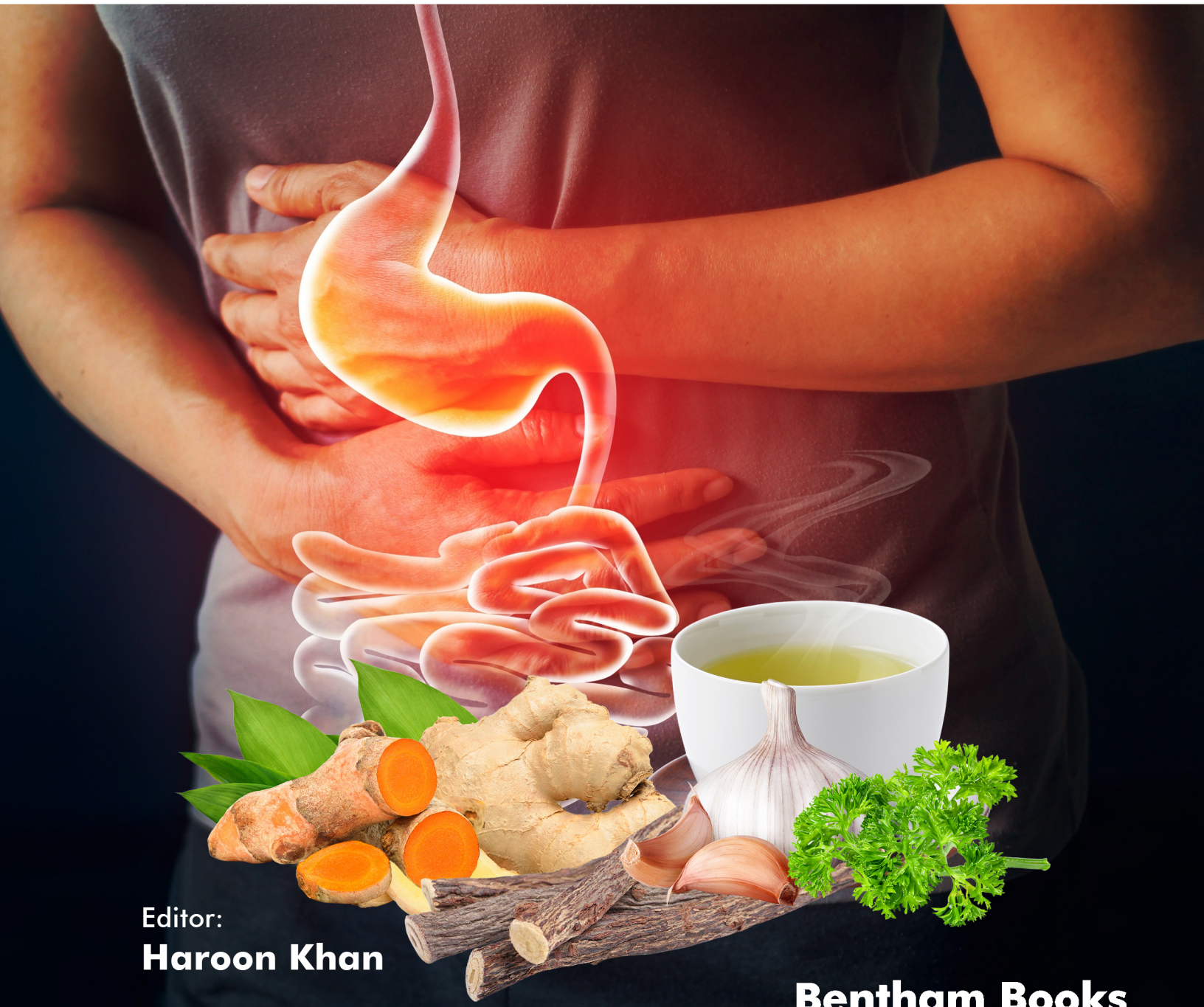
# PHYTONUTRIENTS IN THE TREATMENT OF GASTROINTESTINAL CANCER



Editor:
**Haroon Khan**

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# Phytonutrients in the Treatment of Gastrointestinal Cancer

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Editor: Haroon Khan

ISBN (Online): 978-981-5049-63-3

ISBN (Print): 978-981-5049-64-0

ISBN (Paperback): 978-981-5049-65-7



First published in 2023.

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# CONTENTS

# FOREWORD

Professor Khan has compiled an outstanding book covering contemporary issues in gastrointestinal tract cancers and therapy. It discusses Phytonutrients/Nutraceutical as anticancer and their US Food and Drug Administration (FDA) approval process, flavonoids, saponins, terpenoids, plants volatile oils, phytosterols, plant peptides and glycosides in the treatment of gastrointestinal tract cancers.

The book is highly encompassing. Beyond the conceptualization of various topics, it also offers insight into study methods and contemporary tools for research in the subject matter.

The book represents a compilation of multiple topics and should deepen the reader's understanding of this discipline. Professor Khan has assembled internationally recognized experts in the field, all of whom have made a valiant contribution to the book.

The reader will be treated to the latest developments in this fast-moving field, and updated on the latest scientific breakthroughs in the area.

The book should be of interest to researchers, healthcare providers, and pharmaceutical companies.

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# PREFACE

Cancers of the gastrointestinal tract (GIT) are the most common human malignancies. The prevalence of esophageal cancer, pancreatic ductal adenocarcinoma, gastric cancer, hepatocellular carcinoma, colorectal cancer and gallbladder cancer are on the rise now a days. Despite advances in cancer treatment, increasing reports are focusing on finding novel therapies possessing lower side effects and higher potency. From the mechanistic point of view, several dysregulated factors are behind the pathophysiology of GIT cancers. Multiple studies have shown molecular targeted therapies in various GIT cancers, including epidermal growth factor receptor pathway (EGFR), vascular endothelial growth factor pathway (VEGF), Wnt/β-catenin pathway and insulin-like growth factor receptor (IGFR). The aforementioned mediators are the critical targets of monoclonal antibodies and small molecules in treating GIT cancers. Accordingly, providing the exact dysregulated mechanisms behind GIT cancers could pave the way in the treatment of cancers.

Phytochemicals have been important resources of preventive and curative entities for various diseases, such as cancer. To a certain extent, enough investigation has been made over the last few decades to investigate natural compounds that possess anti-cancer properties. Phytochemicals used in the management of malignancies appear to be obligatory, serving as the cornerstone for the latest medicine as well as a rich reserve of novel medicines. Phytonutrients are the main principles present in plants that possess a great role in their protection against certain bacteria, viruses, and fungi and as a result of certain detoxification processes within the plant. There are many recommendations to increase the intake of high amounts of fresh colored vegetables and fruits, besides whole grains (cereals) and beans, which contain phytoconstituents that participate in lowering the risk of certain cancers, diabetes, hypertension, in addition to certain heart diseases. The effect of phytonutrients differs according to their chemical class and amount. They may act as antioxidants, which mainly prevent carcinogens' effects on the healthy body.

This book focuses on the types of available phytonutrients and their regimens, comprehensive knowledge about phytonutrients, their targeted mechanism of action in the management of GI cancer, clinical findings of phytonutrients, synergistic effect with other anti-cancer medicines and future prospects of phytonutrients in treating GI carcinoma.

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# CHAPTER 1

# Pathophysiology of Gastrointestinal Tract Cancers and Therapeutic Status

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**Abstract:** Cancers of the gastrointestinal tract (GIT) are the most common human malignancies. The prevalence of esophageal Cancer, pancreatic ductal adenocarcinoma, gastric Cancer, hepatocellular carcinoma, colorectal Cancer and gallbladder Cancer are on the rise now a days. Despite advances in cancer treatment, increasing reports are focusing on finding novel therapies with lower side effects and higher potency. From the mechanistic point of view, several dysregulated factors are behind the pathophysiology of GIT cancers. Multiple studies have shown molecular targeted therapies in various GIT cancers, including epidermal growth factor receptor pathway (EGFR), vascular endothelial growth factor pathway (VEGF), Wnt/β-catenin pathway, and insulin-like growth factor receptor (IGFR).The aforementioned mediators are the critical targets of the existence of monoclonal antibodies and small molecules in treating GIT cancers. Accordingly, providing the exact dysregulated mechanisms behind GIT cancers could pave the road in the treatment of cancers. This chapter reveals dysregulated signaling pathways and potential therapeutic agents in the treatment of GIT cancer.

**Keywords:** Colorectal cancer, Esophageal cancer, Gastrointestinal tract, Gastric cancer, Gallbladder cancer, Growth factor, Hepatocellular carcinoma, Pancreatic ductal adenocarcinoma, Signaling pathway, Therapeutic target.

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**Haroon Khan (Ed.)**

## 1. INTRODUCTION

The cancers of gastrointestinal tract (GIT) are heterogeneous malignancies. Of those, pancreatic Cancer (PC), gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), esophageal cancer (EC), gallbladder cancer (GBC) and liver-bile duct malignancies are common GIT cancers which are on the rise [1, 2]. More than one in six affected patients with GIT cancers experience malignant tumors, leading to life-threatening events [3]. Also, evidence indicated that GIT neoplasm, as the most common mesenchymal tumor [4], arises from interstitial cells in the myenteric plexus followed by platelet-derived growth factor receptor A (PDGFRA), which encode tyrosine kinases receptors towards uncontrolled cell replication [5]. There are different GIT classifications based on tumor size and associated risk of progression, including those with high, intermediate, low, and very low [6].

