



Curcumin: Modern Applications for a Versatile Additive

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Abstract: The recent development of several methods for extracting curcumin from the root of the plant *Curcuma longa* has led to intensified research on the properties of curcumin and its fields of application. Following the studies and the accreditation of curcumin as a natural compound with antifungal, antiviral, and antibacterial properties, new fields of application have been developed in two main directions—food and medical, respectively. This review paper aims to synthesize the fields of application of curcumin as an additive for the prevention of spoilage, safety, and quality of food. Simultaneously, it aims to present curcumin as an additive in products for the prevention of bacterial infections and health care. In both cases, the types of curcumin formulations in the form of (nano)emulsions, (nano)particles, or (nano)composites are presented, depending on the field and conditions of exploitation or their properties to be used. The diversity of composite materials that can be designed, depending on the purpose of use, leaves open the field of research on the conditioning of curcumin. Various biomaterials active from the antibacterial and antibiofilm point of view can be intuited in which curcumin acts as an additive that potentiates the activities of other compounds or has a synergistic activity with them.

Keywords: curcumin; antibiofilm; antibacterial activity; food additive; additive for health care

1. Introduction

Curcumin has been known since antiquity and used as a spice, preservative, dye for dyeing fabrics, and in traditional medicine. It is one of the three main colored compounds (demethoxy and bisdemethoxy derivatives) which are extracted from *Curcuma longa* plant roots grown in Asian countries. It is found in the Color Index with the names: Yellow 3 (natural compound) and Gelb 6 (synthetic), it is also known as: turmeric, curcumin, Indian saffron, and saffron of Indians, with the reference number C.A.S. number: 458-37-7 [1].

Considering the epidemiological events caused by the appearance of the COVID-19 virus, in the last two years, there has been an intensification of studies on the methods to obtain [2–20] curcumin and its bioactivity properties [21–30]. If, in 2017, the global curcumin market was valued at USD 52.45 million, due to the diversification of application areas, it is estimated that the size of the global curcumin market will reach USD 151.9 million by 2027. The estimates were made after an evaluation of the increasing number of articles published (Figure 1) on the antioxidant, anti-inflammatory, or anticancer properties, increasing the availability and accessibility of Ayurvedic medicinal products, cosmetics, food supplements, and the natural additives consumer market in developed countries. In this regard, in North America, which is the largest market followed by Europe, food, nutritional supplements, and cosmetics with the main ingredient as curcumin had the biggest sales in 2019, while India is the most important producer of curcumin extracted from turmeric and represents more than 78% of its global production [31–34]. However, the forecasts made have a high degree of uncertainty due to operational problems regarding the supply of raw materials [35-37] and the distribution of finished products on the consumer market, affected by the COVID-19 pandemic [38–40]. Curcumin is used extensively as a phytochemical in studies of various diseases [28,41] and, in particular, in cancer treatments [6]



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Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). targeting its antioxidant [42,43] and anti-inflammatory properties [43]. The current revision is made to highlight the new fields of application regarding the exploitation of antiviral, antifungal, and antibacterial properties. We will discuss methods of conditioning curcumin to increase its solubility in water and the influence or synergistic action of the compounds found in delivery systems. This study updates the conditioning methods for curcumin to improve the photostability and solubility properties, which are important in medical and food applications. In addition, the advantages and the need to use natural compounds in areas related to the protection of, and contribution to, human health will be discussed.



Figure 1. Total number of articles on "curcumin", published between 2016 and 2020, in different databases.

2. Methods of Obtaining and Antiviral, Antifungal, and Antibacterial Activity

The study of the different types of turmeric species in the Zingiberaceae family [2–4,7] regarding the content of bioactive compounds suggests a growing trend in the production of curcumin in the coming years due to the development of new areas of use (Figure 2). Due to its antioxidant and anti-inflammatory properties, curcumin is presented in many specialized studies as a potential adjuvant for treating cancer [6] and neurodegenerative diseases [21]. The applications of curcumin, which reflect the antioxidant properties, are also found in the field of textile dyeing and, as a consequence, textiles with antimicrobial or anti-UV properties were obtained [22,44]. The diversity of the application purposes of curcumin demonstrates its versatility and the tendency for it to be used in as many areas as possible where the presented properties can be exploited.



Figure 2. Areas of use of curcumin.

