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Review

# Therapeutic potential and limitations of curcumin as antimetastatic agent

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ABSTRACT

Treatment of metastatic cancer is one of the biggest challenges in anticancer therapy. Curcumin is interesting nature polyphenolic compound with unique biological and medicinal effects, including repression of metastases. High impact studies imply that curcumin can modulate the immune system, independently target various metastatic signalling pathways, and repress migration and invasiveness of cancer cells. This review discusses the potential of curcumin as an antimetastatic agent and describes potential mechanisms of its antimetastatic activity. In addition, possible strategies (curcumin formulation, optimization of the method of administration and modification of its structure motif) to overcome its limitation such as low solubility and bioactivity are also presented. These strategies are discussed in the context of clinical trials and relevant biological studies.

## 1. Introduction

Treatment of metastases is a major challenge in cancer therapy. It was proved that most deaths in oncology patients are not caused by the primary tumours but by their metastasis [1]. Nevertheless, therapeutic strategy of classical neoadjuvant therapeutic regimens is primarily focused on the reduction of tumour mass by using cytostatic drugs and less focused on the repression of metastasis [2]. In the present time, a new therapeutic method that targets metastasis formation via the use of migrastatic drugs (inhibitors of cell migration) instead of reducing the tumour mass are intensively studied and developed [3,4]. In the case of nonmetastatic castration-resistant prostate cancer, some androgen receptor inhibitors (e.g., apalutamide, enzalutamide, and darolutamide) can delay metastases formation [5]. Besides, the application of some therapeutic agents such as tyrosine kinase inhibitors and immuno-checkpoint inhibitors or inhibitors of IL-6 signalling could be used for the metastasis suppression. [6–9] Gkountela et al. published that $Na^+/K^+$ ATPase inhibitors ouabain and digitoxin (FDA approved agents) induce dissociation of circulating tumour cell (CTC) clusters into single cells and thereby repress metastatic formation [10]. After entry into the bloodstream, CTCs (known as inherent metastatic factors) can infiltrate healthy tissues that are distant from the tumour [11]. Nevertheless, CTC clusters display metastatic potential of 20- to 100-fold greater metastatic potential than single CTCs [12–14]. Other possible targets of migrastatic agents are mechanisms of cell mobility (e.g., cytoskeletal dynamics and cell contractility) and energy provisions (e.g., ATP availability, mitochondrial metabolism) [15].

However, oncological diseases display high heterogeneity and oncogenic signalling pathways, or factors are at least partially substitutability in the metastasis formation [16,17]. Which both lead to a loss of response to the therapy. However, high impact works suggest, that multifunctional agents have a better chance of avoiding the development of resistance than focusing on the single molecular target [18–21].

Curcumin (polyphenol product turmeric from Curcumin longa) [22] and other natural and synthetic curcuminoids display many antitumour and antimetastatic effects. Structure of curcumin and other natural turmeric curcuminoids with similar anticancer effects is showed on the Fig. 1.

Curcumin targets activity/expression of oncogenic signalling pathways and factors (e.g., NF-κB, EGFR, PI3K/Akt/mTOR, Wnt/β-catenin,

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JAK/STAT-3, Hedgehog and Hippo signalling pathways, MAPK, AR, IL-6, IL-8, TNF-α, IL-1β, VEGF) [23–28]. It was proved, that curcumin application decreases migration and invasiveness of cancer cells, quantity of stem cancer cells, angiogenesis, recruitment and functionality of tumour associated cells, tumour development and metastatic activity. Its possible effect on the tumour growth and development are showed on the Fig. 2.

The clinical potential of curcumin is shortly introduced below. Section 2 summarizes results from in vitro and in vivo studies of curcumin with emphasis on its antimetastatic effects. Section 3 discusses possible approaches used in the curcumin formulation with emphasis on clinical trials. Section 4 is focused on the usability of the various strategies of curcumin administration such as oral, inhalation and intratumoural routes. Section 5 summarizes limitations of curcumin application and provides possible solutions to overcome them. Section 6 introduces studied strategies for improvement of curcumin antimetastatic efficacy (e.g., advanced nanoformulation and structural derivatization) and discusses its possible effect on the intratumoural microbiota.

In clinical trials, it was observed that curcumin induces the conversion of Treg cells into Th1 cells and increases IFN-γ level [29,30]. In oncological patients, Treg cell levels can be correlated with the abundance of CTCs, and higher CD8 + T cell and IFN-γ levels can induce a decrease in CTC count [31,32]. The application of curcumin in combination with other nutrients (garlic, green tea, grape seed extract, modified citrus pectin, and medicinal mushroom) decreased CTC count in patients with oncological diseases [33].

Curcumin is also a very suitable agent for boosting other used therapeutic modalities [27,34,35]. For example, NF-κB (strongly repressed by curcumin) is deeply associated with metastatic activity and resistance against therapeutic modalities such as chemotherapy, radiotherapy, immunotherapy, and photodynamic therapy [36–39]. Long-term use of anticancer drugs can induce multidrug resistance and limit therapeutic efficiency. Repression of drug resistance by curcumin application was observed in many high impact studies representing various types of serious cancers including liver, pancreatic, lung, cervical, prostate, breast cancers, leukemic diseases and so on. Besides, curcumin in combination with multiple anticancer drugs (e.g., doxorubicin, 5-fluorouracil, paclitaxel, berberine, docetaxel, metformin, gemcitabine) displays potent synergic effects in the inhibition of proliferation, invasion and metastasis [40].

In addition, curcumin toxicity is selective for cancer cells and tissue and displays protective effects against healthy tissue and normal cells. Its applications display only mild side effects and can alleviate side effects caused by other therapeutic methods. For example, its incorporation with chemotherapy and radiotherapy can strongly improve quality of life of patients with solid tumours [41].

## 2. Curcumins antimetastatic effects: results from in vitro and in vivo studies

Metastatic formation is a complex process and curcuminoids can suppress its individual parts. Firstly, cancer cells change their cellular phenotype (from epithelial to mesenchymal, called epithelial-mesenchymal transition). This process is supported by tumour associated cells (TAM M2 phenotype, CAFs, and TECs) which cause polarity loss and cell/matrix adhesion of cancer cells, and aids in the digestion of the extracellular matrix. Subsequently cancer cells travel up the bloodstream and are transported to the metastatic sites. In the bloodstream or at the site of metastasis, cancer cells revert their phenotype (mesenchymal-epithelial reverting transition (MErT)) and acquire increased cell adhesion and infiltrate the target tissue [42]. Primary tumours besides CTCs can liberate exosomes (nano-sized membranous structures liberated from the cells) into distant organs [43]. They can transport various factors (e.g., RNA, DNA, miRNA, and lipids) [44], which can increase the chance of acceptance of the cancer cell into target organs [43].

