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Review

Colon Cancer: Overview on Improved Therapeutic Potential of Plant-Based Compounds Using Nanotechnology

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Abstract: Colon cancer (CC) is the third most frequent neoplasm, with a considerably high mortality rate. Due to the side effects of conventional forms of CC treatment (surgery, chemotherapy, and radiotherapy), several studies have focused on the use of medicinal plant derivatives to provide a green therapy for CC; although phytochemicals have shown promising results against CC, translating the results obtained in vitro and in vivo to the clinical setting remains a challenge. Indeed, like other orally applied medicines, medicinal plant derivatives have to cross different physiological barriers to reach the CC microenvironment, which considerably limits their dose-dependent therapeutic efficacy. On the other hand, phytocompounds are not free from biopharmaceutical drawbacks, so novel strategies using nanoparticles (NPs) have been proposed to overcome the physiological barriers of the body and provide controlled release of actives of interest. Accordingly, the current review provides an overview and discussion on the predisposing factors to CC and conventional treatment, the use of medicinal plants in CC treatment, and the advantages provided by NPs in the treatment of CC.

Keywords: colorectal cancer; phytochemicals; therapeutic efficacy; physiological barriers; nanoparticles

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1. Introduction

Colon cancer (CC) is the second most lethal type of cancer, with an incidence of 4–5% in the Western population [1]. CC is a disorder that occurs in the colon or rectum caused by the uncontrolled proliferation of glandular epithelial cells. CC can be induced by hereditary, colitis-associated, sporadic, genetic, and environmental factors [2]. Inflammatory bowel diseases, such as ulcerative colitis (UC) and Crohn's disease (CD), are diseases that can lead to the development of CC. In fact, prolonged suffering from UC and CD increases the risk of developing CC by 2 to 3 times [3]. However, there are risk factors that, if modified, reduce the probability of developing CC, such as bad habits like smoking, poor diet, high alcohol consumption, physical inactivity, and overweight [4]. The development of CC takes

years: a polyp requires 10 to 15 years to form a cancerous tumor, so regular screening, polyp detection, and the removal of polyps at an early stage are crucial to avoid the development of CC [2].

Advances in the understanding of CC have led to the development of a wide variety of treatments, including endoscopy, surgical excision, radiotherapy, palliative chemotherapy, extensive surgery, and ablative therapies for metastases, which have successfully inhibited CC and extended the life expectancy of patients [5]. However, several studies have reported the adverse effects that these conventional forms of treatment can have; thus, the growing interest in the use of medicinal plants is due to their reduced side effects. Indeed, plants have biologically active metabolites, many of which have been naturally used and have been exploited industrially and traditionally for the treatment of diseases [6–8]. Their proper use and follow-up in terms of quality control is of worldwide relevance; thus, the World Health Organization (WHO) describes a list of plants with biological activity in order to identify them correctly (to avoid confusion when using their common names only) and lists adverse health effects. Also, it should be taken into account that 25% of modern drugs and 60% of antitumor agents come from natural products [9]. The treatment of cancer, with its varying etiology and population distribution, involves the investment of large amounts of capital in public and private health services. This is a reason for the study of the properties of plants as anticancer agents as a major line of scientific research. Therefore their potential use as adjuvants in cancer treatments is of great significance [10,11]. This research study investigates colorectal cancer, its risk factors and diagnosis, and standards treatments compared with new technologies. It also examines the potential of plant-derived compounds as safe and effective therapeutic alternatives; the significance of nanoparticles as delivery systems for active agents within the tumor microenvironment is also explored. This review highlights the importance of green alternatives combined with nanotechnology for the treatment of CC.

2. Search Methodology

To carry out this review, searches were performed in specialized electronic databases such as PubMed, SCOPUS, Google Scholar, and EMBASE for articles generally associated with colon cancer, as well as alternatives approaches to its treatment, emphasizing the use of vegetable derivatives and green nanoparticles. In total, 144 selected articles from 2000 to 2024 were selected. To carry out the search, different combinations of terms were used: (1) “colon cancer”, “epidemiology”; (2) “colon cancer”, “conventional treatment”; (3) “colon cancer”, “predispositions factors”; (4) “colon cancer”, “conventional treatments”, “phytocompounds/plant extracts”; (5) “colon cancer”, “Green nanoparticles/nanoparticles loaded with phytocompounds”; (6) “colon cancer + diagnosis”; (7) “colon cancer + treatment”. It should be noted that only articles published in English were selected. Review articles, theses, conference papers, letters to the editor, expert opinions, and full texts that were unavailable were excluded. Only articles written in English were selected, focusing on those that, due to the studies conducted or their relevance, represented the most significant advances in the field addressed in this article.

3. Colon Cancer Risk Factors

According to the WHO, cancers induced by genetic and environmental factors represent the diseases of the future, with CC being the most commonly diagnosed and globally responsible for more than 600,000 deaths per year. Indeed, the global incidence of CC is expected to increase by 60% between now and the year 2030, i.e., more than 2.2 million new cases, with mortality increasing by approximately 1.1 million [10,12–17]. Current epidemiological research suggests that lifestyle (eating habits such as high consumption

of red and processed meat and low intake of fruits and vegetables, smoking, alcoholism, obesity, and lack of physical activity), age (colon cancer is most frequently diagnosed in patients older than 50 years), family history, and personal history represent the main predisposing factors to CC, as shown in Figure 1 [18,19].

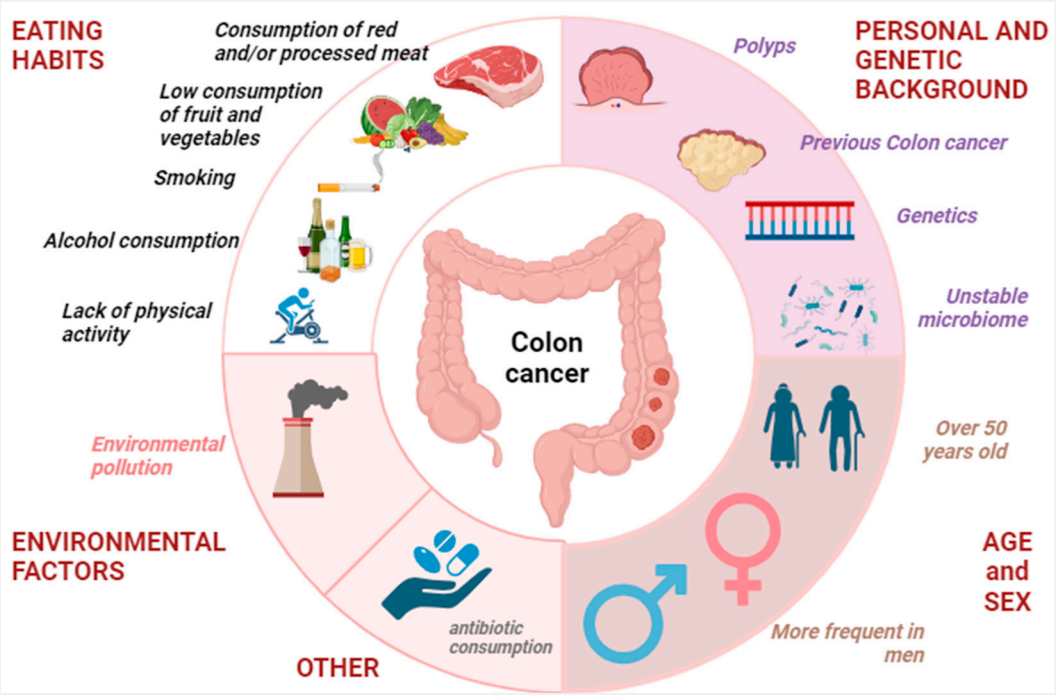


Figure 1. Risk factors for the development of colon cancer.

