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PROOF
REVIEW

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Nanotechnology assisted natural antioxidants: Applications of Propolis loaded nanocarriers in cancer therapy

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Abstract

Apitherapy products, including honey, propolis, royal jelly, pollen, bee venom, and bee bread, are regarded as natural medicines with therapeutic effects on a variety of diseases. Among these, propolis has gained significant attention in medicine and pharmaceuticals due to its antioxidant, antimicrobial and anticancer properties, mainly attributed to its flavonoid and phenolic content. Its strong antioxidant and anticancer effects are associated with multiple mechanisms (apoptosis induction, cell proliferation suppression, antiangiogenesis, etc.). However, the clinical use of propolis remains restricted because of its poor solubility together with its unstable nature and inconsistent chemical composition. Nanotechnology offers effective solutions to these challenges by improving propolis stability, bioavailability, and targeted delivery. Therefore, incorporation of antioxidants derived from natural products with modern nanocarrier systems will provide a more effective and safer way to mitigate the impact of cancer therapies. This review aims to highlight current developments in propolis nanoencapsulation for cancer therapy, focusing on polymeric nanoparticles, lipid nanocarriers, nanoemulsions, etc. It further examines current nanoencapsulation methods and evaluates recent *in vitro* and *in vivo* studies on propolis nanoparticles as anticancer agents.

Introduction

Nanotechnology serves as an advanced technology, which improves natural bioactive compound stability, bioavailability, targeted delivery and effectiveness. The multidisciplinary field of nanotechnology enables precise control over drug release through its ability to engineer materials at the nanoscale (1-100 nm), while also offering promising opportunities in medical applications (Chibuye et al., 2024). The field of nanobiotechnology provides substantial benefits to overcome traditional therapy limitations through the creation of nanocarrier systems, which solve problems related to poor water solubility and nonspecific delivery of active compounds. Nanotechnology has achieved significant progress in pharmaceutical and nanomedical applications through the use of biocompatible materials, simple synthesis methods and adjustable surface characteristics. It is particularly prominent in regenerative medicine, tissue engineering, cell therapy, and cancer treatment applications (Asadi et al., 2023; Ma et al., 2024).

Honeybees (*Apis mellifera*) create propolis by mixing enzymes and beeswax saliva with plant secretions obtained from leaves, buds, trunks, and bark cracks. The bees use this mixture to defend their hives against disease agents. Propolis shows poor solubility while displaying high viscosity and powerful odour

characteristics. Moreover, it is rich in phenolic compounds, including polyphenols, flavonoids, aromatic acids, esters, and other bioactive substances that give it antioxidant, anticancer, antimicrobial, and anti-inflammatory properties, which has made it a valuable component in traditional medicine for many years (Escriche & Juan-Borrás, 2018; Kocot et al., 2018). The effectiveness of propolis can be enhanced by synthesizing it in nano or micro structures through different encapsulation methods and nanocarrier platforms including polymeric nanoparticles, lipid nanocarriers, liposomes, nanofibers, and nanoemulsions. These have been developed to stabilize propolis, improve its pharmacokinetics, and facilitate controlled delivery to tumour sites. Research indicates that the phenolic compounds of propolis remain stable against pH alterations and ionic stress. The encapsulation of propolis at the nano level enhances its bioavailability by up to 50% more than unencapsulated propolis. Propolis demonstrates potential as a tumor regulator through its cytotoxic properties which could replace chemotherapy in cancer treatment (Alanazi et al., 2021; Jayakumar et al., 2013).

The evaluation of nanoformulation strategies for propolis and similar compounds remains limited despite growing interest in apitherapy and natural product-based interventions. Nanomaterials improve the effectiveness of standard cancer treatments including surgery, radiotherapy, and chemotherapy, while also supporting the development of innovative treatment modalities, including biotherapy, photothermal therapy, and photodynamic therapy (Sun et al., 2023). The clinical application of propolis and other natural compounds faces obstacles because of their solubility, stability, and limited bioavailability despite increasing research interest. Moreover, although it has potential use in apitherapy and natural medicine the research on nanoformulated propolis is inadequate. Moreover, the scientific literature shows increasing interest in nanoformulated propolis for cancer research yet a thorough structured review remains absent. Therefore, this review investigates nanocarrier-based delivery methods to overcome these limitations while discussing their therapeutic applications and aims to bridge the gap between nanotechnology and natural compounds to show the potential of propolis in future therapeutic applications.

Chemical Structure and Biological Properties of Propolis

Propolis is a natural composite mixture, which may contain more than 300 chemical bioactive components, serving the purpose of bioactivities. These bioactive components give rise to the various biological properties that propolis possesses such as antimicrobial, antiviral, antibacterial, antifungal, anticancer, antioxidant, and anti-inflammatory properties (Asadi et al., 2023; Silva etal., 2019). Propolis by itself does not provide long-lasting protection; hence it is best used in conjunction with nanocarriers, which would enhance the efficacy of propolis through nanotechnology. The structures will facilitate controlled propolis release and formulations for effective control of the intended condition. Propolis is a mixture of a wide variety of components including phenolic acid, terpenes, aromatic aldehydes, alcohols, amino acids, fatty acids, important vitamins such as A, B1, B2, B6, B7, C and E, beneficial minerals such as magnesium (Mg), calcium (Ca), potassium (K), sodium (Na), copper (Cu), zinc (Zn), manganese (Mn), and iron (Fe); esters, volatile oils and flavonoids (flavones, flavonols and flavanones) (Pasupuleti et al., 2017; Vagish Kumar, 2014). In addition, some enzymes such as succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase, and acid phosphatase are also found in propolis (Pasupuleti et al., 2017). Propolis is an important compound because it suppresses tumor growth by triggering programmed cell death (apoptosis) in cancer cells, increasing the permeability of the mitochondrial membrane, and balancing intracellular oxidative stress. The composition of propolis varies depending on many factors, from plant species to where it is grown, making it difficult to identify the actual molecular mechanisms of propolis' anticancer activity. Caffeic acid phenethyl ester (CAPE) is one of the most significant bioactive components obtained from honeybee hive propolis, and has cell cycle regulating, apoptosis inducing, and anti-inflammatory effects. A lipophilic derivative of caffeic acid and potent antioxidant, CAPE is structurally related to 3,4-dihydroxycinnamic acid (Kuo et al., 2015). CAPE is notable for its hepatoprotective, neuroprotective, antidiabetic, and particularly anticancer properties. It induces apoptosis in cancer cells by increasing reactive oxygen species (ROS), disrupting mitochondrial function, and influencing cancer-related molecular pathways such as PI3K/Akt and AMPK. Additionally, CAPE inhibits metastasis by suppressing epithelial-mesenchymal transition (EMT), and diminishes the aggressive behavior of tumors. It enhances the sensitivity of cancer cells to chemotherapy, thereby improving treatment efficacy. However, due to its low bioavailability, efforts are being made to enhance the potential of CAPE in cancer therapy through the development of nanocarrier systems (Mirzaei et al., 2021). CAPE is also a well-known NF-κB inhibitor. CAPE treatment (50–80 μM) inhibits the activation of NF-κB by preventing the translocation of the p65 unit of NF-κB and blocking the binding between NF-κB and DNA (Natarajan et al., 1996). Treatment with the anticancer agent CAPE suppresses the proliferation of various human cancer cells including breast, prostate, lung, head and neck, cholangio, and cervical cancer cells, as well as preventing the transformation of normal cells into cancer cells (Kuo et al., 2015). Different types of propolis exhibit various biological properties depending on their origin and chemical composition, among which

