Review

Green Chemistry Application in Nanoparticles for Biomedical Therapy: Anticancer Medicine

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Green Chemistry Application in Nanoparticles for Biomedical Therapy: Anticancer Medicine

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Abstract: Latterly, the development of green synthesized polymeric nanoparticles with anticancer studies has been an emerging field in academia, and in the pharmaceutical and chemical industry. Vegetable oils are potential substitutes for petroleum derivatives, as they present themselves as a clean and environmentally friendly alternative and are available in high quantities at relatively low prices. Biomass-derived chemicals can be converted into monomers with unique structures, generating materials with new properties for the synthesis of sustainable monomers and polymers. In this way, the production of bio-based polymeric nanoparticles appears as a great application of green chemistry for biomedical uses. There is an increasing demand for biocompatible and biodegradable materials for specific applications in biomedical as cancer therapy, encouraging scientists in working on research towards designing polymers, with enhanced properties and clean processes, containing oncology active pharmaceutical ingredients (APIs). The nanoencapsulation of these APIs in bio-based polymeric nanoparticles can control the release of the substances, increase bioavailability, reduce problems with volatility and degradation, reduce side effects, and increase treatment efficiency. Thus, this review aims to discuss the use of green chemistry for bio-based nanoparticle production and its application in anticancer medicine. The use of vegetable oils for the production of renewable monomers and polymers will be discussed, bringing castor oil as an ideal candidate for such application, as well as more suitable methods for the production of bio-based nanoparticles and some oncology APIs available for anticancer application.

Keywords: green chemistry; vegetable oils; bio-based nanoparticles; oncology APIs

1. Introduction

The polymer industry plays a significant role in our society as polymers have become essential materials in modern societies. But issues with the extensive use of fossil-based raw materials, large amounts of reagents, and the accumulation of polymeric materials in the environment have increased. The necessity of releasing the polymer industry from its dependence on depleting resources represents a significant concern, pushing the search for industrially applicable renewable alternatives [1].

Materials in the environment give scientists and engineers the possibility to change the polymerization process intend to develop a sustainable society. Research has focused mainly on replacing fossil raw materials with renewable alternatives and on developing end-of-life options that generate materials that are suitable for recycling or biodegradation [2].

The development of sustainable technologies has been dealt with in several ways, one of which is the application of the principles of green chemistry to various processes. The design of chemical

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products and processes, that reduce or eliminate the use and generation of hazardous substances, is essential to living without having a negative impact to the environment. The sustainability evaluation of a product's manufacture starts from the analysis of the employed feedstock and its extraction. This consideration highlights the importance of the 7th principle of green chemistry: "a raw material or feedstock should be renewable rather than depleting, wherever technically and economically practicable" [3].

A collaborative effort by industry, academia, and the government is needed to promote the adoption of the green chemistry technologies necessary to achieve a sustainable civilization. The progress of chemistry research, associated with the industrial revolution, created a new scope for the preparation of novel polymeric materials based on renewable resources.

Biomass-derived chemicals can be converted into monomers with unique structures, leading to materials with novel properties, or modified in order to substitute commercial petroleum-based. Vegetable oils represent one of the most interesting classes of renewables for the synthesis of sustainable monomers and polymers and it can undergo polymerization by different polymerization processes, as emulsion solvent evaporation and miniemulsion polymerization via thiol-ene. Miniemulsion polymerization is a heterogeneous polymerization process used for the production of polymers in the form of nanoparticles, aiming at different applications of polymeric material. The thiol-ene reactions can be used in polymer and monomer synthesis and modification, side-chain/end-group modification, and preparation of various types of branched macromolecules. In the solvent evaporation technique, polymer solutions are prepared in volatile solvent and emulsions are formulated. These kinds of polymeric nanoparticles can be used in biomedical and pharmaceutical applications as antitumor therapy [1,4–6].

Nanoparticles have been of significant interest over the last decade as they offer great benefits for drug delivery to overcome limitations in conventional chemotherapy for anticancer treatments for example. Nanoparticles for use as antitumor drug carriers have been in development due to their many advantages as prolonging the biological circulation time, minimizing non-specific uptake, preventing undesirable side effects, improving cellular penetration, and allowing for specific cancer-targeting [7].

A considerable amount of works has been conducted in search of novel cancer therapies using nanoparticle technology. Combined treatments employ either naturally active ingredients or drugs already intended for other uses, with the aim to increase cell sensitivity to therapy and reduce drug toxicity, using a particular pharmaceutical combination and nanotechnology to develop drug delivery systems for targeting drugs to specific tumors [8].

2. Green Chemistry: monomers and polymers from renewable resources

The term green chemistry, as adopted by the IUPAC, is defined as: the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances. Since their initial appearance in the scientific literature, the terms "green" and "sustainable" have been increasingly used and are nowadays present in several research areas. Green chemistry may be considered in the scientific and economical context in which academia, industry and government are attempting to converge their efforts for the development of a sustainable civilization [9].

Green chemistry, also called sustainable chemistry, dates from 1991 when the U.S. Environmental Protection Agency (EPA) launched the Alternative Synthetic Pathways for Pollution Prevention research program under the auspices of the Pollution Prevention Act of 1990. But the name green chemistry was officially adopted in 1996. American chemistry Paul Anastas, one of the principal founders of green chemistry, claimed that by improving how chemicals are synthesized, it might be possible to prevent the production of pollutants. Also helped, together with John Warner in 1998, to create green chemistry´s 12 principles: as prevent waste wherever possible; design chemicals that break down into harmless products after they are used; or; use renewable feedstocks [10].

Fossil oil is consumed both in supplying energy as well as in the production of chemicals and polymers. Its extensive exploitation over the last 60 years has led to the cost-effective easy

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manufacture of daily life products. The increase in the world population and economic development, along with the decrease of the economically available amount of fossil oil, highlights the issue of its finite availability. With a regeneration time of several million years, fossil resources are faster extracted and consumed than they are produced and are thus considered as non-renewable. Furthermore, environmental concerns related to their production and use, such as greenhouse gas emission and the disposal of these non-degradable materials that led to serious environmental pollution, motivate researchers to develop sustainable solutions [3,11].

