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Recent Advancement of Colorectal Cancer and Their Herbal Essential Oil Treatment

Aditya Kumar[1], Mrs. Yashika Uniyal[2] and Roshan Kumar[3]

[1]Research Scholar, Department of Pharmacy, Guru Nanak College of Pharmaceutical Sciences, Dehradun-248007, Uttarakhand, INDIA.

[2]Assistant Professor, Department of Pharmacology, Guru Nanak College of Pharmaceutical Sciences, Dehradun-248007, Uttarakhand, INDIA.

[3]Assistant Professor, Department of Pharmacology, Guru Nanak College of Pharmaceutical Sciences, Dehradun-248007, Uttarakhand, INDIA.

[1]Corresponding Author: adityakumar857884@gmail.com

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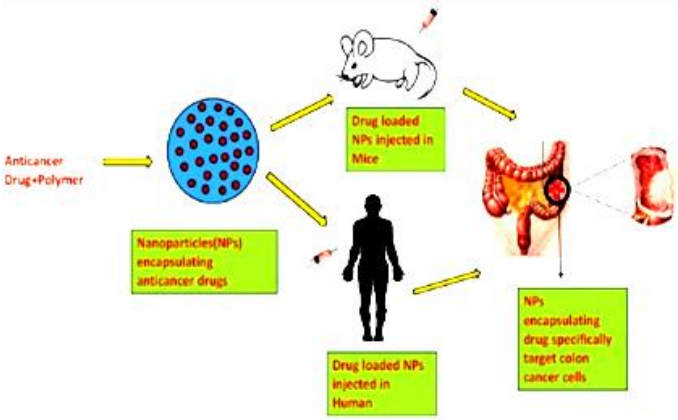
GRAPHICAL ABSTRACT



ABSTRACT

Colorectal cancer is the second most deadly type of cancer (CRC). In the upcoming decades, death and incidence rates would surely increase globally. Despite being disproportionately high in high-income countries, CRC-related mortality is also on the rise in low- and middle-income countries. Early diagnosis of CRC allows for both surgical and medicinal treatment options. Due to the high likelihood of recurrence and the rising rate of treatment failure brought on by cancer medicine resistance, it is regrettable that there is a significant treatment failure rate. Due to early discovery and treatment of CRC, there is a chance of survival in wealthy nations. Contrarily, these resources are noticeably scarce in less developed countries. It is crucial to inform the public about CRC's current situation, its cause, progression, risk factors, and therapy. As a result, we have included in this review all of the most recent data on the global epidemiology, drug resistance, challenges, risk factors, and preventative and therapeutic approaches for CRC. Guidelines for CRC prevention and therapy are briefly reviewed, as well as pathways of CRC developments.

Keywords- Colorectal, Cancer, Chemical therapy, Herbal treatment.

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I. INTRODUCTION

One of the most common causes of cancer-related death is colon cancer. Around the same number of women (47,820) as men (47,700) are expected to be affected by colon cancer incidence, while men will be afflicted at a greater rate (16,190 vs. 4,590). The development of colorectal cancer is influenced by a number of factors, including inactivity [1], heavy drinking [2], old age [3], family history [4], high-fat diets high in red meat and poor in fibre, diabetes [5], and inflammatory bowel diseases such ulcerative colitis and Crohn's disease [6].