By processing fresh or dried turmeric root, several methods (Table 1) for obtaining curcumin have been developed and optimized—by extraction with solvents [2,4,5], in microwaves [4,6], in supercritical fluids [4,7,10,12], or using ultrasound [4,8,9,12]. Curcumin derivatives can also be obtained by synthesis, the classic method being Knoevenagel condensation [16–18], by alternative methods in the microwave field [19], or by ultrasound irradiation [20]. However, for food applications, compounds obtained from natural sources by extraction with ethanol or propanol are preferred. Thus, extraction methods were studied and optimized by utilizing the principles of green chemistry [6,9], based on microemulsion extraction processes [45,46] without surfactants or using eutectic solvents [47–49]. The results of the studies led to the increase in the obtaining efficiency, decrease in product price and the development of the market of its sale and of the derived products.

The extracts obtained were structurally characterized and biological activity was evaluated. The three main polyphenolic compounds are 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (curcumin, 60–70%), 1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxy phenyl)-1,6-heptadiene-3,5-dione (demethoxycurcumin, 20–27%), and 1,7-bis(4-hydroxyph enyl)-1,6-heptadiene-3,5-dione (bisdemethoxycurcumin, 10–15%), along with other compounds, such as heptanoide, phenylpropanoid, and terpene derivatives. Depending on the turmeric species and the extraction method used, mixtures with different proportions of bioactive compounds are obtained which differ in the antibacterial and antifungal activity tested. As curcumin is the major compound among the extracted phenolic derivatives, its structure has been the most studied. Its antioxidant, anti-inflammatory, antiviral, antibacterial, or antifungal properties are determined by the presence in the structure of three active areas, namely, the ketone central groups with keto-enol tautomerism, the two double bonds with cis-trans isomerism, and phenolic groups at the ends of the heptanoid chain (Figure 3).

No. crt	Turmeric Species (Type of Sample)	Methods	Curcuminoids Yield % (mg/g) or Particle Size (mm)	Ref.
1.	Curcuma longa (dried turmeric powder)	Surfactant-free microemulsion	(1.92)	[3]
2.	Curcuma longa (dried turmeric powder)	Soxhlet extraction ternary system	76.82 (88.96) 15.48	[2,8] [15]
3.	Curcuma longa (dried turmeric powder)	Ultrasound	(67.15)	[8]
4.	Curcuma longa (dried turmeric powder)	Ultrasound/deep eutectic solvents	(58.87)	[9]
5.	Curcuma longa (dried turmeric powder)	Microwave	88(105.3)	[6]
6.	Dried rhizomes of C. longa (Rajapurivariety)	Supercritical fluid extraction	(1.68)	[7]
7.	Curcuma aromatic Salisb	Soxhlet extraction	8.34	[10]
8.	Curcuma aromatic Salisb	Supercritical carbon dioxide	7.54	[10]
9.	Curcuma xanthorrhizaRoxb	Solvent extraction	4.98	[3]
10.	Curcuma longa (dried turmeric powder)	Pressurized liquid extraction	0.125–0.45	[11]
11.	Curcuma longa (fresh turmeric)	Solid phase	-	[13]
12.	Curcuma longa (extract the essential oil)	Subcritical water extraction	90.19	[14]

Table 1. Methods for obtaining curcumin derivatives.



Figure 3. Isomeric forms and mechanisms by which curcumin manifests some of its properties.

Numerous clinical and pharmacological studies have been conducted on curcumin over time, and it has been known since 1910 that the active ingredients in turmeric extract are curcuminoids, especially curcumin, which has been shown to be a powerful antioxidant. A diet containing curcumin decreases oxidative stress, through a process of the inhibition of peroxidated lipids and the neutralization of superoxidized and hydrolyzed radicals [7,8,43]. Despite these beneficial properties, curcumin has limited applications due to its low solubility in water. To improve the photostability and solubility properties, different methods of encapsulating curcumin have been experimented with. The antiviral activity of curcumin has been studied since the 1990s, in laboratory experiments on cells, and the results of studies have shown that this compound is active against the human immunodeficiency virus and the hepatitis C virus; nowadays, studies are being conducted on both RNA and DNA viruses [26,27]. In 2007, the antiviral properties were confirmed following a study in which curcumin was tested, along with another 220 phytocompounds, on acute respiratory syndrome associated with coronavirus (SARS-CoV). Of these, curcumin is among the 20 phytocompounds, along with some diterpenes and triterpenes, that have had significant and specific anti-SARS CoV activity [28]. In the following years, the research improved the initial results, thus developing new types of antiviral agents in which curcumin is linked to carbon dots [29]. The new structures act through a mechanism of suppression of viral RNA synthesis and modification of viral protein. The coronavirus infections can also be reduced by stimulating the production of interferon-simulating and pro-inflammatory cytokine genes. Another method applied in antiviral treatments consists of photodynamic inactivation using, as a photosensitizing agent, curcumin deposited on reduced graphene oxide [30]. The potential uses of curcumin for treating the currently circulating virus COVID-19 are currently being proposed [50,51].