The progress of chemistry research, associated with the industrial revolution, created a new scope for the preparation of novel polymeric materials based on renewable resources, first through the chemical modification of natural polymers from the mid-nineteenth century, which gave rise to the first commercial thermoplastic materials, like cellulose acetate and nitrate and the first elastomers, through the vulcanization of natural rubber. Later, these processes were complemented by approaches based on the controlled polymerization of a variety of natural monomers and oligomers [12].

The utilization of renewable raw materials, taking advantage of the synthetic potential of nature, can meet other principles of green chemistry, such as a built-in design for degradation or an expected lower toxicity of the resulting products [13].

Biomass-derived chemicals can be either converted into monomers with unique structures, leading to materials with novel properties, or modified in order to mimic commercial petroleum-based key molecules and monomers. Some of the most widely applied renewable raw materials in the chemical include plant oils, polysaccharides, sugars, wood, and others. For instance carbon dioxide is copolymerized with propylene oxide to generate propylene carbonate polyols; Terpenes, such as limonene, are chemically transformed to limonene oxide and copolymerized with carbon dioxide to generate poly(limonene carbonate); Triglycerides, from vegetable oils, are transformed into long chain aliphatic polyesters; Natural carbohydrate polymers, such as starch, are broken down to glucose, which is subsequently transformed to polymers such as poly(ethylene furoate), polylactide, bio-derived poly(ethylene terephthalate) or bio-derived polyethylene. Products obtained from these renewables are as diverse as pharmaceuticals, coatings, packaging materials or fine chemicals [2,3,13].

Vegetable oils represent one of the most interesting classes of renewables for the synthesis of sustainable monomers and polymers, as they are available in high amounts, and relatively low prices make them industrially attractive. Their long aliphatic chain contributes as a major element to the polymer backbone [1,3,13].

Biodegradable polymers are defined as polymers that are degraded and catabolized, eventually to carbon dioxide and water, by naturally occurring microorganisms such as bacteria, fungi or algae. In addition, when they are degraded, these polymers should not generate any substances that are harmful to the natural environment. Generally, natural materials or synthetic polymers which contain hydrolysable bonds in the backbone, such as polyamides, polyesters and polyether are interesting candidates for biodegradation. Several parameters have been reported to influence the degradation behavior of biodegradable polymers as the chemical composition, the molecular weight, and the crystallinity of the polymer. Although the biodegradability of a material is independent of the origin of the starting raw materials used, biomass represents an abundant renewable resource for the production of biodegradable materials [11].

3. Synthesis of monomers from vegetable oils

Oils of vegetable origin are historically and currently the most important renewable feedstock of the chemical industry [14]. Due to their universal availability, inherent biodegradability and low price, vegetable oils have become an area of intensive interest for both academic and industrial research as platform chemicals for polymeric materials [15].

The major components of vegetable oils are triglycerides (tri-esters of glycerol with long-chain fatty acids) with varying composition of fatty acids depending on the plant, the crop, the season, and the growing conditions [13]. Vegetable triglycerides are among the most renewable resources

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exploited in science, in addition to other reasons, because of their unsaturated varieties [12]. A general molecular structure of triglycerides is demonstrated in **Figure 1**.

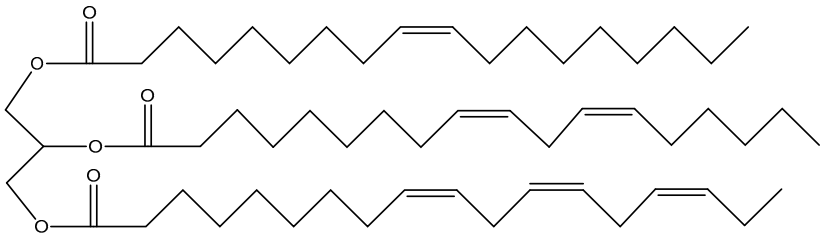

Figure 1. Structure of polyunsaturated triglyceride.

Although triglycerides are found in almost all plants, the quantity that is available varies, and even common crops such as soybeans are estimated to yield only 20 wt% of triglycerides. Another challenge is that the chemical compositions of triglycerides vary both between and within a particular crop [2].

The physical and chemical properties of vegetable oils are mainly determined by the fatty acid chain length and the numbers and locations of double bonds in the fatty acid chains. Usually, the length of the fatty chain is between C12 and C20, with oleic acid (C18:1), linoleic acid (C18:2) and linolenic acid (C18:3) being the most common [15].

The fatty acids account for 95% of the total weight of triglycerides and their content is characteristic for each plant oil [1]. The structures of some frequently studied fatty acids are depicted in **Figure 2**.

