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"Confronting Colon Cancer: A Comprehensive Review on Development, Risk Factor, Treatment, Advancements in Therapeutic Strategies"

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ABSTRACT
Cancer, a multifaceted disease, continues to challenge the medical community worldwide. In this review, we explore key aspects related to cancer research and management. Colorectal cancer (CRC) stands as the third most fatal cancer worldwide, with projected increases in both incidence and mortality over the forthcoming decades. While high-income countries bear a significant burden of CRC-related deaths, developing nations are also witnessing a concerning rise in both CRC incidence and fatalities. Early detection of CRC offers a path to complete cure through surgical intervention and subsequent medications. Nonetheless, the recurrence of CRC is alarmingly high, compounded by the emergence of drug-resistant strains that escalate treatment failure rates. While access to early diagnosis and treatment is relatively feasible in developed nations, such crucial facilities remain scarce in many developing regions, exacerbating the challenge of survival from CRC in these areas. The aim of the study is to highlighting the development, risk factor, treatment and advancements in therapeutic strategies for colorectal cancer.

Keywords: Colon cancer, adenocarcinoma, risk factors, therapeutic strategies.

I. INTRODUCTION

A malignancy or cancer affecting the colon or rectum, situated at the distal part of the gastrointestinal tract. Colon cancer originates from the abnormal proliferation of cells within the colon, which constitutes the initial and lengthiest segment of the large intestine. The large intestine, encompassing the final portion of the digestive system, which is responsible for the breakdown of food to facilitate absorption and utilization by the body[1].

Colorectal cancer ranks as the third most prevalent cancer globally, constituting about 10% of all cancer diagnoses. Moreover, it stands as the second principal contributor to cancer-related mortality on a global scale[1]. Colon cancer primarily impacts older individuals, although it can manifest at any stage of life. The development of colon cancer typically originates from small clusters of cells known as polyps within the colon[2]. While polyps are generally benign, certain types have the potential to progress into colon cancer with the passage of time.

Colorectal carcinoma (CRC) initially manifests in the mucosal lining of the colon before advancing to cause significant symptoms related to the rectum. These symptoms may include rectal bleeding, changes in bowel habits such as diarrhea or constipation, abdominal pain, the formation of abscesses, fistulas, and alterations in dietary habits[3]. As the disease progresses, it can profoundly impact an individual's nutritional intake and overall quality of life.

Among various diseases afflicting humanity, cancer stands out as a formidable threat on a global scale. In India, it ranks as the second most prevalent disease, claiming a staggering 0.3 million lives annually, making it a leading cause of mortality. This alarming statistic is largely attributable to inadequate access to preventive measures, diagnostic tools, and treatment options for the disease across the country. The spectrum of cancers affecting the Indian population is diverse, encompassing malignancies of the skin, lungs, breast, rectum, stomach, prostate, liver, cervix,

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esophagus, bladder, blood, and mouth, among others. Notably, lung, breast, colon, rectum, stomach, and liver cancers are among the most frequently observed types in India. Colorectal cancer (CRC) holds a significant position within this landscape, ranking as the third most common cancer in men globally, with 663,000 reported cases (constituting 10.0% of total cancers), and the second most prevalent in women, with 570,000 cases (representing 9.4% of total cases) worldwide. This underscores the urgent need for enhanced efforts in cancer prevention, early detection, and treatment interventions to mitigate the profound impact of this disease on individuals and communities[1].

The American Joint Committee on Cancer (AJCC) has established a five-stage classification system for colon cancer, ranging from Stage 0 to Stage IV. Stage 0 boasts a remarkable 100% cure rate following surgical resection. Stages I to IIC also typically undergo surgical resection, with 5-year survival rates ranging from 37% to 74%. However, advanced stages (IIIA to IV) necessitate surgical resection followed by adjuvant chemotherapy, yet patients face a persistent high risk of metastasis and recurrence, with a mere 6% survival rate. Adjuvant chemotherapy is conventionally delivered intravenously, leading to severe systemic side effects due to the nonspecific distribution of chemotherapeutic agents to healthy tissues[4].