The cornerstone of colorectal cancer prevention is the use of screening programmes for adenomatous polyps, precancerous tumours of the colon that can be surgically removed [7]. The cornerstones of traditional oncology care include chemotherapy, radiation therapy, cytotoxic drugs, and surgery [8]. Cancer treatment and cancer-slowing medications are both based on antiangiogenic compounds [9]. Early detection and treatment have been shown to increase cancer survival rates. However, the majority of people in impoverished countries, particularly those who reside in rural areas, lack access to reliable and cutting-edge diagnostic tools and infrastructure [12]. As a result, according to the WHO, about 80% of people worldwide take conventional therapies [13]. One such treatment is phytotherapy, also referred to as phytomedicine, which includes giving a patient a plant extract or a combination of plant extracts to cure their ailment. By restoring the body's natural defences, regulatory mechanisms, and healing processes, the usage of medicinal plants has been found to improve physical, mental, and emotional health [14, 15]. A few of the ailments that have been shown to benefit from plant therapy include infertility and fertility [17], hormonal disorders [18], hyperlipidemia [19], liver diseases [20], anaemia [21], renal diseases [22], and neurological and psychiatric disorders [23]. Many studies have suggested using medicinal herbs to cure and prevent cancer because they have so many alleged health benefits [23–25]. Because it is the second most common cancer in the world and the third most common cause of cancer-related death, colorectal cancer (CRC), which includes cancer of the colon and/or rectum, is a serious health problem [26]. About 9.4% of all cancer-related deaths occurred from CRC in 2020 [27]. However, it is anticipated that the incidence of CRC would more than double globally by 2035 [28], with emerging nations experiencing the highest increase due to an increase in cases among the elderly.

The abnormal proliferation of glandular epithelial cells in the colon is a feature of the disease known as colorectal cancer (CRC). Only the colon and rectum are impacted by CRC. The three most typical subtypes of CRC are sporadic, familial, and colitis-related. The prevalence of CRC is increasing globally. Environmental and inherited factors can influence the chance of developing CRC. Long-term Crohn's disease and ulcerative colitis patients also have a higher risk of developing colorectal cancer as they age [28]. Chronic inflammation, family history, diet and lifestyle, and colorectal cancer risk factors have all been identified [29,30].

The best method to prevent CRC and lower mortality from CRC in the general population, however, is to screen persons who have a moderate risk of acquiring it [31]. As a result, population-based screening programmes have been put into place in a number of European nations, Canada, and regions of North and South America, Asia, and Oceania [32]. Only those who fit the criteria for age and geography are eligible for colorectal cancer screening. According to microsimulation modelling, CRC morbidity and mortality have been declining in the United States [33]. The extensive usage of screening techniques may be responsible for this drop. In order to enable early-stage therapies and reduce the danger to individuals and communities, population-based screening also makes an effort to find latent disease in the population at average risk [34].

Screening is particularly helpful in this condition because CRC is both common and is thought to follow the adenoma-carcinoma sequence [35]. The best statistics now available indicate that it takes at least ten years [36] for an adenoma to fully develop into a CRC, giving ample time for screening and therapy. Additionally, colorectal adenomas can be surgically removed to prevent CRC [37], and early identification of CRC increases survival rates [38]. Therefore, interventions along the adenoma-carcinoma pathway can enhance therapeutic results. Examples of high-risk populations that can be successfully identified and monitored include people with inflammatory bowel disease, families with hereditary CRC syndrome, people with a family history suggesting a genetic predisposition to CRC but lacking detectable genetic markers, and people whose phenotypic characteristics indicate high risk. The metabolome has been used to identify significant biological processes that genetic variation has an impact on [39]. The two methods that are most frequently used to screen for colorectal cancer are lower endoscopy and faecal occult blood tests (FOBTs) [40].

A CRC's creation can take a very long period. It typically takes between 10 and 15 years for a benign polyp to develop into a malignant tumour. The removal of polyps, vigilant screening, and early discovery are all necessary for colorectal cancer (CRC) prevention. Current diagnostic techniques can only identify 40% of CRC cases at an early stage, and even after surgery and additional treatment, the disease may recur [41]. Cancer is treated with chemotherapy medications, which also kill the healthy cells that surround the tumour. Modern chemotherapies were resistant to almost all CRC patients, which decreased the effectiveness of the anticancer medications and ultimately resulted in

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chemotherapy failure. It will be crucial to have a detailed discussion about its epidemiology, risk factors, and preventive evaluation utilising the most recent evidence-based knowledge in order to address the future challenges of CRC. In this study, we examined the current global epidemiology of CRC, as well as its issues, risk factors, problems with medication resistance, and preventative and therapeutic choices. The causes of CRC cancer are briefly discussed, along with remedies for curing and preventing it.[42,43,44]