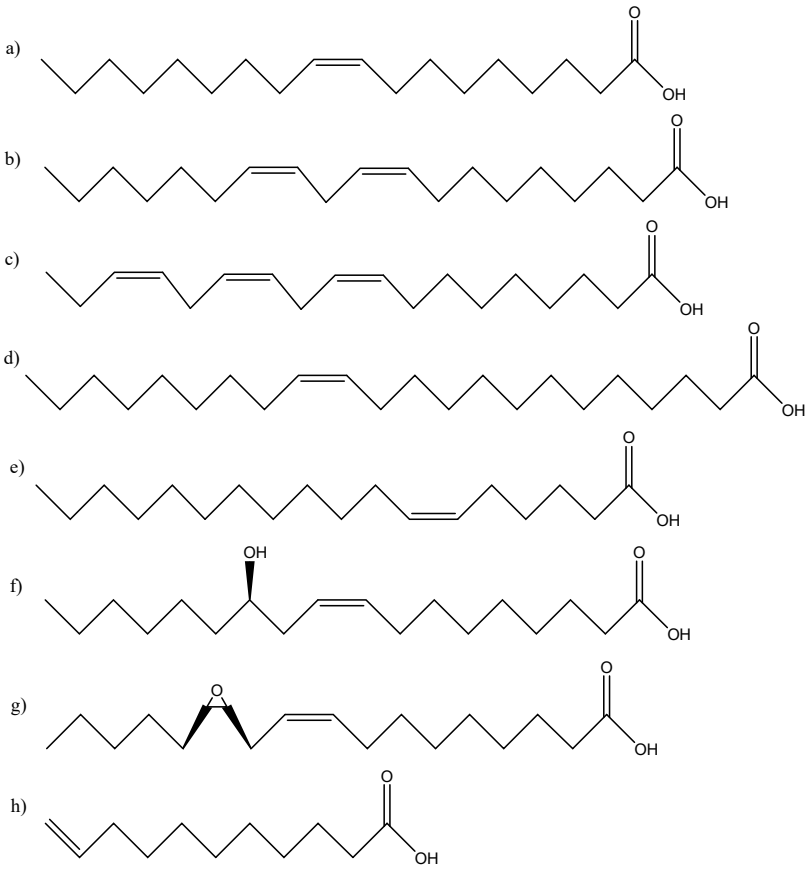

Figure 2. Fatty acids commonly used in polymer chemistry: a) oleic acid, b) linoleic acid, c) linolenic acid, d) erucic acid, e) petroselinic acid, f) ricinoleic acid, g) vernolic acid, h) 10-undecenoic acid.

Fatty acids and esters can be easily obtained either by simple hydrolysis or alcoholysis of triglycerides. They are valuable renewable building blocks for the synthesis of designed monomers

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in the search for specific polymer properties that do not require extensive chemical modification prior to their application [1].

There a growing interest in the use of fatty acids as precursors of monomers, not only because of their renewability, but also because of the properties they can provide to the final molecule [1]. The most common oils used in this kind of studies are castor oil, due to the hydroxyl group presence, and soybean oil, due to the low cost and high availability. Castor oil is a very versatile renewable feedstock for all kinds of polymeric materials, including polyesters, polyamides, polyurethanes, and many others [16].

A process that has considerable potential is reacting the alkene groups found in unsaturated fatty esters to produce α, ω-diene or α,ω-diols. Methyl 10-undecenoic acid, a castor oil derived, was shown to be a suitable starting material for the preparation of esters with alkene groups that can be lead in biodegradable polymers [16].

4. Castor oil as renewable raw material

Castor oil, from castor plant (*Ricinus communis*), a native of tropical Asia and Africa, is one of the most exploited vegetable oils as raw material for the chemical industry. It is naturalized and cultivated on commercial scale all around the world in temperate zones. Like other plant oils, castor oil has to be extracted by a variety of processes or a combination of processes, such as different pressures and solvent extraction followed by a refining process.

The fatty acids of castor oil consist of up to 90% ricinoleic acid and varying small amounts of saturated and unsaturated fatty acids as oleic acid, linoleic acid and linolenic acid. The high content of ricinoleic acid is the reason for the high value of castor oil and its versatile application possibilities in the chemical industry. From castor oil processing, like from other applications of vegetable oils, glycerol is obtained as a byproduct, being a platform chemical with widespread application possibilities in cosmetics, pharmaceuticals, detergents, the manufacture of resins and additives, and also in the food industry [17].

As mentioned, castor oil is a very useful renewable resource and finds a wide range of applications for material synthesis in industry. For instance, certain characteristics of castor oil, like high lubricity, high viscosity over a wide range of temperatures, and insolubility in aliphatic petrochemical fuels and solvents, make it directly applicable as lubricant; coatings and inks, polymers and foam. Biotechnology offers ways to alter the composition of castor oil fatty acids with a focus on processes in the chemical industry with emphasis on development and application in polymer science. There are several possible chemical transformations of castor oil depending on the reacting functional group. Ester reaction: hydrolysis, esterification, alcoholysis, saponification, reduction, amidation, halogenation; Double bond reaction: oxidation, polymerization, hydrogenation, epoxidation, halogenation, addition reactions, sulfonation, metathesis; Hydroxyl group reactions: dehydration, hydrolysis, caustic fusion, pyrolysis, alkoxylation, esterification, halogenation, urethane formation, sulfonation [18].

The pyrolysis of ricinoleic acid at high temperatures (>350 ºC) splits the ricinoleate molecule at the hydroxyl group to form heptaldehyde and undecenoic acid (**Figure 3**) which is a platform chemical that can be used to synthesize a large variety of renewable monomers and polymers [18–20].

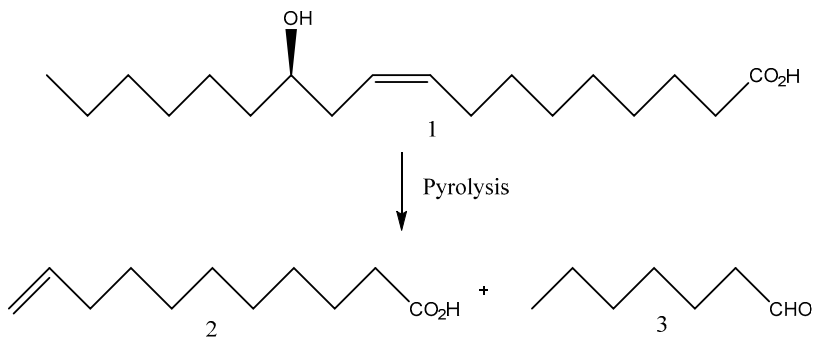

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Figure 3. Products of the thermal fragmentation of ricinoleic acid. 1) Ricinoleic Acid, 2) 10-undecenoic acid, 3) Heptanal.

The use of castor oils as a raw material in the synthesis of polymeric materials is very well established. Polymers of castor oil are applied in various fields such as wound dressing, drug delivery, bone tissue engineering and membranes for fuel cell fabrication [21].

A vast array of copolymers is viable when castor oil (or ricinoleic acid) is combined with other monomers. Materials with varied properties could be obtained by tweaking the chemistry of these copolymers. Altering of comonomer compositions leads to polyesters with controlled mechanical, thermal, viscoelastic properties, as well as degradation profiles [22].

Laurentino *et al.* (2018) synthesized a biobased monomer acrylated ricinoleic acid from castor oil and copolymerized with methyl methacrylate in miniemulsion forming polymeric nanoparticles. The addition of the biobased monomer led to a decrease in the glass transition temperature of the copolymer and to the formation of a small fraction of gel, resulting in materials with interesting properties for future applications as pressure sensitive adhesives [23].

