibitors:

5-alpha reductase inhibitors are not recommended for males with benign prostatic hyperplasia signs and symptoms without a diagnosed enlarged prostate gland. 5-alpha reductase inhibitors may be ordered for males who experience bothersome, slightly moderate symptoms of benign prostatic hyperplasia.

Most patients who take 5-alpha reductase inhibitors describe approximately a 3-point reduction in their American Urologic Association (AUA) symptom index.

5-alpha-reductase inhibitors are also called anti-androgen therapy or hormone therapy.

3.1.2 Side Effects of 5-alpha Reductase Inhibitors:

5-alpha reductase inhibitors seem to be extremely safe and greatly tolerated compared to many other similar drugs. Side effects demonstrated in the first year of consumption include diminished sex drive and breast soreness or expansion.

5-alpha reductase inhibitors decrease PSA (prostate specific antigen) amounts. PSA storages are used to observe early-stage prostatic adenocarcinoma (a form of cancer) Because these drugs affect your sex hormones, sexual problems are the most common side effects. Most of these side effects are caused by the drop in DHT. You may find that you get:

- Problems getting or keeping an erection. Doctors call this **erectile dysfunction**. About 5 in every 100 men taking finasteride get this problem
- A loss of sex drive. Doctors call this **loss of libido**. About 3 in 100 men taking finasteride have less urge to have sex

**Problems ejaculating.** You may produce less fluid (semen) when you have an orgasm or no fluid at all. Doctors call this **ejaculatory dysfunction** or **retrograde ejaculation**. It's more commonly known as dry climax. About 2 in 1,000 men taking finasteride get this problem.
MATERIALS AND METHODS:

Literature and review:

1. **Cichoric acid** is an organic compound which is found in members of the Echinacea species of plants. It is a derivative of both caffeic acid and tartaric acid. It has the chemical formula C22H18O12. Cichoric acid has been found in the roots, stems, flowers and leaves of Echinacea pallida, Echinacea purpurea, and Echinacea angustifolia. Cichoric acid has been shown to stimulate phagocytosis in both in vitro and in vivo studies, to inhibit the function of hyaluronidase (an enzyme which breaks down hyaluronic acid in the human body), protect collagen from damage due to free radicals, and inhibit the function of HIV-1 integrase.

2. **Cynarin** is a phenolic acid compound found in the green leaves and seeds of artichokes (Cynara cardunculus). It has the chemical formula C25H24O11, a molecular weight of 516.45, and the official name 1,3-dicaffeoyl quinic acid. Green artichoke leaves contain about 2% cynarin but exact content varies with season, region, and extracting practices. Fennel (Foeniculum vulgare) and echinacea species also contain at least trace amounts of cynarin. Artichokes are considered to have cholagogue and choleretic properties. They signal the liver to increase the production of bile and then stimulate the gallbladder to secrete this bile into the duodenum of the small intestine. These actions prevent the build up of sludge and stones in the gallbladder and help the body to absorb lipid-soluble nutrients like vitamins A, D, E, and K.

   Cynarin has the following properties: Antimicrobial, Antioxidant, Anti-inflammatory, Bile stimulating (cholagogue and choleretic), Liver supportive & protective, Hepato-regenerative, Lowers cholesterol and triglycerides, Diuretic, Kidney protective, Sweetener, Reduce blood sugar.

   In vitro and vivo studies involving human and animal models have substantiated the protective and regenerative effects of cynarin on the liver. Mixed reviews remain regarding its effectiveness in lowering cholesterol and triglycerides. Some studies show positive results while others allude that a fellow compound in artichokes called luteolin is more statin-like in its cholesterol lowering effects. Cynarin has been indicated anecdotally and in human trials as a gentle and effective treatment for bloating, flatulence, nausea, abdominal pain, and diarrhea.
3. **Delphinidin 3-rutinoside**: is a natural colorant found in blackcurrants and other fruits and flowers. It is produced from natural sources (extraction processes). The product will release hydrochloric acid in water. The product is hygroscopic. The chemical formula is C27H31O16Cl. The molecular weight is 647.0 g/mol. The product belongs to the anthocyanins, which is a class of natural chemicals belonging to the flavonoids. It is highly water-soluble and is easily degraded by hydrolysis and/or hydrogenation at temperatures >40°C. The product shall be dark red/purple in colour, and shall normally be powdered. The product has a purity >97% as detected by high-performance liquid chromatography (HPLC) connected to UV/Vis detector at 280nm and 520nm. The rest is impurities of other anthocyanins, flavonoids or polyphenols. The product should be kept in darkness and at low temperatures for storage more than a few days (< -5°C). This product is intended for research in chemical laboratories. Only qualified individuals shall be considered treating this product. The purchaser should recognize that the supplier of this product under no circumstances is responsible for the applications of the product in the field of human or animal consumption or tests related to human or animal health. The supplier is not responsible for this product as part of drugs, cosmetics, food additives, products for domestic use or veterinary products. The purchaser is responsible for the use and storage of this product as soon as he receives the product.

