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REVIEW ARTICLE

Solid Lipid Nanoparticles for the Delivery of Plant-derived Bioactive Compounds in the Treatment of Cancer Disorders – A Review

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Abstract

Background: The study explores phyto-bioactive compounds in Solid Lipid Nanoparticles (SLN) and their potential use in cancer therapy. **Objective:** Most phyto-bioactive compounds have properties such as anti-inflammatory agents, antioxidants, anti-microbe agents, anti-arthritic agents, hypoglycemic agents, cardioprotective agents, and anti-cancer agents. Phyto-bioactive compounds are abundant in fruits, vegetables, and whole grains, and may impact metabolic processes improve health, and prevent illness. Breast, colon, and prostate cancers, as well as other malignancies, are now being studied for their potential prevention and treatment using therapies based on phyto-bioactive compounds in *in vitro*, *in vivo*, and clinical studies. **Methods:** More than 10 million individuals have lost their lives to cancer this year alone. Cancer is one of the most malignant and deadly diseases afflicting mankind today, and its death toll continues to rise. SLNs have been extensively used by several research groups to efficiently transport phyto-bioactive substances with enhanced anticancer effects. Now is the time for really groundbreaking ideas and innovations in the field of medicinal nanocarriers. **Conclusion:** Lipid nanoparticles' size-dependent properties might lead to new therapeutics. Small size, large surface area, high drug loading, control pattern release, targeted drug release, and interface phase interaction are their benefits. Nanoformulations are undeniably powerful resources for therapeutic delivery applications; the current difficulty is in ensuring their safety, efficacy, and scalability for industrial production and eventual clinical use. Our review offers a novel perspective by focusing on the phyto-bioactive chemicals carried by these SLN nano-carriers, describing recent advancements and their potential applications to cancer therapy.

Keywords: Anticancer, Non-small-cell Lung Cancer, Paclitaxel, Phyto-bioactive Compounds, Solid Lipid Nanoparticles

1. Introduction

The crucial role of nutrition in disease both in prevention and treatment has been emphasized by the classic phrase "Let thy food be thy medicine and medicine be thy food"[1]. The term "bioactive compound" is applied to describe extra nutritional tiny molecules found in food that can control different metabolic processes for the benefit of health. Natural foods that provide additional benefits to health or disease prevention abilities beyond their nutritional value are considered medicinal foods. Bioactive compounds in food are the many nutrient components that only exist in trace amounts. In

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addition to offering a fundamental nutritional profile, many foods additionally possess trace quantities of bioactive compounds. There is a natural possibility that several foods contain bioactive chemical compounds[2]. Medicinal plants often include bioactive nutritional elements including alkaloids, glycosides, flavonoids, phytosterols, polyphenols, terpenoids, carotenoids, etc., which have major pharmacological activities against diseases. Phyto-bioactive compounds have been the subject of extensive research because of the potential benefits they may have in treating human diseases relating to inflammation, cardiovascular disease, diabetes, neurodegenerative disorders, along cancer as well as boosting the immune system[3].

Notwithstanding this, there exists enough data to support the recommendation of including food sources abundant in bioactive substances in one's diet. This leads to a pragmatic recommendation for a diet high in different kinds of produce, vegetables, fruits, grains, beans, and nuts. Thus, this topic desires to identify and assess how bioactive chemicals in food affect human disorders[4]. Researchers have hypothesized that leading an unhealthy lifestyle and experiencing high levels of stress together weakens the immune system and increases the possibility of developing a variety of illnesses, including cancer. People's interest in medicinal foods and nutraceuticals has increased greatly as they realize more about the relationship between diet and health[5].

When treating long-term illnesses in humans, nanoparticle medication administration systems work wonders. They serve pharmacological and biopharmaceutical purposes well. The most effective medication delivery methods in biomedicine use biodegradable and biocompatible nanomaterials. Nanoscale lipid carriers and SLN are promising as colloidal drug delivery systems. Lipid-based nanocarriers and other nanotechnology-based medication delivery technologies have shown remarkable efficacy in this context[6]. Due to the disease's severity and mortality rate, as well as the difficulties in effectively delivering therapeutic agents, researchers worldwide are focused on developing new drug-delivery systems to combat cancer. Anticancer drug delivery methods and treatment approaches for different types of cancer have advanced greatly in recent years. The distribution of medications with difficulties that traditional drug delivery methods cannot mitigate continues to rely on novel drug delivery systems as its base[7,8]. The pharmacokinetics and the place of delivery of medications determine how successful they are therapeutically.

In contrast to traditional dosage forms, nanoparticulate dosage forms disperse the medicine or active ingredient into tiny particles called nanoparticles. They are one of several dosage forms that are designed to administer drugs sublingually or buccally, such as films, patches, gels, and sprays. These nanoparticulate formulations can release drugs through various routes of administration, such as oral, parenteral, nasal, ophthalmic, rectal, etc. These formulations have several advantages, such as:

- Improving the drug's bioavailability.
- Improving the drug's distribution in the body.
- Modifying the drug's release kinetics (e.g., controlled release or sustained release).
- Targeting the drug to specific organs, tissues, and cells.
- Providing solubilization (i.e., to deliver compounds with physicochemical properties that strongly limit their aqueous solubility).
- Protecting compounds that are susceptible to degradation, like peptides[9,10].

2. The Current Global Cancer Status

Cancer is the world's leading cause of death, killing 10 million people in 2020. Cancer is one of the deadliest and most severe disorders known to humans, and its mortality rate is rising. Millions are in danger. The malignancies with the highest incidence rates include breast cancer (2.26 million cases), prostate cancer (1.41 million cases), lung cancer (2.21 million cases), skin cancer (1.20 million cases), and colon cancer (1.93 million cases). In the Indian context, it is projected that a total of 1,461,427 new cases of cancer will manifest in the year 2022. On March 14, 2023, the government notified Parliament that the number of cancer cases in the nation was expected to increase from 14.6 lakhs in 2022 to 15.7 lakhs in 2025, based on data from the Indian Council of Medical Research-National Cancer Registry Programme (ICMR-NCRP). There are expected to be 1,958,310 new cases of cancer and 609,820 deaths from cancer in the United States in 2023. The design, monitoring, and assessment of cancer prevention efforts rely heavily on up-to-date cancer data. General

treatment consists of surgical procedures, radiation therapy, and systemic medication. Systemic treatment is often administered in the form of chemotherapy, hormone medications, or targeted biological therapies[11-13].