In the medical field, biodegradable aliphatic polyesters are the preferred materials as biomaterials because of their biodegradation and biocompatibility. Cardoso *et al*. (2018) obtained biocompatible polymeric nanoparticles via thiol-ene polymerization in miniemulsion using a fully renewable α,ω-diene monomer obtained from 10-undecenoic acid and 1,3-propanediol, both derived from castor oil [24].

Also in the biomedical application of polymers nanoparticles, Machado *et al*. (2017) synthesized a poly(thioether-ester) nanoparticles via thiol-ene miniemulsion polymerization using a biobased α,ω-diene monomer, namely dianhydro-d-glucityl diundec-10-enoate, synthesized from 10-undecenoic acid (derived from castor oil) and isosorbide (derived from starch) [25]. These kinds of polymers nanoparticles have tremendous scope for further fabrications for the biomedical application area, including studies for anticancer treatments.

5. Polymeric nanoparticles and some production techniques

Nanoparticles are frequently defined as solid, colloidal particles in the range 10-1000 nm. This is a collective term given for any type of polymer nanoparticle, but specifically for nanospheres and nanocapsules. Nanocapsules act as drug reservoirs, due to their vesicular structure, in which the retained active pharmaceutical ingredients are reserved in an aqueous or non-aqueous liquid core placed in the vesicle cavity and enclosed by the solidified polymeric shell. On the other hand, nanospheres are matrix particles, particles whose entire mass is solid and molecules may be adsorbed at the sphere surface or encapsulated within the particle [6,26].

The field of polymer nanoparticles plays an important role in a wide spectrum of areas ranging from electronics [27], conducting materials [28], medicine [29,30] and biotechnology [31].

The polymeric nanoparticles are promising vehicles for drug delivery by easy manipulation to prepare carriers with the objective of delivering the drugs to a specific target and has advantages such as increases the stability of any volatile pharmaceutical agents; offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness and delivers a higher concentration of pharmaceutical agent to the desired location. The choice of polymer and the ability to modify drug release from polymeric nanoparticles have made them great candidates for cancer therapy, delivery of vaccines, contraceptives, and delivery of targeted antibiotics [32].

Polymers are very convenient materials for the manufacture of nanoparticles with many potential medical applications. The polymers used in preparation of nanoparticles should be compatible with the body in the terms of adaptability and biodegradable. The most commonly used natural polymers in preparation of polymeric nanoparticles are chitosan, gelatin, sodium alginate and albumin. The synthetic polymers are mostly represented by Polylactides (PLA), Polyglycolides (PGA), Poly (lactide co-glycolides) (PLGA), Polyanhydrides, Polyorthoesters, Polycyanoacrylates, Polycaprolactone, Poly glutamic acid, Poly malic acid, Poly (N-vinyl pyrrolidone), Poly (methyl

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methacrylate), Poly (vinyl alcohol), Poly (acrylic acid), Poly acrylamide, Poly (ethylene glycol) and Poly (methacrylic acid). Although there are many possibilities of polymers, the application of derivatives of castor oil, as 10-undecenoic acid, for preparation of monomers used on production of polymer nanoparticles has been increased [26,32].

Polymers nanoparticles can be conveniently prepared either from preformed polymers or by direct polymerization of monomers using classical mechanisms. Methods like solvent evaporation [33], salting-out [34], dialysis [35], and supercritical fluid technology [36], can be utilized for the preparation of polymers nanoparticles from preformed polymers. On the other hand, polymers nanoparticles can be directly synthesized by the polymerization of monomers using various polymerization techniques such as microemulsion, miniemulsion, and interfacial polymerization (**Figure 4**) [6].

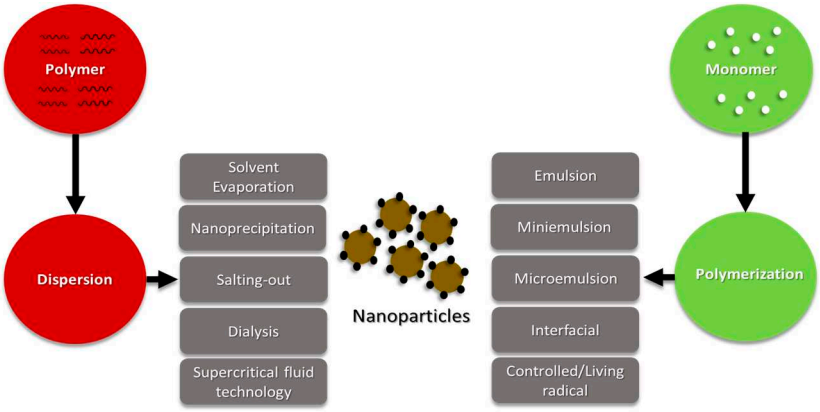

Figure 4. Schematic representation of various techniques for the preparation of polymer nanoparticles.

5.1. Solvent evaporation technique

The emulsification solvent evaporation technique was first reported by Gurny *et al*. (1981). Hydrophobic polymer (synthetic, semi-synthetic or natural) and drug (usually lipophilic) are dissolved in an organic solvent (e.g. chloroform, dichloromethane, ethyl acetate) which is volatile and water-immiscible. This solution is then emulsified in an aqueous stabilizer solution. Emulsification is carried out by sonication or under high-energy homogenization to reduce the size of the emulsion droplets and an emulsion is formed. The organic solvent is then removed by evaporation at room temperature under stirring or under reduced pressure. Afterward, the solidified nanoparticles can be collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants (**Figure 5**) [6,37–40].

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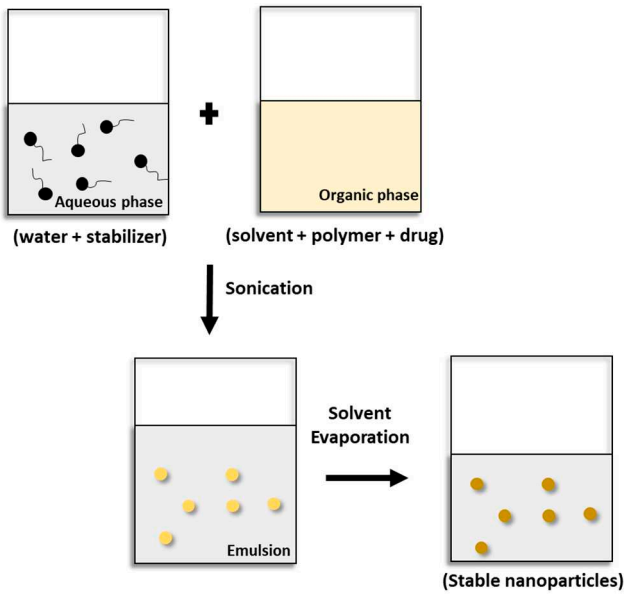

Figure 5. Scheme of the emulsification-solvent evaporation technique.