antioxidant and anticancer effects are two important properties that we want to highlight in our article. The therapeutic properties of propolis are determined by the presence of polyphenols and flavonoids, and interestingly, there are 38 different types of flavonoids in propolis (Elumalai et al., 2022). Flavonoids include flavone and flavonol derivatives such as quercetin, galangin, pinocembrin, and kaempferol. They play a key role in antioxidant activity and free radical scavenging. Phenolic acids and their esters form compounds such as caffeic acid, p-coumaric acid, CAPE, etc. They have cell cycle regulating, apoptosis inducing, and anti-inflammatory effects. Aromatic compounds and terpenoids stand out as various volatile or semi-volatile components that support antioxidant capacity and increase antimicrobial activity.

Propolis is a beehive product characterized by a complex chemical structure, comprising approximately 30% beeswax, 50% resin and herbal balsam, 10% essential and aromatic oils, 5% pollen, and 5% other substances (Ali & Kunugi, 2020; Anjum et al., 2019). The color, odor, and specific chemical profile of propolis are primarily influenced by factors such as geographical location, plant sources, and bee species. This variability complicates the standardization of propolis products across different batches. Consequently, chemical characterization, standardization, and quality control are crucial for the industrial and pharmaceutical applications of propolis. Propolis has a very complex chemical composition and a wide variety of biological properties depending on the plant species and bee species on which the bees are hosted. Numerous types of propolis have been identified to date. These include poplar-type European propolis, Mediterranean propolis, Brazilian green propolis, Brazilian red propolis, Canadian, Venezuelan, Chinese, Argentinian, Turkish, Algerian, Egyptian, Mexican, and Greek propolis. Each kind of propolis and their characteristics may vary due to differences in the environmental changes, the plants that the bees collect, and bee species (Wieczorek et al., 2022). The ratio of biologically active compounds that various propolis types contain changes with time and geography. All types of propolis contain different biologically active components, which depend on the climatic conditions of the region (Sahar, 2020).

Antioxidant and Anticancer Properties of Propolis

Antioxidant Effect

Natural antioxidants consist of enzymatic and non-enzymatic types, which include vitamins, polyphenols, and flavonoids that neutralize reactive species while preventing oxidative damage. Nanotechnology enhances natural antioxidant delivery through improved stability and bioavailability, which results in promising medical applications (Chibuye et al., 2024). The safety profiles of natural antioxidants need thorough evaluation because their excessive consumption or the drug interactions may lead to adverse effects and toxic reactions.

Propolis demonstrates a strong ability to eliminate ROS and to stop their generation. The chemical composition of propolis requires thorough evaluation because this substance lacks stable and predictable chemical properties. Propolis stands as a natural material which brings both scientific value and commercial importance to the market. The antioxidant properties of propolis stem mainly from its phenolic acids and flavonoids, which represent the primary bioactive compounds that scientists have studied extensively (Bezerra et al., 2023). The chemical structure of propolis extracts contains numerous active compounds mostly composed of phenolic acids and flavonoids which belong to the secondary metabolite group. The disruptive effects of phenolic compounds on bacterial cell walls result in adenosine triphosphate (ATP) molecule interference and membrane potential changes, that ultimately cause bacterial cell death. Propolis extracts demonstrate antioxidant properties through their phenolic content which neutralizes free radicals that generate oxidative stress.

Conversely, the impacts of flavonoids are credited to their ability to inhibit DNA and RNA synthesis and proteins in bacteria, as well as their capacity to change membrane permeability. Based on research in the literature, it has been stated that propolis obtained from temperate climate regions is rich in flavonoids and aromatic acids, while propolis collected from tropical regions generally has a high phenolic acid content (Fritea et al., 2021). The combination of flavonoids and phenolic acids maintains cell membrane stability through lipid peroxidation prevention while simultaneously boosting the activity of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) (Oršolić & Jazvinšćak Jembrek, 2022). Furthermore, encapsulating antioxidants into nanoparticles can protect antioxidants from degradation during storage and digestion, which leads to better bioavailability. Also, the antioxidant properties help prevent degenerative diseases that result from free radicals by controlling oxidative stress. The application of nanoparticle systems protects antioxidant effects while enhancing beneficial compound delivery to propolis. These technological advances enable these components to be used more widely in pharmaceutical and functional food products (Khalil et al., 2019). Propolis antioxidant properties depend on multiple variables, including bee species, plant species, hive location, geographical area, temperature fluctuations, seasonal conditions, storage techniques, and post-harvest handling methods. The composition of propolis proves difficult to standardize because of these factors. The antioxidant properties of *Apis mellifera* propolis exceed those of all other propolis samples and demonstrate the strongest antioxidant properties (Irigoiti et al., 2021; Kocot et al., 2018).

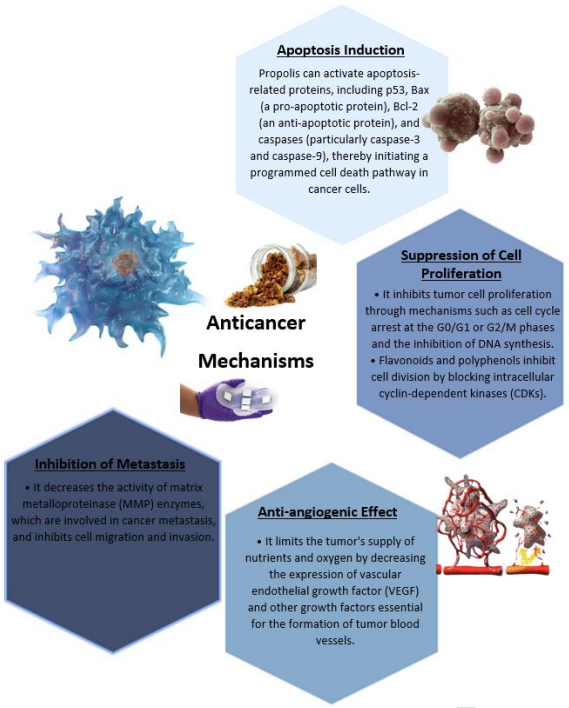

Figure 1. Anticancer effect mechanism of propolis

Moreover, different extraction solvents lead to major modifications in both chemical composition and biological activity of propolis extracts. The extraction of propolis typically uses 70-75% aqueous ethanol as the standard solvent. The extraction process employs different solvents, which include methanol, hexane, and chloroform, as well as ethyl ether and water (Sun et al., 2015).