With fewer adverse effects than traditional treatments, plants and plant extracts can be beneficial in the treatment of colon cancer. This review aims to present and evaluate information on plants that have been shown to be effective in treating colon cancer, to investigate and pinpoint the most important compounds present in plant extracts, and to decipher the underlying molecular mechanisms of action. Cancer occurs when cell division in the body becomes unchecked. [45] Malignant neoplasm of the large intestine Colon cancer onset. CRC grows slowly and may not cause symptoms until it is several centimetres in diameter, at which point it may block the passage of faeces and cause cramping, pain, or bleeding, which may manifest as visible bleeding with bowel movements or, rarely, dark "tarry" stools, highlighting the importance of screening. Most colon cancers form gradually over time as a result of a cascade of alterations in histology, morphology, and genetics. Here we describe the histological, morphological, and genetic changes that occur at each step of CRC progression (see fig.1 for an overview). [46]

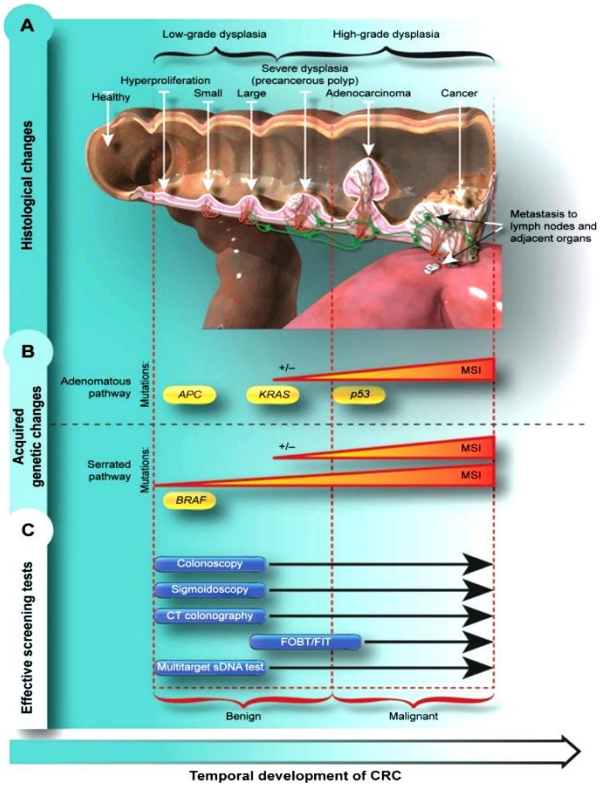

Figure 1: Development of colorectal cancer

II. COLORECTAL CANCER SCREENING

Table 1: Effect of screening on reducing incidence and mortality from Colorectal Cancer

Screening Intervention	Study design	Internal validity	Consistency	Magnitude of effect on CRC incidence	Magnitude of effect on CRC Mortality
Fecal occult blood test	RCTs.	Good	Fair	Small to none	15-33%
Fecal immunochemical test	RCTs.	V. good	Fair	Fair	Fair
Sigmoidoscopy	RCTs.	Fair	Good	22-31%	20-25%
Digital rectal exam	Cases-control study	Fair	Good	No effects	No effects
Colonoscopy	No RCTs.	Poor	Poor	About 60-80%	About 60-80%

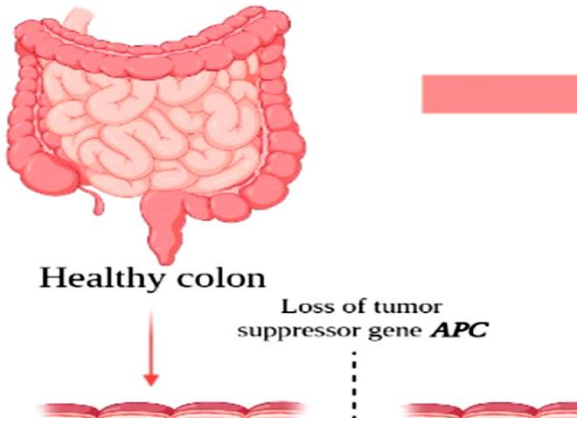

Figure 2: Colorectal cancer (CRC) stages and development.