4. **Docosahexaenoic acid (DHA)** is an omega-3 fatty acid. In chemical structure, DHA is a carboxylic acid with a 22-carbon chain[1] and six cis double bonds; the first double bond is located at the third carbon from the omega end. Its trivial name is cervonic acid, its systematic name is all-cis-docosa-4,7,10,13,16,19-hexa-enoic acid, and its shorthand name is 22:6(n-3) in the nomenclature of fatty acids. Fish oils are rich in DHA. Most of the DHA in fish and more complex organisms originates in photosynthetic and heterotrophic microalgae, and becomes increasingly concentrated in organisms as it moves up the food chain. DHA is also commercially manufactured from microalgae; Cryptothecodinium cohnii and another of the genus Schizochytrium. DHA manufactured using microalgae is vegetarian. Most animals make very little DHA through metabolism; however small amounts are manufactured internally through the consumption of α-linolenic acid, an omega-3 fatty acid found in plants, animals, and milk. DHA is metabolized to form the docosanoids, which comprise several families of potent hormones. DHA is a major fatty acid in sperm and brain phospholipids, particularly in the retina. Dietary DHA may reduce the risk of heart disease by reducing the level of blood triglycerides in humans. Low
levels of DHA have been associated with Alzheimer's disease. DHA was found to inhibit growth of human colon carcinoma cells, more than other omega-3 PUFAs. The cytotoxic effect of DHA wasn't caused by increased lipid peroxidation or any other oxidative damage, but rather decrease in cell growth regulators. However, different cancer lines handle PUFAs differently and display different sensitivities towards them. Such preliminary findings point to the need for further research and are not proof that DHA does or does not provide any benefit for intended treatment, cure, or mitigation of cancer. However, in 2008, DHA was shown to increase the efficacy of chemotherapy in prostate cancer cells, and in 2009, a chemoprotective effect in a mouse model was reported.

5. **GALLOTANNINS**: Source Plant: Anti-HIV galloylquinic acids were isolated from Lepidobotrys staudtii Engl. that was originally collected between Ekombe and Bekondo in the Southwest Province of Cameroon in January of 1987 (Etuge & Thomas 478). Activity: 1,3,4,5-tetra-O-galloylquinic acid protected target cells from the cytopathic effects of HIV-1 and HIV-2 and also exhibited potent inhibition of cellular DNA polymerases, as well as of the reverse transcriptases of HIV-1 and HIV-2. The gallotannins are a class of hydrolysable tannins polymers formed when gallic acid, a polyphenol monomer, esterifies and binds with the hydroxyl group of a polyol carbohydrate such as glucose. Gallate 1-beta-glucosyltransferase uses UDP-glucose and gallate to produce UDP and 1-galloyl-beta-D-glucose. Beta-glucogallin O-galloyltransferase uses 1-O-galloyl-beta-D-glucose to produce D-glucose and 1-O,6-O-digalloyl-beta-D-glucose. Beta-glucogallintetraisgalloylglucose O-galloyltransferase uses 1-O-galloyl-beta-D-glucose and 1,2,3,6-tetrais-O-galloyl-beta-D-glucose to produce D-glucose and 1,2,3,4,6-pentakis-O-galloyl-beta-D-glucose (1,2,3,4,6-penta-O-galloyl-beta-D-glucose, the common precursor of gallotannins and the related ellagitannins).

