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Natural drugs in the treatment and prevention of prostate diseases

Diploma thesis

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Statement:

"I declare that this thesis is my original copyrighted work. All literature and other resources I used while processing are listed in the bibliography and properly cited. The thesis was not misused for obtaining the same or different academic Degree."

I would like to thank my professor Doc. PharmDr. Lenka Tůmová, CSc. in the Pharmacognosy department, whose passionate teaching inspired me to select this topic for my thesis. I would also like to thank my supervisor, Pharm. Dr. Jan Martin, Ph.D. for all the support that he has given me during my work on the thesis.

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Summary

1. INTRODUCTION

Prostate cancer (PC) is one of the most common and frequent cancer conditions in men in the United States and beyond. Compared to other non-cutaneous neoplasm cancer conditions, PC is classified as the second leading in mortality rates. According to the American Cancer Society (ACS), one in every seven men is diagnosed with cancer in their lifetime. This demonstrates the importance of continuous screening and diagnosis of the condition. Different clinical therapeutic approaches have been the development for the management of cancer with little success. However, the condition continues to cause suffering for men of all ages (1).

Though cancer research has led to the development of various tools that can be used to manage PC in men, natural medicine presents a greater opportunity. Natural medicine has been used in the management of different conditions in different parts of the world. Most of the modern medicines marketed in enhanced formulations have strong natural basis. In ancient times, herbal medicine was used in the management of conditions that resembled modern day cancer. For example, Asians used natural drugs in the management of various malignancies (1).

Research has also shown that plants possess a number of complex molecules which can prevent or prevent the spread of tumor cells in the body. A number of plant-based chemicals have been shown to play a major role in regulating cell division, the inhibition of DNA topoisomerase enzyme and ant protease or antioxidant activity. This can contribute to the delay or prevention of PC initiation in men.

Natural remedies in the management of PC have a number of merits over the modern approaches. The cost of using a natural method to manage or prevent the

metastasis of PC is lower as compared to modern methods. Chemotherapy, for instance, is expensive, and this limits the number of people who can comfortably access them. The negative implications of adopting natural methods in the management of PC are also low as compared to other common methods. For example, chemotherapy of PC has other side effects that affect the normal development and wellbeing of the patient (3).

Radiotherapy is dangerous to germ line cells thus making this intervention and management approach ineffective. Modern PC management equipment is also costly thus reducing the number of facilities that have them. On the contrary, natural medicine does not need most of the costly chemotherapy machines. However, the adoption of natural medicine in the management of PC has other demerits. First, research on the chemical and medicinal values of most natural drugs has not been conducted. This has limited their acceptance in different parts of the world including the United States (3). Most active chemical compounds in plants are complex and cannot be synthesized in the laboratory. This limits their commercialization and uses to address multiple cases of PC (1).

2. AIM OF THE WORK

This work will provide a review of natural drugs used in the treatment and prevention of PC. To achieve this, the paper will evaluate the application of different drugs of natural origin in cancer management, especially PC

The aim of this work is:

1. To discuss the anatomy and physiology of the prostate gland
2. To highlight common prostate diseases apart from PC
3. To highlight the prevalence of PC in men
4. Provide a review of PC in men
5. Describe other conditions that affect the prostate gland leading to inflammation
6. Discuss conventional therapeutic approaches in the management of PC
7. Discuss emerging issues in natural drugs in the treatment of PC

3. ABBREVIATIONS

PC	prostate cancer
DNA	deoxyribonucleic acid
ACS	American Cancer Society
PIN	Prostate Intraepithelial Neoplasia
ACA	American Cancer Association
PSMA	Prostate specific membrane antigens
PSA	Prostate-specific antigen
FDA	Food and Drug Agency
DNA	deoxyribonucleic acid
RNA	Ribonucleic Acid
CPT	Camptothecin
HC	Heptaocellular Carcinoma
MDC	Maryland Medical Centre
TRF2	Telomeric Repeat-Binding Factor 2
HSA	Human Serum Albumin
GSK	GlaxoSmithKline
ACA	Antiprostate Cancer Activity

4. THEORETICAL PART

4.1. Physiology and anatomy of the genitourinary system

Genitourinary or urogenital system comprises of the reproductive and urinary systems. Due to their proximity to each other, similar embryological origin and a shared pathway in the urethra, the two systems are grouped together. The two systems develop from the intermediate mesoderm of a fertilized ovum. Genitourinary system is made up of the kidneys, the penis, prostate, ureter and the urinary bladder. While the kidney, bladder and ureter forms part of the urinary system, the penis, and the prostate are part of the genital system (3).

The penis is the external excretory and sex organ in male and is an extension of the urethra. The penis has flexible tissues that allow it to increase in size during sexual stimulation. The prostate is a tissue that is only found in men and has a walnut-sized shape. The prostate grows throughout the life of men, and this increases its susceptibility to attack by cancerous chemicals. The prostate gland contributes significantly in the ejaculation of semen during sex (1).

The prostate is located in the inferior region of the urinary bladder within the pelvic cavity region. Prostate is pseudostratified and is made up of columnar and basal cells. The urethra from the bladder is known as the prostatic urethra. Prostate is divided into several zones that vary in size and function. The peripheral zone makes up 70% of the total prostatic organ in young men. This section is important in prostatic cancer diagnosis as it associated with 70-80% of PCs. The central zone is beneath the ejaculatory duct and is associated with 2.5% of PC cases across the world. The transition zone is the third region and accounts for over 20% of PC

cases. It is beneath the proximal urethra and grows throughout the entire life of men (2).

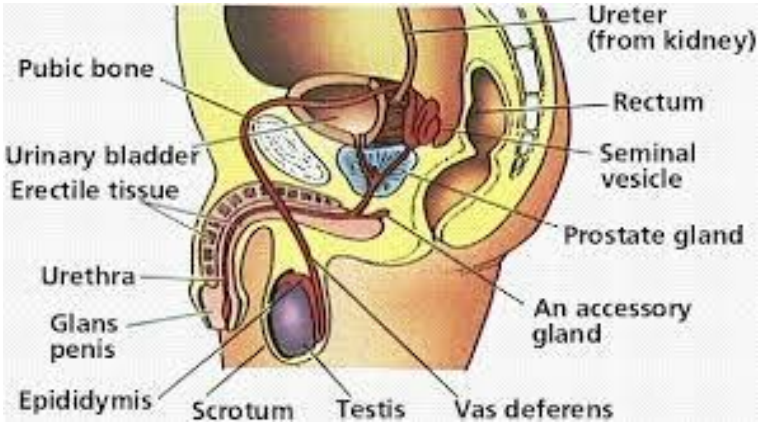

Figure 1: Anatomy of male genitourinary system (81).

4.2. Physiology and anatomy of the prostate

The prostate we made up of difference types of cells which facilitate its various functions in men. The gland cells are responsible for the production of the fluid part of the semen while the muscle cells control the flow of urine and ejaculates during sexual intercourse. Fibrous cells function as support for the structure of the gland. Other structures that are integral to the function of the prostate include the seminal vesicles that are the glands responsible for semen production (1).

The vas deferens is tubes that are responsible for carrying sperms from the testes to the prostate region when it mixes with the semen. The prostate is also made up of nerve bundles that are responsible for controlling the bladder and erectile function at all times. The prostate is divided into different zones that are loosely known as the

peripheral, transition and central zones as shown in figure 2.

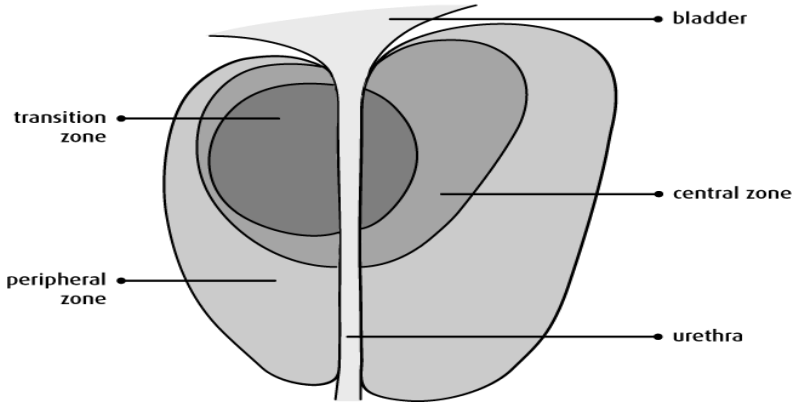

Figure 2: Anatomy of the prostate (82).

The peripheral zones are located next to the rectum and are used during digital rectal examination to identify the presence of any deformities or growth. It is also the largest zone of the prostate gland and is responsible for over 75% of PC cases. The central zone is beneath the ejaculatory duct and is associated with 2.5% of PC cases across the world. The transition zone is the third region and accounts for over 20% of PC cases. It is beneath the proximal urethra and grows throughout the entire life of men. Research has associated this region with the development of benign prostatic enlargement in men. Other classification of prostate includes the anterior, posterior, lateral and medial lobes (2).

The prostate function as the site for semen fluid formation in men and is surrounded by cells that are rich in proteins and mineral salts to nourish the sperms. Semen fluid is manufactured continuously during the lifetime of a male and is excreted in the urine. Large amounts of the fluid are produced whenever a man is sexually aroused, which later mixes with the sperms before ejaculation (2). The prostate is also used in the control of urine flow through the urethra that runs from the bladder to the exterior through the penis. Muscle fibers within the prostate are

wrapped around the urethra and controlled by the involuntary nervous system. Slow contraction and relaxation of these fibers lead to control of the flow of urine (4).

4.3. Diseases of the prostate

Prostate is affected by a number of pathophysiological conditions including cancer and prostatitis. Most of these conditions are influenced by the age and nutrition of the patient. Benign prostatic hyperplasia (BHP) is a common disease of the prostate that arise from the enlargement of the prostate gland. The chances of developing BPH depend on the age of the patient. In men aged 30-40 years, BPH occurs in one out of every 12 patients while the prevalence of the condition is older men is high. One out of two men aged 51 years and above has a higher risk of developing BPH. However, the condition is benign in men and is for this reason, rarely treated. Benign prostatic hyperplasia has symptoms such as difficulties in urination, continuous urge to urinate and frequent nocturnal urination (4).

PC is the common physiological defect that affects the PC. One in every six men will be diagnosed with PC in their lifetime, statistics that show the high prevalence of the condition. However, PC takes a long time to grow, thus reducing the mortality rates from the condition. As witnessed in BPH, the risk of developing PC increases as men ages. Two-thirds of patients suffering from PC are aged 65 years and above (2). Though the exact cause of PC is unknown, a number of possible causes have been discussed.

Genetics is highly associated with the development of PC. Fathers that suffer from the condition indicate the risk levels that their sons face. Race is also considered in the development of this condition, with Caucasians placed at a high risk of developing the condition. PC patients experience symptoms including urination and ejaculation difficulty. Blood can also be sighted in urine and semen of

patients suffering from PC. Pain and stiffness in the back, neck, and upper thighs are also common in PC patients (1).

Prostatitis is also a common disease of the prostate and results in the inflammation of the prostate. This condition is prevalent in young and middle-aged men as compared to other conditions that affect the organ. However, the overall prevalence of the condition is low as only 5-10% of men are at a risk of developing the condition. Prostatitis symptoms are also similar to BPH and are characterized by chills and fever during urination.

4.4. Pathophysiology of prostate cancer

Prostate cancer is an adenocarcinoma or glandular carcinoma and leads to the mutation of a normal sperm producing prostate gland into a tumor tissue. At the early stages of prostate cancer development, a small lump of tumor is formed within the normal prostate gland forming a carcinoma in situ. This is also known as the prostate intraepithelial neoplasia (PIN) (4).

Though the research has not conclusively associated PIN with prostate cancer, it is a known precursor to various cancer diseases in human beings. The small tumor formed in the prostate begins to multiply over time, invading other surrounding prostate tissues. The tumor formed might increase in size to later invade other nearby organs like the seminal vesicle or even the rectum. Other tumors metastasize and travel through the blood streams to other parts of the body. Prostate cancer metastasizes to bones, lymph, nodes, the rectum or even the bladder (4).

Though prostate gland is a zinc accumulating organ, tumor cells lack this essential metal. Zinc plays a role in the regulation of cell metabolism and the production of citrate that is an essential component of semen. Without adequate zinc, prostate cancer cells cannot produce citrate, leading to energy accumulation.

This energy is used by the tumor cells to grow and invade other tissues of the body. Prostate specific membrane antigens (PSMA) are also important in the growth of prostate tumor cells. PSMA acts by increasing the level of folate in the cancer cells that act as a source of food for growth and survival (4).

The spread of prostate cancer cells to the bones leads to the production of the prostatic acid phosphatase. These act on bone remodeling cells to facilitate the formation of the plastic lesions. This information has led to the development of blood borne biomolecular markers for prostate cancer. Prostate-specific antigen (PSA) is also involved in the cleavage of factors within the semen that helps in liquefaction and fertilization. However, PSA also plays a role in the carcinogenesis of the prostate. It acts on various molecules to improve proliferation, detachment, invasion and metastasis of cells (4).

4.5. Conventional treatment of prostate diseases (cancer)

Conventional prostate cancer treatment approaches have varied depending on the severity of the condition and whether it is localised or affecting other parts of the body. Stage one and two prostate cancers are subjected to radical prostatectomy, external beam radiation therapy and interstitial implantation of radioisotopes. Such approaches are meant to reduce the angiogenesis and progression of the cancer to other cells of the prostate. At stage three, hormonal manipulation such as the use of luteinizing hormone-releasing hormone agonist is introduced. Stage five adopts more radical approaches as the condition is now serious and may affect other cells of the body. Extra approaches adopted at this stage are the use of bisphosphonates, palliative radiation therapy and palliative surgery with transurethral resection of the

prostate. Immunotherapy and chemotherapy for hormone resistant prostate cancer can also be adopted for recurrent prostate cancer conditions.