Curcumin and its natural derivatives, in the form of essential oil [52,53], aqueous [54] or alcoholic extracts [55–59], and nanocomposites [41,60–63], have been tested to evaluate both antifungal activity and synergistic activity with other compounds [54,55,62] against several types of fungi found in the food field (*Penicillium* family, *Cladosporium* and *Aspergillus*) [52,53,59] or in the medical field (*Candida albicans*) [60,61]. Thus, curcumin, following in vitro tests, showed a strong antifungal effect through mechanisms associated

with damage of the plasma membrane. The minimum antifungal inhibitor concentration for the *C. albicans* strain is $125 \ \mu g/mL$ [61].

Studies on the antibacterial activity of curcumin have made significant progress in the last decade on the types of bacteriological strains tested and the development of their areas of use as an antibacterial and antibiofilm compound [64–118]. Biofilm is an important problem in the food and medical sectors due to the microorganisms included in the extracellular polymer matrix attaching to different surfaces and becoming a source of contamination. These microbial communities become very resistant to antibiotics and hygienic products, leading to the search for new types of antimicrobial agents that are able to alter the polymer matrix and destroy the structure of the biofilm, or for surface treatments to prevent biofilm formation [64–66]. Several studies [67–70] in which curcumin along with other phytochemicals (flavonoids, quercetin, and lutein) have been tested on different types of bacteria (Acinetobacter baumannii (A. baumannii), Chromobacterium violaceum (C. violaceum), and Pseudomonas aeruginosa (P. aeruginosa)) have demonstrated an ability to inhibit biofilm formation and decrease their virulence. Following antibacterial [71,74–78] and antibiofilm [64–71,85–88] tests, performed against more than 100 strains, curcumin was confirmed as an antimicrobial agent, but with selective activity. This is based on the properties of curcumin as an active initiator of free radicals and the photogenerated reactive oxygen species (ROS). The increase in ROS production was possible due to the structural modification of curcumin in the form of nanoemulsions [61,90,114] or nanoparticles [62,74,87–91,96], increasing the solubility, photostability, and permeability of its cell membranes [88,89,96,118]. Microemulsions obtained by encapsulating curcumin form phospholipid acid micelles [98] (biodegradable biosurfactant used to increase the solubility of hydrophobic drugs), which showed antimicrobial activity for both types of bacteria, Gram positive and Gram negative. In addition to reducing the degradation of curcumin by approximately 95%, a synergistic effect of curcumin with the biosurfactant was observed against P. aeruginosa strains. Several metal complexes (Ag, Fe, Zn, Cu, and Mo) [77–83] of curcumin were tested for the evaluation of anti-quorum and biofilm formation. Among them, copper and molybdenum complexes showed antiviral and antimicrobial activity for a series of multidrug-resistant strains, P. aeruginosa and Klebsiella pneumoniae (K. pneumonia), through a mechanism of action on the dynamics, permeabilization, and depolarization of the bacterial cell membrane. In order to improve bioactivity, curcumin was conjugated to gold nanoparticles by a new method of nanoparticle biosynthesis. Composites with a median diameter of 20 nm, obtained from the green synthesis of gold nanoparticles to which curcumin structures are attached, showed higher antioxidant activity than free curcumin. Tests have shown that antibacterial activity against Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis and Escherichia coli, and in vitro results, are promising for use in the treatment of liver disease [119,120]. Another mode of the antibacterial action of curcumin was tested by loading it into (meso)porous nanocomposites [96,110] and metal oxides [99–101] with a sustained release. These showed antibacterial and antibiofilm activity through different mechanisms of damage to the structure of the bacterial cell wall, leading to the cytoplasm discharge and reduced cell metabolism or the production of virulence factors. Photodynamic inactivation is an effective non-thermal sterilization technique. The method is applied by means of blue light emitted by a diode and curcumin [102-106], as such or encapsulated [107-114], used as a sensitizer (Figure 4). The mechanism underlying the photodynamic therapymediated photoinactivation (PDT) process depends on ROS (e.g., singlet oxygen and free radicals). Studies have found that the results of the method are based on the action of curcumin to generate singlet oxygen [102], while PDT potentiates the activity of curcumin against bacteria and biofilm formation [30,103–114].



Figure 4. Types of curcumin encapsulations used as a sensitizer in antimicrobial photodynamic therapy (aPDT).