In the primary tumour, curcumin can supress EMT transition and migration of the cancer cells and recruitment of tumour associated cells. In the mice model, it was observed that curcumin repolarizes the phenotype of tumour associated macrophage from M2 to M1 (protumour to antitumour). [45,46] Suppression by curcumin in the cancer associated fibroblast phenotype (α-SMA and vimentin) was associated with lower EMT and the migration of pancreatic cancer cells and lung metastasis in the mice model [47]. In the coculture tumour endothelial cells and colon cancer cells, curcumin supressed TEC transition, migration and phenotype [48]. In this case of the patients with colon and lung cancer, curcumin administration resulted in the conversion of the Treg cells (immune suppressive cells) into Th1 cells [29,30]. In the mice model with Ehrlich's carcinoma, this effect (induced by curcumin) was associated with the increase of IFN-γ-secreting CD4 + and CD8 + T cells (antitumour) in the circulation and at the tumour site [49].

Curcumin could also effectively target CTC in the bloodstream. Mirza et al. reported that curcumin (10 μM) displayed potent cytotoxicity against circulating metastatic primary adenocarcinoma cells [50]. In comparison, gemcitabine (100 μM) did not display any significant cytotoxicity. In this section, it should be mentioned, that curcumin could also decrease levels of IL-8 [48,51–53]. Some high impact studies suggest, that higher IL-8 levels could be associated with higher activity and viability of CTC and IL-8 targeting could supress CTC spreading [54–56]. For example, Arnoletti et al. reported, that the CTC model derived from patients with pancreatic ductal adenocarcinoma expressed higher IL-8 RNA [56]. Application of IL-8 antibodies lead to impaired CTC cluster formations and increased CTC apoptosis. On the other hand, relevant clinical trials did not find any correlation between IL-8 and CTC levels in breast and prostate cancer patients [57,58]. However, triple negative breast cancer patients with liver metastasis against nonmetastatic ones display increase in CTC levels and inflammatory markers (IL-6, IL-8 and C-reactive protein) [59]. Similarly, in patients with osteosarcoma, IL-8 levels significantly correlated with the Enneking stage and metastasis [55]. In accordance with the presented hypothesis, in a mouse model, CTC implantation was strongly associated with increased IL-8 levels and its suppression of primary and metastatic tumours and CTC seeding. This

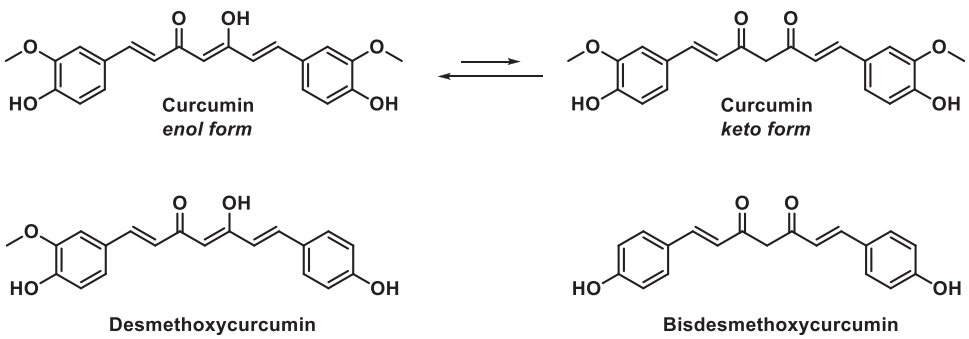


**Fig. 1.** Turmeric curcuminoid structure.

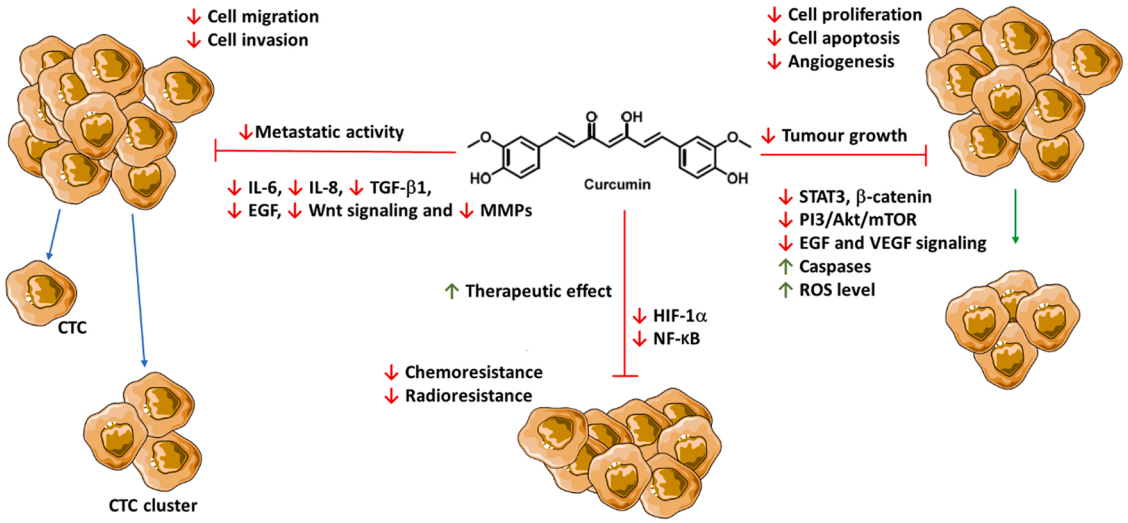


**Fig. 2.** Anti-tumour effect of curcumin. Curcumin display inhibition effects of proliferation cancer cells and induce their apoptosis. Curcumin represses angiogenesis via downregulation of VEGF. All these effects lead to decrease tumour growth and mass. Curcumin is also potent anti-metastatic/migrastatic agents via inhibition of oncogenic signalling (e.g., IL-6, IL-8, EGF and others) and matrix metalloprotease expression decrease migration and invasion of cancer cells and thereby CTC level formation CTC cluster. Curcumin application thank inhibition of NF-κB and HIF-1α activity decrease resistance of cancer cells against therapy. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

suggests that curcumin application could also significantly repress CTC infiltration into the premetastatic site. Palange et al. reported, that curcumin significantly decreased cell adherence of MDA-MB-231 by almost half [60]. In addition, curcumin (NANOCurc™) also repressed TNF-α activation of the HUVECs (in vitro model of inflamed endothelial cells). Combined exposition of both HUVECs and MDA-MBA-231 cells resulted in a 70% reduction of tumour cell adherence.