4.6. Plants considered for treatment and prevention of prostate diseases (cancer)

Different plant species have been studied for their ability to treat prostate cancer and control the spread of prostate tumor to other parts of the body. Though the research on their active components is still undergoing, various publications have listed these plants as potential targets for the elimination of prostate cancer. The following are some of the plants that have been shown to eliminate the development and metastasis of prostate cancer in human beings:

a) *Ficus pseudopalma*

b) *Nelumbo nucifera*

c) *Camptotheca acuminata* (happy tree, cancer tree or the tree of life)

d) *Rauvolfia vomitoria* (poison devil's pepper)

e) *Podophyllum peltatum*

f) *Taxus brevifolia* (California Yew, Pacific Yew or Western Yew)

g) *Viscum album*

h) *Capsicum annum* (capsicum, cayenne, chili pepper, hot pepper or long pepper)

Other plants with biological activity on prostate disease include the following:

- *Serenoa repens* (saw palmetto)
- *Cucurbita pepo* (pumpkin)
- *Borago officinalis* (stinging nestle)
- *Urtica dioica*

- *Brassica oleracea*
- *Nerium oleander*
- *Allium sativum*
- *Camellia sinensis*
- *Oenothera paradoxa*
- *Amaranthus spinosus*
- *Rubus coreanus*
- *Annona muricata*

4.6.1. Botanical description

a) Ficus pseudopalma

Ficus pseudopalma commonly referred to as the fig tree is an erect, glabrous and unbranched shrub growing tree with an approximate height of five meters. The leaves of this tree tend to be crowded towards the stem and are relatively short petioled. Niyog-niyogan, as it is referred to in Philipines has cordate bases and an acute apex (46).

The blades of the leave are coriaceous and dark green in color. The edges are coarsely toothed and are more than 25 centimeters in length. *Ficus pseudopalma* produces ovoid and angular fruits which are four centimetres long with short peduncles. The fruits tend to be crowded at the axil of the leaves. Once the leaves and the fruit mature and drop, they leave a pattern of scars on the trunk of the tree. The plant is indigenous to Philippines where it is cultivated in large volumes (46).

Ficus pseudopalma has high concentration of phytochemicals, flavonoids, unsaturated sterols, triterpenes and other compounds which have been shown to have medical value. other commonly targeted compounds within the plant include steroid glycosides, saponin, tannin and phenols. The leaves, seed and back of the

plant has high concentration of the target molecules as compared to the roots or flower.

It also dominates thickets and forests found within low altitudes or as ornamental plants in some countries due to the patterns left on the trunk. In Hawaii, the plant is sparingly cultivated, having been domesticated from other parts of the world. The leaves are targeted for medicinal purposes and nutrition in Philippines and other parts of the world.

Figure 17: *Ficus pseudopalma (83)*.

b) Nelumbo nucifera

Nelumbo nucifera, commonly referred to as the scared lotus is a symbolic plant that is commonly used in Buddhism and Hinduism. It is native to Asia and Australia and is cultivated for different reasons. It produces large flowers and grows up to three feet tall with widespread and thickened rhizomes. The plant grows in heavily watered regions with the rhizome performing well in water logged mud surfaces. As a result, the plant grows as a marginal aquatic perennial plant (22). *Nelumbo nucifera* has parasol like, upward cupped and waxy green leaves which grow above the water surface. It produces flowers which can bloom for about three days before they wither and get replaced. Like the primrose plant, flowers of *nucifera* open

during the night and close at daytime. After the flowers with, nutlike fruits emerge which are imbedded within the flat surface of the turbinate spectacle. In Asia, the rhizomes, leaves and even seeds of lotus plant are edible and can also be used as spices for cooking different meals.

Figure 19: Sacred lotus (89).

c) Camptotheca acuminata

Camptotheca is a deciduous plant that grows in different parts of China and Tibet. Within the indigenous Chinese, the plant is referred to as *xi shu*, directly translating to happy tree. The branches of camptotheca only grow near the top of the tree and have a reddish green coloration as shown in figure 3. In traditional Chinese society, the plant has been used during times of antiquity to help in the management of diverse medical conditions. These include psoriasis, liver and stomach ailments. It was also used in the treatment of leukemia in ancient Greek and China. Recent studies commissioned by the national cancer institute in the United States have led to the identification of the anticancer agent in the tree (7).

Figure 3: Flowing happy tree (93).

d) Rauvolfia vomitoria

Rauvolfia vomitoria is a naturally occurring plant that occupies equatorial and tropical forests in different parts of the world. It is a shrub of less than eight meters in length with whorled branches interspaced with nodes and enlarged lumps as shown in figure four below. The leaves of the *R. vomitoria* exist in triplets and accumulate to form lanceolate. The plant also produces fleshy and red colored fruits that are poisonous (13).

In different parts of Africa and Asia, *Rauvolfia vomitoria* is planted as an ornamental plant or a source of energy. The bark of the plant has high fiber levels and yellow die which is used in the fashion industry. The seeds of the plant are also used in the making of decorative necklaces common in West Africa. In Gabon, the root and bark powder of the plant is mixed with palm oil and used an insecticide and vermin. Other parts of Africa also use the plant for the treatment of leprosy and other lunatic patients. Rheumatic pain management has also been done using *Rauvolfia vomitoria* extract. Jaundice and gastrointestinal disturbances is also controlled using extracts from the plant.

Figure 4: *Rauvolfia vomitoria* shrub showing unripe fruits (84).

e) Podophyllum peltatum

*Podophyllum peltatum i*s an herbaceous plant that was identified by Linnaeus, the father of the modern taxonomic classification. Commonly referred to as the May apple, the plant grows up to 30-40 centimeters and has an umbrella-like leaves. May apples produce multiple stems that emerge from an underground rhizome. The plant produces white, yellow or red flowers of varying sizes which have been used for medicinal purposes over the years. The plant is relatively poisonous except the fruit that has however been associated with unpleasant indigestion challenges. May apples belong to order *Ranunculales* and the *Berberidaceae* family (11).

Figure 7: *Podophyllum peltatum (87)*.

f) Taxus brevifolia

The Pacific or Western yew belongs to the coniferous plants and is cultivated in different parts of South America. The plant grows under other trees and can tolerate shady canopies. The Pacific yew is a hard wood and can grow for over 60m for a long period. The plant produces seed cones that are used for its propagation within the natural habitat. The plant can grow in different environments though it performs better in moist and cool environment. The Pacific yew is more shade tolerant as compared to other strains of the yew (12).

Figure 8: The Pacific yew (8).

g) Viscum album

Viscum album belongs to the mistletoe species and is common in Europe and other parts of southern Asia. The plant grows as a hemiparasite that dominates certain species of trees to enable it draw water and nutrients. The stems of the plant can grow up to 100 centimeters with dichotomous branching. The plant is dioeciously with insect pollinated flows which have a green cultured background. *Viscum album* produces a white or yellow berry fruit with several embedded seeds which have been used for different medicinal activities.

Figure 14: *Viscum album (94).*

h) Capsicum annum

It belongs to the Solanaceae family and is native to Mexico and Central America. However, capsicum is currently cultivated in different parts of the world for food and spices. Capsicum is a white flowered plant with dense branches that grow up to 6o centimeters. The fruit is classified as a berry and has different colors while in the ripe state. These include green, red for the common capsicum or even yellow. Though the plant can tolerate and survive in different climatic conditions, it thrives better in a warm and dry environment (9).

Figure 5: A ripe *Capsicum annum* plant (85).

4.6.2. Chemical substances and biological activity

Medicinal plants with the ability to effectively manage prostate cancer as has been discussed in the previous section have different active chemical component.

a) Ficus pseudopalma

Ficus pseudopalma has high concentration of phytochemicals, flavonoids, unsaturated sterols, triterpenes and other compounds which have been shown to have medical value. Other commonly targeted compounds within the plant include steroid glycosides, saponin, tannin and phenols. The leaves, seed and back of the plant has high concentration of the target molecules as compared to the roots or flower. Terpenoids is a large and diverse class of organic chemicals which have structural and functional similarity to terpenes (46).

The compound is multicyclic and has five carbon isoprene units which can be modeled and assembled in different ways. Just like other lipid terpenoids, *Ficus pseudopalma* has been used as a traditional remedy to various conditions in Philippines. Research has established the antibacterial, antineoplastic and anticytotoxic properties of the plant extract which has high concentration of terpenoids (46).

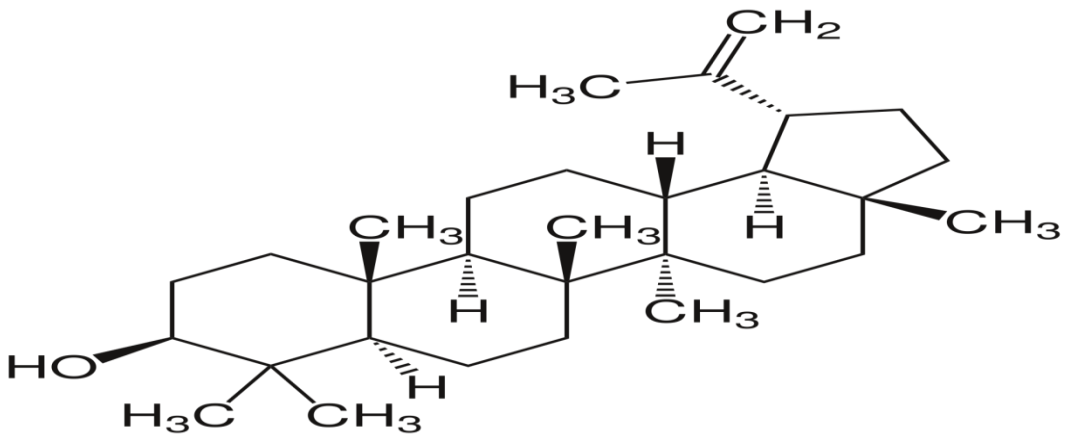

Figure 37: Lupeol (117).

Ficus species has been shown to act against renal carcinogenesis, human glioma and human heptaocellular carcinoma (HC). Other studies have also associated the plant with anticancer activity on HeLa cells, breast cancer cells and colorectal cancer cell lines. The naturally occurring flavonoids and terpenes in ficus have the ability to prevent the oxidative stress within cells which is associated with diseases such as cancer (46).

Triterpernoid lupeol have antioxidant properties which rid the cell of any reactive oxygen species which can lead to the generation of cancer cells in specialized tissues. In model studies conducted with cancer cells from lab mice, lupeol was shown to suppress the growth of hepatocellular carcinoma and even the prostate specific antigen secretion. Lupeol also inhibits the growth of tumours and the metastasis of cancer cell, a property that gives an indication that the plant can be exploited for the control of prostate cancer (50). Squalene significantly suppresses colonic ACF formation and crypt multiplicity. This strengthens the hypothesis that squalene possesses chemopreventive activity against colon carcinogenesis.

Squalene has cardioprotective effect which is related to inhibition of lipid accumulation by its hypolipidemic properties and/or its antioxidant properties. Lutein and zeaxanthin may have roles in protecting against age-related macular degeneration. β-Sitosterol has been shown to inhibit proliferation and induce apoptosis in human solid tumors such as colon and breast cancers. Stigmasterol lowers plasma cholesterol levels, inhibits intestinal cholesterol and plant sterol absorption, and suppresses hepatic cholesterol and classic bile acid synthesis in Winstar as well as WKY rats.

b) Nelumbo nucifera

Nelumbo nucifera has different active compounds which have been extracted and tested for antitumor properties. Compounds such as liriodenine, lysicamine, anonaine, caaverine among others have been tested in various studies to determine their antitumor properties. Most of these compounds have been shown to possess antiradical scavenging, metal chelating and ferric reducing properties. Aporphine alkaloid is the most dominant alkaloid in *Nelumbo nucifera* and is involved in most of the antitumor reactions. Aporphine belongs to the quinolone alkaloids and is found in other plants apart from the sacred lotus. Other pharmaceutical properties of the plant include dopamine antagonist at different concentrations, antinociceptive activity and as an anticonvulsant.

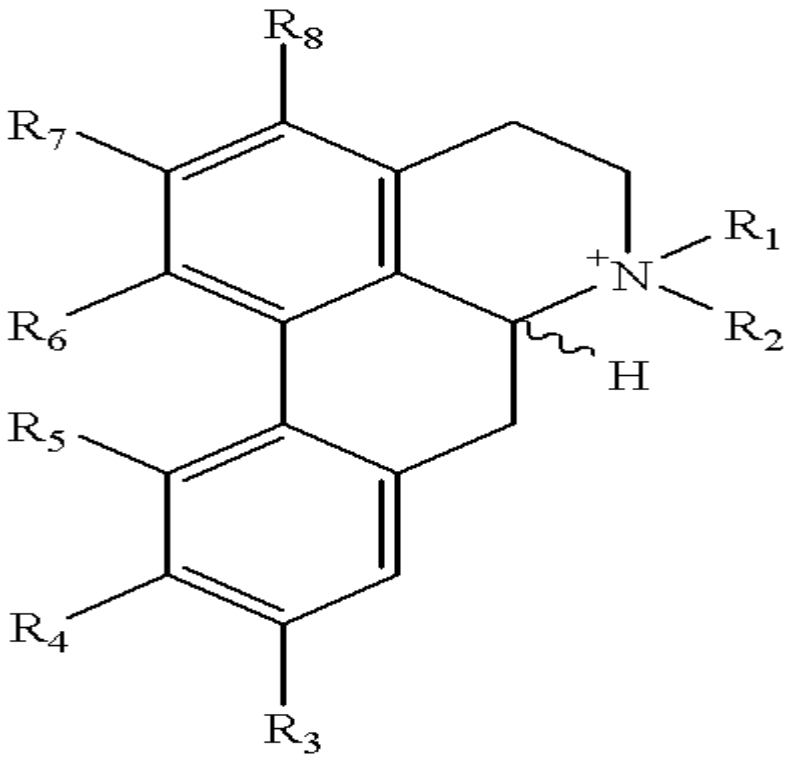

Figure 39: Aporphine alkaloid (119).