In 2016, curcumin came to the attention of researchers as a potentiator of the effect of antibiotics through studies [115] that demonstrated the synergistic effect between curcumin and ciprofloxacin against Gram-positive bacteria. The mechanism by which the process occurs is due to its ability to induce ROS. Curcumin demonstrated better antibiofilm activity than the drug nisidine and had an effect compared to that of chloramphenicol [116], with a proven antibiofilm effect on *A. baumannii* following in vitro tests [67,117]. *A. baumannii* is one of the most common microorganisms found in nosocomial and chronic infections, with a high resistance to antimicrobials and antibiotics [115–118].

In this way, the direct effect of potentiating the activity of antibiotics, such as amikacin, gentamicin, meropenem, and vancomycin, or widening their antimicrobial spectrum, has been tested in vitro [115].

Based on these properties, the applications of curcumin have been developed in important areas, such as in the food and medicine fields, focused on preventing disease and maintaining human health.

3. Additive for the Prevention of Spoilage, Safety and Quality of Food

Curcumin (E100) is a food coloring, yellow-orange, with a hot and bitter taste, approved by the FAO (Food and Agriculture Organization). Restrictions imposed on the products used in food coloring or as a color additives refer to the content of arsenic (calculated as free arsenic) max. 5 mg/kg and lead (calculated as free lead) max. 20 mg/kg. The rhizome extract of the plant, curcumin powder, has over time been used in Southeast Asia in food preservation [1,4]. Recently, the recognition of curcumin as belonging to the category of antifungal and antibacterial agents of natural origin has led to the diversification, on the one hand, in the way of conditioning curcumin [121–125] and, on the other hand, to new sectors of use, for example, as a sensor/pH indicator [126–128] in the food field or in packaging [129–135] (Figure 5).



Figure 5. Applications of curcumin in food, due to its antiviral, antibacterial, and antifungal properties.

Chuacharoen and Sabliov [121] conducted a comparative study of several models of curcumin delivery. In this regard, the encapsulation systems were made in the form of nanosuspensions, zein-based nanoparticles, and nanoemulsions, keeping the same initial amount of curcumin and surfactant concentration for all systems. After evaluating in in vitro systems, it was found that stability depends on certain factors, of which temperature affected the nanoemulsions the most, but the highest antioxidant effect was in curcumin encapsulated in zein. The results of the study showed the advantages and disadvantages of each type of encapsulation, to ease the process of choosing the delivery system of curcumin, depending on the specific application in the food industry (Figure 6).



Figure 6. Types of polymers for the conditioning of curcumin used as an additive in the food industry.

The antifungal properties [42,57] and insecticidal effects [58,123] are capitalized on by using curcumin in the form of natural extracts [42,57], nanocomposites [63,125], or deposited on nanoparticles with metal-organic structures [45,110] to combat a series of pathogens in the process of preserving and preventing fruit and vegetable rot [42,57,62,63] degradation.

Marchi et al. [54] tested the aqueous curcumin extract on inhibiting the growth of the fungal biomass of some types of fungi, Penicillium paneum, Cladosporiumo xysporum, Cladosporium subliforme, and Aspergillus chevalieri, isolated from bread. The results showed that, due to the antifungal activity, curcumin can be used as a food additive, leading to the extension of the shelf life of food [59]. At the same time, curcumin encapsulated in β -cyclodextrin [122] is used in the cheese-making process or encapsulated in sodium alginate [124] for the edible membranes of matured cheeses, without modifying their initial characteristics. For the preservation and extension of the shelf life of meat and fish products, packaging films are used based on gelatin [125], carboxymethylcellulose [126], or vinyl acetate [107], with curcumin as an antimicrobial agent. Curcumin embedded in polyvinyl acetate films has been used to obtain thin coatings with antimicrobial photodynamic activity under white light irradiation. Embedding curcumin in polymer matrices prevents the isomerization processes, increasing the stability and fluorescence lifetime of curcumin. Photodynamic therapy has shown great efficiency, both in vitro and in vivo, in the process of inactivating planktonic cells. This method can be used as a technique in the control of pathogenic microorganisms and biofilm formation, aiming at decreasing the safety risk of food products [42,102,107,127]. The tendencies to increase durability and improve food safety, as well as to reduce food waste, have resulted in the development of different types of smart packaging. These can monitor the quality of packaged products through data carriers, indicators, or built-in sensors [128–130].

Therefore, another property of curcumin, which has found application, is the change in color from yellow to red, as the pH changes from acidic to basic medium. Curcumin has been used as a colorimetric indicator for food packaging [128,131] to detect alkaline compounds produced during food spoilage. Non-woven materials with curcumin made through the electrospinning process have been use for the detection of amines, the main degradation compounds of fish and fishery products. Non-woven materials [128] of polyvinylpyrrolidone (PVP) or ethylcellulose/poly (ethylene oxide) with incorporated curcumin have been exposed to various types of volatile amines. The results showed that, although the loading efficiency with curcumin was lower in the PVP fibers, the detection and quantification limits were higher than in the cellulosic fibers. Intelligent packaging with data carriers (barcode, QR-code) are widespread due to the low cost of production, while packaging with indicators or sensors are uncommon due to the high costs of design and production processes [129,130].

