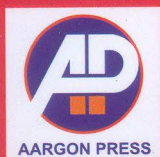


# Frontiers in Cancer Research

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Snober Shabnam Mir





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## CHAPTER 1

### NATURAL PRODUCTS: TARGETED MOLECULAR THERAPEUTIC OPPORTUNITIES IN CANCER THERAPY

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According to World Health Organization (WHO), cancer is a leading cause of death worldwide. Several approaches are implicated to treat cancer, whereas one of the major effective modality against most of the cancers is chemotherapy but due to drug resistance, lack of specificity limits successful outcomes in most cases a major problem that is further augmented by subsequent relapse. The utilization of plants for the treatment of diseases has been in practice for a very long time, as the herbal drugs constitute a major part in all the traditional system of medicines. An important and unique feature of higher plants is their ability to produce a large number of organic chemicals of high structural diversity, called as secondary metabolites. Screening and pharmacological assay of compounds obtained from plants is usually done to evaluate their immense therapeutic potential which represents molecular diversity engineered by nature. Natural compounds i.e. phytochemicals, minerals, and vitamins have shown promising results in chemoprevention and their efficacy against various malignancies in a number of studies *in vitro* and *in vivo* conditions. Extensive research has been carried out on the phytochemicals for their beneficial effect in promoting human health and signifying it as important assets for drug development. They have been found in tea, fruits, herbs, vegetables, spices nuts, seeds, stems and flowers etc. This chapter discusses different natural sources and their targeted molecular therapeutic opportunities in cancer therapy.

**Keywords:** Cancer, chemotherapy, drug resistance and phytochemicals.

## CHAPTER 2

### CYANOBACTERIA: A POTENTIAL SOURCE OF ANTICANCER DRUG

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Cancer is currently one of the most lethal diseases on the planet. Natural medical compounds have been the focus of previous cancer research endeavors. Pharmaceutical businesses and research organizations have devoted a lot of resources in isolating and discovering new marine metabolites over the last few decades. Secondary metabolites are seen as a promising source of potentially novel pharmaceutically active molecules, with a wide structural diversity and a wide range of biological activities; as a result, this is an incredible source of potential new anticancer therapy. Gram-negative photoautotrophic prokaryotes, cyanobacteria are found all over the earth. They are one of the finest places to get bioactive secondary metabolites. More than half of all cyanobacteria are produced commercially for the extraction of bioactive compounds with anticancer potential. By causing apoptosis or changing cell signalling, such as protein kinase-C family members, cell cycle arrest, mitochondrial dysfunctions, and oxidative damage, natural substances or their counterparts evoke cytotoxicity and may destroy a variety of cancer cells. These therapeutic capabilities allow them to be used in the pharmaceutical and healthcare industries to benefit future generations. Heat shock proteins have been linked to tumour cell proliferation, differentiation, invasion, metastasis, death, and immune response recognition and have been found to be overexpressed in a variety of human malignancies. Yet the role of heat shock proteins in oral cancer is ambiguous. In this chapter, we have focused on various bioactive anticancer metabolites reported in cyanobacteria and also showed the involvement of heat shock protein in preventing cancer through an insilico approach. This may improve our knowledge of current advancements in the development of anticancer drugs for human welfare.

**Keywords:** Anticancer, cyanobacteria, heat shock protein, dacarbazine.



## CHAPTER 3

### BIOACTIVE CONSTITUENTS OF SPICES AS POTENTIAL ANTICANCER AGENTS

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Cancer occurs due to mutation in genes, radiation, chemical exposure, DNA damage repair failure. Many genes play significant roles in the cell cycle pathway, and some of these are altered in cancer cells. Different types of treatments and combination therapies have been developed nowadays to fight cancer by inducing apoptosis. However, none of the therapies proved to be successful as cancer cells acquire resistance to them. Natural dietary agents including fruits, vegetables, and spices have drawn a great deal of attention from the scientific community due to their various health-promoting effects. Biologically active phytochemicals derived from spices may have chemotherapeutic activity, as suggested by epidemiologic and animal model studies. Consuming a diet rich in such phytochemicals can possess health-protective effects. Biologically active constituents mediate their positive health benefits directly, by affecting specific molecular targets such as genes, or indirectly, as stabilised conjugate affecting metabolic pathways. Keeping the above points in mind, in this study, we have illustrated various health benefits of some common spices and their major active constituents, with a special focus on anticancer and antioxidant potential.