In summary, the therapeutic potential of bee products, including propolis, royal jelly, honey, bee venom, bee pollen, and polyphenols, exists in their ability to regulate inflammatory mediator production through tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-2 (IL-2), and interleukin-7 (IL-7) while decreasing ROS levels. Furthermore, *in vitro*, *in vivo*, and clinical studies demonstrate that the immune response is enhanced through the activation of B and T lymphocyte cells. For these reasons, the anti-inflammatory, immunoprotective, antioxidant, antiapoptotic, and antimicrobial properties of bee products warrant further research in the clinical field (El-Seedi et al., 2021).

Anticancer Effect

Cancer is a complex and challenging disease to treat. Traditional cancer treatment methods, such as chemotherapy and radiation therapy, often result in severe side effects and do not yield satisfactory outcomes. The development of better treatment options has become essential as a result. In this context, nanotechnology is emerging as a promising solution methodology for cancer detection and treatment purposes. Nanotechnology enables innovative targeting methods through nanomaterials, interacting with cells and tissues to improve cancer diagnosis and treatment. Current challenges in cancer treatment underscore the critical need for innovative methods. (Chehelgerdi & Doosti, 2020).

In the research conducted so far, propolis and its components have been the focus of many studies due to their antimicrobial and anti-inflammatory activities. However, with further studies, it is understood that these substances also exhibit anticancer activity and have many therapeutic effects (Sawicka et al., 2012).

Researchers have shown interest in propolis because it demonstrates specific binding properties to cancer cells. The antitumor properties of its components lead to tumor cell growth suppression, which indicates their potential as chemotherapeutic drug alternatives (Masadah et al., 2021). The anticancer mechanisms of propolis include apoptosis induction, inhibition of metastasis, suppression of proliferation, and anti-angiogenic effects. These mechanisms are shown in Figure 1. Propolis inhibits DNA synthesis while halting fast-growing tumor cells and it activates natural killer cells. The compounds containing tumor suppressor proteins protect against radiation damage by stimulating glutathione production (Anjum et al., 2019).

The biologically active components of propolis, along with propolis itself, demonstrate potent anticancer and antitumor effects against cancer cells through cytostatic mechanisms. The research shows these effects occur both in laboratory tests and animal experiments. Caffeic acid, CAPE, artepillin C, quercetin, naringenin, resveratrol, galangin, genistein, and chrysin are primary constituents of propolis, which have antineoplastic properties and are suitable agents for cancer treatment. The chemopreventive capabilities of its flavonoid components enhance chemotherapy and