With an emphasis on lifestyle, it is reported that a high consumption of red meat and/or processed meat (e.g., sausages, bacon, ham, jerky, corned beef) cooked at high temperature (fried, grilled, etc.) could contribute to the induction of CC due to the production of polyaromatic hydrocarbons resulting from protein denaturation in the cooking process [20,21]. It should be noted that the International Agency for Research on Cancer states that the daily consumption of 50 g of processed meat may increase the risk of developing CC by up to 16%, compared to a 12% increase for a daily consumption of 100 g of unprocessed red meat [22]. In the same vein, Yu Min-Huang [23] and co-workers report that tobacco use may increase the risk of developing CC by 15 to 60%, while alcohol consumption is estimated to increase the risk of developing CC by 8 to 29% [24]. Based on the above, it is clear that meat consumption, as well as smoking and alcohol consumption, are associated with the risk of developing CC.

With respect to sex and age, although a high incidence of CC is reported in postmenopausal women, some research reports that the mortality rate from large bowel cancer is higher in men, being approximately 33% higher (mortality) in men than in women [25–27]. In the past 20 years, there has been an overall 15% increased incidence of this type of cancer in people aged 18–50 years, according to the National Cancer Database. Predominantly, increased incidence is occurring at the younger ages of 25–29 years ($\geq$68%) and 30–34 years ($\geq$71%). However, CC is more prevalent in the older population, with an average age of 67 years [26].

An important factor in the development of CC is personal history, in which a main factor is the history of polyps, specifically adenomatous polyps larger than 1 cm in diameter, which can increase the risk of developing the disease by 3.5 to 6.5% [28]. Along the same lines, family history is a determining factor in the development of cancer, i.e., the risk of

developing the disease is increased through autosomal dominant transmission if a direct relative has had a similar event in the past (i.e., father, mother, children, siblings) [29]. Accordingly, several countries, including Canada, Australia, and China, suggest that it is important to screen relatives of patients with adenoma as a preventive measure [30–32]. Although current studies do not quantify the impact of stress on the induction of colon cancer, it is worth noting that it could have a significant impact on health status, in particular on the development of CC. On the other hand, a high consumption of antibiotics could represent an important predisposing factor, as this significantly affects the intestinal microbiota, which plays an important role in protecting the large intestine. In the same vein, it is reported that patients with a history of infection with *Enterococcus faecalis*, *Streptococcus gallolyticus*, *Bacteroides fragilis*, *Clostridium septicum*, *Escherichia coli*, or *Fusobacterium nucleatum* may increase colorectal carcinogenesis, preventing, for example, intestinal epithelial cells from activating protective TGF-β/Smad [25,33]. It is also reported that toxins produced by *C. septicum* can promote metastasis and the spread of cancer cells to the colon [25]. Another mechanism of colon cancer is the genotoxic effect of cobalactin, a molecule produced by *E. coli* and other enterobacteria, which enhances tumor cell proliferation and promotes the tumoral activity of immune cells [25,34]. Of the exogenous factors that do not depend on the individual, it is important to emphasize that high exposure to environmental pollutants could also constitute a current or modern factor in this type of neoplasm [35,36].

4. Current/Innovative Diagnosis Techniques for Colon Cancer

Traditional CC Diagnosis Methods. The traditional method for diagnosing colorectal cancer (CC) is a complete endoscopy, considered the gold-standard technique for CC diagnosis. This is because, in addition to screening the colon, it allows for the removal of polyps that could develop into CC [37]. However, this procedure is costly and invasive, requiring an uncomfortable process for the patient and potentially causing serious complications [37]. This has led to the search for less-invasive, lower-cost, and safer alternatives, resulting in the development of diagnostic techniques for CC that meet these objectives.

Biomarkers. Biomarkers are a useful tool for CC diagnosis. The ideal biomarker should have high sensitivity and specificity, be low in cost, be safe, and be easy to measure [38]. Colorectal mucus, saliva, urine, and exhaled air are additional sources of biomarkers [39]. Biomarkers can be categorized based on their origin: blood or stool. Examples of blood-derived biomarkers include proteins, tumor DNA, cancer-derived cells, and miRNA, which are found in the bloodstream [38]. An important technique for detecting biomarkers in stool is the guaiac-based fecal occult blood test (gFOBT), which has been used for many years as it is inexpensive and non-invasive. This test identifies rectal blood loss greater than 10 mL per day, though its low sensitivity in the early stages of colorectal cancer and low acceptance rate are significant drawbacks [40]. Another current method is the use of volatile organic compounds (VOCs) as biomarkers. These are low-molecular-weight compounds (<1500 Da) with high vapor pressure at room temperature. They are naturally produced in the body, but the presence of cancerous cells alters VOC production, making them a useful tool for CC detection. They can be obtained from urine, stool, and breath [38].

The Role of Artificial Intelligence (AI). The development of artificial intelligence (AI) has significantly impacted the medical field with great success. In this context, AI has become a useful tool for screening, diagnosing, and treating CC [41]. In 2019, Wang et al. used AI algorithms and The Cancer Genome Atlas (TCGA) database to improve CC diagnosis, constructing four diagnostic models: cancer/normal, M0/M1, carcinoembryonic antigen test, and clinical stage (I-II, III-IV). The results demonstrated that the proposed model has strong predictive abilities, robust stability, and notable accuracy and sensitivity values [42]. In the same year, Zhang et al. proposed a sensitive, rapid, and low-cost

method for detecting the fibrosarcoma mutation gene using near-infrared spectroscopy in conjunction with an artificial neural network. This model showed 100% sensitivity, 87.5% diagnostic specificity, and 93.8% accuracy, making it a promising tool for diagnosing CC through BRAF V600E gene mutations [43]. In another study, Lia et al. evaluated the performance of an artificial intelligence (AI)-assisted image classifier to determine the feasibility of the curative endoscopic resection of large colonic lesions. The image classifier was trained with 8000 endoscopic images of large colonic lesions. The overall accuracy of AI in predicting curative resection was 85.5%. Narrow band imaging (NBI) images demonstrated significantly higher accuracy and area under the receiver operating characteristic curve (AUROC) compared to white light imaging (WLI). AI outperformed junior endoscopists in terms of accuracy and AUROC [44].

The search for non-invasive, low-cost, and highly sensitive CC diagnostic alternatives continues to be a key area of research, and with the implementation of AI, this area is expected to see significant advancements in the coming years.

5. Treatments of Colon Cancer

Conventional treatment for colon cancer varies according to cancer stage, the patient's health, and the objective of the treatment. In general, treatments start with primary surgical therapy, followed by adjuvant treatments such as chemotherapy and radiation therapy [45].

5.1. Surgery Therapy

Surgical therapy is the resection of part or all of the colon, polyps, or lymph nodes, and varies depending on the stage of cancer. In stages 0 to III, there is little possibility of metastasis; thus, the treatment may take the form of an endoscopic resection of the tumor and nearby lymph nodes with the patient kept under surveillance [46]. However, if endoscopic resection is impossible or the cancer is deeply invasive, then surgical resection must be followed.

In stage IV, cancer cases are frequently accompanied by a long distal spread from the primary tumor, known as metastasis; thus, an individualized treatment must be followed. For example, the 2021 American Society of Colon and Rectal Surgeons established [47] that in cases of liver metastasis, it is strongly recommended to start chemotherapy in order to attempt to make unresectable colon cancer resectable. This is supported by clinical evidence [47]. Using chemotherapy as a first-line treatment when there is metastasis is a common regimen for slowing down cancer cell growth [48]. When other organs experience metastases, such as in the liver, peritoneum, and lungs, the resection of the metastases is strongly recommended [46]. After resection, patients must undergo regular follow-up observation, including endoscopic or colonoscopy examinations, computed tomography (CT) examinations, and measurements of tumor biomarkers [48]. From 2000 to 2004, the curative resection rate, calculated from the JSCCR cancer registry, was 99.1% vs. 83.6 at stage I vs. III, respectively [46].

During surgery, some risks include bleeding, infection, and blood clots [45]. Thromboembolic events have been reported at a cumulative risk of 1.57 at 1-year post-resection (95% CI 1.50–1.65) [45]. In the first days after the surgery, patients may not be able to eat as before due to the effect of the anesthesia, or if they have not handled the surgery well [4]; therefore, nausea and vomiting may occur, so special liquid diets should be introduced by specialized nutritionists.