Solvent evaporation is the most employed technique to prepare nanoparticles of polymers in the current literature on techniques using a dispersion of preformed polymers [41–43]. In the polymerization of monomers, the publications on the miniemulsion polymerization and the development of a wide range of renewable polymer materials have recently increased substantially [6].

5.2. Miniemulsion polymerization

The miniemulsion is part of the emulsified polymerization systems and has as main characteristic the size of the drops and the stability of the final emulsion. A nanoemulsion can be considered as a conventional emulsion containing very small particles (size ranging from 50 to 500 nm) [44,45].

Ugelstad et al. (1973) were pioneers in the study of polymerizations in miniemulsions describing the polymerization process in monomer drops. Their discussions led to speculation about the possibility of nucleation and polymerization in very small monomer droplets during emulsion polymerization [46].

Asua (2002) defined miniemulsions as dispersions of small monomer drops in water, stabilized by a surfactant against the coalescence of the drops by the action of the Brownian motion (union of two or more drops, occurring the rupture of the interface and resulting in a larger drop) and a co-stabilizer, to minimize diffusional degradation (Ostwald Ripening, a process in which small drops are grouped by the difference of pressure, leading to an increase in the average size of droplets)[47]. A typical formulation includes water, monomer, co-stabilizing (when used), surfactant and initiator (which can be soluble in the aqueous or organic phase). The surfactant is dissolved in water, the active to be encapsulated is dissolved in the monomer and both are mixed under agitation. A shear mechanism (homogenization) is required to ensure the submicrometric size of the drops [44].

The mechanical homogenization of miniemulsions can be obtained by different methods. Initially, simple agitation was used as the main means of homogenization. Subsequently the use of omni-mixers and ultra-turrax was cataloged. However, the energy transferred by these techniques is not enough to obtain small drops distributed homogeneously. A much higher energy for fragmentation of large drops into small ones is required. Currently, ultrasonication is used especially for homogenization of small quantities. While micro-corrugators or high-pressure homogenizers are favorable for large quantities of emulsion [44].

In the first stage of the miniemulsion polymerization process, small drops are formed by a system containing the dispersed phase (monomer, active to be encapsulated and co-stabilizer) and

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continuous phase (aqueous phase with a surfactant). The initiator can be added in the dispersed phase or continuous phase, depending on whether it is hydro or organic soluble. The surface area of droplets in these systems is very large, and most surfactant is adsorbed on the surface of the droplets [48]. In the second step the drops are nucleated and polymerized [49,50]. In **Figure 6**, the scheme of the miniemulsion polymerization process is demonstrated.

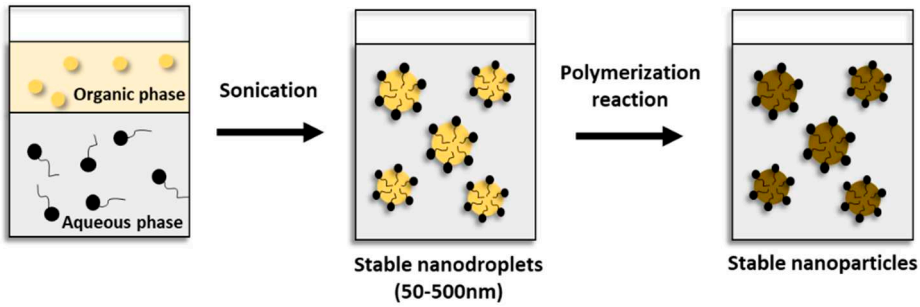

Figure 6. Scheme of the miniemulsion process. Source: Adapted from [49].

6. Thiol-ene polymerization for nanoparticles production

Thiol chemistry, a versatile tool, was first described in 1905 by Posner. The author reports the thiol coupling to different types of mono and bi unsaturated compounds such as aliphatics, aromatics, terpenes, and hydroaromatics. The thiol-ene free radical addition drags special interest due to its application range and simplicity. Early work on this field has appeared in late 1930s to early 1950s [51].

A patent concerning the polymerization of dithiols and dialkenes via radical additions dates back to 1941. The reaction is well known to proceed via free-radical mechanism. Generally, radical reactions are known to be quite fast reactions, and thiol-ene additions offer some additional features such as robustness and efficiency, which have made this reaction to be considered as one of the click reactions and very popular during the last years [52].

Like a traditional free-radical polymerization, thiol-ene polymerization reaction proceeds divided into three stages: initiation, propagation, and termination, plus a chain transfer step. At initiation, the formation of thiol groups occurs by removing hydrogen. During propagation, the thiol radical is added to the unsaturated moiety (ene) group of the olefin, which generates an unpaired electron in the central carbon of the chain. Chain transfer occurs when the central carbon donates the electron to the thiol group, producing another thiol group, thereby restoring the mechanism (**Figure 7**). Termination occurs through radical-radical coupling [53].