6. **Leucocyanidin** is a colorless chemical compound related to leucoanthocyanidins. Leucocyanidin can be found in Aesculus hippocastanum (Horse chestnut), Anacardium occidentale (Cashew, acajou), Arachis hypogaea (Earth Nut), Areca catechu (Areca nut), Asimina triloba (American custardapple), Cerasus vulgaris (Cherry), Cinnamomum camphora (Camphor), Erythroxylon coca (coca), Gleditsia triacanthos (Honey locust), Hamamelis virginiana (American Witch Hazel), Hippophae rhamnoides (Hippophae berry Sanddorn), Hordeum vulgare (Barley), Humulus lupulus (bine), Hypericum perforatum (perikon Amber), Laurus nobilis, Magnolia denudata (Hsin-I Yulan-Magnolie), Malva silvestris (Blue mallow), Musa x
paradisiaca (Banana), Nelumbo nucifera (Baladi bean), Pinus strobus (Eastern white pine), Prunus serotina ssp. serotina (black cherry), Psidium guajava (Common guava), Quercus alba (White oak), Quercus robur (Common oak), Rumex hymenosepalus (Arizona dock), Schinus terebinthifolius (Brazilian pepper tree), Terminalia arjuna (arjun), Terminalia catappa (Indian almond), Theobroma cacao (Cacao), Urginea maritima (European Squill), Vicia faba (bell-bean), Vitis vinifera (Common Grape Vine), Zea Mays (Corn, mais), Ziziphus jujuba (jujube, Chinese date). (+)Leucocyanidin can be synthesized from (+)dihydroquercetin by sodium borohydride reduction. Metabolism: Leucocyanidin oxygenase uses leucocyanidin, 2-oxoglutarate, and O2 to produce cis-dihydroquercetin, trans-dihydroquercetin (taxifolin), succinate, CO2, and H2O. Leucoanthocyanidin reductase (LAR) uses (2R,3S)-catechin, NADP+, and H2O to produce 2,3-trans-3,4-cis-leucocyanidin, NADPH, and H+. Its gene expression has been studied in developing grape berries and grapevine leaves. The C-4 stereochemistry of leucocyanidin substrates affects anthocyanidin synthase (ANS) products. This enzyme is an iron(II) and 2-oxoglutarate (2OG) dependent oxygenase. Leucocyanidin reductase (LCR) uses 2,3-trans-3,4-cis-leucocyanidin to produce (+)-catechin and is the first enzyme in the proanthocyanidins (PA)-specific pathway. Its activity has been measured in leaves, flowers, and seeds of the legumes Medicago sativa, Lotus japonicus, Lotus uliginosus, Hedysarum sulfurescens, and Robinia pseudoacacia.

7. **Monocaffeyltartaric acid** were found to be the major phenolic constituents in flowers, roots, leaves and involucral bracts and also in the medicinal preparations tested. Caftaric acid is a non-flavonoid that impacts the color of white wine. Many believe this molecule is responsible for the yellowish-gold color seen in some whites wines. Caftaric acid and caffeic acid are in a class of chemicals known as cinnamates. Caftaric acid is formed when caffeic acid and tartaric acid undergo esterification. But during fermentation, caftaric acid is oxidized into its principle components. In wine: Winemakers measure caftaric acid levels as their primary method to estimate the oxidation levels that a wine has undergone.
Databases:

Protein Data Bank

The Protein Data Bank (PDB) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. (See also crystallographic database). The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, can be accessed at no charge on the internet. The PDB is overseen by an organization called the Worldwide Protein Data Bank, wwPDB. The PDB is a key resource in areas of structural biology, such as structural genomics. Most major scientific journals, and some funding agencies, such as the NIH in the USA, now require scientists to submit their structure data to the PDB. If the contents of the PDB are thought of as primary data, then there are hundreds of derived (i.e., secondary) databases that categorize the data differently. For example, both SCOP and CATH categorize structures according to type of structure and assumed evolutionary relations; GO categorize structures based on genes.

The principle method to access and search the holding of the PDB is via its web interface using internet browsers:-

direct your browser either to the main RSCB pdb location at URL http://pdb.weizmann.ac.il.

In either place, the next step is to select ‘search the pdb’ to bring up the browser.

The Brookhaven interface supports two search tools, the full PDB Browser, and simplified PDB-lite browser for casual users and lab biologist whichever browser you use, you fill in the blanks with appropriate search question or by sequence in a FASTA like interface.