From the mechanistic point of view, several tumoral signaling pathways play an important function in GIT cancers, such as phosphoinositide 3-kinases (PI3K), mitogen-activated protein kinase (MAPK), transforming growth factor beta (TGF-β), Wnt/β-catenin, and Janus kinase (JAK) /signal transducer and activator of transcription (STAT) [7, 8]. In the Wnt signaling pathway, there are several dysregulated genes, such as β-catenin, phosphatase and tensin homolog (PTEN), Wnt1-inducible signaling protein 3 (WISP3), adenomatous polyposis coli (APC), and T-cell factor 4 (TCF4), which has major functions in carcinogenesis [8]. Based on the experimental evidence, natural killer (NK) cells have cytotoxicity and immune-modulatory properties involved in GIT cancers [9]. They are also activated *via* the natural killer group 2D receptor and its ligands in GC, indicating that the NK cell has a promising cytotoxicity effect on GC cell line [10]. Studies indicated that interleukin (IL) -15 can increase the maturation and function of NK cells in cancers [11]. In this line, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR) and IGFR are upstream receptors that begin the aforementioned signaling cascades in GIT cancers [12]. Recently, abnormal DNA methylation has been correlated to GIT tumorigenesis and progression through the regulation of tumor suppressor genes [13, 14]. Consequently, immunotherapy plays critical roles in checkpoint inhibitors of cancers through anti-programmed cell death protein 1/programmed death-ligand 1 (anti-PD-1/PD-L1] and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4] [9]. Evidence suggested that generation of free radicals and reactive oxygen species (ROS) in GI tract can cause oxidative damages in GIT, leading to a variety of different pathological conditions and clinical signs.

Of the therapeutic candidates, although surgery is the critical way of stopping GC, it does not sufficiently work in patients with advanced stages of disease [15]. In

such cases, chemotherapy is a suitable candidate; however, the response rate is 20-40%, with a median overall survival (OS) time of 6-11 months. Besides, it could not be ignored the serious side effects of chemotherapy [3]. It urges the need to find novel multi-target agents regarding the modulation of several dysregulated pathways in GIT cancers. Accordingly, providing the exact pathophysiological mechanisms behind GIT cancers could pave the road in cancer therapy.

In the present chapter, we investigate different types of GIT cancers, as well as related epidemiology and precise molecular pathology. Additionally, promising therapeutic targets and associated treatments are provided in GIT cancers.

## 2. ETIOLOGY AND PATHOLOGY OF GIT CANCERS

Several factors are behind the etiology of GIT cancers, including inflammation, multiple dysregulated pathways, Epstein-Barr virus (EBV), virus mutation of the E-cadherin gene (*CDH1*), mutations of tumor protein p53 (*TP53*) and catenin (*CTNNB1*) genes [16] and *Helicobacter pylori* (*H. pylori*). Evidence has shown that *H. pylori* as a bacteria can be colonized in the gastric mucosa, leading to chronic active gastritis [17]. In this line, *H. pylori* can disrupt gastric acid secretion and then impair the function of GIT. Additional studies suggested that *H. pylori* infection can lead to abdominal pain, discomfort, satiation, fullness, epigastric pain and also irritable bowel syndrome [18, 19]. Evidence also observed that *H. pylori* infection is involved in the progression of esophageal adenocarcinoma (EA) [20]. In an analysis of patients with PC, Guo *et al.* indicated an increased rate of PC following infection with *H. pylori* [21]. Other studies indicated that CRC is associated with *H. pylori* in affected patients [22]. Studies indicated that *H. pylori* activate a growth factor-like response in gastric cells by complexing with the Src homology 2 domain (SH2)-containing tyrosine phosphatase (SHP-2) in a phosphorylate ion-dependent effects [23].

In addition to the role of *H. pylori* in GIT cancers, reports indicated that inflammation has an important function in the stomach, development of GC and dysfunction of the GIT [18, 19]. Hypermethylation and increased levels of inflammatory markers (TNF-α, IL-1β) correlated to EBV and *H. pylori* [24]. El-Omar *et al.* reported that the levels of IL-1β and IL-1 are increased in GC [25]. It has also been indicated that in PC, there is an elevated expression of cytokeratins 7, 8, 13, 18 [26]. Studies also showed that EBV correlated to GCs [27 - 29]. Evidence has shown EBV and human herpesvirus 4 (HHV4) are associated with cancers such as gastric/nasopharyngeal carcinoma, transplant lympho proliferative disorder (PTLD), non-Hodgkin and Hodgkin lymphomas [29]. EBV is correlated to hypermethylation in many cancers and also miRNA abnormalities [30, 31]. It

CHAPTER 2

# Phytonutrients as a Therapeutic Modality: An Overview

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**Abstract:** Phytonutrients in plants play a great role in their protection against certain bacteria, viruses, and fungi resulting from certain detoxification processes within the plant. There are many recommendations to increase the intake of high amounts of fresh colored vegetables and fruits, besides whole grains (cereals) and beans, which contain phytoconstituents to lower the risk of certain cancers, diabetes and hypertension, in addition to certain heart diseases. The effect of phytonutrients differs according to their chemical class and amount. They may act as antioxidants which prevent the effect of carcinogens on the healthy body. The sources constituents and mechanisms of the phytonutrients are summarized in this chapter.

**Keywords:** Colon cancer, GIT cancer, Nutraceuticals, Phytonutrient, Phyto-medicine.

## 1. INTRODUCTION

Food features a great role in supporting the traditional duties of the physical body. Natural products that resemble a high percentage of our daily food intake are considered health-promoting principles that recently received considerable attent-

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ion from both researchers and consumers. Phytonutrients are plant secondary metabolites in our food, that possess protection and preventive potentials against many diseases and even their effective cure, including anti-cancer effects, which may be an honest solution for this serious health-threatening problem. Their main aim is to revive the ability of the body to guard, regulate, and heal itself from different ailments. Dietary phytonutrients lower the danger of cancer mainly due to the protective effect of their active principles possessing chemo-preventive effects. These phytochemical classes include phenols, polyphenols, flavonoids, terpenes and glucosinolates.

Cancer, a complicated ailment worldwide, was considered for many years the main reason for top mortality rates. Over the past centuries, the cancer mortality rate has been increasing despite the great use of many conventional therapies. Traditionally used strategies to treat cancer include surgery, radiation, chemotherapies, besides other protocols that haven't reduced the number of deaths [1]. Therefore, checking out new sources for therapy or maybe complementary therapies are in great demand to extend the entire relief from cancer and reduce the death rate. Since phytonutrients are of natural origin, so considered useful in clinical therapy compared to chemotherapy or radiotherapy due to their low adverse effects and are very useful in decreasing the health care cost.

## 2. HEALTH BENEFITS OF PHYTONUTRIENTS

Phytonutrients, also called phytochemicals, are present mainly in fruits, vegetables, cereal grains and edible macro-fungi. One of the principal regulations from the 2010 Dietary Guidelines is mainly related to the intake of more vegetables, fruits and whole grains in our daily diet [2]. Main phytoconstituents are classified according to their chemical structures, which participated in their activity as free radical scavenging candidates.

## 3. SOURCES OF PHYTONUTRIENTS

In nature, 4,000 phytochemicals are assembled and are mainly grouped depending on their chemical, physical and pharmacological properties [3, 4]. There has been an enormous increase in the total number of isolated and identified secondary metabolites of plant origin in the last decades. These main classes and their chemistry are discussed as follows:

### 3.1. Phenolics

Phenolics constitute the major and most important class of phytoconstituents present in the plant kingdom. Flavonoids, phenolic acids and stilbenes (tannins) are the most important phenolics that are present in different concentrations in many types of food [16]. They are generally hydroxyl ions (-OH) containing active principles during which the hydroxyl (-OH) is directly attached to an aromatic hydrocarbon moiety ($C_6H_5OH$). Phenolics possess several beneficial activities with antioxidant properties attributed to their role in suppressing free radical-mediated disease processes, including cancer.

### 3.2. Phenolic Acids

These groups of active principles are very strong antioxidants and are studied for their affinities against oxidative damage that results in different degenerative diseases. Chlorogenic acid is perhaps the main phenolic acid present in nature. Numerous examinations stated that phenolic acids adequately restrained mouse pre-adipocytes with an expansion in apoptosis [5]. Dietary phenolics assume an incredible part in diminishing the weight acquired and blocking the biosynthesis of carboxylic acids [6, 7]. Ferulic acid, one of the important phenolics found in rice-wheat, has been suggested for its cancer-prevention agent effects [8]. Besides, in fluctuating amounts, ferulic acid is available in wheat, oats, coffee, apples, artichoke, peanuts, oranges, and pineapples. Hypolipidemic impacts of ferulic acid are useful in decreasing weight gain connected to a high-fat eating regimen [9], decreasing serum cholesterol, preventing liver injury, and, most essentially, an intense tumor inhibitory impact [10].