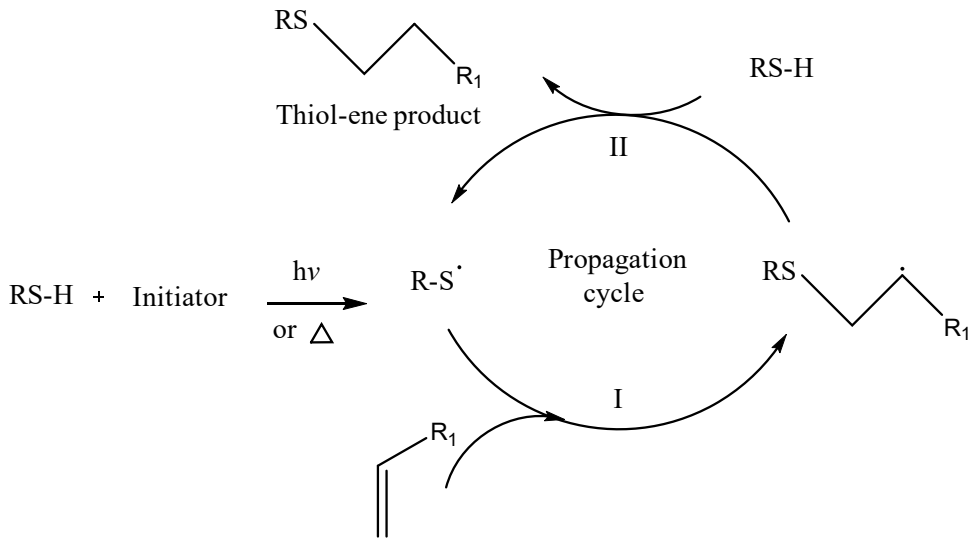

Figure 7. The mechanism for the hydrothiolation of a C=C bond in the presence of an initiator.

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The efficiency of this reaction, therefore, requires the unsaturation in terminal position and strongly depends on the thiol compound used. As mentioned above, the propagation step of this reaction is the addition of a thiyl radical to a C=C double bond and the subsequent abstraction of a hydrogen atom by the formed carbon radical from another thiol compound, forming a new thiyl radical. The formation of the carbon radical is reversible and a rate-determining step, which explains the low reactivity of internal alkenes [52].

There has been impressive growth in the use of the thiol–ene reaction in polymer synthesis and modification as the use in monomer synthesis and side-chain/end-group modification, preparation of various types of branched macromolecules, the preparation of inorganic-organic composites, nanoparticle modification, surface modification, bio-related applications, and crosslinked polymers [4].

Cases of reactions between vegetable oils or derivatives and thiols are found in the scientific literature, such as the work made by Turunç *et al.* (2010) that described the use of methyl-10-undecenoate, a castor oil derived, in thiol-ene reactions [16]. A variety of renewable monomers was obtained in high yields. Their polymerization was also studied, and the material properties of the resulting polyesters were investigated revealing good thermal properties, making them possible candidates for the substitution of petroleum-based materials. Lluch *et al.* (2010) developed a methodology that was applied in a biomass-derived monomer of 10-undecenoic acid [54]. Thiol-ene click step growth polymerization was used to prepare alkene-functionalized linear polymers with variable molar mass.

Hu *et al.* (2017) developed a multi-responsive crosslinked-core poly(thioether ester) micelles. Firstly, a poly (thioether ester) was synthesized by the thiol-ene polymerization using ethanedithiol and glycidyl methacrylate as monomers [55]. The resultant poly (thioether ester) was then coupled with carboxyl terminated poly (ethylene glycol) (PEG) and lipoic acid to give a graft copolymer that could self-assemble into micelles in the aqueous media and turn into crosslinked-core nanoparticles in the presence of dithiothreitol. The crosslinked-core micelles showed a more compact structure and higher drug loading efficiency as compared with non-crosslinked micelles. These results indicate that the cross-linked micelles may provide huge potential for controlled drug delivery in cancer therapy.

In the work of Chen *et al*. (2014), cationic polymeric nanocapsules were generated as potentially therapeutic nanocarriers [56]. These nanocapsules were synthesized from allyl-functionalized cationic polylactide (CPLA) by efficient UV-induced thiol-ene interfacial cross-linking in transparent miniemulsions. These nanocapsules can effectively bypass the multidrug resistance of cancer cells, thereby resulting in increased intracellular drug concentration and reduced cell viability.

In virtue of some already mentioned advantages of thiol-ene reactions, as the possibility that be carried out under mild conditions, the possibility of producing cros-linked and functionalized structures and improvement of degradability, this kind of reaction is considered a great environmentally friendly candidate for synthesizing biocompatible and biodegradable polymers for biomedical application as cancer therapy [24,57–59].

The use of in situ miniemulsion polymerization (polymerization of monomer and encapsulation of active at the same time) by thiol-ene have been evidenced. The nanoparticles have several applications: pharmaceutical, biomedical, and cosmetic. These can be administered in different routes such as intravenous, ocular, oral, intramuscular, subcutaneous and cutaneous. The development of polymeric nanoparticle formulations containing anticancer-like actives, for example, is a relevant strategy. This kind of system can increase the bioavailability of encapsulated substances and reduce problems related to early degradation. In addition, it is possible to functionalize the surface of the nanoparticles, with a coupling of proteins, for example, focusing on increased circulation in the biological environment and the possibility of targeted site delivery.

7. Application of polymeric nanoparticles in cancer therapy

Nanoparticles have been of significant interest over the last decade as they offer great benefits for drug delivery system. In recent times, nanoparticles are extensively employed as biomaterials because of their favorable characteristics in terms of simple elaboration and design, good

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biocompatibility, and a broad structure variety [7]. Nanoparticles can be considered ideal candidates for cancer therapy in comparison with other possibilities as chemotherapy [26].

Chemotherapy is a predominant treatment strategy against cancer wherein anticancer drugs are used to induce cell death in cancer cells. However, it has several limitations such as the requirement of high drug dose, adverse effects, and multidrug resistance that reduce the efficacy of the therapy. To overcome the limitations associated with chemotherapy, nanomedicine strategies employing the formulations of anticancer drugs in various nanocarriers forms have been reported [60].

Nanoparticles for anticancer drug delivery had reached the first clinical trial in the mid-1980s, and the first nanoparticles (e.g., liposomal with encapsulated doxorubicin) had entered the pharmaceutical market in 1995. Since then, numerous new nanoparticles for cancer drug delivery are under development due to their many advantages as enhancing solubility of hydrophobic drugs, prolonging circulation time, preventing side effects, improving intracellular penetration, and allowing for specific cancer-targeting [7].