If only a single structure is found, the browser returns an Atlas Page for the structure including a summary of its header information, and options to download some or all the entry, to display the protein in various ways and to locate related information on other databases.

if the search returns several entries, these are returned in a combined atlas page, with an abbreviated entry for each structure found. You can then which structure to examine in more detail.
PubMed is a free search engine for accessing the MEDLINE database of citations, abstracts and some full text articles on life sciences and biomedical topics. The United States National Library of Medicine at the National Institutes of Health maintains PubMed as part of the Entrez information retrieval system. Listing an article or journal in PubMed is not endorsement. In addition to MEDLINE, PubMed also offers access to

- OLDMEDLINE for pre-1966 citations. This has recently been enhanced, and records for 1951+, even those parts in the printed indexes, are now included within the main portion.
- Citations to all articles, even those that are out-of-scope (e.g., covering plate tectonics or astrophysics) from certain MEDLINE journals, primarily the most important general science and chemistry journals, from which the life sciences articles are indexed for MEDLINE.
- In-process citations which provide a record for an article before it is indexed with MeSH and added to MEDLINE or converted to out-of-scope status.
- Citations that precede the date that a journal was selected for MEDLINE indexing (when supplied electronically by the publisher).
- Some life science journals that submit full text to PubMed Central and may not have been recommended for inclusion in MEDLINE although they have undergone a review by NLM, and some physics journals that were part of a prototype PubMed in the early to mid-1990s.

Many PubMed citations contain links to full text articles which are freely available, often in the PubMed Central digital library. In late 2007, President George W. Bush signed the Consolidated Appropriations Act of 2007 (H.R. 2764) into law; this law included a provision requiring the NIH to modify its policies and require inclusion into PubMed Central complete electronic copies of their peer-reviewed research and findings from its funded research. This is the first time the US government has required an Agency to provide open access to research and is an evolution from the 2005 policy, in which the NIH asked researchers to voluntarily add their research to PubMed Central. With an effective date of April 7, 2008, the Department of Health and Human Services has given notice: "The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine’s PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: Provided, That the NIH shall implement the public access policy in a manner consistent with copyright law."
PubMed is one of a number of search engines through which it is possible to search the MEDLINE database; the National Library of Medicine also leases the MEDLINE information to a number of private vendors such as Ovid and SilverPlatter – as well as many other vendors. PubMed has been available free on the Internet since the mid-1990s.

Information about the journals indexed in PubMed is found in its Journals Database, searchable by subject or journal title, Title Abbreviation, the NLM ID (NLM's unique journal identifier), the ISO abbreviation, and both the print and electronic International Standard Serial Numbers (pISSN and eISSN). The database includes all journals in all Entrez databases.

As of 17 May 2009, PubMed has approximately 18,900,000 citations going back to the year 1865. To see the current size of the database simply type "1800:2100[dp]" into the search bar and click "go".

**PUMCHEM**

PubChem is a database of chemical molecules. The system is maintained by the National Center for Biotechnology Information (NCBI), a component of the National Library of Medicine, which is part of the United States National Institutes of Health (NIH).

PubChem contains substance descriptions and small molecules with fewer than 1000 atoms and 1000 bonds.
**SOFTWARES:**

**Marvin sketch 4.1**

Marvin sketch is a customizable GUI with a brand new design. The features of Marvin sketch are Configuration choices (including ISIS/Draw and ChemDraw like menu and icon arrangements), Chain drawing, displaying the last carbon number, Enhanced Query, S-group and R-group drawing features, Global IME support in Textboxes (allows entering East Asian characters) etc. The Lipinski properties were also calculated using Marvin Sketch.

Marvin Sketch is an advanced chemical editor for drawing chemical structures, queries and reactions. It has a rich (and growing) list of editing features, is chemically aware and is able to call ChemAxon's structure based calculation plugins for structures on the canvas.

Marvin is an applet package for drawing and visualizing chemical structures and substructures. MarvinSketch is a tool for drawing chemical structures. It supports valence checking, query atoms and bonds, stereochemistry, and user-defined templates. On the example below, the user can select templates from four sets: "Generic", "Rings", "Amino acids", and "Polycyclics". Template sets are stored in standard SDfiles.

A few special features are multi-level undo/redo, "visual fragment placement", easy chain drawing, branching at a single click. The applet can be displayed in a separate window that has a menu bar. It can also be used like a viewer, the viewing area can be maximized by hiding the buttons. These two features can be controlled with applet parameters, and also at runtime (try the top left buttons).

A chemist can configure MarvinSketch in such a way that it will allow the users to draw structures containing only a subset of all available atom and bond types. For example, one might have an online program that predicts a chemical property for molecules that contain only C, N, and O atoms. The rest of the atoms can be disallowed by setting applet parameters. "Extra" bond types like the aromatic or the stereo bonds can also be enabled or disabled.

MarvinSketch is the ideal tool also for drawing the query structure for a database search. It supports many query atom types like "atom list", "NOT list", SMARTS query properties like H (number of hydrogen’s), v (valence), X (number of connections), R (rings), r (smallest ring size), A (aromatic), and a (aliphatic). It is also possible to enter any SMARTS expression to describe an atom. The web developer
can decide which functions are needed to be enabled, according to the capabilities of his search engine.