There are four stages in the development of CRC carcinogenesis: initiation, promotion, progression, and metastasis. The liver is the most common metastatic site, followed by the lung and bone. Although it is difficult to determine the duration required for each stage, decades will likely be required to form CRC.

III. CURRENT GLOBAL EPIDEMIOLOGY OF COLORECTAL CANCER

In India, there would be 104,810 new cases of colon cancer and 43,320 new cases of rectal cancer in 2021. (Table 2). Although persons over the age of 55 make up the majority of CRC cases, cases in those under

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the age of 50 will total 27,830 this year. That equates to 49 new cases daily. In 2021, 53,220 people are predicted to pass away from CRC; 3,640 of these deaths will be men and women under the age of 50. [47]Accurate data on mortality from these two illnesses are lacking since nearly 40% of rectal cancer deaths are mistakenly listed as colon cancer on death certificates. The high prevalence of misclassification is caused in part by the fact that some people confuse colorectal and colon cancer.[48,50]

Table 2: Estimation of colorectal cases and death rate in India, in 2021, by age group

	Cases of Cancer			Death rate*
AGE GROUP	COLORECTUM	COLON	RECTUM	COLORETUM
0-49 Years	17,899	11,870	6,560	3,870
50-64 years	50,0145	32,950	17,960	13,902
65+ years	80,012	60,790	19,540	36,480
All age groups	148,980	104,640	43,450	53,150

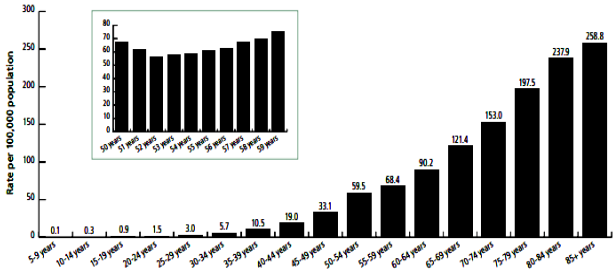

Figure 3: With According to Age group colorectal cancer incidence rate

IV. CANCER DRUG RESISTANCE AND ITS PROSPECTIVE CHALLENGES

Despite significant progress, cancer remains a substantial global burden, as the second largest cause of death worldwide [51]. Surgery, radiation therapy, and chemotherapy are the mainstays of cancer treatment [52,53]. In addition, medications have been developed that target particular signalling pathways thought to have a role in the initiation, development, and spread of cancer, known as targeted therapies [54,55,56]. Recently, immunotherapy (i.e., immune checkpoint inhibitors) has emerged as a game-changer in the treatment of cancer, with the goal of enhancing patients' own immune systems to combat cancer [57,58]. However, this therapeutic approach has been linked to a number of immune-related side effects.

The taxanes (paclitaxel, docetaxel, cabazitaxel) are a well-known family of chemotherapeutic drugs that are still widely used to treat various types of cancer (mostly epithelial-derived cancers) due to their ability to suppress microtubule dynamics, thereby blocking mitosis and triggering apoptosis in tumour cells [59]. Unfortunately, most patients experience the development of resistance to these medications despite their initial significant efficacy in suppressing tumour growth. Maloney et al. [60] provide a thorough summary of the molecular mechanisms underpinning the emergence of taxane resistance across a variety of tumour types in their review. Among these mechanisms are the enhancement of taxane metabolism, the upregulation of pro-survival, anti-apoptotic, and epithelial-to-mesenchymal transition (EMT)-inducing pathways, the increased activity of drug export transporters, which reduces intracellular drug levels, and the upregulation of taxane receptors. Furthermore, this paper explores the role of non-coding RNAs in these resistance-related pathways.[61,62,63,64,65]

