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Recent Advances on Large-Scale Manufacture of Curcumin and Its Nanoformulation for Cancer Therapeutic Application

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Abstract: Considerable amount of research is going on the role of plant species that exhibit anti-cancer properties. One such plant species is turmeric, which has been used in the human diet for centuries. The main active component/polyphenol in turmeric is curcumin. Recently, curcumin has been considered for cancer therapy. The initial challenge with curcumin is its large-scale production and purification of curcuminoids from turmeric. Most of the strategies are not fully effective due to the involvement of many organic solvents, time consumption, and inadequate separation between similar derivatives and crystal structures. Some of the methods to avoid using organic solvents are explained in this entry. The second challenge is that the isolated curcumin is unstable under various environmental and physiological conditions and degrades easily. Various strategies have been proposed and investigated to improve its aqueous solubility, stability, bioavailability, and potential therapeutic applications. Among them, nanoformulation is utilized to fill the gaps between clinical application and production. This review summarizes recent advances in curcumin's large-scale production and purification protocols, the necessity of nanoformulation, recent patents, and its anti-cancer mechanism. Emphasis is given on applying safe and green-tech methods of nanoformulation, including Mozafari and Heating methods.

Keywords: anti-cancer; curcumin; encapsulation; large scale production; nanoformulation; green technology; clinical applications.

1. Introduction

Curcuma Longa (Linn.), commonly termed turmeric, belongs to the Zingiberaceae family and is mostly used as a food ingredient because of its health-promoting properties [1]. It has been part of Indian culture since the Ayurvedic era and has been used for food, skincare, and medicinal applications. Raw turmeric contains three major components: (*i*) Curcumin, (*ii*)

dimethoxy curcumin (DMC), and (*iii*) bisdemethoxycurcumin (BDMC), in which approximately 2–5% is curcumin [2]. From various studies, researchers found out that the main active component/polyphenol of turmeric is curcumin [3]. The structure of curcumin was first discovered in 1910 by Milobdzka and co-workers [4]. The medicinal benefit of curcumin was recorded centuries ago, but the first documented usage as a drug was in 1937 in which it was applied for biliary disease [5].

Cancer has become a major cause of mortality worldwide, affecting approximately 10 million lives in 2020 [6]. The most common type of cancer cases (according to WHO) reported in 2020 were: Breast cancer (2.26 million cases); Lung cancer (2.21 million cases); Colorectal cancer (1.93 million cases); Prostate cancer (1.41 million cases); Skin malignancy (1.20 million cases); Stomach cancer (1.09 million cases).

The most common approaches for targeted tumor therapy are suppressing tumor formation, metastasis, and progression by minimizing the side effects. A high quantity of research and literature on plant species exhibit anti-cancer properties, including curcumin [7]. Recently, curcumin has been targeted towards cancer therapy mainly for the treatment due to its high therapeutic potentials against various tumors [8]. According to the published reports, the mechanism behind the anti-cancer properties of curcumin is due to its triggering of tumor apoptosis, obstruction of proliferation, anti-angiogenesis, hindering of mitotic catastrophe, differentiation/autophagy, inhibition of chemokines, metastasis, and genomic modulation [9].

In this current review, we focus on different studies and approaches on the largescale production of curcumin, the need for nanoformulation to deliver curcumin and its derivatives in cancer treatment, emphasizing their formulation properties, experimental evidence, and general bioactivity and discussing the challenges and opportunities in developing these systems.

2. Properties of Curcumin

Curcumin has a crystalline structure with bright orange-yellow color. The IUPAC name for curcumin is [1,7-bis (4-hydroxy-3 methoxyphenyl) 1,6-hepta diene- 3,5-dione] [10]. Some of the main physicochemical attributes of curcumin pertained to its nanoformulation are described in the following sub-sections.

2.1. Solubility.

Curcumin is poorly soluble in water and other aqueous media at normal pH conditions. However, it is highly soluble in polar/nonpolar organic solvents and alkaline / extremely acidic solvents such as glacial acetic acid [11,12].

2.2. Stability of curcumin in acidic, alkaline, and biological media.

The stability of curcumin is reported to be pH-dependent, observed through the change of color in various pH ranges. For example, the solution exhibits red color when the pH < 1, which is due to the protonated form of the compound. From pH 1–7, curcumin exhibits yellow color due to its neutral structure. When the pH is raised above 7.5, the solution will show orange-red color [13].

The stability/degradation of curcumin in buffer solution has also been monitored. Curcumin exhibited a second-order kinetic reaction in phosphate buffer solution when pH varied from 1–11 (at 31 °C). In another study, the stability of curcumin was monitored in

citrate, phosphate, and carbonate buffers, and first-order reaction kinetics was observed [14,15]. The preliminary degradation product of curcumin with time was ferulic acid (FA) and feruloyl methane, followed by vanillin, the primary degradation product [16]. From the human blood studies, the degradation rate of curcumin was reported to be much slower (< 20% in 1 h). Researchers also found that the addition of glutathione (1mM), N-acetyl-L-cysteine (50 µM), or ascorbic acid (25 µM) was able to protect curcumin from degradation [15][17][18].

2.3. Thermal and photochemical stability.

Photostability of curcumin or any drug is a concern for the acceptable shelf life of the product. Tonnesen *et al*. [13] studied the photostability of curcumin in an isopropanol medium (λexc = 400–510nm) for 4h. The primary degradation product identified had a chemical component of $C_{12}H_{18}O_6$ (from mass spectra). The research group concluded that this structure resulted from the cyclization process that irradiated light (within 15 min). The other side products were vanillin, vanillic acid (VA), ferulic aldehyde (FA), and 4-vinyl guaiacol. In another study, the stability was monitored in ethanolic and methanolic solutions for 120h under sunlight. The degradation products were vanillin, p-hydroxy benzaldehyde, ferulic aldehyde, p-hydroxybenzoic acid [14]. It is also reported that curcumin is more stable in dried form than in the solution state (under sunlight) [19]. In conclusion, the photodegradation mechanism was said to be first-order kinetics, and curcumin stability was in the following order: methanol > ethyl acetate > chloroform > acetonitrile (λexc = 400–750 nm) [20].

Curcumin is reported to be highly stable up to 70 °C when exposed continuously for 10 min. When the temperature is raised above 70 °C, curcumin will start to decompose, which can be observed through UV-absorbance spectra [21]. Then curcumin is also boiled for approx. 10 to 20 minutes will affect the curcumin content, and processing turmeric under pressure (~15 psi) will result in the loss of curcumin content from the material [22].

3. Large Scale Extraction of Curcumin and Its Challenges

As Explained earlier, the average amount of curcuminoids in the raw turmeric is ~ 3-5%, of which 50–60% is curcumin [23]. The large-scale production and purification of curcuminoids is a challenge.

