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Plant Extracts-Loading Nanoparticles: A Promising Therapeutic Strategy for Colon Cancer

Nanopartículas Cargadas con Extractos Vegetales: Una Estrategia Terapéutica Prometedora para el Cáncer de Colon

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Technological innovation: Applications of natural products extracts. In this work we provided information about new methods and applications for natural products as extracts or their isolated active compounds loaded in organic nanoparticles against Cancer.

Area of industrial application: Biotechnology; Pharmacology; Medicine.

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Resumen

En la actualidad, la comunidad científica reconoce ampliamente el potencial terapéutico de las plantas medicinales. Numerosos estudios han demostrado la eficacia de las plantas y sus metabolitos secundarios en el tratamiento y prevención de diversas enfermedades, incluyendo las enfermedades inflamatorias y el cáncer. Sin embargo, la extracción de metabolitos secundarios de las plantas utilizando disolventes puede limitar la composición química de los extractos, lo que podría afectar su eficacia terapéutica. Además, la estabilidad y la biodisponibilidad de los derivados de plantas medicinales pueden ser limitadas, lo que reduce su potencial farmacológico. Para abordar estas limitaciones, se ha propuesto el uso de nanotransportadores como una forma de

mejorar la eficacia terapéutica de las plantas medicinales. La búsqueda fue llevada a cabo en enero 2025 en buscadores como Google Scholar, PubMed y SCOPUS, se utilizaron palabras como “cáncer de colon”; “alternativas terapéuticas para CC”; “plantas medicinales para tratamiento de CC” y “nanopartículas como transportadores de fitocompuestos para CC”. La presente revisión destaca la importancia de las nanopartículas cargadas con extractos de plantas como una alternativa prometedora para el tratamiento de enfermedades inflamatorias y cáncer.

Palabras claves: Plantas medicinales; Cáncer; Eficacia terapéutica; Activos; Nanopartículas.

Abstract

Currently, the scientific community widely recognizes the therapeutic potential of medicinal plants. Numerous studies have demonstrated the efficacy of plants and their secondary metabolites in treating and preventing of various diseases, including inflammatory diseases and cancer. However, the extraction of secondary metabolites from plants using solvents can limit the chemical composition of the extracts, which may affect their therapeutic efficacy. Furthermore, the stability and bioavailability of medicinal plant derivatives can be limited, reducing their pharmacological potential. To address these limitations, the use of nanocarriers has been proposed as a means of enhancing the therapeutic efficacy of medicinal plants. The search was conducted in January 2025, in electronic databases such as Google Scholar, PubMed, and SCOPUS, keywords used included “colon cancer”, “therapeutic alternatives for CC”, “medicinal plants for CC treatment”, and “nanoparticles as carriers for phytocompounds in CC therapy”. This review emphasizes the potential of plant extract-loaded nanoparticles as an effective and innovative approach for the treatment of cancer and inflammatory diseases.

Keys word: Medicinal plants; Cancer; Therapeutic efficacy; Active ingredients; nanoparticles.

1. Introduction

The World Health Organization (WHO) estimates that around 80% of people worldwide use traditional medicine as their main approach to managing health conditions. [1]. Also, the pharmacological potential of plants has been scientifically proven, thus evidencing their antimicrobial, antioxidant, anticancer, and anti-inflammatory activity, among others [2–6]. According to various authors, approximately 60% of commercial drugs are derived or inspired by phytocompounds, which makes plants an important target for modern pharmacology [7].

In contrast to the above, it is difficult to widely exploit the healing potential of plants, due to factors such as the toxicity of the extraction solvent, low physicochemical stability, no modifiable pH and low bioavailability *on-site* [8]. It should be noted that more than 70% of commonly marketed medicinal plant derivatives have low water solubility, which considerably limits their absorption into human tissues [9]. Therefore, there is a need to investigate more efficient dosage forms, to take full advantage of the pharmacological effectiveness of natural products is essential.