**KEYWORDS-** Cancer, DNA damage, apoptosis, spices and active constituents.

Plants provide food and medicine to over 80% of the world's population. Flowers, flower stalks, roots, and juvenile shoots, as well as young leaves, can be used as herbs, vegetables, spices, and for a variety of other medicinal uses<sup>1</sup>. Herbal medicines may treat age-related ailments such as memory loss, osteoporosis, immunological problems, and other diseases such as cancer, for which no exact treatment exists<sup>2</sup>. Spices may be used not only as food flavorings but also as



## CHAPTER 4

### The Anticancer Activity of *Nigella sativa* L. Nanoemulsion on Liver Cancer Cell Line

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Plants provide abundant resources of anticancer compounds and have been used for centuries to inhibit cancers. The seed of *N sativa* L. of Ranunculaceae family, commonly known as black seed or black cumin are used in various traditional systems of medicine. The extract was prepared using Soxhlet apparatus and its nanoemulsion was developed. The nanoemulsion was prepared by aqueous titration method. Lipid nanoemulsions have enhanced the drug solubility, reduced effects of various strong drugs and increased the bioavailability of medications. Effect of seed and its extract on the cell viability of normal and cancerous cell lines was determined by MTT assay. The results showed that 5d sprout extract was the highly potent inhibitor of HepG<sub>2</sub> cancer cells. It significantly affected the viability of cells till 48 h, after which there was no effect. Furthermore, seed and 5d sprout extracts of *N. sativa* did not show cytotoxicity against normal human liver cell line.

**Keywords:** *Nigella sativa*, nanoemulsion, medicinal, cytotoxicity, bioavailability.

Natural bioactive compounds derived from medicinal plants have been recognised as a potential candidate for therapeutic uses since the existence of mankind. There are several religious belief and cultural traditions based on this<sup>1</sup>. *Nigella sativa* L. (*N. sativa*) is plant belonging to Ranunculaceae family, which is commonly used a spice in India, Pakistan and Middle East as a flavouring agent in many recipes. It is found in Southern Europe, Middle East and South West Asia. It is commonly known as black seed or kalaunji in vernacular language. For thousands of years, it has been in use for the prevention and treatment of various illnesses in classical system of medicine. The seed of this plant is referred to by the prophet Mohammed as

## CHAPTER 5

### MOLECULAR PLAYERS INVOLVED IN CHAPERONE MEDIATED AUTOPHAGY AND THEIR ROLE IN CANCER

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**Autophagy is a highly conserved mechanism for transporting cytoplasmic components to lysosomal degradation. Among the three major autophagic pathways, chaperone-mediated autophagy (CMA) is a type of autophagy that is specialized in protein degradation and is based on the individual translocation of a cargo protein across the lysosomal membrane. Recent discoveries have revealed not only the physiological but also the pathological role of CMA in a variety of organs and different disorders including cancers, via the accumulation of unwanted proteins or increased degradation of target proteins, with concomitant metabolic alterations caused by CMA malfunction. In the context of cancer, CMA induction may limit tumor development, experimental evidence also indicates that inhibition of this pathway can attenuate the growth of established tumors and improve the response to cancer therapeutics. In this study, we describe and discuss the evidence supporting the role for impaired CMA function in cancer, as well as this study provides a rationale for further exploring manipulation of the CMA pathway as a strategy for treating cancer.**

**Keywords:** Autophagy, chaperone-mediated autophagy, cancer, lysosomal degradation.

Cancer "The Voldemort of illnesses" is considered to be the second leading cause of mortality, due to involved epigenetic changes and procreation of mutations mainly because of environmental agents that override programmed cell death mechanism and cell cycle arrest that were previously supposed to prevent tumor development. There are many causes of cancer due to which different pathways get affected leading to development of cancer (Figure 1). Recently it has been estimated that about 1,898,160 new cancer cases were identified in the United States and approximately 608,570 people will die due to cancer in 2021<sup>1</sup>. Many cancer therapies such as