The most-reported conventional method for curcumin extraction was the Soxhlet extraction protocol with a heating time range of 12h [24]. This method is unfavorable because it is time-consuming, uses many organic solvents, and risks thermal decomposition of active components (due to prolonged heating) [25]. The time consumption is because curcumin is protected in tightly packed cork cells, making the contact of solvents difficult. Therefore, the researchers moved to microwave-assisted extraction (MAE). MAE employs extraction of active components through localized heating followed by the disruption of the cell wall, which protects curcumin. This led to the faster extraction of active ingredients [26]. The heating mechanism in the MAE protocol depends mainly on the dielectric properties of the solvent and the matrix [27]. Mandal *et al*. [26] have proposed an efficient microwave-assisted extraction protocol to extract curcumin through a synergetic heating mechanism (Figure 1).

For the extraction protocol, the raw powder was modified with methanol. Then the methanol absorbed powder was dissolved in the extracting solvent (acetone). MAE was conducted through varying times of irradiation and power (irradiation-cooling-irradiation sequence). Acetone was chosen as the solvent because of its high solubilizing capacity for

curcumin [28] due to its good heating up property under microwave irradiation. The research team concluded that the MAE protocol had better accuracy than conventional methods from the obtained results. Moreover, the extraction rates obtained were very high for MAE.

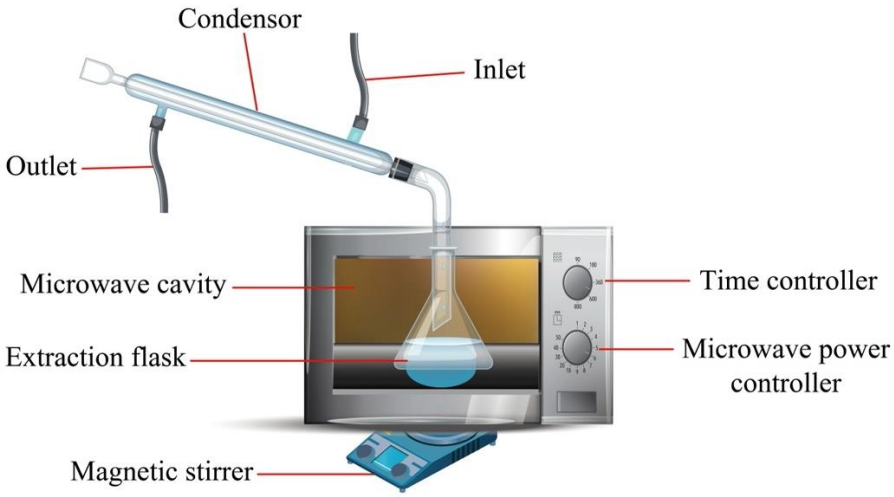

Figure 1. A representative illustration of microwave-assisted extraction setup.

Initially employed common isolation and separation methodologies were silica gel column chromatography, reverse-phase-HPLC (RP-HPLC), and high-speed countercurrent chromatography [29–31]. Silica gel column chromatography suffers from utilizing a large volume of solvents (e.g., chloroform) and inadequate separation between similar derivatives. The large-scale purification by RP-HPLC/high-speed countercurrent chromatography is restricted by low sample loading because of the poor aqueous solubility of curcuminoids. Hence, there was a need for efficient and scalable separation of curcuminoids.

Supercritical fluid chromatography (SFC) has been proposed as an alternative and powerful tool for separating natural components [32]. Supercritical CO_2 is the primary mobile phase in the setup. Compared to HPLC, supercritical CO_2 has a low density and high flow rate with low back pressure, beneficial for efficient separation. Moreover, this can be considered a greener approach due to the minimal utilization of organic solvents compared to conventional methods [33]. Due to this, SFC is greatly preferred for both qualitative and quantitative separation of similar derivative (e.g., steroids, terpenoids, and isoflavones) [34–36]. Even though SFC is utilized to separate curcuminoids, the three derivatives (curcumin, bisdemethoxy-curcumin, and demethoxy-curcumin) couldn't be separated and thus affected the large-scale separation [36]. Song *et al*. [37] proposed using an ultra-high-performance SFC instrument to separate curcuminoids to solve this hurdle. They separated curcumin, DMC, and BDMC using methanolic extract of turmeric. This methodology involved the elution with supercritical CO_2 fluid with 8–15% methanol (modifier) and 10 mM oxalic acid (additive). The three components were separated with a high sample loading capacity. They were able to isolate highly pure curcumin (20.8 mg), DMC (7 mg), and BDMC (4.6 mg) after 5.5 h of separation. The extracted fraction contained curcumin (brownish yellow), DMC (light yellow), and BDMC (yellowish-green), which were detected and isolated automatically using UV (λabs = 410 nm). The residual supercritical CO_2 with the sample evaporated quickly, and the remaining methanol was removed using a rotary evaporator. The calculated recoveries of the three derivatives were 70% (curcumin), 71.4% (DMC), and 88.5% (BDMC), with the purities of 97.9%, 91.1%, and 94.8% respectively (Figure 2). This method resulted in low consumption of solvents and a larger sample loading capacity [37].

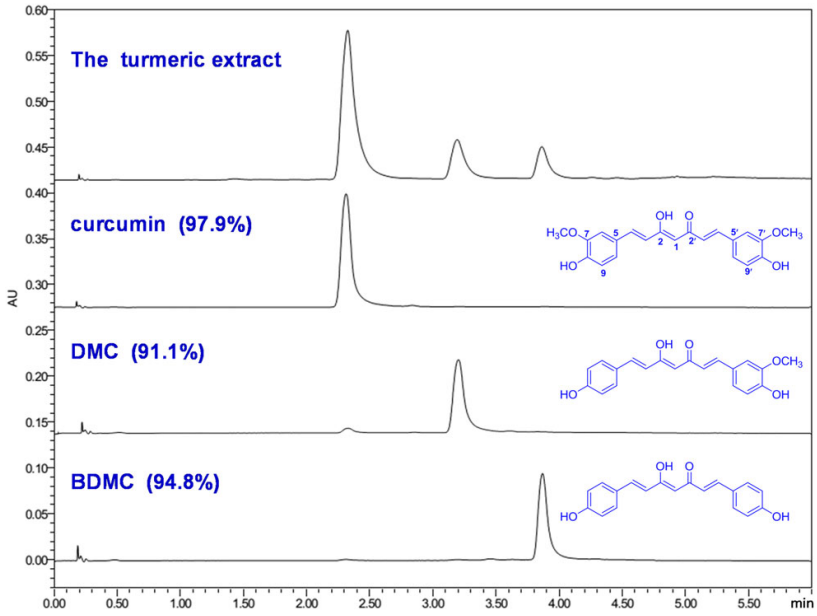

Figure 2. Ultra performance convergence chromatography (UPC2) chromatograms of turmeric, curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) purified by preparative SFC (UV 410 nm). Adapted with permission from Ref. [37].