High concentration of free radicals within the cells is destructive to DNA, proteins and even cell membranes. Most damages caused by such free radicals lead

to the development of cancer related conditions. As an antioxidant, arpophine alkaloid is a scavenger and eliminates any free radicals in the body that can cause the formation of cancer cells. Hydroxydehydronuciferine, a category of aporphine has a potent antiprostate cancer activity (ACA).

The inhibitory effect of isoliensinine isolated from the seeds of *N. nucifera* was studied on bleomycin-induced pulmonary fibrosis in mice. Administration of isoliensinine remarkably suppressed the increase in hydroxyproline content and abated the lung tissue injury induced by bleomycin. It enhanced SOD activity and decreased the malondialdehyde level in a concentration dependent manner. Moreover, isoliensinine significantly inhibited the over-expression of TNF-α and transforming growth factor- β (TGF- β) induced by bleomycin. These results indicated that isoliensinine possesses significant inhibitory activity against bleomycin -induced pulmonary fibrosis, probably due to its antioxidant and/or anti-inflammatory activities and inhibitory effect on TNF-a and TGF-b induced by bleomycin.

c) Camptotheca acuminata

According to the food and drugs agency of the United States, it is safe to consume camptothecin products. However, the use of the botanical products of the plants must be consumed under the direction of a qualified and competent medical practitioner. The plant should not be used for treatment of any form of cancer unless directed by a physician.

In camptotheca, the alkaloid camptothecin (CPT) has been shown to have antitumor activity that can be used in the management of prostate cancer. Companies like the GlaxoSmithKline (GSK) have developed various chemotherapeutic drugs based on camptothecin. Research has established that

camptothecin acts by inhibiting topoisomerase enzyme. This process can be effective in the management of other cancers as has been employed in both ovarian and lung cancers (7).

Camptotheca is popularly known for the production of pentacyclic quinolones camptothecin and 10-hydroxycamptothecin. These are secondary substrates which are produced through the indole alkaloid pathway. Camptothecin inhibits the activity of DNA polymerase 1 and has been shown to be very effective against cancer cells in vitro. However, the application of camptothecin in the control of prostate cancer has been limited by its severe side effects.

However, research has led to the introduction of less toxic variants through genetic manipulation of the plant and chemical synthesis. Semi-synthetic derivatives of camptothecin include topotecan and irinotecan which have strong anticancer activity but have fewer side effects on the other normal cells. Such semi-synthetic camptothecins have been used in the control of colorectal, prostate and other gynecological cancers.

Camptothecin is made up of a lactone ring which is highly susceptible to hydrolysis in the presence of an aqueous environment. However, the compound is inactive in the open ring state and must be enclosed for the topoisomerase inhibition activity to occur. When in the close configuration, CPT is stable in acidic environment which is the characteristic of the carcinogenic environment within the prostate region. The compound is transported to the prostate cells by passive diffusion due to its high hydrophobicity and lipophilicity within the acidic environment. Camptothecin also has a high affinity for human serum albumin (HSA) when in the carboxylate form which increases the absorption and bioavailability of the compound within the target tissues.

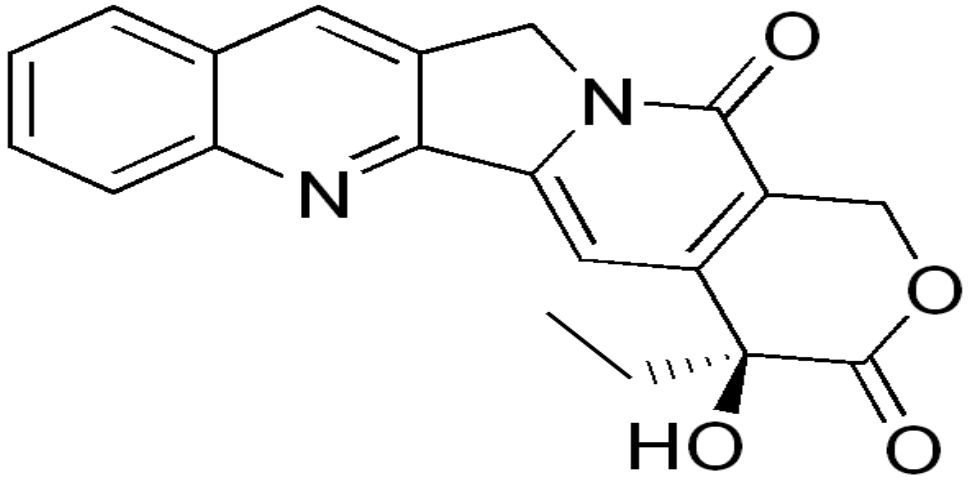

Figure 23: Camptothecin (103).

By inhibiting topoisomerase action, camptothecin inhibits DNA replication processes by increasing the strain on double-stranded DNA during unwinding. This creates an intercalation that affects the DNA duplication machinery, thus preventing the prostate cells from further division. Most mammalian cells have no repair mechanism for correcting double strand breaks. Cells with a high level of double strands breaks are directed to programmed cell death or apoptosis.

Camptotheca plant extract has also been found to act against brain tumor, liver cancer, leukemia and cancer conditions of the gastrointestinal tract. The main cancer agent within the plant is found in high concentration on the tender leaves, roots and back of the leaves. Pentacyclic quinone alkaloid is the main component of the plant though other alkaloids are also present including camptothecone, venoterpine, tannins and salicyclic acids.

Camptothecin also triggers apoptosis in tumor cells by arresting the DNA replication fork. This results into breaks within the DNA double strands through the action of caspase-3 and caspase-7. Diagnostic advances have identified the cleavage of caspase-3 and 7 as a potential protein market in PD (68). Apart from the inhibition of DNA topoisomerase, CPT also inhibits a number of retroviruses which

are associated with numerous carcinomas. For example, the human immunodeficiency and the equine infectious anemia virus activity are inhibited by CPT from camptotheca plant.

CPT acts by inhibiting Tat-mediated transcription from the viral promoters in HIV. Such discoveries have increased the demand for CPT in different parts of the world as efforts to develop the right therapeutic interventions for cancer and viral conditions increases. The secretory structures of the plant have been attributed to the production of bioactive secondary products which in biological scenarios, serve as growth regulators. In plants, CPT is also a defense chemical found in high concentration in leaves, barks, woods and fruits to protect against infections and herbivorous plants.

d) Rauvolfia vomitoria

Despite being able to grow in different weather conditions, *R. vomitoria* is an endangered species. It is common in most African countries including the republic of Congo, Nigeria, Senegal, Sudan among others. *R. vomitoria* produce sweetly scented flowers that are frequented by honeybees among other insects. The back of the tree is also known for the production of good best fiber. Though most parts of the tree are considered poisonous for normal human and plant consumption, it has been used for medicinal purposes in various parts of Africa. For example, traditional healers in Nigeria use the herb for the management of psychiatric conditions among others (8).

The antitumor chemical component of vomitoria that has been isolated and shown to act against prostate cancer is alstonine. Alstonine is an indole alkaloid that has previously been used to manage other conditions such as memory deficit and social withdrawal. Though anticancer activity of alstonine has not been

comprehensively provided, preliminary studies show that it can help manage different type of lymphomas.

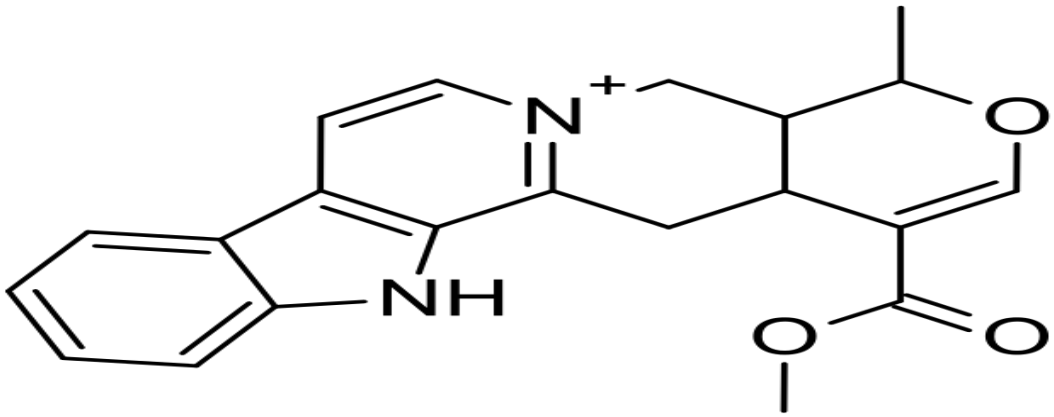

Figure 23: Alstonine (104).

According to 8, R vomitoria acts by inhibiting the PANC-1 tumor in prostate cancer and this contribute to over 50% of tumor inhibition. The inhibitory actions against PANC-1 also lower the rate of metastasis and formation of metastasis lesions within the prostate region. The duo also demonstrated that the use of Rau has relatively low toxicity against other adjacent cells. The conclusion was made after adjacent cells from the mice were subjected to pathological tests to determine the level of damage after treatment with Rau extracts (56).

The admission of the right dose of Rau also induces DNA damage which affects the normal cell cycle within prostate cancer cells. By activating the damage pathways, Rau can be used to induce apoptosis of prostate cancer cells and the control of further metastasis. Just like in CPT, Rau also increase the cleavage of caspase proteins, with caspase-3 and 8 targeted in the case of Rau (68).

Alstonine, the main alkaloid found in *Rauvolfia vomitoria* is a byproduct of tryptophan metabolism in plants. With an indole ring, alstonine has been used in the treatment of numerous mental conditions by traditional psychiatrists. Schizophrenia, a condition associated with abnormality in gama-aminobutyric acid and dopamine neurotransmitter has been controlled in the past with alstonine alkaloid. In mice

models with schizophrenia, the action of alstonine has been shown to depend on dose and potent of the compound. Apart from antipsychotic activity, alstonine also have anxiolytic activity. Traditional and modern healers have used alstonine formulated medication to relieve anxiety in patients. This is due to the interaction of the alkaloid with the 5HT2 receptors on mice models.

In vitro tests with alstonine have also shown that the chemical has a high binding affinity to other cancer cells. The high alstonine binding affinity for cancer cells as opposed to normal cells has been explored in the development of targeting chemotherapies in which case alstonine is tagged with a cancer cell poison. After the binding of the chemical to cancer cells, inhibition of growth occurs in vitro. Experiments carried using the chemical in mice demonstrated its high potency in vivo.

Results from such studies have led to increased research on other cancer classes including ovarian and colon cancer. Despite the benefits of alstonine as has been highlighted in previous texts, scientists have faced the challenge of extracting and purifying the active component from *Rauwolfa vomitoria* plant. High tincture extracts of the chemical completely eliminate cancer cells through the inhibition of replication process. Alstonine has also been studied with brain cancer cells in vitro to determine its potency and future applicability. Positive results posted so far has contributed to an increased demand for the extracts within health facilities and research institutions. Further in vitro and in vivo studies on alstonine can provide the breakthrough that is needed in the management of cancer diseases including prostate cancer.

e) Podophyllum peltatum

The American Indians used the May apple as emetic, cathartic and anthelmintic. Such traditional uses formed the basis of current research for the use of *Podophyllum peltatum* in the management of different cancer conditions including prostate cancer. As a plant that has high concentration of podophyllotoxin, residents boiled the plants to reduce the poison level before applying for different traditional medicinal purposes. For example, *Podophyllum peltatum* disease is a gastro-enteritis disease that is characterized with colicky pain and nausea (21).

Podophyllotoxin, a non-alkaloid, is the main anticancer agent in *Podophyllum peltatum.* The compound has been studied extensively and is currently used by various pharmaceutical companies for the management of cancer. It is one of the few plant-based non-alkaloids that have been successfully synthesized in the lab for large-scale pharmaceutical applications (22). The biosynthetic route of Podophyllotoxin is yet to be fully elucidated though there is indication it is formed from coniferyl alcohol conversion into pinoresinol.

The successful application of this non-alkaloid toxin in the management of other cancers and lymphomas portends successful application in the management of prostate cancer (56). The production of androgens in LNCaP in prostate cancer cells facilitates the entire progression process. In men, the formation of excess androgen has been attributed to the induction of excessive cell proliferation. Such activities within the prostate lead to the development of tumour which progresses to cancer. Podophyllotoxins have been shown to target the androgen production process by inhibiting the synthetic pathway. A reduction in the level of androgen production in prostate cells reduces the possibility of developing full blown cancer. Proliferation

cannot take place in the absence of enough androgens thus leading to the death of the cancer cells.

Podophyllotoxin is currently used as a precursor in the formulation of common cancer drug known as etoposide. This further demonstrates that it presents significant opportunities for the management of prostate cancer. However, further research needs to be conducted to demonstrate the mode of activity of the non-alkaloid in the management of tumor cells (11).