### 3.3. Stilbenes

Stilbenes are small relative molecular mass phenolics, naturally present as plant monomers and oligomers. They are used commercially in aromatherapy products and as dietary supplements. Commonly referred to as tannins, they are classified into 2 main classes, *i.e.*, hydrolyzable and condensed tannins. Stilbenes are produced in plants due to ecological factors, contamination, or subjection to extra UV light and to limit the harm caused [11]. Stilbenes are always related to phytoestrogen as they possess great structural resemblance to estrogens and are furthermore ready to respond with estrogen receptors [12]. Dietary stilbenes have several health benefits; however, their extremely limited bioavailability, quick digestion and discharge in incompletely processed forms restrict their utilization as potential nutraceuticals [13]. Resveratrol, a crucial stilbene, is present mainly in the skin of grapes and has anti-inflammatory, anti-tumor and antioxidant effects

CHAPTER 3

# FDA Approval for Phytochemicals in the Treatment of Cancer

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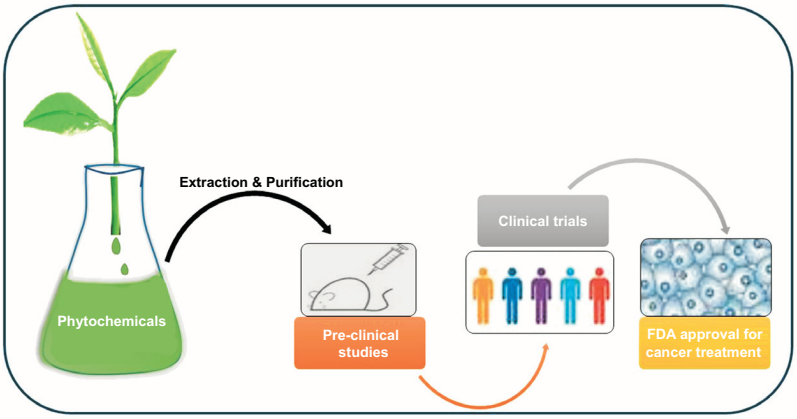
**Graphical Abstract**




**Abstract:** Cancer is considered one of the primary causes of death all over the world; Thus, there is an urgent need for its management. Anticancer drugs available in the market target rapidly growing cells while unable to distinguish between healthy and tumor cells producing significant side effects resulting in discontinuation of therapy after a few months. On the other hand, phytochemicals can induce similar potential effects on cancer cells with less or no side effects deliberately leaving non-cancer cells. However it takes a relatively more extensive period for noteworthy results. The United States Department of Health and Human Services governs Food and Drug Administration (FDA), which accounts for public healthcare, food, and drug product endorsement. Particularly a drug product approval requires ultra-precautions; therefore,

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multiple safety measure steps are followed right from target-based high-throughput screening process to clinical trials. In the past few decades, the FDA has approved several anticancer drugs, either phytochemicals or derived synthetic drug molecules; thus, using phytochemicals isn't a new idea in biomedical research. Due to the very stringent criteria of the FDA for drug approval, many potential phytochemicals and molecules fail to pass clinical trial phases. In this book chapter, we have discussed the stepwise drug approval process followed by enlisting approved or potential phytochemicals in the drug discovery pipeline and their limitation in approval.

**Keywords:** Phytochemicals, FDA, IRB, Cancer, Clinical trials, Drug, Phenol, Terpenoids, Flavonoids, Alkaloids.

## 1. INTRODUCTION

### 1.1. What is FDA

The Food and Drug Administration (FDA or USFDA) is a federal agency of the United States Department of Health and Human Services, among the policy-making departments of the United States of America (www.fda.gov). The United States governs the FDA to implement the Federal Food, Drug, and Cosmetic Act as the prime focus [1, 2]. The FDA accounts for the safety and endorsement of public health through the supervision and control of food products, including pharmaceutical products and dietary supplements such as medicines, medical devices, cosmetics & feed, vaccines, biopharmaceuticals, animal foods, blood transfusions, and veterinary products [1]. It also implements other laws indirectly linked to drugs or food, including regulating cellular phones, lasers, birth control, and disease control products [2, 3]. The FDA is directed by the Commissioner of Food and Drugs, selected by the President with an agreement from the Senate. The Commissioner informs the Secretary of Health and Human Services. Robert M. Califf M.D. has been named as the Commissioner of Food and Drugs on February 17, 2022. The headquarters of the FDA is situated in White Oak, Maryland [4]. It owns almost 223 field offices and thirteen laboratories localised all over the 50 states of America. After 2008, the FDA commenced posting personnel to foreign countries, including India, Costa Rica, China, Chile, the United Kingdom and Belgium [5].

### 1.2. FDA Principles and Procedures for New Drug Approval

The FDA approval for a new drug starts with stepwise research strategies shown in Fig. (**1**), particularly involving target-based basic research followed by animal testing [6]. During the preliminary stage, the invention and development of

research methodologies, including preclinical and clinical studies of a novel therapeutic drug-like molecule, is studied and approved by an established Institutional Review Board (IRB) [7, 8]. These IRBs are present in medical centers, hospitals, universities, and clinical research institutions where clinical studies occur. Earlier to the initiation of the clinical trial, the potential risk *versus* benefit ratio of the course gets anticipated either in selected individuals or in the clinical population [8, 9]. The clinical trial is only initiated or processed if the clinical benefits are more than the risks [9]. Afterwards, proceeding of the FDA process filing and premarket applications take place consisting of the following groups:

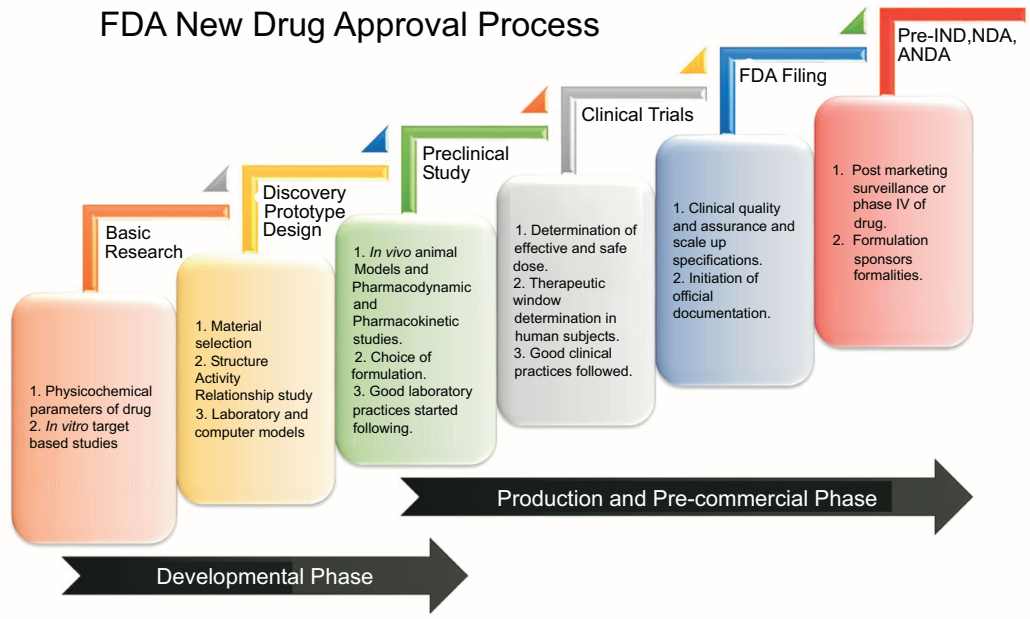


**Fig. (1).** Drug approval process by FDA.

1. Investigational New Drug Application (IND) 2. New Drug Application (NDA) 3. Abbreviated New Drug Application (ANDA)

A multiphase procedure is followed for introducing a drug product into the market for clinical application [10]. The process starts with preclinical studies on animal models, followed by three phases of human trial [1]. Novel drug moieties requiring additional trial data are further considered for the fourth clinical trial phase during post-market surveillance [11]. Comprehensive information on the drug development procedure is also available on the FDA official site (www.fda.gov/cder/handbook/develop.htm) [12]. The published report provides

# CHAPTER 4

# Flavonoids in the Treatment of Gastrointestinal Tract Cancer

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**Abstract:** Globally, cancer is a leading cause of death next to cardiovascular disease. Gastrointestinal malignancies (GI) are extremely widespread malignancies, but their prevalence varies significantly amongst nations and communities. Existing cancer treatments are primarily concerned with low tissue availability, adverse drug reactions related to the demand for larger dose levels and non-specificity of the medicine. Phytochemicals have been important resources of preventive and curative entities for a variety of diseases, such as cancer. To a certain extent, enough investigation has been made over the last few decades to investigate natural compounds that possess anti-cancer properties. Phytochemicals used in the management of malignancies appear to be obligatory, serving as the cornerstone for the latest medicine as well as a rich reserve of novel medicines. Flavonoids are plant-derived secondary metabolites, which are readily available and considered safe, depicting perfect agents for cancer therapy or as adjunctive options in clinical practice. Flavonoids have already received increasing attention as anti-cancer entities, with promising findings as cytotoxic anti-cancer entities that induce apoptotic cell death in malignant cells. Flavonoids, such as kaempferol, Quercetin, Curcumin, myricetin, apigenin, luteolin and silymarin, are among the phytochemicals that have been revealed to be potential agents for the prevention and treatment of malignancies. Flavonoids like Kaempferol and luteolin are reported as potential therapeutic agents for the management of ovarian and GI malignancies. Flavonoid metabolism in major areas of the hepatic and colon cells, unveils reasonably considerable variations in the anti-cancer potential, presumably as a result of exposure to multiple metabolites with multiple functions. Luteolin and apigenin have a real insight into cervical cancer. Flavonoids are now explored to have an inhibitory action on cell cycle development at the G1/S or G2/M stages of the cell cycle *via* modifying several regulatory proteins of the cell cycle. This chapter is designed to provide comprehensive knowledge about flavonoids, their targeted mechanism of action in the management of GI cancer, clinical findings of flavonoids,

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synergistic effect with other anti-cancer medicines and future prospects of flavonoids in treating GI carcinoma.