Curcumin can target infiltrated cancer and suppress micrometastases development. In the survival of dormant cancer cells, hypoxia plays a significant part, and their activation is controlled by the Wnt/β-catenin signalling pathway [61,62]. Curcumin can effectively target cancer cells hypoxia phenotype [63,64] and is a potent inhibitor of Wnt/β-catenin signalling [65–69]. Curcumin could also suppress oxidative stress (essential factor for metastasis formation) [70] in the affected tissue [71].

Some recent studies also imply, that curcumin could also suppress formation of premetastatic niches in the distant organs via tumour exosomes. Their application did not lead to a decrease in exosome formation but stimulated their production by cancer cells. Nevertheless, their biological effect is the opposite and displays an antitumour and metastatic properties, for example the activation of NK cells, suppression of angiogenesis and recruitment of cancer associated cells [72–74]. The effect of curcumin on the metastatic process is shown in more detail in Fig. 3.

The presented model clearly shows that curcumin is a potent anticancer agent with strong and robust antimetastatic effects in many oncological diseases. However, is it sufficiently supported by relevant studies? We can say that results obtained from the numerous experimental studies are consistent with this hypothesis. Numerous in vitro studies have shown that curcumin suppresses migration and invasiveness in various cancer cell models (e.g., breast, lung, colorectal, thyroid, pancreatic, liver and others) (Table 1).

Some studies imply (Table 1), that curcumin effects on cell metastatic activity are significantly higher than on cell proliferation. For example, 20 μM curcumin has no significant effect on MCF-7 mammosphere proliferation, but 15 μM curcumin reduces cell migration by up to a quarter [86]. In this case of MDA-MB-231, the $IC_{50}$ value was 28.7 μM, but application of 20 μM curcumin reduced cell invasion by approximately up to 10% of the original value [79]. Similarly, also in this case, the effect on cell proliferation was sometimes lower than the effect on cell migration and invasiveness in SCC25 head and neck cancer cell lines [112–114]. In this case of SCOV3 spheroids, a reduction of proliferation by up to half was observed at relatively high levels of curcumin (60 μM), however a reduction in cell adhesion and invasion by up to a quarter and less than half was found for the half-dose of curcumin [96].

Some published results suggest, that curcumin could effectively, or preferentially target cancer stem cells (CSCs) like phenotype [93], drug resistance, [100,101] hypoxia [63,64,106] or activated cancer cells (e.g., TPA, phthalate, lipopolysaccharide, neurotensin and autocrine growth hormone signalling) [65,66,82,85,102,118]. In this case of primary human pancreatic cancer cells, curcumin had a significantly higher effect on the inhibition of cell invasiveness, which was observed in cells under hypoxia conditions compared to cells under normoxia [64]. These cell phenotypes display higher metastatic activity and lower sensitivity against typically used drugs. It is well known that tumours that display strong heterogeneity and mechanisms of metastatic activity are associated with displaying similar mechanisms of drug resistance [130,131]. It could be suggested that curcumin can selectively target cells with high metastatic activity and thereby significantly suppress tumour metastatic activity.

Significant antimetastatic effects were also observed in in vivo studies (Table 2). Curcumin applications lead to the suppression of metastatic tumours (e.g., decrease in the number of metastatic nodules, or metastatic mass and volume) and to the down expression of metastatic factors in the primary and metastatic tumour.

Results from various cancer models (e.g., melanoma, colorectal and breast cancer) clearly indicate that curcumin can also target metastasis formation, especially in lung tissue, in addition to suppressing primary tumours. Some studies suggest that curcumin applications could at least decrease development of bone metastasis (incurable in the present time).

Nevertheless, some recent studies have shown possible limitations of curcumin anticancer/antimetastatic effectivity. Prakobwong et al. reported, that during the late stages (5–6 months) of the study, curcumin lost inhibition against NF-κB (golden hamsters infected by *Opisthorchis viverrini* and treated with N-nitrosodimethylamine) [142]. It could imply, that curcumin and other curcuminoids are mostly effective in the early stages of cancer, or as preventive agents. Numerous in vivo studies reported that curcumin application suppresses carcinogen induced