Tyrosine kinase inhibitors (TKIs) were developed and introduced as an oral therapy in clinical settings for the treatment of various cancers, where they are known as "targeted therapies" due to the unique role of receptor tyrosine kinases (RTKs) in tumour development and progression towards its most aggressive phase. [66] It is widely acknowledged that anticancer drugs require adequate absorption at the gastrointestinal (GI) level in order to enter the circulation and, ultimately, to reach the tumour cells. Honeywell et al. use an optimised CaCo2 gut epithelial model to show that different TKIs are poorly absorbed by these cells because of the drug transport systems expressed at the membrane level and the presence of unique metabolising enzymes within the cells. These results provide further evidence that poor absorption of these drugs may play a significant role in the development of the TKI-resistant phenotype seen in several tumour types [67]. It has long been believed that a tumor's ability to develop a blood supply and spread from one location to another is a defining characteristic of malignancy. The recent discovery that antiangiogenic medications, rather than halting cancer growth, actually encourage cancer cells to expand blood vessel production, leading to recurrence and drug resistance, has shed light on the complicated and diverse role of tumour vascularization. Belotti et al. discuss the role of alternative mechanisms of therapy-induced vessel formation in tumour recurrence and drug resistance, in addition to the various mechanisms underlying vascularization in tumours (vasculogenesis, glomeruloid proliferation, intussusceptive angiogenesis, vasculogenic mimicry, and vessel co-option). [68]

Self-renewal, tumor-initiating potential, and the ability to adapt are hallmarks of cancer stem cells (CSCs), a highly aggressive minority of cells within the tumour mass. A growing body of research indicates that CSCs are a critical contributor to treatment resistance and tumour relapse. It has been found that the existence

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of these cells is linked to poor overall survival, decreased time without disease, tumour progression, and tumour recurrence. Marzagalli et al. [69] provide a detailed discussion of the various molecular mechanisms (growth factors, their receptors, and intracellular signalling pathways) that mediate CSCs' ability to escape the antitumor activity of chemotherapeutics, targeted therapies, and immunotherapies, highlighting their plasticity as a stealthy feature responsible for the development of drug resistance in various tumour types.

Nanoscale vesicles called extracellular vesicles (EVs) play a significant role in intercellular communication across a wide range of tissues. It has been widely reported that they mediate a violent cell-to-cell cross-talk in tumour tissues by transporting various molecular cargos (proteins, mRNAs, and microRNAs) between cancer cells and cells in their microenvironment. The most up-to-date research on EVs and their function in the development of treatment resistance in cancer is summarised in a recent review article by Fontana and colleagues. Hunt et al. highlight the unusual, recently documented cell-to-cell communication between cancer cells and the neurons in their surroundings. In order to train neurons to adopt a protumoral phenotype, tumour cells secrete growth factors (such as nerve growth factor, NGF) and microRNAs (miRNAs). Neurite outgrowth toward the cancer site is also facilitated by the expression of chemokine receptors on cancer cells, such as the CCR2 receptor, which is activated by its neuron-derived specific ligand CCL2. While cancer cells secrete axon guidance molecules, guiding nerve expansion in the tumour microenvironment, neurons emit neurotransmitters and neuropeptides that promote tumour progression. However, it has recently been discovered that EVs and their chemical payload (in particular, miRNAs) play a significant role in this form of communication between neurons and tumour cells. The authors draw the conclusion from their findings that elucidating this cross-talk could be a target for effective anticancer medicines to overcome treatment resistance in solid tumours. [70][71]