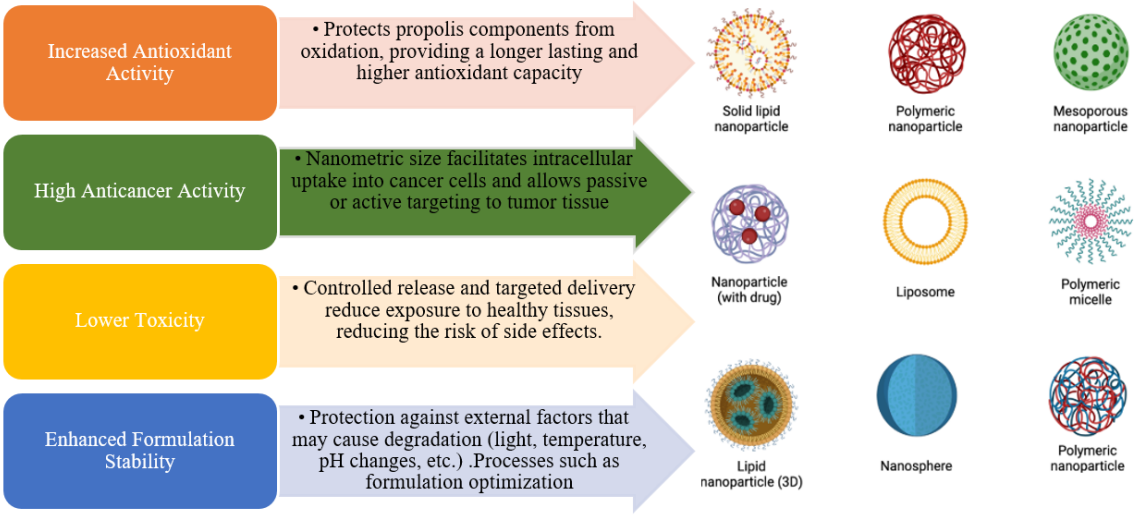

Figure 2. Preclinical applications of nanopropolis

radiotherapy effectiveness, which indicates propolis compounds could serve as diverse cancer treatment solutions. This approach establishes novel directions for preventing and treating cancer (Orsolik and Jembrek, 2022). The active compound of propolis, CAPE, is considered a popular cancer treatment agent (Masadah et al., 2021). The substance stands as one of the primary compounds responsible for propolis' anticancer properties while exhibiting numerous biological activities. Research conducted in laboratory settings demonstrates that CAPE triggers cancer cell death through apoptosis and generates toxic effects. Substances such as CAPE and artepillin C, in particular, cause tumor cells to undergo apoptosis, arresting the cell cycle and strengthening the immune system. The apoptosis rate in fibrosarcoma cells increases when treated with CAPE, and the compound triggers cell death in cancerous cells by modifying p53, p38 MAP kinases, and NF-κB pathways. Through its action on the intrinsic apoptosis pathway, the compound generates ROS while downregulating apoptosis inhibitors. The compound demonstrates potential as a cancer treatment agent through its ability to stop cancer cell growth by downregulating proteins linked to carcinogenesis (Bava et al., 2024). Research demonstrates that CAPE exerts dose-dependent and concentration-dependent cytotoxic effects on cancer cells, while the duration of exposure also influences its effects (Masadah et al., 2021). The analysis of literature reveals that propolis targets essential molecules involved in apoptosis through the intrinsic pathway. The process works through caspase cascade activation and cytochrome C release from mitochondria to cytosol and pro-apoptotic protein action. Watabe and colleagues showed that CAPE blocks NF-κB activation, which serves to block apoptosis and enhance proliferation and angiogenesis. CAPE triggers apoptosis in cancer cells without harming normal WI-38 fibroblast cells (Watabe et al., 2004). Research into the activity mechanisms of propolis and its active compounds CAPE and chrysin triggering apoptosis in cancer cells reveals that these substances activate cancer cell death pathways. The antiproliferative effects of propolis, CAPE, or chrysin in cancer cells are the result of cell cycle arrest as well as suppression of cyclin complexes. The results of *in vitro* and *in vivo* studies suggest that propolis, CAPE, and chrysin may inhibit tumor cell progression and may be useful as potential chemotherapeutic or chemopreventive anticancer drugs (Sawicka et al., 2012). Many studies in the literature have indicated that propolis activates pro-apoptotic proteins (e.g. Bax, p53) in cancer cells, suppresses antiapoptotic proteins (Bcl-2, survivin), plays a role in suppressing cell proliferation, causes cell cycle arrest (G0/G1 or G2/M) and DNA synthesis inhibition, and plays a role in inhibiting angiogenic factors (VEGF, etc.) and MMP (matrix metalloproteinase) enzymes (Czyżewska et al., 2016; Motomura et al., 2008; Park, et al, 2014; Valivand et al., 2024). All these studies have suggested that propolis and its components inhibit cell proliferation, survival, and cell cycle in various cancers by altering various signaling pathways (PI3K/Akt, MAPK, TNF-α/NF-κB, Wnt/β-catenin, and STAT-3/PLK-1) (Czyżewska et al., 2016; Motomura et al., 2008; Park et al., 2014; Elumalai et al., 2022 Valivand et al., 2024). These properties have led to the interest of propolis as an adjunctive treatment agent in cancer research. However, in order to fully utilize propolis at preclinical and laboratory levels, stable and highly bioactive formulations need to be developed. The preclinical effects obtained as a result of formulation development are illustrated in Figure 2. The anticancer effect of propolis is the result of its antioxidant, anti-inflammatory, immunomodulatory, cytostatic, antineoplastic properties, suppression of proliferation in cancer cells, reduction of cancer stem cells and populations, inhibition of specific oncogene signaling pathways, provision of antiangiogenesis, regulation of tumor micro-environment and enhancement of chemotherapeutic activity.

In addition, propolis appears to alleviate the side effects associated with various drugs. It stimulates the induction of lymphocytes and certain cytokines,

influencing IL-1 and TNF. While supporting cancer treatments such as chemotherapy and radiotherapy, it also protects healthy cells from the damage these therapies can cause (İpek et al., 2022; Meneghelli et al., 2013; Patel, 2016). The literature reveals that propolis is a promising candidate in cancer treatment due to its antitumor activity, which is mediated by the induction of apoptosis (programmed cell death) in breast cancer cells. Furthermore, propolis exhibits selective cytotoxic effects against tumor cells, demonstrating low or negligible toxicity toward normal cells. These characteristics position it as a potentially significant agent in breast cancer (Xuan et al., 2014). Turkish propolis has been reported to have a selective cytotoxic effect by increasing endoplasmic reticulum stress, triggering apoptosis (programmed cell death) and caspase activity, and also decreasing mitochondrial membrane potential in human lung cancer cells. These results demonstrate that propolis exhibits potential to slow down cancer cell growth (Demir et al., 2016). Propolis compounds like quercetin and CAPE with chrysin activate cell cycle progression inhibitors, including p21 and p27, together with cyclins, which cause cell cycle halt at multiple stages (Sawicka et al., 2012). Researchers studied how propolis ethanolic extract affected HCT15 human colon carcinoma cells and found dose- and time-dependent cytotoxic effects (Valença et al., 2013), and research shows that the compound reduces glucose consumption and lactate production while changing glycolytic metabolic pathways.

Northern Morocco-derived propolis samples exhibited cytotoxic properties against MCF-7, HCT116, and THP-1 cell lines. Propolis samples demonstrated an increase in the production of interleukin-10 (IL-10), while the levels of TNF-α and IL-6 were reduced. (Touzani et al., 2019).

In another study, the analysis of pre-osteoblast cell behavior after alcoholic extract of propolis treatment revealed that this extract boosted cell growth while enhancing protein kinase B (AKT) and extracellular signal-regulated kinase (ERK) survival protein expression. The propolis extract enhanced cellular differentiation and upregulated bone morphogenetic protein 7 (BMP7) gene expression, which controls osteogenic differentiation. The activities of matrix metalloproteinases (MMP2 and MMP9) demonstrated increased expression during this time. Propolis influences inflammation through its ability to enhance the production of inflammatory cytokines IL-6 and TNF-α. The results demonstrate that propolis extract stimulates growth, differentiation, and tissue reconstruction of osteoblasts. The molecular investigation of propolis extract effects on bone tissue repair and regeneration demonstrates its potential therapeutic application. The molecular modulation of hypoxia inducible factor-1 alpha (HIF-1α) and TNF-α explains how propolis affects bone repair and inflammatory processes. The obtained results indicate that propolis is a promising therapeutic agent for tissue engineering and bone regeneration applications. Additional *in vitro* and *in vivo* studies must be conducted to validate these findings for clinical practice implementation (de Morais et al., 2025).

In summary, the natural product, propolis, demonstrates multiple functions through its strong antioxidant and anticancer effects, which stem from various molecular pathways. The direct clinical application of propolis faces challenges because of its physical and biological characteristics. Nanotechnology provides a promising method to unlock the complete therapeutic value of propolis in oncology by improving its stability, bioavailability, and tumor-targeting ability.

Importance of Nanoencapsulation Technology and Nanocarrier Platforms

Importance of Nanoencapsulation Technology

The encapsulation methods operate as a basic protective system that prevents bioactive compounds from degrading. The encapsulation methods consist of two categories based on material size, which include microencapsulation and nanoencapsulation. Nanoencapsulation is a better option than microencapsulation because its tiny dimensions enhance both bioavailability and controlled release of its contents. The system uses biodegradable nanocarriers to enclose bioactive compounds mainly in the gastrointestinal tract through delivery methods such as nanoparticles, nanoemulsions, nanofibers, or nanotubes. The selection of encapsulation technique depends on two main factors, which include the core material structure and the coating material's chemical structure, size, thickness, solubility, permeability, and delivery rate. The encapsulation methods consist of two main categories, which include physical and chemical methods such as emulsification and coacervation and physical mechanical methods that include spray drying, spray cooling, spray freezing, prilling, freeze drying, electrodynamic methods, and extrusion (Noore et al., 2021; Perinelli et al., 2020).

