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# Emerging Strategies and Obstacles in Colorectal Cancer Therapy: Mesenchymal Stem Cell-Coated Inorganic Nanoparticles as A Novel Approach

**Srinivasa Reddy Karri[1], Vinay Kumar Dangeti[2], Vijaya Lakshmi Ketha[3]**

[1,2,3]School of Pharmaceutical Sciences and Technologies, Institute of Sciences and Technology, Department of Pharmaceutics, Jawaharlal Nehru Technological University, Kakinada, 533003, Andhra Pradesh, India.

Corresponding Author: Srinivasa Reddy Karri

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## ABSTRACT

Colorectal cancer is the second leading cause of death worldwide. Chemotherapy for cancer often results in severe side effects and has a higher mortality rate compared to alternative treatment methods. Mesenchymal stem cells (MSCs) have been adopted as a potential drug delivery system targeting cancer and tumor cells. MSCs possess special features such as low immunogenicity, homing ability, and tumor tropism. There are several approaches for cancer therapy using MSCs, including migration towards irradiated tumors, chemotaxis-mediating factors, genetic engineering, priming with anticancer drugs, and derivation of Micro vesicles. These MSCs are formulated with chemotherapeutic agents to deliver drugs directly to the tumor site. With increasing rates of unhealthy lifestyles, poor food habits, and people may more easily accept genetic predispositions, mesenchymal stem cell therapy as it reduces the frequent use of conventional medications. Nanotechnology has emerged as a favorable approach in cancer treatment, managing the limitations of existing therapies. In recent decades, inorganic nanoparticles have demonstrated significant potential in the fight against colorectal cancer. Unlike organic nanoparticles, inorganic nanoparticles possess unique characteristics such as thermal efficiency, electrical conductivity, magnetic properties, and photosensitivity. These nanoparticles primarily made from materials like carbon, silica, metals and metal oxides are known for their enhanced dru-loading capabilities and effectiveness in advanced photo thermal and photodynamic therapies. This review summarizes the pathophysiology of colorectal cancer, loading ability of MSCs and highlight the crucial role of inorganic nanoparticles in photo thermal and photodynamic therapy and drug delivery, while also searching several types of inorganic nanoparticles utilized in colorectal cancer treatment based on recent studies.

***Keywords:*** Colorectal Cancer, Chemotaxis, Micro vesicles, Tumour tropism, photo thermal therapy, photodynamic therapy

## INTRODUCTION

Cancer rates are steadily rising due various factors such as modern lifestyles, dietary habits, genetic predispositions, and unhealthy behaviors. Colorectal cancer (CRC) is particularly concerning, ranking as the third most commonly diagnosed and the second deadlist cancer worldwide [(1)]. The incidence and mortality rates of CRC have been increasing, especially in developing nations [(2)]. Early stage of CRC is often treated with surgery, accompanied by medication [(1)] .This cancer typically affects the colon and rectum, with abnormal

proliferation of glandular epithelium cells predominately occurring in the colon [(1)]. As one of the most commonly observed cancers, CRC is leading cause of cancer-related deaths globally. Obesity, as measured by body mass index, is a well-known risk factor for developing colon cancer. In 2020, CRC accounted for 0.94 million deaths worldwide, with 1.93 million new cases diagnosed [(2)].

As the individuals age, those with colorectal cancer (CRC) often develop long-term conditions like ulcerative colitis and crohn's disease. In 2020, CRC was responsible for 0.94 million deaths globally, with 1.93 million new cases diagnosed. Research shows that men are more significantly affected by CRC than women, with an estimated 515,367 male death compared to 419,536 female death[(2)]. Modifiable risk factors for CRC include alcohol consumptions, smoking, obesity, high intake of red and processed meats, a sedentary lifestyle, and psychological stress. Non modifiable risk factors include age, gender, a personal history of inflammation bowel disease (IBD) and the composition of intestinal microbial[(3)].

**Epidemiology:**

***Mortality:***

GLOBOCAN estimate from the International Agency for Research on Cancer (IARC) indicates that colorectal cancer (CRC) was the second leading cause of cancer- reacted mortality globally. In 2020, CRC was responsible for approximately 935,173 deaths, resulting in an age-standardized mortality rate (ASMR) of 9.0 per 100,000 person-years. Europe had the highest ASMR at 12.3, while Africa reported the lowest at 5.6, closely followed by Eastern Mediterranean region (EMRO) with an ASMR of 5.3. Mortality rates were similar across other region, with oceania at 9.3, Asia at 8.6, and both Latin America and North America at 8.2[(3)].

***Incidence:***

In 2020, colorectal cancer (CRC) was identified as the third most prevalent cancer globally, following breast and lung cancers. The estimated number of new CRC cases was 1,931,590, resulting in an age-standardized incidence rate (ASR) of (19.5) per 100,000 person-years. Europe reported the highest ASRs at 30.4, followed by Oceania at (29.8) and North America at (26.2). In contrast, Asia had an ASR of (17.6), Latin America recorded (16.6), while the Eastern Mediterranean Region (EMRO) and Africa had the lowest rates at (9.1) and (8.4), respectively [(3)].