The reports on the isolation of curcuminoids through an aqueous two-phase system (ATPS) were rare. The ATPS protocol has several advantages, such as being non-toxic and integrated with different protocols to design ultrasonic-assisted ATPS (UA-ATPS) and microwave-assisted ATPS [38,39]. Applying ultrasonic-assisted extraction (UAE) to natural compounds has been widely reported [40,41]. UAE, combined with ATPS, proposed to have advantages such as greener and low solvent consumption protocol. Xu *et al*. [42] used UA-ATPS combined methodology using ethanol and $(NH_4)_2SO_4$ to isolate curcumin on a large scale (Figure 3). In a typical procedure $(NH_4)_2SO_4$ and ethanol were mixed with water to form a two-phase system. The top phase of the solution was mainly composed of ethanol, and the bottom phase was high in salt. The turmeric powder was added to the mixture and ultrasonicated. The ultrasonication helped separate proteins and polysaccharides to the bottom phase, while curcumin isolated to the upper phase. The scale-up strategy was also employed. The yield of scale-up was maintained between 45.77 mg/g to 47.01mg/g with a purity between 43.98–47.01%. After purification through HPLC, the purity increased up to 85.58%. The yield was compared with the conventional methodologies employing constant time. The conventional extraction yield of UAE was around 42.74 mg/g, which is much lower than UA-ATPE. Moreover, the solvent consumption was much lower for UA-ATPE. The extraction using stirring methodology was the lowest (35.07 mg/g) with a more extensive extraction time (12h).

A solid-liquid extraction assisted by high-intensity ultrasound (HIUS) has been proposed to improve the existing extraction efficiency. This methodology has been hypothesized to isolate bioactive compounds from plant matrices, which have a quick processing time and good extraction yield compared to the previous methods [43]. This methodology involves cavitation phenomenon using high shear stress with an extreme level of localized turbulence [36,44]. This protocol dramatically affects the microstructure by reducing the size of the particle and facilitates good mass transfer. It also helps rupture cell walls similar to the MAE methods discussed above [41]. Generation of less residue and the low processing

time are other advantages [40]. Moreover, the HIUS technique is considered the most preferred technique for the scale-up application [45].

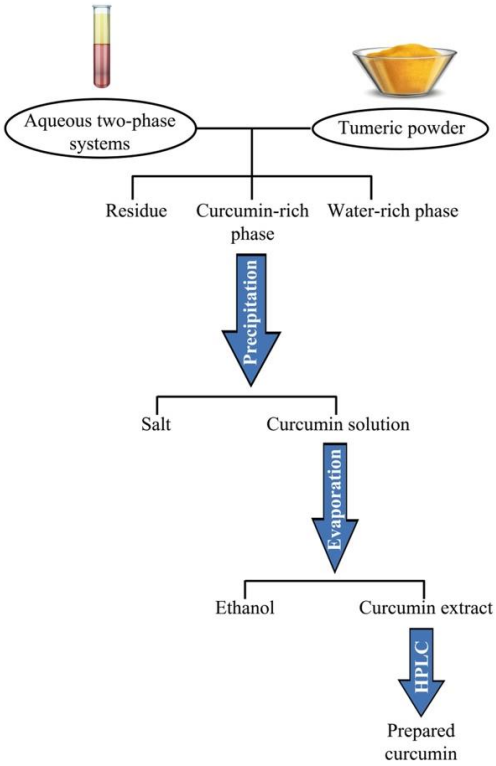

Figure 3. The flow diagram of the large-scale production protocol of curcumin using an ultrasonic-assisted two-phase system (UA-ATPS).

Neves *et al*. [46] proposed solid-liquid extraction assisted by HIUS integrated to extract curcumin from turmeric through a nonthermal and clean emerging approach (Figure 4). In the typical process, the raw turmeric powder was initially subjected to supercritical fluid extraction (SFE), in which two products are obtained: volatile oil extract and unflavored turmeric. The unflavored turmeric was then subjected to solid-liquid extraction-assisted HIUS methodology. They observed curcumin recovery of 40 mg/g at a solvent to feed ratio of 7, comparable to the UA-ATPE method. The most significant advantage of this method is its short processing time of 5 min.

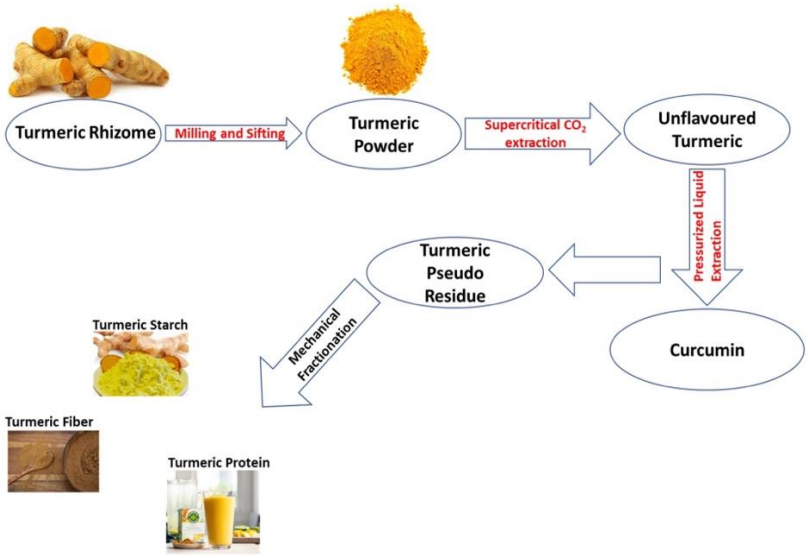

Figure 4. Turmeric's biorefinery from solid-liquid extraction assisted by HIUS clean emerging technologies (see text for details).

Another vital factor to consider for food and pharmaceutical applications is the particle size distribution, crystallinity, purity, and stability [47]. Among them, control over the structure of a crystal is essential concerning the shelf life and the performance. For example, the variation in the ratio of polymorphs in the formulation will affect the active agents' solubility, bioavailability, and bioequivalence [48]. Also, these variations can affect the ability to grind and hence can influence tablet formation [49]. Even though there are three structures of curcumin (monoclinic form I, orthorhombic form II and III), a monoclinic form I is reported to be a more stable structure [50]. Due to the weaker hydrogen bonding, the orthorhombic crystals have a higher solubility and faster dissociation rates in aqueous solutions than form I [51]. Even though orthorhombic crystals are preferred due to their excellent bioavailability and dissociation, the form I is prevailing in the market due to the requirement of complex procedures.

Dense gas protocol (DG) using CO_2 to tune the crystallinity and polymorphism of the crystals has been reported [52–54]. The DG protocol allows tuning the crystal structures through a precipitation and purification process in a single step [55].

Kurniawasyah *et al*. [56] proposed a commercial way to precipitate curcumin through the gas antisolvent (GAS) method and atomized rapid injection solvent process (ARISE) (Figure 5). They observed a higher recovery process for ARISE (60%) than GAS (36%). From Table 1, we could see that under the optimal condition, the isolation of curcumin using ethanol was unsuccessful for GAS, while ARISE setup was successful. This is due to the immediate contact of feed solution and DG antisolvent in ARISE compared to the GAS setup (where the injection of antisolvent is a gradual process).