In **Table 1** recent uses of nanoparticles for cancer therapy are given. The Polyhydroxyalkanoates (PHAs) are natural, non-toxic, biodegradable, and biocompatible polyesters. The Cyclodextrin (CDs) and its derivatives are natural cyclic oligosaccharides and Poly(lactic-co-glycolic acid) (PLGA) is a copolymer of lactic acid and glycolic acid.

Table 1. Demonstration of currently developed nanoparticles as drug delivery systems for anticancer application.

Polymeric nanoparticles	Oncology APIs	Nanoparticles production	Biological study	Ref.
Polyhydroxyalkanoates (PHAs) nanoparticles	Ellipticine	Emulsification/Solvent evaporation	*in vitro*	[61,62]
	Cisplatin	Emulsification/Solvent evaporation	*in vitro*	[63]
	Thymoquinone	Emulsification/Solvent evaporation	*in vitro*	[64]
	Paclitaxel	Double emulsification/Solvent evaporation	*in vitro*	[65]
	5-Fluorouracil	Double emulsification/Solvent evaporation	*in vitro*	[66]
	Etoposide	Solvent evaporation	*in vitro*	[67]
	Doxorubicin	Double emulsification/Solvent evaporation	*in vitro*	[68]
	Rhodamine B isothiocyanate (RBITC)	Emulsification/Solvent evaporation	*in vitro*	[69]
Cyclodextrin (CDs) nanoparticles	Docetaxel	Nanoprecipitation	*in vitro*	[70]
	Camptothecin	Nanoprecipitation	*in vitro*	[71]
	Acyclovir	Nanoprecipitation	*in vitro*	[72]
	Paclitaxel	Emulsification/Solvent evaporation method	*in vivo*	[73]
Poly(thioether-ester) nanoparticles	Zinc phthalocyanine	Thiol-ene miniemulsion polymerization	*in vitro*	[74]
	Full-spectrum cannabis extract	Thiol-ene miniemulsion and Emulsification/Solvent evaporation	*in vitro*	[75]
	4-nitrochalcone	Thiol-ene miniemulsion polymerization	*in vitro*	[76]
Polymeric nanoparticles	**Oncology APIs**	**Nanoparticles production**	**Biological study**	**References**

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	Paclitaxel	Emulsification and Nanopracipitation	Pre clinical (mice)	[77]
	Topotecan–tamoxifen	Double emulsification/Solvent evaporation	*in vitro*	[78]
	Lupeol	Emulsification/Solvent evaporation	*in vitro*	[79]
	Gemcitabine	Emulsification/Solvent evaporation	*in vitro*	[80]
	9-nitro-camptothecin	Nanoprecipitation	*in vitro*	[81]
	Paclitaxel, Doxorubicin	Double emulsification/Solvent evaporation	*in vitro*	[82]
	Paclitaxel	Nanoprecipitation	*in vitro*	[83]
	Cisplatin	Emulsification/Solvent evaporation	*in vitro*	[84]
Poly-(lactic-co-glycolic acid) (PLGA) nanoparticles	Paclitaxel/superparamagnetic iron oxide	Emulsification/Solvent evaporation	*in vitro*	[85]
	Tamoxifen, Quercetin	Emulsification/Solvent evaporation	*in vitro*	[86]
	Docetaxel	Nanoprecipitation	*in vitro*	[87]
	Δ^9 - Tetrahidrocannabinol	Nanoprecipitation	*in vitro*	[88]
	Doxorubicin	Solvent displacement	*in vitro*	[89]
	Paclitaxel	Nanoprecipitation	Pre clinical	[90]
	Bicalutamide	Nanoprecipitation	*in vitro*	[91]
	siRNA, Paclitaxel	Emulsification/Solvent evaporation	*in vitro*	[92]
	Paclitaxel, Doxorubicin	Double emulsification/Solvent evaporation	*in vivo*	[93]
	Methotrexate	Emulsification and diffusion	*in vivo*	[94]
	Cisplatin	Nanoprecipitation	Pre clinical	[95]

Polymeric nanoparticles	**Oncology APIs**	**Nanoparticles production**	**Biological study**	**References**
	Doxorubicin	Solvent displacement	*in vitro*	[96]
	Paclitaxel	Nanoprecipitation	Pre clinical (mice)	[97]
	Curcumin	Nanoprecipitation	*in vivo*	[98]
	PE38KDL	Double emulsification/Solvent evaporation	Pre clinical (mice)	[99]
	Paclitaxel and magnetic fluid	Emulsification/Solvent evaporation	*in vitro*	[100]
Poly-(lactic-co-glycolic acid) (PLGA) nanoparticles	Gemcitabine	Double emulsification/Solvent evaporation	*in vitro*	[101]
	Paclitaxel	Emulsification/ Precipitation	*in vitro*	[102]
	Capecitabine	Emulsification/Solvent evaporation	*in vitro*	[103]
	SN-38	Emulsification/Solvent evaporation	*in vitro*	[104]
	BSA	Double emulsification/Solvent evaporation	*in vitro*	[105]

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Chitosan nanoparticles	Quercetin	Coordination reaction	*in vitro*	[106]
	Curcumin	Ionic gelation method	*in vitro*	[107]
	Metformin	Ionic gelation method	*in vitro and in vivo*	[108]
	Chlorin e6	Nonsolvent-aided counterion complexation	*in vitro*	[109]
	Adriamycin	Dialysis method	*in vitro and in vivo*	[110]
Polycaprolactone (PCL) nanoparticles	Docetaxel	Emulsification/Solvent evaporation	*in vitro*	[111]
	Thalidomide	Dialysis method	*in vitro and in vivo*	[112]
	Docetaxel	Nanoprecipitation technique	*in vitro and in vivo*	[113]
	Dihydroartemisinin	Self-assembly method	*in vitro and in vivo*	[114]
	Oxymatrine	pH gradient method	*in vitro*	[115]
Polymeric nanoparticles	**Oncology APIs**	**Nanoparticles production**	**Biological study**	**References**
Polycaprolactone (PCL) nanoparticles	Paclitaxel and curcumin	Self-assembly method	*in vitro and in vivo*	[116]
	Flutamide	Nanoprecipitation method	-	[117]
	5-fluorouracil	Double emulsion technique	*in vitro*	[118]
	Silibinin	Solvent displacement process	*in vitro and in vivo*	[119]
Cellulose Nanoparticles	Doxorubicin	Self-assembly method	*in vitro and in vivo*	[120]
	5-Fluorouracil	co-precipitation method	*in vitro*	[121]
	Coumarin and curcumin	oil in water emulsion technique	*in vitro*	[122]

Nanoparticles utilization in conventional chemotherapy is recognized and have been accepted by the FDA (Food and Drug Administration) for broader usage. Anticancer drugs entrapment within nanoparticles guards them against efflux transporters and the nano-sized range accelerates its entrance through biological membranes. Besides, the polymer shell affords protects the drug against the body enzymes. Current developments in nanotechnology have revealed many types of targeting strategies for augmenting drug accumulation into the tumor while restricting the undesirable toxicity to normal cells. As the nanoparticles designed for targeted drug delivery systems, that increase the anticancer active ingredients delivered in tumors and no affecting non-cancerous regions [26].