Anticancer drugs exhibit toxicity towards both healthy and malignant cells, typically demonstrating broad distribution throughout the body. Therefore, to achieve precise medication administration to highly particular targets, it is necessary to miniaturize the delivery systems to a size much smaller than the targets. The use of nanotechnology is enabling the precise delivery of medicinal drug molecules to their intended site of action, hence facilitating the development of personalized medicine. This phenomenon enhances the therapeutic effectiveness of the medicine while simultaneously reducing its toxicity in non-target areas[14,15]. Currently, the standard approach for the management of solid tumours involves surgical resection followed by adjuvant radiation therapy and chemotherapy. However, these treatment modalities are associated with significant adverse effects and may greatly diminish the overall quality of life experienced by patients. In addition, the intrinsic toxicity of many medicines restricts their effectiveness and scope of use. Herceptin has promise as a treatment for several cancers, including breast cancer. It is important to note, however, that these medications are quite costly and their effectiveness is generally limited to certain kinds of tumors[16].

3. A Historical Perspective: Plant-derived Drugs

The first use of plants as medications is difficult to identify. There is evidence that people have been cultivating edible plants as medicine for thousands of years. Since the beginning of time, people have used nature to heal themselves. Charaka, Sushruta, Hippocrates, and Theophrastus are just a few of the ancient thinkers who recorded extensive documents on the medicinal uses of plants. Ancient knowledge of plant selection, collection, medication preparation, and usage skills was passed down verbally[17]. Early nineteenth-century plant active ingredient isolation, synthesis, and analysis started. This accelerated medication development and spurred medical miracles. This propensity led to the first-ever discovery of morphine and codeine from *Papaver somniferum* L. (opium), cocaine from *Erythroxylum coca* Lam, the cardiac glycoside digitoxin from *Digitalis purpurea* L., vincristine and vinblastine as anti-cancer drugs from *Catharanthus roseus* L, quinine from *Cinchona officinalis* L. with antipyretic and antimalarial properties, and many others. Many of these compounds are still in active use today[18-20]. This shows the immense therapeutic potential of herbs used in traditional medicine for millennia. Table 1 lists several important chemicals derived from plants that treat different disorders.

Table 1. Some important plant-based drugs for treating different disorders

Plant Source	Drug	Disorders	References
Artemisia annua L.	Arteether	Malaria	21
Artemisia annua L.	Artemisinin	Cancer and Type I diabetes	22
Atropa belladonna	Tiotropium	Asthma and COPD	23 24
Azadirachta indica A. Juss	Azadirachtin	Antimicrobial and insecticidal	25
Berberis vulgaris L.	Berberine, Palmatine,	Anticancer, antidiabetic and antibacterial	26
Callistemon citrinus	Nitisinone	Hepatorenal tyrosinemia	27
Capsicum annuum	Capsaicin	Pain relievers	28
Cleome	Kaempferol, Kaempferitrin	Anticancer	29
Curcuma longa L.	Curcumin	Antioxidant, anti-inflammatory, arthritis, Antibacterial	30
Galanthus woronowii	Galantamine	Alzheimer	31
Genista tinctoria L.	Genistein	Anticancer, Alzheimer's disease	32
Papaver somniferum L.	Apomorphine	Parkinson	33,34
Piper nigrum L.	Piperine	Nanotheranostic agent for cancer treatment	35
Silybum marianum L.	Silymarin	Hepatoprotective activities	36
Taxus brevifolia Nutt.	Paclitaxel	Lung, ovarian and breast cancer	37

4. Solid Lipid Nanoparticles (SLNs)

Solid lipid Nanoparticles (SLNs) are regarded as innovative colloidal nanocarriers for the delivery of medications, characterized by a size range spanning from 1 to 1000 nm. These nanoparticles possess the ability to encapsulate a combination of hydrophilic and hydrophobic medicines, thereby merging the desirable attributes of liposomes and polymeric microparticles[38]. Physiological lipids can be dispersed in a solution of aqueous surfactant to form submicron colloidal systems called "solid lipid nanoparticles," which are stable inside the body despite their size. In recent years, SLNs have emerged as a promising nano-delivery carrier for use in cancer therapy. SLNs can increase medication bioavailability because they have better cellular absorption, smaller size, a greater surface area, high drug loading, longer and targeted drug release, reduced toxicity, and fewer side effects than conventional colloidal carriers[39]. The rapidly expanding field of nanotechnology includes SLN, which have many potential applications in clinical treatment, drug delivery, research, and other related sciences. Due to their unique size-dependent features, lipid nanoparticles offer the possibility of developing novel therapies.

Currently, SLNs are used for a wide variety of medical and cosmetic purposes, including the treatment of infections, cancers, diabetes, heart disease, neurological disorders, and cosmetics. In pharmaceutical applications, however, the best carriers for drug delivery systems are nanomaterials that are both biodegradable and biocompatible. Some examples of innovative drug delivery technologies that offer prolonged and regulated release include polymeric microspheres, liposomes, nanoparticles, hydrogels, transdermal and buccal systems, and implants[40]. Since SLNs have the potential to increase the efficacy of medications, they are of interest as researchers evaluate the viability of many novel molecular targets for treating a variety of malignancies. Solid lipid nanoparticle carriers have emerged as a promising strategy for elucidating certain obstacles associated with certain cancers. Natural phyto features, therapeutic disciplines of cancer concerns, and contemporary initiatives for the surface modification of lipid-based NPs were prioritized during data stockpiling and dissemination. Researchers, those studying the utilization of phyto-bioactive compounds in SLN for the treatment of cancer will find this article informative[41]. Phyto-bioactive substances have been used successfully to treat various cancers for several years. The phyto-bioactive compounds that were loaded into the SLNs and then delivered to the target cancer cells are shown in Figure 1. Lipid-based transport of synthetic medications' active ingredients has been widely explored to develop a wide range of cancer therapies, as many of these drugs have problems with conventional therapy as well. Several research groups have used SLNs to efficiently transport phyto-bioactive chemicals with enhanced anticancer effects[42].