Conversely, the oral route emerges as a safer and more logical option for administering treatment for colon-related diseases such as colon cancer. Besides promoting enhanced patient compliance, oral chemotherapy facilitates direct access to the site of the disease, potentially increasing drug bioavailability while minimizing the necessary dosage. Consequently, patients are at a significantly reduced risk of experiencing chemotherapy-related side effects, thereby improving the overall therapeutic experience and outcomes[4].

DEVELOPMENT OF COLORECTAL CANCER

Colorectal cancer (CRC) exhibits remarkable genetic diversity, with its development governed by various unique mechanisms. For instance, numerous CRC cells showcase numerous somaclonal mutations arising from distinct gene expression profiles. Consequently, CRC is recognized for harboring one of the most extraordinary mutational burdens among malignancies. The extent of somaclonal mutations classifies CRC broadly into hypermutated or non-hypermutated. Moreover, a novel categorization scheme for CRC has emerged from parallel endeavors to classify it based on gene expression profiles, with these classifications continually updated and refined by integrating data on gene expression profiles with tumor genotypes[5].

CRC initiates when epithelial cells undergo a series of genetic or epigenetic alterations, propelling them towards hyperproliferation. These rapidly proliferating cells give rise to benign adenomas, which can progress to cancer and metastasize through several distinct pathways, including microsatellite instability (MSI), chromosomal instability (CIN), and serrated neoplasia. The adenoma–carcinoma sequence delineates the progression of cancer, with the traditional pathway accounting for the majority of sporadic CRC cases. In this pathway, cancer evolves from a small adenoma to a large adenoma before manifesting as cancer. This progression is strongly linked to the development of the chromosomal instability (CIN)-positive subtype. The National Cancer Institute attributes 10–15% of sporadic CRC to this model, characterized by the transition from normal cells to hyperplastic polyps, sessile serrated adenomas, and ultimately leads to cancer[5].

When an adenocarcinoma becomes invasive, it gains the ability to metastasize, spreading to other parts of the body through the bloodstream and lymphatic system. Adenocarcinomas comprise approximately 96% of all colorectal cancers (CRC). However, the progression from developing a polyp to invasive cancer can span up to 18 years. On average, it takes nine years for metastases to form. CRC, like other tumors or cancers, is categorized into stages ranging from stage 0 (carcinoma in situ) to stage IV.

Typically, the development of colorectal cancer (CRC) stems from the progression of non-cancerous abnormalities, resulting in dysplastic tissue formation and eventually leading to CRC. Initially, a benign soft tissue tumor, which doesn't metastasize, forms due to hyperproliferation, presenting as a (benign) polyp or adenoma (stage 0). Around ten percent of adenomatous polyps may progress to malignancy, evolving into an adenocarcinoma that penetrates the muscularis propria (stage I). Subsequently, the tumor expands and infiltrates surrounding tissue, reaching the serosa (stage II) and eventually the visceral peritoneum (stage III). At this juncture, the potential for lymphatic or blood vessel metastasis

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arises (stage IV). The staging dictates the disease's severity and the therapeutic interventions available. Although surgery remains the primary treatment for stages 0–II CRC, stage III necessitates both surgery and adjuvant chemotherapy. For stage IV and recurrent CRC, a combination of surgery, chemotherapy, and targeted therapy is employed. Unfortunately, to date, no definitive cure has been established for advanced stages of CRC[4].

RISK FACTORS FOR COLORECTAL CANCER

Various risk factors are linked to the incidence of CRC, a disease known for its heterogeneity. Genetic and environmental factors prominently contribute to CRC's etiology, elevating the risk, while other factors are associated with a modest increase in CRC risk.

1. Inherited Genetic Risk:

Hereditary factors represent a subset of CRC risk factors beyond individual control. Several hereditary CRC syndromes, notably FAP and HNPCC or LS, significantly elevate CRC risk. Approximately 5% of all CRC cases are attributable to these hereditary conditions.

2. Personal and Family History:

The personal and family history of CRC patients, along with adenomatous polyps' presence, correlates with heightened risks for synchronous and metachronous primary CRC. Additionally, a personal history of IBD (Crohn's disease and ulcerative colitis) escalates CRC risk.

3. Race and Ethnicity:

CRC survival disparities are observed along racial and ethnic lines. In the USA, Native Americans and African Americans face higher CRC risks and lower survival rates across all stages compared to Hispanic and white Americans.