**Keywords:** Clinical standings, Effect and Future prospects, Flavonoids, GI cancer, Mechanistic pathways, Synergistic.

## 1. INTRODUCTION

Cancer is a leading cause of mortality worldwide following cardiovascular disease. Gastrointestinal malignancies (GI) are one of the extremely widespread malignancies, but their prevalence varies significantly between communities. The inaccessibility of cancer cells in traditional cancer treatments is a key problem [1]. Existing cancer treatments are primarily concerned with low tissue availability. Moreover, a number of adverse drug reactions are related to the demand for larger dose levels and non-selectivity of the medication. Diverse phytochemicals isolated from plants are correlated to cancer prevention and therapeutic interventions [2, 3]. Quite enough investigation has been made over the last few decades to explore natural compounds that could have anti-cancer properties [4, 5]. Many such phytochemicals, including vincristine, vinblastine, docetaxel, paclitaxel, irinotecan, etoposide, and topotecan, are being reported to cure cancer patients effectively [6 - 8]. Medicinal plants have a wide variety of biochemical compositions, thus, phytonutrients would most certainly strive to play a part in the management of malignancies [9 - 11].

Phytochemicals used in the management of malignancies appear to be unavoidable, serving as the cornerstone for the latest medicine as well as a rich resource of novel medicines [12, 13]. Nutrition is being described as a key configurable determining factor of the likelihood of malignancy and the prevalence and prevention of various forms of malignancies [14, 15]. So many researchers reported that vegetarians have a lower incidence of various kinds of cancer [16]. In particular, 30-40% occurrence of cancer might be decreased while having lifestyles lavish with vegetables and fruits; maintaining physical activity, and sufficient body mass [17 - 19]. World Cancer Research finds “persuading” justification for vegetables and fruits' preventive role towards tumors of the lungs, stomach and upper aerophagic tract, as well as vegetables' preventive role towards cancers of the rectum and colon, and there is still a persistent prevailing view in favor of vegetables and fruits' preventive function against tumors of the GI tract [20].

Phytochemicals extracted from plants are of specific importance because of their potential efficacy, high safety profile, lesser side effects, lower cost and high

bioavailability. Flavonoids already have received increasing attention as anti-cancer compounds, with promising findings as cytotoxic anti-cancer entities that induce apoptotic cell death in malignant cells [21]. Flavonoids are plant-derived secondary metabolites, which are readily available and considered safe, rendering them perfect agents for cancer therapy or as adjunctive options in clinical practice [22, 23].

Worldwide, researchers have established that flavonoids inhibit the development of multiple types of cancerous cells' proliferation, regulated by diverse molecular targets *via* specific biochemical mechanisms [24, 25]. Flavonoids like Kaempferol and luteolin are reported as potential therapeutic agents for the management of ovarian and GI malignancies. Flavonoid metabolism in major areas of the hepatic and colon cells unveils fairly substantial variations in the anti-cancer potential, presumably as a result of exposure to multiple metabolites with multiple functions. Luteolin and apigenin have a realistic insight into cervical cancer [26]. This chapter briefly describes flavonoids and their underlying mechanistic pathways for the management of GI cancers. Moreover, this chapter focuses on the clinical status of flavonoids and future insights.

## 2. FLAVONOIDS

Flavonoids are an essential group of Polyphenolic compounds (secondary metabolites). Flavonoids have the chemical composition of diphenylpropane (C6-C3-C6) with 2 aromatic rings at each corner and a 3 carbon ring at the center, forming an oxygenated heterocyclic structure (Fig. **1**). The GI and colonic microbiota perform a significant role in the conjugation and metabolism of flavonoids, allowing the hepatic and systemic distribution of flavonoids in humans [27, 28]. An overview of the structure of flavonoids and their derivatives is shown in Fig. (**1**).

# CHAPTER 5

# Glycosides in the Treatment of Gastrointestinal Tract Cancer

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**Abstract:** Gastrointestinal (GI) carcinomas are tumors that impact the digestive system and its supporting organs. Esophageal, gastric and colorectal cancers are among the common cancers in the gastrointestinal tract. GI cancers are responsible for about 2.7 million deaths of the 8.2 million mortalities that occur from cancers every year around the globe. Chemoprevention is the method of intervening in this mechanism by essential dietary control or the addition of nutraceuticals to the daily nutritional intake. The initial stages of cancer growth, known as oncogenesis, have sparked a lot of emphasis on the function of dietary food. The intensity of the epidemiological studies attracted research scholars' interest in the mechanisms underlying the anti-proliferative activities; however, investigation has indeed discovered lots of new phytochemicals in vegetables and fruits which might prevent the development of carcinogenesis. In cancer treatment, drugs obtained from plant sources have a significant role in cancer treatment. The plant alkaloids isolated from *Catharanthus roseus,* such as vincristine and vinblastine, are clinically used to treat testicular carcinomas, leukemia, and breast cancer. Paclitaxel is isolated from *Taxus brevifolia* and is used in the management of lung cancer, breast cancer and ovarian cancer. In the 1960s, there has been initial proof of the *in vitro* cytotoxic impact of glycosides on human cancer cell lines and their *in vivo* anti-tumor activities. Cardiac glycosides are $Na^{+}/K^{+}$ATPase inhibitors and elevate the $Ca^{+2}$ concentrations, which in turn leads to a positive inotropic effect and is thus used as cardio-tonic in the management of congestive heart failure. Cardiac glycosides have recently been documented to play roles in initiating, developing and metastasizing the tumor by controlling cell viability and mortality pathways. It has been reported that $Na^{+}/K^{+}$ATPase inhibitor causes cell death by inducing autophagy, apoptosis and synthesis of free radical species. Notwithstanding the advances in cancer treatments, the need for new medicinal products and treatments to enhance their effectiveness and to decrease the toxicity of existing regimes is strong and unequaled, although a broad objective is to improve the therapeutic results of GI cancers. This chapter briefly describes the glycosides, gastrointestinal malignancies and the diverse types of glycosi-

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des involved in the management of GI malignancies and the clinical trials under progress for the clinical efficacy.

**Keywords:** Clinical status, GI cancer, Glycosides, Mechanistic pathway.

## 1. INTRODUCTION

Tumors of the gastrointestinal tract (GIT) are hereditary abnormalities induced by a series of changes in genes that regulate the differentiation, development and repair of DNA [1]. Though the highest incidence tends to be sporadic, very few GI tumors appear to be inherited, as documented by the well-known genetic syndromes and the family background linked to an increased menace of such syndromes [2, 3]. GI cancer is becoming more prevalent across the globe, having a detrimental effect on society's resources. Gastric cancer contributes to about 8% of all cancers and 10% of all cancer casualties. Furthermore, the occurrence of colorectal cancer is raised dramatically in the last decades, making this the most prevalent cancer worldwide [4]. Dissimilar geographical areas have diverse risk factors for GI carcinomas. According to epidemiological survey, the dietary source is the main contributing risk factor. Japanese people are largely vulnerable to gastrointestinal cancer as a result of their high salt intake in their diets, whereas Americans seem to be more susceptible to produce colorectal cancer as a result of their high cooked meat intake [5 - 7].

The preventive potential of an increased nutritional vegetable and fruit intake has gained considerable attention over several decades, including both scholars as well as from primary healthcare authorities, as one of several environmental factors believed to affect the etiologies of GIT carcinomas [8]. The initial stages of cancer growth, known as oncogenesis, have sparked a lot of emphasis on the function of dietary food. Chemoprevention is the method of intervening in this mechanism by essential dietary control or the addition of nutraceuticals to the daily nutritional intake [9]. In 1997, the World Cancer Research Fund published in their Food, Nutrition, and the Prevention of Cancer reports that excessive intake of nutritious dietary food has a promising role in the prevention of carcinomas [10]. The intensity of the epidemiological studies attracted research scholars' interest in the mechanisms underlying the anti-proliferative activities, however, investigation has indeed discovered lots of new phytochemicals in vegetables and fruits which might prevent the development of carcinogenesis [11].

In cancer treatment, drugs obtained from plant sources play a significant role in cancer treatment. The plant alkaloids isolated from *Catharanthus roseus,* such as

vincristine and vinblastine, are clinically used to treat testicular carcinomas, leukemia, lungs cancer, lymphoma, Kaposi's sarcoma and breast cancer. Paclitaxel is isolated from *Taxus brevifolia* and is used in the management of lung, breast, and ovarian cancer [12]. Notwithstanding the advances in cancer treatments, the need for new medicinal products and treatments to enhance their effectiveness and to decrease the toxicity of existing regimes is strong and unequaled, although a broad objective is to improve the therapeutic results of GI cancers. This chapter is designed to briefly describe the diverse glycosides involved in managing GI malignancies.

