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"Integrative Approaches in Cancer Management: Bridging Herbal and Modern Medicinal Systems"

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ABSTRACT:

Cancer is among the leading causes of millions of deaths worldwide every year, even though much progress has been made in medicine and many studies are still underway to improve cancer therapy. Significant strides in cancer (oncological) research are directed toward discovering novel and efficient therapies aimed at mitigating the severe side effects induced by conventional treatments, incorporating a fusion of herbal and allopathic-based therapeutic approaches. Herbal-origin medicines play a pivotal role in this endeavor, offering potential solutions that combine the inherent benefits of natural compounds with the rigorously tested methodologies of modern medicine. By integrating herbal remedies into conventional oncological treatments, researchers seek to leverage their diverse pharmacological properties to enhance treatment efficacy while minimizing adverse effects. This integrative approach underscores a commitment to holistic patient care, striving to optimize outcomes and improve the overall quality of life for individuals undergoing cancer treatment.

Shogaol, Allicin, Apigenin, Baicalein, Baicalin, Curcumin, Quercetin, Emblica Officinalis, and Camptothecin could be a ray of hope for managing cancer. Advancements in the development of biocompatible materials have significantly contributed to both diagnostic and therapeutic purposes in cancer treatment. This includes targeted therapy, immunotherapy, and gene therapy. This review comprehensively examines recent innovations within both herbal and allopathic medicinal systems, specifically focusing on their utilization in cancer management. By analyzing the integration of these two medical paradigms, the review sheds light on promising strategies for effectively combating cancer while minimizing adverse effects. This exploration underscores the potential of combining traditional herbal remedies with modern allopathic approaches to optimize patient outcomes and pave the way for more personalized and comprehensive cancer care.

1. Introduction

In broad terms, cancer is described as a collective term for diseases or conditions that have the potential to affect any organ system within the body. It ranks as the second most prevalent non-communicable disease globally, following ischemic heart disease (IHD). However, despite ongoing medical advancements, the cure rate for cancer remains relatively low, estimated at approximately 20%. This statistic highlights the persistent challenges in effectively treating and managing this multifaceted disease. (1)

Cancer may be caused by many foreign objects like chemicals, radiation, smoking, tobacco chewing, and infectious organisms, and some internal factors as well like: inherited mutations, hormones, immune conditions, and random mutations [2]. The cancerous cells divide abnormally, due to the higher proliferation speeds displacing normal tissue. The tumor blood vessels are often described as structurally and functionally abnormal. Cancer arises from abnormal cell growth, often manifesting as lumps that can develop into malignant tumors. These tumors can spread to other regions of the body, potentially infiltrating lymph nodes or other organs, and may disrupt their normal functions. Conversely, benign tumors do not metastasize, but cancerous cells from malignant tumors can detach and migrate from the primary site, leading to the formation of secondary tumors. This process, known as metastasis, plays a

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significant role in the progression and dissemination of cancer throughout the body [3].

Cancer classification presents a challenge due to the diverse range of cancers originating from various human tissues. These cancers can be categorized based on their primary site of origin or their tissue types. Histologically, there are five primary types of cancer: Sarcoma, Myeloma, Lymphoma, and Mixed Types. Each type exhibits distinct characteristics based on the tissues involved and their microscopic features. This classification system aids in understanding the nature of cancer and guides treatment decisions tailored to specific cancer types [4]. At the cellular level, cancer is characterized by alterations in deoxyribonucleic acid (DNA), leading to abnormal genetic expression. This can affect the transcription process, wherein DNA is transcribed into messenger ribonucleic acid (mRNA). Changes in genetic expression can result in the production of abnormal mRNA, leading to alterations in the sequence of amino acids during protein synthesis. Consequently, this abnormal protein synthesis contributes to the pathogenesis of cancer. These molecular changes underline the complexity of cancer development and progression. (5)

Currently, the widely used treatment landscape involves use of potent cytotoxic drugs targeting rapid proliferating cancerous cells. These conventional methods cause serious adverse effects to normal cells, gradual development of multidrug resistance due to long-term treatment approach and suboptimal drug level at tumor site concerning pharmacokinetic profile. Therefore, advancement in cancer research is important to overcome these adverse effects. [6] [7]. Various approaches like gene therapy, immunotherapy, phototherapy, and thermal therapy have been developed recently and studied for minimizing cancer. However, their efficacy varies significantly from patient to patient due to the different types of drug resistance mechanisms in patients.

Tailoring the drug doses and targets based on the molecular characteristics of tumors has the potential to enhance treatment outcomes and provide targeted therapies aimed at minimizing cancer progression. [8].

Herbal treatments offer a promising avenue for managing cancer progression in situations where traditional therapies such as chemotherapy, radiotherapy, or surgery led to adverse reactions or are not viable options. Rasayana therapy, known for its cell-protective properties, plays a significant role in enhancing the comfort and quality of life for cancer patients [9]. This review discusses the comparison between recent advancements in drug delivery sciences for herbal drugs and modern allopathic in the context of cancer management.

Herbal treatments offer a promising avenue for managing cancer progression in situations where traditional therapies such as chemotherapy, radiotherapy, or surgery led to adverse reactions or are not viable options. Rasayana therapy, known for its cell-protective properties, plays a significant role in enhancing the comfort and quality of life for cancer patients [9]. This review discusses the comparison between recent advancements in drug delivery sciences for herbal drugs and modern allopathic in the context of cancer management.

Treatment of Cancer-

Cancer treatment strategies focus on mitigating the advancement of this life-threatening illness, aiming to afford patients a semblance of normalcy. While complete eradication may not always be attainable, therapies endeavor to either reduce tumor size or impede its growth, thereby extending patient longevity. Various avenues such as chemotherapy, radiation therapy, immunotherapy, surgery, and bone marrow transplants offer treatment options. Nonetheless, these methods often encounter critique due to challenges associated with drug bioavailability at the intended site, leading to a spectrum of severe adverse effects that can prove fatal [35]. It is very difficult to treat the cancer as it is an aggressive disease due to several reasons. These include the major inter and intra-tumor heterogeneity and the mutations in hundreds of different genes contributing to cancer. Furthermore, cancer can affect a wide range of cells (e.g., epithelial, stromal, blood-based) and organs in the body. In addition, cancer is generally not a static disease, but evolves and progresses over time accumulating new mutations [11- 12]. Hence, with cancer increasing in incidence, related clinical management continues to be a challenge in the 21st century. The utilization of medicinal herbs and their derived extracts, rich in polyphenolic compounds, holds promise for cancer management. Therefore, herbal

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medicinal systems can complement conventional chemotherapy and radiation therapy, potentially enhancing therapeutic outcomes and quality of life (QoL) while mitigating adverse effects and complications [13-14].

Ayurvedic medicine identifies numerous herbal combinations that hold significant promise for cancer treatment. Scientifically, these concoctions show their effect through various enzymatic pathways dynamically affecting human components. By promoting overall nourishment, these herbal combinations facilitate total healing while mitigating side effects and complications associated with cancer [15]. Numerous plants have been scientifically studied for their anticancer properties, including Raphanus sativus, Barleria prionitis, Prosopis cineraria, Amorphophallus campanulatus, Oxoxylum indicum, Tinospora cordifolia, Semecarpus anacardium, Vitis vinifera, Baliospermum montanum, Madhuca indica, Pandanus odoratissimum, Pterospermum acerifolium, Basella rubra, Flacourtia romantchi, Moringa oleifera, Ficus bengalens Many herbal substances are currently being clinically evaluated and phytochemically analyzed to better understand their potential as cancer treatments. According to recent studies, more than 25% of medications used in the last 20 years are derived from plants, with the remaining 25% being chemically modified natural compounds. Notably, nine plant-derived compounds— teniposide, taxol, vincristine, vinblastine, etoposide, navelbine, taxotere, topotecan, and irinotecan—have been licenced as cancer treatments. Colchicinamide, curcumol, 10-hydroxycamptothecin, monocrotaline, d-tetrandrine, lycobetaine, indirubin, curdione, gossypol, and homoharringtonine are some of the promising natural plant-derived cancer treatments. [16,17]

The active compounds found in these herbal plant species work synergistically to increase the therapeutic efficacy and reduce side effects with enhanced pharmacokinetics. This synergy can minimize the need for additional supplementary therapies in cancer management. Therefore, raising awareness and encouraging physicians to integrate herbal therapies into cancer treatment protocols is essential for optimizing patient care. By advocating for an integrated approach to tumor management, healthcare professionals can harness the potential benefits of herbal remedies alongside conventional treatments, ultimately aiming to minimize the impact of cancer on patients' lives**.** Herbal therapies have long been utilized in various cultures for their medicinal properties, and recent research has highlighted their potential role in cancer prevention and treatment. However, it's crucial to approach the integration of herbal remedies into cancer care with caution and expertise. The role of physicians is to keep abreast with the latest evidence- based practices and potential interactions between herbal treatments and conventional cancer therapies to ensure patient safety and efficacy.

Furthermore, fostering collaboration between traditional and alternative medicine practitioners can enhance the effectiveness of integrated cancer treatment plans. By combining the strengths of both approaches, healthcare professionals can tailor treatment strategies to individual patient needs, addressing not only the physical aspects of cancer but also the emotional and psychological well-being of patients.