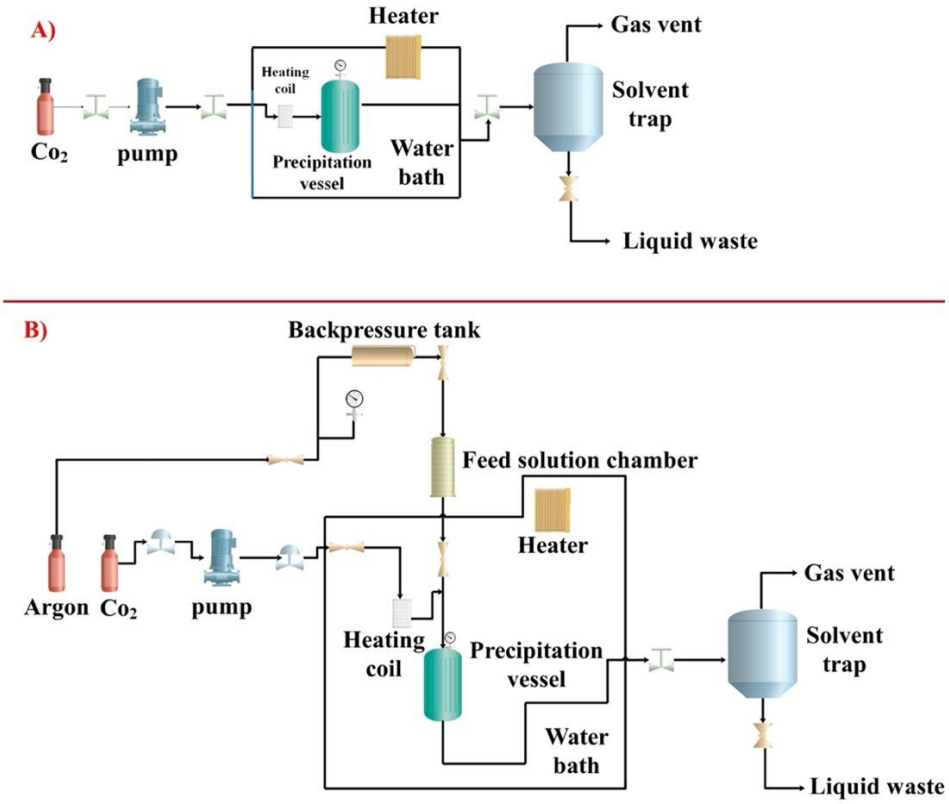

Figure 5. Representative illustration of (**A**) GAS and (**B**) ARISE experimental setup.

These results are favorable for scale-up applications in the industries. Another advantage of ARISE is the requirement of lower operating pressure. The unprocessed curcumin was in irregular shape, and after the process, the products were in uniform morphology without

any organic solvents. The ability to control the crystal structure enables control over the therapeutic application.

Table 1. The extraction of different forms of curcumin crystal structures by changing the parameters of DG antisolvent precipitation protocol. Conc = concentration of feed solution; P-CO_2 = final pressure (GAS) or pressure before solution injection (ARISE).

Type of Process	Conc. (mg/mL)	P-CO_2 (MPa)	Temp. (K)	Crystal form
Unprocessed	–	–	–	I
GAS^{E}	1	10	313	I
GAS^{E}	2	10	313	I, III
GAS^{A}	10	10	313	I
GAS^{AE}	10	10	313	I
GAS^{AE}	10	10	298	I
$ARISE^{E}$	1	9.5	313	I
$ARISE^{E}$	2	9.5	313	I, III
$ARISE^{E}$	2	9.5	298	I
$ARISE^{M}$	1	9.5	313	I
$ARISE^{A}$	10	9.5	313	I, (II)*, III
$ARISE^{AE}$	10	9.5	313	I, (II)*, III
$ARISE^{AE}$	10	9.5	298	I

Notes: E: ethanol; A: acetone; AE: acetone-ethanol 1–1 (v/v); M: methanol.

4. Challenges Involved in The Therapeutic Applications

Curcumin has found many therapeutic applications against various diseases. It has been reported that the curcumin molecule is unstable under various environmental and physiological conditions and degrades easily [57,58]. Kunati *et al*. [59] performed clinical trials using curcumin at an 8 g/day concentration. They found out that the material is rapidly converted to metabolites and observed only small curcumin content in plasma (< 2.5 ng/mL). Curcumin has a poor water solubility in acidic/neutral pH (3 × 10−8 μM), and > 90% of curcumin will degrade under 30 min in PBS at pH 7.2 [60]. The low aqueous solubility, stability issues, and low bioavailability restrict its medical and non-medical applications. Consequently, various studies have been reported to improve/enhance these parameters. To enhance its solubility, stability (physical and biological), bioavailability, and clinical translation, multiple methodologies have been proposed. Some of the significant modifications include its formulation with nanoparticles, liposomes, solid dispersions, micro/nanoemulsions, and complexation with phospholipids and cyclodextrins [61–63].

Nanoparticles and other nanosystems exhibit advantages over conventional carriers/ matrices due to their small size and large surface area. Nanoformulation strategies can be applied to obtain slow and sustained release, which helps attain desired drug delivery. Through nanoformulation, it is possible to increase the circulation time, enhance bioavailability and achieve targeted delivery of bioactive compounds. Therefore, nanoformulation will be an excellent choice for biopharmaceutical classification system (BCS) class IV drugs such as curcumin [64]. There are various studies on the nanoformulation of curcumin for various diseases, such as tumor therapy [65–67], neurodegenerative diseases [68,69], wound healing [70], diabetes [71], and inflammatory diseases [72]. Adahoun *et al*. [73] prepared curcumin nanoparticles with a size range of 34–359.4 nm to improve the absorption, cellular uptake, bioavailability, and efficiency. Bai *et al*. [74] prepared pectin-curcumin (PEC-CCM) conjugates and created nanosized micelles in an aqueous medium. The conjugate exhibited acceptable antioxidant activity and stability. There are various reports on the nanoformulation

of curcumin for cancer application [57,75,76]. Table 2 shows the recent patents filed between 2017 to 2021 on the nanoformulation of curcumin for various applications.

Table 2. Recent patents involved in the nanoformulation of curcumin (2017–2021).