5. Role of SLNs in the Delivery of Phyto-bioactive Compounds

Over the past three to four decades, scientists in academia and industry have paid increasing attention to lipid-based nanocarriers for bioactive compounds delivery. There are many problems with the conventional approaches to dosing and administering drugs, including low patient compliance, quick metabolism, low bioavailability, dose variations, unpleasant side effects, and drug toxicity. Nanocarrier systems designed for a specific goal, such as liposomes, bilosomes, niosomes, SLN, ethosomes, herbosomes, and polymeric nanoparticles, can circumvent these constraints[43,44]. The use of lipid nanoparticles has been shown to significantly increase absorption, and bioavailability, and decrease adverse side effects. This highlights the great promise of these novel drug-delivery vehicles for therapeutic applications. The Solid Lipid Nanoparticle (SLN) is a primary nano-delivery method that has been widely employed for modulated release in the oral administration of phytocompounds for the treatment of diverse chronic ailments[45].

6. Phyto-bioactive Compounds with Anticancer Properties

So, there is no question that there is an actual desire for new anti-cancer drugs that work well and have fewer adverse effects. Plants are a good place to look for such drugs. There is a lot of scientific proof that plants can

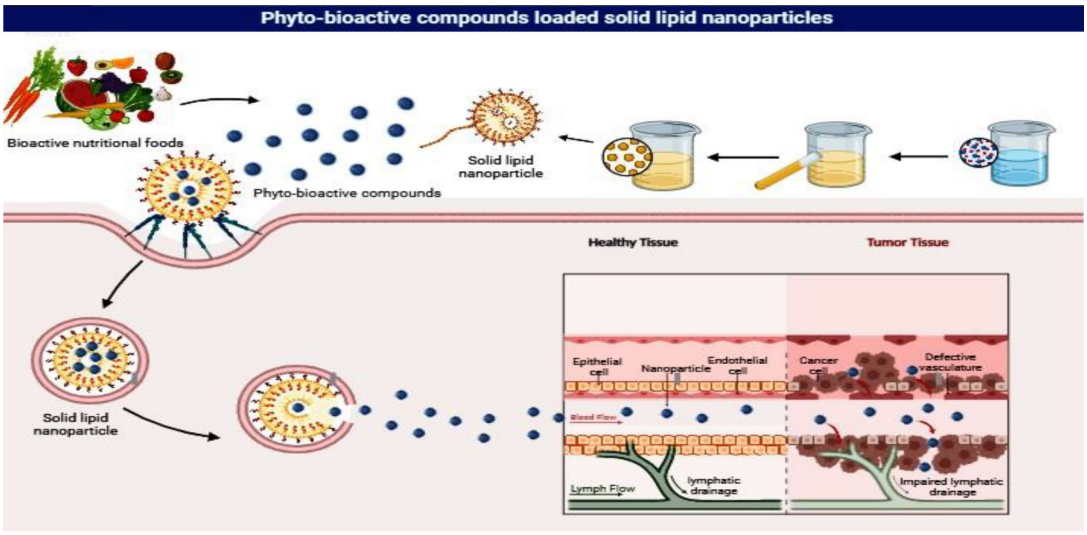

Figure 1. The schematic representation of phyto-bioactive compounds loaded SLNs delivery to the target tumour cell.

help fight cancer. 50–60 % of the anticancer drugs that are approved come directly or indirectly from natural sources[46,47]. In this study, some of the most interesting phyto-bioactive compounds that fight cancer are talked about. Both *in vitro* and *in vivo* tests have shown that these nutrients are effective against cancer. Phyto-bioactive compounds, for the most part, have the potential to serve as effective alternative therapies for the prevention and treatment of cancer[48].

The categorization of therapeutically used plant-based anticancer drugs encompasses four primary types: taxane diterpenoids, vinca alkaloids, epipodophyllotoxin, and camptothecin derivatives. Other plant-derived anticancer medicines, such as combretastatin (natural phenols), cephalotaxine (alkaloid), and ingenol mebutate, etc., are employed in addition to those in the aforementioned families of phyto-bioactive chemicals (Table 2). Some phyto-bioactive compounds utilized in cancer treatment are briefly described here. Several commercially available phyto-compounds have been shown to have anti-cancer effects, and their active natural phyto-bioactive substances are summarized in Table 3.

6.1 Taxane Diterpenoids

Paclitaxel (Taxol) is widely recognized as one of the most prominent examples of an initial plant-derived anti-cancer medication. The first discovery of the cytotoxic properties of diterpene, a taxane compound extracted from the bark of *Taxus brevifolia* Nutt (commonly known as Western yew), was documented by Wani *et al*[49]. In the year 1992, the Food and Drug Administration (FDA) approved the use of Taxol as a therapeutic intervention for ovarian cancer. Taxol demonstrated similar outcomes on many forms of cancer, including lung and breast cancer. It is also effective in treating a wide variety of other malignancies, such as those of the head and neck, endometrium, bladder, oesophagus, and cervix. Paclitaxel is an anticancer drug that works by binding to tubulin subunits and preventing them from depolymerizing within cells, thereby stabilizing microtubules and halting the progression of mitotic division and, ultimately, causing apoptosis[50,51].

Paclitaxel is a diterpene alkaloid with a complex ring system and several chiral centres in its chemical structure. It has a stiff ring structure containing four rings, including cyclodecane and oxetane[52,53].

Subsequently, docetaxel, a semi-synthetic derivative of diterpene, has emerged as a prominent therapeutic agent in the treatment of several cancers including breast, ovarian, pancreatic, prostate, and lung cancers. A variety of semisynthetic compounds have been synthesized to enhance the cytotoxicity against resistant tumours, reduce toxicity, and increase solubility. Taxanes demonstrate an anticancer mechanism via the stabilization of microtubules, leading to the interruption of the cell cycle and the occurrence of abnormal mitosis. Researchers have discovered that paclitaxel may also target mitochondria and block the activity of the apoptosis-inhibiting B-cell Leukemia