Multiple essential factors need to be evaluated when selecting nanocarrier production techniques. The selection of nanocarrier production methods depends on the release mechanism and rate as well as stability and solubility and production costs (Noore et al., 2021).

The encapsulation of bioactive propolis components requires binding through chemical reactions or physical trapping methods to achieve nanoscale encapsulation. The delivery system provides controlled tissue targeting and protects bioactive compounds from environmental factors, including oxidation, pH changes, and enzymatic breakdown. Nanoencapsulation technology has various applications across dietary supplements, drug delivery systems, cosmetics, and agricultural products. Nanostructured carriers decrease toxicity levels, which enhances the therapeutic potential of bee products. The

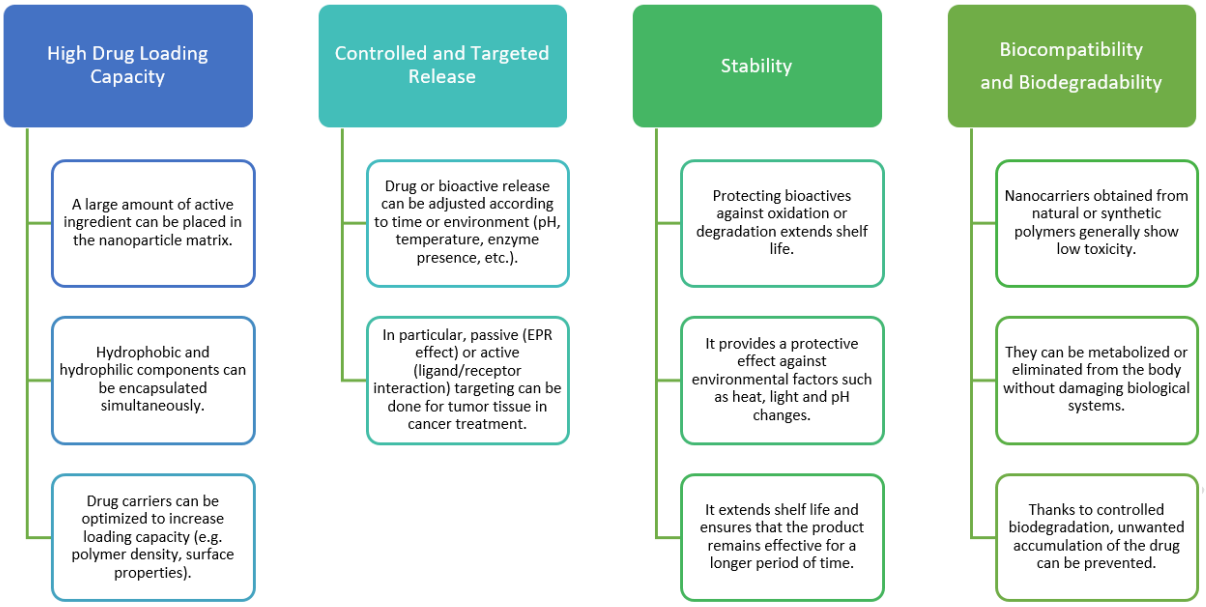

Figure 3. Advantages of nanocarrier systems in solving the problems of low solubility and rapid degradation of natural products such as propolis.

characteristics suggest that bee products could serve as effective treatments for cancer and other diseases (El-Seedi et al., 2021).

Nanocarrier Platforms

The delivery of bioactive compounds to their targets requires nano-delivery systems that use nanoscale materials as their fundamental components. Nanoscale materials serve as a preferred technology in modern cancer research because their surface modification capabilities enable them to pass through tumor blood vessel large pores and evade immune system detection. The small dimensions of nanoscale materials enable drug absorption and tissue targeting while protecting drugs from degradation, enhancing solubility and bioavailability, reducing side effects and enabling controlled drug release (see Figure 3). The research field continues to advance at a rapid pace. Several nanocarrier platforms are listed below.

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) originate from polymers, which consist of monomer units that repeat sequentially. The main material used in nanoencapsulation applications consists of polymeric nanoparticles derived from biocompatible polymers, including chitosan, alginate, gelatin, polylactic acid, polyvinyl alcohol, and poly (lactic-co-glycolic acid). PNPs function as pharmaceutical delivery matrices in various pharmaceutical applications to encapsulate medications and active ingredients. PNPs function as drug carriers through surface adsorption and encapsulation to enhance drug solubility while protecting drugs from environmental factors and enabling controlled drug delivery. The release of bioactive compounds from PNPs depends on the physical and chemical properties of both the polymer material and the bioactive compound. The characteristics that affect these traits include molecular weight, degradability, hydrophilicity, hydrophobicity, chemical structure, and crystallinity. The parameters of particle size, encapsulation efficiency, and drug release profiles can be precisely controlled through techniques such as emulsion-solvent evaporation, nanoprecipitation, coacervation, and ionotropic gelation. Polymeric nanoparticles can trigger drug release at the tumor site through reactions with tumor microenvironment stimuli, including pH, temperature, or enzymatic activity (Mendez-Pfeiffer et al., 2021; Revadihal et al., 2025). These systems are unique because they have large surface areas together with adjustable physical and mechanical characteristics and natural elasticity. The creation of targeted biomolecule binding sites becomes possible by modifying monomers through various combinations and chemical alterations (Moulahoum et al., 2023).

Nanoemulsions

Nanoemulsions (NEs) function as drug carriers in vaccine delivery and cancer therapy applications. The water-insoluble molecules are transported through colloidal dispersion formulations of NEs. The stability of these formations receives enhancement from surfactants, which typically create water droplets dispersed in oil or oil droplets dispersed in water. The main benefit of NEs involves protecting drugs from hydrolysis and enzymatic degradation through encapsulation, which extends their effectiveness duration. The stability of NEs reaches its peak between 20 and 200 nm in size, but NEs larger than 500 nm

become thermodynamically unstable. NEs achieve stability through their size range, which makes them appropriate for multiple drug delivery methods. The modification of NEs through ligand attachment enables them to target particular diseases, including cancer. The receptor-targeting capabilities of NEs conjugated with ligands enable better penetration into tumor cells because these receptors appear in high numbers on cancer cell surfaces. The described features show promise to boost NEs' cancer treatment performance while helping to minimize tumor expansion (Jaiswal et al., 2015; Rai et al., 2018; Sánchez-López et al., 2019).