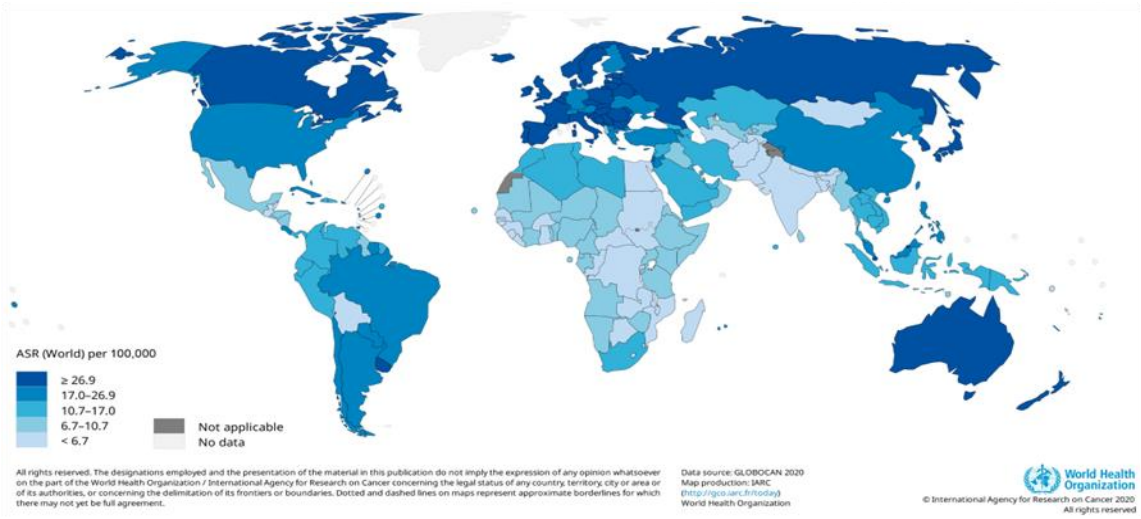


**Figure 1. Estimated age-standardized incidence rate for colorectal cancer, 2020 (Data source: GLOBOCAN 2020; Map production: IARC, http://gco.iarc.fr/today, accessed on 10 October 2023).**

The rate of colorectal cancer (CRC) incidence and mortality are on the rise in developing nations for both genders, despite being notably higher in high- income countries. Upper- middle- income countries represent the highest proportions of CRC cases, accounting for 45.94% of incidences and 49.37% of deaths. In contrast, high-income countries report lower incidence rates at 42.43%, but their mortality rates are also reduced at 36.40% (Fig2). This discrepancy may be attributed to superior healthcare and treatment options available in these regions [(1)].

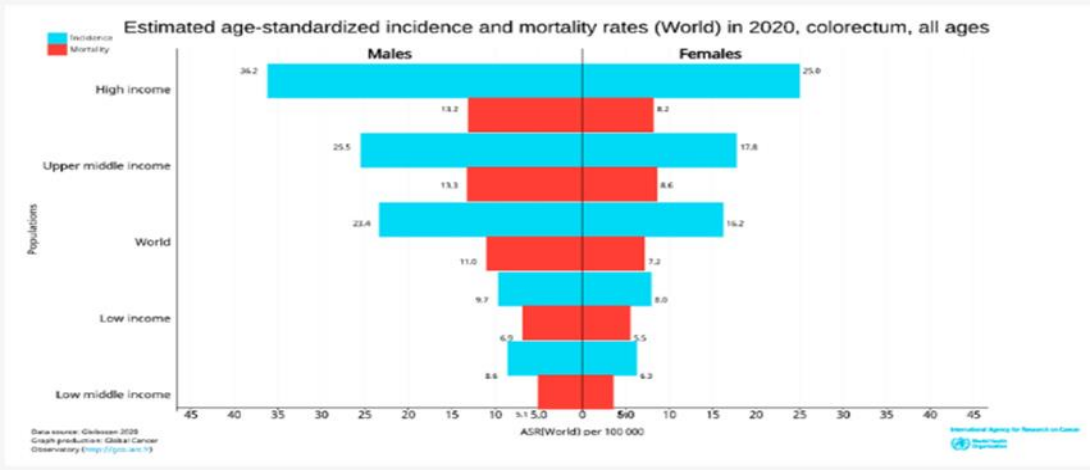


**Figure - 2: World CRC incidence and mortality rates in 2020**

**Colorectal Cancer Development:**

In colorectal cancer (CRC), genetic alterations in epithelial cells result in abnormal growth, leading to Hyper proliferation. The stage of colorectal cancer (CRC) plays a crucial role in determining the severity of the disease and the available treatment options. For stages 0 to II, surgery is typically the primary treatment approach. In contrast, stage III CRC necessitates both surgical intervention and adjuvant chemotherapy. For stages IV and recurrent CRC, a combination of surgery, chemotherapy, and targeted therapies is often employed. However, it is important to note that, as of now, there is no definitive cure for these advanced stages of the disease.

**Stages of colon rectal cancer:**

1. Initiation-Adenocarcinoma that burglarize into muscularis propria.
2. Promotion- The size of the tumour increases and invades the tissue in the serosa.
3. Progression- The tumour slowly penetrates into visceral peritoneum.
4. Metastasis - This the final stage in this the cancer cells spreading to the lymphatic/ blood vessels [(1)].

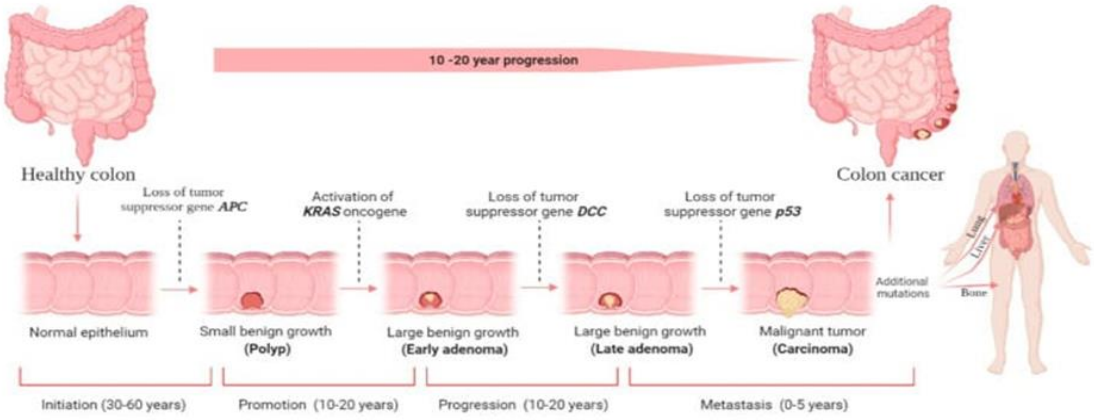


**Figure - 3: Colorectal cancer (CRC) stages and development**

Classification of colon rectal cancer [4].:
These are classified according to the histological, location, and molecular pathway involved.