4. Sex:

Men exhibit a slightly elevated risk of CRC compared to women. Globally, men are 1.5 times more likely to develop CRC across all age groups. Furthermore, women tend to be more prone to right-sided colon cancer, characterized by a more aggressive phenotype than left-sided colon cancer.

5. Age:

Age serves as an unmodifiable CRC risk factor. Over 90% of CRC cases manifest in individuals aged ≥50 years. The incidence of CRC is over 50 times higher in those aged 60-79 years compared to those under 40 years.

6. Comorbidities:

Various comorbidities heighten CRC risk, including diabetes mellitus/insulin resistance, abdominal irradiation in childhood cancer survivors, uncontrolled acromegaly, cholecystectomy, long-term immunosuppression post-kidney transplantation, cystic fibrosis, and androgen deprivation therapy in prostate cancer patients.

7. Environmental Factors and Lifestyle:

Strong associations exist between environmental/lifestyle factors and CRC development. Low socio-economic status, coupled with inadequate medical care, increases CRC risk. Dietary factors such as high meat consumption, particularly red and processed meats, along with diets low in fruits, vegetables, and fiber, are implicated in CRC risk. Moreover, low physical activity, obesity, and excess body weight contribute to CRC risk. Cigarette smoking and heavy alcohol consumption may also elevate CRC risk[6].

TREATMENT OF COLORECTAL CANCER

Early detection plays a pivotal role in enhancing the survival rates of patients with CRC. Many cancers are potentially treatable if caught in their early stages, prior to the onset of metastasis. Typically, standard cancer treatments include chemotherapy, surgery, radiation therapy, or a combination thereof, especially for advanced-stage diseases. The selection of treatment modalities for CRC entails a multimodal strategy contingent upon tumor-specific characteristics such as location, size, metastatic spread, and patient health status[7]-[8]. Over time, a range of treatment options has evolved for both primary and metastatic CRC (mtCRC), affording patients greater therapeutic choices. These options encompass laparoscopic surgery for early-stage primary CRC, aggressive resection of mtCRC (including metastases in organs like the lungs and liver), radiotherapy for rectal cancer (RC), neoadjuvant chemotherapy, and palliative chemotherapy[9]-[10]-[11]. Surgical resection stands as the primary modality for patients with potentially curable and localized early-stage CRC. Nevertheless, depending on the stage of the disease, neoadjuvant chemotherapy and/or radiotherapy might be administered prior to or following surgery. Notably, among various solid tumors, CRC uniquely exhibits increased survival rates through the surgical excision of distant

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metastases. For patients with unresectable mtCRC, systemic chemotherapy offers a means to enhance survival. In CRC treatment, chemotherapy is often coupled with monoclonal antibodies targeting EGFR (Estimated Glomerular Filtration Rate) and VEGF (Vascular Endothelial Growth Factor) to impede tumor growth and angiogenesis[12],[13],[14].Non-surgical CRC cases, particularly those with late-stage mtCRC, adopt a palliative systemic approach aimed at enhancing quality of life and extending life expectancy. Efforts to enhance treatment efficacy and mitigate the side effects of conventional chemotherapy have led to investigations into alternative therapies such as anti-inflammatory medications, gold-based compounds, agarose macrobeads, and probiotics. However, despite advancements in CRC treatment, delayed diagnosis and the challenges of ensuring the safety and efficacy of chemotherapy persist as significant hurdles[15],[16].

ADVANCEMENTS IN THERAPEUTIC STRATEGIES FOR CRC

1. AGAROSE MACROBEADS

Organs and tumors often exhibit growth patterns that follow a Gompertzian curve, which is characterized by a decremented exponential curve approaching an asymptote or declining as it enlarges. This observation suggests that tumors, much like organs, are subject to both positive and negative growth-regulatory mechanisms[17]. The well-established phenomenon of positive regulation in tumor growth is supported by extensive evidence in the literature. For instance, partial surgical removal of a tumor can often lead to tumor progression due to compensatory hyperplasia. Additionally, biological signals indicating the presence of a tumor mass can inhibit or halt tumor growth even when the mass of cells is absent. This understanding forms the basis for utilizing hydrophilic agarose macrobead culture cells in the context of colorectal cancer (CRC) outgrowth[18].