However, to compensate for these disadvantages, active packaging [131–135] has been developed, based on materials with antioxidant [83,132,133], antimicrobial [83,132,133,135], or anti-UV [132,135] properties which protect the packaged products from perishable factors and extend their expiration date. To obtain these packages (Figure 7), cellulose materials were most often used in the form of nanofibers or films, in the composition of which curcumin was integrated (bacterial cellulose-curcumin [131]; carboxymethylcellulose-ZnO-curcumin [133]) or in encapsulated form (cellulose bacterial-protein nanoparticles zein/curcumin [134]; cellulose nanofibers-chitosan-curcumin [135]). The treatment of composite materials with curcumin led to the modification of their physico-chemical structures by improving the elongation properties at break, thermal stability, depending on the concentration and type of curcumin delivery system. At the same time, the antibacterial and antioxidant properties of biocomposites have been improved without changing the properties of the water vapor barrier, which is an important factor for controlling humidity in obtaining an unfavorable environment for the growth and development of mold, yeast, and bacteria. The films based on different polyvinyl polymers in which curcumin was incorporated showed a slight decrease in the properties of the water vapor barrier, but without significantly affecting the other properties. These films have been used to

obtain coatings that show antimicrobial photodynamic activity [107,132]. Depending on the concentration of curcumin and temperature, an antibacterial efficiency of 93% was obtained against *S. aureus* and *Salmonella typhimurium* (*S. typhimurium*) [119]. From the point of view of the natural additives used in the food industry, curcumin is the ideal example due to its antioxidant, antifungal, antiviral, and antibacterial properties. However, its disadvantage, as with most phytochemicals, is its sensitivity to photodegradation and its low solubility in aqueous media. To improve these shortcomings, research is continuing to find curcumin delivery systems that are non-toxic and compatible with the use environments.



Figure 7. The main ingredients of active packaging.

4. Additive for Health Care Products

Curcumin is known in traditional medicine, especially in India, for use in treating fever, skin infections, and to facilitate digestion due to its anti-inflammatory [6–8], antiviral [26–50], and antibacterial [63,117] properties. In the last two years, because of the COVID-19 pandemic, the congestion of hospitals has led to an increased level of nosocomial infections [136–139]. This situation has triggered new approaches regarding the dispersion of biofilm and in finding new ways to prevent the initial formation by modifying the surfaces [64,65] (Figure 8). Therefore, a nanocomposite based on metal oxides [82] or chitosan nanoparticles [127] containing curcumin have been tested. The results of the studies showed that curcumin deposited on copper oxide nanoparticles had higher antimicrobial activity against Gram-positive bacteria compared to Gram-negative bacteria, whereas in vitro tests of curcumin-releasing chitosan nanocomposites showed high activity against mono and polymicrobial biofilms of C. albicans and S. aureus, which can proliferate on medical silicone surfaces. Curcumin loaded on polyvinyl materials [91] or silicone rubber [93,95] used in catheters or cosmetic implants showed high antibiofilm activity. The results of tests performed on S. aureus strains showed antibiofilm activity of 99% at a concentration of 500 μ g/mL of curcumin nanoparticles. The action of limiting bacterial colonization is achieved by the process of complete lysis of the bacterial cells, which has more effective antibiofilm activity than the drug nystatin and has effects comparable to those of chloramphenicol [116].



Figure 8. The main fields of use of curcumin in the medical field and its types of formulations in applications.