Podophyllotoxin blocks cell division by inhibiting the microtubule assembly process within the mitotic apparatus. The interaction of the toxin with DNA has been considered as the main effect cancer cells division. Exposing cancer cells to this toxin affects the cell progression into the late phase S or early G2 interacting with the enzyme topoisomerase II. Topoisomerase enzymes are used in the reduction of the strain during DNA double strand separation.

Topoisomerase enzymes are therefore important in replication, transcription, chromosomal segregation and DNA recombination which are important in cell division. The production of androgens in LNCaP in prostate cancer cells facilitates the entire progression process. In men, the formation of excess androgen has been attributed to the induction of excessive cell proliferation. Such activities within the prostate lead to the development of tumour which progresses to cancer. Podophyllotoxins have been shown to target the androgen production process by inhibiting the synthetic pathway. A reduction in the level of androgen production in prostate cells reduces the possibility of developing full blown cancer. Proliferation cannot take place in the absence of enough androgens thus leading to the death of the cancer cells.

Synthetic podophyllotoxin analogues have been used to evaluate the impact of the toxin on cancer cells in vitro. Podophyllotoxin analogues have similar inhibitory impact on the growth of cancer cells which make it a powerful potential anticancer agent. Agents such as etoposide, teniposide and etopophos have been studied to evaluate their impacts on the pathogenesis of different cancer categories. However, Podophyllotoxin is poisonous to other normal cells in the body. To effectively use it as an anticancer agent, specific targeting of the cancer cells with antibody conjugated to the Podophyllotoxin can be adopted in order to reduce the harmful impacts on healthy cells in the body.

f) Taxus brevifolia

In *Taxus brevifolia*, paclitaxel is the main antitumor agent based on previous studies that have showed that it acts against leukemia and cancer cells. Paclitaxel or paclitaxel has been used in the management of other cancer conditions such as breast, ovarian, lung and pancreatic. Success in these cancer cases have demonstrated that it can be successfully used in prostate cancer (12).

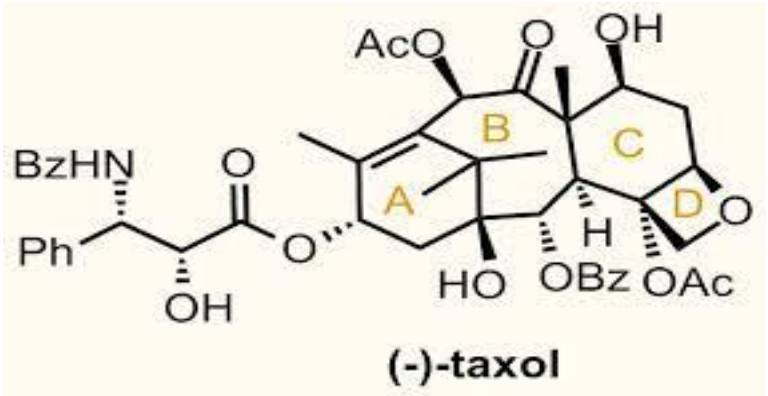

Figure 27: Paclitaxel (117).

Paclitaxel acts against tubulin that are cytoskeletons used by locomotion and cell division in cells. As a result, this compound can initiate the formation of defective mitotic spindles during cell mitosis. The cell can also affect the normal

chromosomal segregation during cell division, resulting in the formation of an abnormal cell. However, the use of paclitaxel in the management of prostate cancer presents other health challenges based on results from studies with other cancer cases (12).

Paclitaxel is a common cancer medication that is extracted from Taxus plant. Studies have confirmed that paclitaxel can be used in the management of a number of cancer conditions including ovarian cancer, breast cancer, lung and pancreatic cancer. Discovered in 1962, paclitaxel has been extensively studied and formulated in different forms for therapeutic applications in the management of cancer. Paclitaxel functions through the stiffening of the microtubules in cells which are important for the inner skeleton and shape. Locking the microtubules into place affects cell malleability, leading to crumble and inability to divide at interphase. As a result, cancer cells exposed to paclitaxel undergo apoptosis, leading to a decline in population.

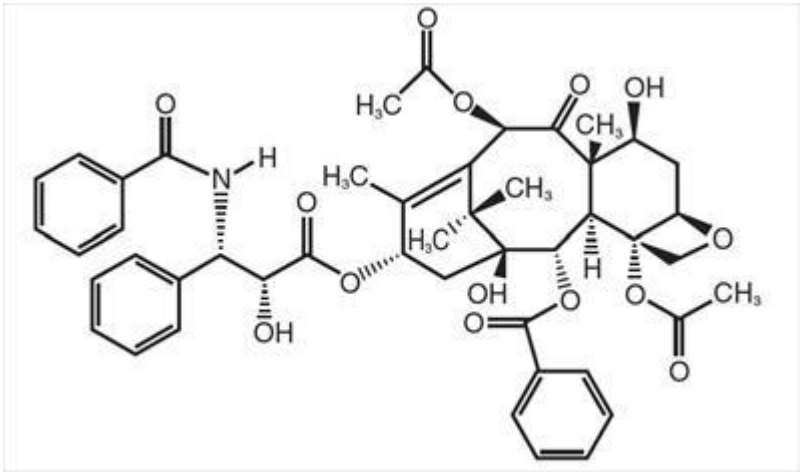

Figure 34: Paclitaxel (113).

Doxetaxel is the second taxane from the taxus plant that has been shown to have anticancer activity. The FD approved docetaxel as an anticancer agent for use in breast, neck and gastric cancers but studies have recently shown that it has activity against prostate cancer. Doxetaxel is twice as potent as paclitaxel due to its

ability to affect both the microtubules and the centrosome of the mitotic spindle. Doxetaxel has been shown to be effective against refractory prostate cancer thereby increasing the life expectancy and quality of life for cancer patients as compared to other therapeutic approaches.

Docetaxel has a 1.9-fold higher affinity for the site than paclitaxel does and it induces tubulin polymerization at a 2.1-fold lower critical tubulin concentration (5). The initial slope of the assembly reaction and the amount of polymer formed is also greater for docetaxel. In addition, docetaxel is more potent than paclitaxel is at inducing cytotoxicity in vitro and in tumor xenograft. These differences do not imply that docetaxel has a greater therapeutic index because greater potency may also portend greater toxicity, and pharmacologic differences between the agents must be considered.

The taxanes inhibit cell proliferation by inducing a sustained mitotic block at the metaphase/anaphase boundary, as well as formation of an incomplete metaphase plate of chromosomes and an abnormal organization of spindle microtubules, which occur at much lower drug concentrations than those required to increase microtubule mass. Aberrant mitotic spindles and mitotic block due to stabilization of microtubule dynamics which results from inhibitory drug effects on intrinsic microtubule. This involves the equilibrium between tubular dimers and microtuble polymers such as dynamic instability and treadmilling. After the disruption of microtubules, particularly those comprising the mitotic spindle apparatus, the precise means by which cell death occurs are not clear. However, morphologic features and DNA fragmentation patterns characteristic of programmed cell death or apoptosis have been documented in 354 tumor cells after taxane treatment.

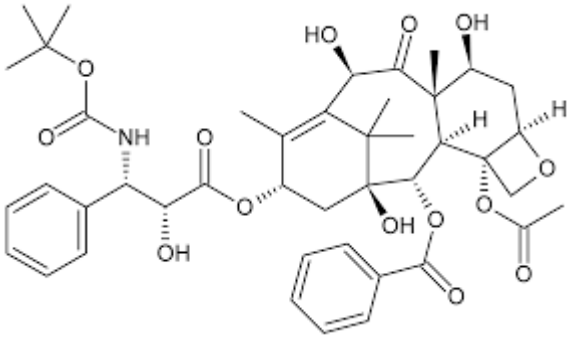

Figure 35: Doxetaxel (114).

g) Viscum album

The European mistletoe aqueous extracts has been shown to possess anticancer activity and used in some setting for cancer therapy. Clinical trial studies in different parts have shown that the extracts from the plant improve quality of life in cancer patients. Biological active component examination had shown that the plant has high concentrations of mistletoe lectins, viscotoxins, polyphenols and branched polysaccharides.

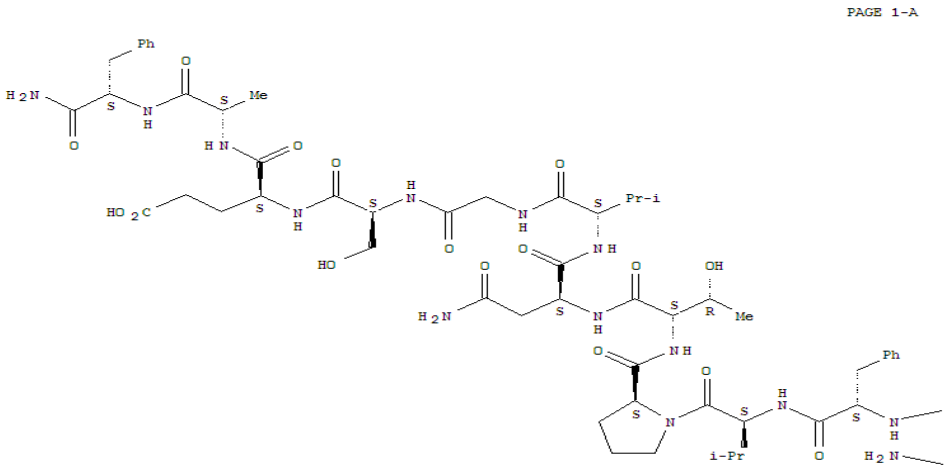

Figure 36: Viscotoxins (114).

The European mistletoe aqueous extracts induce apoptotic cell death in cancer cells. Though the complete mode of action has not been fully elucidated, reports from different clinical trials have supported the assertion that these extracts have antitumor activities. Cancer development is reliant on angiogenesis and

metastatic progression of the cancer cells. Currently, research has focused on preventing angiogenesis as a way of eliminating tumor cells from the body (3).

Viscum album preparations commonly (mistletoe extracts), are used as complementary treatment approaches in cancer and also in the treatment of several inflammatory human conditions. Despite their extensive applications in human health, their mode of action has not been extensively understood through biochemical studies. Studies have shown that these preparations exert anti-tumor activities, which involve the cytotoxic properties, induction of apoptosis, inhibition of angiogenesis and several other immune-modulatory and anti-inflammatory mechanisms. These properties collectively define the mechanistic basis for the therapeutic benefit of VA preparations.

Studies have also shown that VA preparations exert a potent anti-inflammatory effect by selectively down-regulating the COX-2-mediated cytokine-induced secretion of prostaglandin E2 (PGE2), one of the important molecular signatures of inflammatory reactions. However, the molecular mechanisms associated with the vascular mediated COX-2 inhibition are not clear. VA preparations are shown to inhibit the COX-2 protein expression without modulating its expression at mRNA level suggesting a possible effect of VA on post-transcriptional events of COX-2 regulation. Several molecules and phytotherapeutics are known to interfere with the post-transcriptional and post-translation regulation of COX-2 in order to inhibit the COX-2 expression and subsequent reduction of PGE2. The discovery of several novel natural products from European mistletoe shows the need for more studies on this plant for use in other condition.

European mistletoe has been used for the treatment of prostate cancer with success though studies indicate that it can be used in other conditions. Failure to effectively characterise the plant has affected has affected its application to other pathological conditions. This is particularly valid with respect to medium-sized organic molecules belonging to the main molecular regime relevant in the search for new drug candidates.

Mistletoe's lectins are cytotoxic glycoproteins of approximately 10,000 molecular weight; they cause cells to agglutinate14 and inhibit protein synthesis on the ribosomal level. The lectins, also known as viscumin or agglutinin, are dual chain molecules. Chain A inhibits protein synthesis and chain B activates macrophages and releases lymphokines from lymphocytes. Both the A and B chains of mistletoe lectin I also inhibit allergen-induced histamine release from leukocytes and collagen-induced serotonin release from platelet.

Lectins are structurally similar to two highly biologically active toxic proteins, ricin and abrin. The amounts and biological activity of V. album lectins are dependent on the host tree, manufacturing process, and time of harvest. Viscotoxin is a 46-amino acid peptide that damages cell membranes. Viscotoxin is found only in V. album. A similar constituent of Phoradendron is phoratoxin, a polypeptide about twice the weight of viscotoxin; it makes up 0.01% to 0.23% of Phoradendron leaves and stems.

The compound also targets other cancer types such as gastric and skin cancer cell lines. Other classes of arpophine have apoptotic activity on cancer cells thus reducing the progressive invasiveness of the cancer condition. Cancer cells are subjected to programmed cell death in the presence of some of these alkaloids, thus reducing metastatic spread into other parts of the body in the case of prostate cancer.

The major constituents isolated from the lotus plant are alkaloids and flavonoids ((+)-1(R)-coclaurine, (-)-1(S)-norcoclaurine and quercetin 3-O-b-D-glucuronide. One of the most potent mechanisms by which flavonoids inhibit platelet aggregation is by mediating increase in platelet cyclic AMP levels by either stimulation of adenylate cyclase or inhibition of cAMP phosphodiesterase activity. The composition of flavonoids, polyphenols, alkaloids and natural antioxidants present in pink and white flowers is completely different. Furthermore, it is a well-known fact that many patients taking aspirin continue to have adverse cardiovascular events.

h) Capsicum annum

Capsaicin is the main anticancer agent in *Capsicum annum* and has also been used in the management of various other conditions. Capsaicin is a secondary metabolite that is produced by capsicums and is categorized under the capsaicinoids. In its pure form, the product is highly volatile, hydrophobic and forms crystals at room temperature (9). Naturally, capsaicin is used as an analgesic applied topically and through the nasal routes. In dermal patches, capsaicin is used in the management of pain in patients suffering from different conditions.