Lipid-Based Nanoparticles

Liposomes are a traditional class of vesicular lipid-based nanoparticles and are often used in drug delivery systems. They are made up of phospholipid and cholesterol layers, enclosing a water-based core. The original formulation used natural lipids, but the technology now includes synthetic lipids and surfactants. The carriers demonstrate versatility because they can contain water-soluble compounds in their core and fat-soluble drugs within their lipid layers. Medical applications of liposomes typically range in size from 50 to 450 nanometers. The drug delivery system benefits from their cell membrane-like structure and drug transport capabilities. Liposomes are widely used for drug delivery, nutritional supplements, and the delivery of biological agents, showing high encapsulation efficiency and prolonged circulation properties. These characteristics allow liposomes to accumulate at disease sites, such as tumors, via the EPR effect (Bozzuto & Molinari, 2015; Najahi-Missaoui et al., 2020).

Solid Lipid Nanoparticles (SLN)

The drug delivery system employs SLN as stable carriers, which are solid at room temperature and human body temperature. The colloidal carriers are in the form of small particles with a size range of 50 nm to 1 µm. The drug is stabilized by a solid lipid core that has surfactants to encapsulate the drug. The release rate of the drug is highly dependent on the structure of the solid lipid core. The solid lipid nanoparticles have high lung tolerance and low toxicity (Himri & Guaadaoui, 2018; Loira-Pastoriza et al., 2014).

The nanocarriers, solid lipid nanoparticles, have a unique characteristic of being biocompatible and biodegradable and also modifying drug properties. The technology has many advantages due to its ease of operation, low cost, absence of solvents in manufacturing, durability, and controlled delivery system (Gulati et al., 2022).

Silica Nanoparticles

Silica nanoparticles represent nanoscale materials that consist of silicon dioxide (SiO_2). The abundant natural material found in sand and rocks exists for synthesis through chemical vapor deposition, hydrolysis, and sol-gel synthesis methods. The distinctive features of silica nanoparticles include their high surface area together with chemical stability, biocompatibility, and low toxicity. Their high melting point together with chemical and heat resistance makes them suitable for industrial and structural applications. Medical applications of silica nanoparticles include drug delivery, imaging, and tissue engineering (Moulahoum et al., 2023). The drug delivery capabilities of silica nanoparticles make them promising candidates because their large surface area and pore volume enable them to transport high drug doses (Castillo & Vallet, 2021).

The selection of an appropriate nanocarrier platform is critical to maximize the therapeutic benefits of propolis in oncology. Among the various options, polymeric nanoparticles and nanostructured lipid carriers have shown the most promise due to their favorable safety profiles, controlled release kinetics, and tumor-targeting capabilities. Future research should continue to refine nanoencapsulation techniques while prioritizing scalability, biocompatibility, and regulatory compliance for clinical translation (Bruckmann et al., 2022).

Efficacy of Nanocarrier Systems in Propolis Based Anticancer Therapies

The advantages of encapsulation of bioactive compounds are more than protection against external factors like oxygen, light, and heat. It can also assist in prolonging shelf life and avoiding interference with product performance by removing unpleasant odours and tastes. Nanoparticles (NPs) enhance the efficacy of both traditional and modern medicine by improving drug delivery, solubility, and stability. Herbal medicine could undergo a revolution as a result of this integration, especially when it comes to viral diseases. Because of their varied pharmacological characteristics, natural products, which have long been used as a source of therapeutic agents offer a great deal of promise. These organic substances can be further enhanced by combining them with nanotechnology. By improving bioavailability, stability, and targeted drug administration, nanotechnology opens the door to more potent therapies. (Herdiana, 2025).

CAPE is a promising compound for therapeutic applications; however, it presents pharmacokinetic challenges due to its poor water solubility and species-specific metabolic differences. While CAPE is rapidly cleared in rats, with a half-life of approximately 21 to 27 minutes, its half-life in humans is significantly longer, averaging around 18.5 hours following oral administration. The deficiency of carboxylesterase in human plasma may inhibit the hydrolysis of CAPE, thereby preserving its therapeutic effects. Nevertheless, the issue of poor solubility can be addressed through advanced formulation techniques, such as nanostructures. The application of CAPE in controlled and targeted release systems may enhance its biological

activities (Yordanov, 2019). Table 1 presents some of the studies that have investigated various encapsulation methods aimed at preserving the bioactive compounds of propolis over the past decade.

In the encapsulated propolis study conducted by Diab et al., the effects of a novel nanoformulation containing sericin, propolis, and 5-fluorouracil (5-FLU) on colorectal cancer were investigated. The nanoformulation demonstrated cancer cell growth suppression and apoptosis induction in both *in vitro* and *in vivo* studies. Through PI3K/AKT/mTOR pathway inhibition and FOXO-1 pathway activation, it caused