1. Colorectal adenocarcinoma:
   This type of CRC greater than 90% of CRC worldwide.
2. Mucinous Colorectal adenocarcinoma:
   In this type, the cancer is characterized due to the presence of extracellular mucinous pools at least 50% of the tumour volume. A considerable proportion of mucinous adenocarcinomas occur in individuals with hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome (LS), and are characterized by high-level microsatellite instability (MSI-H). Carcinoma that displays a significant mucinous component are commonly referred to as 'adenocarcinomas with mucinous features' or mucinous adenocarcinomas. These tumours generally present large glandular formation accompanied by pools of extracellular mucin.
3. Medullary CRC:
   In this case, the frequency of medullary CRC is mainly 4% only. Medullary carcinoma is closely associated with high-level microsatellite instability (MSI-H) and frequently presents alongside mutations in the BRAF gene, which encodes the B-Raf proto-oncogene serine/threonine protein kinase.
4. Signet ring cell CRC:
   It is rare type of CRC the 50% of cancer cells with signet ring-like morphology. This type of carcinoma is characterized by the presence of greater than 50% of cancer cells with a signet ring-like morphology (31). Some signet ring CRCs may be MSI-H tumours'.

**Treatment of colorectal cancer:**

A range of treatment strategies for both primary colorectal cancer (CRC) and metastatic colorectal cancer (mtCRC) has developed, offering patients increased options. These strategies include laparoscopic surgery for early- stage CRC, more extensive resections for mtCRC, such as those involving lung and liver metastases, as well as radiotherapy for rectal cancer. Additionally, neoadjuvant chemotherapy and palliative chemotherapy are also utilized. Surgical resection remains the primary treatment for patients with localized early-stage CRC that is potentially curable. However, based on the disease stage, neoadjuvant chemotherapy and or radiotherapy may be recommended either before or after surgical intervention. In colorectal cancer (CRC), chemotherapy is often used alongside monoclonal antibodies targeting EGFR and VEGF to impede tumour growth and angiogenesis. For patients with late-stage metastatic CRC who are not candidates for surgery, a palliative systemic approach is employed to enhance quality of life and extend survival. To improve the efficacy of traditionally chemotherapy while minimizing side effects, various alternative therapies are being explored, including anti-inflammatory agents, gold- based compounds, agarose macro beads, and probiotics.

**Mesenchymal Stem Cells:**

Mesenchymal stem cells (MSC) are predominantly sourced from bone marrow, adipose tissue, dental tissues, and placental/ umbilical cord blood, releasing growth factor essential for tissue repair. MSCs are known to home to tumour sites, where they differentiate into tumour-associated fibroblasts (TAFs) and secrete trophic factors like vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), transforming growth factor-beta, epidermal growth factor, and platelet-derived growth factor (PDGF) (5). Additionally, MSCs can inhibit tumour growth by inducing cell cycle arrest and reducing proliferation through interference with the PI3K/AKT pathway and expression of tumour suppressor genes. They also migrate to areas of tissue damage, enhancing chemoattractant activity in the extracellular matrix and peripheral blood. MSCs, also referred to as stromal cells, can be derived

from various sources and possess the ability to differentiate into multiple cell types, including osteoblasts, chondrocytes, and myocytes. Their self-renewal capacity and multi- lineage differentiation potential make them valuable in regenerative medicines and cell- based therapies (6). The tropism exhibited by MSCs allows them to target tumors and deliver therapeutic molecules to tumour site and metastatic niches (5) MSCs are just one type of stem cell, alongside embryonic stem cells, adult stem cells, and induced pluripotent (7). These cells treat a wide range of conditions, including dermatological, musculoskeletal, neurological, cardiovascular, and urological disorders [(7)]. MSCs are mainly derived from bone marrow, adipose tissue, teeth, and placenta/umbilical cord blood [(6).] Various diseases have been treated using MSC-based drug delivery systems.

Self-renewal and differentiation capabilities of MSC in MSC- based drug delivery:

The self-renewal and differentiation abilities of mesenchymal stem cells (MSCs) are essential for their application in drug delivery systems. Overall, the distinctive characteristics of MSCs position them as promising candidates for developing effective drug delivery systems in regenerative medicine and various other therapeutic fields. MSCs, recognized for their self- renewal and differentiation potential, are being modified to improve their survival, retention, migration, and production of growth factor, which are vital for regenerative medicine and drug delivery applications. The adult stem cells are recognized for their capacity to replicate and transform into various cell types, which makes them highly valuable in regenerative medicine and therapeutic delivery. These engineered MSCs are specially tailored to enhance their therapeutic effectiveness by increasing their survival in vivo through genetic modification that pro-survival, pro-angiogenetic, or anti- apoptotic gene expression[(3)].

**Immunosuppressive functions of MSCs:**

Mesenchymal stem cells (MSCs) can be genetically modified to produce specific immunomodulatory agents, thereby enhancing their capacity to modulate immune responses and allowing them to deliver significant amounts of cancer-targeting biologics in a single administration. The interactions between mesenchymal stem cells (MSCs) and immune cells, resulting in immunomodulation and suppression of immune responses. They mainly inhibit T-cells proliferation and regulate dendritic cell maturation, and interact with regulatory T cells and monocytes to facilitate their immunomodulatory effects.

Homing of mesenchymal stem cells (MSCs) toward tumour site and damage tissues:

The migration of stem cells to damage tissues, often referred to as “homing” is driven by chemotactic gradients created by chemotactic gradients created by chemokines. These gradients stimulate the proliferation of stromal cells and trigger immunomodulatory and angiogenic effects through factors released in a paracrine manner.