In conclusion, raising awareness among physicians about the benefits of herbal therapies in cancer treatment and advocating for an integrated approach to tumor management is essential. By embracing herbal remedies alongside conventional treatments, healthcare professionals can provide patients with a more comprehensive and personalized approach to battling cancer, ultimately striving for improved patient outcomes and quality of life. [18]

The established standard treatment modalities for cancer, encompassing surgery, chemotherapy, radiotherapy, and targeted therapy, often entail side effects that might inadvertently exacerbate the patient's condition. Hence, there is a critical imperative to pioneer advanced treatment approaches that offer heightened efficacy and precision. Conventionally, the typical treatment regimen for individuals afflicted with malignant tumors entails surgical resection aimed at tumor removal, followed by a chemotherapeutic regimen and radiotherapy. While these interventions have demonstrated efficacy in numerous cases, their potential side effects pose significant challenges, and they may not consistently A diverse array of surgical techniques is at the disposal of healthcare practitioners, ranging from conventional to minimally invasive approaches. Among the less invasive options are endoscopic and laparoscopic surgeries, which offer patients benefits such as reduced postoperative pain and

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shorter recovery times. In addition to these established methods, newer surgical techniques have emerged, broadening the scope of treatment options available. These include microwave ablation, cryosurgery, radiofrequency ablation, and high-intensity focused ultrasound (HIFU)deliver optimal outcomes. To confront these issues, researchers and clinicians are actively exploring innovative avenues in cancer treatment. These may encompass precision medicine methodologies, which tailor therapies to the unique molecular characteristics of the tumor, immunotherapy approaches that harness the body's immune system to combat cancer, and sophisticated radiation techniques designed to minimize harm to surrounding healthy tissues. Additionally, there is burgeoning interest in complementary and alternative therapies, including herbal medicine, acupuncture, and mind-body interventions, which promise to mitigate treatment-related side effects and enhance overall patient well-being.

By embracing these progressive approaches and integrating them into the conventional framework of cancer care, healthcare practitioners can offer patients a more tailored and holistic treatment paradigm. This not only endeavors to augment treatment effectiveness but also places a premium on patient-centered care by mitigating side effects and optimizing quality of life throughout the cancer treatment [19].

Surgery stands as one of the earliest methods employed for cancer treatment, dating back to eras predating the advent of anesthesia and antisepsis. Despite its ancient origins, surgery remains a cornerstone of cancer management and care. The evolution of medical imaging technologies, such as radiography and CT scanning, has significantly enhanced the precision of tumor localization. This advancement has notably contributed to the increased efficacy of surgical tumor removal across various cancer types. Furthermore, the timely detection and removal of precancerous lesions through screening initiatives hold substantial promise in facilitating the surgical excision of invasive cancers at their nascent stages. By preemptively addressing precancerous abnormalities, healthcare providers can potentially intercept the progression of malignancies and intervene with surgical interventions when the disease burden is minimal. Overall, the enduring relevance of surgery in cancer treatment underscores its indispensable role in the comprehensive management of the disease. Leveraging advancements in imaging technology and early detection strategies not only enhances the precision of surgical interventions but also enables proactive measures to mitigate cancer progression, ultimately improving patient outcomes [20]. A diverse array of surgical techniques is at the disposal of healthcare practitioners, ranging from conventional to minimally invasive approaches. Among the less invasive options are endoscopic and laparoscopic surgeries, which offer patients benefits such as reduced postoperative pain and shorter recovery times. In addition to these established methods, newer surgical techniques have emerged, broadening the scope of treatment options available. These include microwave ablation, cryosurgery, radiofrequency ablation, and high-intensity focused ultrasound (HIFU). Each of these techniques harnesses distinct mechanisms to target and eliminate cancer cells. Microwave ablation employs focused microwave energy to generate heat and induce tumor cell death. Cryosurgery, on the other hand, utilizes extreme cold to freeze and destroy cancerous tissues. Radiofrequency ablation relies on high- frequency electrical currents to heat and eradicate tumors. Finally, HIFU delivers focused ultrasound waves to precisely heat and destroy cancer cells while sparing surrounding healthy tissues. These innovative surgical modalities offer the advantage of inducing localized alterations in temperature, effectively targeting and eliminating cancer cells within the treatment area. By harnessing the unique properties of each technique, healthcare providers can tailor treatment strategies to individual patient needs, optimizing outcomes while minimizing the impact on surrounding healthy tissues. (20)

Despite the success achieved in local control through surgical resection, long-term mortality and side effect rates remain consistently high, mostly due to cancer metastasis [20]. As the incidence of malignant diseases continues to rise, radiotherapy has emerged as a crucial management tool for cancer patients. It is estimated that over half of all cancer patients receive radiotherapy at some stage of their treatment journey. Radiotherapy typically employs ionizing radiation, which includes various forms such as X-rays, gamma rays, and particle radiation (including electrons, protons, neutrons, carbon ions, alpha particles, and beta particles). These forms of radiation are utilized to target and eliminate

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cancer cells within the body. By delivering controlled doses of radiation to specific areas of the body affected by cancer, radiotherapy precisely delivers high-energy radiations at targeted cancer cells. This targeted approach helps to shrink tumors, alleviate symptoms, and ultimately improve patient outcomes. [19].

The fundamental principle underlying radiotherapy involves the ionizing effect of radiation, which disrupts and damages the DNA of cancer cells, leading to their demise and subsequent reduction in tumor size. For instance, in brachytherapy, radiation emanates directly from a radioactive isotope like radium-223, typically positioned within or near the nucleus of the tumor cells. Predominantly, radiotherapy serves as adjuvant therapy, often complementing surgical interventions to enhance treatment effectiveness and mitigate the risk of cancer recurrence. By delivering precise doses of radiation to residual cancer cells post-surgery, adjuvant radiotherapy aims to eradicate any lingering malignant cells, thereby diminishing the probability of disease resurgence. This integrated approach of combining surgery with adjuvant radiotherapy is pivotal in comprehensive cancer management, offering patients improved treatment outcomes and reduced rates of relapse. [23].

Recent Advances in Cancer Therapies Utilizing Herbal-Based Anti-Cancer Agents:

Herbal-derived drugs are recognized as an effective treatment for reducing cancer. Numerous herbal plants from around the world possess compounds that could potentially be used in cancer therapy. Several investigations are underway employing these nanofibers encapsulating herbal-based drugs for cancer therapy. A portion of the herbal-drug- encapsulated nanofibers used in cancer treatment are:

Shogaol

Shogaol, a bioactive compound extracted from ginger (Zingiber officinale, Roscoe), exhibited significant inhibition of lung cancer cell growth in a mouse model of non-small cell lung cancer when administered at a dosage of 10 mg/kg. This effect was linked to decreased cell proliferation and increased apoptosis, as indicated by a reduction in positive cells and an elevated count of terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick-end labeling positive cells. [101].

Allicin

Allicin is an organ Sulphur bioactive compound found in garlic (Allium sativum)). It has been studied for its effects on a mouse model for cholangiocarcinoma. It was observed that allicin considerably inhibited the growth of human liver bile duct carcinoma at the dose of 10mg/kg. In an in vitro molecular analysis, allicin at a concentration of 20 μM reduced matrix metalloproteinase levels by inhibiting the activity of the signal transducer and activator of the transcription signaling pathway. This inhibition led to a decrease in migration, invasion, and epithelial-mesenchymal transition of human liver bile duct carcinoma cells [102].

Apigenin

Apigenin is a naturally occurring flavonoid present in fruits and vegetables with diverse anticancer properties. In the mouse model of chondrosarcoma cells, Apigenin, administered at a dosage of 5 mg/kg, inhibited tumor growth, correlating with a reduction in apoptosis. Apigenin impacts the molecular level by modulating the expression of B-cell lymphoma 2 family proteins and initiating the caspase cascade. This process results in G2/M phase arrest and apoptosis. [101].

Baicalein and baicalin

Baicalein and baicalin are naturally occurring flavonoids and the active components of Scutellaria baicalensis (Lamiaceae). In the mouse model of colon cancer, baicalein (50 mg/kg) and baicalin (50 mg/kg) inhibited tumor growth and induced apoptosis. It suppressed p38 signaling, extracellular signal-regulated kinase, and mitogen-activated protein kinase expression in vivo. It also reduced the expression of human telomerase reverse transcriptase [103].

Curcumin

Turmeric contains a bioactive phenolic component called curcumin, which has profound anticancer effects. Researchers evaluated curcumin's anticancer activity on carcinoma cells after incorporating it into poly(lactic-co-glycolic) acid (PLGA) nanofibers. Curcumin-loaded electrospun nanofibers showed a noteworthy initial quick release followed by a sustained and continuous release in the treatment of breast cancer, suggesting its potential safety for therapeutic usage. A unique method of treating breast cancer includes the use of chitosan (CS) nanofibers loaded with curcumin as a medication delivery vehicle. Recent research studied the delivery of curcumin and chrysin (CH) by electrospun PLGA-PEG nanofibers on breast cancer cells, which exhibited a sustained and continuous drug release without any burst release. Because of its potent antibacterial, antioxidant, anticancer, anti-inflammatory, and anti-infective qualities, curcumin is highly appreciated for a variety of medical applications. [28]

Quercetin

Quercetin, a polyphenolic component found in plants such as apples and tea, has been shown to prevent or diminish the growth of tumor cells. An early study examined quercetin release utilizing biodegradable poly(lactide-co-glycolide)-polycaprolactone (PLGA/PCL) nanofibers on human hepatocellular cancer cells. The in vitro release investigation revealed that the PLGA/PCL nanofibrous matrix facilitated and maintained drug release. There were also improvements in quercetin's aqueous permeability, system degradation, and diffusion rate.