These hormone-related tumours include breast, ovarian, and prostate cancers, and this Special Issue contains a variety of studies that focus on the molecular pathways that contribute to the emergence of medication resistance in these malignancies. Tsoi et al. found that in breast cancer, the splice variant BQ323636.1 upregulates IL-6 and IL-6R expression and stimulates STAT3 activation by favouring the binding of the oestrogen receptor (ER) to the IL-6 promoter. Tamoxifen resistance in breast cancer cells can be efficiently reversed in vitro and in vivo by targeting the IL-6/STAT3 signalling pathway with IL-6R knockdown or therapy with the targeted IL-6R antibody tocilizumab [72]. HER receptor family signalling alterations play a significant role in the evolution of treatment resistance in breast cancer. Even though lapatinib (a particular HER2 inhibitor) is commonly used to treat HER2+ breast cancer, the prognosis is dismal because most patients develop resistance to the drug. Drug-resistant breast cancer cells have been shown to have elevated levels of Heat Shock Protein 90 (HSP90), as shown by the work of Lee et al. According to the authors, HSP90 inhibitors combined with lapatinib could be an effective new treatment for HER2+ patients [73]. The upregulation of the HER3 receptor isoform is another mechanism involved in the development of resistance to anti-HER2 treatments. Cruz et al. show in their research that JAM-A, a junctional adhesion protein, increases HER3 expression in breast cancer cell and tissue models through a biochemical mechanism involving -catenin and FOXA1. Based on these findings, JAM-A should be regarded a good target for blocking the emergence of resistance to HER2-targeted treatments [74]. We now know that abnormal changes in cellular metabolism are a common feature of malignancies, including breast cancer. The development of drug resistance to standard drugs like cisplatin, paclitaxel, tamoxifen, and doxorubicin, as well as the progression of cancer towards its most aggressive phases, have all been linked to increased glucose uptake, hyperactivated glycolysis, and dysfunctional oxidative phosphorylation. In this Special Issue, authors Varghese et al. [75] present a thorough overview of the current state of knowledge about innovative therapeutic techniques that aim to correct the abnormal glucose metabolism seen in chemoresistant breast tumours. Well recognised and proved to play a crucial role in the development of resistance to anticancer therapies is the presence of a vicious cross-talk between cancer cells and cells in their microenvironment, such as fibroblasts, adipocytes, and immune cells. This harmful communication in breast cancer has been shown to involve a wide variety of soluble biofactors and extracellular vesicles.

Cosentino et al review's [76] delves further into the unique function of microRNAs in mediating the formation of protumoral characteristics in stromal cells as well as the stromal cell-mediated promotion of cancer's aggressiveness and progression into a drug-resistant phase. Due to its aggressive characteristics and rapid growth towards the drug-resistant stage, ovarian cancer continues to be one of the leading causes of death among gynaecological cancers. The molecular mechanisms (i.e., regulatory elements from the non-coding RNA families) involved in these processes are discussed by Seborova et al. in their review. In this article, the authors address the unique function of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in the metastasis of ovarian cancer, and how this could be a useful tool in tracking the efficacy of treatment [77]. Ovarian cancer patients are often treated with platinum-based chemotherapy, such as cisplatin; nevertheless, toxicity and acquired resistance to this drug have presented significant treatment challenges. Therefore, it would be helpful to find molecular

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biomarkers that predict the response to cisplatin so that new, successful medicines can be created. Drug resistance has long been believed to be influenced by a tumor's innate ability to repair DNA damage. The original article by Guffanti and colleagues explores the possibility that the expression of nucleotide excision repair (NER) proteins (ERCC1, XPF, ERCC1/XPF complex) and base excision repair (BER) protein DNA polymerase could serve as a biomarker of cisplatin response in a platform of established patient-derived ovarian carcinoma xenografts. They note, however, that none of these proteins were able to foretell cisplatin's efficacy in ovarian cancer models. DNA functional tests may be a more accurate way to predict the response to platinum-based therapy in ovarian cancer, the authors conclude [78]. Because of its need on androgens in its early stages, prostate cancer patients are typically treated with androgen deprivation therapy (ADT), also known as suppression of the androgen receptor (AR). [79]

V. HERBS IN TREATMENT OF COLORECTAL CANCER

TNBC tumours have a shorter overall survival time and higher recurrence risk than other subtypes of breast cancer [75-76]. Although there are no clearly established molecular targets for treating metastatic TNBC, standard chemotherapy is frequently used [80]. Though safety and toxicity to tissues other than the target remain challenges with this therapy. Finding innovative chemicals (natural or synthetic) with greater selectivity and fewer side effects than the current chemotherapy drugs is thus one of the biggest challenges in the treatment of cancer. The effectiveness of new medications in this situation must be determined using preclinical models that evaluate heterogeneous populations of cells derived from patient malignancies.