The homing process of mesenchymal stem cells (MSCs) consists of several key steps

1. Initial anchorage: Through selectins, allowing for rolling along the vessel wall.
2. Adhesion and activation: Mediated by chemokines, such as CXCR4 and cell adhesion molecules like VCAM-1(vascular cell adhesion molecule-1)
3. Retention: Facilitated by integrins
4. Diapedesis: Transmigration across the endothelial barrier.
5. Extravascular migration: Guided by the CXCR4/SDF-1 α chemotactic gradient, which directs MSCs toward the tumour site.
6. Release of CXCR4/SDF-1 chemokines by stromal or mesenchymal MSCs

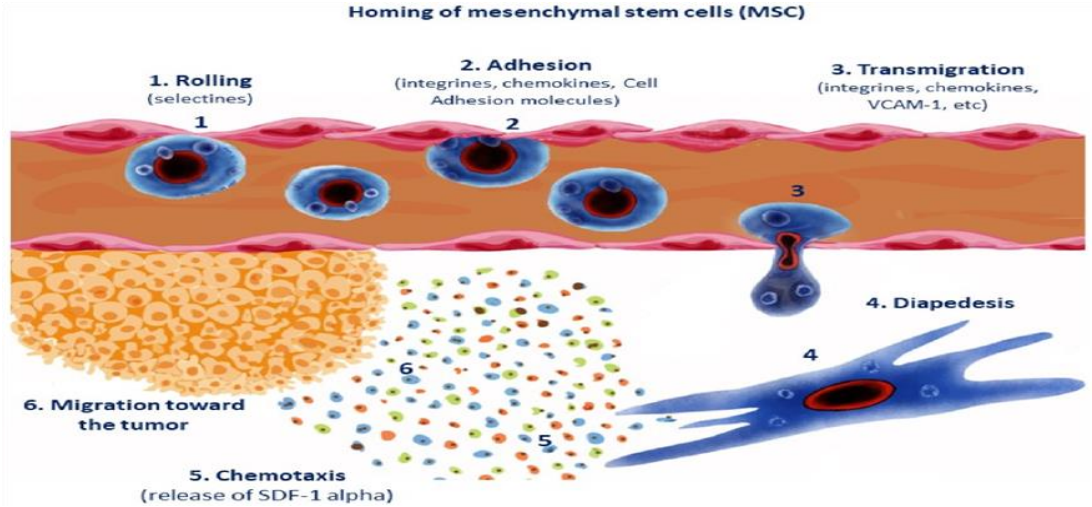


**Figure - 4: Homing of mesenchymal stem cells toward the tumour site**

Main method for loading of contents into MSC and EV's are broadly classified into 2 types:

1. Cell- based loading
2. Non cell based loading.

1. Cell- based loading: In this type the MSC are act as donor to loading the cargo and by using transfection method packed &produce the cargo within the EV's. The biomolecules like small RNA, m RNA, DNA, proteins into MSC are used in the transfection method.
2. Non Cell- based loading:
   In this method, the isolated EV's are directly loading cargo into MSC. Small molecules and biomolecules can be loaded by using the electroporation, sonication, and freeze thaw [(6)].

**Mechanism of Action:**

These stem cells show their mode of action through paracrine factors, mitochondrial factors, and extracellular vesicle secretion. Earlier studies have proposed that mesenchymal stem cells (MSCs) can migrate to areas of injury, where they may either differentiation into fully functional cells or fuse with damaged cells to aid in tissue regeneration.

1. Paracrine Effects:
   These cells primarily prompt paracrine factors (chemokines, cytokines, microRNA, and growth factors), producing effects of immunomodulation, tissue regeneration, repair, anti-fibrosis, and anti-apoptosis. Due to their immunomodulatory properties, mesenchymal stem cells (MSCs) represent a promising therapeutic approach for various inflammatory diseases, such as multiple sclerosis, graft-versus- host disease, systemic lupus erythematosus, Crohn's disease, and type 1 diabetes. After transplantation or the injection of isolated secreted factors, paracrine factors released by mesenchymal stem cells (MSCs) can help restore a normal microenvironment in injured tissues, facilitating their recovery. These factors have a substantial impact on immunomodulation, tissue regeneration and repair, anti-fibrosis, anti-apoptosis.

| **Factors Involved in Tumour Promotion** | |
|---|---|
| IL6, TGF-β1, IL-8 | Cytokines |
| SDF-1, CXCL1, CCL2, CCL5 | Chemokines |
| VEGF, Ang-1, PDGF, IGF | Angiogenic factors |
| NRG1 | Growth factor |
| periostin, PAI-1, Sema-7A | Other factors |
| "miR-21-5p, miR-410, MiR-142-3p, miR-23b" | microRNAs |

**Table 1: The role of tumour- promoting factors**

2. Mitochondrial Effects:
   Nanoparticles coated on the mitochondrial membrane can bind ligands to the membrane, rendering them impotent poisons. Nanoparticles enter the stratum cornea through the tight junctions of proteins and keratin. Consequently, using, mesenchymal stem cells (MSCs) as a source for mitochondria transfer has emerged as a promising therapeutic strategy, as it may help restore or replace dysfunctional mitochondria in damaged cells. Evidence suggest that under inflammatory or hypoxic condition, the transfer of mitochondria from MSCs to injured epithelial or endothelial cells promotes the formation of tunnelling nanotubes (TNT) and gap junctions, while also providing protection against apoptosis in the recipient cells.
3. Extracellular Vesicles Transfer:
   This technique reduces the possible drawbacks of lineage differentiation. MSCs may discharge various extracellular vesicles when activated, consisting of membrane-enclosed exosomes, micro vesicles, and apoptotic bodies. These contain various substances, including proteins, miRNA, and MRNA (7). As a result, employing mesenchymal stem cells (MSCs) for mitochondria transfer has shown potential as a therapeutic approach, potentially restoring or replacing dysfunctional mitochondria in damaged cells. Research indicates that in inflammatory or hypoxia environments, the transfer of mitochondria from MSCs to injured epithelial or endothelial cells facilitates the development of tunnelling nanotubes (TNT) and gap junctions, while also helping to protect recipient cells from apoptosis.

**Signalling pathways regulated by MSCs[8]:**

The onset, progression, and advancement of cancer are linked to a diverse range of signalling pathways.