## CHAPTER 6

### **The Anticancer Potential of *Linum usitatissimum L.* and its Health Benefits**

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Globally, cancer is a disease that has a significant impact on the human population. There is an ongoing need for novel medicines to cure or prevent this potentially fatal condition. Natural-derived chemicals are attracting scientific and research interest. Flaxseed or linseed is pharmacologically active. Since, conventional treatments for cancer can be quite useful in treating certain cancers but synthetic drugs used during the treatment and chemotherapy may have several side effects. Also, there are many different protocols for cancer treatment, which are extremely expensive. So, as the herbal drug it is low cost, and possesses anticancer potential and various other health beneficial properties with minimum side effects. Collectively this chapter comprises of all the above mentioned aspect also, we have present data of the extract preparation and yield gained which is the initial step in any such study.

**Keywords:** Flaxseed, cancer, herbal, health, anticancer.

Cancer is a terrible illness, and every practical method to fighting it is critical for public health. Therefore, in addition to reasoned allopathic medications, it is worthwhile to evaluate folk medicine, a plant-based treatment that has not been the subject of a systematic investigation. An alternative to allopathic therapy, which is associated with significant side effects, is the use of folk medicine plant concoctions to combat the disease's insidious nature. Numerous herbs have been tested in clinical trials and are now being researched phytochemically to acquire a better understanding of their anti-tumor effects against a variety of malignancies. Thus, cancer patients who have already been handicapped by the illness and are now plagued by drug-induced hazardous side effects have resorted to complementary and alternative medicine in the hope of

## CHAPTER 7

### CANCER PROGRESSION VIA HSP90 AND MATRIX METALLOPROTEINASES

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Cancer is an unusual and uncontrolled proliferation of cells due to DNA replication errors or mutations in genes due to exposure to harmful radiation, carcinogens and mutagens. Chemotherapeutic resistance develops in cancer cells due to the suppression of several cell death pathways and high expression of various oncogenic proteins. HSPs are molecular chaperones that properly fold unfolded or misfolded client proteins and ultimately reduce protein stress in the cancer cells. HSPs have a main role in the development of resistant phenotype and aggressiveness in cancer. Invasiveness is the development of malignancy in terms of migration and metastatic potential. Heat shock protein 90 (HSP90) is ATP-dependent molecular chaperone that modulates different kinases and transcription factors of apoptosis. It is responsible for cell viability. Matrix metalloproteinases (MMPs) regulate cell-signaling pathways that inhibit inflammation, cell growth and angiogenesis in migration of cancer cell and ECM degradation. MMPs promote carcinogenesis by cleavage of receptors or ligands responsible for the transduction of pro-apoptotic signals and inhibit apoptosis. The expression of MMP2 and MMP9 is majorly mediated by the PI3K/AKT pathway. Moreover, MMPs secretion stimulates the activation of AKT which leads to metastasis and invasion of cancer. MMPs not only act in HSP90 dependent manner but are also stabilized by HSP90. Additionally, AKT, which is a downstream protein of HSP90, is responsible for the stimulation and secretion of MMPs.

**Keywords:** Cancer, metastasis, HSP90, MMPs, PI3K/AKT

Cancer is a sequence of consecutive alterations in genes affecting the cell functions. Generally, cancer disturbs the living relations of the cells resulting in the abnormality of fundamental genes.