The ginger plant's rhizome is made up of chemicals called gingerols, which are also what give ginger its biological and pharmacological properties [81-85]. We have already shown, in vitro, that SSi6 is effective in causing cell death in the MDA-MB-231 cell line. We show in this study that SSi6 increases specific cytotoxic effects in the triple-negative line (MDA-MB-231). Comparatively to the original natural compound (6G), SSi6 induced apoptosis without the involvement of caspases, autophagy, and the formation of reactive oxygen species. This strategy, which involves inducing many mechanisms of cell death, may be useful for treating triple-negative tumours that are resistant to treatments that induce classical apoptosis [86]. By include preclinical models that would enable us to evaluate the potential therapeutic benefit of this unique chemical, we intended to advance this research. This is a significant discovery because no prior studies have demonstrated that the SSi6 has anticancer or antimetastatic capabilities in vivo. This investigation was contrasted with others that looked at the in vitro and in vivo therapeutic effects of unmodified gingerols like 6G and [87]-gingerol.

Xu et al. [88] shown that high dosages of 6G (10, 30, and 50 M) are cytotoxic in kidney cancer cell lines. After 7 days of treatment, 6G was found to have a concentration-dependent effect on ACHN, 786-O, and 769-P cell lines, especially at 30 and 50 M. Furthermore, Luo et al. [39] documented the impact of 6G on HGC-27 human gastric cancer, which was treated with 300 M of 6G in conjunction with ionising radiation to sensitise the cells and enhance this chemical's activity. The IC50 value remained still high (386.3 M) even after 48 hours of 6G treatment, showing that the radiosensitization was inefficient. Our findings imply that SSi6 is more potent at suppressing colony formation at low concentrations in TNBC lines than its unmodified equivalent 6G, demonstrating its cytotoxic potential. Additionally, the computed IC50 values demonstrated that SSi6 was selective in how it affected the MDA-MB-231 cell line.

Numerous studies have claimed that 6G has no acute toxicity in animal models. Rastogi et al. [89] shown in a xenograft experiment using cervical cancer HeLa cells that 6G dosages of 2.5 and 5 mg/kg had no effect on the bodyweight of athymic mice. Based on investigations of the enzymes alanine aminotransferase and aspartate aminotransferase, the same study concluded that 6G is not hepatotoxic. Our research, which showed that SSi6 did not cause toxic effects in FVB mice even at 15 mg/kg, was based on an examination of histology and blood parameters, is consistent with these findings. In other words, whereas the molecular structural modification employed to make SSi6 is essential for enhancing the compound's selectivity and cytotoxic actions towards TNBC cells, it has little influence on the acute toxicity of 6G.

After the primary tumour reached a volume of 200 mm3, it was treated with SSi6, and in the initial xenograft model (without the primary tumour being removed), we permitted metastases to develop in the axillary lymph nodes. SSi6 significantly outperformed the control group in terms of anticancer activity, slowing the growth of the primary tumour. Additionally, in most of the animals in the treated group (15 mg/kg), SSi6 demonstrated potent antimetastatic activity by preventing spontaneous metastasis from spreading from the axillary lymph nodes to the lungs. Since 6G has relatively little in vivo activity, the majority of studies examining its antimetastatic effects probably use extremely high dosages. In a xenograft model using the MCF-7 breast cancer line, Zhong et al. [90] demonstrated that only dosages of 100 and 200 mg/kg of 6G (ten times more than used in this work) were effective in suppressing tumour formation and lung and liver metastases. In contrast to our study, treatment started when the tumour volume was only around 10 mm3, which indicates that the illness had not yet metastatically progressed to the lymph nodes.