## 2. GASTROINTESTINAL TRACT CANCER

Gastrointestinal (GI) carcinomas are tumors that impact the digestive system and its supporting organs. Esophageal, gastric and colorectal cancers are among the common cancers in the gastrointestinal tract [13]. Every year, 14 million of the world's population is diagnosed with cancer, about 1/4$^{th}$ of which includes GI carcinomas. GI cancers are responsible for about 2.7 million deaths of the 8.2 million mortalities that occur from cancers every year around the globe [14, 15]. According to mounting evidence, microbial infections may contribute globally to 33% of all malignancies. Enterotoxigenic *Bacteroides fragilis*, which causes colorectal carcinomas, *Opisthorchis viverrini* and *Clonorchis sinensis*, which cause bile duct carcinoma, *Helicobacter pylori*, which causes stomach cancer, are just few examples of microbial induced GI malignancies. Although the involvement of infections in the growth of certain GI malignancies is newly understood, the clinical assessment reveals that many carcinomas (particularly GI and pancreatic) are not considered immunogenic. In comparison to neo-antigens derived from infectious diseases, the controlled development of somatic genetic variations, translating healthy cells into cancerous cells, produces cancer proteins, which generally are modified self proteins. These proteins are inhibited by immune system *via* immune modulatory mechanisms [16, 17].

The key focus of the treatment strategy for initial tumors is a surgical incision. Modern management approaches and therapies are attributed to the absence of specificity for malignant cells and available treatment toxicities, which prevent anticancer agents from reaching their full potential. New anticancer approaches are therefore highly needed. Phytomedicine is a relatively new and innovative area in cancer treatment [18, 19].

# CHAPTER 6

# Terpenoıds in the Treatment of Gastrointestinal Tract Cancer

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**Abstract:** Gastrointestinal cancers are the most common cancer group, accounting for approximately one-fourth of the total cancer incidence and one-third of cancer-related deaths in developing countries. Treatments for the disease include surgery, radiation, and administration of chemotherapy components, such as docetaxel, mitomycin, and cisplatin injection. However, due to the side effects seen in these treatments and for the purpose of supporting the treatment, the trend towards medicinal herbs and phytonutrients, which have certain biological activities and potential benefits to human health, including the prevention of diseases, has increased. Natural products and their derivatives are consistently the most successful source of phytonutrients and pharmaceutical leaders. Terpenoids are one of the most important families of natural compounds known for their medicinal value. Terpenoids are found in higher plants, algae, mosses, liverworts, and lichens, as well as insects, microbes or marine organisms; and have been shown to exhibit anti-infective, anti-inflammatory, and antitumoral properties. Recently, research activities on the preclinical and/or clinical potential of this class of components in cancer have continuously risen. In this review, the molecular basis of the antitumoral effect of terpenoids is presented, with special emphasis on the latest developments in this field, comprising recently enlightened findings of the potential of monoterpenoids, diterpenoids, triterpenoids and tetraterpenoids as antitumoral agents. Furthermore, this review will summarize promising terpenoid compounds in combination therapy with conventional chemotherapeutic agents.

**Keywords:** Cancer, Gastric cancer, Phytonutrients, Pharmaceuticals, Molecular mechanisms, Terpenoids.

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## 1. INTRODUCTION

Cancer is a multifactorial disease characterized by the transformation and uncontrolled proliferation of a number of normal cells. Carcinogenesis includes three main steps: initiation, promotion, and progression. Activation of oncogenes and promoting cell survival and proliferation are some of the major events involved in the initiation and progression of cancer. Cells play a crucial role in progress by invading other organs and tissues and forming metastasis [1].

The world population is aging, and cancer remains one of the leading causes of death worldwide. With respect to the World Health Organization (WHO), it is estimated that the number of new cases will increase by about 70% in the next two decades and reach 23.6 million new cancers worldwide by 2030 [2]. Gastric cancer also continues as one of the deadliest malignancies. Considering many advances in understanding this complex disease, few signs of progress have been noted in improving existing therapies, and the survival of patients with advanced disease remains depressing. The recent emergence of drug-targeted therapies will undoubtedly reduce the incidence of cancer in the coming years. However, the incidence of such chronic diseases as cancer will continue to increase. Thus, there is an urgent need to seek a safer and lower-cost treatment [3].

Natural products play an increasing role in drug discovery and the development of new candidate molecules for the treatment of cancer. They are obtained from microbes, fungi, marine organisms, higher plants, and animals and display a wide variety of chemical diversity and many different biological properties [4]. It is a fact that terpenic substances such as taxol have been used in the treatment of cancer in the past. Taxol (paclitaxel) and its derivatives are microtubule-stabilizing drugs commonly used in the treatment of various types of cancer, including mammary, prostate, ovarian, and non-small-cell lung carcinoma, as well as AIDS-associated Kaposi's sarcoma and other types of tumor [5].

Recently, terpenoids have gained significant acceptance as potential chemotherapeutic agents. A lot of research has also been done on evaluating these compounds as effective agents because they can act on specific and/or multiple molecular and cellular targets. This chapter reviews the antitumor activity of terpenoids as promising agents against GIT cancers, as well as criticizes the knowledge about naturally occurring terpenoids and their mechanisms of cancer therapeutic activity.

## 2. POTENTIAL THERAPEUTIC STRATEGIES OF PHYTONUTRIENTS IN CANCER

It has been determined in epidemiological and preclinical studies that both nutritional and behavioral factors significantly affect the prevalence of various cancers. Therefore, there has been increasing interest in phytonutrients [6, 7]. Hence, plant-based rich health diets have been found to have protective effects against cancer [8]. Many dietary phytochemicals contain bioactive chemicals that may be effective independently or in combination in the chemoprevention of cancer [9, 10]. Phytochemicals are often required to be used in high doses to be effective, and these doses cannot usually be achieved through diet alone [11].

In general, all types of cancer cells exhibit abnormal gene expression due to mutations in the epigenome due to epigenetic modifications involved in cell proliferation, differentiation, and survival [12]. Therefore, the epigenetic diet was presented as a chemopreventive approach correlated with delineating the efficiency of dietary bioactive compounds and their effect on modulating the epigenome [12].

Nutrigenomics, another hopeful cancer chemopreventive approach, includes the modulation of gene expression in response to dietary compounds. Consequently, a holistic and intuitive approach to chemopreventive treatment makes use of these bioactive dietary compounds to regulate epigenomic variations and prevention. Especially, realistic approaches emphasis more on the combinational efficiency of these promising dietary phytochemicals [12].

Chemopreventive dietary phytochemicals are naturally occurring bioactive substances in vegetables, fruits, herbs and spices. They have antioxidative, anti-inflammatory, anti-proliferative and pro-apoptotic effects and, in particular, inhibit the growth of several cancer cells. It has been reported in previous studies that increased consumption of fruit and vegetables prevents the development of cancer [12]. In addition, dietary phytochemicals have both chemosensitizing and chemotherapeutic effects [13].

Through drug-interaction, the pharmacological properties of dietary phytochemicals exhibit a positive interaction promoting the effectiveness of the bioactive compound by molecular interaction with adjuvant substance. They demonstrate a combined efficacy which is equivalent to additive effects, or combined efficacy, which is greater than synergistic effects, and lastly, the combined efficacy which is less than the sum of individual effects [14, 15].

CHAPTER 7

# Saponins in the Treatment of Gastrointestinal Tract Cancer

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**Abstract:** The natural glycosides with triterpenoid or spirostaneaglycones are the saponins, which are associated with a wide range of therapeutic activities, inclusive of gastrointestinal anticancer activities. To promote research and development of novel cytotoxic agents against GIT cancer, this chapter focused on the anticancer potentia l of the naturally occurring triterpenoid and steroidal saponins. The *in vitro* assays and *in vivo* studies authenticated the anticancer potential of these compounds through anti-angiogenic, anti-proliferative, anti-metastatic and anti-multidrug resistance activities. The protein targets and signaling cascades behind the anticancer effect of these compounds in GIT cancer are also discussed in this chapter.

**Keywords:** Anti-proliferative and Anti-metastatic, Gastrointestinal cancer, Signaling cascades, Signaling cascades, Target, Triterpenoid saponins.

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## 1. INTRODUCTION

A broad group of saponins belongs to glycosides, widely occurring in higher terrestrial and marine plants and low marine organisms. Saponins are a diverse group exhibiting steroidal or triterpenoid aglycones and sugar chains [1]. Steroidal saponins naturally exist in a favorable amount in monocotyledons, and triterpenoid saponins commonly exist in dicotyledons [2]. From ancient times, mankind has implemented the surface active and micelle-forming characteristics of saponins as soaps [3]. Saponins have had broad medicinal usage for hundred years as anti-inflammatory, antimicrobial and hemolytic agents in Chinese and Japanese medicines. Nowadays, saponins are used in the pharmaceutical and cosmetic industry in the fabrication of semi-synthetics costly products [4, 5]. The pharmacological activities of saponins were reported in 1927 as hemolytic, anticancer, antidiabetic, antifungal, antioxidative, antihyperlipidemic, expectorant, insecticidal and anti-inflammatory [6]. The primary physiological role of saponins is to boost the immune system against the antigen and increase the absorption of vaccines [7 - 9].

## 2. CHEMISTRY

Saponins contain lipid-soluble aglycone steroidal or triterpenoid portion and water-soluble sugar chains, which define their water solubility [9] Tables (**1** and **2**). Naturally, these are soluble in water and form a colloidal solution. The chemical structures of saponins derived from plants and animals are different. The triterpenes are composed of a pentacyclic structure of 30 carbon atoms [10].