5.2. Chemotherapy

Chemotherapy is a method used for cancer treatment, involving a single drug or a combination of two or more drugs delivered orally, intravenously, subcutaneously, intra-

muscularly, intrathecally [49,50], or topically, presenting several mechanisms of action leading to efficacy [51]; however, chemoresistance is one of the main concerns in colon cancer treatment [52].

Adjuvant chemotherapy is recommended if there is a higher risk of cancer recurrence, such as in the presence of lymph node metastasis or cancer cells that could not be removed and remain in the organs. The timing for adjuvant chemotherapy is strongly recommended to be within 8 weeks of colon resection [47], although typically it is delayed by 2 weeks post-surgery [53]. A significantly higher 5-year overall survival has been shown in patients receiving postoperative chemotherapy (94%) than in those with stage II colon cancer ($p = 0.01$) without adjuvant therapy (84%) [54].

The disadvantages of chemotherapy (Table 1) include its toxicity, as it may affect other tissues [53]. The main toxicity effects have been reported as fatigue (80%); those on the digestive system, such as loss of appetite (76%), diarrhea (72%), and constipation (28%) [55]; affection of the hair follicles; damage to reproductive cells, resulting in infertility; cognitive effects, including memory loss and lack of concentration; and damage to stem cells in the bone narrow, which may lead to mild or moderate leukocytopenia or severe haematotoxicity [56]. Other side effects that could develop during treatment, or months or years after chemotherapy, include heart problems, damage to the lungs and kidneys, and an increased risk of cancer recurrence [57]. Peripheral sensory neuropathy has also been reported, lasting for 3 years in 24.3% of stage III patients that followed a 6-month chemotherapy treatment [58].

Table 1. Chemotherapy agents against colon cancer.

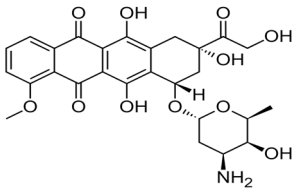
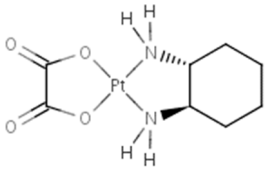
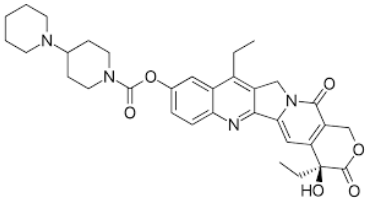
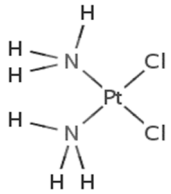
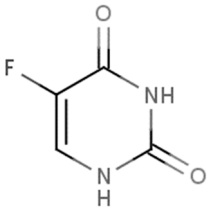
Chemotherapy Agents	Drug Structures	Disadvantages
Doxorubicin		It is associated with cardiac side effects; the most common drawback is the development of heart failure.
Oxaliplatin		Side effect profile of oxaliplatin regimens.
Irinotecan		Acquired resistance to irinotecan in patients with advanced CC is still a major clinical issue.
Cisplatin		Its toxicity and acquired resistance limit its clinical applicability.

Table 1. *Cont.*

Chemotherapy Agents	Drug Structures	Disadvantages
5-Fluorouracil (5-FU)		The clinical use of 5-FU is limited due to the development of drug resistance.

This table was made based on data from Gavrilas et al., 2022 [58].

5.3. Radiation Therapy

Radiation therapy consists of a high-energy X-ray beam delivered to downsize or shrink the tumor [59], although it is more often used to treat rectal rather than colon cancer [59]. Radiotherapy is used as palliative care to relieve symptoms and prolong the survival time of patients with unresectable colorectal cancer [46], and may decrease the need for colostomy [59,60].

There are two main radiotherapy techniques: three-dimensional conformal radiation (3DCRT), which uses a three-dimensional imaging technique to simulate the tumor, and intensity-modulated radiation therapy (IMRT) [61], an advanced version of 3DCRT [59]. Radiation therapy is also considered an adjuvant therapy and could be delivered as preoperative, intraoperative, or postoperative radiotherapy [46].

Palliative care radiation therapy has the purpose of relieving symptoms such as pain, hemorrhage, and bowel dysfunction caused by tumors (Japanese); however, radiation at fractionated levels of 25 Gy to 50 Gy could also result in induced delayed toxicity. Some patients' side effects include fatigue, skin issues, diarrhea, proctitis, bladder toxicity, and sexual dysfunction [62]. In addition, resistance to radiotherapy is also a disadvantage. As cells become radioresistant over time, several conditions may lead to inadequate treatment, such as hypoxia in the tumor microenvironment and the presence of tumor-associated macrophages and cancer-associated fibroblasts, which release growth factors promoting the survival of cancer cells [61].

5.4. Other Therapeutic Strategies for CC

5.4.1. Monoclonal Antibodies

As explained above, CRC is an extremely complex and diverse disease at the molecular level, characterized by the presence of recurrent mutations that frequently result in resistance to conventional treatments. Although significant progress has been made in identifying therapeutic targets and creating monoclonal antibodies, significant challenges remain in the treatment of CC [63]. Monoclonal antibodies (mAbs) are proteins designed to specifically target antigens on tumor cells, allowing them to be marked for destruction by the immune system or to block growth receptors. Since the introduction of rituximab in 1997, mAbs have played a crucial role in the treatment of cancer. As of 2023, the US FDA has approved 79 therapeutic mAbs, of which 48 are indicated for the treatment of cancer [64]. For example, cetuximab and panitumumab target EGFR, while bevacizumab targets VEGF. Ramucirumab inhibits both VEGF and its receptor. Rituximab, ofatumumab, tositumomab, and ibritumomab tiuxetan are used to target CD20. Other examples include trastuzumab, pertuzumab, and emtansine, which target HER2/neu. Alemtuzumab binds to CD52, and brentuximab vedotin targets CD30. Ipilimumab binds to the CTLA4 molecule. In addition, monoclonal antibodies are in development that target new or older targets, but have not yet been approved for use in patients [65]. However, in many cases, patients

treated with therapeutic antibodies eventually relapse or develop progressive disease. This suggests that tumors possess or acquire intrinsic resistance mechanisms that allow them to escape treatment. Drug resistance is a significant challenge in cancer treatment; it is not limited to chemotherapeutic drugs, and also affects antibody-based therapies. Tumors treated with antibodies may evolve in ways that evade the signaling associated with a specific receptor or develop variants that do not express the target antigen [66].

5.4.2. Photodynamic Therapy

Photodynamic therapy involves the use of a drug that is activated by light exposure, called a photosensitizer or photosensitizing agent, to destroy cancer cells. The light is provided by a laser or another source, such as light-emitting diodes, known as LEDs [67]. Although several studies report significant advantages in treating cancer with this technique (e.g., reduced invasiveness, low toxicity to healthy cells and tissues, overcoming multidrug resistance barriers, activation of the immune response against cancer), it is important to note that it presents certain challenges. Specifically, these include the low water solubility of photosensitizers, difficulty in treating deep tumors due to limited light penetration, and low effectiveness in tumors with low oxygen levels [68].

5.4.3. Cryotherapy

This is a treatment that uses extremely low temperatures to destroy cancer cells, also known as cryosurgery or cryoablation. This procedure can be performed in different ways, depending on the location of the cancer in the body [66]. For skin cancers, liquid nitrogen is applied directly to the affected area, while for internal cancers, a probe called a cryoprobe is used, which is inserted near or into the abnormal cells and connected to a supply of argon gas to freeze the cancer cells. It should be noted that, before performing cryotherapy, it is essential to perform a biopsy to characterize the tumor. Tumor types that are highly invasive, such as poorly differentiated adenocarcinoma and signet ring cell carcinoma, are not recommended for this treatment, while moderate- or high-grade adenocarcinomas are more suitable. In addition, tumor size influences the effectiveness of the treatment. The diameter of the ice ball is required to increase as the tumor size increases to ensure complete ablation [69].

To achieve cell necrosis, cryotherapy generally requires temperatures below −40 °C. However, tumor cells are usually destroyed when the temperature drops below −25 °C. The ice ball formed during treatment must extend at least 5 mm beyond the edge of the tumor to be effective. There are risks associated with cryotherapy, such as significant bleeding upon thawing of the ice ball and systemic response related to thermal injury. In addition, cryotherapy is not recommended in cases where the tumor has invaded adjacent structures or in the presence of lymph node metastasis, as this may increase the rate of tumor recurrence [65].

