applied sciences

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Review

Curcumin Innovative Delivery Forms: Paving the 'Yellow Brick Road' of Antitumoral Phytotherapy

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Received: 23 November 2020; Accepted: 11 December 2020; Published: 16 December 2020

Abstract: This review deals with the various aspects involved in the medicinal action of curcumin, from the photosensitivity and its relevance to storage and shelf-life, to the different routes of administration, which influence the bioavailability. The focus of the review is on the antitumor properties of curcumin and the currently available solutions for their amelioration. The work starts by presenting a brief historical perspective on the origins and uses of curcumin, from early days until the present time. The following sections describe the physico-chemical properties of curcumin and their impact on the biological activity and pharmacokinetics, raising awareness to the need for formulations able to improve the bioavailability. The last section is focused on research efforts being made to circumvent curcumin's instability and low availability due to the extensive hepatic first pass metabolism, describing innovative scientific advances and new patented formulations and emerging products on the market.

Keywords: cancer chemotherapy; clinical trials; bioavailability; dosage forms; encapsulation; metal complexes

1. Introduction

1.1. Curcumin Overview

The history of curcumin dates back about five thousand years. This strong yellow pigment is the main active component of *Curcuma longa*, a perennial Zingiberaceae plant native to southwest India, but now grown across the South and Southeast Asia, especially in China and India [1–3]. The rhizomes of this plant are dried and powdered to obtain the spice commonly known as turmeric, referenced in Ayurvedic medicine, the characteristic medicinal system of Ancient India, as a home remedy for various diseases [4]. The expansion of the therapeutic use of curcumin to the Western civilizations dates from the time of the Portuguese "State of India", in the XVI century. Garcia de Orta, the physician of the Viceroy of India, mentioned turmeric in his compendium on Indian plants and principles, as "a medicine for jaundice" used widely across Asia [5].

Turmeric dry rhizome is composed mainly of starch, having also, in lesser extent and in varying composition according to geoclimatic factors, carbohydrates, proteins, lipids, fiber, curcuminoid pigments, sesquiterpenes (turmerone, atlantone, zingiberone, turmeronol, germacrone, α-curcumene, β-sesquiphellanderene, bisacurone, curcumenone, dehydrocurdione, procurcumadiol, bis-acumol, curcumenols, zedoaronediol, bisabolene, and curlone), and caffeic acid [6,7]. The curcuminoid content typically varies between 2% and 9%. Curcuminoids are biosynthesized by condensation of malonic acid with cinnamoyl CoA or *p*-coumaroyl CoA. Curcumin is the most abundant curcuminoid in

turmeric, but traces of its precursors, desmethoxycurcumin and bisdemethoxycurcumin (Figure 1), are also present [8]. Curcumin and its analogues can be found in several other *Curcuma* species as well as in a few species from other genera. Sources of curcuminoids include *Curcuma mangga, Curcuma zedoaria, Costus speciosus, Curcuma xanthorrhiza, Curcuma aromatic, Curcuma phaeocaulis, Etlingera elatior,* and *Zingiber cassumunar* [9]. *C. mangga*, commonly named mango ginger, is indicated as a good dietary source of curcumin, but it is still far from reaching the widespread reputation of turmeric as a dietary supplement and functional food.

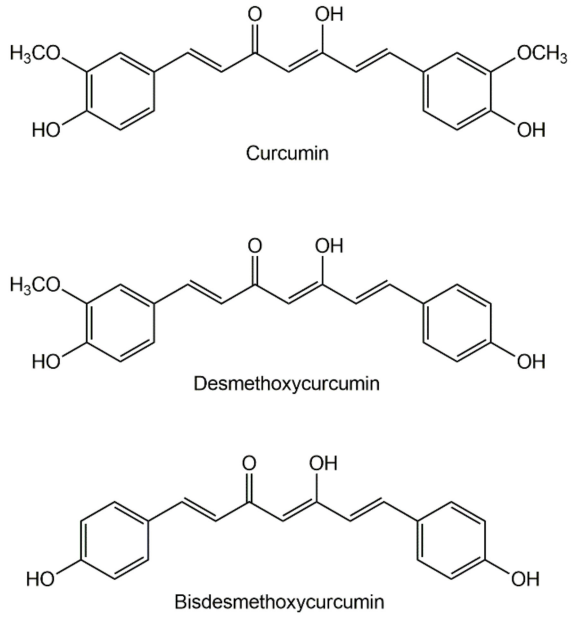

Figure 1. The three main curcuminoids found in *Curcuma longa*.

In western societies, turmeric consumption is a growing trend due to the recognition of its therapeutic properties against inflammation and cancer [10,11]. Turmeric has been granted the GRAS status ('Generally Recognized as Safe') by the FDA [12], with an acceptable daily intake (ADI) limit of 2.5 mg/kg of body weight; for pure curcumin, the ADI is of 0.1 mg/kg weight [13]. The official acknowledgement of turmeric as a safe dietary supplement contributed strongly to its widespread use. Turmeric is, since 2013, the top-ranking herbal supplement in North America, having had, in that year, a most impressive sales growth of 26.2% [14]. The applications of curcumin in commercial products are expanding beyond the field of food supplements and tending to grow into other areas, such as cosmetics. While India is the largest producer of curcumin, North America is the largest curcumin market. Market revenue in 2014 was superior to US$20 million [15]. Future market predictions, from now up to 2022, estimate a shift in the demand towards Europe, with Germany and Denmark expected to grow by 17% and to become the largest market. By 2022, the global curcumin market is predicted to reach $94.3 billion [16].

1.2. The Chemistry of Curcumin

The isolation of the active phytochemicals in turmeric dates back to 1815, when the first crude extract was obtained and described as "a matter of yellow color" [17]. Many of the properties of curcumin could already be observed in this extract: it was insoluble in water, solubilizing upon the addition of alkali to form a reddish-brown solution, and able to react with salts of metals such as lead and tin [17]. The extract was later found to contain a mixture of curcuminoids along with some oils and resins, and only in 1870 was curcumin first purified and isolated in the form of orthorhombic crystals [18]. Its chemical structure was determined in 1910 [19]. Curcumin has the chemical formula $C_{21}H_{20}O_6$ (Mw of 368.38) and it is also referred to as diferuloylmethane, since its IUPAC denomination is quite

long: (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Its chemical structure comprises two aromatic ring systems with *o*-methoxy phenol groups connected by a seven-carbon linker consisting of an α,β-unsaturated β-diketone moiety that exhibits keto-enol tautomerism in solution [20]. Due to extended conjugation, the π electron cloud is distributed all along the molecule and thus curcumin is quite hydrophobic, with a log *p* value of 3.38 and an extremely low solubility in water (1.34 ± 0.02 mg/L) [21]. According to the Biopharmaceutics Classification System (BCS) [22], curcumin is a class IV drug; that is, a compound having low solubility and low permeability. Class IV drugs usually are "not well absorbed over the intestinal mucosa and a high variability [in the absorption profile] is expected".

Curcumin is reasonably stable in water at pH < 7.0 due to structural stabilization by the conjugated diene; in PBS and at pH > 8 it may degrade rapidly (10 min) [2]. In fact, curcumin possesses three ionizable protons with pKa values of approximately 8.5 (enolic proton) and 10–10.5 (two phenolic protons) [23,24].

Curcumin absorbs light from the near ultraviolet (around 340 nm) to the indigo-blue spectral region (450–460 nm), with absorption peaking at 410–430 nm (violet light) [25]. It presents a fluorescence band between 460 and 560 nm. Furthermore, curcumin is sensitive to ultraviolet radiation and its degradation is accelerated by exposure to sunlight [26,27]. When irradiated with light above 400 nm, curcumin undergoes a self-sensitized photo-decomposition where singlet oxygen is involved, but when reactive oxygen species are not available, other decomposition mechanisms are triggered. Photodegradation products include vanillin, vanillic acid, 4-vinyl-guaiacol, ferulic aldehyde, and ferulic acid [28].