**Quantum 3.3.0**

Quantum is a software package of drug discovery and computational chemistry tools. Quantum’s computational platform is based on direct modeling of biochemistry processes by using advanced methods of quantum and molecular physics. These simulation models are controlled by a graphic user interface, which is used to load and modify 3D molecules and set important parameters of the models. Quantum can be run both on parallel clusters and a workstation. The platform were the quantum runs are Linux and windows 2000/XP. The memory space needed is 1 GB RAM.

The QUANTUM molecular docking software was developed using a new paradigm in molecular modeling applying quantum and molecular physics instead of statistical approaches (scoring function-like and QSAR-like methods).

In QUANTUM, the binding affinity of a protein-ligand complex is estimated on the basis of free binding energy calculations.

A successful free binding energy calculation consists of three key parts:

1. a vacuum force field for internal molecular energy calculations (conformational changes)
2. a model of intermolecular interactions in solution (water model), and
3. Fast and accurate machinery for thermodynamic calculations (evaluation of entropy losses). All these approaches and methods were developed in-house and applied in QUANTUM protein ligand docking software.

Quantum Pharmaceuticals’ drug hit identification tool calculates the IC50 (Kd, Ki, pKd) value of any protein-ligand complex, docks a small molecule in the active site of a protein and screens a library of compounds against a target protein or DNA/RNA. The hit identification tool consists of three modules: The IC50 module, 2) Ligand Docking software and 3) Library Screening modules. The drug hit identification tool can run in both Windows and Linux environments.

**Key Quantum Benefits:**

- Outstanding precision of molecular modeling and calculations
- Unrivaled ability to discover novel classes of inhibitors.
ADME - TOX

http://pharma-algorithms.com/

ADME is an acronym in pharmacokinetics and pharmacology for absorption, distribution, metabolism, and excretion, and describes the disposition of a pharmaceutical compound within an organism. The four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug.

3.1.3 Absorption/Administration

Before a compound can exert a pharmacological effect in tissues, it has to be taken into the bloodstream — usually via mucous surfaces like the digestive tract (intestinal absorption). Uptake into the target organs or cells needs to be ensured, too. This can be a serious problem at some natural barriers like the blood-brain barrier. Factors such as poor compound solubility, chemical instability in the stomach, and inability to permeate the intestinal wall can all reduce the extent to which a drug is absorbed after oral administration. Absorption critically determines the compound's bioavailability. Drugs that absorb poorly when taken orally must be administered in some less desirable way, like intravenously or by inhalation (e.g. zanamivir).

3.1.4 Distribution

The compound needs to be carried to its effector site, most often via the bloodstream. From there, the compound may distribute into tissues and organs, usually to differing extents.

3.1.5 Metabolism

Compounds begin to be broken down as soon as they enter the body. The majority of small-molecule drug metabolism is carried out in the liver by redox enzymes, termed cytochrome P450 enzymes. As metabolism occurs, the initial (parent) compound is converted to new compounds called metabolites. When metabolites are pharmacologically inert, metabolism deactivates the administered dose of parent drug and this usually reduces the effects on the body. Metabolites may also be pharmacologically active, sometimes more so than the parent drug.
3.1.6 Excretion/Elimination

Compounds and their metabolites need to be removed from the body via excretion, usually through the kidneys (urine) or in the feces. Unless excretion is complete, accumulation of foreign substances can adversely affect normal metabolism.

There are three sites where drug excretion occurs. The kidney is the most important site and it is where products are excreted through urine. Biliary excretion or faecal excretion is the process that initiates in the liver and passes through to the gut until the products are finally excreted along with waste products or faeces. The last method of excretion is through the lungs e.g. anaesthetic gases.

Excretion of drugs by the kidney involves 3 main mechanisms:

- Glomerular filtration of unbound drug.
- Active secretion of (free & protein-bound) drug by transporters e.g. anions such as urate, penicillin, glucuronide, sulphate conjugates) or cations such as choline, histamine.
- Filtrate 100-fold concentrated in tubules for a favourable concentration gradient so that it may be reabsorbed by passive diffusion and passed out through the urine.

3.2 Toxicity

Sometimes, the potential or real toxicity of the compound is taken into account (ADME-Tox or ADMET). When the Liberation of the substance (from protective coating, or other excipients) is considered, we speak of LADME.