Camptothecin

Camptothecin, a naturally occurring chemical produced from the bark and stem of the Camptotheca acuminata tree, mostly found in China and Tibet, has been employed in combination with peptide amphiphile (PA) nanofibers. Camptothecin encapsulated in PA nanofibers has significant antitumor potential, according to studies conducted in vitro on breast cancer cells [33]. Emblica Officinalis

Emblica Officinalis, commonly known as Indian Gooseberry or Amla, is extensively utilized in modern medicine and holds a pivotal position in the Indian traditional medical system, Ayurveda. Acquired through natural means via plant extracts, it exhibits noteworthy therapeutic properties with minimal adverse effects. When formulated as polycaprolactone nanofibersPromising antiproliferative actions against human breast cancer cell lines are demonstrated by Emblica officinalis. Its various advantages are demonstrated by preclinical evaluations. These include its ability to be a radiomodulator, chemomodulatory agent, chemopreventive agent, antioxidant,anti-inflammatory, cardioprotective, antipyretic, analgesic,antianemic,wound healing,antidiarrheal,nephroprotective,and neuroprotective. [34]. Current developments in cancer treatments by using allopathic-based Cancer treatment strategies:

Nanomedicine

Nanoparticles are minuscule entities, usually within the range of 1 to 1,000 nanometers in diameter, distinguished by their unique physicochemical attributes stemming due to their size and increased surface area-to-volume ratio [36]. Certain nanoparticles are utilized in cancer treatment to overcome challenges associated with traditional therapies, such as limited specificity and the availability of drugs or contrast agents [37]. Hence, employing the encapsulation method for active agents within nanoparticles can improve their solubility and biocompatibility, enhance their stability within the body, and increase their retention time in tumor vasculature. [38]. Furthermore, nanoparticles exhibit remarkable selectivity towards specific targets. [39, 40] and release the drug in a controlled manner in response to specific stimuli within the body [41, 42]. Inorganic nanoparticles play a crucial role as substitutes in diagnostic applications, with quantum dots standing out prominently. These quantum dots are tiny semiconductor nanocrystals recognized for their powerful fluorescence, resilience against photobleaching, and outstanding sensitivity in tasks related to detection and imaging [43]. Through integration with active ingredients, nanoparticles offer promising potential for therapeutic applications [43]. In a recent study, semiconductor nanoparticles like quantum dots coated with polyethylene glycol (PEG) were conjugated with anti-HER2 antibodies to target specific tumor cells. [44].

Liposomes are sphere-shaped particles composed of at least one lipid bilayer, resembling cell membranes, and they are extensively used as drug delivery systems. Liposomes are primarily used to encapsulate hydrophilic drugs within their aqueous core, but they can also accommodate hydrophobic drugs within the bilayer or through chemical attachment [45]. Agents with hydrophobic cores can effectively encapsulate hydrophobic drugs. Notably, Doxil, the first FDA approval of nanoparticle agents occurred in 1995 for the treatment of AIDS-associated Kaposi’s sarcoma, which involved doxorubicin-loaded PEGylated liposomes. [47]. This formulation significantly reduces the side effects associated with doxorubicin. Subsequently, additional liposomal formulations, including Myocet and

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DaunoXome, have obtained FDA approval for cancer treatment. [48], Several other formulations have gained FDA approval, such as Abraxane (albumin-bound paclitaxel particles for metastatic breast cancer and pancreatic ductal adenocarcinoma treatment) and Ontak (a fusion protein of interleukin-2 and diphtheria toxin for non-Hodgkin's peripheral T- cell lymphomas treatment).

Targeted therapy and immunotherapy-

A significant challenge in cancer management is the lack of selectivity of chemotherapeutic medicines for cancer cells. Studies indicate that many drugs affect both healthy and diseased cells and tissues, resulting in severe side effects. Researchers are exploring alternative methods to specifically target cancer sites. Nanoparticles have gained substantial interest because they tend to aggregate more in tumor tissues and cells, which is attributed to the improved permeability and long-term action [50]. This mechanism is known as passive accumulation, relying on the small nanoparticle size and the compromised vasculature and reduced lymphatic drainage of cancerous cells or tissues [51]. Nevertheless, passive targeting is challenging to control and may lead to the development of multidrug resistance (MDR). [52]. Conversely, active targeting improves absorption by tumor cells through the targeting of specific receptors that are excessively expressed on their surface [53,54]. Nanoparticles are modified with ligands that specifically bind to cancer cells or sites, facilitating targeted delivery [51]. Various types of ligands can serve as vehicles, including chemical compounds, short chains of amino acids, biological macromolecules, nucleic acid ligands, and immune system proteins can be employed for this objective. Among the smallest molecules are folic acid and biotin, whose receptors are frequently upregulated in tumor cells. Many nanoparticles have been modified with folic acid to specifically target ovarian and endometrial cancers [55]. Nanoparticles composed of polyethylene glycol-poly (lactic-co- glycolic acid) conjugated with folic acid, delivering docetaxel, demonstrated an increase in the uptake of drugs by cervical carcinoma cells [56]. Compact ligands are economical and are readily attached to nanoparticles using straightforward conjugation techniques [57].

Immunotherapy can also be implemented through a strategy known as adoptive cell transfer (ACT). This approach involves isolating T-lymphocytes (T-cells) with the greatest anti- cancer activity directly from the patient's blood, expanding them ex vivo, and subsequently reintroducing them into the patient's system [58]. Autologous T-cells can undergo genetic modification in vitro to express a chimeric antigen receptor, enhancing their specific antigens of cancer cells [59]. Various chimeric antigen receptors can be tailored to target specific cancer antigens Various methods can be utilized to genetically modify T-cells, such as viral transduction, some non-viral methods such as DNA-based transposons, CRISPR/Cas9, or alternative techniques, such as electroporation and encapsulation in nanoparticles for DNA and mRNA transfer [60]. ACT protocols are integrated into clinical practice for advanced or relapsed acute lymphoblastic leukemia and specific hostile forms of non-Hodgkin's lymphoma [59]. Research shows that administering CAR T-cell therapy to end-stage patients with acute lymphocytic leukemia led to complete remission in as many as 92% of cases [60]. Despite the highly promising outcomes, ongoing research is dedicated to comprehending acute adverse effects of CAR T-cell therapies, their persistence within cancerous cells, and enhancing technologies for CAR T-cell expansion.

Gene therapy: An Approach for cancer treatment-

Gene therapy involves the insertion of a functional copy of a mutant gene into the genome to address the disease of interest. This approach aims to correct genetic abnormalities by providing the body with the genetic information it needs to produce functional proteins or restore normal cellular functions. By introducing a functional gene, gene therapy has the potential to treat various genetic disorders and other diseases at their fundamental cause [61]. The initial application of gene therapy occurred with the use of a retroviral vector to transport the adenosine deaminase (ADA) gene into T-cells of individuals diagnosed with severe combined immunodeficiency (SCID). This groundbreaking approach aimed to address the underlying genetic defect causing SCID by providing a functional ADA gene to the patient's cells, thereby restoring their immune system functionality [62]. Recent research has explored the potential application of gene therapy in various rare and chronic human disorders, with a significant focus on cancer treatment. Presently, there are approximately 2,900 ongoing clinical trials investigating gene therapy, with around 66.6% of these trials specifically targeting cancer-related conditions. This underscores the growing interest and potential of gene therapy as a promising approach in the fight against cancer and other diseases [63]. Various strategies are being assessed for cancer gene therapy, including

1.Inducing the expression of genes capable of eliciting targeted antitumor immune responses.

2.Introducing wild-type tumor suppressor genes to restore normal cellular functions and inhibit tumor growth

3.Expressing proapoptotic and chemo-sensitizing genes to enhance cancer cell death and sensitize tumors to chemotherapy.

4.Employing targeted approaches to silence oncogenes, which are genes that promote cancer development and progression.

The wide array of strategies underscores the intricate nature of gene therapy in addressing cancer, leveraging various pathways and mechanisms to efficiently combat the disease [64]. One proposed methodology involves the introduction of the thymidine kinase (TK) gene, combined with the subsequent administration of the prodrug ganciclovir, which is designed to activate TK expression and generate specific cytotoxic effects [65] This approach has undergone clinical testing for the treatment of glioma and prostate cancer, demonstrating its efficacy in targeted therapy for these conditions. [66, 67].

Adenoviral vectors engineered to selectively replicate in cancer cells lacking functional p53 tumor suppressor genes have recently been studied for potential clinical applications. One such vector, ONYX-015, has been investigated in patients with non-small cell lung cancer (NSCLC). Promising results have been observed when ONYX-015 was administered as a monotherapy or in combination with chemotherapy, with a notably high response rate reported in these NSCLC patient trials" [68].

The gene therapy product Gendicine, an adenoviral vector engineered to deliver a functional copy of the wild-type p53 gene, has exhibited encouraging results in the treatment of head and neck squamous cell carcinoma. When administered as an adjuvant therapy alongside radiotherapy, Gendicine has displayed the ability to induce complete remission of the disease in some patients. This mirrors the positive outcomes reported for the adenoviral vector ONYX-015, which selectively replicates in p53-deficient cells when used to treat non-small cell lung cancer either as a monotherapy or in combination with chemotherapy [69].