On the other hand, studies report that the use of nanoparticles for the application of derivatives of medicinal plants could represent an invaluable solution to overcome the limitations that the latter present when applying to humans [1,9]. Indeed, due to the structural modulation of the characteristics of nanocarriers their pharmacological effects can be optimized by adjusting factors like composition (organic, inorganic, or hybrid), dimensions (ranging from small to large), morphology (such as spherical, rod-shaped, or cubic), and surface characteristics (including charge, functional groups, and targeting moieties). Currently, nanotechnology is regarded as a highly valuable approach for advancing medical applications, including their use as carriers for plant extracts in the treatment of diseases such as colon cancer. [9-11].

Colon cancer (CC) is one of the most prevalent cancers worldwide and represents a serious public health issue [10]. With an incidence of approximately 1.93 million new cases per year, it is the third leading cause of cancer-related death globally, reflecting the magnitude of this health challenge [12]. Despite advances in diagnosis and treatment, the overall survival rate for patients with CC remains limited [13], underscoring the urgent need to develop more effective therapeutic strategies.

Currently, conventional treatments for CC include surgery, chemotherapy, radiotherapy and immunotherapy. However, these approaches have several significant disadvantages. Chemotherapy, for example, is effective in reducing tumors, but is often accompanied by severe side effects such as nausea, immunosuppression, and toxicity to healthy organs [14]. Additionally, chemotherapy and radiotherapy do not always manage to selectively eradicate tumor cells, which can lead to the development of tumor resistance and cancer relapse [15]. Furthermore, these treatments are expensive and not always accessible in all geographic regions. These drawbacks have driven the search for new therapeutic alternatives with fewer side effects and greater selectivity toward tumor cells.

In this context, nanoparticles loaded with phytochemicals have emerged as a promising therapeutic strategy. Nanoparticles offer controlled and targeted release of therapeutic agents, enhancing the bioavailability of phytochemicals and reducing the adverse effects associated with conventional treatments. Moreover, nanoparticles can improve penetration into tumor tissues, allowing for greater specificity in the destruction of cancer cells [13]. This approach offers the potential to overcome the limitations of current treatments, such as widespread toxicity, lack of tumor selectivity, and the development of resistance [16], thus justifying its investigation as a strategy for the treatment of colon cancer.

In accordance with the above mentioned, this work highlights the relevance of the use of nanoparticles in the delivery of natural products with anticancer activity.

2. Methodology

This study was conducted through exhaustive searches in electronic databases such as Google Scholar, PubMed, and SCOPUS, focusing on articles related to colorectal cancer, therapeutic alternatives using medicinal plants, and the application of nanoparticles as carriers of phytocompounds for the treatment of this disease.

3. Epidemiology of colon cancer (CC)

CC is the third most common malignant disease according to the World Health Organization (WHO), with 1.85 million new cases reported per year, which is equivalent to 10.2% of all cancer cases, preceded by breast

and lung cancer at 2.26 million new cases per year in 2020 [17]. CC is also the third most common type of cancer in men with 1.3 million new cases per year, behind lung and prostate cancer, while in women it is in second place with 820 thousand new cases per year, behind breast cancer [18]. The number of deaths caused by CC in 2016 was estimated at 794 thousand, while by 2020 it was estimated to be over 930 thousand deaths, representing an increase of 17% [19]. It is predicted that by 2040 there will be 3.2 million new cases per year, an increase of 63% [20].

The highest incidence of CC is in Australia and New Zealand with 36.7 cases per 100 000, second highest in Europe with 28.8-32.1 cases per 100,000, followed by East Asia with 26.5 cases per 100,000 and North America with 26.2 cases per 100,000, the regions with the lowest incidence are Africa, South and Central Asia [21].There are several factors that influence the incidence of CC in each region, including the fact that areas with greater economic development have greater access to processed foods, including red meat, one of the main factors for the development of CC, and that in areas with high economic growth it is easier to detect and treat CC, while in underdeveloped areas often lack of the necessary conditions for a correct diagnosis, so the figures may be underestimated in these regions [20]. Additionally, lifestyle factors such as obesity, physical inactivity, and low fiber intake, as well as limited access to health care services, cultural habits, and even genetic predispositions, may contribute to the differences in CC incidence observed across the various continents and countries [21].

In the Americas, the highest incidence is found in Canada and Uruguay, in Europe the countries with higher incidence are Slovakia, Slovenia, Hungary, Norway, Spain, England, among others, while for Asia the highest incidence is found in Japan, the Republic of Korea and Singapore, in Oceania the highest incidence is found in Australia and New Zealand, the incidence of CC is low in the African continent (figure 1) [22].