Recently, research on the treatment and prevention of dental diseases has made significant progress, especially in treatments involving photodynamic therapy [105]. In this regard, there are many studies with significant results in which curcumin is delivered as microemulsions [106,108,109] or encapsulated as nanoparticles of poly lactic-co-glycolic acid (PLGA) [111], graphene oxide [30], or silver [80]. Composites are used as sensitizers in photodynamic therapy (Figure 4) with antibacterial and antibiofilm effects on several types of bacteria (Enterococcus faecalis (E. faecalis), Streptococcus mutans (S. mutans), Porphyromonas gingivalis (P. gingivalis), and Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)) commonly found in periodontitis, tooth decay in children, or endodontic treatments [69,71,84,85,112–114]. However, the most intense use of curcumin is found in skin treatments. In the past, it was used in poultices and compresses to cure various skin diseases, and as its antioxidant, antifungal, and antibacterial properties were confirmed, curcumin came to the attention of cosmetic manufacturers [140,141]. Subsequently, loading systems [142–149] were developed to increase the skin penetration effect and the photostability of curcumin. Thus, after conditioning, it was introduced in cosmetics as an active ingredient to protect the quality of the skin [59,142,143] and for the treatment of acne, psoriasis, or eczema [140,141]. Furthermore, studies have been directed to the field of the prevention and treatment of chronic wound infections, especially for diabetic patients where the healing process is slow [90]. However, to improve the solubility of curcumin, o/w nanoemulsions stabilized with PLGA [88] or N-oxide [90] have been made, which were tested against several types of strains (C. albicans, E. coli, and S. aureus) and showed antibacterial and antibiofilm activity. Mirzahosseinipour et al. [110] encapsulated curcumin in silica nanoparticles and used it as a sensitizer in antimicrobial PDT against planktonic systems and the biofilm of *P. aeruginosa* and *S. aureus*. The results of in vitro tests demonstrated antimicrobial and antibiofilm activity, without any significant cytotoxic effect of nanocomposites on normal human fibroblasts; while Varaprasad et al. [75] demonstrated the synergistic effect between silver and curcumin by increasing the antimicrobial activity against *E. coli* as carboxymethylcellulose nanocomposite films. Thus, considering the healing properties of curcumin, which is attributed to the presence of myofibroblast and enhancing fibronectin and collagen expression, the study authors developed composites with increased antibacterial efficacy. The results of the study, in vitro, showed 86% inhibition growth for composites loaded with silver nanoparticles and curcumin, compared to other film composites which showed only 25% inhibition growth of E. coli.

The encouraging results of studies on the action of curcumin in skin treatments has led to the development of another field, that of dressings and biomaterials carrying drugs for treating infected wounds (Table 2). Studies have continued to design different types of structures and platforms which allow them to be loaded with drugs or adjuvants to speed up the healing process.

Table 2. Types of composite materials used as a support loaded with curcumin, used in bandages or dressings.

No. crt	Polymer Support	Target Microorganisms/Potential Application	Ref.
1.	chitosan/pluronic membranes	<i>S. aureus, P. aeruginosa</i> / healing applications	[150]
2.	chitosan/polycaprolactone	S. aureus/healing properties	[151]
3.	hyaluronic acid modified pullulan polymers	E. coli, S. aureus/accelerating skin wound healing	[152]
4	lactide-co-glycolide /chitosan/β-cyclodextrin/poly(vinyl alcohol)	blend films	[153,154]
5.	chitosan-collagen, gelatin, sodium alginate	S. aureus, E. coli	[155–157]
6.	polyvinyl pyrrolidone(PVP)-cerium nitrate hexahydrate	<i>S. aureus, E. coli/</i> dressing material-anti-scar property	[156]
7.	cellulose hydroxypropyl-β-cyclodextrin-silver nanoparticle	<i>S. aureus, P. aeruginosa, C. auris</i> /healing properties	[158]
8.	Metal oxides-NPs-cotton	MERSA, S. aureus, E. coli	[159–162]
9.	cellulose-zinc oxide	<i>S. aureus, T. rubrum/</i> skin infection	[161]
10.	graphene oxide	S. aureus, E. coli	[163]
11.	3-methyl-1- (hexadecyloxycarbonylmethyl)imidazolium bromide	hydrogel used for the wound healing	[164]
12.	sodium alginate	wound healing applications	[165]
15.	thiocarbohydrazide gelatin nanofibers	<i>E. coli</i> /wound healing applications	[166]
16.	bacterial nanocellulose	S. aureus, E. coli	[167]
17.	oleic acid based polymeric bandage	wound healing	[168]

Simultaneously, the mechanical properties of resistance, cytotoxicity, absorption capacity, and release of bioactive compounds must be monitored. For this, composites based on curcumin-loaded chitosan have been designed and incorporated into Pluronic [150] or polycaprolactone [151] copolymers that lead to membranes with good thermomechanical properties and sustained release of curcumin. Test results in vitro against *S. aureus* and *P. aeruginosa*, most commonly present in chronic wounds, showed that curcumin retention was higher in the epidermis than in the dermis. Pullulan-type polymers [152] modified with hyaluronic acid have been used to make films with specific properties, to speed up the wound healing process and fight infections. The addition of curcumin to the composition of the films and their testing, in vivo, showed an improvement in biocompatibility, and antibacterial and antioxidant activities.