**Table 1. Classification of triterpenes saponins.**

| # | Triterpenes Classes | Ring Structure |
|---|---|---|
| 1 | Dammaranes | Contain four 6-membered rings |
| 2 | tirucallanes, | |
| 3 | curcubitanes, | |
| 4 | Lanostanes | |
| 5 | Cycloartanes | Cyclopropane attached to four 6-membered ring structure |
| 6 | Lupanes | Cyclopentane ring attached to four 6-membered ring structure |
| 7 | Hopanes | |
| 8 | Oleananes | Consisted of 5 membered ring skeleton |
| 9 | taraxasteranes | |
| 10 | Ursanes | |

**Table 2. Classification of steroidal saponins.**

| # | Classes of steroidal saponins | Aglycone Skeleton |
|---|---|---|
| 1 | Spirostan | Four 6-membered and two 5-membered ring structures |
| 2 | Furostan | Three 6-membered and two 5-membered ring structures |
| 3 | Cholestane | Three 6-membered and one 5-membered ring structures |

Saponins have wide applications as starting material in the synthesis of steroids. Partial hydrolysis yields biologically active compounds. Saponins like Dioscin, polyphyllin D and balanitis are associated with significant anticancer activity.

## 3. ANTICANCER ACTIVITY OF SAPONINS AGAINST GIT CANCERS

Cancer is a multi-step genetic defect in cell proliferation, differentiation and cellular apoptosis induced by genetic and epigenetic factors [11]. The complex process of programmed cell death is regulated by enzymatic activities [12]. Gastrointestinal tract (GIT) cancer describes a malignant state of digestive organs, including the esophagus, stomach, liver, pancreas, biliary tract, small and large intestine, rectum and anus [13]. GIT cancer symptoms are concomitant to the organ affected, generally associated with difficulty in swallowing and unusual bleeding. Pancreas, liver and gall bladder are generally associated with most GIT cancers and death [14]. Cancer of the stomach is known as gastric cancer, and the most common is adenocarcinoma. Gastric cancers are the most prevalent, highly morbid type of cancer worldwide [15]. Various environmental factors are also involved in etiopathogenesis of cancer, like diet, bacterial infection and poor lifestyle [16]. Pancreatic cancer is 5$^{th}$ common cause of cancer-related deaths and is associated with smoking and advanced age [17]. Liver cancer occurs due to prolonged hepatitis B and C infection and due to alcoholism-induced cirrhosis [18 - 20]. Gallbladder usually targets elderly women and is usually linked to gallstone and polyps formation [21]. Colorectal cancer generally occurs in old age due to the intake of a diet poor in vegetable fibers and rich with fats, in secretory cells lining the gut [22, 23]. Anal cancer is usually squamous cell carcinomas generally linked to ulcerative colitis and due to sexually transmitted viral infections [24]. It is evident from various *in vitro* and *in vivo* studies that steroidal, triterpenes saponins and diosgenin are associated with remarkable antitumor activity. Steroidal saponins naturally exist in plant extracts, and synthetic or semisynthetic have significant antitumor activity [25]. It is reported that the favorable amount of steroidal saponins in *Asparagus officinalis* L. extract have anticancer activity against hepatocellular carcinoma cells HepG2 through induction of apoptosis [26, 27]. Likely, steroidal saponins isolated from *Paris polyphylla* are associated with

# CHAPTER 8

# Alkaloids in the Treatment of Gastrointestinal Tract Cancer

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**Abstract:** Alkaloids, nitrogen-containing compounds, are found in living organisms ranging from microbes to seed-producing plants all over the world. About more than 20,000 alkaloids have been discovered, mostly occurring in higher plants of the families Ranunculaceae, Papaveraceae, Leguminosae, Loganiaceae and Menispermaceae. These compounds are able to inhibit cancer proliferation, especially gastrointestinal cancer, which constitutes the highest incidence rate all over the world. The most diversified group of phytochemicals, alkaloids offer a mighty series of chemical scaffolds and moieties which can be harnessed to ameliorate the devastating consequences underlying cancer. Gastrointestinal (GIT) cancers constitute the malignancies of esophageal, gastric, pancreatic, colorectal and anal tumors, which possess aberrant metabolic signals giving rise to uncontrolled cell proliferation. These cancers are the most frequent of all cancers and account for the high mortality rates worldwide. Conventional therapeutic options carry the risks like being non-economical as well as they possess severe side effects. Natural products offer a wide spectrum of pharmacological properties which can overcome these risk factors by providing cheaper products and are reliable regarding their bio-safety profiles. Alkaloids can be

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investigated in detail to investigate their pharmacological potential against GIT cancers. Several alkaloids are known to modulate the cell signaling pathways by inducing cell cycle arrest at G0/G1, S and G2/M phases in addition to being the apoptosis inducers. In addition to that, they are also known to target various metabolic pathways, such as p53, β-catenin, MAPK and PIM3. The chapter intends to investigate the biological as well as pharmacological profiles of various alkaloids with special reference to GIT cancers in order to update scientists and researchers about the pharmaceutical potential of these compounds.

**Keywords:** Alkaloids, Cell cycle arrest, Clinical potential, Gastrointestinal cancer, GIT cancers, Modulation of singling pathways.

## 1. INTRODUCTION

Cancer, the major reasons of mortality around the globe, has been indicated to cause an incidence of 14 million cases in 2012, as per the data published by the World Health Organization (WHO). It has been a general estimate that this figure may exceed 22 million in the next two future decades [1]. Regardless of sharing usual abnormal alterations, cancer is not a single disease, but it is even a heterogeneous type of tumor formation with variable clinical histories, pathological stages, grading, morphological expressions, and variable cytotoxic response to available chemotherapeutics [2].

Gastrointestinal tract (GIT) cancers mainly comprise gastric, colorectal, esophageal as well as anal tumors, and represent 20% (approx.) of all cancers. In addition to their high incidence, these types of cancers exhibit high mortality rates, putting great health concerns about these types of cancers [3]. According to estimated data, 1,500,000 new cases of GIT cancers were reported in 2005 all over the world, and this number is predicted to reach up to 2,110,000 by the year 2025 [4]. Esophagus and stomach carcinoma are accounted as the most lethal of all malignancies [5]. In 2008, gastric and colon tumors were ranked as the second and third most fatal cancers, respectively, representing over one million deaths worldwide. Since its incidence, esophageal cancer usually has no remarkable epidemiological data, but it has become an aggressive tumor with a bleak of five years with an overall survival rate of less than 15% [4].

## 2. TYPES AND PATHOGENESIS OF GASTROINTESTINAL TRACT CANCERS

According to the cancer Institute Cancer Research Centre and the cancer registry program, most gastrointestinal cancers occur in the stomach. The next most susceptible parts of the GIT cancers are the colon and rectum (colorectal cancers), pancreas, esophagus and liver [6]. Gastric, esophageal, and cardiac cancer are the three most common malignant tumors of upper GIT cancer. Gastric cancer is an ailment with high mortality and high morbidity as well (Fig. **1**). Two-thirds of

gastric cancer cases occur in developing countries. One of the most aggressive neoplasms of GIT cancers is esophageal cancer, with its incidence diversity, which is higher in Asian countries and lower in European and American continents [7].


**Fig. (1).** Types of gastrointestinal tract cancers.

## 2.1. Gastric Cancer (GC)

Gastric cancer is ranked as the third most fatal cancer in the world. Epidemiological, molecular and morphological characteristics identify the two major subtypes, intestinal-type gastric cancer and diffuse gastric cancer (DGC) [8]. Gastric carcinomas had different pathological characteristics. However, they fall into two categories on the basis of invasiveness and growth patterns: infiltrative type and expanding type [9]. Most gastric cancers are related to

CHAPTER 9

# Plant Essential Oils in the Treatment of Gastrointestinal Cancers

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**Abstract:** Gastrointestinal malignancies are well-known terms in the pathogenesis of the alimentary canal. They have been prevalent in different organs of the gastrointestinal tract system. Gastric tumor is the second most common cause of death due to cancer in the world. The epidemiology of cancer has changed within the last few decades. A significant deal with such carcinomas is done using essential plant constituents like alkaloids, volatile oils, and glycosides. They involve various mechanisms for eliminating these carcinomas. Many plant essential oils, such as thymol, lemon oil, limonene, carvacrol, and lavender oils, have been investigated for their anti-inflammatory, anti-oxidant, and anti-carcinogenic properties been shown to modulate numerous immunological and cellular functions. Many types of research have proven that a large number of volatile oils and aromatic compounds present in various plants have important anti-cancer activities. They showed the anti-cancer effect on cell lines and cancer cells in animals. The use of various plant volatile oils may alter or affect the pathogenesis of several types of gastrointestinal cancer like liver cancer, esophageal cancer, gastric cancer, pancreatic cancer, *etc.* In this chapter, the anti-cancer activity of plant essential oil components against GIT cancers has been discussed, with a focus on their possible mechanism of action.

**Keywords:** Carvacrol, Essential oils, GI cancers, Limonene, Pathogenesis, Thymol.

## 1. INTRODUCTION

Gastrointestinal cancer is a malignant condition associated with the organs of the GIT. It involves a variety of functional changes in the organs [1]. Gastrointestinal (GI) cancer is the fourth most common type of cancer. This is the second leading

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cause of death across the world. Its incidence and prevalence rates differ in different areas of the world. Each year 4000-6000 adults are diagnosed with GIT cancers. The most common type of GIT cancer is stomach cancer which is about 60%, and then is intestinal cancer which is almost 35%. The other types are rare in people below 40 and mostly occur in people over 40 years of age [2].