While gene therapy approaches like adenoviral vectors have shown promise in cancer treatment, significant hurdles remain to be overcome. Key challenges include achieving optimal therapeutic gene expression levels and developing delivery systems that can precisely target cancer cells. Limitations have arisen due to issues with genomic integration in certain patient subgroups and immune system neutralization of the gene delivery vectors, hampering overall efficacy. As a result, targeted gene silencing strategies have gained substantial interest as an alternative approach. RNA interference (RNAi) technology has proven to be a advantageous tool for both research and therapeutic applications. Small interfering RNAs (siRNAs), composed of double-stranded RNA molecules, represent a promising modality for regulating gene expression and developing novel cancer therapies by silencing specific disease-driving genes. [70] Targeted gene silencing is achieved through intracellular mediation by the RNA-induced silencing complex (RISC). This complex is tasked with cleaving messenger RNA (mRNA), thereby disrupting protein synthesis processes. [71].

The RNAi pathway is a naturally occurring biological process found in many eukaryotic organisms, including animals. After the initial discovery and characterization of RNAi, researchers rapidly translated this mechanism into therapeutic applications. Notably, within just a few years of its discovery, an RNAi-based treatment for eye disease wet age-related macular degeneration had advanced into phase I clinical trials. This swift progression from basic research to early-stage clinical testing highlighted the immense potential of harnessing RNAi for developing novel therapies targeting various diseases. [72]. Cancer is driven by the dysregulation of specific molecular pathways. Small interfering RNAs (siRNAs) offer a targeted therapeutic strategy by allowing selective silencing of key genes that promote uncontrolled cell proliferation and metastatic dissemination. This RNAi-based approach relies on the ability of siRNAs to induce gene knockdown of anti-apoptotic proteins, which are often overexpressed in cancer cells and contribute to their survival and resistance to cell death. By precisely targeting these pro-survival factors with siRNAs, researchers aim to tip the balance towards apoptosis and impede the oncogenic processes fueling tumor growth and spread. [73], Small interfering RNAs (siRNAs) can also target transcription factors, such as the c-myc gene, or mutated genes commonly associated with cancer, such as K-RAS [74]. Presently, the majority of clinical trials are underway, focusing on either local administration of small interfering RNA oligonucleotides in specific tissues or organs, or systemic delivery throughout the entire body. [75]. Utilizing drugs based on small interfering RNAs offers several advantages: 1) Reduced occurrence of side effects compared to conventional therapies; 2) Ability to be tailored for specific targets; 3) High efficacy, as even small amounts can lead to significant downregulation of genes; 4) Safety, as they do not integrate with the genome; and 5) Cost-effectiveness in production. [76, 77].

While siRNAs hold promise as a therapeutic modality, there in vivo application faces several hurdles. These molecules exhibit relatively low stability and are susceptible to various clearance mechanisms in the body, including phagocytic uptake by immune cells during circulation, renal filtration, and enzymatic degradation. Furthermore, siRNA therapy carries the risk of unintended off-target gene silencing effects as well as the potential to elicit innate immune responses, particularly inflammatory reactions. Overcoming these challenges related to stability, specificity, and immunogenicity is crucial for the successful clinical translation of siRNA-based therapeutics [79].

Small interfering RNAs (siRNAs) face a critical obstacle in their therapeutic application due to their molecular properties. As negatively charged and hydrophilic molecules, unmodified siRNAs cannot passively cross cell membranes to reach their intracellular targets. To overcome this cellular barrier, researchers are actively exploring various siRNA delivery strategies. These include chemically modifying the siRNA structure, encapsulating them within lipid or polymer-based nanocarriers, and conjugating siRNAs to different organic molecules such as polymers, peptides, lipids, antibodies, or small molecule ligands. These delivery approaches aim to facilitate cellular uptake, protect siRNAs from degradation, and potentially enable tissue or cells specific therapeutic drug delivery. [80], Achieving effective targeted delivery of siRNAs often requires modifying their chemical structure through various means. Chemical alterations to the siRNA molecules are commonly employed as part of targeting strategies designed to improve their therapeutic efficacy.[81]. Among these modifications is the incorporation of a phosphorothioate at the 3’ terminus of the small interfering RNA (siRNA) molecule, aimed at mitigating exonuclease degradation [82],

One chemical modification strategy to improve the stability and bioavailability of siRNAs involves incorporating a 2' O-methyl group into the molecular structure. This alteration has been shown to extend the circulating half-life of siRNAs in plasma. Alternatively, researchers have explored modifying siRNAs with moieties like 2,4-dinitrophenol to facilitate their membrane permeability and enhance cellular uptake [83]. These types of chemical modifications aim to overcome key challenges associated with siRNA delivery and enable more effective therapeutic applications. [84]. However, the deterioration of engineered small interfering RNAs frequently induces cytotoxic reactions. Hence, it is more advantageous to develop customized nanocarriers. Various positively charged lipid nanoparticles, including liposomes, micelles, and solid lipid nanoparticles, can serve this purpose effectively [81], Various strategies have been employed for loading small interfering RNAs. Cationic liposomes, for instance, interact with negatively charged nucleic acids, facilitating their transfection through straightforward electrostatic interactions [85]. Liposomal nanoparticles composed of cationic lipids like 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) and N-{1-(2,3-dioleoyloxy) propyl]-N, N, N-trimethylammonium methyl sulfate (DOTMA) have been extensively explored as delivery vehicles for siRNAs. Researchers have developed a theragnostic agent that encapsulates survivin-targeting siRNAs within PEGylated liposomes [86]. This multifunctional design combines two key features: precise tumor localization enabled by entrapped magnetic resonance imaging and fluorescent probes, and the ability to induce anti-proliferative effects in vivo through the silencing of the survivin gene by the encapsulated siRNAs. This approach aims to leverage the diagnostic and therapeutic

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capabilities within a single nanoparticulate platform. [87].

Liposomes composed of neutral lipids, such as 1,2-dioleoyl-sn-glycero-3- phosphatidylcholine (DOPC), have shown promising efficacy as siRNA delivery vehicles in preclinical studies. Specifically, these neutral liposomal formulations have exhibited significant therapeutic potential in mouse models of ovarian carcinoma and colorectal cancer when used to deliver gene-silencing siRNAs. The favourable outcomes observed in these disease models highlight the potential of neutral liposome-based systems for siRNA delivery and anti-cancer applications. [88, 89]. In addition to lipid-based carriers, siRNAs can be formulated using cationic polymeric materials that condense and protect the negatively charged siRNA molecules. Examples of such polymers employed as siRNA delivery vectors include chitosan, cyclodextrin derivatives, and polyethyleneimine (PEI). Chitosan, a naturally derived cationic polysaccharide, has garnered significant interest and has been widely explored for drug delivery of nucleic acid. Demonstrating the potential for both in vitro and in vivo siRNA delivery. The cationic nature of these polymers enables electrostatic complexation with siRNAs, forming condensed nanoparticles suitable for cellular uptake and gene silencing. [90]. Notably, researchers have demonstrated successful targeted delivery of siRNAs using polymeric nanocarriers in preclinical mouse models of breast cancer xenografts. By employing polymer-based siRNA delivery systems, they were capable of effectively transport and release the therapeutic siRNAs within the tumor microenvironment, leading to gene silencing and anti-tumor effects in these in vivo models. [91]. Cyclodextrin- based polymeric nanocarriers have been engineered to deliver a specific small interfering RNA (siRNA) termed CALAA-01. These nanocarriers are coated with polyethylene glycol (PEG) and conjugated with human transferrin, a protein involved in iron transport. This delivery system has demonstrated the ability to effectively inhibit tumor growth by reducing the expression of the M2 subunit of ribonucleotide reductase (R2), a crucial enzyme involved in the synthesis of deoxyribonucleotides required for DNA replication and repair. By silencing the R2 subunit, the nanocarrier-mediated delivery of CALAA-01 siRNA can interfere with the tumor's ability to proliferate and grow. [92].