In summary, the use of monoclonal antibodies and cryotherapy is a treatment option that may be effective for certain types of cancer, but its application must be carefully evaluated based on the characteristics of the tumor and the patient's condition.

5.4.4. Immunotherapy

Immunotherapy aims to restore the innate antitumor immune response by revitalizing and maintaining the tumor-specific immune pathway [70,71]. In 2024, Chalbi et al. conducted a Phase 2 study investigating the efficacy and safety of neoadjuvant immunotherapy with nivolumab and ipilimumab in patients with mismatch repair-deficient (dMMR) colon cancer. Of the 115 enrolled patients, 113 underwent timely surgery, and 109 showed a pathological response, including 105 with a major response and 75 with a complete response. No patients experienced recurrence during the median follow-up period of 26 months.

The treatment demonstrated an acceptable safety profile, with five patients experiencing grade 3 or 4 immune-related adverse events. These results suggest that neoadjuvant immunotherapy may be a promising approach for patients with dMMR colon cancer [72]. In the same year, Yu et al. investigated the correlation between αvβ6 and PD-L1 expression in colon cancer tissues. The results demonstrate that αvβ6 mediates immune escape by upregulating PD-L1 through the ERK/MAPK pathway. αvβ6-positive tissues exhibited increased PD-L1 expression, and the inhibition of αvβ6 reduced PD-L1 expression. Furthermore, αvβ6 suppressed CD8+ T-cell infiltration and granzyme B expression in CD8+ T cells. Mice engrafted with αvβ6-expressing colon cancer cells showed an unsatisfactory response to anti-PD-1 therapy. These results suggest that αvβ6 mediates immune escape in colon cancer and could serve as a marker for anti-PD-1 therapy efficacy. αvβ6 may be a valuable biomarker for predicting response to immunotherapy [73]. Although this therapy has shown promising results in the treatment of various cancers, it has been reported that only a minority of patients exhibit a positive response. Indeed, the efficacy of immunotherapy can vary, depending not only on the patient, but also on the immune characteristics of the cancer [58,71], which lowers the reliability of this type of therapy.

5.4.5. Personalized Therapy

Personalized therapy emphasizes the adaptation of medical treatment to the individual characteristics of the patient, with the aim of discriminatingly affecting cancer cells; that is, personalized or targeted therapy is designed to interfere with specific molecular targets that are involved in the growth, progression, and spread of cancer [71]. In fact, thanks to the emergence of new genomic technologies, the identification of signaling pathways important for the permanence and proliferation of cancer cells has been facilitated. According to several authors, these signaling pathways dictate the malignant phenotype, the immune response, and the tumor microenvironment, influencing the efficacy of therapeutic therapies [57,58]. Therefore, by focusing on them, personalized therapy can limit the growth and spread of tumors in a specific way, minimizing the side effects of the dosed drug [71]. With an emphasis on colon cancer, the main molecular signaling pathways associated with its tumor microenvironment include the Wnt/β-catenin, RAS/RAF/MEK/ERK, phosphoinositide 3-kinase (PI3K)/AKT, and transforming growth factor beta (TGF-β) pathways [71]; so, the main personalized therapies used to combat CC are implemented with the aim of blocking one of these signaling pathways. On the other hand, it is important to mention that, although personalized therapies represent precise and effective alternatives to combat CC, their application in clinical settings may present important limitations, such as the development of resistance mechanisms such as the compensatory upregulation of Wnt ligands and receptors [74], or resistance to MAPK pathway inhibitors; it should be noted that the development of extrinsic resistance to anti-EGFR therapies has been reported in more than 40% of patients exposed to such therapy [75]. These limitations in personalized therapies represent an important warning to encourage the search for other reliable alternatives that are capable of overcoming biological barriers between individuals.

6. Medicinal Plants in the Prevention and Treatment of Colon Cancer

The use of plants has accompanied mankind since the dawn of civilization; indeed, there are records of the use of plants in papyri and codices, and above all, their use is described in oral traditions. This predilection goes hand in hand with the fact that they offer to improve the quality of life of human beings, as they are used as raw materials in food, buildings, clothing, and as active ingredients important for health [76]. At present, the biological activity of a large number of plants is known; as inducers of apoptosis, they reduce the expression of important proteins in the phases of cell division, such as

PI3K, Bcl-2, and Bcl-XL, and also promote decreases in nuclear cell proliferation, as reflected in the Nuclear Cell Proliferation Antigen (PCNA), cyclin A, cyclin D1, cyclin B1 and cyclin E [77]. This is relevant to CC treatment. Nelson et al. (2020) mentioned that about 50% of chemotherapy treatments consist of drugs that are primarily related to plant metabolites that have been isolated and subsequently modified, indicating that they are an important source of new anticancer pharmacological agents [78]. The most important biologically active compounds derived from plants that are known as phytochemicals belong to several families of organic compounds, including flavonoids, polyphenols, carotenoids, anthocyanins, saponins, polysaccharides, triterpenoids, alkaloids, glycosides, phenols, and terpenes (Table 2). Resveratrol, genistein, quercetin, caffeic acid, epigallocatechin, luteolin, rosmarinic acid, carnosic acid, emodin, eugenol, kampferol, oleanolic acid, and β-sitosterol have demonstrated activity against CC [79–81]. As the main in vitro models for testing biological activity against colon cancer, cell line models such as HT-29, HCT116, and CaCo-2 are used. For example, in HT-29, extracts of *Allium sativum* and *C. sinensis* (root and leaves, respectively) induced cell apoptosis via two pathways. The ethanolic extract of *A. sativum* induced cell apoptosis via PI3K/Akt at concentrations of 20, 50, and 100 mg/mL. In CaCo-2 cells, antiproliferative activity has been demonstrated by blocking the G2/M phase with methanolic extracts of *V. vinifera* at a concentration of 365 mg/g (important compounds are catechin, epicatechin, quercetin, and gallic acid) [81–85]. As for HCT116 cells, studies on aqueous extracts of American ginseng (Panax quinquefolius) at concentrations of 0–2.0 mg/mL induced cell-cycle arrest at different control points. The important compounds involved were ginseng and its derivatives: ginsenosides and polysaccharides [86]. In terms of animal models, the most widely used is the murine model, where the effects of medicinal plants and their extracts have been found to be the same in vitro [81].

Table 2. Main plants with compounds showing biological activity against colon cancer and their clinical study phase.

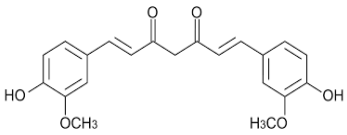
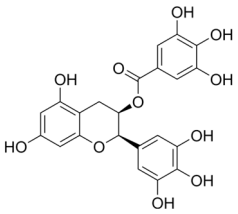
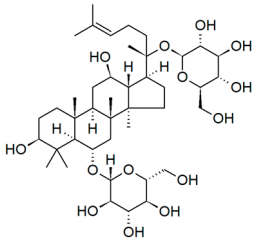
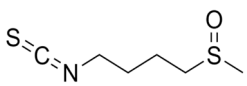
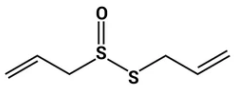
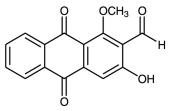
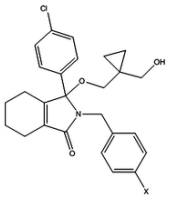
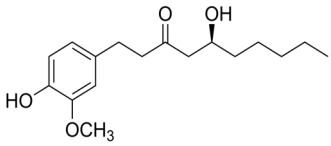
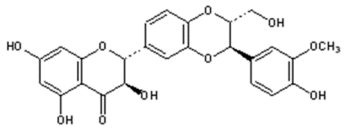
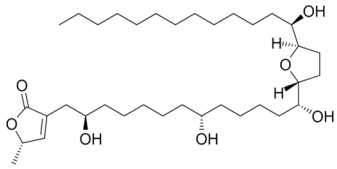
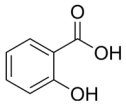
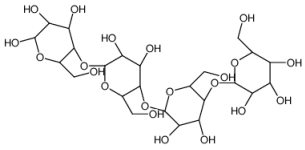
Plant	Metabolite	Chemical Structure	Compound Group	Clinical Study Phase	Reference
Curcuma longa	Curcumin		Polyphenol	Phase II and III	[84]
Camellia sinensis	Epigallocatechin gallate (EGCG)		Flavonoid	Phase I and II	[85]
Panax ginseng	Ginsenosides		Triterpene saponins	Phase I and II	[86]
Brassica oleracea	Sulforaphane		Isothiocyanate	Phase II	[87,88]