2. Biological Actions of Curcumin

Curcumin is indicated in ayurvedic medicine for an enormous variety of pathologies and ailments [29]. Most of this knowledge is, however, empirical, or it has not been demonstrated by studies on human subjects. Most of studies available in the literature have been conducted either in vitro or in animal models (mostly rodents). They provide information on possible therapeutic indications of curcumin for conditions as varied as viral infections, scleroderma, atherosclerosis, myocardial infarction, brain ischemia, and Alzheimer's [30], but such activities may not necessarily be manifested in human patients. Only in the latest decades has evidence from clinical trials been gathered on curcumin. This section presents the most relevant results of clinical trials, with highlight on cancer therapy.

2.1. Medicinal Activity in Humans

Turmeric has well-documented anti-inflammatory [31,32], antioxidant [33–36] and antitumor activities [37–40] that are associated with the extraordinary performance of its main active component, curcumin. Research conducted over the last decades has demonstrated that curcumin is a strongly pleiotropic molecule, able to modulate the activity of numerous signalling biomolecules, to interfere with different cellular and molecular cascades [41,42] and to interact with transcription factors, growth factors or their receptors, nuclear factors, cytokines, and hormone receptors. Curcumin is even able to regulate the expression of genes associated with the processes of cell proliferation and apoptosis [43]. Details on the different biochemical targets of curcumin are given in the Section 2.2. The complexity of mechanisms underlying the action of curcumin allows understanding its efficacy in the treatment of multi-factorial pathologies such as cancer.

2.1.1. Curcumin against Inflammation and Oxidative Stress

Curcumin acts on inflammation at various levels of the arachidonic acid inflammatory cascade, inhibiting the enzymes phospholipase, cyclooxygenase II, and lipo-oxygenase, and having also effects on cytokines [44,45]. Curcumin was shown to reduce post-operative inflammation in patients having had surgical repair of inguinal hernia and/or hydrocele [46], to ameliorate symptoms of chronic inflammation pathologies such as arthritis [47,48], psoriasis [49], and bowel conditions (IBS, Crown's

disease, and ulcerative colitis) [31,50–53] and to treat eye inflammations such as the "idiopathic orbital inflammatory syndrome" [54] and uveitis [55].

The antioxidant activity of curcumin is also the result of a multiplicity of actions. Not only does curcumin stabilize superoxide and hydroxyl free radicals due to the electron-donating properties of its phenolic groups [20,56–58], but it also induces the expression of antioxidant enzymes. In vitro tests with beta cells of human pancreas islets incubated with curcuminoids have shown increased levels of heme oxygenase 1, gamma-glutamyl-cysteine ligase, and NAD(P)H:quinone oxidoreductase and a consequent increase in glutathione levels [59]. Curcumin protects against oxidative stress caused by advanced glycation end products in patients with diabetes, being under evaluation as a new anti-diabetes drug candidate in a series of clinical and pre-clinical studies [60]. It should also be highlighted that the antioxidant benefits of curcumin do not cease with its metabolization, as many of the metabolites present significant antioxidant properties [61].

2.1.2. Antitumoral Action

The first report on the anticancer activity of curcumin, in 1987 [62], rekindled the interest in this compound and brought it to the spotlight of the western society. Curcumin has been the subject of over 30 clinical trials in the context of cancer, some of them still ongoing. This clearly demonstrates its significant chemo-preventive and anticancer potential.

- In colorectal cancer, curcumin was studied for both tumor prevention and chemotherapy. In cancer prevention, it was demonstrated to reduce by 40% the formation of aberrant crypt foci in smoking patients (intake of 4 g/day for one month) [63]. In a combination study, curcumin, and quercetin (1440 + 60 mg/day for six months) were shown to reduce the number and size of polyps in patients with familial adenomatous polyposis, a hereditary disorder characterized by the development of hundreds of colorectal adenomas which turn malign when left untreated [64]. In chemotherapy, 1 g/day curcumin for up to one month (prior to surgical removal of the tumor) was shown to improve the patient's body weight and to increase the apoptosis rates of the patient's tumor cells [65].
- In prostate cancer, a trial has demonstrated that curcumin/flavone association reduces the chances of developing cancer by lowering the levels of prostate-specific antigen (PSA). PSA levels are increased due to the presence of chronic inflammation in the prostate, which is one of the most significant causes of tumorigenesis [66]. Association of curcumin (5.4 g/day for seven days around chemotherapy) with docetaxel/prednisone (75 mg/m^2 + 24 mg, once every three weeks, for six cycles) demonstrated encouraging results, with a tumor objective response in 40% and a PSA response in 59% of the patients in a group having castration-resistant prostate cancer [67]. There is also preliminary evidence on the ability to reduce the formation of metastases. An association of polyphenols (pomegranate seed, green tea, broccoli, and turmeric), taken over six months, has lowered PSA by 63.8% (compared to placebo) in prostatectomized patients [68]. Note that, since these men have no prostate, PSA is produced only by neoplastic cells, thus being a good indicator of metastasis growth. Curcumin can confer radioprotective effect in patients with prostate cancer who undergo radiation therapy, reducing the severity of radiotherapy related urinary symptoms. Patients were given 3 g of curcuminoids per day (corresponding to ca. 2 g/day of curcumin) for one week before the onset of radiotherapy and until completion of radiotherapy [69,70].
- In breast cancer, curcumin was used in co-therapy with both chemotherapeutic agents and radiation. A combination therapy with docetaxel and curcumin (in escalating doses of up to 6 g/day) was found to afford better therapeutic results than docetaxel used alone: histological improvements were observed in the fourteen patients under study, all having reduction or elimination of disseminated foci [71]. Curcumin was evaluated in two clinical trials regarding protective action against radiation-induced dermatitis during radiotherapy of breast cancer patients. Despite promising results on a pilot study, with slightly less severe dermatitis in the

curcumin group, a second trial on 686 patients showed no significant changes in pain, symptoms, and quality of life of the patients taking curcumin (1.5 g daily) in regard to those taking placebo [72].

- Pancreatic cancer, in the advanced stage, is a condition with very poor prognosis. In a phase II study with twenty-one patients taking curcumin (8 g/day for up to 18 months), partial regression was observed during the treatment period; after treatment, patient responses varied, one of them having become stable and another having shown a strong tumor response [73]. Another trial evaluated the association of curcuminoids (8 g/day, corresponding to 6.14 g/day of curcumin) with a gemcitabine-based chemotherapeutic treatment. A total of 21 patients was divided into two groups: one, with 2 patients, received gemcitabine monotherapy; the other, with 19 patients, received a combination therapy of gemcitabine and S-1. S-1 is a novel oral antitumor formula based on fluorouracil, comprising three pharmacological agents: (i) tegafur, a prodrug of 5-fluorouracil, (ii) 5-chloro-2,4-dihydroxypyridine, which inhibits dihydropyrimidine dehydrogenase activity; and (iii) potassium oxonate, which reduces gastrointestinal toxicity was also evaluated. Eighty-one percent of the patients died during the study period. In the surviving patients, the treatment was able to stabilize the disease [74].

2.2. Molecular Targets of Curcumin

Curcumin has an immense range of molecular targets, being proven to interact with transcription factors, growth factors and their receptors, cytokines, enzymes, and genes that regulate cell proliferation and apoptosis, as reviewed elsewhere [75,76]. The various effects are summarized in the Table 1 and described with more detail in the following sub-sections.

2.2.1. Curcumin Modulates the Activity of Transcription Factors

Three main families of transcription factors are involved in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy and radiotherapy. They are:

i. the families of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and of the activated protein-1 (AP-1),
ii. signal transducers and activators of transcription (STAT), and
iii. steroid receptors [77].