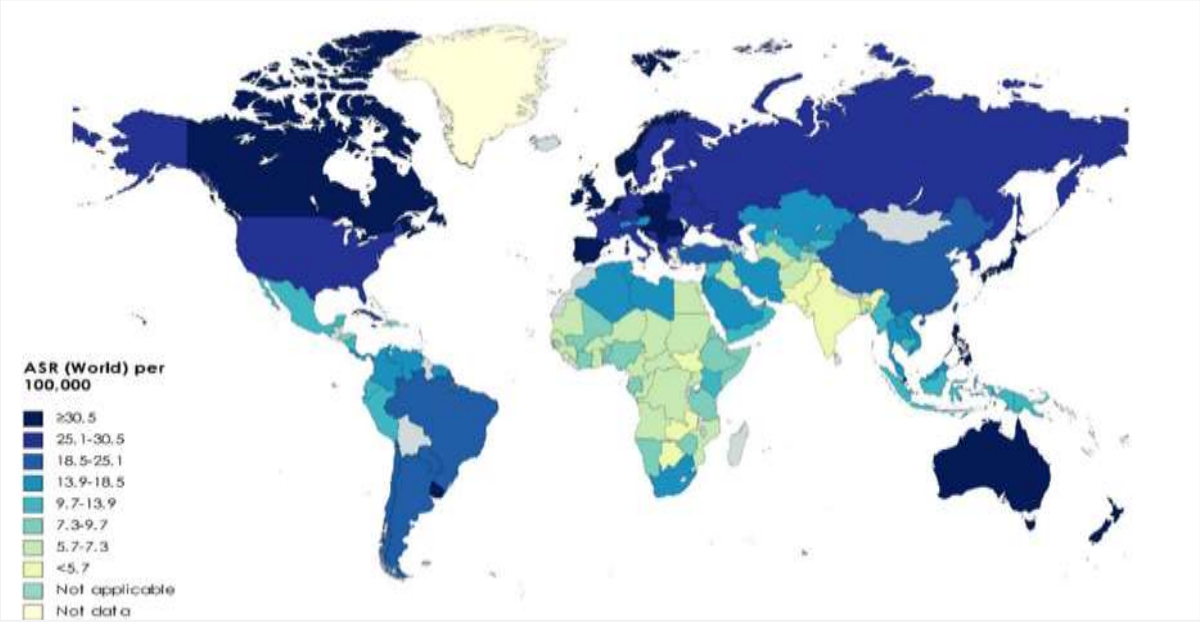


Figure 1. Age-standardized incidence of CC in the world.

Deaths caused by CC and the incidence have been increasing in developed countries, both for men and women, but the increase is more significant in countries with high development; countries with medium-high economic development have the highest incidence (45.94 %) and mortality rates (36.40 %) (figure 2). On the other hand, countries with high development have a slightly lower incidence than the previous countries (42.43%), but the mortality rate is significantly lower, probably due to easier access to better treatment [23]. The incidence of CC is directly related to the economy of the countries; in rich countries there is a higher incidence because the environmental conditions and customs of the population predispose them to the development of CC, although, they have better infrastructure and therefore better access to control and cure CC, resulting in upper-middle income countries having a higher mortality rate [24].