Computational chemists try to predict the ADME-Tox qualities of compounds through methods like QSPR or QSAR.

The route of administration critically influences ADME.
Mol inspiration is an independent research organization focused on development and application of modern chemoinformatics techniques, especially in connection with the Internet. Mol inspiration offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modeling and drug design, high quality molecule depiction, molecular database tools supporting substructure search or similarity and pharmacophore similarity search. Our products support also fragment-based virtual screening, bioactivity prediction and data visualization. Mol inspiration tools are written in Java, therefore are available practically on any computer platform.
Mol inspiration supports also internet chemistry community by offering free on-line cheminformatics services for calculation of important molecular properties (for example logP, polar surface area, number of hydrogen bond donors and acceptors), as well as prediction of bioactivity score for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors) and possible molecular toxicity. Mol inspiration software is used by hundreds of users in industry and academia to produce high-quality cheminformatics science.

Fig No. 11 Home page of molinspiration for Finasteride
Fig No. 12 Molecular properties for Finasteride

Fig No. 13 Calculation of drug likeliness for Finasteride
PROCEDURE:

Step 1:- Collection of molecules via literature study.

1. Collecting information regarding chemoprevention of prostate cancer.

2. Searching for chemopreventive molecules using databases, journals and articles.
   - Pubmed
   - Oxford journals
   - AACR journals
   - Nature
   - Interscience
   - Springerlink
   - Biomed Central
   - Science Direct
   - Aspet journals

Fig No. 14 home page of springerlink
3. Filtering the search by selecting only naturally derived chemopreventive molecules which are not commercialized.

Step 2: Retrieval of structure for the collected molecules.

**Fig no: 15** Structure were retrieved for the molecules using PUBCHEM database.

**Fig No: 16** Now Get the Details on the Structure you have selected

Structure for molecules that are not published in pubchem were retrieved using Marvin Sketch.
Step 3:- Perform energy minimization

1. Energy minimization was done for all the chemoprevention was done for all the chemopreventive molecules using Marvin Sketch.

2. Conformers were found for each molecule and the best one with the least energy was selected.

Steps of Energy minimization of each molecules:

1. Load the structure in SDF format in Marvin Sketch.

2. Save the structure as extended mol file(mol).

3. Open the mol file in Marvin view.

4. Perform energy minimization.

5. From the conformers obtained select the least energy.

6. Save the file in SDF format (.sdf)

Marvin sketch is a customizable GUI, where energy minimization and partition coefficient (LogP) values of all the natural molecules under study were obtained.
Step 4: Retrieval of 3D structure of the 5-alpha reductase by homology modelling.
The PDB structure of drug targets is not available. So, modeling of the target proteins were performed using MODELLER. A template search has been performed through BLAST and PSI-BLAST programs. Global alignment method was used for comparison between the target-template sequences. Gaps with variable gap penalty function are included for structural loops and core regions, in order to get maximum correspondence between the sequences. Alignment file for MODELLER was prepared by CLUSTALW. Fold recognition was done through mGenThreader and LOMETS server for fold assignment. Energy minimization of generated 3D-model was done through GROMACS (OPLS force field) by using Steepest Descent and Conjugate Gradient Algorithms. Parameters like covalent bond distances and angles, stereochemical validation, atom nomenclature were validated using PROCHECK and overall quality factor of non-bonded interactions between different atoms types were measured by ERRAT program. RMSD (root-mean-square deviation) and RMSF (Root Mean Square Fluctuation) was calculated for modeled structures. Functionally important residues (Active-site) were identified through comparative result of POCKETFINDER and SURFACE RACER 4.0.

Fig No: 20 modeled target protein

Step 5:- Docking of chemopreventive molecules in Quantum Software.

Steps in Quantum:-

1. Load the ligand.
2. prepare the ligand then load the protein and prepare the protein.
3. Generate active site on protein for ligand binding
4. start docking.

5. Calculation of Docking score

Fig No: 21  Ligand finasteride loaded in quantum
Fig No: 22 Target protein loaded in quantum

Fig No: 23 Preparing protein for active site calculation
Fig No: 24 Running active site calculation on protein structure

Fig No: 25 Active sites of protein shown in red balls pattern
Fig No: 26  Running docking for the protein-ligand

Fig No: 27  Result of docking of ligand finateride shown
Hex 4.5

**Fig No:28** Open the homepage & go to file → open → receptor...

**Fig No:29** Hex after loading the molecule
Fig No: 30 Open the homepage & go to file → open → Ligand...

Fig No: 31 Go to controls→ docking→ enter.
Fig No: 32  Docking control—activates ---hex progress.