Agarose macrobeads are composed of two concentric layers of agarose, creating an inner space where cancer cells can be contained. While various tumor cell lines can form colonies after encapsulation in agarose macrobeads, RENCA cells (a mouse renal cortical adenocarcinoma cell line) have been specifically chosen for this application. Following encapsulation, these cells form colonies starting from single cells that progressively grow in size to contain several hundred cells. As the colonies expand, their growth rate slows until they reach a stable size, typically around 6 to 24 months post-encapsulation[19]. During this period, the encapsulated cells undergo a transformation process wherein at least two subpopulations of cells are selected to form the tumor colonies. The growth-restrictive agarose environment prompts the production of tumor-inhibitory molecules, which can inhibit the proliferation of non-encapsulated cancer cells both in vitro and in vivo[20]. These molecules include Gelsoin (GSN), Fibulin (FBLN1), nucleolin (NCL), Prosaposin (PSAP), pigment epithelium-derived factor (PEDF), Serpine1 (Serbp1), secreted protein acidic and rich in cysteine (SPARC), tissue inhibitor of metalloproteinase 2 (TIMP2), phosphatidyl ethanolamine-binding protein (PEBP1), and peroxiredoxin 1 (PRDX1).Although the precise mechanism of growth inhibition by RENCA macrobeads remains unclear, it is hypothesized that these secreted proteins collectively induce multiple signals that ultimately increase the cell-cycle time of exposed cancer cells[21]. Notably, experimental results indicate that RENCA macrobeads prolong the S-phase cycle time and reduce the number of mitoses. Given the nonspecific nature of the mechanism of action of RENCA macrobeads, this regulatory system is potentially applicable to various epithelial-derived tumor types across different species and cell lines.

RENCA macrobeads have undergone testing in a phase I/II clinical trial for advanced epithelial-derived cancers. Overall, the treatment was well-tolerated by patients, with common adverse effects including fatigue and anorexia lasting from a few days to three weeks. Less common adverse effects included abdominal pain, constipation, pyrexia, nausea, vomiting, dyspnea, localized fluid accumulation around the macrobeads, ascites, abdominal distension, and peripheral edema. Most treated patients exhibited a positive response to the treatment, showing reductions in tumor markers, disease stabilization, alleviation of pain, and improvements in quality of life. A phase II/III clinical trial is currently ongoing, and the future prospects for this treatment appear promising[1],[22],[23].

2. METAL- BASED DRUGS FOR CRC TREATMENT

The utilization of metals for therapeutic purposes traces its roots back to ancient civilizations. For instance, cinnabar powder, derived from mercury, found widespread application in traditional Chinese and Indian medicine[1],[24],[25]. Silver sulfadiazine is another example commonly found in topical creams for treating burns. Additionally, Tianmai Xiaoke

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Tablet, containing chromium picolinate as its primary component, is employed in China for managing type 2 diabetes. However, one of the most significant advancements in inorganic chemistry in the medical field is the accidental discovery of cisplatin's anticancer properties in the 1960s[26]. Cisplatin, represented chemically as cis-PtCl2(NH3)2, revolutionized cancer treatment. Subsequently, numerous other metal-containing compounds have been synthesized and explored for their potential in cancer therapy[27].

In this discussion, we will focus on two particularly promising candidates: platinum and gold, and their applications in colorectal cancer chemotherapy.

a. Platinum

Cisplatin pioneered the use of metals in chemotherapy and has demonstrated effectiveness against various cancer types, including testicular, ovarian, and solid tumors of the head and neck[28]. Its success lies in its mechanism of action: cisplatin binds to DNA, inducing apoptosis. Upon entering the cell, cisplatin interacts with DNA at the N7 position of major groove guanines, forming mono- and bifunctional adducts through inter- and intra-crosslinks[29].

However, despite its efficacy, cisplatin usage is associated with significant side effects. Kidney damage and hearing loss are the most notable adverse effects[30]. Nephrotoxicity results from cisplatin accumulation in the kidney proximal tubule, while ototoxicity is caused by the death of cochlear sensory hair cells due to increased reactive oxygen species[31]. Moreover, resistance to cisplatin treatment has emerged, primarily attributed to enhanced repair of cisplatin-DNA adducts, along with cytosolic drug inactivation and reduced drug uptake[32].