Table 2. Phyto-bioactive compounds used in the treatment of cancer

Phyto-bioactive compounds	Molecular targets	Cancer type	Pharmacological action	References
Taxanes: Paclitaxel*(Taxus brevifolia* Nutt.*)* Cabazitaxel, Docetaxel *(Taxus baccata* L.*)*	Tubulin	Breast, ovarian, pancreas, gastric, prostate (hormone refractory), head and neck, and non-small-cell lung cancer	The inhibition of microtubule activity leads to cell cycle arrest and abnormal mitosis.	55,57,105
Vinca alkaloids: Vincristine Vinblastine Vindesine Vinflunine Vinorelbine *(Catharanthus roseus)* (L.) G. Don	Tubulin	Breast cancer, lung cancer, leukemia, Hodgkin and non-Hodgkin lymphomas, testicular cancer, Kaposi's sarcoma, and urothelial cancer in the second line.	It primarily inhibits microtubule polymerization by interacting with β tubulin, causing anticancer effects.	68,106
Podophyllotoxin: Etoposide Teniposide *(Podophyllum peltatum* L.*)*	Topoisomerase II	Breast, prostate, bone sarcoma, Non-Small Cell Lung Cancer (NSCLC), cervical, colon, nasopharyngeal, and testicular cancers.	Complex formation with topoisomerase II and DNA results in the inhibition of DNA synthesis.	71,107
Camptothecin: Irinotecan Topotecan *(Camptotheca acuminate* Decne*)*	Topoisomerase I	Small cell lung cancer (SCLC), colorectal, ovarian, and cervix malignancies.	The topoisomerase I-DNA complex is stabilized, limiting the relegation of single-strand breaks that would otherwise lead to deadly double-stranded breaks.	108,109
Curcumin *(Curcuma longa* L.*)*	Apostasies	Breast, lung, head and neck, liver, prostate, ovary, and skin cancers.	Curcumin suppresses cellular signaling pathways to induce apoptosis and decrease tumour development and invasion.	92
Homoharringtonine *(Cephalotoxus fortunei)*	Protein translation	Acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and lung cancer.	It competes with the ribosomal A-site, inhibiting protein synthesis during translation.	98
Ingenol mebutate *(Euphorbia peplus* L.*)*	Immune/ neutrophil activation	Actinic Keratosis (AK)	The active componentmay suppress tumour cell development or kill them in numerous ways. This may include protein kinase C or neutrophil activation.	104

2 (Bcl-2) protein[54-56]. Cabazitaxel, a derivative of docetaxel belonging to the second generation, demonstrates cytotoxic effects against different types of tumours that have developed resistance to docetaxel while exhibiting reduced overall toxicity. One notable attribute of cabazitaxel is its capacity to effectively traverse the blood-brain barrier in live organisms, a feat that is not attainable with other taxanes. Several paclitaxel analogues, including larotaxel, ortataxel, milataxel, and tesetaxel, are now receiving clinical assessment[57].

In a notable development, Taxol was discovered in 1993 to be synthesized in limited quantities by the endophytic fungal organisms *Taxomyces andreanae*, located inside the Taxus plant. It can now be grown from several endophytic fungi, reducing production time and cost. Subsequently, additional endophytic fungi were also revealed to have the capability to make Taxol, hence opening up the potential for its production by microbial fermentation in the future[58-60]. Since all Taxus species only generate a small quantity of Taxol, researchers have tried a variety of methods to increase production. Two separate groups at the tail end of the 20th century reported finding a significant quantity of two Taxol precursors, 10-deacetyl baccatin III and baccatin, in the needles of the European Taxus, *Taxus*

Table 3. Phyto-bioactive compounds used in pharmaceutical delivery systems with commercial approval

Phyto-bioactive class	Active Phyto-bioactive compound	Trade name	Drug Delivery System	Company	References
Taxanes	Paclitaxel	Abraxane®	Albumin Nanoparticle	Celgene and Abraxis	105,110
		Lipusu®	Cholesterol/lecithin liposomes	Luye Pharma	
		Opaxio®	Polymeric nanoformulation	Cell Therapeutics	
		Taxol®	Polymeric micelles	Polysciences, Inc	
		PICN®	Polymeric lipidic nanoparticles	Sun Pharma	
		Cynviloq®	Polymeric micelles	Samyang and Nantpharma	
		Nanoxel®	Polymeric micelles	Dabur	
		Paclical®	Polymeric micelles	Oasmia	
		Liporaxel®	Emulsion	Daehwa	
	Cabazitaxel	Jevtana®	Injection Concentrate	Sanofi	55, 57
	Docetaxel	Taxotere®	Injection Concentrate	Sanofi-Aventis	111
Vinca alkaloids	vincristine	Marqibo®	Sphingomyelin/cholesterol Liposomes	Spectrum	112
Camptothecin	Irinotecan	Camptosar®	Injection Concentrate	Pfizer and	113
	Topotecan	Hycamtin®	Submicron colloidal particles (capsules)	GlaxoSmithKline	
Curcuminoids	Curcumin	Theracurmin®	Submicron colloidal particles (capsules)	Theravalues	92, 114-116
		Meriva®	Curcuminoids and phosphatidylcholine phytosome	Indena S.p.A	92,117
Homoharringtonine	Omacetaxine mepesuccinate	Synribo®	Injection Concentrate	Teva Pharmaceuticals	118
Ingenol mebutate	Ingenol mebutate	Picato®	Gel	Leo Pharma	119

baccata L.[61]. Currently, Taxol and its semisynthetic soluble analogue Docetaxel (commercially known as Taxotere™) are produced by a multi-step semi-synthetic procedure. However, more enhancements are required to meet the future market requirements for this significant pharmaceutical [62,63].

6.2 Vinca Alkaloids

Vinca alkaloids are a category of pharmaceutical compounds derived from the *Catharanthus roseus* L. (commonly called *Vinca rosea*) plant, often known as pink periwinkle and classified under the Apocynaceae family. Vinca alkaloids are the second most often utilized class of anticancer medications in the treatment of different cancers. The cytotoxic effects of Vinca alkaloids are accomplished by their binding to β tubulin at a separate position relative to that found in taxanes. This binding inhibits the polymerization and assembling of microtubules, resulting in metaphase arrest along with subsequent cell death [64,65].

It was indeed one of the first anticancer drugs produced from plants to be permitted by the FDA. The FDA first gave its approval to its usage in cancer treatment in 1963. Vincristine is an alkaloid that belongs to the class of terpenoids called bis-indoles. Vincristine is a non-symmetric dimeric compound comprised of two indole-type nuclei (one of vindoline and one of catharanthine) connected by a carbon-carbon bond. Vincristine and vinblastine are two naturally derived alkaloids that have been used in the field of therapeutic malignancy for about the past fifty years. A collection of partially synthetic derivatives of these two alkaloids

has been created. Vinorelbine and vindesine are two semisynthetic counterparts that have been licensed for clinical use due to their shown efficacy. These drugs are often included in chemotherapy combination regimens for the management of various malignancies, such as leukemia, breast and lung cancers, Hodgkin and non-Hodgkin lymphomas, advanced testicular carcinoma, and Kaposi's sarcoma[66,67].