***PI3K/AKT signaling pathway:***

These alterations in the PI3K/AKT pathway are associated with the acquisition of neoplastic traits by tumors, including increased cell proliferation, drug resistance, and stem cell-like characteristics. As a group of heterodimeric lipid kinases, PI3Ks are activated by numerous upstream factors, such as cytokines, chemokines, antigens, and growth factors [54]. Additionally, the PI3K/AKT pathway is connected to a wide array of signaling molecules and cascades that have been implicated in cancer development. The effective strategy to suppress the pro- tumour effect of mesenchymal stem cells (MSCs) by targeting the PI3K/AKT pathway

***Wnt signaling pathway:***

MSC- mediated alterations in Wnt signaling may have dual roles in cancer progression. This variation could be due to difference in cancer type, the source of MSCs, and the activation status of Wnt proteins. The role of Wnt signaling has been extensively studied in various cancers. In the context of colon cancer, research has shown that cancer cells secrete Wnt signalling, such as Wnt3, which helps sustain Wnt activity. From a mechanistic perspective, β-catenin, a key signaling molecule in the Wnt pathway, enhances the expression of telomerase reverse transcriptase (TERT), a ribonucleoprotein that safeguards telomeres in cancer stem cells from degradation.

***JAK/STAT signalling pathway:***

This pathway is an evolutionarily conserved signaling mechanism. Disruption in this pathway is linked to the progression of several diseases, including cancer. Numerous studies have explored how mesenchymal stem cells (MSCs) interact with tumours via the JAK/STAT pathway. For instance, interleukin- 6 (IL-6) produced by MSC derived from colorectal cancer has been shown to activate JAK2/STAT3 signaling pathway thereby promoting the advancement of colon rectal cancer.

***Hippo signalling pathway:***

This pathway act as a tumour suppressor, activation is associated with the inhibition of YAP/TAZ activity. This pathway comprises various proteins they are Yes-associated protein/WW-domain-containing transcription regulators (YAP/TAZ), large tumor suppressor 1/2 (LATS1/2), and mammalian Ste20-like kinases 1/2 (MST1/2). Consequently YAP/TAZ is regarded as an oncogene due to its overexpression in many types of cancer. Moreover, the Hippo pathway has been shown to be downregulated during colorectal cancer development, contributing to tumor metastasis. In the context of MSC-based cancer therapies, there is limited evidence suggesting that MSCs can modulate the Hippo pathway to influence tumorigenesis. However, studies have demonstrated that MSCs secrete prostaglandin E2 (PGE2), which activates YAP in liver cells and promotes hepatocyte proliferation as a result.

***MYC signalling pathway:***

The MYC gene family includes three transcription factors: c- myc, n- myc, l –myc. It acts as therapeutic target for cancer treatment by the c- myc by significant oncogene. Recent studies shown that the Myc sinaling pathway mainly influence the cancer progression and drug resistance. This pathway it also disrupts pro-tumour activity with directly suppress tumour development.

***NF-KB signalling pathway:***

This family of genes mainly encodes five members RelA, RelB, c-Rel, NF-κB1/p50 and NF-κB2/p52, and these genes are mainly involved enhancing the enhancing the expression of a various genes. For previous research describe that reducing the NF-κB signalling tends to inhibiting the risk of colitis-associated cancer. Additionally, in gastric cancer, increased NF-κB signaling correlates with enhanced tumor invasiveness and is regarded as a prognostic indicator for patients with the disease.

**Recent strategies in MSC- based Cancer Therapy [8]:**

The researchers giving the awareness about the using of MSC in anticancer treatment due to their complicated pattern of interactivity between MSC and tumour. In this gene engineering technique, the MSC cells are stocked with the viral vector, non-viral vector and transfusion tools to produce the anti-tumour effects. The exosomes are obtained for MSC can be produced the potential cell-free cancer treatment. MSC act as medium for therapy delivery:

In this technique, these act as agent for delivery of anti-tumour drugs.

They usually suppress the extension and the advancement of cancer; these cells are genetically altered by producing the variety of agents.

The agents used in MSC could be categorized into 3 major types.

1. Therapeutic proteins
2. Suicide genes
3. Oncolytic gene

***Delivery of therapeutic protein:***

These several of proteins such as cytokines, growth factor, interferon, transcription factor these acts as potential regulators of the development of cancer. The therapeutic proteins mainly reduce the tumour growth and restrict the pro-tumour factors characterized as novel form of anticancer drug [8].

Example: Interferon act as potent anti-tumour agents due to this reason these decreases proliferation of tumour cells and regulate the immune response [9].

***Delivery of suicide of gene:***

These MSC have been incorporated the suicide genes these could convert nontoxic reagents into toxic anti- tumour drugs. MSC are reveal a cytosine deaminase: uracil phosphoribosyltransferase (CD: UPRT) tends to effective in models of colon cancer. These suicide gene have the capability to convert the nontoxic 5-fluorocytosine into toxic 5-fluorouracile [10,11,12].

***Delivery of oncolytic viruses:***

This virus should subsequently kill cancer cells and supposed the prospective anti-cancer agents.

OVs identify and attached to cancer cells mainly targeting the surface proteins on the cancer cells, tends to oncolytic [13,14].

Mesenchymal stem cells (MSCs) are a type of multipotent cell that can self-renew and have the capacity to differentiate into various cell lineages. MSCs can be extracted from different tissues, and using MSC- coated nanoparticles can lower macrophage uptake, which helps reduce clearance by the reticuloendothelial system. This approach enhances targeted cellular uptake and promotes selective accumulation in tumours. Building on previous research, this study employed MSC membrane coating as a method to disguise a Nano drug for treatment of colon cancer. For example: Anti- cancer drug (doxorubicin), iron oxide nanoparticles coated with mesenchymal stem cell (MSC) membrane (DOX-SPIO@MSCs) demonstrated enhanced tumour cell uptake, reduced immune response, and amplified anti-tumour effects, while exhibiting minimal side effects.