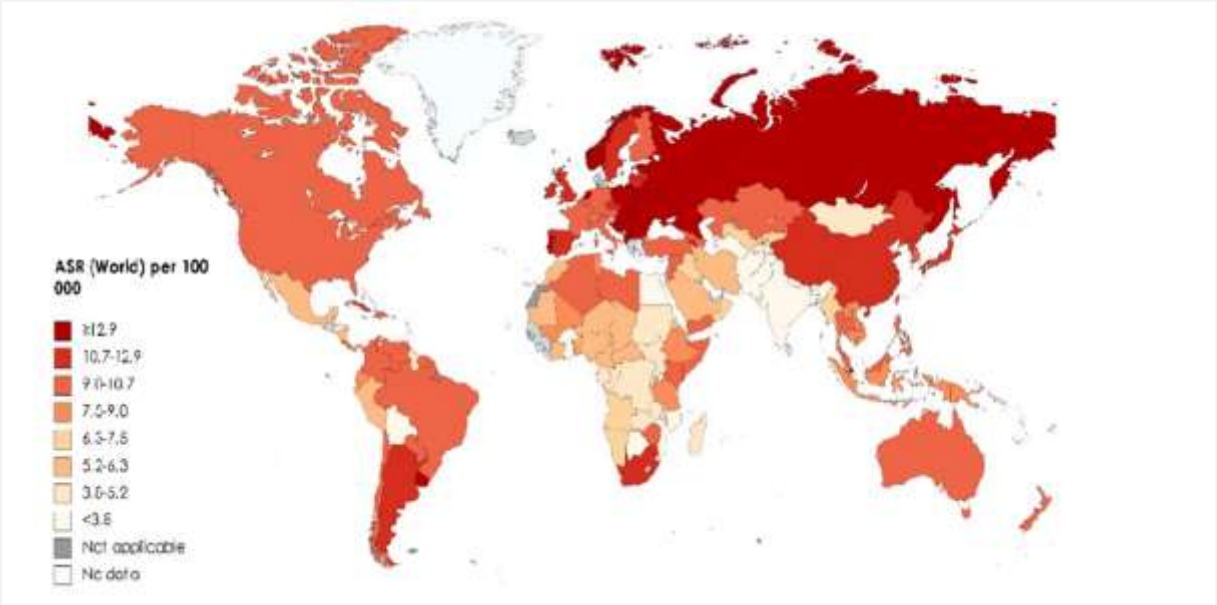


Figure 2. Age-standardized death rates from CC in the world.

According to the 2020 GLOBOCAN study, for each continent the data for both incidence and mortality by region are as follows: North Africa is the region with the highest new cases with 12,033 and 6,876 deaths for both gender, respectively. North America reports 117,379 new cases and 44,265 deaths, East Asia reported 436,272 and 220,945 deaths, in Central and Eastern Europe 100,909 new cases and 56,048 deaths were reported, in Oceania Australia and New Zealand reported 13,153 new cases and 4,798 deaths [6]. The worldwide risk of developing CC is 2.27 % between ages 0-74 years, it is more prevalent in nations with a high Human Development Index (HDI) compared to those with a lower HDI [24], and the risk increases with age, being more common in people over 50 years, the average age at diagnosis was 72 years for females and 68 years for males [21].

4. Types of nanomedicines/nanocarriers used in cancer

Nanotechnology is the science that deals with the study of materials and systems whose structures and components exhibit novel and significantly improved physical, chemical, and biological properties, phenomena and processes due to their nanometer-scale size [14,15], on the other hand, their applications to medicine with the purpose of preventing,

diagnosing, and treating diseases is known as Nanomedicine [25]. In recent years there have been problems in the treatment of CC. These problems are due to several factors, including limited health care resources, shortage of trained health care personnel, high costs of treatment, delayed diagnosis, and poor access to specialized care centers. Various conditions have led to the search for strategies that require an increase in the efficacy and selectivity of therapeutic agents, as well as a decrease in their toxicity in normal tissues [26]. With the continuous development and innovation of nanomedicines, nanoparticles have been proposed for drug administration, capable of offering targeted delivery to specific tissues, in addition to conferring different characteristics to the active ingredient such as the ability to incorporate hydrophilic and hydrophobic drugs, protect them from degradation by environmental factors, modify the pharmacokinetic profile, in addition to improving penetration and intracellular distribution [27]. These characteristics of nanoparticle-based delivery systems directly address many of the limitations associated with current colon cancer treatments. For instance, while conventional chemotherapy often leads to systemic toxicity and poor tumor selectivity, nanoparticles can enhance the accumulation of therapeutic agents specifically at tumor sites, thereby minimizing adverse effects on healthy tissues [28]. Additionally, the ability of nanoparticles to protect phytocompounds from degradation and to improve their solubility and bioavailability provides a means to overcome the pharmacokinetic drawbacks of many plant-derived molecules [29]. Thus, the use of nanoparticles not only improves the therapeutic performance of phytocompounds but also represents a promising strategy to circumvent the limitations of current therapies, such as drug resistance, nonspecific distribution, and high toxicity [30].