Some of the applications of nanoparticles in cancer therapy can be seen in the work of Vivek *et al.* (2014) that developed a novel biodegradable antibody conjugated polymeric nanoparticles designated for targeted delivery in breast cancer receptors [60]. The formulated nanoparticles were capable of sustained pH depended drug release. The results indicated that the formulated nanoparticles were found to provide better anticancer and inhibitory activity against breast cancer cells than the free anticancer agent by in vitro and in vivo evaluations.

Han *et al.* (2012) evaluated the inhibition of glioma growth in vivo by combining the interstitial chemotherapy and the targeting drug delivery strategy [123]. They developed 3-bis(2- chloroethyl)-1-nitrosourea-loaded wafers that were implanted in the tumor and 3-bis(2- chloroethyl)-1-nitrosourea-loaded poly(lactic acid) nanoparticles decorated with transferrin that were administrated by intracarotid perfusion. The results showed that the combined therapy significantly prolonged the survival time of glioma-bearing rats in comparison with either treatment alone.

Feuser *et al.* (2016) synthesized and characterized Zinc (II) phthalocyanine loaded poly(methyl methacrylate) obtained by miniemulsion polymerization for photodynamic therapy in leukemic cells [124]. The cytotoxicity and phototoxicity studies indicated that the nanoparticles improving the photobiological activity of zinc phthalocyanine on leukemic cells. Although good results of Zinc (II)

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phthalocyanine loaded poly(methyl methacrylate) were obtained for photodynamic therapy, the poly(methyl methacrylate) is not a biodegradable polymer. Boosting other works with new kinds of renewable and biodegradable polymer as poly(thioether-ester).

Due to reasons exploited, nanoparticles present many applications in cancer remediation. There are a lot of possibilities of nanoparticle technology that need to be explored to harness their remarkable perspective as a new class of targeted remediation for cancer therapy.

8. Oncology Active Pharmaceutical Ingredients (APIs)

According to the World Health Organization (WHO), an active pharmaceutical ingredient (API) is any substance or combination of substances used in a finished pharmaceutical product, intended to furnish pharmacological activity or to otherwise have a direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings [125].

Oncology or anticancer APIs also called antineoplastic drugs refer to the biologically active components present in anti-cancer drugs. They are effective in the treatment of malignant, or cancerous, disease. There are several major classes of oncology APIs. These include alkylating agents, antimetabolites, natural products, hormones, and a great number of assets that demonstrate anticancer activity and are used in the treatment of malignant diseases.

Nanoparticles containing oncology APIs offer a different alternative to conventional treatments, mostly due to their targeted delivery and action. They also can be used as biosensors, allowing cancer detection or carriers in targeted drug delivery to specific locations [126].

The nanoencapsulation of APIs exhibits other advantages over conventional medical methodologies.

The nanoparticles have the ability to target and enter into selective tissue at the molecular level; Provide a large surface area and high absorption rate; Increase cellular uptake and drug localization; Accurate and targeted drug delivery to cancerous cells without interactions with healthy cells; Use lower dosage due to the encapsulation of drugs or small molecules; Improve uptake of poorly soluble drugs; Decrease medicinal toxicity; Minimize or suppress the resistance arising from the physiological barriers in the body [126,127]. For these and other reasons already mentioned, new oncology APIs have been studied in cancer treatment strategies. **Table 2** brings examples of new oncology APIs for cancer treatment.

Table 2. Examples of new oncology APIs for cancer treatment.

Oncology (APIs)	Kinds of Cancer	Biological study	References
Quercetin	Breast, lung, liver, colon cancers, intestine	*in vitro and in vivo*	[128–131]
Bevacizumab	Colorectal, glibastoma	*in vitro and vitro*	[132–135]
Catharanthus roseus extract	Breast, cervical, liver	*in vitro*	[136–138]
Irinotecan	Colorectal, colon, gastric	*in vitro*	[139–141]
Isolated cannabinoids or full-spectrum cannabis extract	Melanoma, glioma, ovarian, leukemia, adenocarcinoma, lung	*in vitro, in ovo and in vivo*	[75,88,142,143]
Olaparib	Prostate, pancreatic, breast, ovarian	*in vitro and vitro*	[144–146]
Podophyllum extract	Carcinoma, breast	*in vitro*	[147–149]
Temozolomide	Glioma, gliobastoma, lung	*in vitro and vitro*	[150–152]
Vemurafenib	Resistent melanoma	*in vitro and vitro*	[153,154]

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Zinc phthalocyanine	Breast, liver, carcinoma, cervical adenocarcinoma	*in vitro and in vivo*	[74,155,156]

9. Conclusions

The necessity of releasing the polymer industry from its dependence on non-renewable resources represents a significant concern. In this way, vegetable oils represent one of the most interesting renewables classes for synthesizing sustainable monomers and polymers that can be applied for biomedical as nanoparticles containing active pharmaceutical ingredients for anticancer therapy. Nanoparticles are rapidly changing the direction of cancer treatment, they can deliver the oncology APIs to a specific target, such as a tumour region, and control the delivery release, increasing the effectiveness of treatments and reducing possible side effects. Incorporating the enhanced properties of green synthesized nanoparticles loaded oncology APIs into cancer treatment and diagnosis has opened new possibilities for biomedical applications and presents itself as a promising future.

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