In order to prolong the circulation time and facilitate efficient cellular entry, small interfering RNAs can be chemically coupled with biomolecules such as peptides, antibodies, and aptamers. These conjugated systems leverage the properties of the attached moieties to improve the stability of the siRNA cargo in biological fluids and promote targeted uptake into desired cell populations. [93]. The aptamer component of Chimera chimeras binds to PSMA (prostate-specific aminotransferase), a receptor overexpressed on the cell surface of prostate cancer cells and tumor vasculature. Additionally, the small interfering RNA component targets the expression of survival genes, yielding positive results in the treatment of prostate cancer [94]. The utilization of nanocarriers has significantly enhanced the stability, pharmacokinetics, biodistribution properties, and targeting specificity of small interfering RNAs. [95, 96]. Currently, researchers are developing smart nanomaterials that respond to external stimuli such as magnetic fields and ultrasounds, as well as tumor-specific cues like acidic pH and redox conditions. These materials are designed for controlled release, aiming to minimize undesired negative effects [97, 98]. This Research has innovative approaches to augment the therapeutic potential of small interfering RNAs (siRNAs) by covalently linking them with various biological molecules. These hybrid constructs, comprising peptides, antibodies, or aptamers, offer several distinct advantages. They prolong the siRNA's circulatory residence time by shielding it from degradative mechanisms present in bodily fluids. Additionally, the attached biomolecules facilitate targeted delivery and cellular internalization of the siRNA cargo into specific cell types or tissues of interest, exploiting the intrinsic properties of the conjugated moieties. This strategy aims to enhance the stability, biodistribution, and uptake efficiency of siRNA therapeutics, thereby improving their therapeutic efficacy. [99]. It's have developed poly(allylamine) phosphate nanocarriers, capable of maintaining structural integrity at physiological pH levels. These nanocarriers have been meticulously engineered to facilitate the release of small interfering RNAs (siRNAs) into the cytoplasm, triggered by the nanocarrier's disassembly at the low pH conditions encountered within endosomal compartments. This strategic design aims to leverage the natural cellular machinery for efficient

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delivery and subsequent cytoplasmic dissemination of the siRNA cargo, enhancing its therapeutic potential. While the siRNA- based approach has demonstrated numerous promising outcomes, several challenges continue to hinder its clinical translation. Determining the appropriate dosages for patient administration and addressing the considerable variability observed among individuals and disease stages remain unresolved issues. [100]

Though allopathic medicines show adverse side effects they are a promising candidate in clinical use due to their efficacy and robust research background which ayurvedic system lacks. Integrating ayurvedic system with allopathic system to manage the side effects of allopathic medicines and improve quality of life of cancer patients could be one strategy worthy to explore.

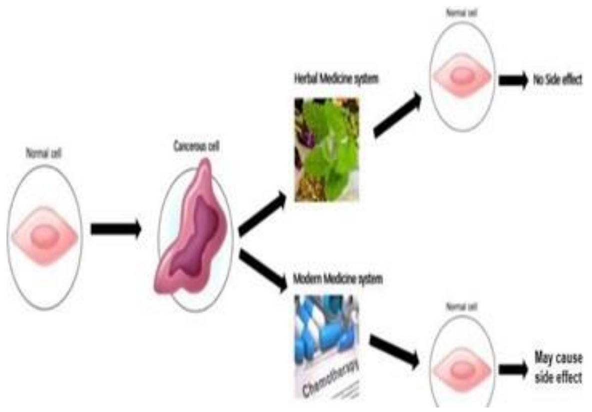
Both the systems emphasize patient-centric medical care but in different ways. Ayurveda focuses on individualized treatment plans based on a person's unique constitution, while allopathic medicin**e**

IMPACT OF AYURVEDIC AND ALLOPATHIC SYSTEM OF MEDICICNES ON CANCER TREATMENT.

The table below describes the way both ayurvedic and allopathic system of medicines approaches the cancer treatment. [15,19]

Ayurvedic system of medicines	Allopathic system of medicines
Holistic approach Ayurveda tries to restore the energies of bodies present in the form of doshas through Satvik diet, changes in lifestyle, herbal remedies and practicing yoga.	**Surgical interventions** For the first line of treatment the affected area or the source of cancer is removed surgically with improved outcomes.
Herbal Remedies Ayurvedic herbs are utilized for their anti-cancer-like properties such as ashwagandha (Withania somnifera) and many more.	**Chemotherapy** Synthetically derived medicines are used which are potent, toxic and has adverse drug reaction to kill the cancer cells. Although the normal healthy cells are also affected.
Supportive care Ayurveda treatments help to minimize the adverse effects of allopathic treatment through meditation, herbal supplements, and improve digestion and weak immune system.	**Radiotherapy** This treatment approach involves using high energy radiation to destroy cancer cells without affecting normal healthy functional cells.

increasingly moves towards personalized medicine based on genetic pool the individual possess and molecular profiling In summary, while the allopathic system remains the primary approach for treating cancer due to its evidence-based methods and technological advancements, the Ayurvedic system offers valuable complementary strategies that can enhance quality of life and potentially improve treatment outcomes when used alongside conventional therapies. Integrative approaches that combine both systems are gaining popularity, reflecting a more holistic view of cancer care. Further research endeavours, with a focus on achieving controlled release to target specific sites and developing optimal personalized therapies tailored to each cancer patients, will be crucial in the coming future. Overcoming these hurdles through continued scientific exploration and innovation will be essential for realizing the full therapeutic potential of this approach.



1. **Title: Comparison of Cancer Cell Treatment: Herbal vs. Modern Medicine**
2.Flow Diagram Elements:
•Normal Cell: Start with a simple illustration of a normal cell.
•Cancerous Cell: Show a transformation from a normal cell to a cancerous cell, indicating mutation or malignancy.
•Herbal Medicine System:
•Image/Illustration: Use an illustration of a plant or herbs (make sure it's a different plant or illustration style).
•Description: Show the pathway leading from the cancerous cell to a restored normal cell, labeled "Herbal Medicine Treatment."
•Outcome: Label the outcome with "No Side Effects."

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•Modern Medicine System:
•Image/Illustration: Use an illustration of chemotherapy drugs (ensure it's a different style or specific to avoid direct copying).
•Description: Show the pathway leading from the cancerous cell to a restored normal cell, labeled "Modern Medicine Treatment."
•Outcome: Label the outcome with "May Cause Side Effects."
3.Annotations and Arrows:
•Use arrows to indicate the progression from the normal cell to the cancerous cell and from the cancerous cell to the treated cells in both pathways.
•differentiate the two treatment methods with distinct visual styles or colours.

Diagram: Comparison of Cancer Cell Treatment Approaches

- Normal Cell --> Cancerous Cell
- Herbal Medicine Treatment:
- Image: Herb illustration.
- Arrow: Cancerous Cell --> Normal Cell
- Label: No Side Effects
- Modern Medicine Treatment:
- Image: Chemotherapy illustration.
- Arrow: Cancerous Cell --> Normal Cell
- Label: May Cause Side Effects

Conclusions and Future Perspectives-

This review concisely outlines a comparative analysis of various cancer treatment modalities and protocols, evaluating their benefits and potential challenges across herbal and allopathic systems of medicine. The relentless rise in cancer-related fatalities with each passing year casts a sombre shadow, leaving an indelible mark on those who emerge victorious in their battle against this formidable foe. However, the arduous journey through treatment and recovery, marred by excruciating adverse effects and lingering vulnerabilities, underscores the pressing need to delve into alternative, less detrimental approaches to cancer management. Exploring such avenues could pave the way for a future where the triumph over cancer does not exact an exorbitant toll on those who have already endured immeasurable hardships.

Numerous herbal plants from around the globe harbour compounds that hold promise for cancer therapy, including Curcumin, Quercetin, Emblica Officinalis, and Camptothecin, which exhibit notable potential in minimizing cancer with fewer adverse effects. In recent times, even modern allopathic medicine has been associated with significant adverse effects in cancer management. Our research has delved into various potential delivery systems aimed at the safe and effective administration of anticancer drugs. Drug delivery systems offer greater efficacy and fewer adverse effects compared to natural medicines. Despite being derived from naturally occurring sources, their synthesis costs are lower. Nonetheless, further studies are warranted. Numerous studies and validated findings advocate for the use of allopathic medicines in slowing tumor growth. Their controlled release properties contribute to minimizing adverse effects. Previous research has shown that while the initial release rate may be high, it shifts to a slower release over time, leading to reduced side effects. Electrospun nanofibers are an example of a drug delivery system that effectively meets numerous essential criteria for successful drug administration. Recent years have witnessed remarkable advancements in cancer medicine research, driven by a relentless pursuit for more effective, precise, and minimally invasive treatment modalities. The convergence of nano medicine and targeted therapy has unlocked promising avenues for enhancing the biodistribution of both novel and existing chemotherapeutic agents, directing them to specific tissues and cells under treatment. Simultaneously, cutting-edge strategies such as gene therapy, delivery of small interfering RNAs (siRNAs), immunotherapy, and the utilization of antioxidant molecules have opened new frontiers in the battle against cancer. These multifaceted approaches hold the potential to redefine the landscape of cancer treatment, offering hope for improved outcomes and a better quality of life for those affected by this formidable disease.

The dynamic realm of cancer research unveils a vast expanse of opportunities, not merely confined to facilitating patient recovery but also encompassing the effective mitigation of adverse effects, thereby ensuring holistic well-being during the course of therapy. This comprehensive review primarily juxtaposes herbal-based therapeutic modalities with allopathic anti-cancer interventions, with the overarching objective of identifying treatment

approaches that minimize collateral damage, thus paving the way for a more tolerable journey in the management of cancer. By exploring these contrasting paradigms, the review seeks to illuminate pathways that harmonize therapeutic efficacy with a reduced burden of undesirable side effects, ultimately empowering patients to navigate the arduous challenges posed by this formidable disease with fortitude and resilience.