Steps involved in the loading of anticancer drug via nanoparticles disguised with mesenchymal stem cell membrane:

1. *Loading of anticancer drug on Nanoparticles:*
   Anti-cancer drug (Doxorubicin) is loaded on Nanoparticles (SPIO). The quantity of DOX loaded was determined by measuring the difference for DOX before and after the conjugation process.
2. *Preparation of MSC Membrane- Derived Vesicles (MSVs);*
   Following multiple freeze- thaw cycles, the cell was gently sonicated on ice. The energy from sonication facilitates the separation of MSCs into their nuclei, cytoplasm, and cell membrane.
3. *Synthesis of DOX-SPIO @ MSCs:*
   A co-extrusion technique, with minor adjustment, was employed to produce DOX-SPIO @ MSCs

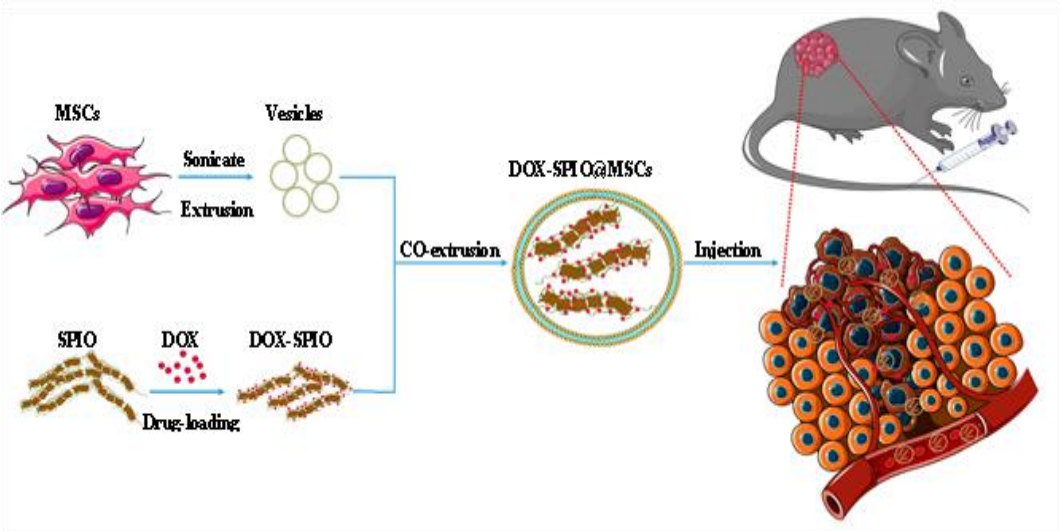


**Figure 5: Schematic of the preparation of DOX-SPIO@MSCs**

**Nanoparticles used in cancer therapy [15]:**

Nanotechnology is recently used techniques by the science and engineering for the targeting the cancer cells. These NP's is mainly targeting the tumour cells and deliver anticancer drug to the tumour site. When compared to the organic nanoparticles the inorganic nanoparticles show the efficient activity and prefer both function like drug carrier and therapeutic agent. While using the inorganic nanoparticles first mainly identify the potential of inorganic nanoparticles.

Based on the therapy.

A. Photo thermal therapy
B. Photodynamic therapy

A. Photo thermal therapy:
Hyperthermic - based cancer therapies consist of exposing targeted tissues to higher temperature, which can either lead to cancer cell death through thermal ablation ( at temperature) or increase the sensitivity of cancer cells to other treatments through mild hyperthermia (at temperature ranging between 40 and 45°C)[16]. Thus, NIR-II (1000-1700 nm) is better suited for reaching deeper tumour and minimizing damage to nearby healthy tissues [17]. In standard hyper thermic methods, the increase in temperature within targeted tissue is usually accomplished through external techniques, including regional hyper thermic, superficial hyper thermic and whole-body hyper thermic, using thermal baths, microwaves, or radiofrequency [18,19]. Nanoparticles that can produce heat when exposed to external stimuli have surfaced as promising alternatives, offering solutions to the draw backs of traditional hyperthermia techniques [20]. This is due to the low absorption of biological material in this spectrum, resulting in reduced off-target interactions and enhanced penetration within the human body, which ultimately boosts therapeutic efficacy [2]

B. Photodynamic therapy :
Photodynamic therapy (PDT), regraded as a novel approach for tumour ablation, provides a sophisticated method with reduced long- term morbidity. Inorganic nanoparticles (INP) – based photosensitizer represent a significant advancement over conventional organic photosensitizer. They offer several distinct advantages: first, they possess high extinction coefficients, enabling efficient energy transfer for photosensitization. Second, their surfaces are highly versatile, allowing for the conjugation of targeting ligands and functional groups, which enhances their selectivity for tumour cells [22]. Additionally, their small size results in large surface-to-volume ratios, making them more effective at accumulating in solid tumour tissues through the enhanced permeability and retention (EPR) effect [23]. In the Type-I mechanism, the excited triplet state of the photosensitizer (PS) interacts directly with surrounding biomolecules with cancer cells, forming radical cation or anions. These radicals can further react with oxygen (O2) to generate reactive species (ROS) such as superoxide anion hydroxyl radical (. OH) (H2 O2) etc [24,25]. In the type-II mechanism, the excited triplet state PS directly sensitizes O 2 (the ground state is a triplet) and generates highly cytotoxic ($^1$ O2) inside cancer cells [26].