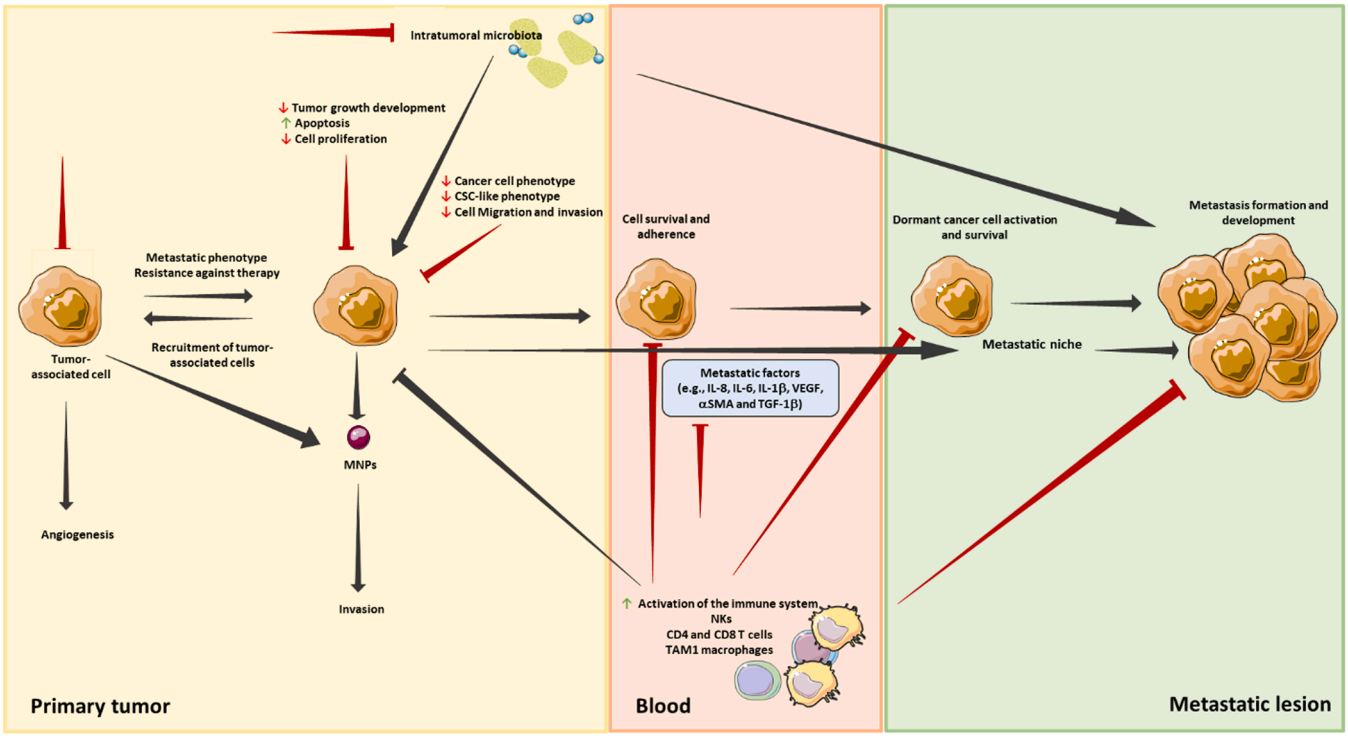


**Fig. 3.** Curcumin anticancer effect with emphasis on antimetastatic activity. Metastasis formation is a complex process. Potentially metastatic cancer cells are activated by stimuli produced by the tumour microenvironment. Tumour associated cells can induce the mesenchymal phenotype (migrated and metastatic phenotype of cancer cells). In addition, tumour associated cells can migrate with circulating tumour cells and protect them from the immune system and drugs or protect them against Anoikis apoptosis caused by stress in the bloodstream. On the other hand, cancer with the mesenchymal phenotype displays more potent abilities in recruitment and activation of cancer associated cells and in suppression of the immune system, higher resistance to drug and greater similarity with the phenotype of cancer stem cells. Primary tumours can also support metastasis formation via preparation of metastatic niches through exosomes and metastatic factors. Tumour microbiota may have a significant role in this. In the present time, it has been shown, that primary and metastatic tumours can contain their own specific microbiota, which stimulate tumour development and progression.Curcumin can target tumour growth and metastases through independent mechanisms. It suppresses the phenotype of tumour associated cells and can activate the immune system to kill cancer cells. Curcumin also displays direct cytotoxic effects on cancer cells and decreases their proliferation, migration, and invasiveness. It decreases tumour growth and angiogenesis enhances sensitivity of the tumour to chemotherapy and other used anticancer regiments. Curcumin application can decrease the subpopulation of stem cancer like cells in the tumour. Some works suggest that curcumin could be hacking the tumours exosome system and inducing the production of exosomes with antitumour and antimetastatic properties. Curcumin also displays potent cytotoxicity against some typical representatives of the tumour microbiota. In the bloodstream, curcumin directly targets CTCs and activates immune cells to kill them. Curcumin decreases the adherence of cancer cells and thereby most probably decreases their infiltration into distant tissues. In the metastatic niche, curcumin reduces survival and activation of inactive tumour cells and suppresses metastasis. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

cancer. In addition, several clinical trials reported, that curcumin decreased DNA damage after exposition to chemical pollutants [144–146]. Nevertheless, Yan et al. surprisingly reported, that a curcumin rich diet before and after tumour implantation (Lewis lung carcinoma in the mice model) and surgical removal did not display any effect on the primary tumour and increased angiogenesis and metastatic volume [137]. However, in the other studies with the mice model, curcumin displayed potent effectivity against Lewis lung carcinoma, including metastatic activity [147–150]. Fan et al. reported, that although curcumin induced the HIF1α/mTOR/VEGF/VEGFR cascade in ischemic tissue (obtained from mice bearing Lewis lung carcinoma), its efficacy in cancer tissue was reversed [148]. A possible explanation could also be that curcumin resistant cells represent more aggressive cancer lines. Nevertheless, Yan et al. reported that curcumin-surviving subpopulation of Levis lung cancer cells display lower expression of ALDH1A1 and NF-κB and their metastatic activity (after mice implantation) is low [151].

In short, it could be said, that curcumin and most probably also other curcuminoids could suppress various stages of the metastatic process by various independent mechanisms (Fig. 1). On the other hand, it is appropriate to admit here that the presented model is mostly based on the results of in vitro and in vivo studies (Tables 1 and 2, respectively) and its verification or rebuttal is not possible clinically without appropriate clinical studies.

## 3. Curcumin formulations: data from clinical trials

Some relevant clinical trials have shown indisputable limits of possible curcumin application [152]. For example, incorporation of curcumin powder into docetaxel therapy of patients with metastatic castration-resistant prostate cancer did not lead to any positive results and the clinical trial had to be terminated [153]. A possible explanation could be based on the low solubility (456 μg/L) [154,155] and biostability of natural curcuminoids and thereby their limited bioactivity. Healthy volunteers' serum curcumin levels were 57.6 ng/mL two hours after oral application of 12 g curcumin (standardized powder) [156]. To improve curcuminoid solubility and biostability, other curcuminoid formulations of applications (nano/micro) are being intensively studied.

Unlike classical materials, nanoparticles can display significantly different properties such as higher solubility and bioactivity [157]. In this case, bulk particles $< 1\%$ of contained atoms co are localized on the surface. Whereas $> 80\%$ of total atoms are on the surface of nanoparticles because of their small size, large surface area and polydispersity.

In accordance with the above, suitable nanoformulation can strongly boost therapeutic effectivity of curcumin [158]. Paradoxically, first

**Table 1**
Examples of antimetastatic effects of curcumin with emphasis on migration and invasiveness of tumour cells in in vitro studies.