In recent times, concerning the tedious and expensive nature of their extraction processes, a range of semi-synthetic derivatives of vinca alkaloids have been synthesized. These semi-synthetic vinca alkaloid derivatives include vinorelbine, vinfosiltine, vindesine, and vinflunine, which are currently being utilized in clinical settings[68]. Reportedly, vinblastine was synthesized by the fungus *Alternaria* species, while vincristine was produced by the fungus *Fusarium oxysporum*. Fungus *Fusarium* solani, isolated from the phloem of *Catharanthus roseus* L., produces a mixture of these alkaloids[69].

6.3 Podophyllotoxins

Podophyllotoxin is a naturally occurring compound that has been extracted from the plant's *Podophyllum peltatum* L. and *Podophyllum emodi* Var., which belong to the Berberidaceae family. Podophyllotoxin has been identified as a compound that may impede cell development by reducing the polymerization of tubulin, hence disrupting the formation of mitotic spindles. Podophyllotoxin has reversible binding to tubulin, whereas its primary derivatives, etoposide, and teniposide, exert their effects by inhibiting Topoisomerase II, hence causing DNA cleavage mediated by Topoisomerase II. Additionally, podophyllotoxin has shown promise in inhibiting Multidrug Resistance (MDR) in many types of drug-resistant tumor cells[70,71]. These plants produce podophyllotoxin predominantly in their roots and rhizomes, but it has also been identified in their stems, roots, seeds, fruits, leaves, woody portions, and endophytic bacteria. Compared to other podophyllotoxin-producing plant species, *Podophyllum hexandrum* Royle contains 4.3%[72].

Consequently, this development has created an opportunity for the virtual design of a wide range of podophyllotoxin derivatives to enhance their clinical effectiveness. These investigations need a comprehensive examination of the latest developments in the field of podophyllotoxin. In addition, the depletion of podophyllotoxin plant resources has prompted a change in attention towards alternate sources, such as the manipulation of microorganisms for this purpose[73]. Biotechnological methods were developed to tackle large-scale production obstacles such as the extinction of podophyllotoxin-plant sources, sluggish plant development, precise constructions, and poor yields[74]. Fungal sources are more productive than other options for embryogenesis from somatic cells, tissue culture, and macro propagation procedures[75]. The primary fungal species used in the commercial manufacture of podophyllotoxin are *Fusarium oxysporum*, *Fusarium solani*, *Trametes hirsuta*, *Alternaria* fungus, *Mucor fragilis*, *Phialocephala fortinii*, and *Aspergillus fumigatus*. The results indicate that *F. oxysporum* shows potential as a viable candidate for the commercial production of podophyllotoxin[76-78].

6.4 Camptothecins Derivatives

Camptothecin, a pentacyclic quinoline alkaloid, is derived from the wood and bark of the Chinese tree *Camptotheca acuminate* Decne, *C. lowreyana* S.Y.Li (Nyssaceae) and *C. grandiflora* (Apocynaceae). The establishment of complexes between camptothecin and type I DNA topoisomerase inhibits the processes of DNA cleavage and relegation, ultimately resulting in the occurrence of a DNA double-strand break and subsequent cytotoxic effects. The effect results in DNA damage and cancer cell death because a single-strand break is converted into a double-strand break when the replication fork collides with the cleavable complex[79,80]. Camptothecin and its congeners are a class of medicines that exhibit specificity for the S-phase of the cell cycle and have a broad range of effectiveness against neoplastic cells. For the tumor cells to have an impact, they need an extended duration of exposure to a concentration of camptothecin that is above the minimum threshold[81].

Currently, the only FDA-approved therapeutically active and less toxic than camptothecin semi-synthetic derivatives are irinotecan and topotecan. Advanced malignancies of the gut or rectum are treated with irinotecan. Topotecan, on the other hand, is a proven method for dealing with recurrent malignancies like

those found in the cervix, lung, and ovary. Those two congeners were sold in the United States by Pharmacia and GlaxoSmithKline, respectively[82]. In addition to plant sources, camptothecin is synthesized by several endophytes that have been extracted from camptothecin-producing host plants, as well as when these endophytes were cultivated in culture conditions[83]. The current supply of camptothecin derived from plants does not satisfy the demands of the worldwide market. Consequently, there have been ongoing efforts to discover other sources of camptothecin. Entrophospora infrequent is an endophytic fungus that was obtained from the inner bark of *N. foetida (Wight)* in the Konkan Ghats region, located on the West coast of India[84].

6.5 Curcumin

Turmeric, or *Curcuma longa* L., Zingiberaceae, is a plant native to the tropics of Southeast Asia that is most often used as a spice. The rhizome of this plant contains the phytopolylphenol chemical curcumin. Traditional Indian and Chinese medicine uses turmeric powder that contains 2-5% curcumin. In 1910, Lamp and Milobedeska were the first to determine the chemical structure. It contains a seven-carbon linker with two enone moieties, a -dicarbonyl moiety, and two aromatic O-methoxy phenolic groups; its IUPAC name is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione[85,86].

Many studies have looked into the possibility of curcumin's chemopreventive and anticancer activity against different types of cancer due to its acknowledged pharmacological properties, such as its antibacterial, anti-inflammatory, antiviral, antioxidant, and wound-healing ability[87]. The relationship between the low incidence of gastrointestinal mucosal malignancies in Southeast Asian cultures and frequent turmeric usage in their diet has sparked research interest in curcumin's anticancer effects. Curcumin acts as a chemosensitizer for certain clinical chemotherapeutic drugs (e.g., gemcitabine) and synergistically along with other natural products (e.g., epigallocatechin-3-gallate) to overcome tumor resistance and prevent a recurrence. Several scientists have analyzed the most recent data from anticancer studies utilizing curcumin, both in laboratory animals and in humans. Recently, it was shown that giving patients with metastatic pancreatic cancer curcumin Meriva® (2,000 mg/day) as an adjuvant therapy to gemcitabine improved gemcitabine's effectiveness without increasing its severe side effects[88,89].