Item	Title of Patent / Inventor(s)	Significant findings	Ref.
1	Curcumin-sophorolipid complex. Singh, Prabhune, Ogale	• Improved aqueous solubility. • Therapeutic application in breast cancer.	[77]
2	Pharmaceutical compositions for the delivery of substantially water-insoluble drugs. Singh, Sandhu	• Water solubilized PVP-curcumin nanoparticles are fabricated.	[78]
3	Preparation method of curcumin-carrying nanoemulsion. Xu *et al*.	• Safe and low-cost preparation method.	[79]
4	Liposomal curcumin for treatment of diseases. KurzrockLan *et al*.	• A practical method of treating skin, pancreatic, or breast cancer using PEGylated curcuminoids.	[80]
5	Formulation of curcumin with enhanced bioavailability of curcumin and method of preparation and treatment thereof. Antony	• Increase in bioavailability by the addition of 5% turmeric oil. • Increase in water dispersion through gelatin capsule encapsulation.	[81]
6	Esterase response type curcumin-polymerized thiodipropionic acid copolymer prodrug nano-micelle and preparation method and application thereof. Chang, Dong, Yuxin	• Esterase-responsive curcumin-thiodipropionic copolymer prodrug nanomicelle for treating colorectal cancer, pancreatic cancer, ovarian cancer, or multiple myeloma.	[82]
7	Curcumin solubilisate. Behnam	• The average diameter of aqueous soluble micelles loaded with curcumin is 5 nm to 40 nm.	[83]
8	Lipid nanoparticle complex containing curcumin comprising ginsenosides. Yoo *et al*.	• The pharmaceutical composition exhibits anti-cancer activity against colon cancer, lung cancer, breast cancer, or melanoma.	[84]
9	Curcumin hyaluronic acid nano-micelle for treating rheumatoid arthritis as well as preparation method and application thereof. Bin	• Low in cost; the medicine has good biocompatibility and no toxic or side effect *in vivo*.	[85]
10	A kind of soluble soybean polysaccharide-soybean protein-curcumin complex and preparation and application. Feiping, Chen	• Improved curcumin stability in aqueous and slow-release effect, has a good application prospect in the exploitation of functional food and medicine.	[86]
11	Curcumin composite particles and its preparation method and application. Fangyi	• Significantly improved water solubility, bioavailability and the stability of curcumin.	[87]
12	A kind of curcumin colon specific drug preparation and preparation method thereof. Cao *et al*.	• Colon specific delivery of curcumin. • Aqueous soluble.	[88]

5. Nanoformulation of Curcumin Towards Cancer Therapeutic Application

5.1. Breast cancer (BC).

According to WHO, in 2020, 2.3 million women were reported with breast cancer, and 685,000 deaths were reported globally, making it the world's most widespread cancer [89]. The classification of BC is based on immunohistochemistry, tumor grade, lymph nodes' states, and the markers of expressions which include progesterone (PR), estrogen (ER), and human epidermal growth factor 2 (HER 2) receptors [90]. The choice of therapeutic approach depends upon the target/expression.

Encapsulating curcumin in polylactic glycolic acid (PLGA) nanoparticles has been one of the potential approaches to combat BC. The PLGA-curcumin complex improved chemical stability in the cellular environment and expressed a more significant antiproliferative effect against estrogen-dependent MCF 7 BC cells [91]. Among various nanoformulations, Solid lipid nanoparticles (SLN) are vastly applied in drug delivery applications. SLNs are reported

to have a smaller particle size, good biocompatibility, high stability, and surface tunability [92,93]. The other characteristics are a desirable release profile, increased blood circulation time, and improved therapeutic efficiency of anti-cancer drugs [94,95]. Wang *et al*. [96] fabricated SLN to encapsulate curcumin and applied it on the SKBR3 cell line. The cell proliferation result observed dose-dependent toxicity for curcumin and SLN-curcumin, in which SLN-curcumin had the lowest IC_{50} value (18.78 µM). The higher cellular uptake of curcumin-SLN explains this observation. They also observed an increase in ROS generation and a decrease in Bcl-2/Bax expression in SKBR3 cells after SLN-cur administration. From cell cycle analysis, they observed a lower level of cyclin D and CDK4 expressions after administration of SLN curcumin, leading to apoptosis. Another proposed methodology uses human serum albumin (HSA) as a nanocarrier for drugs [97]. The molecular structure of curcumin is similar to the fatty acid so that the albumin can interact easily with curcumin [98]. Also, after the release of the drug, albumin can be utilized by the body. Matloubi *et al*. [58] conjugated curcumin with HSA and evaluated its effects on MCF 7 and SKBR3 cell lines. From cell viability studies, they observed that the toxicity of HSA-curcumin on normal cell lines was less than curcumin alone. However, the anti-cancer effect was much higher than curcumin.

Sampath *et al*. [99] fabricated curcumin-loaded PLGA NPs with various capping groups such as chitosan, dextran, polyethyleneglycol, and emulsifier Tocopherol Poly (ethylene glycol) (TPGS) and evaluated it on MCF 7 breast cancer cell line. The PLGA NPs encapsulated with curcumin and the different capping agents exhibited high MCF 7 cell growth arrest from *in vitro* anti-cancer analysis. When the nanoformulation particles were conjugated with TPGS, they observed a higher cellular uptake. This is due to the enhancement of cell adhesion and hydrodynamic properties by Vitamin E TPGS.

One type of BC called triple-negative breast cancer (TNBC) lacks some receptors, making them chemo-resistive to some drugs and bypassing some of the tumoricidal mechanisms [100]. Therefore, a better therapeutic agent was required. H-ferritin (HFn) based biomimetic nanoparticle has been proposed as a nanocarrier [101]. HFn is a globular protein that can unfold into individual subunits under acidic conditions (pH < 3) or alkaline conditions (pH = 11–12) and can retain its original structure when pH is neutral [102]. Furthermore, the higher affinity of HFn towards transferrin receptor 1 (TfR1) can be utilized for higher cellular uptake, which is also over-expressed in tumors [103,104]. Pandaffi *et al*. [105] encapsulated curcumin in Hfn nanoparticles and assessed the biological activity in the TNBC cell line. The encapsulation enhanced the solubility, chemical stability, and bioavailability of the curcumin. From the binding experiments, Hfn nanocages were internalized more quickly in TNBC cell lines and confirmed that the TfR1 receptor influenced the process. Also, the curcumin encapsulated Hfn nanoparticles at lower concentrations were more effective compared to the drug alone.

Greish *et al*. [106] encapsulated curcumin metal complexes in polystyrene-co-maleic acid (SMA) micelles to solve the issues of stability and targeted delivery. Two curcumin complexes were synthesized (Cu^{2+} -curcumin and Fe^{3+}-curcumin) and were evaluated on MCF 7, MDA MB 231, and 4T1 cell lines. They observed a higher cytotoxicity effect for Cu^{2+}-curcumin complex even in the sub-micromolar range than bare curcumin, which has a higher IC_{50} value (25.6 µM) on the MDA MB 231 cell line [107]. This cytotoxicity involves the binding with beta-diketo function [108]. To increase the bioavailability, the Cu^{2+}-curcumin complex was encapsulated in SMA NPs. SMA is biodegradable, easily binds to plasma

albumin, and has a higher enhanced permeation and retention (EPR) effect [109]. After encapsulation, they observed a decreased cytotoxic effect on the MDA-MB-231 cell line. The biodistribution profile on the 4T1 tumor murine model of TNBC revealed comparable results for Cu^{2+}-curcumin and SMA Cu^{2+}-curcumin. The SMA Cu^{2+}-curcumin reduced the tumor growth by 61% at 10 mg/kg in 10 days compared to Cu^{2+}-curcumin, which required 20 mg/kg. This was explained by the high biological stability and EPR effect of NP formulation.