Table 1. Studies on the effects of propolis-loaded nanocarrier structures

Encapsulation material	Method	Effect	Result	Reference
Propolis Encapsulation	Emulsion chemical crosslinking	Anticancer effect-MCF-7	Cell viability was further reduced, indicating higher level of cytotoxicity.	(Jayakumar et al., 2013)
PLGA/Propolis NP	Emulsification solvent diffusion method	Antimicrobial effect (inhibition of biofilm formation for Staphylococcus aureus and Pseudomonas aeruginosa)	It inhibited both Gram-positive and Gram-negative bacterial biofilm formation, the effectiveness of PLGA-HERP NPs is higher against Gram-positive strains.	(Silva et al., 2019)
Brazilian red propolis extract (BRPE)/PLA nanoparticle	Nanoprecipitation Method	Antimicrobial, antioxidant and anticancer effect (OVCAR-3 ovarian cancer)	It showed high bioavailability, antimicrobial activity and anticancer properties, inhibited the proliferation of cancer cells and promoted apoptosis. In addition, NCBRPE controlled bacterial infections in the ovarian cancer micro-environment, reduced oxidative stress by showing high antioxidant capacity.	(Justino et al., 2024)
Propolis loaded niosome formulation	Thin film hydration technique	Anticancer effect (in MCF7, A549, MDA-MB-231, SK-MEL, SK-BR-3, DU145 and L-929 cell lines)	By increasing the bioavailability and targeting ability of propolis, it showed significantly higher cytotoxic effect compared to EEP, especially in SK-MEL and A549 cell lines. It showed a strong antitumor effect with very low IC50 values in SK-MEL, A549 and DU145 cell lines. It strengthened the antitumor effect by reducing the spheroid dimensions of PLN.	(Cetin et al., 2022)
Propolis loaded Chitosan coated PLGA Nano-Microparticle carrier	Nanospray drying	Anticancer effect HepG2(liver) and HCT 116(colon)	Propolis loaded NIMs induced more cytotoxic effect on HepG2 cells than HCT-116 cells and mediated three times higher therapeutic efficacy than free propolis, propolis loaded NIMs induced apoptosis of HepG2 cells and significantly reduced their numbers in proliferative G0/G1, S and G2/M phases (it shows antiproliferative effect against HepG2 and HCT116 cell lines by inducing apoptosis and cell cycle arrest due to the effect of propolis extract)	(Elbaz et al., 2016)
Propolis-loaded nanostructured lipid carrier	High-Shear Homogenization method for nano lipid carriers	Anticancer effect (Breast cancer)	Significantly reduced tumor growth in mice, increased antioxidant levels, suppressed angiogenesis and inflammatory pathways, and induced apoptosis. In addition, the increase in miRNA-223 expression inhibited the proliferation of breast cancer cells and increased apoptosis	(Shaker et al., 2023)
Propolis loaded PVA/PAA hydrogel	Cryogel system	Antibacterial activity *Staphylococcus aureus, Escherichia coli, Salmonella typhimurium*, and *Pseudomonas putida*	Antimicrobial studies revealed highly effective inhibition of all bacteria studied. Furthermore, bacterial inhibition increased with increasing propolis concentrations.	(de Lima et al., 2016)
sercin/propolis/ fluorouracil loaded nanoparticle	Self assembly method	Anticancer effect Colorectal cancer (CaC0-2)	Sercin/propolis/5-FLU nanoformulation showed high anticancer activity in the treatment of colorectal cancer. The nanoformulation triggered apoptosis and autophagy processes via inhibition of PI3K/AKT/mTOR pathway and activation of FOXO-1 pathway.	(Diab et al., 2024)
Propolis Loaded Liposome	Modified Ethanol Injection Method for Liposome	Antimicrobial and Antioxidant Activity	It was found that propolis-loaded liposomes have high antioxidant capacity. Antimicrobial activities were effective against Gram-positive and Gram-negative bacteria, and minimum inhibitory concentrations varied between 512-128 µg/mL for bacteria and 256-128 µg/mL for fungi. It was concluded that propolis-loaded liposomes may offer an effective alternative in wound treatment with their antioxidant and antimicrobial properties.	(Aytekin et al., 2020)
Propolis loaded soy protein/pectin microcapsule	Coacervation and freeze drying	Antioxidant and antimicrobial activity	Encapsulation process preserved the antioxidant activity of the material as well as its inhibitory activity against S. aureus.	(Nori et al., 2011)
PVA/Propolis NP	Electrospraying method	Antioxidant and antimicrobial activity	Using the electrospray method, different concentrations (0, 0.4, 0.8, 1.0 and 1.2 %) of propolis extract PVA nanoparticles produced showed antioxidant activity (DPPH radical scavenging activity) in the range of 80-89%. In antimicrobial activity tests, propolis loaded nanoparticles showed strong inhibition against Gram-positive bacteria (especially *S. aureus*), but not against Gram-negative bacteria (*E. coli* O157:H7). has been found to be less effective against	(Subaşı-Zarbaliyev et al., 2023)
Malaysian propolis/chitosan NP	Ionic gelation	Antibacterial effect (Enterococcus faecalis-gram positive bacteria)	Propolis-chitosan nanoparticles exhibited better effect against preformed biofilm compared to free propolis, indicating the penetration capacity of nanoparticles, Malaysian propolis extract showed anti-biofilm effect not only by reducing the viability of E. faecalis cells but also by decreasing the expression of biofilm-related genes such as gelE, ace, asa, fsrB, fsrC, ebpA, ebpB, ebpC, efa	(Ong et al., 2017)
Propolis loaded PLGA NP	Emulsion chemical cross-linking	Antifungal effect-antifungal effects on C. albicans	It has an increased effect on metabolic activity of C. albicans by up to 20% compared to free propolis	(Iadnut et al., 2019)

cells to die faster and experience autophagy. An *in vivo* study showed that the nanoformulation led to diminished tumor growth while simultaneously lowering oxidative stress and activating antioxidant systems. The nanoformulation demonstrated low toxicity while it increased the 5-FU bioavailability. Research findings established the nanoformulation as a potential therapeutic solution for colorectal cancer treatment (Diab et al., 2024).

In another study, the researchers assessed nanostructured lipid carriers with propolis extract to determine their effectiveness in breast cancer treatment. The research showed that treated mice developed smaller tumors while their antioxidant levels rose as well as their angiogenesis, and their inflammation and apoptosis pathways became blocked. The research demonstrated that elevated miRNA-223 expression levels led to decreased breast cancer cell proliferation and increased programmed cell death. The therapeutic value of the 5-fluorouracil (5-FU) chemotherapy drug increased when combined with propolis extract nanolipid carriers, while its adverse reactions decreased. The research demonstrated that breast cancer treatment benefited from nanotechnology-based propolis combinations and identified miRNA-223 as a crucial molecular target (Shaker et al., 2023). The nanoencapsulated Brazilian red propolis extract showed better bioavailability, antimicrobial, and anticancer activity than propolis extract in ovarian cancer research and also inhibited cancer cell proliferation and induced apoptosis. Nanoencapsulated Brazilian propolis inhibited the formation of biofilm in ovarian cancer cells, reduced bacterial infections in the tumor microenvironment, and had strong antioxidant activity to reduce oxidative stress. Nanoform simultaneously targeted cancer cells and reduced infection and inflammation in the microenvironment, which presented a diverse treatment solution (Justino et al., 2024).

Propolis exhibits natural antioxidant and anti-inflammatory properties along with immunomodulatory characteristics that affect autophagy mechanisms. Autophagy represents a cellular system that breaks down damaged proteins and organelles through lysosomal degradation to preserve cellular equilibrium. Propolis displays dual functions in autophagy regulation since it either enhances or suppresses the process across different disease models, including cancer, infections, and cellular damage. Autophagy effects depend on both propolis component concentration levels and the particular cells under examination, such as galangin, artepillin C, and chrysin. It is understood that certain components of propolis can induce apoptosis in cancer cells by promoting autophagy, particularly in the context of cancer treatment. Furthermore, propolis is believed to regulate excessive inflammation by activating autophagy processes in response to infections and oxidative stress-related diseases. The immunomodulatory effects of propolis may also indirectly influence autophagy by modulating inflammatory signaling pathways, such as IL-6 and TNF-α (Lesmana et al., 2024).