Table 2. *Cont.*

Plant	Metabolite	Chemical Structure	Compound Group	Clinical Study Phase	Reference
Allium sativum	Allicin		Organosulfur compound	Preclinical, Phase I	[89]
Morinda citrifolia	Damnacanthal		Anthraquinones	Preclinical	[90]
Uncaria tomentosa	Pentacyclic oxindole alkaloids		Alkaloids	Preclinical	[91]
Zingiber officinale	Gingerol		Phenols	Preclinical, Phase I	[92]
Silybum marianum	Silymarin		Flavonolignan	Phase I and II	[93]
Annona muricata	Acetogenins		Annonaceae	Preclinical	[94]
Salix alba	Salicylic acid		Phenols	Preclinical	[95]
Aloe vera	Glucomannan		Polysaccharide	Preclinical	[96]

As a mechanism of action, phytochemical compounds play an important role in some metabolic pathways. Essential nutrients, such as vitamins and minerals, as well as some sulfur-containing amino acids, such as cysteine, modulate mitochondrial activity in cells and may also protect cells from oxidative damage due to their antioxidant potential [97]. The most important metabolic pathways in carbohydrate metabolism, as well as the formation of amino acids with aromatic rings, coenzymes, and high-energy molecules—such as NAD-, FAD-, and Coenzyme A, among others, in which phytochemicals such as epigallocatechin and genistein are regulated—are the pentose phosphate pathway, the Krebs cycle, and lactic acid production, which promote apoptosis and attenuate tumor growth.

The use of plants for the development of new drugs is of global importance, as the cost–benefit they offer is much better than that of patent medicines due to their availability and low purchase price. It is necessary to take into account that, in Mexico, 13% of cancer

cases occur in women of reproductive age and that more than 50% of young male survivors want to become fathers after treatment [98]. For example, the average cost of breast cancer care per patient is MXN 99,280.36 (USD 5230.78) and MXN 148,023.60 (USD 7789.92) for the early and advanced stages, respectively [99]. Thronicke et al. (2020) conducted a study on 118 stage 4 lung cancer patients who were divided into two groups—one with conventional chemotherapy treatment and the second with a combination treatment of conventional treatment with the addition of the plant *Viscum album*—and concluded that the combined use of chemotherapy and *V. album* was clinically effective and comparatively cost-effective (MXN 65,783.60; EUR 3586 difference) to chemotherapy alone in the patient sample, analyzed from a hospital perspective [100]. This gives us a clear picture of the advantages in terms of cost-effectiveness and lower costs compared to allopathic medicine. Another point is that it is available without prescription and, as already mentioned, the combination with conventional medicine is another of its advantages, as well as the fact that traditional medicine has the potential to cure most diseases (Table 2) [101]. Research on these medicinal plants gives confidence in their use, as abuse or ignorance of their compounds can cause serious damage to health. Phytopharmaceuticals such as acetylsalicylic acid, digitalin, and vincristine, among others, have been successfully administered in a favorable way; therefore, we urge researchers to continue with the development of research on the biological activity of plants before suggesting their use [102,103].

7. Green Nanoparticles Against Colon Cancer

7.1. Types of Nanoparticles Used in Colon Cancer Treatment

Nowadays, the role of nanotechnology in the administration of drugs with specific action at a specific site and target is well known, with an improved success rate compared to conventionally formulated actives. The development of nanoformulations includes different bases, such as organic bases (liposomes, polymeric, micelles, dendrimers, etc.) and inorganic bases, as the coating material for the administration of nanodrugs (Table 3) [104,105]. To counteract CC, several studies widely report the use of silica nanoparticles, gold nanoparticles, silver, zinc oxide, liposomes, polymeric, micelles, and dendrimers (Table 3) due to their potential advantages in active dosing in the CC microenvironment [104–108].

Table 3. Types of nanoparticles most commonly used in colon cancer therapy.

Types of Nanoparticles	Structural Components	Possible Advantages	Possible Disadvantages	References
Metallic Nanoparticles	Silver, gold, silica, iron oxide, etc.	Highly toxic to cancer cells; high contact surface due to its nanometric size; ease of interaction with cellular systems due to its size and surface charge; moldability of its shape.	Induce apoptosis in healthy cells, non-specific release, etc.	[105]
Liposomes, Micelles	Phospholipids and cholesterol	Accumulation in tumor cells; ability to incorporate hydrophilic or hydrophobic substances; the phospholipid bilayer facilitates interaction with cell membranes; low toxicity in healthy cells.	Limited physicochemical stability, etc.	[106]
Polymeric Nanoparticles	Polymers	Capacity to incorporate hydrophilic or hydrophobic substances; controlled release of the active ingredient; facilitating interaction at the cellular level; pH-dependent; capacity to bind ligands to the surface to offer specific delivery of the active ingredient.	Variability in loading kinetics, stability problems during storage, are only spherical in shape, etc.	[102,106,108]

7.2. Nanoparticles Loaded with Plant Derivatives Against Colon Cancer

While medicinal plants have proven benefits in the prevention and treatment of human diseases such as colon cancer, the application of phytocompounds in the clinical setting

remains a challenge due to their solubility and stability [107], which considerably affects the bioavailability of these compounds at the desired site, as well as their dose-dependent efficacy. However, the use of nanotechnology in phytotherapy could revolutionize the delivery system of plant compounds, allowing their therapeutic efficacy to be efficiently harnessed through their controlled release at the desired site [108]. With an emphasis on CC, several studies have shown that the formulation of phytocompounds in NP systems increases their antitumor potential (Table 4) [109]. In 2016, You et al. conducted a study on silver nanoparticles loaded with Vitex negundo extracts; evaluated against HCT15 strain human DC cells, it was found that this formulation possessed an IC50 of 20 μg/mL at 48 h. The possible mechanism of inhibition is through the suppression of cell growth and the arrest of the G0/G1 phase, which reduces DNA synthesis and induces apoptosis [109]. Following the same order of ideas, in vitro studies have shown that revelatrol and quercetin formulated in nanoparticles confer considerably greater anticancer activity than conventional chemotherapeutics due to the increase in their bioavailability and absorption in situ. Indeed, the in vitro study by Boxu et al. in 2021 found that a micronized formulation of resveratrol had a Cmax of 8.51 μM at a Tmax of 1.5 h, which is an encouraging value with respect to the chemotherapeutic potential of resveratrol [110,111]. Additionally, they found that quercetin nanoemulsion, prepared using different oils by high-pressure homogenization, had a two-fold lower IC_{50} of 18 μM for inducing cytotoxicity in the colon cancer cell lines HCT-116 and HT-29 [112]. In 2022, Cristina Mesas evaluated calcium phosphate NPs loaded with esculetin and euphorbetin (curcumin derivatives), obtained from the seeds of *Euphorbia lathyris*, and proved this formulation to be non-toxic to human blood cells, in addition to presenting cytotoxic selectivity against DC cells (T-84 cells) with an IC50 of 71. 42 μg/mL and showing lower cytotoxicity against healthy cells (CCD8) with an IC_{50} of 420. 77 μg/mL. A possible mechanism of action is through the inhibition of carbonic anhydrase and autophagy. In this same study, an in vivo study of loaded NPs in mice was conducted. The mice were induced with CC via two different models, and the results showed a 62% reduction in tumor volume and a significant decrease in the number and size of polyps [113]. According to the work published by Mostafa and his collaborators, NP-PLGA loaded with a powdered cranberry nutraceutical extract had anticancer activity against CC. Indeed, in this study, it was proven that a formulation of blueberry extract in the NPs enhanced their therapeutic efficacy due to an increase in permeability, increasing from 2.19 to 3.10 times compared to the crude extract; on the other hand, this presented significant inhibition in terms of the vascular endothelial growth factor (VEGF). According to these studies, it can be concluded that the use of NPs loaded with plant extracts is a useful tool for the formulation of drugs, enhancing efficacy and efficiency in the treatment of CC [114].