Wang *et al*. [110] fabricated curcumin encapsulated in methoxy poly(ethylene glycol) polycaprolactone (MPEG-PCL) and evaluated it on MDA MB 231 (triple-negative) cell lines. The cell viability of Curcumin-MPEF-PCL was lowered compared to the free curcumin. The higher cytotoxicity was explained using mitochondrial morphology. When the nanoformulation curcumin was administered, they observed fragmentation of mitochondrial morphology, as depicted in Figure 6. This process was followed by the cell nucleus's total collapse and apoptosis of the breast cancer line. *In vivo* analysis revealed inhibition in tumor growth for curcumin nanoparticle formulation compared to the bare curcumin. Western blot analysis showed that cleaved caspase-3 increased significantly for nanoformulation curcumin compared to the free curcumin, indicating apoptosis induction [110].

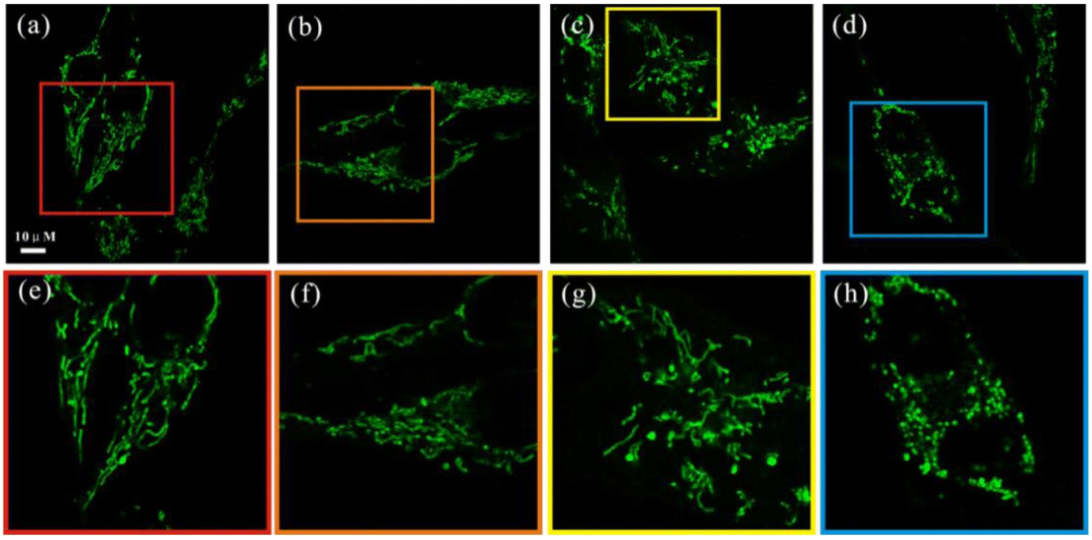

Figure 6. Confocal imaging of breast cancer cells mitochondria morphologies after N-CUR (10 μM) administration. **a.** Control; N-CUR treatment for **b.** 1h; **c.** 4h; **d.** 24h. **e–h.** Enlarged images corresponding to the color box area from **a** to **d**. Adapted with permission from Ref. [110].

Tumor-targeted therapeutic application using magnetic nanoparticles is a promising method with more drug accumulation that can be achieved at the desired target. Moreover, the magnetic field can be used as a physical trigger for the release of drugs [111]. Song *et al*. [111] prepared magnetic Fe_3O_4 NPs alginate/chitosan composites to deliver curcumin on MDA-MB 231 and HDF normal cell lines. There was a higher cellular uptake for nano formulated curcumin with dose-dependent uptake. The higher concentration of chitosan coating also improved the cellular uptake due to the protonation of the amino group.

On the other hand, normal HDF cells' uptake was comparable for both the curcumin and nano formulated curcumin. In conclusion, cancer cells have a higher metabolism than normal cells and overexpress some receptors [112]. Also, the nano formulated curcumin exhibited higher toxicity on a cancer cell line which can be due to the higher cellular uptake and controlled release of curcumin.

Some cancer cells, especially triple-negative breast cancer, overexpress Programmed Death-ligand 1 (PDL1) protein, which helps it to camouflage from immune cells [113]. This overexpression of PDL1 has been utilized for tumor imaging and targeted therapeutic application [114]. The PDL1 can be easily targeted by various antibodies/peptides [115]. Hasan poor *et al*. [116] prepared HSA/curcumin NPs, conjugated them with PDL1 binding peptides, and evaluated them on breast cancer cell lines (MDA MB 231, MCF 7, SKBR 3). RT-PCR analysis confirmed that the PDL1 was overexpressed in MDA MB 231 cells (triple-negative) compared to other normal breast cancer cell lines. As expected, nano-formulated curcumin's cellular uptake was higher than the curcumin alone (not encapsulated). Moreover, the cellular uptake of peptide conjugated HSA/cur was high for MDA MB 231 cells compared to HSA/Cur. The cytotoxicity assay observed higher toxicity for HSA/Cur NPs and peptide-HSA/Cur NPs than free curcumin. As discussed above, this is due to the EPR effect of nanoformulation. Also, the PDL1 conjugated NPs expressed higher cytotoxicity on MDA MB 231. Nevertheless, there was no substantial difference between HSA/Cur NPs and peptide HSA/Cur NPs cytotoxicity on other cell lines due to the low expression of PDL1.

Even though PLGA has been widely applied, the blood circulation time is low. It is easily identified by plasmatic opsonin (an extracellular protein that tags/labels to get phagocytosed) and cleared. As an alternative, researchers started to coat the polymeric NPs with PEG, making the particles invisible to the mononuclear phagocytic system (MPS) [119–121]. Prabhuraj *et al*. [117] fabricated PEGylated PLGA NPs loaded with curcumin and studied the different conjugating ligands (Folic acid, hyaluronic acid, transferrin) and evaluated on triple-negative MDA MB 231 and normal fibroblast (L929) cell lines. When the curcumin was dissolved in PBS buffer, there was no cytotoxicity observed due to the insolubility. But cytotoxicity was observed when the curcumin was dissolved in DMSO. This explains the importance of the solubility of curcumin in therapeutic application. The PEGylated PLGA-curcumin showed higher toxicity compared to PLGA-curcumin due to the increase in solubility by PEG [118]. The order of toxicity towards cancer cells when conjugated with different moieties were as follows HA-PEG-PLGA-Cur (HA targets CD44) > Tf-PEG-PLGA-Cur (Tf targets TfR1) > FA-PEG-PLGA-Cur (FA targets FOLR1).