GI cancer is an aggregate term used to depict diseases that influence the alimentary system [3]. Around the world, the most usually analyzed GI tumors incorporate colorectal cancer, gastric malignancy, liver malignancy, oesophageal malignant growth and pancreatic malignancy. GI malignancies, which occur rarely, incorporate those influencing the anus, bile duct, gallbladder, and small intestine [4]. GI malignant growths account for more tumor-related passing than some other sort of malignant growth. In 2018, epidemiologists represented an expected 3.4 million people who died around the world, with a further 4.8 million new cases analyzed around the same time. A colorectal malignant tumor is the most widely recognized kind of GI disease, with 1.85 million new cases analyzed around the world in 2018, making it the third generally basic of all organ tumors after lung and breast. Around the same time, gastric and esophageal tumors were positioned as the fifth and seventh most generally determined malignancies individually to have 1.03 million new instances of gastric cancer and 0.6 million new instances of esophageal malignancy around the world [5].

There is a general idea that early diagnosis can reduce the mortality from cancer; however, few screening trials have included persons over 60 years of age. For colorectal cancer screening, a fecal obstruction blood test has the strongest evidence of benefit in elderly patients; few studies have supported the affinity of colonoscopy, virtual colonoscopy, and double-contrast barium X-ray because of the poor tolerability of these tests [6].

## 2. PATHOGENESIS OF GASTROINTESTINAL CANCERS

Cancer arises due to cancer cell proliferation in the organ lining. Any causative agent of gastrointestinal cancer initiates a sequence of events that leads to cancer (Fig. **1**). The sequence includes chronic non–atrophic inflammation of the affected area to atrophic inflammation, metaplasia, and then dysplasia, leading to cancer [7].

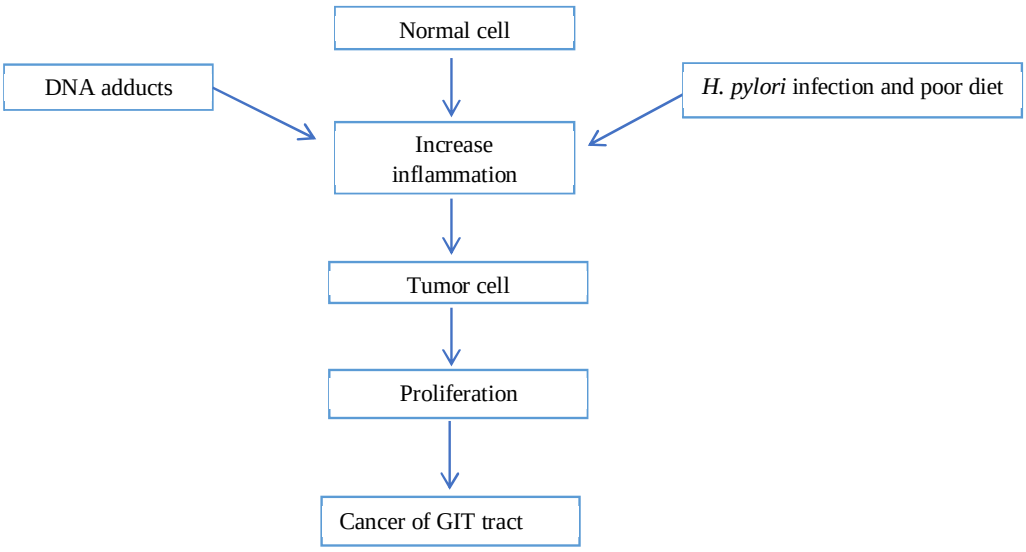


**Fig. (1).** Pathogenesis of GI cancers [Adapted from 5].

## 2.1. Gastric Cancer

Gastric cancer (GC) is the fourth most common cancer worldwide and ranks second in the mortality rate among cancers [8]. The most important environmental risk factor for GC is chronic gastritis secondary to *Helicobacter pylori* (*H. pylori*) infection. The interplay between the bacterium and the host immune reaction might be complex, whereas about two out of third of the world population (mostly living in developing countries) is infected with *H. pylori*, and only a small proportion develops GC [9].

Most GC cases are sporadic. About 10% of cases are familial, a minority of which are hereditary (HGC) [10]. Mutations in the Cadherin-1 (CDH1) gene are the most frequent cause of hereditary diffuse gastric cancer and sporadic diffuse gastric cancer [11]. The occurrence rate of CDH1 gene mutations shows an inverse relationship with the incidence of gastric cancer. In low-incidence countries, such as North America, the mutation rate in the CDH1 gene is about 51.6%, while it is reduced to 25% in medium-incidence countries and 22.2% in high-incidence countries, such as Italy [5].

## 2.2. Liver Cancer (Hepatocellular Carcinoma)

The liver is one of the largest organs in our body. It is present in the upper right portion of the abdomen. It has many important functions, such as clearing toxic

# CHAPTER 10

# Phytosterols in the Treatment of Gastrointestinal Tract Cancers

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**Abstract:** Phytosterols and related derivatives phytostanols are naturally occurring bioactive compounds present mainly in plant cell membranes. These lipophilic steroid alcohols contain a tetracyclic cyclopenta [a] phenanthrene structure which is substituted with a hydroxyl group at position C3 and have a side chain at position C17, usually containing one or more double bonds in the steroid skeleton. Phytosterols derived from isopentenyl pyrophosphate belong to the terpene family and are generally synthesized by the mevalonate pathway. They have similar structural and biological functions to cholesterol. It is not possible to synthesize by a human; as a result of their intake in diet, they are present in the human body as cereals, legumes, vegetables, fruits, nuts, vegetable oils, oilseeds, cereal grains, cereal-based products and related products which contain phytosterols in relatively high amount, consumed daily by the whole world population. Phytosterols are known as part of the normal human diet. Increasing interest has been given to phytosterols in recent years as epidemiological and experimental studies suggest that they have an important role in the protection from cancer besides their several beneficial effects, such as anti-inflammatory, antioxidative, anticarcinogenic, antifungal, antibacterial, antipyretic, antineoplastic, anti-ulcerative activity and cholesterol-lowering capacity. Inhibition tumor cell growth, multiplication, invasion and metastasis; reducing cell proliferation and increasing apoptosis; decreasing tumor size; inhibition of carcinogen production; reduction of angiogenesis and adhesion of cancer cells; inhibition of reactive oxygen species production and oxidative stress and increased antioxidant enzymes have been suggested as responsible mechanisms for anticancer activity of phytosterols. The current review aims to summarize the occurrence, safety, toxicity and chemistry of phytosterols to explain their potential activities in cancer with suggested mechanisms in detail. Furthermore, epidemiological and experimental studies related to treating the activity of phytosterols in gastrointestinal system cancers have been described.

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**Keywords:** Gastric cancer, Molecular mechanisms, Phytonutrients, Phytosterols, *β*-sitosterol.

## 1. INTRODUCTION

The cancer prevalence and the number of cancer deaths are increasing progressively worldwide, which is expected to rise to an estimated more than 10 million deaths in ten years [1 - 3]. One out of every 5 men and 6 women in the world gets cancer during their lifetime, and one out of 8 men and 11 women dies due to cancer. Gastrointestinal cancers (GI) are the most common cancer group, accounting for approximately one-fourth of the total cancer incidence and one-third of cancer-related deaths in developing countries [1].

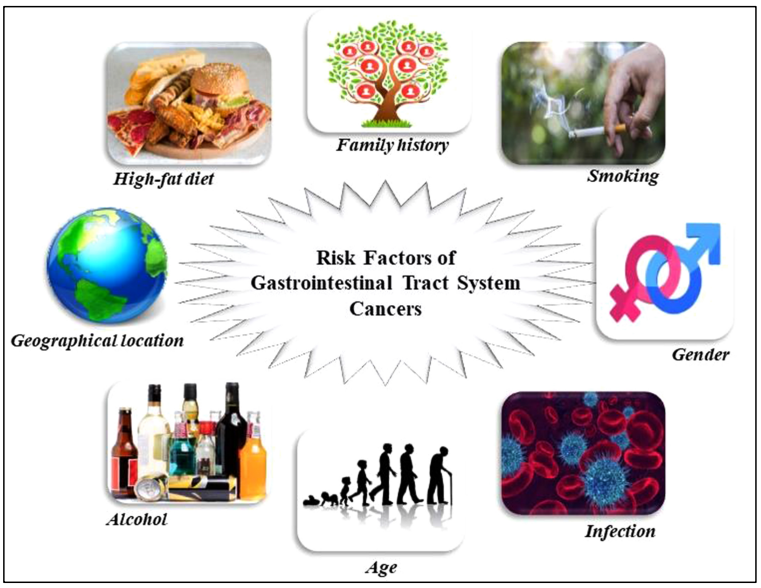


**Fig. (1).** Risk factors of gastrointestinal tract system cancers.

High-fat diet, smoking, alcohol, family history, infection, gender, age, and geographical location are important factors in the development of gastrointestinal cancers (Fig. **1**), of which incidence is higher in developed countries [4]. Studies have revealed that lifestyle changes are an important factor in the prevention of all these cancers. Calorie restriction, increased consumption of fruits and vegetables, whole grain intake, minimum meat consumption, avoidance of tobacco, moderate use of alcohol, exercise, appropriate vaccines and regular health checks are very important in cancer prevention [5 - 8]. Furthermore, tumor genotyping and signaling pathways like PI3K [9], RAS/BRAF [10], WNT, and ß-catenin stat3 have a significant role in GI cancers [11, 12].