**Inorganic Nanomaterials with Intrinsic Singlet Oxygen Generation for Photodynamic Therapy:**

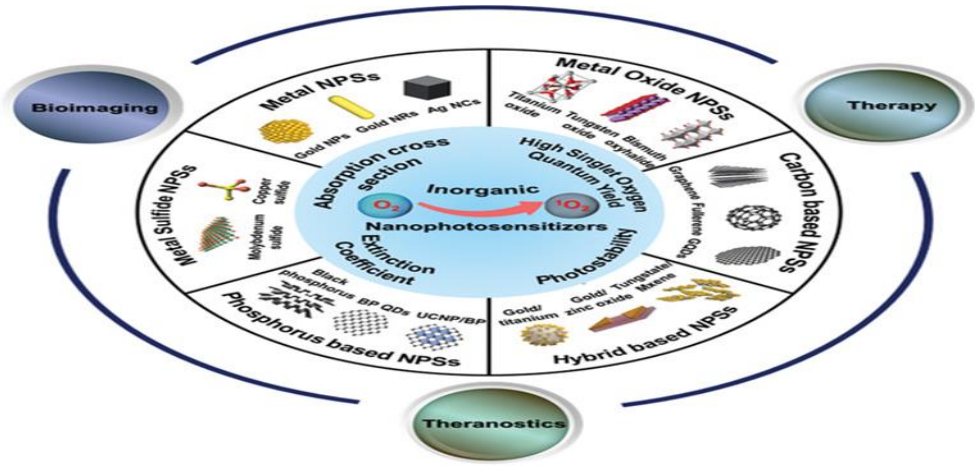


**Figure - 6: Inorganic Nanomaterials with their therapeutic applications**

**Inorganic nanoparticles- based approaches for colon rectal cancer therapy:**

In organic nanoparticles have emerged as central focus in recent cancer therapy research. For example, quantum dots (QDs) possess distinctive properties such as strong fluorescence and a broad emission spectrum, making them ideal for bio imaging applications [(27)]. Their primary characteristics include biocompatibility, precise targeting, non-toxicity, thermos ability, distinctive optical properties, small size, increased surface area, tenable structure, exceptional bioavailability, and favourable physicochemical properties [(28)].

1. Carbon nanotubes (CNT's):

These nanotubes are minute tube shaped structure. Carbon nanotubes (CNT's) can be categorized as either single- walled carbon Nano tubes (SWCNT'S) or multi-walled carbon Nano tubes (MWCNT'S) based on the number of graphene layers forming each nanotube. The distinct physicochemical characteristics of carbo nanotubes (CNT's), namely high surface area and length-to-diameter ratio, optimal electrical conductivity, and thermos- chemical stability, make them particularly attractive for biochemical applications [(29)]. It has been demonstrated that carbon nanotubes (CNTs) can cross cellular membranes via either an endocytic pathway or passive diffusion (Fig. 2). In the endocytic process, CNTs are engulfed into vesicles called endosomes, which subsequently transport them to lysosomes located in the perinuclear region [(30)]. On the other hand, passive diffusion of CNT's, often referred to as needle-like penetration, allows CNT's to pass through the cellular membrane without requiring energy expenditure [(31)]. Based on computational and electron microscopy studies, the passive diffusion of functionalized CNTs ($f$-CNTs) through the phospholipid bilayer can be described in three stages: i) adsorption and movement of $f$-CNTs on the membrane surface; ii) insertion into the lipid head groups; and iii) passage through the lipid tail region. [(32)]. The high surface area, chemical stability, and excellent thermal and electrical conductivity of CNT's make them versatile nanoparticles with potential applications in the treatment of colorectal cancer (CRC) [(33)]. Phagocytic cells primarily internalize carbon nanotubes (CNTs) via phagocytosis; however, even when this energy-dependent process is inhibited, CNT uptake can still occur through passive diffusion [(36)]. A study found that single – walled carbon nanotubes (SWCNTs) functionalized with TRAIL - a ligand that targets specific receptors to trigger apoptosis in cancer cells- enhanced cell death by tenfold compared to the delivery of TRAIL alone in carcinoma cell lines [(35)]. Numerous studies have indicated the development of various strategies utilizing carbon nanotubes (CNTs) for the delivery of antitumor drugs. In one approach, single-walled carbon nanotubes (SWCNTs) conjugated with a synthetic polyampholyte were employed to deliver paclitaxel to Caco-2 cells. Treatment with paclitaxel-loaded SWCNTs resulted in enhanced anticancer effects in both Caco-2 and HT-29 cell lines compared to paclitaxel alone [(34)].

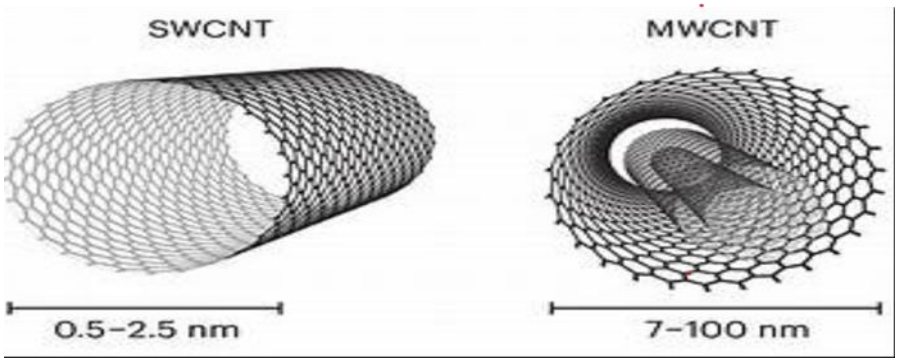


**Figure – 7 Carbon Nanotube**

2. Quantum dots:

Quantum dots (QDs) are fluorescent semiconductor nanocrystals [1] with diameters of the order of 2–10 nanometers. They are referred to as II–VI, III–V, or IV semiconductor nanocrystals, based on the periodic table groups that these elements are from Cadmium selenide (CdSe) and Cadmium telluride (CdTe) nanocrystals are examples of QDs which are group II–VI semiconductor nanocrystal [(37)]. CdSe contains cadmium (Cd) from group II and selenide (Se) from group VI of the periodic table. The fluorescence imaging ability of QDs is because of their higher fluorescence output and photochemical stability [(38)]. The graphene oxide of QD's with peptide name (GILGFVFTL) that has high affinity towards (PLAC-1). In CRC the placenta- specific protein1 (PLAC-1) is over-expressed. QDs probes have been shown to accumulate in tumour by enhanced permeability and retention at tumour sites or by antibody binding to cancer-specific cell surface biomarkers [39].