Gosh *et al*. [66] fabricated curcumin-loaded HA modified mesoporous silica nanostructures (MSN) and evaluated them on MDA MB 231 and MCF 7 cell lines. From the above discussion, we could understand that HA modifications on NPs improve its targeting ability on breast cancer cell lines. They observed a higher cellular uptake for HA-MSN compared to MSN NPs. Also, the uptake on MDA MB 231 was more than MCF 7, which is attributed to the CD44 targeting property of HA. HA also promoted the cancer cell death for nano formulated curcumin. The cell cycle analysis by administration of 12µg/ml of MSN-HA-C leads to a cell cycle arrest at the G2/M phase. One of the challenges of triple-negative breast cancer MDA MB 231 cells is its metastasize capability [119,120]. A wound-healing assay was performed to understand the inhibitory effect of HA-MSN-C on the metastasis nature of the cells. The results observed significant repression of MDA MB 231 cell migration at a dose of 2.5 µg/mL. This repression was high in incase of MDA MB 231 compared to MCF 7 due to the targeting effect of HA. They observed a decreased tumor volume and mass from *in vivo* antitumor activity with MSN-HA-C administration.

5.2. Lung cancer.

Lung cancer (both small and non-small cell types) is the second most common cancer affected in men and women (not counting skin cancer). Among lung cancers, the non-small cell lung cancer type (NSCLC) is responsible for 85% of cases [121]. Only 5% of curcumin reaches the colon area when administered orally.

It has been reported that reactive oxygen species (ROS) are high in certain tumors like lung cancer [122]. Researchers focused on designing ROS responsive systems such as acryl boronic ester, ferrocenyl, selenium, and thioether groups for targeted therapeutic applications [123]. Luo *et al*. [124] fabricated ROS responsive 1,4-(hydroxymethyl) phenylboronic acid (HPBA) modified PEG-PAA nanoparticle (PPHC) loaded with curcumin and evaluated on ROS elevated lung cancer cell line (A549). They used N-acetyl-l-cysteine (NAC) (an antioxidant) on the A549 cell line during the study. They found that PPHC was highly viable even at a higher concentration of 20 µg/mL, and the material showed dose-dependent toxicity when NAC was not added. This result concluded the ROS-dependent release of curcumin by PPHC nanoparticle formulation. They also concluded that the curcumin-induced A549 cells death through ROS signaling pathway.

Zhu *et al*. [125] synthesized curcumin-loaded methoxy polyethylene glycol-polylactide (mPEG-PLA) core-shell structures and evaluated them on A549 cells. mPEG-PLA consists of hydrophilic mPEG and hydrophobic PLA. The main advantage of mPEG is its camouflaging ability to bypass non-specific uptake by the reticuloendothelial systems (RES), which prolongs the material circulation time [126]. The cur-mPEG-PLA had higher cytotoxicity than curcumin alone, which is attributed to the enhanced cellular uptake confirmed through Flow cytometry (FCM) analysis. The cell kinetic analysis on A549 cells observed a retarding of G2/M transition point, which was comparable with curcumin. The inhibition on proliferation and clone formation ability of A549 cells treated with curcumin and cur/mPEG/PLA was studied. They observed a high inhibition with nano formulated curcumin than bare curcumin. They also found that the nano formulated curcumin had a higher inhibition of lung cancer metastasis than curcumin alone.

Pulmonary targeted drug delivery is a non-invasive administration through inhalation/spraying [127,128]. Dry powder inhalers (DPIs) have been used to target drugs in the deep areas of the lungs [129]. DPI is reported to have higher stability compared to aerosols and nebulizers [130]. Zhang and colleagues [131] prepared liposomes loaded with curcumin dry powder inhalers (LCDs) and evaluated lung cancer. The liposome formulated curcumin enhanced the anti-cancer activity through the permeability of curcumin and cellular uptake. Rat lung cancer models were used to test the anti-cancer efficacy of the material. Compared to healthy tissue, tumor tissues had various tumor nodes and bleeding. After administration of curcumin (CP), Liposome curcumin (LCD) and gemcitabine (reference anti-cancer drug) showed decreased bleeding. LCD and gemcitabine-treated tissue had similar structures as healthy tissue. For CPs, LCDs, and gemcitabine, cell proliferation was also inhibited significantly, mainly due to the apoptosis in which the antiproliferation effect of LCDs was the highest. Similar results were observed with VEGF expression.

Liposomes formulated in the mentioned study were prepared by the thin-film hydration method using tetrahydrofuran [131], while other groups used chloroform and/or methanol in this method of liposome preparation. It should be noted that all these organic solvents are potentially toxic, and trace amounts of these molecules remaining in the formulations can lead

to serious health hazards. There are safe and scalable methods for liposome preparation for pharmaceutical applications, which do not require the employment of any potentially toxic solvent or reagent. These include heating method [132,133] and Mozafari method [134,135]. In the heating method, liposomes and nanoliposomes (in addition to some other encapsulation systems) can be prepared using a single vessel in the absence of potentially toxic solvents, as explained in Figure 7. All the steps of preparation of phospholipid vesicles should be carried out under an inert gas atmosphere (such as argon or nitrogen) to avoid oxidation of the ingredient molecules. Solvents and co-solvents used are selected from non-toxic solvents such as de-ionized water, physiological buffers or saline solution, and one or more polyol (e.g., glycerol) [136]. Loading the drug or bioactive molecules such as curcumin to liposomes or nanoliposomes using the Mozafari method can be accomplished through the following three steps: Adding capsule ingredients to a preheated (60 °C) mixture of drugs and a polyol such as glycerol, propylene glycol, or sorbitol (final concentration 3%, v/v) in a heat resistant vessel; Heating the mixture at 60 °C while stirring (e.g., 1000 rpm) for a period of 45–60 min under an inert atmosphere (e.g., argon or nitrogen gas); Following preparation of the capsules, the formulation must be kept at temperatures above the phase transition temperature of the phospholipid ingredients (Tc) under an inert atmosphere for 1 hour to allow the vesicles to anneal and stabilize (Figure 7) [134–136].