As in all solid cancers, early diagnosis is the most important factor determining the survival of the patient in gastrointestinal cancers. Early diagnosis is associated with less morbidity and treatment cost, besides increasing the chances of curative treatment. However, most cancer patients are asymptomatic in their early stages. For this reason, screening programs are needed for early diagnosis of cancer before symptom onset and ideally before metastasis in high-risk populations. On the other hand, when cancer-related symptoms occur in patients, the disease is usually diagnosed at an advanced stage, and the disease prognosis worsens. For this reason, it is of great importance for physicians to question the risk factors and alarm findings of cancer, especially if screening is not performed.

Treatments for the disease include surgery, radiation, and administration of chemotherapy components, such as docetaxel, mitomycin, and cisplatin injection [13]. However, due to the side effects that were seen in these treatments and to support the treatment, the trend towards medicinal herbs and phytonutrients which have certain biological activities and potential benefits to human health, including the prevention of diseases, has increased. Cancer patients are among the most frequent users of complementary and alternative medicine treatments, including herbal foods [14, 15]. The reasons for these include treating or reducing the disease, reducing the risk of recurrence and the negative effects of chemotherapy or radiation, and improving overall health, quality of life, and well-being [16, 17]. Individuals with a previous or current cancer diagnosis are more likely to use phytonutrients than the general population. Phytonutrient use has been studied in many different cancer populations and has been found to have protective effects on the breast [18], lung [19], stomach [20], liver [21], ovarian [22, 23], and prostate [24] cancers.

This chapter reviews and highlights phytonutrients and some phytochemicals, especially naturally occurring phytosterols, as promising agents that are assessed at preclinical and clinical trials and their brief mechanisms for treating cancer in the gastrointestinal tract system.

## 2. GASTROINTESTINAL TRACT SYSTEM CANCERS

Gastrointestinal cancers include the colon, rectum, stomach, pancreas, esophagus, anus, gall bladder, liver, and bile duct tumors. These cancers characterize a heterogeneous array of complex diseases and disorders (Fig. **2**). They can be divided into rare hereditary forms and, more frequently sporadic forms. A critical interaction of environmental and genetic factors encourages the transformation of normal tissue into precursor, premalignant lesions and, ultimately, open malignancy. Although it is clear that certain genetic mechanisms are better respected in a cell type and tissue type-specific context, there are still overarching

# CHAPTER 11

# Plant Peptides in the Treatment of Gastrointestinal Cancer

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**Abstract:** Cancer becomes uncontrolled with conventional therapeutic medications and is, therefore, able to tolerate drug activity, which contributes to increasing the adverse effects during medication therapy. The usage of anti-cancer peptides is a recent clinical technique against cancer cells. The physicochemical characteristics, amino acid composition and the addition to the anti-cancer peptides sequence of chemical groups impact their conformation, net load and secondary structure orientation, which affect the targeted specimen and peptide cell interaction, stability and effectiveness of penetrating peptides. Anti-cancer peptides are formed by replacing cationic amino acid residues with neutral or anionic amino acid residues or by introducing a chemical group, both naturally occurring and modified peptides. Updated peptides improve the potency of cancer treatment. This efficacy has recently allowed anti-cancer peptides to shape medicines and vaccines that were sequentially tested in many phases of clinical testing.

The creation of anti-cancer peptides continues to concentrate on the production of clinically adjusted anti-cancer peptides with a view to decreasing the occurrence of new cancer cases and the mortality rate. The current analysis could help promote the creation of anti-cancer peptides and, in the immediate future, improve successful anti-cancer peptide therapy. Anti-cancer plant peptides are part of several species of plant inborn immune response systems and are attractive candidates for the care of animals and humans against infections. Anti-cancer plant peptides also display anti-cancer acti-

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vities and can inactivate a wide variety of cancer cells. Cancer appears to be a worldwide source of elevated morbidity and mortality. There is a dire need to produce novel methods to treat gastric cancer. Anti-cancer plant peptides like cyclotides, thionines, and defensins which have anti-cancer activities, are appealing alternatives. We have summarized the anti-cancer effect of anti-cancer plant peptides with a focus on their mode of activity, efficacy, and selectivity.

**Keywords:** Anti-cancer, GIT cancer, Natural products, Peptides.

## 1. INTRODUCTION

Cancer is the most prevalent cause of death and the second most widespread and brought out 8.2 million mortality worldwide in 2013 [1]. The incidence is expected to increase in the less developed countries owing to the age factor in their populations and the known risk factors [2]. In developed countries, more than 70% of new cases of gastric cancer and mortality take place, while the highest morbidity rates were observed in East Asia [3]. The prevalence of gastric cancer remains significant; many patients are not usually diagnosed until the last stages of cancer in China [4]. The poor diagnosis and tendency to relapse may be the key reason for a low survival rate of up to 5-year, approximately 20% [5]. The tumours heterogeneity involves cancer cells with stem cells and differentiated tumour cells responsible for the difficulty of treating this cancer. The cancer cells that have stem cell characteristics are also referred to as cancer stem cells [6]. The cells are altered by the important cycle checkpoints, potent DNA damage repair relevant to chemotherapy or radiotherapy, damaged machinery for apoptosis and upregulated proteins for multidrug resistance [7]. Current treatments are also mostly successful at eradicating non-cancer stem cells instead of cancer stem cells. In cancer treatment, the ability of cancer stem cells to avoid radio and chemotherapy is a significant obstacle [8].

The chemotherapeutic drugs for cancer treatment have a significant disadvantage, prompting advancements in anti-cancer therapies. In addition, due to the selection of multidrug-resistant variants [9]. Numerous neoplasms gradually resist traditional chemotherapy. New anti-cancer drugs have contributed to these limitations. Plant peptides represent a new family anti-cancer mediators that resist the side effects of traditional chemotherapy and are an enticing alternative [10].

Plant peptides have a size of 12 to 100 residues, predominantly with either positive, neutral or negatively charged molecules [11]. Plant peptides are categorized according to their structure into four groups: (a) cysteine-rich and beta-sheet ; (b) alpha-helices-possessing such as cecropins, LL-37 magainins and cathelicidin; (c) extended structure that is rich in proline, tryptophan, glycine,

histidine, and arginine; (d) loop peptides with a single disulfide bond such as bactenecin. Several articles were published about the plant peptide mechanisms of action and their resistance [11, 12]. In addition, recent reports were published on anti-cancer effect and efficacy of peptides [13, 14]. Only a few studies were tested using *in vivo* models, considering the promising properties of anti-cancer agents such as an antimicrobial peptide.

## 2. PEPTIDES RELATED TO CANCER TREATMENT

For the production of anti-cancer agents, therapeutic peptides are a new and effective method [15]. Plant peptides are existed naturally and have unique biological functions in all living organisms [16]. They are part of the inherent system of immune defense and have the potential as antimicrobial therapeutic agents like cathelicidins and defensins [17]. Many plant peptides have cationic charges, dissolve in non-polar solvents, and form amphipathic structures [18].

The plant peptides attack cancer cell membranes, which can cause either necrosis or apoptosis to induce cell death. The plant peptides attacked the negatively charged molecules on the cancer cell membrane during necrosis and induced apoptosis, disrupting the mitochondrial membrane [19]. Lehmann *et al.* found that margainin-II induced cytotoxicity in human bladder cancer cells. The induction of pores in the plasma membrane induced magainin to destroy bladder cancer cells [20]. Buforin IIb was cytotoxic *in vitro* against human cervical carcinoma (HeLa) and leukaemia (Jurkat cells) cells and helped to inhibit the development of xenografts in mice for human lung cancer. This peptide interacts with plasma membrane gangliosides was caused the extrinsic apoptotic cascade in these cells [21]. Cell penetration peptides (CPPs) are the second category of therapeutic peptides. CPPs are 5-30 AA in length and translocate from small molecules such as plasmid, siRNA, and DNA to oligonucleotides and proteins to transport through the membrane and provide a promising drug delivery mechanism [22]. These CPPs are hydrophobic in nature and consist mostly of simple residues, playing a significant role in peptide interaction and penetration into the cell membrane [23]. Cell undergoes either energy-independent (direct translocation) or energy-dependent (endocytosis and pinocytosis) processes [24, 25].

Tumour-targeting peptides (TTPs) are the third category of peptides. These peptides target the markers expressed on the tumour cell membrane, such as receptors [19]. Arginine-glycine-aspartate (RGD) peptides include an Arg-Gl--Asp sequence that identifies and binds to the integrin alpha-vβ3 and alpha-vβ5 expressed on the lung cancer membrane, melanoma, breast cancer cells, brain cancer and ovarian cancer [26 - 29]. Owing to RGD ability to be internalized into the cell, this peptide may be used as a drug delivery mechanism [30]. Xiong *et al.*

# SUBJECT INDEX

## A

## B



## C



## D

## E



## F



## G



## H

## I



## J



## K



## L



## M

## N



## O



## P

## R



## S



## T



## U



## V



## W

## X



## Y

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