In peripheral neuropathy such as shingles, capsaicin is applied topically in a controlled environment to avoid unnecessary irritation. In cultured prostate cancer cells, capsaicin has been demonstrated to possess antiproliferative effect. Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is the principal pungent component in the fruits of plants from the genus *Capsicum*, which are members of the nightshade family, *Solanaceae.* Such properties have increased chemopreventive potential research on capsaicin by natural medicine scientists.

Long term topical application of capsaicin cream also reduces carcinoma carcinogenesis in mice that are exposed to tumor promoters. However such effects are concentration dependent, which raises issues of irritation and unwanted side effects in cancer patients. More studies on mice should therefore be conducted to determine any potential side effects of capsaicin in different doses. This discrepancy is as a result of the frequent need to renew primary cultures due to dedifferentiation, in studying the effects of capsaicin in relevant "normal cell" control groups for comparison with cancer cells, which are pathologic.

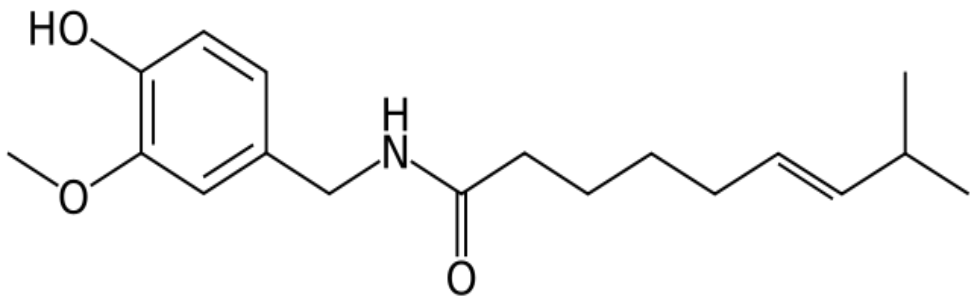

Figure 25: Capsaicin (115).

Despite the lack of adequate research on the use of capsaicin in the management of prostate cancer, previous applications in other forms of cancers have proved beneficial. It was commonly used as a powerful painkiller and exists in topical forms as used and approved by the food and drug agency (FDA) in the United States (56).

During and after chemotherapy, capsaicin can be used to effectively reduce pain and the negative implications of radiation poisoning in prostate cancer patients. Capsaicin has antioxidant abilities and can reduce the negative implications of nitrosamine, a known carcinogen. Capsaicin also improves DNA repair in cells, thus blocking the replication and duplication of damaged DNA. Evidence exists to show that capsaicin can effectively slow the growth of prostate cancer cells in vitro.

Such experimental results have increased the scientific prospect of using the compound in the management of prostate cancer in men (9). However, capsaicin has also been reported to be mutagenic and to result into an increase in the cell viability and proliferation of the androgen-responsive prostate cancer LNCaP cells corresponding with increased androgen receptor expression. The action and potent of capsaicin in other cancer cases also vary depending on the stage of pathogenesis and organ affected. A number of mechanisms for capsaicin-induced apoptosis have emerged for different cell systems within the body. For example, capsaicin induces the apoptosis of leukemic cells through the activation of p53 protein phosphorylation by the reactive oxygen species. In contrast, capsaicin in prostate cancer also induces apoptosis of the cells but in a manner which is independent of the action of p53 protein.

In human colon cancer, capsaicin has been shown to activate and induce the activity of p53 protein. P53 is an important role in the protecting the integrity of human genome and is classified as a proto-oncogene. Mutation on this gene induces the development of 50% tumors in human beings, demonstrating its primary role in the management of cancer epidemiology. Activation of p53 by the capsaicin makes it to act as a transcription factor which lead to the accomplishment of different functions including activation of DNA repair induction of cell cycle arrest in cancer cells and programed cell death in extreme cases.

Exposure of p53 gene to capsaicin leads to the enhancement of its stability. With high level of capsaicin in cancer cells, MDM2-mediated p53 degradation which leads to the development of colon cancer is suppressed. Capsaicin also targets mitochondrial and plasma membrane electron transport systems, leading to the

production of reactive oxygen species. Reactive oxygen species mediate the apoptosis of nearby cancer cells in the body.

Despite the positive results from numerous studies, potential limitations has affected its adoption as an alternative cancer therapy. The positive impacts of capsaicin on cancer cells was only witnessed at high capsaicin concentrations. For example, the highest functioning concentration of capsaicin that can be administered orally to induce apoptosis of cancer cells is 30mg/kg. Oral LD_{50} dose of capsacin from previous studies also indicate that a male dose of 118mg/kg and 98mg/kg for female mice is effective. Such high concentrations cannot be achieved in vivo without affecting the normal function of other cells in the body. For complete treatment of colon and prostate cancer using capsaicin, novel therapeutic approaches developed based on the results currently posted are needed. However, food additives such as *P. annum* have been shown to have positive impacts on colon cancer patients as compared to current chemotherapeutic agents.

4.6.3. Other plants with biological activity on prostate disease (cancer)

Serenoa repens

Saw palmetto is a sole species belonging to the genus S*erenoa* and has been used extensively in the management of different conditions. The plant has palm like leaves and grows up to a maximum of 10 feet. It has sprawling trunk and is mostly found within the dense thick sandy coastal regions of the United States. The plant has sharp edges that can easily break the skin if handled in the absence of protective clothing.

The leaves of the inland plant are green while the coastal strain has silvery white edges. In most cases, the leaves of the plant can grow to a six of 2 meters in length with leaflets on the edges. The plant has yellowish flowers and is produced at the extreme edges of the plant (14). The fruits are the target for alternative medicine and are reddish black as show in figure nine below.

Figure 9: Fruit saw palmetto plant (89).

Serenoa repens or saw palmetto is also a common anticancer plant that has been used in the management of prostate cancer. The plant has beta sitosterol as the main ingredient that acts against tumor cells and prevents further metastasis. Beta sitosterol is categorized under the phytosterols and has a chemical structure similar to cholesterol. When extracted, purified and evaporated, beta sitosterol is white, waxy powder with an identical smell. It is hydrophobic and therefore dissolved and formulated using alcohol. Apart from *repens*, the compound has also been isolated in *cucurbita pepo,* cashew nut and the corn oil. Beta sitosterol has been used in the management of BPH in men and the success has contributed to current research in prostate cancer.

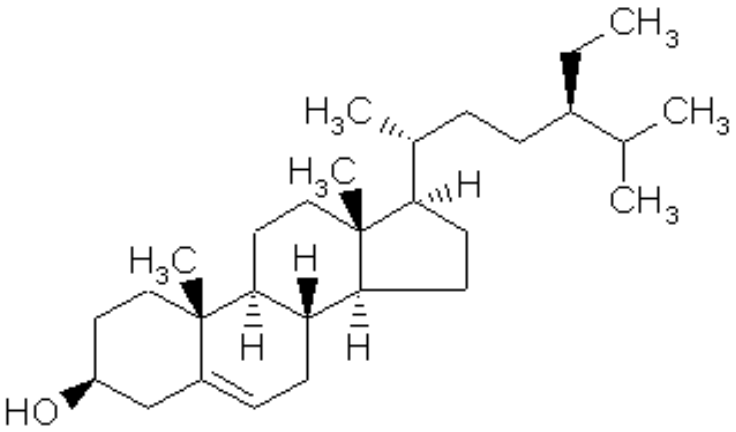

Figure 29: Sitosterol (119).

Beta sitosterols are used to promote the activity of antioxidant enzymes, superoxide demutase and glutathione peroxidase. As a result, the compound can protect cells from destructive actions of antioxidants, processes that are associated with the emergence and progression of prostate cancer cells. Sitesterols and other phytesterols within the same class have also been shown to affect cancer development and progression.

A treatment of prostate and breast cancer cells with 8μm of beta sitosterols reduced the rate of cell growth by 50%. Sitosterols have also been shown to increase to promote apoptosis of cancer cells, a common mechanism that has been adopted in the process of inhibiting carcinogenesis. In prostate cancer cells, treatment with sitosterols decreased their population indicating the most of the cells were killed in the process.

Brassica oleracea

Brassica oleracea belongs to the cabbage family and is edible, cooked or raw. The vegetable has a large and flowery head that is green in color with a tree-like structure. When cut from the top, *Brassica oleracea* takes the shape of a tree with sprouting branches and thick stalk as shown in figure five below. The vegetable was first cultivated in the northern Mediterranean during the 6th BC. There are

different varieties of broccoli that are cultivated and studied for potential anticancer activity. However, sprouting broccoli is the most common variant that is used as a vegetable. However, purple cauliflower which is found in Italy, Spain and other parts of the United Kingdom has gained considerable interests. A number of broccolis have emerged from artificial breeding processes such as the Brussels sprouts. The vegetative components of the new variants have been improved as compared to the wild strains.

It is similar to cauliflower though belong to different cultivar groups and is associated with the Italians who initially used it as a vegetable (10).

Figure 6: A pair of *Brassica oleracea* vegetables (86).

Hot peppers have been used as medicine in Africa and other parts of the globe based on reports by botanists. In Asia, pepper has been used as a spice while fresh, cooked and fresh due to high levels of vitamins A and C. capsaicin, which is the main chemical ingredient in red pepper is an eye and skin irritant. It has been formulated for use by police officers as a defense mechanism. Apart from physical uses, capsaicin has been used in the management of other medical conditions such as topical pain relief, muscle soreness, shingles, skin irritation, rheumatism and as an anti-inflammatory agent. Recent research has provided a new impetus into the cultivation of capsicum as indications show that the plant has anticancer activity.

Sulforaphane is a phytochemical found in *Brassica oleracea* with significant anticancer activity based on results from previous studies. It is biochemically classified as an isothiocyanate that is produced by myrosinase enzyme found in most cruciferous vegetables such as *Brassica oleracea*. Epidemiological studies have shown that people who regularly consume *Brassica oleracea* and associated vegetables have low incidences of developing prostate cancer among other cancer categories. Just like other phytochemicals, sulforaphane can limit further growth of tumor (56).

More research is needed to verify the safety and efficacy of sulfurophane and its synthetic intermediates for use in prostate cancer management especially at high doses. But a growing understanding of how sulforaphane functions and is able to selectively kill cancer cells indicate it may have value in treating metasticized cancer, and could work alongside existing approaches. Sulforaphane is pharmacologically well absorbed through the primary drug routes of administration. This conclusion is based on numerous clinical and preclinical studies involving the chemical extracted from broccoli. Excretion of sulfuraphane also occurs through the renal route, making it a pharmacologically safe drug to be developed for the management and treatment of prostate and other category of cancer. In humans, bioavailability of sulforaphane appears to be 74% and primarily absorbed in the jejunum.

The development of cells into cancer cells lead to the production of phase two enzymes. Sulforaphane is a phase two enzyme inducers which helps in the neutralization of carcinogens before they can transform cells by damaging DNA. The phytochemical inhibits the production of benzopyrene-DNA and other DNA adducts (10). Sulforaphane also inhibits cell cycle progression in cancer cells which

limits metastasis process. Sulforaphane act by inhibiting cytochrome P1A1 which is induced by the benzopyrene ring according to results from HepG2 cells conducted in vitro.

Research has also shown that sulfurophane induce apoptotic cell death and inhibition of angiogenesis in prostate cancer cells. Through the induction of chk2 kinase-dependent cells, the G2/M process is arrested leading to decline in the progression of prostate cancer. In the treatment of prostate cancer, sulfurophane leads to the induction of p21 and down regulation of cyclin D1 and cyclin A. as a result, G1cell cycle is arrested.

LnCap is also arrested in prostate cancer that is treated with sulfurophane due to the arrest of G1/S stage of cell cycle. Treatment with microscale of sulfurophane also induces apoptosis in p53 positive and p53 negative prostate cancer cell lines. DU145 cells are significantly affected with chemical through apoptotic mechanism as caspase 7 and 9 are activated leading to the release of cytochrome C from mitochondria.

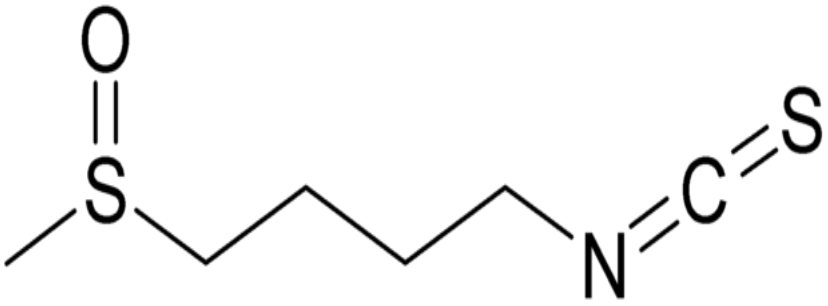

Figure 26: Sulforaphane (116).

Sulforaphane is also a potential antioxidant which inhibits histone deacetylase enzymes (HDAC). HDAC enzymes play a critical role of determining whether or not certain genes will be expressed or not. For example, the tumor suppressor genes are under the control of HDAC enzymes and they function to suppress tumor genes from being activated. Researchers are currently investigating how the concentration of sulforaphane can be

manipulated in order to control the activity of HDAC in different cells. With cancer cells experiencing inappropriate cell growth, HDAC inhibitors can be used to restore normal cell functions.