It exerts its anticancer impact by many modes of action, including the reduction of cancer cell metastasis, inhibition of cancer cell development, and activation of apoptosis in cancer cells. Several signaling pathways involving curcumin have been investigated *in vitro* and *in vivo* for their roles in a wide range of cancers, including colorectal and breast cancer. For example, in HCT-116 and HT-29 colon cancer cells, curcumin-induced apoptosis in response to Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL) by upregulating Death Receptor 5 (DR5)[90,91]. Curcumin's chemotherapeutic role in various cancer cells, including those of the blood, breast, head and neck, liver, prostate, ovary, and skin, has been reported in multiple studies. This is due to curcumin's ability to modulate multiple signaling and gene expression regulatory pathways[92-96].

6.6 Homoharringtonine

Homoharringtonine, an ester derived from the alkaloid cephalotaxine, is a naturally occurring compound found in several species of trees belonging to the Cephalotaxus genus (*Cephalotaxus fortune,* Cephalotaxaceae). Homoharringtonine has been utilized to treat patients with myeloid leukemias in China for over 50 years. It has been officially recognized for the therapeutic management of chronic myeloid leukemia. Homoharringtonine limits protein translation by competing with the ribosomal A-site, therefore blocking the first step in protein synthesis. Patients with intolerance and resistance to hypomethylating agents like azacitidine and decitabine have been shown to benefit from a semi-synthetic version of Homoharringtonine called omacetaxine mepesuccinate in the treatment of Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)[97,98].

Up to 85% full response can be induced in Acute Myeloid Leukemia (AML) with the current regimens, which mix Homoharringtonine with aclarubicin and daunorubicin or cytarabine. Homoharringtonine is an effective anticancer drug that has been shown to work against a variety of aggressive blood cancers, including those that have developed resistance to targeted therapies such as tyrosine kinase inhibitors. Recent studies have

shown that Homoharringtonine can effectively kill all types of lung cancer cells, including those that have developed resistance to tyrosine kinase inhibitors[99,100].

6.7 Ingenol Mebutate

Ingenol mebutate is a hydrophobic ester of the diterpene ingenol isolated from the common Australian sap plant *Euphorbia peplus* L (Euphorbiaceae), which has dermatological benefits including the treatment of malignant tumors. Actinic Keratosis (AK), a common skin condition caused by persistent UV radiation exposure that can develop into squamous cell carcinoma if untreated, is one of the conditions for which ingenol mebutate has been permitted for topical treatment. This substance rapidly induces cell death, making it effective for treating Actinic keratosis lesions. The mechanism(s) by which the active ingredient suppresses tumor growth or causes tumor cell death is called pleiotropic. The effects of ingenol mebutate can be broken down into two categories. First, at higher concentrations, it promotes the rapid beginning of cell death in the specified area. Second, it induces an inflammatory reaction that kills off any residual cells at doses as low[101-104].

7. Additional Anticancer Compounds Derived from Plants

The current overview has gathered extensive data on the efficacy of several phytochemicals from many researches. Brief info on each phytochemical follows.

7.1 EGCG (Epigallocatechin Gallate)

The flavonoid polyphenol epigallocatechin-3-gallate (EGCG) is found in many plant foods. Consuming green tea (*Camellia sinensis* L., Theaceae) and cocoa-based commodities is a great way to get the recommended daily intake of EGCG[120]. Green tea has a long history of medicinal usage in both China and India, where it has been used as a stimulant, astringent, diuretic, and cardiovascular tonic. The ester of epigallocatechin with gallic acid is known as epigallocatechin-3-gallate. Health advantages of EGCG include lowering LDL cholesterol, preventing aberrant blood clot formation, and slowing tumour development, among others. EGCG is the most powerful anti-inflammatory and anticancer agent among the several green tea catechin derivatives[121].

Green tea's ability to reduce the occurrence of cancerous tumours, such as those found in the stomach, colon, lungs and liver has been the subject of many *in vivo* investigations. Among the 10 polyphenols studied for their chemopreventive potential, only EGCG had strong antiproliferative effects, dramatically inducing cell cycle arrest across the G1 phase and cell death[122]. The potential of EGCG as an anticancer drug has been shown in several investigations. It inhibits cell growth, stops metastasis, and promotes cell death. By modulating the Src signaling pathway, EGCG suppressed MMP-2 protein production and hence the metastatic potential of human nasopharyngeal cancer cells[123]. Recent studies using the PDX model have shown that PLGA-encapsulated epigallocatechin gallate nanoparticles are more effective than free EGCG in inhibiting tumour growth in lung cancer via downregulating NF-kB-regulated genes. Furthermore, animals with Ehrlich ascites carcinoma showed remarkable antitumor activity when exposed to gold nanoparticles coated with epigallocatechin-3-gallate[124,125].

7.2 Genistein

The highest concentrations of genistein may be found in food and beverages made from soy. Since it was initially isolated from *Genista tinctoria* L. in 1899, it was appropriately given the name of that plant's genus. However, it serves as the primary metabolic byproduct in Glycine max (soybean) and Trifolium species. *Lupinus perennis* L. (Lupin) a legume has a genistein concentration equivalent to soybeans[126]. Soybeans (and related legumes) contain genistein, a naturally occurring isoflavone that has estrogen-like characteristics. Because of its structural similarity to 17-estradiol, it may bind to and influence the activation of estrogen receptors. Genistein, or [4,5,7-trihydroxyisoflavone], is a phytoestrogen that has a 15-carbon skeletal system[127]. In its aglycone form, genistein exerts its estrogenic, anticancer, and antiosteoporotic effects. The anticancer effects of genistein were demonstrated by a reduction in tumour growth and development in both the bare-skin mice hepatic cell cancer model and the Wistar rat gastric cancer embody, suggesting that genistein induces apoptosis, reduces proliferation, and inhibits angiogenesis and cancer metastasis[128].

7.3 Harringtonine

Cephalotaxus harringtonia var is the source of harringtonine and cephalotaxine, two compounds with anti-cancer properties. These compounds are effective against several forms of leukemia, including Acute Myelogenous Leukemia (AML), myelodysplastic syndrome (MDS), Acute Promyelocytic Leukemia (APL), and leukemia s of the central nervous system and intrathecal sites[129]. Anti-leukemic effects were demonstrated in L1210 cell lines and mouse P388 using the harringtonine esters, which vary in structural side-chain methylene group from harringtonine, homoharringtonine, isoharringtonine, deoxyharringtonine, and homoharringtonine[130,131]. Homoharringtonine's mechanism of action involves its effect on the ribosomes of malignant cells, which inhibits protein synthesis in a dose- and time-dependent manner, preventing the initiation of polypeptides synthesis and halting the progression of the cell cycle through G1, S, and M phases, ultimately resulting in apoptosis[132,133].