| Model | Curcumin effect **Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| **Breast carcinoma** | |
| EMT 6[75] | **Scratch** (1/3; 30/24) |
| MCF-7[76] | **Cell** (↓NF-κB, ↓uPA) **Proliferation** (63%; 20/48), **Adhesion** (3/4; 20/1; 20 min pretreatment) and **Invasion** (1/2; 20/12; 24 h pretreatment) |
| CF-10 F[77] normal immortalized breast epithelial cell line | **Cell** (↓AXL, ↓Twist, ↑Notch1, ↑Fibronectin, ↑Vimentin) **Proliferation** ≥ 30/48; inhibition), **Migration** (1/3; 30/48) and **Invasion** (1/4; 30/48) |
| Tumour2 from Alpha 5 cell line, radiation transformed) [77] | **Cell** (↓AXL, ↓Twist, ↓ZEB2 and ↓STAT3 ↓, ↓Notch1 EZH2 ↓Fibronectin, ↓Vimentin) **Migration** (4/5; 30/48) and **Invasion** (1/2; 30/48) |
| MDA-MB-231[78] | ↓MMP3 secretion ↓Cell migration, **Proliferation** (60–70%; 20/24) and **Invasion** (2/3; 15/8) |
| DMC-MDA-MB-231[78] | ↓MMP3 secretion ↓Cell migration, **Proliferation** (70–80%; 20/24) and **Invasion** (1/2; 7.5/8) |
| BDMC-MDA-MB-231[78] | ↓MMP3 secretion ↓Cell migration, **Proliferation** (80–90%; 20/24) and **Invasion** (2/3; 7.5/8) |
| MDA-MB-231[77] | **Cell** (↓AXL, **0**Twist, ↑ZEB1 and ZEB2, ↑Fibronectin, ↓Vimentin, **0**EHZ and **0**STAT-3, **0**Notch1) **Migration** (1/4; 30/48) and **Invasion** (1/7; 30/48) |
| MDA-MB-231[79] | **Cell** (↓Gli1 and 2, ↓PTCH1 and ↓SMO) **Proliferation** ($IC_{50}$; 28.7/24), **Invasion** (1/10; 20/24 h) and **Scratch** (1/5; 20/24 h) |
| TGF-β induced MDA-MB-231[80] | **Cell** (↓p38, ↓Smad2/3, ↓PTHrP) **Proliferation** (50%; 24/24) |
| MDA-MB-231[67] | **Cell** (↓$CD44^+$ $CD24^-$ subpopulation, ↓β-catenin, ↓Vimentin, ↓Fibronectin, ↓Oct4, ↑E-cadherin, ↓Nanog, ↓Sox2 and ↓mamospheres) **Proliferation** (50%; ~25/24) and **Scratch** (2/3; 15/24) |
| T47D-wt and T47D-$GH^+$ (Autocrine GH expression)[65] | **Cell** (↓pSTAT1, ↓p38, ↓c-jun, ↓NF-κB activation, ↓miRNA-182–96-183, |

(*continued on next page*)

**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/ time (μM/h)[b] |
|---|---|
| | ↑vimentin,<br>↓β-catenin,<br>↓MMP-2<br>↓N-cadherin and<br>↑E-cadherin)<br>**Proliferation** (50%; ~20 and 25/48), **Scratch** (1/3 and <1/10; 20/24)<br>**Migration** (1/2 and 1/2; 20/ 48) and **Invasion** (1/ 3 and 2/3; 20/2) |
| BHMC-MDA-MB-231[81] | **Cell** (<br>↓MMP-9)<br>**Proliferation** (50%; ~50/ 24), **Scratch** (2/3; 12.5 / 24), **Invasion** (1/2;12.5 / 24) and **Migration** (1/2; 12.5 / 24) |
| MCF-7 (normal and indudced12-O-tetradecanoylphorbol-13-acetate (TPA))[82] | **Cell** (<br>↓p-38,<br>↓JNK,<br>↓IkBa,<br>↓IKKab,<br>↓IKKb,<br>↓p65,<br>↓p50,<br>↑P-c-Jun,<br>↓PKCα)<br>**Proliferation** (~90%; 30/24; normal) and **Invasion** (1/4;30/24; TPA induced) |
| MCF-7 and MCF-7-GH$^+$[66] | **Cell (**<br>↓STAT3,<br>↓MMP-2,<br>↓Slug,<br>↓N-cadherin,<br>↓GH)<br>**Proliferation** (50%; ~20 and 25 / 24), **Migration** (1/4 and 1/2; 20 / 24) and **Invasion** (1/2 and 1/4; 20/ 24) |
| MDA-MB-453-wt/MDA-MB-453-GH$^+$[66] | **Cell (**<br>↓STAT3, Akt,<br>↓MMP-2, |

**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/ time (μM/h)[b] |
|---|---|
| | ↓Vimentin,<br>↓GH)<br>**Proliferation** (50%; ~20 and 25/24), **Migration** (3/4 and 1/2; 20/ 24) and **Invasion** s (1/4 and 1/2; 20/ 24) |
| MDA-MB-231-wt/MDA-MB-231-GH$^+$[66] | **Cell** (<br>↓STAT3,<br>↓MMP-2, Slug,<br>↓β-catenin,<br>↓GH)<br>**Proliferation** (50%; ~ 20 and 25/ 24), **Migration** (1/3 and ¼; 20/24) and **Invasion** (1/2 and ½; 20/ 24) |
| MDA MB-231[83] | **Cell** (<br>↑ROS,<br>↑E-Cadherin,<br>↓STAT3,<br>↓VEGF), Paclitaxel synergy<br>**Proliferation** (41% and 63%; 10 μg/mL (27uM) curcumin and curcumin with (5 and 5 μg/mL) paclitaxel/36), **Migration** (1/2 and 1/5; 10 μg/mL curcumin and curcumin with paclitaxel (5 and 5 μg/mL) /36) and **Scratch** (4/5 and 1/2; 10 μg/mL curcumin and curcumin with paclitaxel (5 and 5 μg/mL) /36) |
| 4T1[83] | **Cell** (<br>↑ROS,<br>↑E-Cadherin,<br>↓STAT3,<br>↓VEGF) Paclitaxel synergy<br>**Proliferation** (40% and 56%; 10 μg/mL (27uM) curcumin and curcumin with paclitaxel (5 and 5 μg/mL)), **Migration** (3/5 and 1/3;10 10 μg/mL curcumin and curcumin with paclitaxel (5 and 5 μg/mL)/36) 0 and **Scratch** (1/3 and 1/2;10 10 μg/mL |

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**Table 1** (*continued*)