NF-kB is involved in cell response to several external agents, including physical strain, oxidative stress (free radicals), and cytokines. NF-kB is usually inactive in the cytoplasm, but once activated by the adequate stimuli it can translocate to the nucleus, inducing expression of apoptosis-suppressing genes to promote cell proliferation and even metastasis. Curcumin was shown to inhibit the activation of the NF-kB pathway by studies in vitro [78] and in vivo [79] and in a phase II clinical trial [80].

AP-1 is involved in the differentiation, proliferation, apoptosis, and oncogenic transformations of the cells [81]. AP-1 can be activated by stimuli of growth factors, cytokines, or bacterial/viral infections. Activated AP-1 induces the expression of several genes that code proteins involved in the angiogenesis and growth of cancer cells, such as cyclin-D1, MMP, and VEGF [82]. Curcumin inhibits this pathway by direct interaction with the AP-1 DNA-binding site, namely in human leukemia cells, transformed keratinocytes and prostate cancer cells [83–87]. The effect of curcumin on the expression of NF-kB and AP-1 members was evaluated in an oral cancer cell line [88]. Nuclear extracts obtained from curcumin-treated cancer cell were evaluated regarding binding of the transcription factors AP-1 and NF-kB, to reveal that binding is reduced in a dose dependent manner and that in cells treated with 100 µM of curcumin, the DNA-binding activities of AP-1 and NF-kB were completely lost. These results confirmed the downregulation of several transcription factors and inhibition of NF-kB and AP-1.

The Janus kinase (JAK) signal transducer of activators of transcription (STAT) pathway signalling pathway is a signaling pathway employed by diverse cytokines, interferons, growth factors, and related molecules, allowing these extracellular factors control gene expression and regulate cell growth and differentiation [89]. In cancer cells, this pathway is consistently active, being involved in metastasis.

Inhibition of the JAK/STAT pathway by curcumin was observed in prostate, lung, and glioblastoma cancer cell lines [90–92]. Curcumin was shown to inhibit STAT3 phosphorylation and to lower levels of interleukin-6 (IL-6), a pro-inflammatory cytokine involved in cell proliferation and survival. Curcumin also exhibited antineoplastic effects in K652 chronic leukemia, ovarian, and endometrial cancer cells by suppression of JAK/STAT signalling [93,94].

Table 1. Molecular targets and cell processes modulated by curcumin.

Family	Molecular Target	Effect	Ref
Transcription factors	NF-kB	↓	[78–80,88,95]
	Nrf2	↑	[96]
	AP-1	↓	[83–88]
	STAT-3	↓	[97,98]
	STAT-5	↓	[99,100]
	β-catenin	↓	[101,102]
	EGR-1	↓	[103,104]
	HIF-1	↓	[105]
	Notch-1	↓	[106]
Growth factors	EGF	↓	[107]
	FGF	↓	[108]
	PDGF	↓	[109]
	TGF-β	↓	[110–114]
	VEGF	↓	[115–117]
Cytokines, pro-inflammatory	TNF-α	↓	[95,118–120]
	IL-1	↓	[121]
	IL-2	↓	[122]
	IL-5	↓	[123]
	IL-6	↓	[118]
	IL-8	↓	[121]
	IL-12	↓	[124]
	IL-18	↓	[125]
Enzymes	COX-2	↓	[72,80,126,127]
	iNOS	↓	[127]
	Lipoxygenase	↓	[128]
	MMP-9	↓	[78,129–131]
Kinases	JNK	↑	[132]
	MAPK	↓	[133]
	PKC	↓	[131]
	Akt	↓	[134]
	CDKs	↓	[135]
Receptors	AR	↓	[86]
	EGFR	↓	[79,119]
Adhesion molecules	ICAM-1	↓	[95]
	VCAM-1	↓	[95]
	ELAM-1	↓	[95]
Antiapoptotic proteins	Bcl-2	↓	[136–140]
	Bcl-xL	↓	[136–138,141]
Proapoptotic proteins	Bax	↑	[136–140]
	Bak	↑	[140]
Others	Cyclin D1	↓	[142,143]
	p53	↑	[144,145]

2.2.2. Curcumin Decreases Tumor Angiogenesis

Curcumin has anti-angiogenic properties by inhibition of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [79]. Several in vitro and in vivo studies have demonstrated the association between the suppression of VEGF expression by curcumin with its inhibitory action on tumor growth [115–117]. In vivo studies in mice showed that VEGF expression and angiogenesis suppression is mediated through suppression of the osteopontin gene expression and the NF-κB/ATF-4 pathway [115].

2.2.3. Curcumin Inhibits Inflammatory Cytokines

Tumor necrosis factor (TNF) and interleukins (IL) are two kinds of inflammatory cytokines with an important mediating role in tumorigenesis. Curcumin was shown to have profound effects on TNF inhibition in dendritic cells, macrophages, monocytes, alveolar macrophages, and endothelial and bone marrow cells [118]. The suppression of the TNF-signalling pathway by curcumin is related to the inhibition of NF-kB phosphorylation, as detailed in 2.2.1 [119,120].

Interleukins (ILs) contribute to tumor invasiveness and angiogenesis by induction of the expression of metalloproteinases, adhesion molecules and STATs [146]. Curcumin inhibits the expression of IL-1 [121], IL-2 [122], IL-5 [123], IL-6 [118], IL-8 [122], IL-12 [124], and IL-18 [125], being thus a potent inhibitor of these classes of cytokines.

2.2.4. Curcumin Regulates the Activity of Enzymes with Roles in Inflammation and Cancer

Pro-inflammatory enzymes are linked with various types of cancer. COX-2 is known to participate in uncontrolled cell proliferation and suppression of apoptosis, while inducible nitric oxide synthase (iNOS) and matrix metalloproteinase-9 (MMP-9) are involved in the formation of metastases [147,148]. Several studies, both in vitro and in vivo, demonstrated that the inhibitory action of curcumin on COX-2 expression contributes significantly to its antitumor action [72,80,126]. Curcumin was also shown to inhibit the expression of MMP-9 in orthotopically implanted pancreatic [129] and ovarian [130] tumors in mice and the production of iNOS in chronic colitis [127].

2.2.5. Curcumin and Cell Cycle Regulation

Programmed cell death, or apoptosis, is a mechanism of vital importance in maintaining normal cell growth. Apoptosis is initiated by regulation of protein 53 (p53) and by proteins of the B-cell lymphoma 2 family (Bcl-2). Activated p53 induces activation of two pro-apoptotic proteins, Bcl-2 homologous antagonist killer (Bak), and Bcl-2 associated x protein (Bax), which in turn release cytochrome c into the cytoplasm to activate the caspase cascade. Curcumin is able to induce apoptosis in prostate cancer PC-3, DU-145, and LNCaP cells via p53-dependent mitochondrial pathways [145]. Activation of p53 by curcumin leads to over-expression of Bak, Bax, and several caspase proteins [136–140]. In addition, curcumin inhibits the activity of a few anti-apoptotic proteins, such as Bcl-2 and B-cell lymphoma extra-large protein (Bcl-XL) [136–141].

Cyclin-dependent kinases (CDKs) are also involved in the life cycle of cells, being in charge of its progression through the different stages [149]. Malignant cells have thus frequent alterations in CDK expression, with overexpression of cyclins and suppression of CDK inhibitors. Curcumin induces cell cycle arrest in colon cancer cells (HTC116 line) by CDK2-dependent effects [135]. The mechanism underlying cell cycle arrest by curcumin may involve overexpression of CDK inhibitors and blockage of the expression of cyclin E and cyclin D1 [142,143].