Another type of film obtained from poly nanofibers (lactide-co-glycolide) loaded with curcumin and heparin have been successfully tested for wound healing in diabetic mice [153]. The polyvinyl alcohol-chitosan-curcumin- β -cyclodextrin films also showed antioxidant activity [154]. The patches of polymeric alginate-chitosan-curcumin [155] or PVP-curcumin cerium nitrate [156] have been tested in vivo, showing antimicrobial activity. These bandages are suitable for use in regenerative therapy because the wounds treated with these dressings healed completely without scars. Moreover, other delivery platforms

have been developed which, based on their structural design, create the possibility of the controlled release of curcumin. These are then loaded on cellulosic fabrics used as dressings.

Naghshineh et al. [157] obtained and studied three types of composites with spongy structure based on chitosan-collagen/gelatin/alginate-curcumin. Depending on the composition of the mixtures, structures with different degrees of porosity were obtained, which had a direct effect on the ability to release curcumin. Based on the histological tests, of the three types of structures, chitosan-gelatin-curcumin released curcumin the fastest, resulting in the greatest healing effect on wounds and the highest antibacterial action. The nanocomposite with alginate had the most porous structure, thus presenting the best results on biodegradation, while the collagen composite was the most stable.

The structures of metal nanoparticles [158,159], metal oxides (Ag, Zn, or Ti) [159–162] or graphene oxide [163], were designed as a delivery platform for curcumin. The synergetic action between them was aimed at increasing the regenerating effects of the skin and antibacterial activity. These structures integrated in bacterial cellulose [158,161] or chitosan [160,162] have been used to develop new types of advanced polymeric materials, such as hydrogel [158,161–164] for bandages with improved wound healing properties in chronic infections [159,165–168].

Curcumin is used in passive drug delivery systems to treat skin lesions caused by sunburn or erythema. For this, it is integrated in thermosensitive microgels [169,170] deposited on cotton fabrics that can be used efficiently for the treatment of lesions caused by ultraviolet radiation [44]. Furthermore, the dyeing of natural fibers or polyester fabrics by using alum-type mordants, metal sulfates, or biomordants can reduce the risk of developing allergies to fixing compounds, leading to textiles that have antimicrobial activity against *Staph aureus, Klebsiella pneumonia, Candida albicans,* and *Salmonella typhimurium*. It has been claimed that in the future, the fabrics will be used in the medical field [22,171], especially designed for a daily breast cancer prevention regimen for healthy women [172].

5. Future Developments of Curcumin-Based Materials

Due to the multitude of properties manifested by curcumin analogs, the diversity of applications of the natural compound will be further developed (Figure 2) as many as the issues related to the extraction, solubility, and stability of the parent compound will be solved. Due to its antioxidant and anti-inflammatory properties, modern applications of curcumin in the medical field targeting the treatment of neurodegenerative diseases [173–176] and cancer [177–184] will be further developed. Furthermore, studies have shown that, as a result of the metabolism process, curcumin can undergo two types of transformation. Consequently, by reducing the double bonds, hydrogenated derivatives, di, tetra, hexa, and octahydrocurcumin can be obtained, or it can be conjugated to the phenolic groups with sulfate moiety or glucuronol moiety [185]. Each of these compounds manifesting greater solubility and improved bioactivity compared to curcumin. In vivo studies by Zhang et al. [186] showed that tetrahydrocurcumin and octahydrocurcumin demonstrated more pronounced anti-inflammatory activity than curcumin. These studies will be continued to evaluate its antioxidant, anti-cancer, and antiseptic properties, and the mechanisms by which they act. Simultaneously, studies have been conducted on the protective activity of curcumin based on its antioxidant properties against the neurotoxicity produced by methamphetamine [187], organophosphorus insecticides [188], and aluminum [189]. In vivo results have shown that the mechanisms of action of curcumin include the prevention of lipid peroxidation and an increase in the antioxidant capacity of the enzymes superoxide dismutase and glutathione peroxidase that protect cells from damage caused by ROS [187].

In the case of neurological diseases, nano-curcumin treatments have been tested in vitro/in vivo and in clinical trials. For the development of targeted therapy in the treatment of neuronal diseases, curcumin was encapsulated in micelles, liposomes, or polymeric nanoparticles. Thus, the efficacy of neuronal membrane penetration and the mechanisms of action of "nano"-curcumin in the treatment of Parkinson's disease [173], Huntington's disease, Alzheimer's disease [21,176], multiple sclerosis, epilepsy, and amyotrophic lateral sclerosis were evaluated [174,175]. Furthermore, curcumin and curcumin nanoparticles have been tested as a protector on indicators of oxidative stress in cardiovascular disease [190–192]. Prathipati et al. evaluated the neuroprotective effects of curcumin-loaded lipid nanoparticles on homocysteine-induced oxidative stress in vascular dementia. In vivo test results showed that 25 mg/kg nano-curcumin demonstrated neuroprotective effects on homocysteine-induced oxidative stress [192].