References-

1. .Vyas, P.; Thakar, A. B.; Baghel, M. S.; Sisodia, A.; Deole, Y. Efficacy of Rasayana Avaleha as an Adjuvant to Radiotherapy and Chemotherapy in Reducing Adverse Effects. Ayu 2010, 31(4), 417–423.
2. .Mathur, G.; Nain, S.; Sharma, P. K. Cancer: An Overview. Acad. J. Cancer Res. 2015, 8(1), 1–10.
3. National Cancer Institute. What Is Cancer? 2015. Available at: https://www.cancer.gov/about-cancer/understanding/what-is-cancer (accessed Nov 6, 2020).
4. Guruvayoorappan, C.; Sakthivel, K. M.; Padmavathi, G.; Bakliwal, V.; Monisha, J.; Kunnumakkara, A. B. Cancer Preventive and Therapeutic Properties of Fruits and Vegetables: An Overview. In Anticancer Properties of Fruits and Vegetables: A Scientific Review; Dey, S. K., Ed.; Springer: 2015; pp 1–52.
5. Eggert, J.; Kasse, M. The Biology of Cancer: What Do Oncology Nurses Really Need to Know? Semin. Oncol. Nurs. 2011, 27(1), 3–12.
6. Stortecky, S.; Suter, T. M. Insights into Cardiovascular Side-Effects of Modern Anticancer Therapeutics. Curr. Opin. Oncol. 2010, 22(4), 312–317.
7. Wang, X.; Yang, L.; Chen, Z.; Shin, D. M. Application of Nanotechnology in Cancer Therapy and Imaging. CA Cancer J. Clin. 2008, 58(2), 97–110.
8. Sawant, S.; Shegokar, R. Cancer Research and Therapy: Where Are We Today? Int. J. Cancer Ther. Oncol. 2014, 2(4), 02048.
9. Ganguly, S. Ayurveda for Cancer Therapy. World J. Pharm. Res. 2014, 3(9), 1476–1479.
10. Ahmad, S.; Rehman, T.; Abbasi, W. M. Homeopathic Approach for the Treatment of Cancer. Indian J. Res. Homeopathy 2018, 12(3), 157.
11. Kamphorst, J. J.; Nofal, M.; Commisso, C.; Hackett, S. R.; Lu, W.; Grabocka, E.; Vander Heiden, M. G.; Miller, G.; Drebin, J. A.; Bar-Sagi, D.; Thompson, C. B. Human Pancreatic Cancer Tumors Are Nutrient-Poor and Tumor Cells Actively Scavenge Extracellular Protein. Cancer Res. 2015, 75(3), 544–554.
12. Duffy, M. J. The War on Cancer: Are We Winning? Tumor Biol. 2013, 34, 1275–1284.
13. Cui, Y.; Shu, X. O.; Gao, Y.; Wen, W.; Ruan, Z. X.; Jin, F.; Zheng, W. Use of Complementary and Alternative Medicine by Chinese Women with Breast Cancer. Breast Cancer Res. Treat. 2004, 85, 263–270.
14. L.am, W.; Bussom, S.; Guan, F.; Jiang, Z.; Zhang, W.; Gullen, E. A.; Liu, S. H.; Cheng, Y. C. The Four Herbs in Chinese Medicine PHY906 Reduce Chemotherapy-Induced Gastrointestinal Toxicity. Sci. Transl. Med. 2010, 2(45), 45–59.
15. Thatte, U.; Dhahanukar, S. Ayurveda, the Natural Alternative. Science Today 1991, 12–18.
16. Smit, H. F.; Woerdenbag, H. J.; Singh, R. H.; Meulenbeld, G. J.; Labadie, R. P.; Zwaving, J. H. Ayurvedic Herbal Drugs with Possible Cytostatic Activity. J. Ethnopharmacol. 1995, 47(2), 75–84.
17. Cravotto, G.; Boffa, L.; Genzini, L.; Garella, D. Phytotherapeutics: An Evaluation of the Potential of 1000 Plants. J. Clin. Pharm. Ther. 2010, 35(1), 11–48.
18. Patel, B.; Das, S.; Prakash, R.; Yasir, M. Natural Bioactive Compounds with Anticancer Potential. Int. J. Adv. Pharm. Sci. 2010, 1(1), 1–5.
19. Cao, W.; Gu, Y.; Meineck, M.; Xu, H. The Combination of Chemotherapy and Radiotherapy Towards More Efficient Drug Delivery. Chem. Asian J. 2014, 9(1), 48–57.
20. Wyld, L.; Audisio, R. A.; Poston, G. J. The Evolution of Cancer Surgery and Future Perspectives. Nat. Rev. Clin. Oncol. 2015, 12(2), 115–124.
21. Rees, M.; Sweetland, H. Role of Surgeons in the Management of Cancer. Surgery (Oxford) 2015, 33(3), 112–116.

22. .Brown, S.; Kirkbride, P.; Marshall, E. Radiotherapy in the Acute Medical Setting. Clin. Med. 2015, 15(4), 382–386.
23. Strom, T.; Harrison, L. B. Radiotherapy for Management of Basal and Squamous Cell Carcinoma. Curr. Probl. Cancer 2015, 39(4), 237–247.
24. Molassiotis, A.; Fernandez-Ortega, P.; Pud, D.; Ozden, G.; Scott, J. A.; Panteli, V.; Margulies, A.; Brownell, M.; Magri, M.; Selvekerova, S.; Madsen, E. Use of Complementary and Alternative Medicine in Cancer Patients: A European Survey. Ann. Oncol. 2005, 16(4), 655–663.
25. Montfort, H. A New Homeopathic Approach to Neoplastic Diseases: From Cell Destruction to Carcinogen-Induced Apoptosis. Br. Homeopath. J. 2000, 89(2), 78–83.
26. Rasouli, S.; Montazeri, M.; Mashayekhi, S.; Sadeghi-Soureh, S.; Dadashpour, M.; Mousazadeh, H.; Nobakht, A.; Zarghami, N.; Pilehvar-Soltanahmadi, Y. Synergistic Anticancer Effects of Electrospun Nanofiber-Mediated Codelivery of Curcumin and Chrysin: Possible Application in the Prevention of Breast Cancer Local Recurrence. J. Drug Deliv. Sci. Technol. 2020, 55, 101402.
27. Sampath, M.; Lakra, R.; Korrapati, P.; Sengottuvelan, B. Curcumin-Loaded Poly (Lactic-Co-Glycolic) Acid Nanofiber for the Treatment of Carcinoma. Colloids Surf. B Biointerfaces 2014, 117, 128–134.
28. Sedghi, R.; Shaabani, A.; Mohammadi, Z.; Samadi, F. Y.; Isaei, E. Biocompatible Electrospinning Chitosan Nanofibers: A Novel Delivery System with Superior Local Cancer Therapy. Carbohydr. Polym. 2017, 159, 1–10.
29. .Rasouli, S.; Montazeri, M.; Mashayekhi, S.; Sadeghi-Soureh, S.; Dadashpour, M.; Mousazadeh, H.; Nobakht, A.; Zarghami, N.; Pilehvar-Soltanahmadi, Y. Synergistic Anticancer Effects of Electrospun Nanofiber-Mediated Codelivery of Curcumin and Chrysin: Possible Application in the Prevention of Breast Cancer Local Recurrence. J. Drug Deliv. Sci. Technol. 2020, 55, 101402
30. Gao, X.; Wang, B.; Wei, X.; Men, K.; Zheng, F.; Zhou, Y.; Zheng, Y.; Gou, M.; Huang, M.; Guo, G.; Huang, N. Anticancer Effect and Mechanism of Polymer Micelle-Encapsulated Quercetin on Ovarian Cancer. Nanoscale 2012, 4(22), 7021–7030.
31. Vashisth, P.; Singh, R. P.; Pruthi, V. A Controlled Release System for Quercetin from Biodegradable Poly (Lactide-Co-Glycolide)–Polycaprolactone Nanofibers and Its In Vitro Antitumor Activity. J. Bioact. Compat. Polym. 2016, 31(3), 260–272.
32. Soukasene, S.; Toft, D. J.; Moyer, T. J.; Lu, H.; Lee, H. K.; Standley, S. M.; Cryns, V. L.; Stupp, S. I. Antitumor Activity of Peptide Amphiphile Nanofiber-Encapsulated Camptothecin. ACS Nano 2011, 5(11), 9113–9121.
33. Baliga, M. S.; Dsouza, J. J. Amla (Emblica officinalis Gaertn), A Wonder Berry in the Treatment and Prevention of Cancer. Eur. J. Cancer Prev. 2011, 20(3), 225–239.
34. Mateti, T.; Aswath, S.; Vatti, A. K.; Kamath, A.; Laha, A. A Review on Allopathic and Herbal Nanofibrous Drug Delivery Vehicles for Cancer Treatments. Biotechnol. Rep. 2021, 31, 63.
35. Tinkle, S.; McNeil, S. E.; Muhlebach, S.; Bawa, R.; Borchard, G.; Barenholz, Y. Nanomedicine: A New Era in Cancer Treatment. Nat. Rev. Cancer 2014, 14(10), 589–600
36. Martinelli, C.; Pucci, C.; Ciofani, G. Nanostructured Carriers as Innovative Tools for Cancer Diagnosis and Therapy. APL Bioeng. 2019, 3(1), 1–12
37. Maeda, H. Toward a Full Understanding of the EPR Effect in Primary and Metastatic Tumors as Well as Issues Related to Its Heterogeneity. Adv. Drug Delivery Rev. 2015, 91, 3–6.
38. Shi, J.; Kantoff, P. W.; Wooster, R.; Farokhzad, O. C. Cancer Nanomedicine: Progress, Challenges and Opportunities. Nat. Rev. Cancer 2017, 17(1), 20–37.
39. Shi, J.; Votruba, A. R.; Farokhzad, O. C.; Langer, R. Nanotechnology in Drug Delivery and Tissue Engineering: From Discovery to Applications. Nano Lett. 2010, 10(9), 3223–3230.
40. 4Sinha, R.; Kim, G. J.; Nie, S.; Shin, D. M. Nanotechnology in Cancer Therapeutics: Bio-Conjugated Nanoparticles for Drug Delivery. Mol. Cancer Ther. 2006, 5(8), 1909–1917.
41. Bregoli, L.; Movia, D.; Gavigan-Imedio, J. D.; Lysaght, J.; Reynolds, J.; Prina-Mello, A. Nanomedicine Applied to Translational Oncology:

A Future Perspective on Cancer Treatment. Nanomedicine 2016, 12(1), 81–103.
42. Mathelié-Guinlet, M.; Cohen-Bouhacina, T.; Gammoudi, I.; Martin, A.; Beven, L.; Delville, M. H.; Grauby-Heywang, C. Silica Nanoparticles-Assisted Electrochemical Biosensor for the Rapid, Sensitive, and Specific Detection of Escherichia coli. Sens. Actuators B: Chem. 2019, 292, 314–320.
43. Gao, J.; Chen, K.; Miao, Z.; Ren, G.; Chen, X.; Gambhir, S. S.; Cheng, Z. Affibody-Based Nanoprobes for HER2-Expressing Cell and Tumor Imaging. Biomaterials 2011, 32(8), 2141–2148.
44. Gubernator, J. Active Methods of Drug Loading into Liposomes: Recent Strategies for Stable Drug Entrapment and Increased In Vivo Activity. Expert Opin. Drug Delivery 2011, 8(5), 565–580
45. Narang, A. S.; Delmarre, D.; Gao, D. Stable Drug Encapsulation in Micelles and Microemulsions. Int. J. Pharm. 2007, 345(1–2), 9–25.
46. Singh, S. K.; Singh, R.; Lillard, J. W., Jr.; Singh, R. Drug Delivery Approaches for Breast Cancer. Int. J. Nanomed. 2017, 12, 6205–6218.
47. Markman, M. Pegylated Liposomal Doxorubicin in the Treatment of Cancers of the Breast and Ovary. Expert Opin. Pharmacother. 2006, 7(11), 1469–1474.
48. Nasir, A.; Kausar, A.; Younus, A. A Review on Preparation, Properties, and Applications of Polymeric Nanoparticle-Based Materials. Polym.-Plast. Technol. Eng. 2015, 54(4), 325–341.
49. Alasvand, N.; Urbanska, A. M.; Rahmati, M.; Saeidifar, M.; Gungor-Ozkerim, P. S.; Sefat, F.; Rajadas, J.; Mozafari, M. Therapeutic Nanoparticles for Targeted Delivery of Anticancer Drugs. Multifunctional Systems for Combined Delivery, Biosensing, and Diagnostics 2017, 245–259.
50. Bazak, R.; Houri, M.; El Achy, S.; Kamel, S.; Refaat, T. Cancer Active Targeting by Nanoparticles: A Comprehensive Review of the Literature. J. Cancer Res. Clin. Oncol. 2015, 141, 769–784
51. Barua, S.; Mitragotri, S. Challenges Associated with Penetration of Nanoparticles across Cell and Tissue Barriers: A Review of Current Status and Future Prospects. Nano Today 2014, 9(2), 223–243.
52. Xu, S.; Olenyuk, B. Z.; Okamoto, C. T.; Hamm-Alvarez, S. F. Targeting Receptor-Mediated Endocytotic Pathways with Nanoparticles: Rationale and Advances. Adv. Drug Delivery Rev. 2013, 65(1), 121–138.
53. Hymel, D.; Peterson, B. R. Synthetic Cell Surface Receptors for Delivery of Therapeutics and Probes. Adv. Drug Delivery Rev. 2012, 64(9), 797–810
54. Senol, S.; Ceyran, A. B.; Aydin, A.; Zemheri, E.; Ozkanli, S.; Kösemetin, D.; Sehitoglu, I.; Akalin, I. Folate Receptor α Expression and Significance in Endometrioid Endometrium Carcinoma and Endometrial Hyperplasia. Int. J. Clin. Exp. Pathol. 2015, 8(5), 5633–5641
55. Tao, W.; Zhang, J.; Zeng, X.; Liu, D.; Liu, G.; Zhu, X.; Liu, Y.; Yu, Q.; Huang, L.; Mei, L. Blended Nanoparticle System Based on Miscible Structurally Similar Polymers: A Safe, Simple, Targeted, and Surprisingly High-Efficiency Vehicle for Cancer Therapy. Adv. Healthcare Mater. 2015, 4(8), 1203–1214.
56. Byrne, J. D.; Betancourt, T.; Brannon-Peppas, L. Active Targeting Schemes for Nanoparticle Systems in Cancer Therapeutics. Adv. Drug Delivery Rev. 2008, 60(15), 1615–1626.
57. Ginn, S. L.; Amaya, A. K.; Alexander, I. E.; Edelstein, M.; Abedi, M. R. Gene Therapy Clinical Trials Worldwide to 2017: An Update. J. Gene Med. 2018, 20(5), 3015.
58. McCune, J. S. Rapid Advances in Immunotherapy to Treat Cancer. Clin. Pharmacol. Ther. 2018, 103(4), 540–544.
59. 5Miliotou, A. N.; Papadopoulou, L. C. CAR T-Cell Therapy: A New Era in Cancer Immunotherapy. Curr. Pharm. Biotechnol. 2018, 19(1), 5–18.
60. Friedmann, T. A Brief History of Gene Therapy. Nat. Genet. 1992, 2(2), 93–98.
61. Rosenberg, S. A.; Aebersold, P.; Cornetta, K.; Kasid, A.; Morgan, R. A.; Moen, R.; Karson, E. M.; Lotze, M. T.; Yang, J. C.; Topalian, S. L.; Merino, M. J. Gene Transfer into Human Immunotherapy of Patients with Advanced Melanoma, Using Tumor-Infiltrating Lymphocytes Modified by Retroviral Gene Transduction. N. Engl. J. Med. 1990, 323(9), 570–578
62. Ginn, S. L.; Alexander, I. E.; Edelstein, M. L.; Abedi, M. R.; Wixon, J. Gene Therapy Clinical

Trials Worldwide to 2012: An Update. J. Gene Med. 2013, 15(2), 65–77
63. Roth, J. A. A Clinical Trial of Retroviral Gene Transfer of Wild-Type p53 in Lung Cancer Patients with Mutant p53 Tumor Suppressor Genes. Nat. Med. 1996, 2, 985.
64. Freeman, S. M.; Abboud, C. N.; Whartenby, K. A.; Packman, C. H.; Koeplin, D. S.; Moolten, F. L.; Abraham, G. N. The “Bystander Effect”: Tumor Regression When a Fraction of the Tumor Mass Is Genetically Modified. Cancer Res. 1993, 53(21), 5274–5283.
65. Nasu, Y.; Saika, T.; Ebara, S.; Kusaka, N.; Kaku, H.; Abarzua, F.; Manabe, D.; Thompson, T. C.; Kumon, H. Suicide Gene Therapy with Adenoviral Delivery of HSV-tK Gene for Patients with Local Recurrence of Prostate Cancer After Hormonal Therapy. Mol. Ther. 2007, 15(4), 834–840.
66. Westphal, M.; Ylä-Herttuala, S.; Martin, J.; Warnke, P.; Menei, P.; Eckland, D.; Kinley, J.; Kay, R.; Ram, Z. Adenovirus-Mediated Gene Therapy with Sitimagene Ceradenovec Followed by Intravenous Ganciclovir for Patients with Operable High-Grade Glioma (ASPECT): A Randomized, Open-Label, Phase 3 Trial. Lancet Oncol. 2013, 14(9), 823–833.
67. Ahrendt, S. A.; Hu, Y.; Buta, M.; McDermott, M. P.; Benoit, N.; Yang, S. C.; Wu, L.; Sidransky, D. p53 Mutations and Survival in Stage I Non-Small-Cell Lung Cancer: Results of a Prospective Study. J. Natl. Cancer Inst. 2003, 95(13), 961–970.
68. Raty, J. K.; Pikkarainen, J. T.; Wirth, T.; Ylä-Herttuala, S. Gene Therapy: The First Approved Gene-Based Medicines, Molecular Mechanisms and Clinical Indications. Curr. Mol. Pharmacol. 2008, 1(1), 13–23.
69. Elbashir, S. M.; Lendeckel, W.; Tuschl, T. RNA Interference Is Mediated by 21- and 22-Nucleotide RNAs. Genes Dev. 2001, 15(2), 188–200.
70. Weiss, B.; Davidkova, G.; Zhou, L. W. Antisense RNA Gene Therapy for Studying and Modulating Biological Processes. Cell. Mol. Life Sci. CMLS 1999, 55, 334–358.
71. Whelan, J. First Clinical Data on RNAi. Drug Discov. Today 2005, 10(15), 1014–1015.
72. .Jia, L. T.; Chen, S. Y.; Yang, A. G. Cancer Gene Therapy Targeting Cellular Apoptosis Machinery. Cancer Treat. Rev. 2012, 38(7), 868–876.
73. Fleming, J. B.; Shen, G. L.; Holloway, S. E.; Davis, M.; Brekken, R. A. Molecular Consequences of Silencing Mutant K-Ras in Pancreatic Cancer Cells: Justification for K-Ras-Directed Therapy. Mol. Cancer Res. 2005, 3(7), 413–423.
74. Scanlon, K. J. Anti-Genes: siRNA, Ribozymes and Antisense. Curr. Pharm. Biotechnol. 2004, 5(5), 415–420.
75. Fire, A. Z. Gene Silencing by Double-Stranded RNA (Nobel Lecture). Angew. Chem. Int. Ed. 2007, 46(37), 6966–6984.
76. Bora, R. S.; Gupta, D.; Mukkur, T. K.; Saini, K. S. RNA Interference Therapeutics for Cancer: Challenges and Opportunities. Mol. Med. Rep. 2012, 6(1), 9–15.
77. Van de Water, F. M.; Boerman, O. C.; Wouterse, A. C.; Peters, J. G.; Russel, F. G.; Masereeuw, R. Intravenously Administered Short Interfering RNA Accumulates in the Kidney and Selectively Suppresses Gene Function in Renal Proximal Tubules. Drug Metab. Dispos. 2006, 34(8), 1393–1397.
78. udge, A. D.; Sood, V.; Shaw, J. R.; Fang, D.; McClintock, K.; MacLachlan, I. Sequence-Dependent Stimulation of the Mammalian Innate Immune Response by Synthetic siRNA. Nat. Biotechnol. 2005, 23(4), 457–462.
79. Martina, M. S.; Nicolas, V.; Wilhelm, C.; Ménager, C.; Barratt, G.; Lesieur, S. The In Vitro Kinetics of the Interactions Between PEG-Ylated Magnetic-Fluid-Loaded Liposomes and Macrophages. Biomaterials 2007, 28(28), 4143–4153.
80. Whitehead, K. A.; Langer, R.; Anderson, D. G. Knocking Down Barriers: Advances in siRNA Delivery. Nat. Rev. Drug Discov. 2009, 8(2), 129–138.
81. Czauderna, F.; Fechtner, M.; Dames, S.; Ayguèn, H.; Klippel, A.; Pronk, G. J.; Giese, K.; Kaufmann, J. Structural Variations and Stabilizing Modifications of Synthetic siRNAs in Mammalian Cells. Nucleic Acids Res. 2003, 31(11), 2705–2716.