To address these limitations while maintaining efficacy, several analogues, such as oxaliplatin and carboplatin, have been developed. Oxaliplatin, in particular, is widely used in colorectal cancer chemotherapy[33]. Its significance lies in its lack of cross-resistance with cisplatin, enabling its use in cases of cisplatin resistance. This lack of cross-resistance is attributed to distinct mismatch-repair proteins recognizing each type of adduct, also explaining their differing side effects. Notably, oxaliplatin does not induce ototoxicity or nephrotoxicity[34].

Oxaliplatincommonly administered in combination with infusional 5-fluorouracil/leucovorin, known as FOLFOX regimen. FOLFOX has significantly improved response rates, with a response rate of 50% compared to 20% with 5-fluorouracil treatment alone[35]. Additionally, the combination therapy of both offers better survival rates in metastatic patients.

b. Gold

Numerous metal-based anticancer drugs incorporating gold (I) or gold (III) have been developed in recent decades. These compounds exhibit diverse structures, with the gold atom coordinated to phosphines, carbine ligands, porphyrinates, or dithiocarbamates to enhance their antitumor efficacy and other properties. A well-studied gold-containing anticancer drug is auranofin[1],[29],[35],[36],[37]. Known chemically as [2,3,4,6-Tetra-o-acetyl-1-thio-β-d-glycopyranosato(triethylphosphine)gold], it is a gold(I) compound containing phosphine and thiol ligands, traditionally employed as an antirheumatic drug[38]. Auranofin's mechanism of action involves inhibiting thioredoxin reductase, leading to increased reactive oxygen species (ROS) levels, oxidative stress, and ultimately, intrinsic apoptosis. Consequently, auranofin is effective at inducing apoptosis even in cisplatin-resistant cancer cells[29],[39].

Given that the gold atom in auranofin drug is responsible for inhibiting thioredoxin reductase, other gold-containing drugs also possess the capability to induce apoptosis in cancer cells. Gold atoms have a high affinity for thiol and selenol groups, enabling them to bind to selenium-dependent proteins like thioredoxin reductase, which is upregulated in certain cancers such as colorectal cancer, and is directly involved in tumor progression and survival. Inhibiting this enzyme can lead to cancer cell death[39].

However, inhibition of thioredoxin reductase is not the sole mechanism through which gold-containing drugs combat colorectal cancer. For instance, auranofin can also impede the ubiquitin-proteasome system, which is crucial for maintaining colon cancer cell homeostasis. This affinity is shared by other gold-containing drugs as well. Specifically, gold(I) derivatives disturb the redox balance, elevating ROS levels within the cell, and disrupting the mitochondrial membrane potential. This cascade of events activates the apoptosis pathway, resulting in controlled cell death, without affecting nucleic acids[29],[40].

3. ANTI- INFLAMMATORY DRUGS

Chronic inflammation, a prevalent characteristic in colorectal cancer (CRC), is

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instigated by immune cells along with their secreted factors such as cytokines and chemokines, reactive oxygen and nitrogen species (ROS and RNS), and various arachidonic acid derivatives, primarily synthesized via the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. This inflammatory milieu actively contributes to tumor progression by facilitating growth, proliferation, invasion, and resistance[42],[43],[44].

Given the pivotal role of inflammation in CRC development and advancement, numerous anti-inflammatory drugs have emerged as crucial tools in both prevention and treatment strategies. The predominant class of such agents is non-steroidal anti-inflammatory drugs (NSAIDs), which function by inhibiting COX enzymes, thereby impeding the production of arachidonic acid derivatives. For instance, aspirin has exhibited promising outcomes in CRC prevention, significantly reducing the risk by up to 50%. Another notable NSAID utilized in CRC-associated inflammation is sulindac, which has demonstrated efficacy in reducing colorectal cancer inflammation. Furthermore, the combination of sulindac with atorvastatin has shown inhibitory effects on tumor growth[41].