Fig No: 33  See the Hex progress....
Fig No: 34 See the E total & rms...

Fig No: 35 Save the result...
Step 6:- ADME-TOX

Find the ADME and TOX properties for the best molecules.

Procedure:-

1. ADME-TOX BOX was opened using the URL: http://www.pharma-algorithms.com/webboxes/ 
2. Click on continue. 
3. Paste the canonical smile of the molecules or upload the files which are saved in .mol extention and click on calculate. 
4. ADME/TOX properties were displayed. 
5. Each of the properties were noted and studied.
Fig No: 37 properties of finasteride on ADME-TOX

Fig No: 38 properties of finasteride in ADME-TOX
RESULTS:

Table 1

**COLLECTION OF CHEMOPREVENTIVE MOLECULES:**

<table>
<thead>
<tr>
<th>s.no.</th>
<th>compound name</th>
<th>structure</th>
<th>source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>palmatine</td>
<td><img src="image1" alt="Structure" /></td>
<td>saw palmetto extract</td>
</tr>
<tr>
<td>2.</td>
<td>docosanol</td>
<td><img src="image2" alt="Structure" /></td>
<td>Pygeum (Prunus africanum, Pygeum africanum)</td>
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<td>3.</td>
<td>shikonin</td>
<td><img src="image3" alt="Structure" /></td>
<td>Nettle (Urtica dioica)</td>
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<td>4.</td>
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<td><img src="image4" alt="Structure" /></td>
<td>green tea</td>
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<tr>
<td></td>
<td>Compound</td>
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<td>5</td>
<td>N-methylerythromycin A</td>
<td>emu oil</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Genistein</td>
<td>soy-isoflavonoid</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Gemeprost</td>
<td>evening primrose oil</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Allyl sulfide</td>
<td>garlic</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3,3'-Diindolylmethane</td>
<td>broccoli</td>
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<tr>
<td>10</td>
<td>Indole-3-carbinol</td>
<td>cabbage</td>
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<td>Source</td>
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<td>Acidophilus</td>
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<td>Rat</td>
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<td></td>
<td>Compound</td>
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<tr>
<td>17.</td>
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<td>oregon grape</td>
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### Table 2

**QUANTUM DOCKING RESULT OF CHEMOPREVENTORS FOR 5-ALPHA REDUCTASE TYPE 2 (PROSTATE CANCER)**

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**finasteride** (std drug) -26.84
Table 3

LIST OF SCREENED MOLECULES THAT FOLLOW LIPINSKY’S RULE:

QUANTUM DOCKING RESULT OF CHEMOPREVENTORS FOR 5-ALPHA REDUCTASE TYPE 2 (PROSTATE CANCER)

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<th>details of lipinsky rule followed by molecules</th>
<th>result</th>
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DISCUSSION:

Around 132 potential chemopreventive molecules were selected from pubmed out of which all the 125 were natural or dietary chemopreventive molecules. The 132 molecules were minimized using Marvin sketch and the least score conformer of each molecule was docked using Quantum and Hex. The docking scores were compared with the reference ligand score (-26.84 Kcal/mol). Following 12 molecules had lower docking score than reference molecule.

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Table 5
Details of H bond interaction and IC50 of lead compounds in comparison to standard Drug

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<td>-29.58 Leu154, ile182</td>
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ADME-TOX PROPERTIES:

Table 6
Calculating ADME-TOX properties of 12 best selected chemopreventive molecules.

ADME: Absorption/Administration, Distribution, Metabolism, Excretion/Elimination table for all the 12 molecules:-