Discussion

Improvement of propolis with nanocarrier systems has been shown to significantly increase its anticancer activity. Nanoencapsulation improves the solubility and bioavailability of propolis, enabling its efficient delivery to target cells, which led to increased cytotoxicity and controlled release. Table 1 summarizes the literature in the field by collectively presenting experimental studies of propolis-based nanoformulations in cancer models. In this context, studies using various nanoencapsulation techniques have been examined, and these methods include emulsion chemical crosslinking, emulsification solvent diffusion, nanoprecipitation, thin film hydration, nanospray drying, high shear homogenization, cryogel systems, self-assembly, modified ethanol injection, coacervation by freeze-drying, electrospraying, and ionic gelation. However, when these data are examined, the most frequently investigated cancer types in the analyzed studies are breast (MCF-7), colorectal (HCT-116, HT-29, CaCo-2), liver (HepG2), and ovarian (OVCAR-3) cancers, respectively (Jayakumar et al., 2013; Elbaz et al., 2016; Cetin et al., 2022; Shaker et al., 2023; Justino et al., 2024; Diab et al., 2024). This suggests that propolis has a higher therapeutic potential, especially in tumors of epithelial origin. Indeed, the fact that most of these cancer types have inflammatory and oxidative stress-based pathophysiologies may contribute to the antioxidant and immunomodulatory effects of propolis being more pronounced in these models. The most commonly used nanocarrier systems are polymeric nanoparticles (e.g. natural polymers such as PVA, PLGA, and chitosan), lipid-based systems (SLN), nanostructured lipid carriers (NLC), and nanoemulsions and micelles, which have been used in a limited number of studies (Elbaz et al., 2016; de Lima et al., 2016; Silva et al., 2019; Iadnut et al., 2019; Shaker et al., 2023; Subaşı-Zarbaliyev et al., 2023; Justino et al., 2024). Among the production techniques, methods such as emulsion chemical crosslinking (Jayakumar et al., 2013) and nanospray drying (Elbaz et al., 2016) are only moderately effective in cancer treatment, whereas nanoprecipitation, emulsification-solvent evaporation, and high-pressure homogenization methods stand out in anticancer applications due to their ability to increase bioavailability, provide controlled release, and target tumor microenvironments. These methods exploit the physicochemical properties of polymeric and lipid-based nanocarriers to optimize the delivery of propolis bioactives. The emulsification method, especially used with lipid carriers, provides high encapsulation efficiency and colloidal stability, increasing cellular uptake and bioavailability (Bozzuto & Molinari, 2015; Najahi-Missaoui et al., 2020; Justino et al., 2024). Similarly, PLGA- and chitosan-based systems have been

reported to have higher cytotoxic effects compared to free propolis in HepG2 and MCF-7 cell lines (Elbaz et al., 2016) This reveals the potential of the carrier material to increase controlled release and intracellular targeting. Some studies have shown striking results; polymer-coated nanoparticles provided threefold higher cytotoxicity in HepG2 cells compared to free propolis (Elbaz et al., 2016). Nanoprecipitation of Brazilian red propolis extract (BRPE) into PLA nanoparticles showed superior bioavailability and anticancer activity against ovarian cancer (OVCAR-3 cells). These nanoparticles showed high encapsulation efficiency, inhibited cancer cell proliferation, promoted apoptosis, and reduced bacterial infections in the tumor microenvironment (Justino et al., 2024). Similarly, NLC systems enhanced apoptosis and contributed to tumor suppression in breast cancer models (Shaker et al., 2023). It has been observed that combinatorial nanoformulations in which propolis is used together with chemotherapeutic agents such as 5-fluorouracil exhibit synergistic effects and enhance the therapeutic effect by inhibiting the PI3K/AKT/mTOR pathway and activating the FOXO-1 pathway, triggering apoptosis and autophagy in colorectal cancer (Diab et al., 2024). Therapeutic synergy in these combinatorial systems may be related not only to cellular death mechanisms but also to the oxidative stress-reducing effect of propolis. However, it remains largely unclear through which cellular signals these effects occur. On the other hand, the variation in the extraction method and chemical content of propolis used between different studies complicates comparative interpretations and highlights the need for standardization. Similarly, the fact that the differences in efficacy between production techniques have not been tested in direct comparative studies makes it difficult to determine which method is more suitable for which carrier system. However, it is noteworthy that there are some methodological deficiencies in addition to their positive effects. The lack of direct comparisons between nanoformulation types, the lack of long-term *in vivo* safety data, and the differences in the components of propolis depending on geographical and plant sources make it difficult to standardize formulations and compare results. In addition, the fact that most of the formulations have been tested only *in vitro* ignores clinically critical parameters such as systemic toxicity, biodistribution, and immune response. This situation limits the translational value of the data obtained. The fact that possible side effects on healthy cells have not been evaluated in most studies also prevents a holistic interpretation of the safety profile. In summary, polymeric and lipid-based carrier systems stand out as the strongest candidates in terms of both safety and efficacy. Breast and liver cancer models are among the cell lines most sensitive to nanoencapsulated propolis. However, in order for these systems to be transformed into therapeutic products, multicenter, long-term studies focusing not only on efficacy but also on parameters such as production scalability, shelf life, and toxicity threshold are needed.

Conclusion and Future Perspectives

Propolis serves as a natural compound which exhibits antimicrobial, antioxidant, and anticancer properties. Therapeutic effectiveness of propolis is restricted by its poor water solubility together with its variable chemical structure and limited bioavailability. The challenges related to propolis can be addressed by nanotechnology through nanoencapsulation methods. Nanocarrier systems improve propolis stability through controlled release mechanisms and targeted delivery systems which enhance bioavailability. Particularly, the use of tumor-targeted nanocarriers with specific ligands enables targeted delivery to cancerous tissues which reduces off-target toxicity and enhances therapeutic outcomes. Several *in vitro* and *in vivo* studies have shown that nanoencapsulated propolis exhibits enhanced cytotoxicity against different cancer cell lines while maintaining biocompatibility with normal tissues. The therapeutic efficiency of the treatment is improved. Nevertheless, standardization, safety testing, and industrial scaling are necessary for clinical applications. Furthermore, combining propolis with other natural components or chemotherapeutics may facilitate the development of synergistic treatment strategies. Future research should investigate the *in vivo* efficacy, immune system interactions, and long-term safety profiles of propolis-loaded nanocarriers to establish a scientific foundation for clinical applications. Additionally, advanced nanocarrier designs such as stimuli-responsive systems or multifunctional nanoparticles that can transport propolis in a controlled and tumor-targeted manner need to be investigated. Simultaneously, by ensuring the standardization of production processes and adherence to legal regulations, a diverse array of applications can be developed in the pharmaceutical, cosmetic, and food industries. The integration of nanotechnology with propolis holds the potential to offer a significant therapeutic alternative in the health sector by facilitating a more efficient evaluation of bioactive compounds.

Author Contributions

BS: Investigation, Methodology, Visualization and Writing; AGSC: Supervision, writing, review and editing.

Conflict of Interest

The authors declare that they have no known competing financial or non-financial, professional, or personal conflicts that could have appeared to influence the work reported in this paper.

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