As for in vivo tests, several studies have proven the therapeutic superiority of nanoformulated phytocompounds over free phytocompounds. Following this same line of thought, Gou and his collaborators have shown that, although in in vitro studies there is no significant difference in toxicity results between the free and nanoformulated active ingredients of these compounds, there is pharmacological superiority in vivo studies; in fact, their study entitled "Curcumin-loaded biodegradable polymeric micelles for colon cancer therapy in vitro and in vivo" proved that a group of rats treated with curcumin micelles had a significantly lower tumor weight than those treated with free curcumin, reflecting a stronger antitumor activity in vivo. However, neither treatment presented significant differences in in vitro tests [115]. Furthermore, subpopulations of CD44(+)/CD24(+) tumor cell growth were inhibited by curcumin micelles in vivo through the following mechanisms: the prevention of tumor cell proliferation and angiogenesis; the promotion of apoptosis [115–117]. Additionally, based on an in vivo pharmacokinetic study on a rat model,

Xiang et al. showed that curcumin nanoparticles have an increased half-life by 6 times compared to free curcumin, due to the improvement of the bioavailability of the active ingredient at the desired site [118].

In 2020, Aboulthana and his collaborators verified that *Croton tiglium* nanoextract allows the biochemical and molecular restructuring of azoxymethane-induced colon cancer by regulating the expression level of the TP53 and APC genes [119].

Table 4. Nanoparticles loaded with plant extracts: nosology, mechanism of action, and therapeutic effects.

Nosology	Type of Nanoparticles	Model	Proposed Mechanism of Action	Therapeutic Effect	References
Euphorbia lathyris : laxative	Calcium phosphate NPs	In vitro assay: A CELL proliferation assay was performed on T84 (human colon cancer) and MC38 cell lines. The cells were seeded in 48-well plates at a density of 4×10^3 cells/well. After 24 h, the cells were exposed to calcium phosphate NPs at different concentrations. Finally, the optical density (OD) was measured at 492 nm, and the percentage of cell survival was calculated. In vivo assay: Female C57BL/6 mice (18–20 g, 6 months old) were used. The tumor was induced subcutaneously using MC38 cells, and the treatment with calcium phosphate NPs was administered intraperitoneally for 3 days (seven doses). The tumor volume was measured at the end of the treatment.	Reduction in carbonic anhydrase activity and induction of autophagy likely activated through the formation of autophagic vesicles, potentially driven by modulation of key autophagy-related proteins, including upregulation of LC3-II and Beclin and downregulation of ATG3 and p62.	Reduction in induced CRC volume by 62% and a decrease in the number and size of polyps.	[110,113]
Vaccinium corymbosum: antioxidant and anticancer properties	PLGA nanoparticles surface-modified with chitosan	In vitro: The MTT cytotoxicity assay was performed against CC HT-29 cell lines. The cells were seeded in 96-well plates and incubated for 72 h. Absorbance was measured at 570 nm and the IC50 was calculated. Ex vivo: A permeability study of the three formulations presented by Mostafa was conducted.	Inhibition of vascular endothelial growth factor and the STAT-3 protein; stimulation of the caspase-3 protein.	No data.	[114]
Argemone mexicana: analgesic, diuretic, tumors, inflammation, rheumatism, leprosy	Golden nanoparticles	In vitro: The cytotoxicity study of the loaded nanoparticles was conducted using the MTT assay on HCT colon cancer cell lines. The cells were exposed to the loaded nanoparticles 24 h after incubation, followed by an additional 4 h of incubation, and the absorbance was measured at 560 nm. Additionally, a DNA fragmentation assay was performed to evaluate genotoxicity, and a caspase-3 assay was conducted to examine apoptosis.	Nanoparticles can exert antiproliferative and genotoxic effects by suppressing cell growth and inducing apoptosis through mitochondrial membrane potential disruption, leading to extensive nuclear DNA fragmentation with double-strand breaks and resulting in a time-dependent upregulation of caspase-3 activity. This was confirmed by Western blot analyses, which revealed an increase in p53 and caspase-3 expression, verifying the activation of the intrinsic apoptotic pathway mediated by p53 and executed by caspase-3.	No data.	[117,118]

Table 4. *Cont.*

Nosology	Type of Nanoparticles	Model	Proposed Mechanism of Action	Therapeutic Effect	References
Croton tiglium: used for the treatment of constipation	Silver nanoparticles	In vivo: CRC was induced in 36 adult Wistar rats through a single injection of azoxymethane (AOM), and the induction process was accelerated with dextran sulfate sodium (DSS). The nano-extract was administered orally for 21 days.	Prevention of anti-Keratin 20 antibody expression. Regulation of the genetic expression of the TP53 and APC genes.	Minimization of inflammatory reactions. Regulation of molecular and biochemical alterations caused by cancer induction through AOM.	[119]
Albizia lebbeck: abdominal tumors, cough, ocular conditions, pulmonary conditions	Golden nanoparticles	In vitro: The cell viability study of the nanoparticles was conducted using the MTT assay on the HCT-116 cell line. The cells were incubated for 24 h in 96-well plates, after which the nanoparticles were added and the incubation continued for an additional 24 h. Absorbance was measured at 560 nm. Additionally, assays for ROS, caspases, and Western blot analysis were performed.	Induction of apoptosis through ROS production and a reduction in mitochondrial membrane potential facilitated cytochrome c release and triggered caspase-9 and caspase-3 activation, leading to DNA fragmentation. The latter was reinforced by the upregulation of pro-apoptotic proteins Bax and Bid and the downregulation of anti-apoptotic Bcl-2.	No data.	[117,120, 121]

According to the above, it is evident that nanoformulations derived from medicinal plants have demonstrated their potential in vitro and in vivo against colon cancer. These results have led to interest in transferring them to the clinical setting for human applications; however, it is important to undergo preclinical testing to establish safety measures at the time of application in humans. Following this same line of thought, in a phase II clinical trial on 44 patients, it was reported that first-line treatment with bevacizumab/FOLFIRI and nanoparticles facilitated long-term survival with acceptable toxicity results [122].

These results prove the viability of the alternative use of NPs in the active administration system for the prevention and/or treatment of CC.

7.3. Application of Nanoparticles to Combat Cancer Stem Cells

Although cancer stem cells (CSCs) represent a minor population of cells within the tumor microenvironment, they have been reported to play critical roles in tumor initiation, propagation, and regeneration, particularly in CC [123]. Indeed, they are characterized by their ability to self-renew, differentiate into other types of tumor cells, and exhibit tumorigenicity. Therefore, they play a crucial role in metastasis, drug resistance, and cancer relapse (pharmacological resistance)) [124]. According to several authors, the key factor in addressing these issues lies in exposing CSCs to sufficient pharmacological concentrations; that is, active agents should be dosed using technology that enables them to overcome the barriers of the tumor microenvironment, specifically recognize cancer cells, and facilitate their controlled release. To achieve this, several researchers propose the use of polymeric nanoparticles to dose active agents, such as those derived from medicinal plants (e.g., polyphenols, etc.) [125], due to their excellent pharmacokinetic properties and the possibility of conjugating them (on their surface) with antibodies or specific ligands for CSCs. As reported by Lazer and colleagues, nanoparticles of chitosan conjugated with hesperetin and functionalized with folic acid and DCLK1 have an IC_{50} of 4.8 μM in colon cancer cells. The same study found that these nanoparticles have the ability to induce apoptosis and inhibit the migration and invasion of colon cancer cells. Additionally, they found that this

nanoparticle system can reduce the expression of CSC markers such as DCLK1, STAT1, and NOTCH1, compared to the same non-functionalized nanoparticle system [126].