3. Pharmacokinetics and Bioavailability of Curcumin from Different Administration Routes

Traditionally used as a spice, curcumin is typically taken orally. Nevertheless, this administration route is, most likely, the least effective way to convey curcumin to the human organism, as evidenced by the bioavailability results detailed in the following subsections.

3.1. Oral Administration

Curcumin has extremely poor bioavailability from oral intake, which poses serious limitations to its widespread use as a therapeutic agent. In fact, serum levels following the ingestion of curcumin are so low that a dose-response profile is difficult to establish. When curcumin is taken in low amounts (30 or 180 mg daily), its levels in plasma or urine are null or within the experimental error [150,151], as evidenced by the first two entries in the Table 2. Ingestion of daily doses of 3.6 g caused half of the patients to show serum levels of 11 nM [152], but for higher levels there is not a straightforward dose-response behavior (see also Table 2). Daily doses of 4 or 6 g corresponded to average serum peaks of 510 and 640 nM [153], while daily doses of 10 or 12 g resulted in average serum peaks of 138 nM and 157 nM, respectively [154]. Taken together, the results demonstrate that curcumin has a quite low absorption rate at the intestine, estimated at less than 1%, meaning that most of it is passed through the feces.

The amount of curcumin that does get absorbed is further decreased due to the hepatic first pass metabolism, involving extensive O-conjugation to form curcumin glucuronides (Figure 2) and curcumin sulphate, and bioreduction to tetra-hydrocurcumin, hexahydro-curcumin, octahydrocurcumin, and hexahydrocurcuminol [155,156]. Seric levels of curcumin peak at around 1–2 h after the ingestion, followed by a gradual decline within 12 h [153]. Curcumin and its conjugates are excreted in the urine [156].

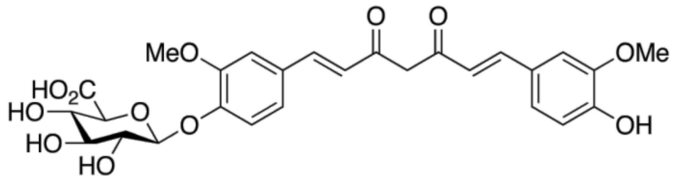

Figure 2. The metabolite curcumin β-D-glucuronide.

Table 2. Reported maximal serum levels (C_{max}) and time (T_{max}) in human subjects after ingestion of different dosages of curcumin.

Daily Dose	C_{max} Mean ± S.D. (nM)	T_{max} (h)	Ref.
0.18 g	n.d. [a]	—	[150]
3.6 g	11.1 ± 0.6	1	[152]
4.0 g	510 ± 110	1.67	[153]
6.0 g	640 ± 60	2	[153]
8.0 g	1770 ± 1870 [b]	1.75	[153]
10.0 g	138 [c]	4	[154]
12.0 g	157 [c]	2	[154]
0.03 g/kg	4.9 ± 7.6	6	[151]
2.0 g/kg	16.3 ± 13.5	1	[157]

[a] n.d. means not detected. [b] The large standard deviation value may be due to the fact that data was collected from only two subjects. [c] No average available because data is from only one subject; no curcumin was detected in the plasma of the remaining subjects.

Some authors claim that serum levels of free curcumin show a deceivingly low bioavailability because a significant fraction of the compound occurs in plasma as glucuronide and sulfate conjugates [72,158]. In the abovementioned clinical study with patients taking 3.6 g of curcumin, serum levels of the conjugates averaged 0.016 μM for curcumin glucuronide and 0.009 for curcumin sulphate [152]. The real therapeutic properties of these metabolites are, however, different from those of curcumin. Curcumin mono- or di-glucuronides have lower anti-inflammatory and anti-proliferative activities [159], and curcumin sulfate inhibits the activity of prostaglandin E2 very poorly when compared with curcumin [160].

3.2. Parenteral Administration

Intravenous (I.V.) injection was one of the first administration routes for curcumin to be tested on human subjects, in the advent of its introduction to Western medicine (the other tested route was oral administration). The studies were conducted by Albert Oppenheimer from 1932 to 1936 [161]. Curcumin, as a sodium salt, was administered in concentrations of 50 mg/mL (5 mL injections, making a total dose of 250 mg) and its emptying effect on the gallbladder was demonstrated by the cholecystograms of the patients. Seric levels of curcumin were not determined in the study and bioavailability in human subjects following intravenous administration of curcumin remains, until the present day, not fully understood. Studies with rats (Table 3) have demonstrated that an I.V. dose of 10 mg/kg of curcumin given affords a maximum serum level of 0.36 µg/mL [162]. For comparison, the authors also conducted oral administration of the same dose in rats and obtained bioavailability values 1800 times lower.

Table 3. Plasma peak levels (C_{max}) in rodents after parenteral administration of curcumin.

Species	Dose	Route	C_{max} Mean ± S.D. (nM)	Ref.
Rat	10 mg/kg	I.V.	977 ± 27	[162]
Mouse	100 mg/kg	I.P.	6107 ± (n.a.)	[163]

Note: I.P. = intraperitoneal, I.V. = intravenous, n.a. = not available (S.D. was not calculated).

It should be noted, however, that serum levels of curcumin in rats and in human are not directly comparable [155], and thus further studies are needed to understand bioavailability from this route.

4. Innovative Curcumin Formulations and High-Performance Delivery Forms

Several curcumin supplements are available in the market [164–168]. These products promise a good availability from oral intake of curcumin, based on different strategies: (i) increasing permeability by formulation with nanoparticles, micelles, or self-emulsifying liposomes; (ii) increasing solubility by micronization or molecular encapsulation with γ-cyclodextrin; and (iii) decreasing metabolization by association with piperine, a substance able to block the metabolic degradation of curcumin. A few oral dosage forms are designed for in situ absorption at the mouth cavity or the colon, easily working around hepatic inactivation. Parenteral and transdermal delivery of curcumin also allow good bioavailability. New formulations in these fields rely on the innovations in micro- and nano-scale carriers.

Further solutions for improving curcumin's biological performance are under research. Many of these involve chemical modifications to afford curcumin prodrugs or metal complexes with superior solubility in aqueous solution and a prolonged stability once inside the human organism.

4.1. Oral Delivery Forms

4.1.1. Marketed Products

There are, at the present day, many curcumin supplements available in the market which promise improved bioavailability when compared with pure curcumin. Albeit these were not specifically developed for (nor tested on) cancer patients, they can still be quite useful for them owing to their claimed superior bioavailability. Optimized for oral delivery, these formulations can offer good systemic action with doses as low as 30 mg/day. Ingestion of such improved formulations is, thus, much more practical than taking pure curcumin, which would theoretically require a patient to have 5–10 g/day, corresponding to 10–20 tablets. The different formulation strategies for curcumin (or curcuminoid mixtures) available from commercial suppliers are systematized in the Table 4 (next page). Many of these products were tested on human subjects, which comprised healthy volunteers in some instances and patients suffering from inflammatory conditions in a few other studies.

Theracurmin is a stable colloidal suspension of curcuminoids formulated as polysaccharide nanoparticles (NPs). It was tested in a dose of 30 mg on seven healthy volunteers, other seven having

30 mg curcumin powder. The nanoparticles were shown to increase the AUC (area under the curve, a measure of the total bioavailability of curcumin over time) by 27-fold (compared to curcuminoid powder), thus pointing to increased bioavailability [151].

In "Biocurcumax", curcumin is dispersed in turmeric oil containing 45% of *ar*-turmerone. This formulation, studied in a group of eight volunteers, showed an absorption maximum after 3 h of ingestion and curcumin levels 5–16-fold higher to those of unformulated curcumin [169]. Blending curcumin with turmeric essential oil is also the strategy used in "Biomor", which is claimed to have bioavailability five times higher than the competitors' brands of bioavailable curcumin (namely those using piperine as an absorption enhancer). The reported plasma peak after the intake of 4 g of "Biomor" is observed at 4 h and has a value of ca. 1.6 μg/mL [14].