Currently, different types of nanoparticles are studied because they facilitate the application of drugs by offering targeted delivery of drugs to different tissues, presenting great advantages over conventional drugs currently used in the treatment of cancer, in addition to their ability to incorporate essential oils, extracts, and compounds isolated from plants provides novel therapeutic options with great perspectives [31]. Currently, various different nanomedicines studied for the delivery of drugs, particularly in the treatment of cancer, due to their characteristics and multiple advantages they provide, they can be applied liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions and metallic nanoparticles. In Table 1 size ranges, main structural components, as well as the advantages and disadvantages of these nanomedicines are described.

Table 1. Advantages and disadvantages of nanomedicines applicable to the treatment of CC.

Types of nanoparticle	Advantages	disadvantages	Ref.
Liposomes	Ability to incorporate hydrophilic or hydrophobic substances; Correct interaction with cell membranes; reduces toxicity.	Limited physicochemical and biological stability.	[26, 32]
Nanoemulsion	Ability to incorporate hydrophilic or hydrophobic substances; masks the bad taste of substances; decreases toxicity versatility in formulations (e.g. cream, patch, liquid); improves the stability of compounds. Protects from oxidative degradation and light.	It needs large amounts of non-toxic surfactants; limitations to incorporate high melting point substances; its stability can be influenced by environmental factors such as temperature and pH.	[33-35]

Polymeric Nanoparticles	Ability to incorporate hydrophilic or hydrophobic substances; high stability of volatile active ingredients, high loading capacity of active ingredients; controlled release capability; high contact surface due to its submicron size; improving the bioavailability of active ingredients; they facilitate interaction at the cellular level; ability to enter cells and release inside; ability to bind ligands to the surface to offer precise delivery of the active ingredient.	The disadvantages are few because they have a great diversity of variables that can be modified, according to the chemical nature of the drug to be encapsulated, the type of polymeric system, the application area, the size requirement, however: Due to its size and large surface area, aggregation between particles makes it difficult to physically handle it in liquid and dry form.	[31, 36]
Metallic Nanoparticles	Biological activity linked to the composition and type of synthesis of the NP; high contact surface due to its nanometric size; ease of interaction with cellular systems due to their size and surface charge; ability to be coated with biogenic surfactants or protective agents to obtain biocompatibility, stability and low toxicity; ability to bind ligands to the surface to induce biological activity at a specific site.	Instability because the nanometric metallic composition is thermodynamically unstable and can undergo transformations. High possibility of obtaining impurities since they are highly reactive during the synthesis. Toxicity and irritation at the cellular level by metallic nanomaterials.	[37]

5. *In vitro* anticancer activity of nanoparticles loaded with medicinal plants.

One of the principal challenges associated with the widespread application of plant extracts in therapeutic contexts is the inherently low solubility of their bioactive compounds, which significantly restricts their pharmacological efficacy. Nonetheless, polymeric nanoparticles loaded with curcumin, commonly referred to as nanocurcumins, have demonstrated a remarkable affinity for aqueous environments without the need for surfactants. This improved dispersibility greatly facilitates their systemic administration, thereby substantially enhancing the pharmacological potential of the extract [38-41].

In an in vitro investigation, Swathi et al. reported that cerium oxide (CeO_2) nanoparticles, when loaded with *Nelumbo nucifera* flower extract rich in flavonoids and phenolic compounds exert pronounced cytotoxic effects against HCT 116 human colon cancer cells, exhibiting an IC_{50} value of 41.5 µg/mL [42]. Similarly, Rahimivand and colleagues encapsulated *Artemisia ciniformis* extract within sodium alginate nanogels and assessed their efficacy against AGS gastric cancer cell lines. The encapsulated formulation induced apoptosis in a manner dependent on both exposure time and dosage, yielding IC_{50} values of 21.5, 18.5, and 15.2 µg/mL at 24, 48, and 72 hours post-treatment, respectively. These values were markedly lower compared to the unencapsulated extract, which exhibited IC_{50} values of 61.9, 40.07, and 28.7 µg/mL over the same time intervals. The observed cytotoxic activity is postulated to be primarily mediated by flavonoids and monoterpenoids present in the extract [43].