## CHAPTER 8

### The Potential Anticancer Effect of *Cichorium intybus* L. on Hepatocellular Carcinoma

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*Cichorium intybus* L. (*C. intybus*) has been commonly used as a coffee substitute and its usage is proven since ancient times in medicine to cure hepatic cancer, renal failure, diabetes, and others. It has several bioactive components, including inulin, sesquiterpene, polyphenols, phytosterols, lactones, caffeic acid derivatives, coumarins, etc. Biologically active compounds derived from *C. intybus* have been investigated for their anti-oxidant and anti-cancer activities against many cancers. In this *in silico* study, we have tried to identify a novel inhibitor against p21 to target hepatocellular carcinoma (HCC). The tertiary structures of target protein and phytochemicals reported in *C. intybus* were retrieved from RCSB and Pubchem respectively. Pharmacokinetic study and Druglikeness analysis was performed by using Pre ADMET and Molinspiration, an online server, followed by molecular docking of selected ligands against protein to analyze their binding affinity. AutoDock analyses revealed that standard compound doxorubicin have the binding affinity of about  $\Delta G = -7.11$  kcal/mol and  $K_i = 6.13$   $\mu$ M against the protein 2X4Z. Comparative to the standard compound's binding score and inhibition constant of two compounds namely Stigmasterol and Chicoralexin shows higher binding potential of -8.68 kcal/mol and -8.83 kcal/mol respectively, and average inhibition constant about 4.35  $\mu$ M and 3.37  $\mu$ M, respectively. The binding energy revealed that the both compounds are having better binding affinity with the target protein as compared to the standard drug. Thus, study suggests that our two best compounds i.e. Chicoralexin and Stigmasterol could be potent inhibitor of P21 (2x4z) against HCC.

**Keywords:** *Cichorium intybus*, anti-cancer, hepatocellular carcinoma, molecular docking.

## CHAPTER 9

### ROLE OF METFORMIN IN THE REGULATION OF AMPK/mTOR PATHWAY IN CANCER

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Cancer is a deadly disease which has affected lots of people around the globe. It mainly occurs due to mutations in either tumor suppressor genes or proto oncogenes as a result of failure in DNA damage repair. Various signaling pathways are modulated in cancer cells which impact cellular proliferation and death rate. Such pathways maintain homeostasis and cellular proliferation even under stressful conditions. Nowadays, cancer therapy aims at modulating the specific oncogenic pathways in tumor cells, so as to prevent normal tissues from the deleterious effects. This “targeted therapy” relies on a better understanding of genes associated with tumor cell proliferation and survival. Autophagy is one of those pathways which have crucial role in cancer cell survival and death. Autophagy balances the cellular conditions by catabolizing the damaged organelles and generating the basic energy supplies. It has complicated roles in cancer as it can either lead to cell death or prevent the cell from the death signals. Autophagy is regulated by autophagy related genes (ATG) which are responsible for formation and maturation of autophagic vesicles known as autophagosomes. Cancer cells multiply rapidly and thus are nutrients and energy deprived. AMPK/mTOR pathway responds towards the stimuli such as availability and deprivation of nutrients, and thus is a major regulator of autophagy. In this study we have discussed the significant role of metformin in the regulation of AMPK/mTOR pathway of autophagy in lung cancer.

**KEYWORDS-** Cancer, apoptosis, autophagy, autophagy genes, chemotherapy, AMPK, mTOR



## CHAPTER 10

### **The anticancer properties of *Cydonia oblonga* L.: an underutilized Indian medicinal plant Elhan Khan, Anjum Rabab, Iffat Zareen Ahmad\***

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Plants have been known to possess enormous potential against a variety of diseases, exhibiting antimicrobial, antiseptic, antifungal, antioxidant and a hundred other properties since time immemorial. They are not only a dietary source but also a gold-mine of various metabolites. *C. oblonga* is one of the Rosaceae family plants known for its therapeutic values. The methanolic extract of quince seed was evaluated through GC/MS techniques, and the analysis reported the presence of 30 compounds. The compounds 9,12-Octadecadienoic acid, methyl ester and hexadecanoic acid, methyl ester are two compounds detected with a high peak area and height. The quince is studied in detail through various research papers about their chemical profiling, presence of phenolics, organic acids and essential oils, and also elaborates on the quince plant's potential against distinct types of cancer. Quince is reported to be a source of various bioactive compounds which need to be isolated and evaluated for their safety, efficacy, and pharmacokinetics properties for the advancement of novel drug development against cancer.

**Keywords:** *Cydonia oblonga*, quince, bioactive compounds, anticancer, fatty acids.

The ease of availability makes medicinal plants the hotspot source for non-industrial societies because of their inexpensive nature. A study conducted in 2017 stated that botanical extracts and medicines have a potential market of around several hundred billion dollars across the globe. Plants are known to produce two types of metabolites: primary and secondary. Whereas primary metabolites are produced under normal conditions and are important for the growth and developmental functions of the plant, secondary metabolites are produced under conditions of abnormal stress. These secondary metabolites act as attractants for pollinators and are valuable