Despite their anti-inflammatory efficacy, NSAIDs are accompanied by adverse effects such as gastrointestinal ulcerations or renal impairment. Consequently, they are predominantly employed for CRC prevention in high-risk individuals, including those with Crohn's disease, ulcerative colitis, or familial adenomatous polyposis (FAP), rather than for treatment purposes. To mitigate these side effects, a newer class of NSAIDs specifically targeting cyclooxygenase-2 (COXibs) has been developed for both preventive and therapeutic interventions. Nonetheless, some COXibs, like rofecoxib, withdrawn from the market inn 2004, have been associated with cardiovascular toxicity. Among COXibs, celecoxib stands out as a significant therapeutic agent, demonstrating efficacy in CRC prevention and adenoma reduction, even in advanced stages. Notably, celecoxib exhibits minimal gastrointestinal adverse effects and does not pose significant cardiovascular risks[44].

Furthermore, efforts are underway to develop novel formulations aimed at further reducing known side effects. An example of such innovations is celecoxib microbeads, designed to selectively target colon cells. Currently, this formulation is undergoing testing using in vitro models, with subsequent studies in animal models anticipated in the near future. Moreover, celecoxib has been investigated in combination with curcumin, a compound derived from turmeric, yielding a synergistic anticancer effect[44],[45].

4. PROBIOTICS

Probiotics, defined as live microorganisms administered in adequate amounts, confer health benefits on the host. Among the extensively studied probiotics in colorectal cancer (CRC) treatment are lactic acid bacteria, including Lactobacillus, Streptococcus, Enterococcus, Lactococcus, Bifidobacterium, and Leuconostoc[46],[47],[48].
The protective function of probiotics stems from the hypothesis that dysbiosis is a primary contributor to CRC. Discrepancies in the microbial composition between CRC patients and healthy individuals suggest that probiotics might aid in restoring normal flora, thus mitigating CRC risk. To examine this hypothesis, Pala and colleagues conducted a study involving healthy volunteers to correlate yogurt consumption with CRC risk. Their analysis, which meticulously accounted for dietary patterns and lifestyle factors, revealed a direct association between yogurt intake and reduced CRC risk, even when considering factors such as yogurt consumption alone or in combination with other dairy products[49].

5. FUNCTIONAL FOODS

Reactive oxygen species (ROS) are oxygen molecules with a missing or unpaired electron, generated as part of cellular metabolism. At low concentrations, ROS serve physiological functions such as pathogen defense, triggering mitogenic responses, and participating in various molecular pathways[50]. However, an overabundance of these reactive compounds, often induced by environmental pollutants, tobacco, drug use, and other stressors, can lead to damage to cellular structures through lipid, protein, and DNA oxidation. Such scenarios have been implicated in various human diseases, including arthritis and cancer. Thus, maintaining and restoring redox balance is crucial for overall organismal health, making redox and antioxidant systems prime targets in functional food science. In this realm, polyphenols derived from natural sources have emerged as a promising strategy to combat oxidative stress[51],[52].

Polyphenolic compounds represent the most abundant secondary metabolites in plants. They are present in a wide array of foods, including cereals, legumes, oilseeds, fruits, vegetables, and beverages[53],[54],[55],[56]. Characteristically, polyphenols feature aromatic rings adorned with

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one or more hydroxyl groups, encompassing diverse classes of compounds from phenolic acids to vibrant anthocyanins, simple flavonoids, and complex flavonoids. Alongside their anticarcinogenic effects, polyphenols exhibit potent antioxidant properties, thus mitigating cancer risk[57]. Indeed, many polyphenols demonstrate chemoprotective, antiproliferative, antioxidative, and estrogenic/antiestrogenic activities, along with the ability to induce cell-cycle arrest or apoptosis and facilitate enzyme detoxification. Moreover, they modulate the host's immune system and cellular signaling pathways[58]. Notably, proanthocyanidins, flavonoids, resveratrol, tannins, epigallocatechin-3-gallate, gallic acid, anthocyanins, and various plant extracts have demonstrated protective effects in several cancer models[59].

II. CONCLUSION

Colon cancer is consistently listed among the most serious and life-threatening cancers worldwide, typically ranking within the top three.In conclusion, colon cancer remains a significant health challenge globally, ranking among the most prevalent and deadly cancers. However, advancements in research, early detection methods, treatment modalities, and public awareness have provided a beacon of hope in the fight against this disease. It is imperative that individuals prioritize regular screenings, adopt healthy lifestyle habits, and seek prompt medical attention for any concerning symptoms. By collectively addressing risk factors, embracing preventive measures, and supporting ongoing research efforts, we can strive towards reducing the burden of colon cancer and improving outcomes for patients worldwide.

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