| Model | Curcumin effect **Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | curcumin and curcumin with paclitaxel (5 and 5 μg/mL)) |
| LPA induced MCF-7[84] | **Cell** (↓RhoA, ↓p-MYPT1, ↓ROCK 1 and 2, ↓MMP-2 and 9) **Proliferation** (60–70%; 75/24) and **Invasion** (2/3; 15/24) |
| MCF-7(normal and LPS induced)[85] | **Cell** (↓EMT, ↑E-Cadherin, ↓Vimentin, ↓Snail, ↓p65) **Proliferation** (70–80%; 20/24; normal) and **Invasion** (1/2 and 1/3; 20/48; 1 h pretreatment) |
| MDA-MB-231 (normal and LPS induced)[85] | **Cell** (↓EMT, ↑E-Cadherin, ↓Vimentin, ↓Snail, ↓p65) **Proliferation** (70–80%; 20/24; normal) and **Invasion** (2/3 and 1/3; 20/48; 1 h pretreatment) |
| Mammosphere of T47D[86] | **Proliferation** (75–100%;15/24) and **Migration** (1/3; 15/24) |
| Mammosphere of MCF-7[86] | **Cell** (↑E-Cadherin) **Proliferation** (Insignificant; (0–20 μM)/24), **Adhesion** (1/4; 15/1) and **Spreading** (3/1; 15/3 h), **Migration** (1/4; 15/24) and **Three-dimensional invasion** (1/2; 15/48) |
| **Lung carcinoma** | |
| H1299[75] | **Scratch** (1/3; 30/24) |
| Mammospheres BT-549[87] | **Cell** (↓Steam like phenotype ($CD44^+$ $CD24^-$), ↓microtentacles and ↓reattachment) **Proliferation** (insignificant;0–50 μM/6 h) |
| 801D[88] | **Cell** (↓Cdc42, PAK1, ↑E-cadherin, ↓actin cytoskeleton reorganization) **Invasion** (4/5; 5/24) |
| A549 and H226[89] | ↑E-cadherin, ↓vimentin, ↓TCF8, ↓Snail, ↓Slug, ↓TLR4/MyD88 and ↓EGFR **Proliferation** ($IC_{50}$; 19.71 and 30.88 / 72), **Colony formation** (2/3 and 1/3; 5/ 2 and 3 weeks) and **Migration** (1/3 and 5/6; 5/48 h) |
| A549[90] | **Cell** (↓PI3K, ↓PKC, ↓VEGF, ↓FAK, ↓Ras, ↓MKK7 ↓MMP 2 and 9, ↓Rho A and ↓FAK) **Migration** (1/3 and 1/10; 10/24 and 48) and **Invasion** (>5% and 1/10; 10/24 and 48) |
| A549[91] | **Cell** (Global change in the mRNA profile) **Proliferation** (90%; 10/48), **Scratch** (6/10; 10/24) and **Invasion** (1/3; 10/24) |

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**Table 1** (*continued*)

| Model | Curcumin effect **Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| A549[92] | **Cell** (<br>↓MMP2 and 9,<br>↓p21)<br>**Proliferation** (50–75%; 20/24), **Scratch** (1/4; 10/24) and **Invasion** (1/4; 10/24) |
| A549 (CD166 +/EPCAM+ and CD166-/EPCAM-)[93] | ↑Cisplatin sensitivity<br>**Proliferation** ($IC_{50}$; 40/48) and **Scratch** (1/2 and 2/4; 40/ 48), (1/3 and ¼; 40 with 30 μM cisplatin) |
| H2170(CD166 +/EPCAM+ and CD166-/EPCAM-)[93] | ↑Cisplatin sensitivity<br>**Proliferation** ($IC_{50}$; 30/48)<br>**Scratch** (1/2 and 3/4; 30/48), (1/10 and 1/7; 30/48 with 7uM cisplatin) |
| BDMC-TGF-β1 induced 95D[94] | **Cell** (<br>↑E-Cadherin,<br>↑WIF-1<br>↓Vimentin,<br>↓Fibrononectin and<br>↓Snail,<br>↓β-catenin nuclear translocation)<br>**Scratch** (>10%; 5/48) and **Invasion** (1/2; 5/48) |
| **Ovarian** | |
| DU145[95] | **Cell** (<br>↓HES-1,<br>↓MMP-2,<br>↓MT1-MMP)<br>**Proliferation** (50%; 25/48 h) and **Scratch** (1/2; 25/24) |
| SKOV3 spheroid[96] | **Cell** (<br>↓ALDH1A1)<br>**Proliferation** (50%; 60/48 and; 35/48 (monolayer)), **Adhesion** (1/4; 30/48), **Invasion,** (4/10; 30/48) and **Mesothelial clearance**[a] (½;30/48) |
| SKOV3[97] | **Cell** (<br>↓STAT3,<br>↑polygonal Appearance and<br>↓filopodia formation)<br>**Proliferation** (50%;30–40/12), **Adhesion** (83%; 10/6 h), **Migration** (76%; 10/6 h) and **Invasion** (75; 10/6 h) |
| **Colorectal carcinoma** | |
| HCT-116 and LoVo[98] | **Proliferation** ($IC_{50}$; 10 and 20/48), **Scratch** (88% and 72%; $IC_{50}$ (10 and 20)/24) and **Invasion** (1/7 and 1/7 $IC_{50}$(10 and 20)/24) |
| HCT-116 cells[99] | **Cell** (<br>↓MMP-9,<br>↓NF-κB,<br>↓claudin-3,<br>↑FAS,<br>↑E-cadherin)<br>**Proliferation** (50%; 10–20/24 h), **Colon formation** (50%; 10/48) and **Migration** (55%; 10/24) |
| HCT-116 (normal and 5-FU resistant)[100] in alginate beads culture | **Cell** (<br>↓CXCR4,<br>↓MMP9,<br>↓NF-κB)<br>**Proliferation** ($IC_{50}$; 9 and 5/14 days) and **Invasion** (1/3 and 1/5; 10/28 day) |
| SW480 and 5-FU-Resistant SW480[101] | **Cell** (<br>↓MYC,<br>↓insulin and IGF-1 receptors)<br>**Proliferation** ($IC_{50}$; 20 and 17/ 72 h), **Colony formation** (<5% and <5%; 20/ 3 weeks) and **Scratch** (>95% and 1/3; 20/48) |
| Neurotensin activated HCT-116[102] | **Cell** (<br>↓AP-1,<br>↓NF-κB, $Ca^{2+}$ mobilization and<br>↓IL-8 secretion) and **Migration** (1/3; 10/16; Neurotensin) |
| Rko and HCT116[103] | **Cell** (<br>↓p-c-Jun and<br>↓c-Fos,<br>↓Pre- and miR-21, |

(*continued on next page*)

**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | ↑Pdcd4)<br>**Proliferation** ($IC_{50}$; 10 and 16/48), **Migration** (1/3 and 1/3; $IC_{50}$ (10 and 16)/13; 24 h preretirement) and **Invasion** (1/2 and ¼; $IC_{50}$ (10 and 16)/13; 24 h pretreatment) |
| **Cervical** | |
| Bisdemethoxycurcumin[c]-Hela[104] | **Cell** (<br>↓Vimentin,<br>↓RAS,<br>↓RHO A,<br>↓N-Cadherin and<br>↑E-Cadherin,<br>↑NF-Kβ,<br>↓Snail)<br>**Proliferation** (50%; 10–15/24), **Scratch** (3/4 and ½; 5/24 and 48), **Migration** (1/5 and 4/5; 5/24 and 48) and **Invasion** (4/5 and ½; 5/24 and 48) |
| **Thyroid** | |
| BCPAP[105] | **Cell** (<br>↑E-Cadherin,<br>↓Vimentin,<br>↓TGF-β1 induced (<br>↓Smad2 and<br>↓Smad3<br>↓MMP2 and 9),<br>↓Cell spreading)<br>**Proliferation** (~50%; 50/24), **Attachment** (53%; 12.5/2) and **Scratch** (66%; 12.5/24; 6 h pretreatment) |
| K1- hypoxia phenotype[106] | **Cell** (<br>↓HIF-1α<br>↓MMP-9,<br>↑E-Cadherin,<br>↓BNIP3)<br>**Proliferation** (Insignificant; 0–50 μM/24, **Scratch** (80%; 25/24; 1 h pretreatment) |