8. Physiological Limitations in the Therapeutic Scope of Treating Colon Cancer with Orally Administered Drugs

The colon is an organ of excellence, facilitating the absorption of water and minerals, and the removal of waste from the body; therefore, an alteration in its function could influence the process of the digestion of food, thus generating a food deficit and possible functional problems in other organs, such as the liver [127]. Among the chronic enemies of the colon, there is colorectal neoplasia, which can destroy its strength by altering its epithelial cells, intestinal mucosa, and pH, among others [4,23,85–100]. Indeed, after the induction of colorectal carcinoma, gradual mutations of critical genes in neoplastic cells give them survival and developmental advantages over epithelial cells [128]. In other words, once induced, cancer cells generate an environment that facilitates their development and spread exponentially faster than normal cells.

The characteristics of the CC microenvironment include high fibrosis, a low number of immune cells, and a considerable number of cancer cells. Indeed, tumor cells are reported to promote the aggression of fibroblasts, the migration of cells responsible for the immune reaction (Figure 2), and the formation of vascular networks through the secretion of cytokines [33]. Together, these activities contribute to the formation of the tumor environment that sustains and promotes tumor cell survival.

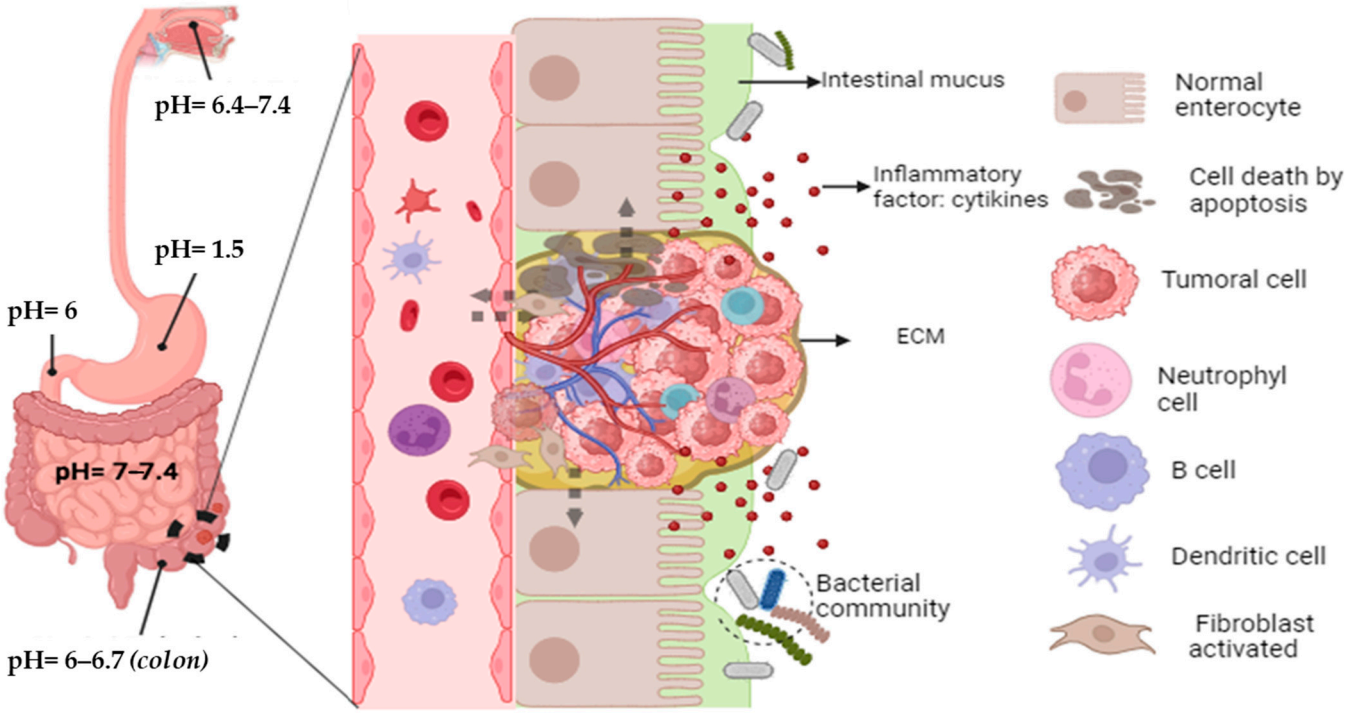


Figure 2. Physiological and tumor microenvironment factors influencing oral drug delivery for colorectal cancer therapy. Gastrointestinal factors such as pH, mucus composition, and microorganisms can present significant challenges to the efficacy of orally administered nanoparticles. Furthermore, the tumor's extracellular matrix (ECM) can pose an additional barrier to drug delivery due to inherent tumor characteristics that can vary between individuals.

As mentioned above, the therapeutic approaches for the treatment of CC currently encompass radiotherapy, chemotherapy, adjuvant therapy, and immunotherapy; although these therapies applied together or individually have shown promising results by increasing the survival rate of colon cancer patients, it should be noted that current studies

report limited efficacy of the latter due to the development of tumor cell resistance to chemotherapeutic biomolecules, as well as their toxicity, among other reasons [128,129]. In addition, due to the characteristics of the CC microenvironment, i.e., its extracellular matrix, immunotherapeutic treatments may have practically no therapeutic efficacy due to their inability to overcome the extracellular matrix of solid cancers. On the other hand, although chemotherapeutic and radiotherapeutic treatments have shown positive contributions against solid cancers, the latter can induce neuropathies, bone marrow suppression, gastrointestinal and skin disorders, hair loss, cardiotoxicity, and pulmonary toxicity.

While such limitations have prompted researchers to seek alternative solutions to colon cancer, e.g., those derived from medicinal plants evidenced above, the latter still face a myriad of limitations. Indeed, although phytocompounds have proven their pharmacological potential against different cancer cell lines in in vitro studies, translating these results into the clinical setting remains a puzzle for researchers due to factors such as low solubility and stability, resulting in low bioavailability at the desired site. According to several authors, the main limitations of phytochemicals when translating them into the clinical picture are the physiological barriers in the human body as a result of oral application being the major dosage form [119–121]. Indeed, during the movement of drugs through the gastrointestinal tract to reach the colon, they have to overcome different barriers such as pH, mucosa, and the gastrointestinal microbiota, among others. Emphasizing pH, it is reported that it can vary from 1.5 in the stomach to 6.7 in the colon, passing through an intermediate pH in the duodenum (Figure 2). According to Homayun et al. (2019) [130], due to the lack of protection of free actives, they may bind non-specifically to proteases and lipases in the gastrointestinal tract, where their pharmacological potential is reduced. Since gastrointestinal microbiota also have the capacity to produce metabolic enzymes, such as hydrolases, they may indirectly contribute to drug degradation and stabilization. Several studies have shown that polyphenols derived from medicinal plants may have a prebiotic effect [97–102], and may therefore directly affect the predefined active ingredient concentration, with potential biological effects.

According to several authors, the gastrointestinal mucosa may also constitute a physicochemical constraint to therapeutic efficacy [122,131], as it can influence the pharmacokinetics and pharmacodynamics of conventionally formulated drugs, as well as the bioactive molecules consumed in free form (infusions). Being a viscoelastic mesh-like structure (found in vaginal and gastrointestinal areas, as well as in the eye, among others), it can present a major physiological obstacle to the biodistribution of actives. It is reported to be difficult for micrometer-sized particles ($\geq$500 nm), as they can be trapped by adhesion [132]; this means that there could be a gradient of particle distribution on the mucosal membrane depending on their size and on the negative charge of the mucosa [133]. Thus, this can limit the biodistribution of positively charged particles by electrostatic attraction. On the other hand, it is well known that mucus is composed of water and glycoproteins (mucins) [132–135], which means that it is largely composed of hydrophilic domains, which may limit the biodistribution of hydrophobic drugs. Additionally, the mucin network can build a steric barrier to macromolecules (peptides, proteins, etc.) of high molecular weight [133].

9. Advantages of Using Nanotechnology in the Treatment of Colon Cancer

From the early 1970s to date, the FDA has shown increasing interest in nanoparticle-based pharmaceutical products due to their low toxicity and other attributes; according to the FDA's Center for Drug Evaluation and Research (CDER), nanodrugs hold promise for the cure of various diseases and should receive special attention. Furthermore, it is reported

that, to date, the FDA has approved more than 60 applications for nanomaterial-based products [136].