Studies should be simultaneously continued on the cytotoxicity of nanoparticles, their biodegradation, and the biocompatibility of curcumin delivery systems.

In cancer treatments, curcumin has been approached from several perspectives. It was primarily used as a chemo-protective, reducing the side effects of cytotoxic drugs used in chemotherapy through various mechanisms of reduction, markers of heart damage, or the degree of lipid peroxidation [177–180]. In vivo studies have shown the hepato-protective and nephrological effect of curcumin administered before and during chemotherapy [178]. The second approach is the use of curcumin as an adjuvant with the effect of the chemosensitization of cancer cells resistant to chemotherapeutic agents, through mechanisms of inhibition of the expression of anti-apoptotic proteins or intracellular transcription factors [181]. Thus, the results of studies performed on patients with colorectal cancer refractory to standard chemotherapy established a daily oral dose of 3.6 g curcumin without adverse effects. Encouraging results were obtained after completion of the first stage of clinical trials conducted in patients with breast cancer where the curcumin was used as an adjuvant in combination with the chemotherapeutic agent docetaxel. The final recommendations are that the maximum dose administered should be 6 g/day curcumin [182,183]. To reduce the dose of administration and increase the bioavailability, curcumin was conditioned in the form of nanoparticles, micelles, liposomes, and phospholipid complexes. Thus, curcumin encapsulated in biocompatible polymers or liposomes in combination with chemotherapeutic agents have been tested for breast cancer, cervical cancer, and pancreatic cancer. The results of in vivo tests demonstrated an efficiency of 76-82.5% in inhibiting tumor growth compared to cells treated with individual compounds [182]. Another way in which curcumin has found use in cancer treatments is its use as a photosensitizer in photodynamic therapy to treat skin [193,194], lung [195], prostate [196], breast [197], or cervical cancers [198]. Due to the ability of curcumin to generate reactive oxygen species, the tests in vitro/in vivo have obtained encouraging results for such applications. In vivo/in vitro studies of the delivery of curcumin encapsulated in liposomal structures [193,197] or mesoporous materials [195,199,200] have shown an increase in cytotoxic activity and have suggested the possibility of efficient use of curcumin in lower doses in PDT of cancer.

All these possible applications require further studies on the optimal conditioning conditions to increase the bioactivity of curcumin and the biocompatibility of the delivery systems used.

The use of curcumin in the field of sensors is already known, but research continues in the development of new structures and detection methods depending on its field of use, either in the medical, food [23–25], or environmental protection fields [201]. Its application in the development of nanomaterials for antimicrobial and antibiofilm coatings for multiple surfaces, necessary in both the food and medical fields, will continue to be given special attention. In addition, there are new uses in the application of products with self-cleaning properties [202] or anticorrosive coatings [203]. Developing new composite materials with curcumin has started to be addressed in areas such as solar cellules [204], nonlinear optics [205] applications in robotics, and artificial intelligence [206]. All this research on increasing efficiency in the use of curcumin for various fields is conducted with the vision of developing new eco-technologies, based on sustainable methods and principles.

The use of the natural compound has been preferred in many applications due to its known properties and the cytotoxicity tests performed, which considerably reduces the research time regarding the application of curcumin in certain fields, such as medical and food. However, curcumin-derived structures must also be tested, with some studies showing modified structures that have improved properties over the natural compound [16–20].

6. Conclusions

Out of a desire to use as much of the bioactive potential of curcumin as possible, the compound has known and continues to know various applications. Starting from the most diverse extraction methods to conditioning the compound in the form of (nano)emulsions, (nano)particles, and delivery nanoplatforms, all aim to increase the light stability and water solubility of curcumin. The diversity of composite materials that can be designed, depending on the purpose of use, leave the field of curcumin conditioning open to research. Various biomaterials active from an antibacterial and antibiofilm point of view can be intuited in which curcumin plays the role of an additive that potentiates the activities of other compounds or has synergistic activity with them. However, the way in which nanomaterials can influence human health must be taken into account, given that they can be ingested when used for food preservation, or can cross the cell barrier by penetrating the skin from compounds intended for dermatological treatments. Depending on their location inside the cell, nanoparticles, by specific mechanisms, can damage the cell structure or DNA, eventually causing cell death. To this end, in vivo studies should be performed to have a clearer view of the effects of nanocomposites in terms of their cytotoxicity. Moreover, the use of nanocomposites in packaging products or dressings/bandages should not be neglected in terms of the biodegradability properties or the effects that may result after use when released into the environment.

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