**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | and **Invasion** (4/5; 25/24; 1 h pretreatment) |
| K1[107,108] | **Cell** (<br>↓MMP-9,<br>↑E-cadherin,<br>↓lamellipodia, phenotype (<br>↑round and<br>↑prominent))<br>↓Cell spreading, **Proliferation** (90%; 12.5/24), **Attachment** (47%; 12.5/24; 24 h pretreatment), **Scratch** (1/2; 12.5/6; in presence VEGF; 6 h pretreatment), **Migration** (87%; 12.5/3 h; 24 h pretreatment) and **Invasion** (84%; 12.5/4 h) |
| **Pancreatic carcinoma** | |
| Primary human cancer cells (normoxia and hypoxia)[64] | **Cell** (<br>↓α-SMA,<br>↓IL-6 secretion,<br>↓MMP-9,<br>↑E-cadherin,<br>↓vimentin<br>↓IL-6/ERK/NF-κB,<br>↓EMT,<br>↓hypoxia phenotype)<br>**Proliferation** (50%; 20/48 (normoxia) and **Scratch** (1/2 and ½; 20/24 h) |
| BxPC-3(normoxia and hypoxia)[64] | **Cell** (<br>↓ERK,<br>↓Vimentin,<br>↓MMP9,<br>↓IL-6 signalling)<br>**Invasion** (½ and 1/3; 20/48; pancreatic stellate cells conditioned media) |
| Panc-1(normoxia and hypoxia)[64] | **CM induced cell** (<br>↓ERK, |

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**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | ↓NF-κB)<br>**Invasion** (½ and 3/4; 20/48; pancreatic stellate cells conditioned media) |
| BxPC-3 and Panc-1[109] | **Cell** (<br>↑ROS, $H_2O_2$ induced factors (<br>↓MMP-2 and 9,<br>↓ERK,<br>↓NF-κB))<br>**Proliferation** (50%; 20/24), **Scratch** (4/5 and ¾; 5/24; in the presence of $H_20_2$) and **Invasion** (2/3 and ¾; 5 / 48; in the presence of $H_2O_2$) |
| Panc-1(normoxia and hypoxia)[63] | **Hypoxia cell** (<br>↓vimentin,<br>↓N-cadherin,<br>↑E-cadherin<br>↓SHH,<br>↓SMO and<br>↓GLI1)<br>**Proliferation** (~75% and 69%; 20/72) **Scratch** (9/10 and 2/3; 20/24) and **Invasion** (7/8 and 2/3; 20/48) |
| TGF-β1 activated PANC-1[110] | **Cell** (<br>↓Shh,<br>↓GLI1,<br>↑E-cadherin,<br>↓vimentin)<br>**Proliferation** (48%; 30/48), **Scratch** (1/3;30/24; 48 h pretreatment) and **Invasion** (1/2;30/48; 48 h pretreatment) |
| **Nasopharyngeal carcinoma** | |
| CNE1[111] | **Cell** (<br>↑p53,<br>↑p21,<br>↓MMP-2 and 9,<br>↓FAK)<br>**Proliferation** ($IC_{50}$; 31/48), **Colony formation** (3/4; 10/24), **Scratch** |

**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | (4/5; 10/48) and **Invasion** (3/4; 10/48) |
| **Oral squamous cell carcinoma** | |
| SCC25[112] | ↓Cellular cohesion in spheroids<br>**Proliferation** (10–20%; 5/24) and **Migration** (3/4; 2/24) |
| SCC-25[113] | **Cell**(<br>↓Snail,<br>↓Twist,<br>↑p53,<br>↑E-Cadherin<br>↓MMP-9 and<br>↓MMP-2)<br>**Proliferation** (50%; 10–15/24) and **Invasion** (5%; 10/24) |
| SCC-25[114] | Cell (<br>↓uPA,<br>↓uPAR,<br>↓MMP-9 and 2,<br>↓EGFR,<br>↓p-Akt,<br>↓ERK1/2,<br>↓STAT3)<br>**Proliferation** (70–80%; 40/24) and **Invasion** (1/2; 40/24; 24 h pretreatment) |
| 5–8 F[115] | **Proliferation** (90%; 50/3 h) and **Scratch** (insignificant; 50/24) |
| **Liver carcinoma** | |
| HepG2[116] | Cell (<br>↓HSP70 and<br>↓TLR4)<br>**Proliferation** (50%; ~50/48), **Scratch** (1/7 and <5%; 50 and 80/24), **Migration** (22% and 2% and 50 and 80/24) |
| HepG2TT (thermal tolerance HepG2)[116] | **Cell** (<br>↑HSP70 and **0**TLR4)<br>**Scratch** (1/7 and <5%; 50/24 and 48), **Scratch** (1/2 and ¼; 80/24 and 48) |
| Hca-F[117] | **Cell** (<br>↓Cav-1,<br>↓CD147,<br>(*continued on next page*) |

**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | ↓EGFR,<br>↓EGF,<br>↓p38MAPK,<br>↓p-44/42MAPK)<br>**Migration** (1/2;10/12) and **Invasion** (1/6; 10/12)16 h |
| Huh7 (normal and phthalate induced)[118] | **Cell** (<br>↓AhR,<br>↓ERK,<br>↓SKI,<br>↓N-cadherin (only for induced cells),<br>↑E-cadherin)<br>**Proliferation** (Insignificant (0–5 μM)/24), **Migration** (9/10 and ½;5/24) and **Invasion** (Insignificant and ½; 5/48) |
| PLC/PRF/5 (normal and phthalate induced)[118] | **Proliferation** (Insignificant (0–5 μM)/24), **Migration** (Insignificant and 2/3;5/24) and **Invasion** (Insignificant and ½; 5/24) |
| Hep3B[119] | **Cell** (<br>↓mTOR,<br>↓β-catenin,<br>↓Akt,<br>↓pGSK3β)<br>**Proliferation** (50%; 20/24) and **Scratch** (significant; 20/48) |
| CBO140C12[120] | **Cell** (<br>↓MMP-9,<br>↓stress fiber formation)<br>**Invasion** (2/3;1/6 h), **Adhesion** (3/4; 1/1) and **Haptotactic migration** (1/2; 1/3; to fibronectin and laminin, without change of integrin expression) |
| **Bladder carcinoma** | |
| T24 and 5637 cancer[69] | **Cell** (<br>↓β-catenin, |