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<th>Toxicity properties</th>
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<td>Oral bioavailability</td>
<td>Drug binding to plasma protein</td>
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<td>solubility</td>
<td>%F(Oral) &gt; 30%: 0.950 %F(Oral) &gt; 70%: 0.773</td>
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<td>%F(Oral) &gt; 30%: 0.950 %F(Oral) &gt; 70%: 0.773</td>
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</tr>
<tr>
<td>2</td>
<td>Berberine</td>
<td>%F(Oral) &gt; 30%: 0.033 %F(Oral)</td>
<td>-6.56</td>
</tr>
<tr>
<td></td>
<td>%F(Oral)</td>
<td>%PPB:</td>
<td>LogKa HSA:</td>
</tr>
<tr>
<td>---</td>
<td>----------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>3.</td>
<td>cichoric</td>
<td>&gt; 70%: 0.008</td>
<td>HSA: 3.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 30%: 0.033</td>
<td>%F(Oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70%: 0.008</td>
<td>%F(Oral)</td>
</tr>
<tr>
<td>4.</td>
<td>cynarin</td>
<td>%F(Oral)</td>
<td>&gt; 30%: 0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70%: 0.008</td>
<td>%F(Oral)</td>
</tr>
<tr>
<td>5.</td>
<td>delphinidin-3-rutinoside</td>
<td>%F(Oral)</td>
<td>&gt; 30%: 0.854</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70%: 0.450</td>
<td>%F(Oral)</td>
</tr>
<tr>
<td>6.</td>
<td>docosahexaenoic acid</td>
<td>%F(Oral)</td>
<td>&gt; 30%: 0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70%: 0.008</td>
<td>%F(Oral)</td>
</tr>
<tr>
<td>7.</td>
<td>Gallotannin</td>
<td>%F(Oral)</td>
<td>&gt; 30%: 0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70%: 0.009</td>
<td>%F(Oral)</td>
</tr>
<tr>
<td>8.</td>
<td>leucocyanidin</td>
<td>%F(Oral)</td>
<td>&gt; 30%: 0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70%: 0.008</td>
<td>%F(Oral)</td>
</tr>
<tr>
<td></td>
<td>Substances</td>
<td>%F(Oral) &gt; 30%:</td>
<td>%PPB:</td>
</tr>
<tr>
<td>---</td>
<td>----------------------</td>
<td>-----------------</td>
<td>-------</td>
</tr>
<tr>
<td>9</td>
<td>Monocaftaric acid</td>
<td>0.033</td>
<td>0.25</td>
</tr>
<tr>
<td>10</td>
<td>Phytic acid</td>
<td>0.033</td>
<td>0.30</td>
</tr>
<tr>
<td>11</td>
<td>procyandin</td>
<td>0.033</td>
<td>0.30</td>
</tr>
<tr>
<td>12</td>
<td>Steric acid</td>
<td>0.854</td>
<td>0.50</td>
</tr>
<tr>
<td>13</td>
<td>Triterpenoids</td>
<td>0.033</td>
<td>0.30</td>
</tr>
</tbody>
</table>

B* = blood, C* = Cardiovascular system, G* = Gastrointestinal system, K* = Kidney, Li* = Liver, Lu* = Lungs
CONCLUSION:

Diagnosis of prostate cancer is quite difficult. In addition to coping with a potentially life-threatening illness, one must make complex decisions about treatments. Hence it’s better to prevent cancer than curing it. At present the best known options for chemoprevention of prostate cancer is Finasteride. This project finds out those naturally derived molecules which can be an effective inhibitor of prostate cancer as better as Finasteride or better than that. Using the various bioinformatics databases and softwares we have checked the efficiency of these chemopreventive molecules and the results suggest that out of the 132 molecules we docked, 12 potent chemopreventive molecules had lower docking score than the reference molecule. Lower the docking score (more negative) of a molecule the more well is its effectiveness as an inhibitor. Thus Berberine and Monocaffeyltartaric acid which has the least docking score may be an effective chemopreventive inhibitor of prostate cancer.

Thus an appropriate use of a chemopreventive agent ultimately depends on the understanding of its mechanism of action at all levels, namely at the molecular, cellular, tissue and organ levels, as well as in the animal as a whole, without this knowledge we can only make intuitive decisions in selecting preventive agents and hope that a useful clinical result will be forthcoming. More data are needed to accurately access risk. A multidisciplinary approach needs to be adopted in field of chemoprevention to yield fruitful data.

This approach should include psycho-social research, epidemiologic data and clinical trials to improve understanding of the biology and identify each potential target.

The need for new agents with novel mechanisms of action to prevent cancer is perhaps the most urgent need in the entire field of chemoprevention. Although proof of principle of chemoprevention has been clearly demonstrated, in both animal and clinical studies, none of the existing chemopreventive agents is ideal, either because of lack of efficiency and potency or cause of toxic side effects that preclude widespread, long term use discovery of new agents is therefore of vital importance.
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Triazolam Substrate Inhibition: Evidence of Competition for Heme-Bound Reactive Oxygen Within the CYP3A4 Active Site

Michael L. Schrag and Larry C. Wienkers

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Phase II trial of daily oral perillyl alcohol (NSC 641066) in treatment-refractory metastatic breast cancer
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