7.4 Rohitukine

The chromone alkaloid rohitukine was first extracted from the leaves and stems of the Meliaceae plant species *Amoora rohituka* (Roxb.) Wight and Arn, and later from the closely related *Dysoxylum binectariferum* Hiern. The compounds rohitukine N-oxide and N-demethylrohitukine-3'-acetate were obtained through the extraction process from the stem bark of *S. magnificum var*. On the other hand, endophytes were sourced from *D. binectariferum* Roxb. However, the alkaloid showed only moderate toxicity against human HL-60 promyelocytic leukemia and HCT-166 colon cancer cells, despite its wide range of bioactivities, such as anti-inflammatory and immunomodulatory effects and anti-fertility activity. Flavopiridol and Riviciclib hydrochloride (P276-00) are two rohitukine congeners currently evaluated in the advanced phase II clinical trials for potential antitumor therapy[134,135].

7.5 Combretastatins

Combretastatins are a group of structurally related compounds found in the bark of the South African Cape bush willow, *Combretum caffrum* Kuntze (Combretaceae). The substances encompassed in this group consist of stilbenes, dihydro stilbenes, phenanthrenes, and macrocyclic lactones, specifically referred to as combretastatin A, combretastatin B, combretastatin C, and combretastatin D, respectivel[136]. Compounds of the combretastatin class block tubulin polymerization in tumor endothelial cells, thereby leading to a rapid vascular collapse in solid tumors. Two of these chemicals have been obtained from nature; they are called combretastatins A1 and A4. The Food and Drug Administration (FDA) has approved the orphan medication combretastatin A4 phosphate (CA4P) for the treatment of several types of ovarian and thyroid cancers[137,138].

7.6 Thalicarpine

Roots of many different species in the genus Thalictrum (*Thalictrum dasycarpum* Fisch. and Lall., *Ranunculaceae*) were analyzed, and a new dimeric alkaloid called thalicarpine was discovered. It was possible to synthesize the alkaloid and learn its three-dimensional structure[139]. In monolayer, cultures of KB cells, the alkaloids thalasine, thalamelatine, thalifoetidine, and berberine exhibited cytotoxicity. A multidrug-resistant efflux pump called p-glycoprotein is bound and inhibited by Thalicarpine. The life cycle of tumor cells is halted in the G2/M and G1 phases after exposure to thalicarpine, which also generates single-strand fragments in DNA[140,141].

7.7 Usambarensine

The tiny tree *Strychnos usambarensis* Gilg, native to southern Africa, yielded cancerous alkaloid usambarensine when its roots were analyzed. This bis-indole alkaloid has been shown to have cytotoxic and antimalarial properties, in addition to its powerful antiamoebic activity[142]. Tertiary and quaternary alkaloids with anhydrous bases may be found in the root bark of Strychnos. Retulines are a class of alkaloids that includes C-calebassine, C-dihydrotoxiferine, C-fluorocurarine, and C-curarine, (in its monomeric form). Although preliminary research on the antineoplastic action of some of these alkaloids has shown promise, further study is needed[143,144].

7.8 Acronycin

The little Australian shrub *Acronychia baueri* Schott (family Rutaceae) was the initial source of acronycine. Subsequently, numerous compounds were identified from *Melicope leptococca* Guillaumin's aerial parts and the bark of *Sarcomelicope argyrophylla* Guillaumin, *Sarcomelicope dogniensis* T.G.Hartley, *Sarcomelicope glauca* T.G.Hartley

and *Sarcomelicope simplicifolia* (Endl.)[145]. Research interest has increased in recent years owing to the great variety of bioactivities shown by acronycin and its congeners. The biological effects of a chemical that intercalates into DNA and disrupts the cell's replication mechanism. They have little effectiveness against murine leukemia models but show cytotoxicity against breast, lung, colon, melanoma, and other solid tumor cell lines[146,147].

7.9 Ellipticine

Researchers in countries surrounding the Indian Ocean gathered *Ochrosia elliptica* Labill, *Aspidosperma*, *Ochrosia*, and some Apocynaceae for their leaves and stems, where they extracted ellipticine, methoxy-ellipticine, and elliptinine. Significant anticancer and biological actions were observed for ellipticines and their derivatives[148]. Breast, colon cancers, melanoma, Leukemia, ependymoblastoma, and Erlich carcinoma are only a few of the tumor types that are susceptible to its powerful cytotoxic activity and anticancer potential. It has been hypothesized that intercalation into DNA and suppression of DNA topoisomerase II activity are the primary mechanisms by which ellipticine exerts its anticancer, mutagenic, and cytotoxic actions[149].

7.10 Matrines

Roots of the *Sophora* species (*Sophora flavescens* Aiton, *Sophora japonica* L., and *Sophora prostrata* Buchanan) and the *Sophora alopecuroides* L. (above ground section) are the sources of the tetracycloquinolizindine alkaloids known as matrines. The Chinese State Food and Drugs Administration has authorized oxymatrine tablets, which are made from an alkaloid extract of the roots of the sophora plant, for use in the treatment of cancer. Matrines have a crucial role in the treatment of leukemia, leukopenia, and cancers of the oesophagus, larynx, and uterine cervix, among others[150,151].

7.11 Resveratrol

Resveratrol (3, 5, 4 – trihydroxy – trans – stilbene) is a polyphenol found in nature that is classified as a stilbene. Resveratrol is abundant in purple or red grapes (*Polygonum cuspidatum* Willd; Polygonaceae), peanuts, blueberries, mulberries, and pomegranates. Resveratrol has a fundamental structure of two phenolic rings connected by a double styrene link. Recent research into resveratrol's anticancer effects has shown that it has a remarkable capacity to attack a wide variety of cancer hallmarks. Resveratrol inhibited cell growth, activated caspase-3 and caspase-9, upregulated Bcl-2 associated X protein, and induced expression of p53 in human cervical cancer cells, demonstrating apoptotic and antiproliferative actions[152,153].