82. Liao, H.; Wang, J. H. Biomembrane-Permeable and Ribonuclease-Resistant siRNA with Enhanced Activity. Oligonucleotides 2005, 15(3), 196–205.
83. Hall, A. H.; Wan, J.; Shaughnessy, E. E.; Ramsay Shaw, B.; Alexander, K. A. RNA Interference Using Boranophosphate siRNAs: Structure-Activity Relationships. Nucleic Acids Res. 2004, 32(20), 5991–6000.
84. Sarisozen, C.; Salzano, G.; Torchilin, V. P. Recent Advances in siRNA Delivery. Biomolecular Concepts 2015, 6(5-6), 321–341.
85. Kim, H. S.; Song, I. H.; Kim, J. C.; Kim, E. J.; Jang, D. O.; Park, Y. S. In Vitro and In Vivo Gene Transferring Characteristics of Novel Cationic Lipids, DMKD (O, O'-Dimyristyl-N-Lysyl Aspartate) and DMKE (O, O'-Dimyristyl-N-Lysyl Glutamate). J. Control. Release 2006, 115(2), 234–241.
86. Kenny, G. D.; Kamaly, N.; Kalber, T. L.; Brody, L. P.; Sahuri, M.; Shamsaei, E.; Miller, A. D.; Bell, J. D. Novel Multifunctional Nanoparticle Mediates SiRNA Tumor Delivery, Visualization and Therapeutic Tumor Reduction In Vivo. J. Control. Release 2011, 149(2), 111–116.
87. .Halder, J.; Kamat, A. A.; Landen, C. N., Jr.; Han, L. Y.; Lutgendorf, S. K.; Lin, Y. G.; Merritt, W. M.; Jennings, N. B.; Chavez-Reyes, A.; Coleman, R. L.; Gershenson, D. M. Focal Adhesion Kinase Targeting Using In Vivo Short Interfering RNA Delivery in Neutral Liposomes for Ovarian Carcinoma Therapy. Clin. Cancer Res. 2006, 12(16), 4916–4924.
88. Gray, M. J.; Van Buren, G.; Dallas, N. A.; Xia, L.; Wang, X.; Yang, A. D.; Somcio, R. J.; Lin, Y. G.; Lim, S.; Fan, F.; Mangala, L. S. Therapeutic Targeting of Neuropilin-2 on Colorectal Carcinoma Cells Implanted in the Murine Liver. J. Natl. Cancer Inst. 2008, 100(2), 109–120.
89. Mao, S.; Sun, W.; Kissel, T. Chitosan-Based Formulations for Delivery of DNA and siRNA. Adv. Drug Deliv. Rev. 2010, 62(1), 12–27.
90. .Pillé, J. Y.; Li, H.; Blot, E.; Bertrand, J. R.; Pritchard, L. L.; Opolon, P.; Maksimenko, A.; Lu, H.; Vannier, J. P.; Soria, J.; Malvy, C. Intravenous Delivery of Anti-RhoA Small Interfering RNA Loaded in Nanoparticles of Chitosan in Mice: Safety and Efficacy in Xenografted Aggressive Breast Cancer. Hum. Gene Ther. 2006, 17(10), 1019–1026.
91. Urban-Klein, B.; Werth, S.; Abuharbeid, S.; Czubayko, F.; Aigner, A. RNAi-Mediated Gene Targeting through Systemic Application of Polyethyleneimine (PEI)-Complexed siRNA. Mol. Ther. 2006, 14(4), 468–477.
92. Urban-Klein, B.; Werth, S.; Abuharbeid, S.; Czubayko, F.; Aigner, A. RNAi-Mediated Gene Targeting through Systemic Application of Polyethyleneimine (PEI)-Complexed siRNA In Vivo. Gene Ther. 2005, 12(5), 461–466.
93. Jeong, J. H.; Mok, H.; Oh, Y. K.; Park, T. G. siRNA Conjugate Delivery Systems. Bioconjugate Chem. 2009, 20(1), 5–14.
94. McNamara, J. O.; Andrechek, E. R.; Wang, Y.; Viles, K. D.; Rempel, R. E.; Gilboa, E.; Sullenger, B. A.; Giangrande, P. H. Cell Type-Specific Delivery of siRNAs with Aptamer-SiRNA Chimeras. Nat. Biotechnol. 2006, 24(8), 1005–1015.
95. Gallas, A.; Alexander, C.; Davies, M. C.; Puri, S.; Allen, S. Chemistry and Formulations for siRNA Therapeutics. Chem. Soc. Rev. 2013, 42(20), 7983–7997.
96. Warden, M. R.; Cardin, J. A.; Deisseroth, K. Optical Neural Interfaces. Annu. Rev. Biomed. Eng. 2014, 16, 103–129.
97. Zhou, J.; Wu, Y.; Wang, C.; Cheng, Q.; Han, S.; Wang, X.; Zhang, J.; Deng, L.; Zhao, D.; Du, L.; Cao, H. Sensitive Nano Micelles for High-Efficiency siRNA Delivery In Vitro and In Vivo: An Insight into the Design of Polycations with Robust Cytosolic Release. Nano Lett. 2016, 16(11), 6916–6923.
98. Sun, C. Y.; Shen, S.; Xu, C. F.; Li, H. J.; Liu, Y.; Cao, Z. T.; Yang, X. Z.; Xia, J. X.; Wang, J. Tumor Acidity Sensitive Polymeric Vector for Active Targeted siRNA Delivery. J. Am. Chem. Soc. 2015, 137(48), 15217–15224.
99. Truong, N. P.; Gu, W.; Prasadam, I.; Jia, Z.; Crawford, R.; Xiao, Y.; Monteiro, M. J. An Influenza Virus-Inspired Polymer System for the Timed Release of siRNA. Nat. Commun. 2013, 4(1), 1902.
100. Cui, Y.; Briscoe, J.; Wang, Y.; Tarakina, N. V.; Dunn, S. Enhanced Photocatalytic Activity of

Heterostructured Ferroelectric BaTiO3/α-Fe2O3 and the Significance of Interface Morphology Control. ACS Appl. Mater. Interfaces 2017, 9(29), 24518–24526.

101. Kim, M. O.; Lee, M. H.; Oi, N.; Kim, S. H.; Bae, K. B.; Huang, Z.; Kim, D. J.; Reddy, K.; Lee, S. Y.; Park, S. J.; Kim, J. Y. Shogaol Inhibits Growth and Induces Apoptosis of Non-Small Cell Lung Cancer Cells by Directly Regulating Akt1/2. Carcinogenesis 2014, 35(3), 683–691.
102. Chen, H.; Zhu, B.; Zhao, L.; Liu, Y.; Zhao, F.; Feng, J.; Jin, Y.; Sun, J.; Geng, R.; Wei, Y. Allicin Inhibits Proliferation and Invasion In Vitro and In Vivo via SHP-1-Mediated STAT3 Signaling in Cholangiocarcinoma. Cell. Physiol. Biochem. 2018, 47(2), 641–653.
103. Dou, J.; Wang, Z.; Ma, L.; Peng, B.; Mao, K.; Li, C.; Su, M.; Zhou, C.; Peng, G. Baicalein and Baicalin Inhibit Colon Cancer Using Two Distinct Fashions of Apoptosis and Senescence. Oncotarget 2018, 9(28), 2008.