Sulforaphane also activates phase 2 enzymes which are found in high concentration within the liver cells. These enzymes have detoxification ability and are used to reduce the risk of developing prostate and colon cancer. Sulforaphane is one of the potent phytochemical to date that has been used to induce the action of phase-2 enzymes in hepatocytes. Broccoli is thus an important anticancer fighting food that nutritionists have focused on in the recent past.

Studies have however, revealed that the potent of broccoli as a source of sulforaphane is dependent on the cooking approach adopted. The formation of sulforaphane requires the presence of myrosinase enzyme which can be destroyed at different temperatures. To retain sulforaphane, broccoli should be steam for only five minutes and not boiled or microwaved. Boiling of broccoli for a minute or less destroys a large concentration of the sulforaphane in broccoli, making it less potent as an anticancer food food (19).

Cucurbita pepo

Cucurbita pepo is a common vegetable plant of the Cucurbita genus and classified into different cultivars. The morphological features of the plant vary depending on the cultivar and the location of cultivation. Pumpkin is an annual crop that spreads on the ground and is grown in different parts of the world depending on the cultivar and water availability. The normal height of the plant is less than 2 feet while the sprout may extend and curl within the garden. It is suitable for light and medium soils which are well drained (14).

Figure 10: Ripe pumpkin vegetable (yellow cultivar) (90).

Pumpkin has flesh and seeds have high presence of phytoestrogens and cucurbitacin E which have been associated with breast and prostate cancer respectively. Cucurbitacins E is an oxidized steroid and is made up of tricyclic triterpenes. Previous studies have associated cucurbitacin E with anti-inflammatory action, as an antioxidant and in the manufacture of insecticide. The compound is found in different plant species belong to cucurbitaceae family like pumpkins.

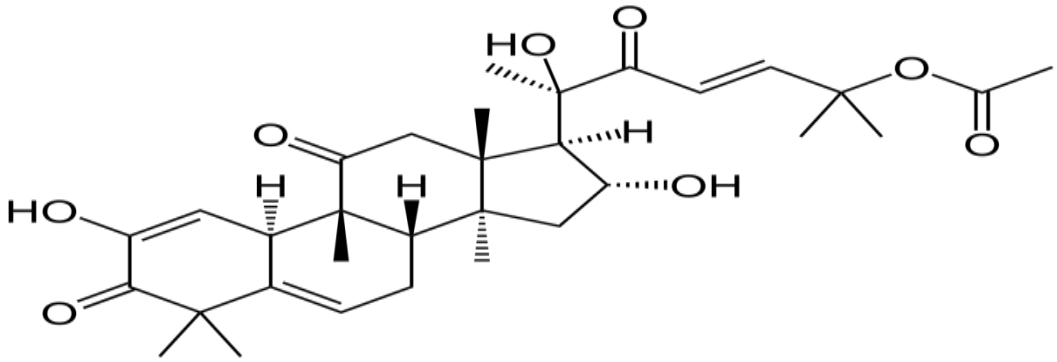

Figure 28: Cucurbitaceae (118).

Cucurbitacin E has the potential to induce antitumor proliferation and apoptosis on tumor cells. In combination with other compounds or in isolation, cucurbitacin can inhibit the phosphorylation of STAT3 and JAK2 leading to their activation. This is important in the control of tumor cell proliferation in human

beings. Cucurbitacin also causes the disruption of cytoskeleton, thus interfering with the process of mitosis and the structures of actin and vimentin (22).

Normal mitogen induced cells in human beings are also inhibited in the presence of cucurbitacin. This leads to the disruption of F-actin and tubulin microfilaments cytoskeleton, thus arresting the motility of the tumor cells. Reduced cell motility is important in the control of cancer cell motility in prostate cancer. Other categories of cucurbitacin have been tested in other cancer subtypes such as breast and colon cancer, cucurbitacin B and I are effective in the control of metastasis and the control of angiogenesis process.

Borago officinalis

Borago officinalis is a common starflower that grows annually and is used in different parts of the world as herbs. Though it is native to the Mediterranean region, the plant has been domesticated in other parts of the world. The weather in the United Kingdom favors its growth and it is a common herb in the region. The herb grows up to a meter in height and has hairy stems and leaves which are arranged in an alternative manner. The flowers have narrow and triangular pointed petals and are often blue in color. However, pink varieties also exist in other parts of the world but the arrangement is common. The blue flower is the genetically dominant variety while the white is recessive. The pink color is a cross from a white and blue flower variety.

Figure 11: Flowering borage (91).

In *Borago officinalis*, the active compound with anticancer activity was identified to be rosmarinic acid. Rosmarinic acid belongs to caffeic acid esters and is common in a number of plant species apart from the stinging nestle. Rosmanic acid has been used in a number of other clinical applications including acting as an anxiolytic and GABA inhibitor. Recent research has associated the compound with anti-prostate cancer activity (30).

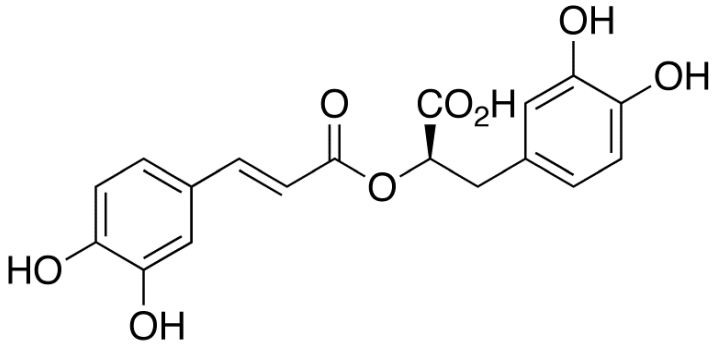

Figure 30: Rosmanic acid (120).

Rosmanic acid at different concentrations act as inhibitors to TPA induced transcription processes. By inhibiting COX-2 activation, the compound has been shown to prevent the development and proliferation of prostate cancer. Increased levels of prostaglandins-2 promote the activation of ERK-signaling pathway, thus promoting the proliferation of prostate cancer cells (30).

Urtica dioica

Urtica dioica or the stinging nestle is also a plant commonly under in the management of prostate disease. The plant is native to different continents including Europe, North Africa and North America. Several subspecies of the plant exist that have been used as medicinal plants in different parts of the world (68). The plant can grow up to seven feet tall and is common during the winter. The rhizomes are widely spreading and the roots of the plant are bright yellow. The leaves are green,

sharped edge and rough on the surface. The plant secretes different chemicals when stimulated through touch including acetylcholine, formic acid and leukotriene (24).

Figure 12: The stinging nestle (92).

The nettle leaf has a dense deposit of micronutrients and is used as a source of food nutrition in some communities. The stinging hair contains histamine, acetylcholine, acetic acid, butyric acids, leukotrienes and 5-hydroxytryptamine. In the management of prostate cancer disease, the hydrophilic components of the plants have appeared to be more essential. From the roots of the nettle, (-)-3, 4-divanillytetrahydrofuran is extracted and used in the treatment of benign prostrate hyperplasia (BPH) among other androgen sensitive conditions such as prostate cancer. The inhibition of prostatic sodium/potassium pump is achieved by the action of stigmasterol, stimast-4-en-3-one and the campesterol (24).

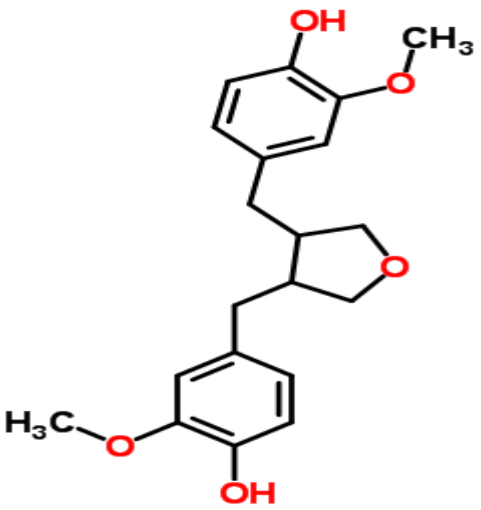

Figure 31: (-)-3, 4-Divanillytetrahydrofuran (121)

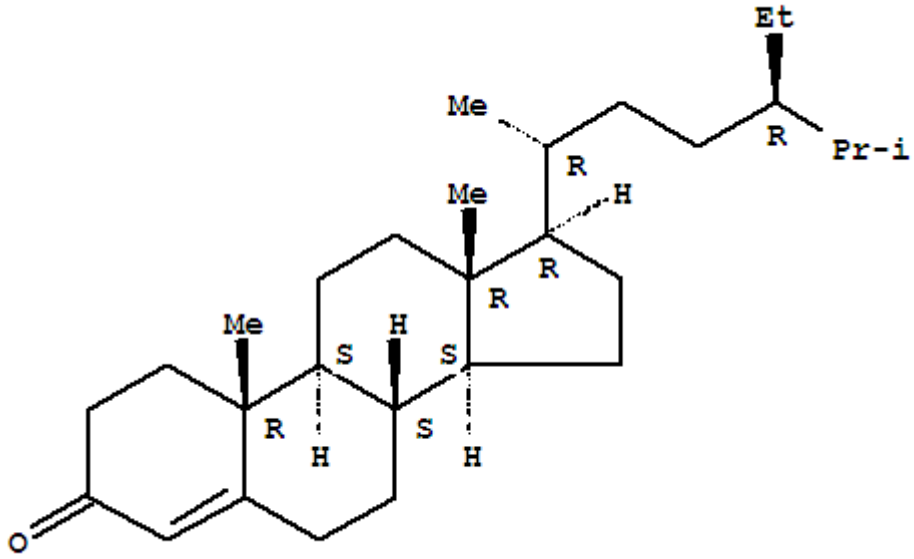

Figure 32: Stimast-4-en-3-one (122).

The level of aromatase enzyme rises as the age of men increases and this increase the level of estrogen which is formed testosterones using the aromatase enzyme. High levels of estrogen contribute to the enlargement of the prostate, leading BPH and other prostate disorders such as prostate cancer. *Dioica* compounds have been shown to possess aromatase inhibitory effects which slow down the production of estrogen within the prostate region (24). *Urtica dioica* therefore has a

number of active compounds that have anti-prostate cancer and BOH activity in men.

Nerium oleander

This is an evergreen shrub that has high poison level and has high fragrant flowers of varying colors including white, red, purple and pink. The plant is found mostly in mild climatic conditions but can also be domesticated and grown indoors despite the high poison levels. The plant grows up to 6 matters tall and has erect stem that is covered with a grey back. The flowers of *Nerium oleander* grows in cluster at the tip of every branch and the leaves are deeply lobed. The plant originated from different parts of the world including Mauritania, morocco and Portugal though it is currently available in different parts of the world including the east coast of the United States. Currently, the extract of the plant are undergoing clinical trials to determine whether it can be used in the control of cancer specifically prostate cancer.

Figure 13: *Nerium oleander* (93).

The search for an effective agent that can effectively kill cancer cells and reduce the likelihood of metastasis in conditions such as prostate cancer has led to the current focus on *Nerium oleander,* a tropical flowering plant that has different flow colors. This plant has been used before in different medical conditions including the induction of abortion, treatment of hemorrhoids, ulcers, leprosy and snake bites. The leaves of the plant are rich in cardiac glycosides, oleandrin, adynerin, aeriatin, and oloroside A. the extraction of anirvel which contain a combination of oleanrigenin and oleandrin has been shown to have cytotoxic and antitumor effects (51).

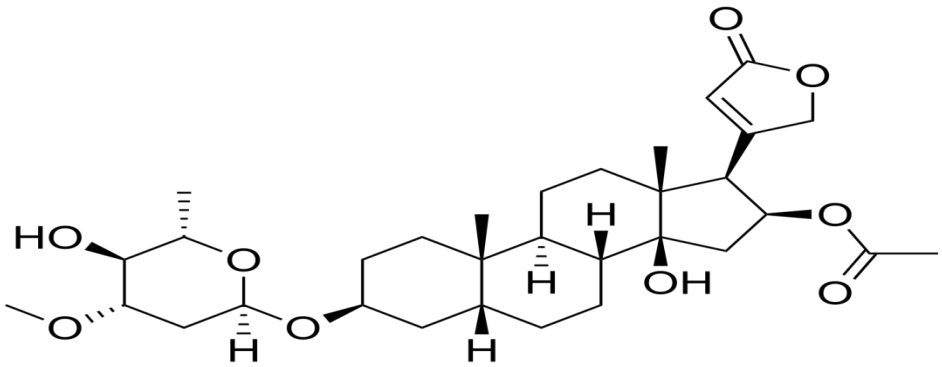

Figure 33: Oleandrin (113).

As a result, current literature indicates that the plant extracts can be used in the effective management of prostate cancer and other cancer categories. In vitro studies of the effects of anrizel and its active component oleandrin, a specific-specific cell killing was reported in different classes of human cells and in cells of murine and canine origin (30). The cell killing of prostate cancer cells by *Nerium oleander* is mediated by the loss of telomeric DNA which results into the inhibition of G_2/M phase of the cell cycle. This action in prostate cancer cells also leads to the induction of endomitosis and extensive fragmentation of DNA and a decline in the levels of TRF2. This will finally result into cell death as mitotic division is arrested through the inhibition of DNA multiplication during the G_2 phase of cell cycle (47).

Allium sativum

Allium sativum or garlic is a common food product that is related to onions, the shallot and other plants which have been historically used in the management of different conditions (22). The plant is natural in Africa, Asia and even Europe and is currently grown in different continents in the world. Garlic is a bulbous plant with a sprout which grows over four feet above the soil surface. Garlic is a hermaphrodite with flowers that are self-pollinated using bees or even insects. The bulb in the soil is used for nutritional and medicinal purposes (56).