In "Meriva", curcumin forms a solid dispersion with "phytosomes" and this blend is dosed in the form of gelatin capsules. Phytosome is the tradename given to liposomes rich in phosphatidylcholine [170,171]. When inside the gastrointestinal (GI) tract, these liposomes facilitate the interaction with biological membranes and increase absorption [171]. Meriva increases the average plasma peak levels of curcumin by roughly five times in male Wistar rats [172]. In humans, it allows lowering daily intake values while keeping a safe and effective action. Two clinical studies with 50 [173] and 100 [174] osteoarthritis patients showed improved mobility upon intake of 200 mg of Meriva curcumin. Liposomal curcumin is also found in several other oral liquid formulations from various manufacturers [175–178].

Molecular encapsulation of curcumin with γ-cyclodextrin affords the inclusion complex denominated as "Cavacurmin", which features increased solubility and bioavailability over pure curcumin. Taken as a dietary supplement (as capsules), Cavacurmin is claimed to be transported unchanged through the stomach into the upper intestinal tract, where it dissociates, and curcumin is absorbed [179]. A study on 12 healthy volunteers taking cavacurmin showed a C_{max} of ca. 190 nM, which is roughly 40-fold higher than pure curcumin.

Micronization of solid curcuminoids to particles with 10 μm average size and blending them with a lipophilic matrix is another simple strategy to improve absorption and achieve sustained release up to 12 h. The product, commercially available as MicroActive® Curcumin, was tested on three healthy volunteers, affording a ten-fold absorption increase [167].

Combination therapy allies curcumin with piperine to address losses in activity caused by glucuronidation, one of the major metabolic pathways responsible for the low oral bioavailability of curcumin. The alkaloid piperine (1-piperoylpiperidine) is one of the major active components of the pepper plants *Piper nigra* and *Piper longa*, known to act as a bioavailability enhancer for a variety of drugs by inhibiting glucuronidation both in the liver and in the small intestine [180]. A comparative study with healthy volunteers taking 2 g/kg curcumin, either alone or in combination with 20 mg/kg of piperine, has shown a 20-fold curcumin bioavailability enhancement for the combined therapy, as well as an earlier plasma peak (T_{max} of 40 min vs. T_{max} of 60 min for curcumin alone) [181].

Table 4. Curcumin oral dosage formulations currently available in the market.

Trade Name	Formulation Strategy	Dosage Form	Product Composition	Ref.
CurcuminRich	Colloidal NP w/curcuminoids (theracurmin)	30 mg capsules	Theracurmin: polysacharide NPs loaded with curcuminoids Excipients: MCC, magnesium stearate, silica	[151]
Biocurcumax	Curcuminoids w/turmeric essential oil	350 mg capsules	Curcuminoids (titrated 95% curcumin) Excipients: Maltodextrin, magnesium stearate, HPMC	[164]
Biomor	Curcuminoids w/turmeric essential oil	500 mg capsules	Curcuminoids (titrated 95% curcumin) in a vegetable capsule	[14]

Table 4. *Cont.*

Trade Name	Formulation Strategy	Dosage Form	Product Composition	Ref.
Cavacurmin	Cyclodextrin inclusion complex w/curcumin	Dry powder	Cavacurmin: curcumin, γ-cyclodextrin	[179]
Meriva	Liposome	500 mg capsules (100 mg curcumin)	Liposome: Turmeric root extract, phosphatidylcholine, phospholipids Excipients: HPMC, leucine, silicon dioxide and MCC	[165]
Liposomal curcumin mango	Liposome	Liquid, 20 g/L	Liposome: curcumin, phospholipids from sunflower Excipients: water, xylitol, mango aroma, ascorbic acid, Preservative: seabuckthorn extract	[177]
Liposomal curcumin	Liposome	Liquid, 41.7 g/L	Liposome: Turmetic root extract, phospholipids from sunflower Excipients: water, glucosylsteviosides, flavors, glycerin, xanthan/acacia gums Preservative: potassium sorbate	[178]
Dr. Mercola Curcumin Advanced	Micronized curcuminoids (microactive)	500 mg capsules	Micronized curcumin Excipients: HPMC, MCC, polyglycerol oleate, silicon dioxide, metolose, medium chain triglycerides and sodium alginate	[167]
Curcumin C^3 Complex	Combined therapy of curcuminoids & piperidine	500 + 5 mg capsules	Complex: Turmeric root extract (73% curcumin), piperine Excipients: rice flour, cellulose and ascorbyl palmitate	[166,168]

Abbreviations: HPMC = hydroxypropylmethylcelluloce, MCC = microcrystalline cellulose; NP = nanoparticle.

4.1.2. Emerging Solutions for Oral Delivery

Curcumin availability from oral delivery can be increased by directing absorption towards specific sites of the GI tract. The incorporation of curcumin into self-micro-emulsion-based capsules is claimed to make the absorption occur only at the colon and to increase absorbability [182]. A gastro-resistant liposome carrier for curcumin is also reported, allowing higher accumulation of curcumin along the intestinal track, particularly at the duodenum [183]. Encapsulation of curcumin into nanoparticles made from fibroin, a silk protein, followed by dispersion into a carrier such as chitosan, is claimed to provide a non-toxic formulation for cancer therapy that can be adapted to oral administration or to other administration routes (by changing the dispersive medium) [184].

4.1.3. Buccal Delivery

Absorption of curcumin in the buccal cavity allows good availability for local action and it has been proposed as a suitable strategy to treat a rare variety of cancer occurring in the mouth, squamous-cell carcinoma of the salivary glands. It is, in fact, an excellent target for local treatment with curcumin. This action was demonstrated in patients treated with chewable tablets of curcumin, which evidenced lower activity of the pro-inflammatory enzymes (IKKβ kinases) in salivary cells [185].

4.2. New Injectable forms of Curcumin

Injectable forms of curcumin are, to the best of our knowledge, currently unavailable in the market. Several parenteral formulations of curcumin are described, including the proprietary formulations named "Lipocurc" and "NanoCurc", but these are still not approved by the FDA. Lipocurc is a liposomal formulation for curcumin [186] with 100 nm mean particle size. It exhibited excellent in vitro antiproliferative activity against several pancreas cancer cell lines (ASPC-1, BxPC-3, Capan-1, Hs766-T, and MiaPaCa2), with half-maximal inhibitory concentration (IC_{50}) values within 2–7 μM, as well as tumor-reducing and anti-angiogenic effects in mice xenografted with human pancreas carcinoma (BxPC-3 and MiaPaCa2) [187]. Clinical trials (phases 1a and 1b) with Lipocurc in 70 human subjects showed no cardiac toxicity and signs of efficacy in end-stage cancer patients who had failed 6–7 prior chemotherapy regimens; results of phase 2 trials should be available soon [188]. Another claimed

application of intravenous liposomal curcumin is in the treatment of neurodegenerative and stress disorders, according to a patent filed in 2011 [189].

Nanocurc is a polymeric nanoparticle formulation of curcumin. The nanoparticles have an average size of 50 nm, being thus smaller than the aforementioned liposomes. They are obtained from the micellar aggregates of cross-linked, random co-polymers of N-isopropylacrylamide (NIPAAM), with N-vinyl-2-pyrrolidone (VP) and poly(ethyleneglycol)-monoacrylate (PEG-A) [190]. Nanocurc showed sustained plasma concentrations of curcumin with T_{max} of 2.75 ± 1.50 h and C_{max} of 46.62 ± 14.05 μM and a good inhibitory effect on Pa03C (human pancreatic cancer) xenografts in mice [191]. It is able to cross the blood-brain barrier [192], which may be useful in addressing brain tumors.