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To more closely mimic the clinical metastatic disease status in women, where the tumour is found, surgical resection is done, and the chemotherapy regimen is started, we designed a preclinical xenograft model in which the primary tumour was excised and SSi6 treatment was started. Our team had previously shown that [91]-gingerol (10G), a different compound produced from gingerol, had antimetastatic properties [92]. In an orthotopic xenograft model, it was discovered that the MDA-MB-231 HMTL.6 line (derived from spontaneous lung metastases) was resistant to 10G (10 mg/kg), suppressing the growth of primary tumours and circulating tumour cells (CTC) in mice [93]. This result was closely related to preventing CTC from growing inside of the lungs (pulmonary metastasis). Here, we demonstrate that SSi6 therapy, which was also successful in preventing visceral metastases, has an effect on this xenograft model in which the primary tumour has been removed (spleen, liver, and kidneys). We specifically demonstrated that SSi6 prevented metastatic spread from axillary lymph nodes to the lungs in the majority of treated animals.

TCM may greatly benefit cancer patients by prolonging their lifetime and improving their quality of life while causing few negative effects, according to growing research. Chinese herbal remedies are now more popular among researchers studying cancer [94,95,96]. Rhein is very effective at halting the growth of tumours, according to several studies [97,98]. The precise mechanism(s) by which rhein causes CRC is/are still unknown. In this study, we demonstrated that rhein blocks EMT, inhibits CRC cell motility and invasion, and causes apoptosis and cell cycle arrest in the S phase. Rhein blocks the growth of cancer in vivo and in vitro by reducing mTOR signalling.

The development of tumours has been linked to mTOR signalling, which is necessary for cell growth and metabolism [99,100]. By blocking mTOR, colorectal cancer (CRC) tumour growth may be successfully inhibited [101]. The letters mTORC1 and mTORC2 stand for two different mTOR complexes. Eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and p70S6K are phosphorylated by mTORC1 to promote cell proliferation [102]. The phosphorylation of Akt at Ser 473 by mTORC2 initiates the Akt signalling pathway. According to research, mTOR is necessary for both the production of heat-shock proteins and the activation of HSF1 [103]. In breast cancer and gastric cancer, HSF1 has been associated with a worse prognosis and quicker tumour growth [104,105]. We also found that rhein treatment reduced the levels of HSF1 and HSP90 and that CRC cells overexpressed HSF1. These findings imply that rhein inhibits the mTOR/p70S6K and the mTOR/HSF1 pathways. The cell cycle is tightly regulated by CDKs and the cyclins with which they interact [106]. The cyclin A/CDK2 complex is necessary for S-phase entry and maintenance [110]. Chemotherapy [107], DNA damage [108], and hypoxia [109] all caused cell cycle stalling in the S phase. The mTOR pathway has been discovered to be involved in the DNA damage response [111]. A fascinating finding we made was that rhein inhibited the production of cyclin A1, cyclin E1, and cyclin-dependent kinase 2 and so increased S-phase cell cycle arrest in CRC cells. The ability of rhein to damage DNA in CRC cells needs to be confirmed in a subsequent investigation.[112]

It is common practise to assess possible cancer treatments using tumour xenograft models created from cell lines. In order to further demonstrate the anticancer properties of rhein, we created an HCT116 xenograft mouse model.[113-115]

VI. CONCLUSION

Plants and their principal compounds have a considerable impact on the transcription process as well as the cell cycle. Examples of such pathways include the induction of superoxide dismutase for free radical removal, DNA oxidation reduction, cell cycle arrest leading to apoptosis, downregulation of PI3K, P-Akt protein, and MMP expression, anti-apoptotic Bcl-2 and Bcl-xL protein expression, and downregulation of PCNA, cyclin A, cyclin D1, cyclin B1, and cyclin E. Additionally, plant compounds increase the expression of the cell cycle promoters p53, p21, and p27, as well as the cell cycle inhibitors BAD, Bax, caspase 3, caspase 7, caspase 8, and caspase 9. Overall, this study's findings suggested that medicinal plants might be able to stop colon cancer cells from spreading. However, more in vivo testing of these medications is required before they may be applied in clinical settings. Clinical trials were infrequently employed, despite the widespread use of in vivo models in research. In fact, clinical studies, in vivo models, and the purification of herbal compounds may offer fresh and effective approaches to the prevention and treatment of colon cancer.

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