Figure 15: Garlic (95).

Preliminary investigations have shown that the consumption of garlic acids can help in reducing the development of prostate cancer in men. According to the American Cancer Association (ACA), garlic is currently under numerous studies to demonstrate its anticancer properties (47). Though scientific evidence is inconclusive on the impacts of garlic acid consumption of different other cancer categories, positive results with prostate cancer has increased interests in the plant (50). The allyl sulphur garlic acids as currently been promoted as potential anti-prostate cancer agents (47).

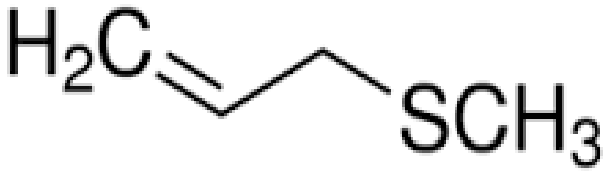

Figure 35: Allyl methyl sulfide (119).

The compound acts by removing oxidants and other reactive oxygen species that contribute towards the emergence of cancer cells in the body. Garlic extract has also been associated with the initiation of apoptosis of prostate cancer cells, thus reducing chances of cancer metastasis.

Camellia sinensis

Camellia sinensis is the source of green tea that has been famously used for the management of various conditions. Green tea is processed by exposure to maximum oxidation process and is sourced from china though other Asian cultures have also used it. The production of a number of modern western beverages and dietary supplement depends on the green tea production process. Different varieties of green tea have been produced and are used for different medicinal and supplementation purposes (22).

Figure 16: Green tea levels (96).

Green tea is a known angiogenesis inhibitor that has been used in the prevention and treatment of prostate cancer according to scientists from the University of Maryland Medical Centre (MDC). Angiogenesis is the process of forming new blood vessels which is critical in the process of cancer cell growth and proliferation. Through angiogenesis, nutrients and oxygen is supplied to cancer cells, allowing further differentiation and growth. The antioxidants phytochemical known as catechins exist in high concentration in green tea which has been associated with cancer growth inhibition (30).

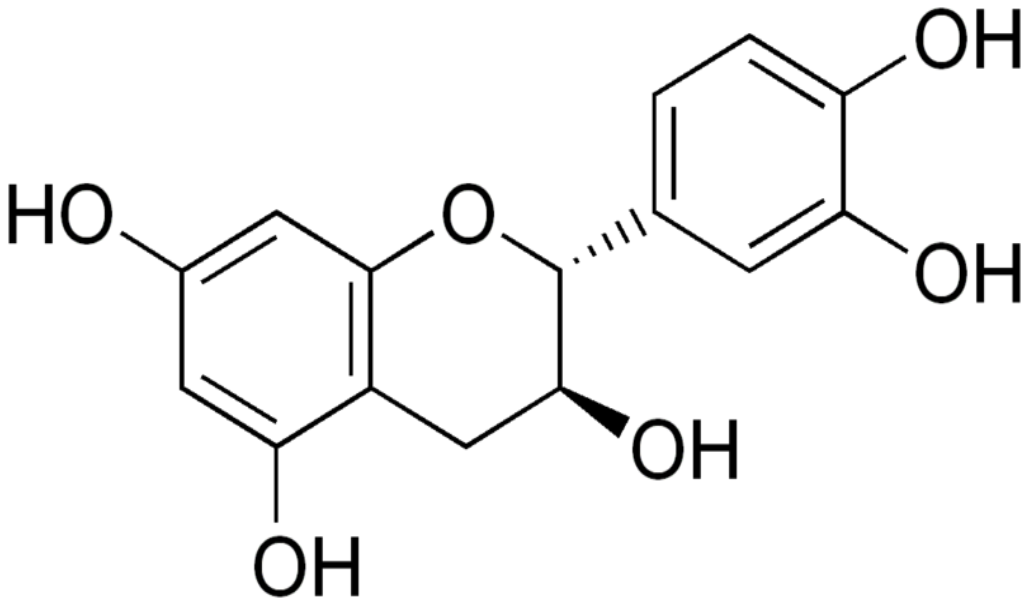

Figure 36: Catechins (118).

Catechin has a high free radical scavenging activity which helps in the reduction in the level of free radicals and reactive oxygen species in the body. The removal of free radicals from the body helps in the reduction in DNA damage by the reactive oxygen species. Tea catechins also inhibit further tumor proliferation and induce apoptosis in prostate cancer cells. Laboratory tests have also confirmed that tea catechins inhibit tumor cells angiogenesis and the invasiveness of tumor cells (47).

Oenothera paradoxa

Oenothera paradoxa is an herbaceous flowering plant that is indigenous and parts of the American continent. The plant has several common names including the evening primrose and sun drops among other names. The size of the plant varies with strains but is relative short shrubs, growing up to ten centimetres in length. However, other vigorous lowland species have been identified in Mexico that can grow for up to three meters in height (56).

The leaves of the plant form a basal rosette while the flowers exist in spiral form, emanating from the stem. Most of the blades are dentate in shape while others are deeply lobed. During the evening, most of the flowers open which explains the common name ‘evening primrose’. Colour carry may vary based on the strain and the location of cultivation but are commonly white, purple, pink or even red. However, the original and wild strain variety of the plant has white flowered colours, which is the dominant trait (22).

Figure 18: Primrose (98).

The search for conventional and complementary treatment for prostate cancer has switched the focus from chemical drugs to plant polyphenols. Plant polyphenols have multiple biological activities in human cells which can help in in the prevention and even control of cancer. The evening primrose plant has high concentration of mono and oligo-polymers of flavanol (30). However, the anticancer

activity of the plant is attributed to catechin in conjunction with other flavanols and polyphenol extracts in the plant. Catechins target cancer susceptible cells and reduce the population of reactive oxygen species and other cancer compound which can increase the development of prostate cancer in men.

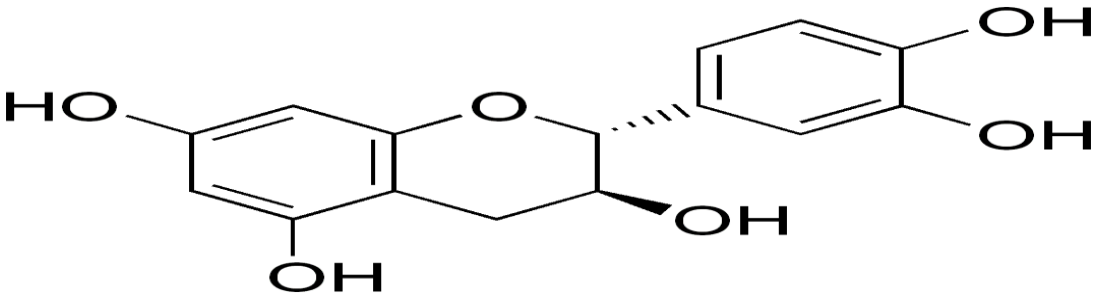

Figure 38: (+)-Catechin (121).

Polyphenols from evening primrose have an antiproliferative activity against human prostate and breast cancer cells. As a result, cells treated with the polyphenol have low proliferation which reduces the spread of prostate cancer cells to other parts of the body. Evening primrose polyphenols have also been shown to prevent the invasiveness of certain cancer cell lines. For example the non-tumorigenic immortalized human prostate epithelial cell lines have low invasiveness in the presence of polyphenols from evening primrose (50).

Amaranthus spinosus

Amaranthus spinosus is a vegetable plant that has different scientific names based on the country of cultivation. It is native to tropical America but has been adopted in other parts of the world including Asia, Africa and Europe. In some countries, the plant is a noxious weed that affects the cultivation of rice for example in Asia. *Amaranthus spinosus* is an annual herb that grows up to one and half meters with laborious leaves which are sparsely haired. The plant has green flowers which are clustered on the axillary and bears branched terminal spikes (68).

Figure 20: *Amaranthus spinosus (100).*

The active chemical constituent in *Amaranthus spinosus* is spinoside, a mew coumaroyl flavone gycoside that has been shown to possess potent anticancer activity especially against prostate cancer cells. Spinoside is categorised under triterpene hydrocarbons cucurbitane with class A and B.

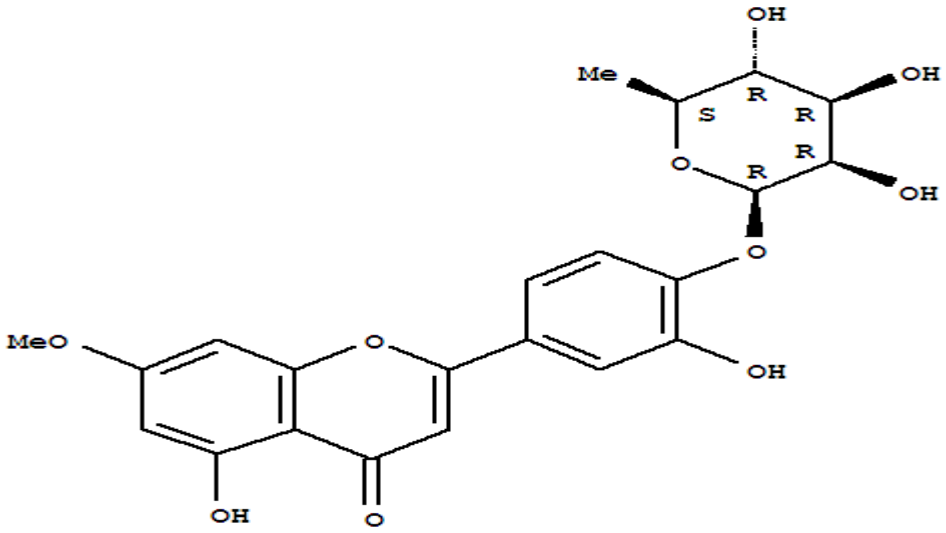

Figure 40: Cucurbitane (104).

The production of androgens in LNCaP in prostate cancer cells facilitates the entire progression process. In men, the formation of excess androgen has been attributed to the induction of excessive cell proliferation. Such activities within the prostate lead to the development of tumour which progresses to cancer. Spinosides

from *Amaranthus spinosus* have been shown to target the androgen production process by inhibiting the synthetic pathway.

A reduction in the level of androgen production in prostate cells reduces the possibility of developing full blown cancer. Proliferation cannot take place in the absence of enough androgens thus leading to the death of the cancer cells. Though further studies should be conducted to determine if the compound has other modes of action of against cancer cell, current literature strongly suggest that *Amaranthus spinosus* is a potent medicinal plant that should be employed in the management of different forms of prostate cancer.

Rubus coreanus

Rubus coreanus also known as the Korean black raspberry is a common raspberry species that is native to Korea, japan and china. The plant produces edible berries which have been used for different purposes including fermentation into wine and for medical purposes. Previous traditional uses have also associated the plant with aphrodisiac properties. *Rubus coreanus* height ranges from 300 to 900 meters and is common within thickets in slopes, montane valleys, riverbanks and other elevated surfaces.

Though the test has not been applied to human beings, the preclinical studies have demonstrated it can have potential impact in the control of prostate cancer. Anthocyanins are water soluble pigments that are associated with a number of flowering plants. The substance belongs to the class of flavonoids and is found in different species of plants. The separation and purification of the substance can be done from leaves, stems and roots of plants that have been associated with the chemical.

In Korea, the plant is commonly referred as Korean bramble and used for brewing of wine. *Rubus coreanus*. The plant begins to flow within the months of July and august and form seeds after every two months. The flowers of this plant are hermaphrodites and are pollinated by insects.

Figure 21: *Rubus coreanus (101).*

Rubus coreanus has attracted focus among cancer researches due to its high concentration of anthocyanins. Previous studies have associated anthocyanins from the plant with treatment of erectile dysnfunction. Preclinical studies conducted on transgenic rats have shown that anthocyanins increase the level of testosterone in male. A high amount of testosterone hormone increases the level of spermatogenesis and the mortality of sperms in lab rats (79).

Though the test has not been applied to human beings, the preclinical studies have demonstrated it can have potential impact in the control of prostate cancer. Anthocyanins are water soluble pigments that are associated with a number of flowering plants. The substance belongs to the class of flavonoids and is found in different species of plants. The separation and purification of the substance can be

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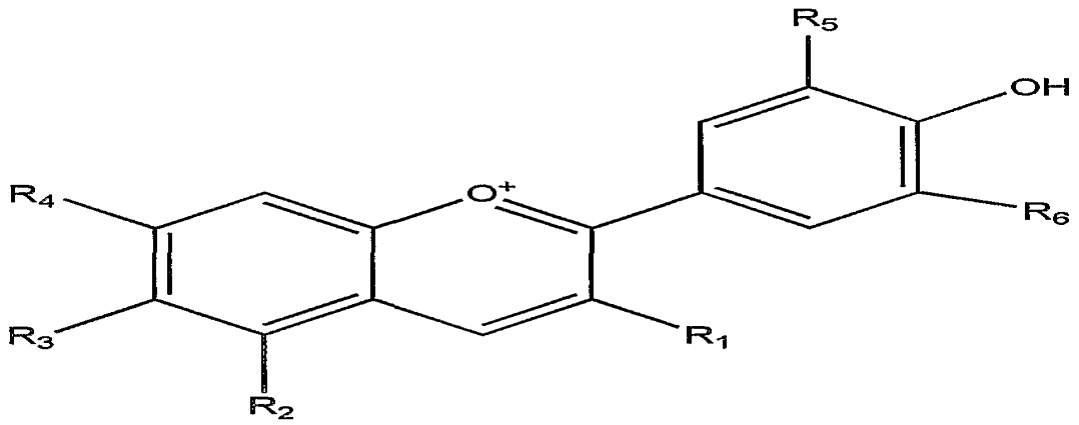

Figure 41: Anthocyanins (115).