Curcumin-loaded biodegradable micellar nanoparticles based on a co-polymer of PEG and poly(ε-caprolactone) were developed for the treatment of colon cancer [193,194]. These particles have an average size around 28 nm, being even smaller than those of Nanocurc (described above). In vitro studies showed their direct cytotoxic effect on murine colon carcinoma cells (CT26 line) and in vivo studies on xenograft mice further confirmed the anticancer effect, associated with anti-angiogenesis. The therapeutic action and improved pharmacokinetics of curcumin carried by these micelles makes this system an excellent intravenously injectable aqueous formulation of curcumin, one that has potential clinical application in colon cancer therapy.

PLGA was also used to encapsulate curcumin, both in the form of injectable microparticles [195] and of nanoparticles [196]. The curcumin microparticles had an average diameter around 22 μm and featured sustained release properties over four weeks (in mice), inhibiting the growth of human breast cancer cells (MDA-MB-231 line), both in vitro and in vivo in xenograft mice treated by intraperitoneal injection. It should be stressed, however, that PLGA microparticles cause acidity and inflammatory response at the site of injection due to partial degradation to lactic and glycolic acids, even though the inflammation is attenuated by the anti-inflammatory properties of curcumin.

Carrier-free injectable curcumin can also be prepared by a simple process of nanocrystalization. A nanocrystalline suspension (NS) containing only the nano-sized crystals of the active ingredient and minimal amounts of stabilizer (usually a surfactant or polymer), is thus a carrier-free system and an excellent method to formulate BSC class IV drugs such as curcumin [197]. Curcumin NS was produced by high-pressure homogenization and it showed solubility values for curcumin increased by over 600-fold, having lower vascular irritability and hemolytic effect in rabbits [198]. In vitro tests against HeLa (cervix epithelial cancer) and MCF-7 (breast cancer) human cell lines showed good inhibitory action, with IC_{50} values around 50 and 35 μM, respectively.

4.3. Inhalable Curcumin Formulations

4.3.1. Dry Powder Inhaler for Pulmonary Delivery

Curcumin delivery by absorption through the pulmonary region aims at achieving high bioavailability with reduced side effects. Curcumin inhalable powders were obtained using carbon dioxide as anti-solvent and polyvinylpyrrolidone and hydroxypropyl-β-cyclodextrin (HPβCD) as excipients [199]. The particles presented good aerodynamic properties and cytotoxicity against the H1299 human non-small cell lung carcinoma line, with an IC_{50} of 17 μM, but also some toxicity on normal lung cells of the MRC-5 line (IC_{50} of 29 μM).

4.3.2. Intranasal Aerosol for Delivery to the Brain

Delivery of curcumin to the brain through the olfactory pathway by means of an inhalable aerosol was proposed as an alternative to injectable formulations. For this, curcumin had to be modified to be sufficiently hydrophilic to traverse blood circulation while maintaining the lipophilicity that allows it to cross the blood–brain barrier (BBB) [200]. The study involved a perfluoro derivative of curcumin (for fluorescence imaging) dissolved in PBS/Tween 20 (1:6 ratio) and atomized by a cross-flow apparatus. Intranasal exposure in mice showed that distribution to the brain (cortex, hippocampus,

and thalamus areas) was achieved, but it also revealed the presence of the compound in major organs such as the lungs, kidney, and liver.

4.4. Transdermal Administration

4.4.1. Curcumin Topical Formulations with Liposomes, Microemulsions, and Polymeric Nanoparticles

The delivery of curcumin across the skin is of enormous interest not only to the cosmetic industry, due to its anti-inflammatory and rejuvenating properties [201], but also in skin cancer prevention, as demonstrated by various studies with skin cancer models [202–206]. In transdermal delivery formulations of curcumin, the liposome strategy is fine-tuned to afford liposome variants such as the "ethosomes", containing ethanol to convey flexibility and to act as permeability enhancer [207,208], the propylene glycol liposomes (PegLs), also quite flexible but without the volatility issues associated with ethanol [209] and the "invasomes", containing a small number of terpenes (0.5 to 1.5%). Terpenes are known to increase diffusivity and partitioning into the skin by disturbing its lipid bilayers [210]. A study comparing PegLs, ethosomes and plain liposomes for curcumin delivery to the skin showed that the PegLs were the best formulation, with superior results in the curcumin loading ability (ca. 93%), the transdermal delivery ratio and curcumin local action, followed by ethosomes and lastly by plain liposomes [211]. Curcumin invasomes were prepared using different terpenes (limonene, fenchone, or neradinol) and HPβCD, to assure a high loading (90%) and tested with an ex vivo skin model (from rat abdominal skin), showing that limonene was the most adequate enhancer for the permeation of curcumin [211]. Formulations containing high amounts of terpenes formed microemulsions due to the oily nature of these compounds. The performance of curcumin microemulsions having 5% or more of limonene, 1,2-cineole or α-terpineol was studied on skin excised from neonate pigs [212]. Once more, limonene proved to be the most adequate penetration enhancer for curcumin.

Another strategy for increasing skin permeability of liposomes is to coat their surface with cell-penetrating peptides (CPPs) by means of a conjugation reaction. CPPs are short peptides, generally not exceeding 30 residues, having both the capacity to ubiquitously cross cellular membranes and very limited toxicity. In comparison with permeation of pure curcumin, CPP-coated liposomes carrying curcumin were able to increase the permeation efficacy by 7-fold, whereas the same liposomes without coating only afforded a 2-fold increase. Distribution and deposition of curcumin following its release from the carriers on mouse skin was also studied. CPP-coated liposomes afforded the highest curcumin content in both dermis and epidermis layers (7.0 and 3.5 μg respectively), followed by conventional liposomes and curcumin solution only (Figure 3). The liposomes coated with CPP are thus a good solution for delivering curcumin in high amounts and helping it reach the deep layers of the skin [213].

Curcumin nanogels for transdermal delivery are also reported. Developed from chitin particles with an average size of 70–80 nm, nanogels offer a good transdermal delivery capacity and the promise of a simple topic formulation for the treatment of melanoma [214]. In vitro studies have demonstrated specific inhibition of the growth of human melanoma cells (A375) with low activity against the non-tumoral human dermal fibroblast cell line (HDF).

4.4.2. Dermal Compositions Containing Silver and Curcumin for Combined Therapy

Combining the activity of curcumin with another cytotoxic agent creates opportunity for more effective treatment of skin pathologies, whether these are the result of infection by bacterial microorganisms or of the uncontrolled growth of the body's skin cancer cells.

Silver-doped hydrogels were tested as vehicles for skin delivery of curcumin and demonstrated good results in vitro, with loading efficiencies up to 80% and in vitro release higher than 70% after 160 h. Furthermore, the curcumin–silver hydrogel demonstrated a cumulative antibacterial action against *Escherichia coli*, being thus a promising new cytotoxic agent that may also be tested for cancer treatment [215]. Typically used as antimicrobial, silver has demonstrated antitumoral activity in various studies. Colloidal silver inhibits in vitro growth of MCF-7 breast cancer cells at concentrations

> 1 nM [216] and in vivo Dalton's lymphoma and lymphosarcoma xenografts were inhibited by nanoparticles of silver [217] and silver oxide [218], respectively.