A wide variety of plant-based substances, including artemisinin, berberine, betulinic acid, gingerol, ginseng, glycyrrhizin, lycopene, nimbolide, pterostilbene, quercetin, and thymoquinone, have been determined due to their anti-cancer properties.

8. Challenges Associated with SLNs

While SLN delivery methods make an effort to meet the parameters necessary for the improved distribution of phyto-bioactive chemicals, a standard delivery system cannot be implemented at this time. Food and pharmaceutical applications may both benefit from the systems' utilization of high-quality lipids, increased loading capacity relative to food bioactive components, and cheaper manufacturing costs per unit. There is further work to be done on understanding how food particles are incorporated into SLNs, how they adapt physiologically to food storage systems, and whether or not they are risky to the target organs. Further study in these areas will boost the food industry's use of SLNs. Given the increasing toxicity of synthetic pharmaceuticals, there will soon be a higher need for medicinal foods. Potentially useful for transporting phyto-bioactive medicines and nutrients, these approaches could assist in enhancing functional fortified food in the future[154].

9. SLN Formulation and Production Strategies for the Improvement of Oral Delivery of Bioactive Compounds

Solid Lipid Nanoparticles (SLN) can improve the transport and stability of phyto-bioactive substances, but only if the formulation and production procedures are appropriate. The lipids, phyto-bioactive substances, surfactants, and cryoprotectants used in the SLN formulation play a role in the product's effectiveness and bioavailability[155]. Lipids included in Generally Regarded as Safe are frequently used in SLN formulations. The advantages of SLNs can be fabricated using a wide variety of lipids, including fatty acids/esters, triglycerides,

cholesterol, waxes, stearic acid, hard fats, and palmitic acid. Sodium cholate, polyvinyl alcohol, poloxamers, and Pluronic F68/F127 are all under consideration as emulsifiers. PEGylation, targeted delivery, and surface charge changes are provided by a selection of organic salts, surface modifiers, and ionic polymers[156].

10. Synthesis of Nanoparticles

A wide variety of techniques may be used to synthesize nanoparticles; nevertheless, these techniques can be roughly classified into two primary categories: (1) the top-down approach and (2) the bottom-up approach.

10.1 Top-down Method

The considerable substance is first reduced to its component nanoparticles or structures. A damaging strategy was used in this procedure. It all begins with more giant molecules broken down into smaller ones; then, they are transformed into appropriate nanoparticles. The methods utilized to create particles smaller than one micron are called top-down synthesis. Top-down methods are more straightforward because they start with eliminating or partitioning large amounts of material or scaling down large manufacturing operations to create a smaller, more manageable structure with the right attributes. The flaws in the surface structure are the main issue with the top-down method. Various decomposition processes, including grinding/milling, chemical vapour deposition (CVD) and physical vapour deposition (PVD) are used in this procedure[157,158].

10.2 Bottom-up Method

This method is used in the other direction, as nanoparticles are produced from considerably less complex compounds. As a result, this strategy is sometimes referred to as the building-up strategy. Techniques such as sedimentation and reduction are examples of this kind of methodology. The 'bottom-up' strategy is an alternate approach that can generate less waste and more significant cost savings. Atom by atom, molecule by molecule, or cluster by cluster is what is meant by the term "bottom-up approach," which refers to the process of constructing material from the bottom up. When it comes to the commercial manufacture of nanopowders, a significant number of these processes are either still in the process of being developed or are just starting to be used[159]. Some of the well-known bottom–approaches that have been documented for the manufacture of luminous nanoparticles include:

- The revere-micelle method.
- The organometallic chemical route.
- The sol-gel synthesis.
- The colloidal precipitation.
- The hydrothermal synthesis.
- The template-assisted sol-gel.
- Electrodeposition.
- Other techniques.

11. Absorption Processes of Phyto-bioactive Compounds Loaded in SLNs in Different Models of Chronic Diseases

Oral Delivery is the most often recommended route for lipid-based nanosystems, followed by parenteral administration. When chronic disorders are treated orally, the phyto-bioactive chemicals included in the SLNs have to be dissolved before absorption in the intestinal tract. While both methods of dosing aim to produce systemic effects from the encapsulated medications, oral dosing is more common and is generally favoured. However, the parenteral route, which includes intramuscular and subcutaneous injections, allows medications to reach the systemic circulation without first having to cross any absorptive barriers[160]. When SLNs are broken down by stomach enzymes, they disperse and release breakdown products that create mixed micelles. The phyto-bioactive compounds placed into these mixed micelles may be more readily absorbed due to their reduced particle size. The effects of SLNs on malignant illnesses are examined, and several recent studies demonstrate the higher absorption of bioactive substances via SLNs for treating diseases including microbiological, carcinogenic, inflammatory, diabetic, neurological, and cardiovascular disorders[161,162].

12. Conclusions and Future Perspectives

Cancer has claimed the lives of more than 10 million people worldwide so far this year. The mortality toll

attributable to cancer, already among the highest of any illness plaguing humanity, continues to grow. Several potential drug sources in nature might be developed into useful biologics for contemporary medical practice. Certain foods may contain phytobioactive substances. The majority of the phyto-bioactive compounds have capabilities that reduce inflammation, prevent heart disease, lower blood sugar, inhibit cancer, and kill bacteria. The vast majority of phytochemicals have therapeutic promise for treating and preventing cancer. We focused on a subset of these phyto-bioactive substance categories to more effectively approach these pharmacological issues. To address the issues associated with the qualities of phytochemicals, we are using this opportunity to expand our study to include these phyto-bioactive substances.

Solid Lipid Nanoparticles (SLN) are an exciting new colloidal delivery technology that may be used for oral or injectable administration of phyto-bioactive substances to numerous organs, including the tumor cell. It has been discovered that the phyto-bioactive compounds contained in SLNs are 10-20 times more bioavailable than they are in their natural state. The prolonged release of phyto-bioactive substances by oral administration allows the development of several novel phytocompounds loaded into SLNs to treat different cancers. Future research in nanomedicine will likely concentrate on enhancing and prolonging the oral administration of phyto-bioactive substances. The current research targets cancer diseases. Preclinical and clinical studies for new anticancer, anti-diabetic, and antihypertensive medications, as well as nanotechnology-based subatomic targets and delivery systems, are being conducted and showing encouraging results. SLN may help detect various malignancy barriers.

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