3. Sliver nanoparticles:

Sliver nanoparticles (Ag NP's) exhibit promising anti-cancer properties through a distinct mechanism of action. Upon entering the cell, Ag NP's release sliver ions ($Ag^+$), which subsequently target the mitochondria. There, these ions interact with thiol group's in proteins, leading to the inhibition of NADPH dehydrogenase enzymes. This interaction promotes the generation of reactive oxygen species (ROS), which can disrupt respiratory chain enzymes, effectively blocking ATP synthesis. Additionally, the ROS produced can bind to DNA and RNA, impairing cell replication and protein synthesis, ultimately resulting in cell death [40]. Nanoparticles offer significant advantages over conventional therapies, as they can be tailored to possess specific proteins and functionalities. They are particularly beneficial for cellular Imaging applications. Silver, in particular, is crucial in imaging systems due to its pronounced and sharp plasmon resonance. Recently, silver-based biosensors have emerged as powerful tools for detecting cytochrome P53 in squamous cell carcinoma of the head and neck [41]. The reusable composite graphene and Ag NP's (GO-Ag NP's) for efficient treatment of CRC. Silver nanoparticles (Ag NP's) can be synthesized using the both top-down and bottom-up approaches. The top-down method involves the mechanical grinding of larger metal particles, often utilizing the colloidal protective agents to stabilize the resulting the nanoparticles. While chemical reduction is noted for its high yield, it presents significant and drawbacks, including high costs and the use of toxic and hazardous materials during the synthesis process [(43)].

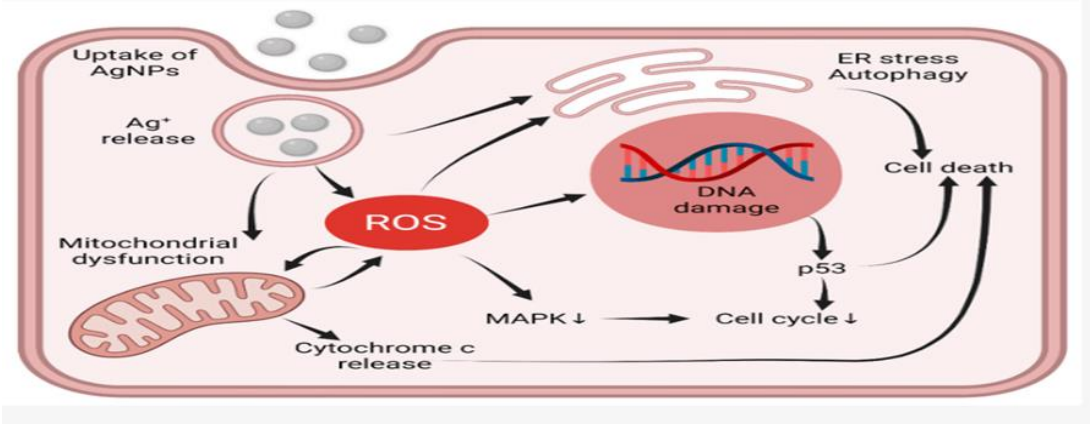


**Figure 8: Sliver nanoparticles released the Ag ions to the generation of Reactive Oxygen Species**

4. Gold nanoparticles:

Gold (Au) is a chemically inert element that is highly favoured for various applications due to its abundance, ease of handling, straightforward fabrication methods, and resistance to corrosion. Additionally, its

chemical stability and biocompatibility make it an ideal choice for many uses [44]. AuNp's have demonstrated significant promise as carrier for drug delivery. When combined with various targeting ligands, AuNp's serve as an effective means for the targeted administration of both novel and establishment treatment for metastatic tumour [45]. The direct attachment of certain medicinal compound to gold particles can be achieved through physical adsorption as well as ionic or covalent interactions [46]. The enhanced permeability and retention (EPR) effect enhances the uptake of nanoparticles in tumours, enabling efficient passive targeting through their accumulation in tumour vasulature[47,48]. AuNp's may enter cells through mechanisms such as passive diffusion, cytosis, receptor- mediated endocytosis, transcytosis, or non- specific receptor- independent endocytosis, depending on these characteristics. Different strategies facilitate the cellular uptake and internalization of gold nanoparticles (AuNp's), influenced by several factors, including particle size, surface properties, morphology, and functionalization.[49,48]). Additionally applying a biodegradable coating to the nanoparticles surface can enhance stability in physiological environments [50,51].

5. Mesoporous silica nanoparticles:

These NP's re appeared as honeycomb-like structure of silica (SiO2). The Mesoporous silica nanoparticles. The High amount of drug is loading into the core of silica NP's. Mesoporous silica nanoparticles (MSNs) can effectively encapsulate therapeutic agents either through covalent binding or electrostatic adsorption. Their mesoporous structure allows for significant drug loading capacity within the core, while exhibiting low toxicity and controlled drug release. These characteristics render MSNs particularly advantageous for targeted drug delivery applications. Additionally, their stability is attributed to the robust Si-O bonds present in their structure [51]. Mesoporous silica nanoparticles (MSNs) have garnered significant interest owing to their distinctive features, such as high porosity, the ability to load dual or multiple drugs, biodegradable nature, biocompatibility, controlled drug release capabilities, and the potential for incorporation with detectable agents. This release mechanism can be regulated through various endogenous and/or exogenous stimuli [53]. The pH level in the tumor microenvironment (TME) is generally lower than that of healthy tissues [54] As a result, functionalized mesoporous silica nanoparticles (MSNs) that utilize pH-responsive gatekeepers, such as gold nanoparticles, can effectively transition from a closed to an open state in response to this endogenous stimulus, thereby modulating the release of encapsulated therapeutic agents [54].

## CONCLUSION

Colorectal cancer (CRC) presents considerable treatment challenges, but inorganic nanoparticles (INPs) offer promising new avenues for therapy. These nanoparticles possess distinctive features—such as increased photosensitivity, electrical conductivity, magnetic properties, and thermal efficiency—that allow them to function both as drug carriers and as direct therapeutic agents.

In contrast to organic nanoparticles, INPs have the potential for greater drug-loading capacities and can facilitate advanced treatment techniques like photothermal therapy (PTT) and photodynamic therapy (PDT). Typically composed of metals, metal oxides, and non-metallic substances, INPs may enhance the effectiveness of treatments while also reducing the adverse effects commonly associated with conventional chemotherapy. A critical aspect of their clinical success involves understanding how INPs are cleared from the body. Most INPs, due to their larger particle sizes and non-biodegradable characteristics, are not eliminated through renal pathways via urine. Instead, hepatobiliary excretion through feces may serve as a more viable alternative. However, this elimination route is significantly affected by the interactions

between INPs and liver cells, which ultimately influences their disposition in the body.

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