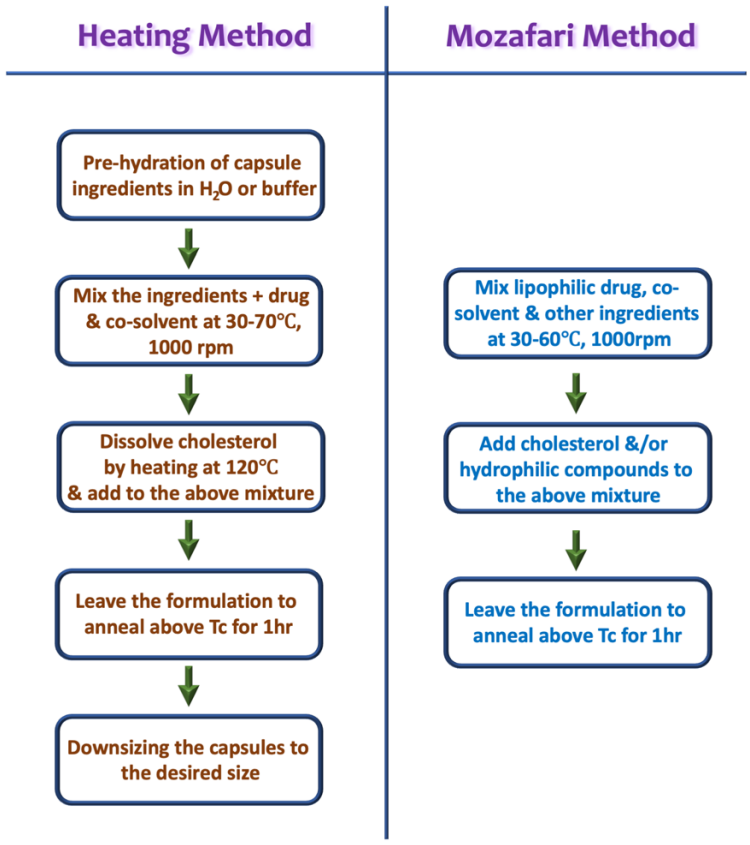

Figure 7. Comparison of "Heating method" and "Mozafari method" with respect to their process steps.

5.3. Colorectal cancer.

Colorectal cancer is ranked third after breast and lung cancer is mainly reported in men. There were over 1.8 million new cases in 2018. Rao *et al*. [137] proposed a nanogel based approach for the treatment of colon cancer. They fabricated nanogel consisting of gelatin and acrylamide glycolic acid monomer through emulsion polymerization protocol. The material

exhibited a higher release profile for curcumin at pH 7.4 compared to pH 1.2. Lizbeth *et al*. [138] loaded curcumin in poly diethylamino ethyl methacrylate (PDEAEM) -core-PEG-shell nanogels for the intravenous injection of colon cancer. The positive surface charge of the gel enhanced the cellular uptake and the anti-cancer effect of the material. Graphene and its derivatives have been proposed as a nanocarrier due to its good cellular interactions and minimal cell damage [139,140]. Lina *et al*. [141] fabricated curcumin-loaded AuNPs-reduced graphene oxide studied the cellular membrane interaction and anti-cancer effect on colon cancer (HT29 & SW948) cell lines. TEM was used to analyze the interaction of as-synthesized material on colon cancer cells. The material was endocytosed into the cell without any aggregation. The type of cell death was also studied using TEM micrographs. The study clearly shows the structural changes of the nucleus accompanied by chromatin condensation and cellular uptake of the material in both cell lines. The apoptotic stage is visible with blebbing of the membrane in both cell types.

Folic acid receptors are extensively expressed in various tumors such as the colon, brain, lungs, and breast, whereas they are expressed in normal tissues too much less extends [142]. Hu *et al*. [143] loaded curcumin in folic acid conjugated mPEG/PCL micelles and evaluated its effect on colon cancer (*in vivo* and *in vitro*). They observed higher toxicity and a lower IC_{50} value of 1.373 µg/mL, which was the lowest compared to the free curcumin and non-folic acid conjugated nanoparticles. Systemic toxicity was evaluated in the vital organs such as the heart, liver, spleen, lungs, and kidney of the mouse through the Hematoxylin-eosin (HE) staining method, and no morphological abnormalities were found. The formulation exhibited an acceptable safety profile. Different strategies for the preparation of nanoformulations of curcumin are listed in Table 3.

Table 3. Various potential nanoformulations of curcumin.

Item	Composition	References
1	Curcumin- human serum albumin (HSA) nanoparticles	[58]
2	Polylactic glycolic acid (PLGA) nanoparticles	[91]
3	Solid lipid nanoparticle formulations of curcumin	[93 - 96]
4	Albumin nanoparticles	[98]
5	Polymeric nanoparticles-Polyethylene glycol (PEG)	[99]
6	H-ferritin (HFn) based biomimetic nanoparticle	[101]
7	Curcumin complexed with copper nanoparticles	[106]
8	Curcumin encapsulated in methoxy poly(ethylene glycol) polycaprolactone (MPEG-PCL)	[110]
9	Liposomes / Nanoliposomes	[131, 136]
10	Graphene-based nanoformulations	[141]
11	Micelles	[143]

6. Conclusions and Future Perspectives

Researchers have found out from a myriad of studies that the main active component/polyphenol of turmeric is curcumin. However, the large-scale production and purification of curcuminoids for industrial applications is still a challenge.

Some of the notable results from large scale protocols are as follows: MAE procedure provides better precision than conventional methods; SFC method results in low consumption of solvents and a larger sample loading capacity; UAE combined with ATPS possesses advantages such as being non-toxic and less solvent requirement; HIUS is a fast process and produces fewer residues compared to many other methods; The DG protocol allows tuning the crystal characteristics in the single-step precipitation and purification process.

Various strategies have been proposed and investigated to improve solubility, enhance stability, increase bioavailability, and expand the range of potential applications of herbal

extracts. Some of the main strategies involve the formulation of the extract in the form of nanoparticles, liposomes, nanoliposomes, solid dispersions, microemulsions, and complexation with phospholipids and cyclodextrins. Most of the patents between 2017–2021 focused on improving aqueous solubility, low-cost preparation methods, improving bioavailability, and targeted therapeutic applications. The most evaluated anti-cancer cell lines were breast, lung, and colon. Among breast cancer cell lines, the triple-negative cell lines were more applied due to their chemo-resistive nature. Studies indicated that nanoformulation has the potential to improve the cellular uptake, IC_{50} value, biological stability, and therapeutic efficacy of curcumin.

The major reasons for the enhancement of therapeutic efficacy of nanoformulations are as follows: An increase in ROS generation and decrease in certain cell expression; Attachment of targeting ligands such as HFn, Folic acid, etc., improves the therapeutic efficacy of curcumin; Some surface modifications such as PEG and its derivatives help the nanoparticle camouflage from macrophages and improve the blood circulation time. Due to these, PEG has been widely used for nanoformulation of active ingredients, including curcumin; The viability of the tumor tissue and its metastasis ability was inhibited more by nanoformulation; Tumors such as lung cancer exhibit higher ROS levels, and targeting curcumin nanoformulations to this ROS signal is considered an efficient strategy to combat cancer.

Even though various large-scale approaches are reported for the extraction and purification of curcumin, a complete large-scale synthesis with a green-tech approach has not been fully established. The authors recommend thorough research in the design of a green synthesis protocol for large-scale curcumin extraction. Since the nanoformulation of curcumin can affect its chemical nature due to the type of the capping agent, the effect of pH, the nature of formulation protocol, a detailed optimization of parameters, and the structural study of the encapsulated curcumin is required. Most of the literature on curcumin and its nanoformulations report them as being biocompatible based on limited observation and histological studies. The authors also recommend more comprehensive and reproducible investigations on this topic using different cytotoxicity assays.

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Conflicts of Interest

The authors declare no conflict of interest.

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