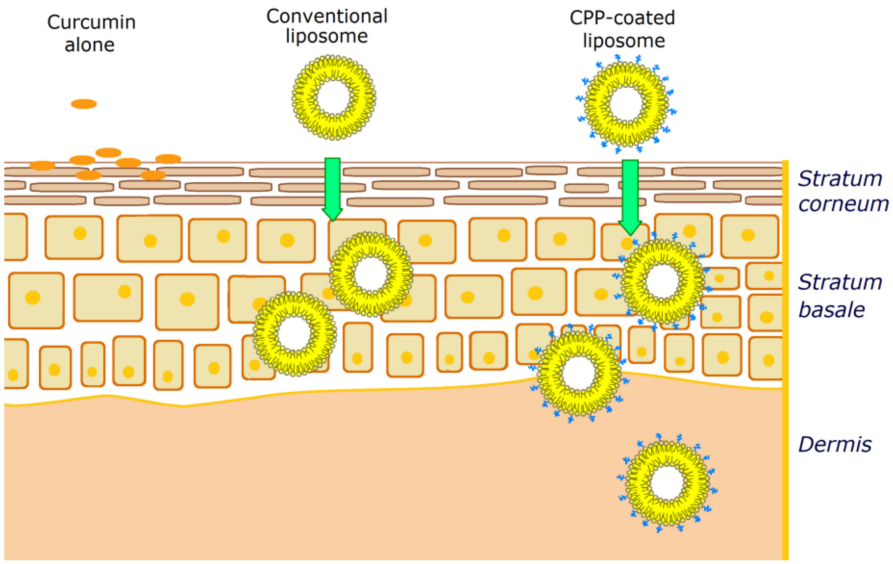

Figure 3. Comparison of the skin penetration rate of curcumin (without any carrier) and curcumin loaded into two different carriers: conventional liposomes and cell-penetrating peptides (CPP)-coated liposomes. Drawn with base on the data reported by Patra et al. [213].

4.4.3. Iontophoresis Techniques

Iontophoresis facilitates the migration of charged compounds across a skin area which is subject to a low-intensity continuous electrical current. The administration of charged curcuminoids by this procedure was first patented in 2009 as a therapy for Alzheimer's disease [219]. Another study aimed at developing a new breast cancer treatment by formulating curcumin into liposomes and promoting their transdermal migration by iontophoresis [220]. In vitro skin permeation studies on newborn pig skin showed that iontophoresis allowed for the permeation of a cumulative amount and flux of liposomes. The cytotoxic action of the curcumin-loaded liposomes was demonstrated by incubation with different cultured lines of breast cancer cells (MCF-7, MDA-MB-231, and MDA-MB-435S), IC_{50} values ranging from 15 to 20 μM.

4.4.4. Photodynamic Therapy for Increased Antitumoral Action on Skin

Curcumin can also be used as a photosensitizer for photodynamic therapy of tumors (PDT) [221]. It was already demonstrated that curcumin in the presence of oxygen can be photocytotoxic against mammalian cells [222,223]. When irradiated by light, curcumin produces reactive oxygen species (ROS), such as singlet oxygen and reduced forms of molecular oxygen, as well as carbon-centered radicals [222]. Indeed, some reports have shown that the combination of curcumin with light increases significantly the antitumoral action of curcumin, particularly at very short incubation times (1–2 h) [224,225]. On HeLa cells curcumin exhibited IC_{50} values of 85.4 μM in the dark and of 8.2 μM under irradiation [225]. Similar situation was reported by Verena et al. using four epithelial liver tumor cells lines (HuH6, HepT1, HepG2, and HC-AFW1), for which the IC_{50} values diminished 9–26 times under blue light irradiation, varying slightly according to the cell density used, but being always significantly lower than those measured under dark conditions [224]. In addition to curcumin, other curcuminoids may be used as photosensitizers, namely, desmethoxycurcumin and bisdesmethoxycurcumin. On the MDA-MB-231 (breast cancer) line, desmethoxycurcumin had IC_{50} values of 4 μM and 33 μM under blue light and dark conditions, respectively [226]. Increased growth inhibitory action was observed in human head and neck cancer cells (AMC-HN3) following a photofrin-PDT treatment combined with

curcumin, which was postulated to result from mitochondrial-dependent apoptosis due to increased ROS generation [227].

4.5. Curcumin Prodrugs and Metal Complexes

Curcumin metabolization occurs, as described in Section 2.2.1., mainly by conjugation at its phenolic hydroxyl groups. This way, curcumin is often functionalized at these two positions to form derivatives with improved physico-chemical, biological, and pharmacokinetic properties [228,229]. A useful strategy is to design curcumin prodrugs that are able to prevent metabolization. This is achieved by protecting the hydroxyls with functional groups such as amino acids, small carboxylic acids [230–232] and even nucleotides [233]. The prodrugs curcumin maleoyl valinate and curcumin maleoyl glycinate were tested against human bladder cancer EJ cells, having shown dose- and time-dependent inhibition [231]. The toxic side effects on healthy human renal proximal cells (HKC) were considerably lower in comparison with pure curcumin. Succinate prodrugs of curcumin with good cytotoxicity against colon adenocarcinoma (Caco-2 cell line) were also reported, with highlight to curcumin diethyl disuccinate, having an IC_{50} of 1.9 μM [232]. Conjugation of curcumin with an oligonucleotidic chain complementary to a sequence of telomerase RNA allows targeting this specific cellular function [234]. Human prostrate tumor cells (DU145) were transfected with this 5′-*O*-curcumin DNA prodrug but the antiproliferative action was very slow (20% cell survival after 75 days).

Another class or curcumin prodrugs comprises nanocarriers. These are obtained by functionalizing the phenolic hydroxyls with oligomers or polymers using linkers that are hydrolyzed in vivo by enzymes or pH [235–237]. The prodrugs aggregate into nanoparticles, forming a carrier system. Curcumin oligo(ethylene glycol) nanoparticles were shown to reduce the size of intraperitoneal SKOV-3 tumors and subcutaneous (mammary fat pad) MDA-MB-468 tumors in xenografted mice [235]. Additionally, nanocarriers made of biocompatible aluminosilicate clays were reported [238]. These materials are named halloysite nanotubes due to their hollow tubular structure. Curcumin is linked to them by a cysteamine arm, hydrolysable at the disulfide bond. This carrier system can thus be considered a prodrug. In vitro studies with two hepatic carcinoma cell lines showed good cytotoxic activity. At 48 h and using a dose of 50 μM, cell viability rates were low, 22% and 16% for Hep3B and HA22T/VGH, respectively, and at the dose of 100 μM zero viability for the Hep3B line was observed (also after 48 h).

Curcumin coordination to a metal center brings advantages to the solubility and stability (both redox and to light). This is very helpful for the biological activity, and positive results have been reported in a varied range of actions, not only with antitumor compounds, but also with reports of better antioxidant and anti-inflammatory agents and even of new complexes to be used in the treatment of Alzheimer's disease [239].

The preparation of metal complexes with curcumin typically involves deprotonating curcumin in a first step to form a stable enol form [240]; then, an appropriate molar ratio of curcuminate is made react with a metal precursor. Suitable precursors include halogenates of zinc(II) [241–244], calcium(II) [244] and iron(III) [244,245], acetates of copper(II) [246,247], palladium(II) [248] and nickel(II), or vanadyl bis(acetylacetonate), $VO(acac)_2$ [249]. The $VO(curcuminate)_2$ complex was very successful in inhibiting mouse lymphoma cells (L1210), with an IC_{50} of ca. 15 μM. It was, however, also toxic towards rat smooth muscle cells (CRL-1444), with an IC_{50} of 2.9 μM [249]. Curcumin zinc complexes with dinonyl-2,2′-bipyridine (bpy-9) and 4,4′-bis(hydroxymethyl)-2,2′-bipyridine as the spectator ligands presented good inhibitory action on the prostate cancer cell lines DU145, PC3, and LNCaP, and the neuroblastoma SHSY-5Y and SD LAN-5 lines, with IC_{50} values in the 12–37 μM range at 72 h [242]. [(bpy-9)Zn(curcumin)]BF_4, a cationic derivative, was also very active against the SH-SY5Y neuroblastoma cell line [243]. A palladium analogue, [(bpy-9)Zn(curcumin)]CF_3SO_3, was tested successfully on prostate cancer cells (LNCaP, PC3, and DU145) having IC_{50} values in the 20–24 μM range [248]. Curcumin palladium complexes bearing cyclohexane-diamine derivatives as the spectator ligand were developed for colon cancer treatment, having IC_{50} values in the 10–34 μM range against the cell lines DLD-1, HT-29 and CRL-1790 [250].