Accordingly, it is evident that reaching colon cancer as a therapeutic target involves crossing different physiological barriers in the body, as well as the barrier imposed by the tumor microenvironment. To overcome these biological limitations, the use of nanosystems in the transport of active molecules has been proposed in recent decades to promote the protection and control the release of active ingredients of interest [107–109]. However, like conventionally applied drugs, NPs have to overcome different challenges to reach their drug target. Among the advantages of using NPs as a drug delivery system is their controlled (pH-dependent) release [94,111]; this particular feature allows them to overcome different pH changes that can affect the stability of drugs as they move through the digestive tract. Moreover, the protection of actives in a nanovehicle system allows them to be protected from potential enzymes produced by the intestinal microbiota (Figure 3), which can bind to biologically active molecules and break them down, thus affecting the dose-dependent pharmacological efficacy. Additionally, due to their moldable characteristics designed according to knowledge of the characteristics of the gastrointestinal mucosa, it is reported that negatively charged NPs of a size less than or equal to 200 nm easily overcome the barrier imposed by the intestinal mucosa (Figure 3) [18].

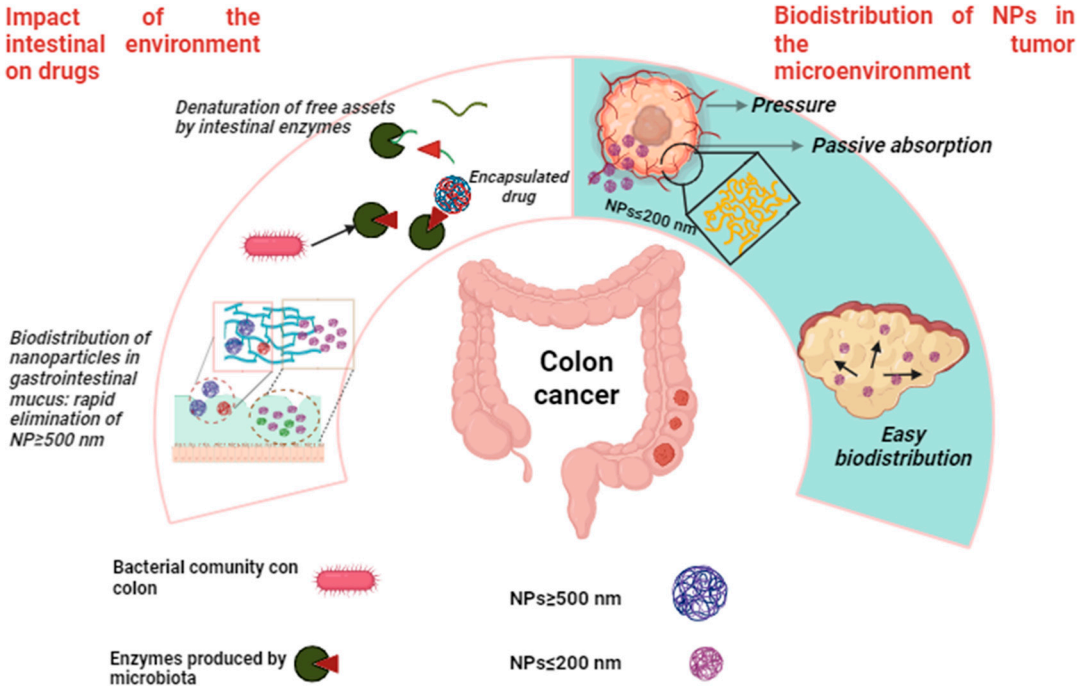


Figure 3. The benefits of using nanovehicles for active delivery over free or conventionally administered actives. In fact, nanoparticles provide protection for the actives against the colon environment, while also enabling passive penetration of the ECM and facilitating uniform distribution, with optimal distribution achieved by nanoparticles of approximately 200 nm in size.

Subsequent to the physiological barriers that can adversely affect orally applied drugs is the barrier imposed by the tumor microenvironment, including the extracellular matrix (ECM), the tumor microenvironment (TME), and endocytosis of the drug by cancer cells [107–117]. There is a significant difference between the absorption rate of nanoencapsulated actives and free actives. According to Scheetz et al. (2019), 10 to 15% of NPs accumulate in the tumor environment, compared to 0.1% of conventionally dosed molecules [137]. Indeed, due to the size and shape of the NPs, they can passively pass through the retinal pigment epithelium (RPE) [138]. Furthermore, it was found that NPs

with a diameter between 5 and 150 nm have a longer circulation time (half-life in blood ~55 h) and, consequently, a more significant accumulation in tumors, contributing to antitumor activity [91,111].

Once inside the tumor environment, drugs have to overcome other barriers, such as interstitial fluid pressure and ECM density, which can considerably influence pharmacological biodistribution, thus limiting accessibility to tumor cells [139–142]. However, due to the high electrostatics of NPs, they can easily reach tumor cells and be endocytosed. Spencer et al. (2008) reported that NP charge is an essential factor for cancer treatment with NP-based approaches, as negatively charged NPs can be easily absorbed because they can pass through the barrier constituted by the tumor EMC [142]. This surface charge also allows them to mechanically approach tumor cells electrostatically, which facilitates their biodistribution in the tumor environment. Moreover, the size of the NPs facilitates their endocytosis by tumor cells [143]. It should be noted that the shape of NPs plays a major role in their internalization, as it dictates their endocytosis by normal and/or cancer cells.

10. Conclusions and Perspectives

The use of plants for therapeutic purposes dates back more than 10,000 years. With growing interest in the search for new medicinal sources that are more friendly than conventional ones, in recent decades, research on the healing potential of medicinal plants, as well as the possibility of using them as adjuvants or co-adjuvants in the treatment of various human and animal pathologies, has increased. Due to satisfactory results, today, about 30% of the drugs used in industrialized countries are synthesized from plant products, so we can consider plants as a reliable source for the production of medicines. However, medicinal plant derivatives, like most products derived from chemical synthesis, are dosed in the same way, i.e., as tablets, capsules, or emulsions, which greatly limits their therapeutic potential; also, the application of medicinal plant derivatives in a conventional way could induce side effects like those experience with synthetic drugs, which represents a possible danger to human health. Beyond these limitations, such derivatives may present difficulties in terms of solubility in organic solvents, which reduces their potential use.

On the other hand, the advent of nanotechnology may represent the solution to all the limitations presented by the use of active ingredients (secondary metabolites) of plant origin due to the possibility of encapsulating insoluble and soluble molecules in organic solvents in target organs and cells. Indeed, the use of NPs as a delivery system for green actives could present several advantages, not only to solve the problems associated with their solubility, but also to allow their delivery to a specific target, helping them to overcome various physiological barriers in the human body. For a disease such as colon cancer, the use of green NP systems could be a promising alternative to fight against this type of disease, since their physicochemical characteristics can be shaped to allow them to reach the tumor microenvironment.

While most polymeric NPs are pH-sensitive and could be affected by pH due to pH similarities in the gastrointestinal tract, there may be other solutions, such as the use of fructans (plant-derived polymers) for the synthesis of NPs. Although researchers have not yet contemplated the possibility of using such biomaterials for the delivery of green and synthetic actives in the treatment of colon cancer, it is well known that the target of fructans is the colon. According to Heya et al., only 10% of conventional nanoparticles, compared to 0.1% of free active agents, manage to overcome the tumor microenvironment; therefore, improving the design of nanoparticles through functionalization with ligands or antibodies could represent a solution to realize drug delivery and increase accumulation in the tumor environment. Additionally, other authors suggest the use of other types of nanovehicles, such as exosomes (widely used in personalized therapy), for drug delivery due to certain

risks that nanoparticles may pose, particularly metallic particles (which can accumulate in healthy cells and be toxic to humans). However, the utopian concept of finding an ideal drug for everyone, i.e., one that can overcome population heterogeneity or differences, remains a challenge that several scientists believe can be overcome with well-designed nanoparticles.

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