Generally, anthocyanins have been used in the management of various categories of cancer. As a result, recent studies have focused on the application of the compound in the management of prostate cancer. Anthocyanins have an antioxidant effect which reduces the level of reactive oxygen species (ROS) from cells. In vivo tests on the antioxidant properties of the chemical have been conducted using endothelial colon and prostate cancer cells. The results from these studies have shown that the substance's ability to scavenge of ROS can help in controlling prostate cancer. Anthocyanin can also chelate heavy metals, thus reducing the concentration of harmful substances from the cell.

Apart from antioxidant activity, anthocyanin has also been shown to have anti-cell proliferation properties. By blocking various stages of cell division, the process of cell proliferation has been arrested. Inhibiting the growth of cancer cells helps in the reduction of tumor cell population within the prostate glands. Anthocyanin also induces apoptosis of cancer cells within the body. Apoptosis is one of the common ways the cell ensures that abnormal and nonfunctional cells are eliminated. However, apoptotic function in cancer cells in deregulated, thus

increasing the concentration of abnormal cells within the body. By facilitating apoptosis, anthocyanin reduces the occurrence of prostate cancer in men (31).

Annona muricata

Annona muricata is a plant categorised under *anona* species and is an edible fruit with high acid levels. Native to the Caribbean and Central America, *annona muricata* is currently found in other parts of the world including Africa and Europe. *Annona muricata* is an erect tree that grows up to 13 feet with hairy branches. The leaves are oblong to oval in shape with a glossy green colour. The fruits are dark green with prickly or rough surface with an oval shape (34).

When ripe, the fruits are juicy, succulent with a whitish and aromatic flesh. Within the flesh of the plant, there are over 1000 seeds weighing averagely 470 grams. The ability of the plant to tolerate poor soil has enabled it to grow in other parts of the world including lowland areas.

Figure 22: *Annona muricata (102).*

A number of biochemical products have been isolated from the planted categorized under phytochemicals and acetogenins. Such phytochemicals have been extracted from the back of the plant, the leaves and the fruit. Acetogenin is the

active compound found in this plant which has been associated with the management of different categories of cancer. Acetogenin is a polyketide natural product that falls under the Annonaceae where the plant belongs.

Native to Caribbean and Central American countries, *annona muricata* has been used for different medical and nutritional roles. The seeds, fruits and leaves of the plant are targeted by researchers for the treatment of various conditions such as fever, parasitic infection, rheumatism and cancer. A number of biochemical products have been isolated from the planted categorized under phytochemicals and acetogenins. Such phytochemicals have been extracted from the back of the plant, the leaves and the fruit. Acetogenin is the active compound found in this plant which has been associated with the management of different categories of cancer. Acetogenin is a polyketide natural product that falls under the Annonaceae where the plant belongs. The compound has 34 linear carbons with oxygenated functional groups such as hydroxyls, ketones, epoxies among tetrahydrofurans. Annonacin is the main chemical found within the custard apple which has anticancer activity.

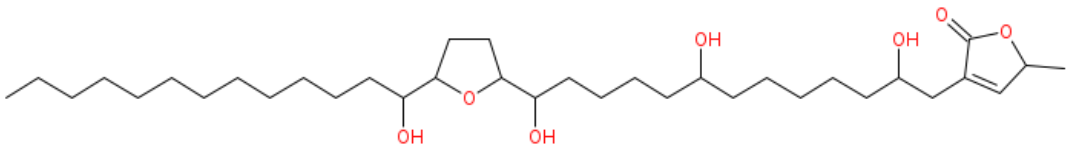

Figure 42: Annonacin (42).

Annonacin species has been shown to act against renal carcinogenesis, human glioma and human heptaocellular carcinoma (HC). Other studies have also associated the plant with anticancer activity on HeLa cells, breast cancer cells and colorectal cancer cell lines. The naturally occurring flavonoids and terpenes in ficus have the ability to prevent the oxidative stress within cells which is associated with diseases such as cancer (46). Annonacin have antioxidant properties which rid the cell of any reactive oxygen species which can lead to the generation of cancer cells

in specialized tissues. In model studies conducted with cancer cells from lab mice, annonacin was shown to suppress the growth of hepatocellular carcinoma and even the prostate specific antigen secretion. Annonacin also inhibits the growth of tumours and the metastasis of cancer cell, a property that gives an indication that the plant can be exploited for the control of prostate cancer.

5.DISCUSSION AND CONCLUSION

Prostate cancer is a major health concern in men and has been the basis of research in different parts of the world. Today, prostate cancer is ranked as the second cancer killer, after lung cancer. Despite the high mortality and morbidity in men, prostate cancer is senile and is more prevalent in men aged 50 and above. Current prostate cancer treatments include surgery, radiation and chemotherapy. However, chemotherapeutics has failed to completely eradicate the condition due to high cost of the drugs.

The prevalence of prostate cancer in different parts of the world varies depending on several factors including race and ethnicity. From 2011, for example, studies have shown that black men are more likely to die from prostate cancer as compared to other races. A recent survey released by the world cancer research fund international indicated that France lead in prostate cancer cases followed by Norway and Trinidad and Tobago in Europe. The United States is a distant 14^{th} together with other countries in Europe such as Switzerland, Finland and Estonia. In the top 20 prostate cancer incidence index, Belgium had the lowest level of the condition as compared to other 20 countries that were polled in the survey (60).

Most of these conventional drugs also have major side effects include hypertoxicity, cardiovascular disorders and synergistic hormonal reaction in the body. Variation in drug target acceptors has also made most of the current treatments ineffective as change in receptor affects ligand binding. Such challenges have contributed to the current search for new treatments for prostate cancer beyond the currently available chemotherapies. Focus has shifted to natural compounds to determine their anticancer activity and positive impacts on the disease control. This

proposal provided a review of different natural compounds with anticancer activity that can be used in the mitigation of prostate cancer disease (64).

Lignans have been used as natural toxins due to their strong anti-tumour activity. Extraction and elucidation of lignans from plants can be done in large scale in order to control the pathogenesis of cancer. In this proposal, *Podophyllum peltatum* plant was shown to have high concentration of lignans which can be extracted, elucidated and purified for prostate cancer management. Podophylotoxins have previously been shown to act against androgen sensitive and androgen independent human prostate cancer cell lines (64).

Nitrogen containing alkaloids are common constituents of secondary metabolites in a number of plants. Alkaloids have considerable activity against prostate cancer cells through the induction of apoptosis of androgen responsive and androgen dependent PC-3 cells. *Nelumbo nucifera* contains quinolone alkaloid which has both anti-inflammatory and anti-tumour activity against PC cells. Inhibition of cell growth of both androgen dependent and androgen responsive prostate cancer cells occurs through the inhibition of cyclin kinase enzyme (62).

Taxus brevifolia is a common anticancer medication that has been used in the management of numerous cancer categories. Current therapeutic focus for paclitaxel and doxetaxel from the plant include the management of breast, ovarian, lung, bladder cancers and other categories of melanoma. Paclitaxel has been attributed to the polymerization of tubulins, leading to the disruption of microtubule movements during cell division. Microtubules are important in the separation of chromosomes at the centromere and movement to the poles before cells divide into two. When the tubulins are interrupted, separation of the chromosomes fail to occur, truncating the process of cell division in the process. However, paclitaxel has been associated with

toxicity such as hypersensitivity reaction, neurotoxicity and hematological toxicities. Paclitaxel also acts on other refractory malignancies such as reemerging lymphoma and small cell lung cancer. Recent applications of paclitaxel include treatment against AIDS associated Kaposi's sarcoma.

Ficus pseudopalma contain flavonoids which animal and clinical studies have demonstrated to prevent oncogenesis. For example, quercetin flavonoid in *Ficus pseudopalma* can reduce tumor progression in prostate cancer through the inhibition of cell growth and induction of apoptotic cell death. Previous studies have demonstrated that quercetin and related alkaloids can down regulate the activity of heat shock protein (Hsp90). *Ficus pseudopalma* also contain triterpenes which have been demonstrated through preclinical studies to inhibit the progression of prostate cancer (69).

Triterpenes inhibit the chymotrypsin-like activity in human prostate cancer proteasome. This results into the accumulation of ubiqutinated proteins which suppress the activity of AR protein in androgen dependent prostate cancer cells. It can also induce apoptosis of cancer cells with the right receptors on its surface. Tricyclic and pentacyclic triterpenes also have antiangiogenic and apoptotic activity against prostate cancer cells in human beings. Both these triterpenes are found in *Ficus pseudopalma* plant and can be isolated for targeting of the condition. Possible targets of this category of triterpenes are the transcription factors specified proteins Sp1, Sp3 and Sp4 which are highly expressed on the surface of prostate cancer cells. *Ficus pseudopalma* holds significant potential in the future eradication of prostate cancer due to its LNCaP activity which helps reduces cancer cells population and prevents metastasis (68).

Nelumbo nucifera also contain considerable amounts of quinones or quinolone alkaloids that can be used for the management of prostate cancer. Quinones also target human prostate cancer cells, resulting in programmed cell death. Death of cells in the presence of quinones occurs due to the activation of receptor pathways such as caspase 8 and 10. Other plants with Quinone's include the endophytic fungi and the mangroves that have been shown to produce SZ-685c. This is an anthracycline analogue that can inhibit cell proliferation of cancer cells (67)

A number of companies have begun extensive research on the use of natural products in anticancer agents. As demonstrated in this thesis, natural products have a huge potential in the management and elimination of prostate cancer in men. However, the complexity of natural products and the difficulty associated with artificial synthesis of such products in large scale has limited the application of such information in addressing medical challenges. However, the development of modern technologies has made it possible for various companies to produce plant based cancer drugs in large scale. Manufacturers are currently unevenly distributed in different parts of the world including India, china, Europe and the united states.

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ABSTRACT

Danial Alaei Faradonbeh, Natural drugs in the treatment and prevention of prostate diseases, Charles University in Prague, faculty of pharmacy in Hradec Králové, 2015, 86 pages.

"Natural drugs in the treatment and prevention of prostate diseases" deals with prostate diseases which are some of the common ailments affecting men in different parts of the world. The etiology of prostate diseases has been identified but little progress has been witnessed as far as treatment is concerned. Of all prostate diseases identified so far, prostate cancer is the most common and affect me aged 40 and above. Prostate cancer affects the prostate gland and affects the normal function of other genitourinary tissues. Conventional prostate disease therapies have yielded minimal results, leading to increased calls for further research. Successful application of plants in the management of other conditions has attracted the interests of cancer researchers. Focus on a number of plants can provide the much needed reprieve and therapy against prostate cancer. Previous studies have identified a number of plants whose active component can act against cancer cells.

Ficus pseudopalma, Nelumbo nuficera, Camptotheca acuminata, Rauvolfa vomitoria and Viscum album are some of the plants which have been identified to act against cancer cells. Lupeol, the main chemical component of F. pseudopalma, is an antioxidant which reduces the concentration of reactive oxygen species within the prostate gland. Nelumbo nucifera has aporphine alkaloid which is also an antioxidant and acts in the same manner as pseudopalma. Studies in the United States have led to the formulation of some of these plants as anticancer agents. Apart from these five plants, other plants exist which can provide remedy to prostate cancer patients. Research on therapeutic application of plants on the management of

prostate cancer will reduce the burden of this disease across the globe. However, clinical trials should be commissioned to evaluate their effectiveness and possible side effects on human despite the success that has been witnessed with preclinical studies.

ABSTRAKT (Czech Version)

Danial Alaei Faradonbeh, Přírodní látky v léčbě a prevenci onemocnění prostaty, Univerzita Karlova v Praze, Farmaceutická fakulta v Hradci Králové, 88 stran.

Diplomová práce s názvem “, Přírodní látky v léčbě a prevenci onemocnění prostaty” se zabývá onemocněními prostaty. Zatímco etiologie těchto onemocnění je dobře známá, možnosti léčby jsou značně omezené. Jednou z nejzávažnějších a bohužel i nejčastějších chorob u mužů nad 40 let je rakovina prostaty. Rakovina prostaty ovlivňuje nejen funkci vlastního orgánu, ale celé genitourinární soustavy. Konvenční terapie této choroby zaznamenala jisté úspěchy, nicméně je zde požadavek na další možnosti léčby. Z literatury je známo mnoho rostlin s antikancerogenním účinkem a jejich úspěšné použití u jiných nádorových onemocnění vyvolalo zájem i u pacientů s nádory prostaty. řada rostlin může dát těmto pacientům naději na záchranu a zlepšení stavu onemocnění.

Ficus pseudopalma, Nelumbo nuficera, Camptotheca acuminata, Rauvolfa vomitoria a Viscum album jsou rostliny s výrazným protinádorovým efektem. Lupeol, hlavní obsahová látka F. pseudopalma, má antioxidační účinky a snižuje koncentraci reaktivního kyslíku v prostatické tkáni. Nelumbo nucifera obsahující aporfinové alkaloidy je rovněž antioxidantem působí na stejném principu jako F. pseudopalma. Kromě těchto pěti rostlin jsou v práci zmíněny i další rostliny s potenciálním účinkem na rakovinu prostaty. Bohužel většina zmíněných studií je pouze preklinických a účinek těchto rostlin teprve musí být potvrzen v klinickém testování.