Curcumin ruthenium(II) organometallic complexes obtained from precursors that share a common "piano-stool" geometry are represented in Figure 4 [251–253].

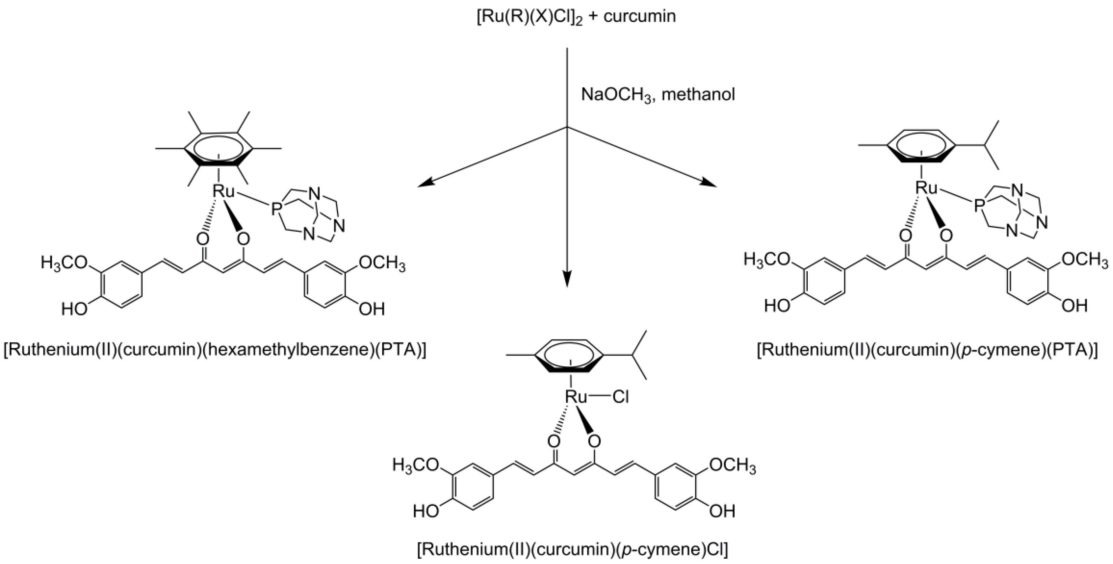

Figure 4. Synthesis and structure Ru(II) arene curcumin complexes, with R = hexamethylbenzene or *p*-cymene, and X = Cl or 1,3,5-triaza-7-phospha-adamantane (PTA).

The arene that comprises the "top" of the piano stool was either a hexamethylbenzene or a *p*-cymene. Curcumin coordinated at the positions of two of the legs and the third leg was a chloride, in some instances replaced by 1,3,5-triaza-7-phospha-adamantane (PTA) for higher aqueous solubility. The complexes with PTA displayed the most promising activities, being able to inhibit the growth of breast cancer A2780 cells (both cisplatin-sensitive and cisplatin-resistant lines) at sub-micromolar concentrations [251]. Their IC_{50} on these cell lines were 0.4 μM, approximately ten times lower than pure curcumin (IC_{50} = 4.3 μM). Safety was evaluated on a healthy embryonic kidney cell line, HEK293. Ru(hexamethylbenzene)(curcumin)(PTA) had an IC_{50} value of 4.3 μM against this cell line while for Ru(*p*-cymene)(curcumin)(PTA) IC_{50} was 9.1 μM [251]. The activity of Ru(*p*-cymene)(curcumin)Cl was inferior or equal to that of curcumin on the tested cancer cell lines [252].

Analogues of curcumin arene complexes can be obtained by replacing the arene with the heterocyclic moiety of 1,4,7-tritiacyclononane (abbreviated as [9]ansS_3), to afford complexes with higher polarity and thus better compatibility with aqueous media. The complex [Ruthenium(II)(curcumin([9]aneS_3)DMSO]Cl was reported as a strong DNA-binding agent, with higher affinity than pure curcumin [254]. Cytotoxicity against the PC-3 prostate cancer cell line was, however, not observed at concentrations as high as 80 mM. This suggests that cell-penetrating abilities of the complex need to be ameliorated.

Two ruthenium polypyridyl complexes with curcumin, with the formulae [Ruthenium(II)(curcumin)(bpy)(N,N'-Lig)]Cl, where N,N'-Lig = 2,2'bipyridine (bpy) or dppn (benzo-[i]dipyrido[3,2-a:2',3'-c]phenazine), were recently reported [255]. Despite being cationic, the complexes were lipophylic, with log *p* values of 0.75 for the one with two bipyridines and 1.06 for the one with dppn. The in vitro inhibitory activity was evaluated on the A549 human non-small-cell lung cancer line, the MCF-7 human breast adenocarcinoma cell line and the SGC7901 human gastric cancer cell line, with the dppn-bearing complex having exhibited higher activity: IC_{50} values were within the 2.1 ± 0.2 to 2.7 ± 0.2 μM range. Compared to curcumin and cisplatin, which inhibited the same cell lines with IC_{50} values of 11.4 ± 0.3 to 15.4 ± 1.0, the complex is quite more potent. Additional biomolecular studies on the A549 line have shown that the mode of action of the complexes involves apoptosis.

5. Conclusions

The present review presents a concise description on the history of curcumin as a therapeutic agent. From the digestive and choleretic aid in the past centuries to the exciting antitumoral new agent which attracts the interest and hope of both patients and scientist of the present day, curcumin has been a constant and much appreciated herbal medicine for mankind. As the pharmacokinetics of curcumin became more well-known, its low bioavailability was evidenced. Since then, many efforts to circumvent it were undertaken. Fruitful results are substantiated by the large number of curcumin-based supplements on the market, eight of which are formulated to assure a superior bioavailability (Table 4), and by the countless oral, injectable, intranasal, inhalable, and dermal formulations which are either pending approval or at the R&D stage.

Future directions along this yellow-brick road will need to address the long-term safety of curcumin, a sine-qua-non-requirement to assure its approval as a drug that is safe for the treatment of oncologic and other diseases, be it ingested, administered parenterally or topically or even implanted, to treat bone cancer [256]. Regarding long-term exposure associated with, thus far only a study in animals raised a slight warning, which involved possible iron deficiency [257]. It is our opinion that the large number of people presently incorporating curcumin supplements into their daily dietary routine will contribute to produce reports and feedback that will serve as a natural database of information of curcumin tolerability and safety. This way, the knowledge of curcumin long-term safety is expected to expand tremendously in the years to come, hopefully dissipating concerns and helping to establish it as a recognized therapy for cancer.

Author Contributions: Conceptualization, M.C.H., M.A.F.F. and S.S.B.; writing—original draft preparation, M.H.C., and S.S.B.; writing—review and editing, M.C.H., M.A.F.F. and S.S.B. All authors have read and agreed to the published version of the manuscript.

Funding: The authors acknowledge the University of Aveiro and FCT/MCTES (Fundação para a Ciência e a Tecnologia, Ministério da Ciência, Tecnologia e Ensino Superior) through national funds and, where applicable, co-financed by the FEDER (European Fund for Regional Development) within the PT2020 Partnership Agreement, for general financial support to LAQV-REQUIMTE (UIDB/50006/2020).

Conflicts of Interest: The authors declare no conflict of interest.

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