Furthermore, Olea et al. explored the therapeutic potential of ethyl acetate and ethanol extracts of *Leptocarphari vularis*, which were incorporated into polymeric micelles composed of Pluronic F127. These micellar formulations were evaluated against HT-29 human colon cancer and PC-3 prostate cancer cell lines [44]. The ethyl acetate extract encapsulated within the micelles demonstrated significantly enhanced

cytotoxic activity, with an IC_{50} of 0.05 mg/mL compared to 10.70 mg/mL observed for the free extract. Similarly, the encapsulated ethanol extract displayed improved efficacy, with IC_{50} values of 6.70 mg/mL versus 14.90 mg/mL for HT-29 cells and 0.30 mg/mL versus 15.60 mg/mL for PC-3 cells. These cytotoxic effects have been attributed to the presence of triterpenes and saponins inherent to the extract [44]. In a separate study conducted in 2022, Cristina Mesas evaluated calcium phosphate nanoparticles loaded with esculetin and euphorbetin, derivatives of curcumin extracted from *Euphorbia lathyris* seeds. This formulation was demonstrated to be non-toxic to human blood cells while exhibiting selective cytotoxicity against colon cancer cells (T-84 line), with an IC_{50} of 71.42 µg/mL, and low toxicity toward healthy cells (CCD8), which had an IC_{50} of 420.77 µg/mL. The underlying mechanism of action is hypothesized to involve the inhibition of carbonic anhydrase activity and the modulation of autophagy pathways. The same investigation included an *in vivo* study in murine models of colon cancer induced via two distinct methods, resulting in a substantial reduction of tumor volume by approximately 62%, alongside a significant decrease in both the number and size of polyps [45].

Moreover, Mostafa and collaborators developed poly(lactic-co-glycolic acid) (PLGA) nanoparticles encapsulating a powdered cranberry nutraceutical extract, which exhibited noteworthy anticancer activity against colon cancer. Their findings demonstrated that the incorporation of blueberry extract within the nanoparticles significantly augmented the therapeutic efficacy, principally through increased cellular permeability, which rose from 2.19 to 3.10 times relative to the crude extract. Furthermore, the nanoparticle formulation elicited considerable inhibition of vascular endothelial growth factor (VEGF), a critical biomarker implicated in tumor angiogenesis [46].

Lastly, nanoencapsulation of plant-derived extracts possessing antioxidant and anticancer properties has emerged as a promising strategy to enhance their systemic bioavailability. For instance, anthocyanins encapsulated within whey protein and citrus pectin matrices have been shown to effectively reduce cancer cell proliferation and impede tumor progression [47]. Clinical trials involving healthy volunteers revealed that these nanoencapsulated anthocyanins exhibited increased bioavailability within the large intestine compared to other delivery systems, thereby suggesting that such encapsulation technologies can markedly improve systemic absorption and therapeutic outcomes [33, 34].

6. Conclusion

CC is a complex disease that requires a comprehensive approach to its treatment. Research into nanoparticles and medicinal plants offers great hope for improving patients' quality of life with CC. The administration of phytocompounds through nanoparticles represents a promising strategy for the treatment of colon cancer, as it helps to overcome many limitations associated with conventional therapies. In this study, various types of nanoparticles such as liposomes, polymeric nanoparticles, metallic nanoparticles, and solid lipid nanoparticles were explored for their ability to deliver bioactive compounds derived from medicinal plants. Phytochemicals such as flavonoids, triterpenes, saponins, and anthocyanins demonstrated significant anticancer potential, and their encapsulation in nanoparticles improved their stability, bioavailability, and selectivity toward tumor cells. Altogether, these nanoformulated systems not only enhanced the therapeutic efficacy of natural

compounds but also contributed to reducing toxicity in healthy tissues, positioning them as a viable and effective alternative for the development of innovative treatments against colon cancer. However, it is essential to continue researching and evaluating the possible undesirable effects of these therapies before their clinical implementation. Collaboration between scientists, doctors, and patients is crucial to advance in the fight against this type of cancer. With research and innovation, we can improve patients' quality of life with CC and offer them a longer life expectancy.

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