**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | ↑Vimentin,<br>↓N-Cadherin,<br>↑ECadherin)<br>**Proliferation** (50% ~20; and 30/72), **Colony formation** (½ and 2/3; 10/ 2 weeks), **Scratch** (2/3 and 2/3; 5 / 24), **Migration** (1/3 and 1/3; 10 / 2) and **Invasion** (½ and ½; 10 / 12) |
| 5637[121] | **Cell** (<br>↓MMP-2 and 9,<br>↑ROS induced HO-1)<br>**Proliferation** (86%; 10/24), **Invasion** (93% and 62%; 5 and 10/24), **Invasion** (1/2 and 1/5; 5 and 10/24; HO-1 knockdown) |
| **Prostrate Carcinoma** | |
| DU145[75]<br>DU-145[122] | **Scratch** (1/3; 30/24)<br>**Cell** (<br>↓MMP 2 and 9)<br>**Proliferation** (~50%; 81/24) and **Invasion** (1/2;13.6/24) |
| PC-3[123] | **Cell** (<br>↓CCL2 and<br>↓MMP-9)<br>**Adhesion** (2/3;30/0.5; CCL2), **Migration** (2/3 and ½; 30/18; normal and CCL2) and **Invasion** (4/5 and 2/3; 30/ 18; normal and CCL2) |
| **Osteosarcoma** | |
| U2OS[68] | **Cell** (<br>↓β-catenin nuclear translocation)<br>**Proliferation** (60–80%; 20/48) and **Invasion** (1/5 and 1/2; 10/48; normal and β-catenin plasmid; 24 h pretreatment) |
| **Brain tumour** | |
| N18[124] | **Cell** (<br>↓MMP-2 and 7,<br>↓FAK,<br>↓Rho A,<br>↓ROCK-1,<br>↓COX-2, |

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**Table 1** (*continued*)

| Model | Curcumin effect<br>**Assay** (value of tested effects in curcumin presence/original value of tested effects[a]; dose/time (μM/h)[b] |
|---|---|
| | ↓iNOS,<br>↓NF-kB p65,<br>↓ERK1/2,<br>↓MKK7 and<br>↓MMP-2 and −7)<br>**Migration** (2/3 and 1/3; 7.5/24 and 48) and **Invasion** (1/2 and 1/3; 7.5/24 and 48 h) |
| A172[125] | **Cell** (<br>↓PI3K, **0**mTOR, **0**AKT Autophagy factors (<br>↑C3B/LC3A<br>↑LAMP-1 and<br>↑Atg5-Atg12))<br>**Proliferation** (~90%; 27/24 apoptosis) **Scratch** (~80%; 1.4/24), **Migration** (~85;1.4/18) and **Invasion** (slightly; 1.4/18) |
| **Melanoma** | |
| Osteopontin induced B16F10[126] | **Cell** (<br>↓IκBα,<br>↓MT1-MMP<br>↓MMP2,<br>↓ p65 nuclear localisation)<br>**Migration** (1/2; 25/16; OPN) **and Invasion** (1/2; 25/16; OPN) |
| B16F-10[127] | **Invasion** (45% and 2.2%;14 and 27 /24), (N. D. and 30.9%; 14 and 27/24; 24 pretreatment) |
| B16F10[128] | **Cell** (<br>↑ROS)<br>**Proliferation** ($IC_{50}$; 38/24), **Invasion** (1/5; 12.5/24) and **Migration** (1/2; 12.5/24) |
| B16F10[129] | **Cell** (<br>↓MMP 2 and 9)<br>**Proliferation** ($IC_{50}$; 41/24) and **Scratch** (1/6; 41/24) |

α-SMA, Alpha smooth muscle actin; AhR, Aryl hydrocarbon receptor; ALDH1A1, Retinal Dehydrogenase 1; AP-1, Activator protein 1; Akt, Protein kinase B; Atg protein, autophagy-related protein; AXL, Tyrosine-protein kinase receptor UFO; BNIP3, BCL2 Interacting Protein 3; C3B, Complement component 3b; CCL2, chemokine (C-C motif) ligand 2; CXCR4, C-X-C chemokine receptor type 4; COX-2, Cyclooxygenase-2; iNOS, Inducible nitric oxide synthase; c-Fos, AP-1 transcription factor subunit; EGFR, Epidermal growth factor receptor; EGF, Epidermal growth factor; ERK 1/2, Extracellular signal-regulated kinase 1/2; EZH2, Enhancer of zeste homolog 2; EMT, Epithelial–mesenchymal transition; FAK, Focal adhesion kinase; GH, Growth hormone; GLI1, GLI Family Zinc Finger 1; HES-1, Hairy and enhancer of split-1; HIF-1α, Hypoxia-inducible factor 1-alpha; HO-1, Heme oxygenase 1; HSP70, Heat shock proteins 70; JNK, c-Jun N-terminal kinase; IGF-1, Insulin-like growth factor 1; IL-6, Interleukin 6; IL-8, Interleukin 8; LAMP-1, Lysosomal-associated membrane protein 1; LC3A, Light Chain 3A; IkBa, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IKKαβ, IkappaB kinase alfa and beta subunits; IKKβ, inhibitor of nuclear factor kappa-B kinase subunit beta; PI3K, phosphatidylinositol 3-kinase; PKCα, Protein kinase C alpha; MAPK, Mitogen-activated protein kinase; MyD88, Myeloid differentiation primary response 88; MKK7, Mitogen-activated protein kinase 7; MMP-2, Matrix metalloproteinase-2; MMP3, Matrix metalloproteinase-3; MMP-9, Matrix metalloproteinase-9; MT1-MMP, Membrane type 1 matrix metalloproteinase; mTOR, Mammalian target of rapamycin; MYPT1, Myosin phosphatase target subunit 1; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NOTCH1, Notch Receptor 1; PAK1, P21 (RAC1) Activated Kinase 1; pGSK3β, Glycogen Synthase Kinase 3 Beta; PTCH1, Protein patched homolog 1; PTHrP, Parathyroid hormone-related protein; ROS, Reactive oxygen species; ROCK 1, Rho-associated, coiled-coil-containing protein kinase 1; uPA, Urokinase-type plasminogen activator; SHH, Sonic Hedgehog; SMO, Smoothened, Seven Transmembrane Spanning Receptor; STAT1, Signal transducer and activator of transcription 1; STAT3, Signal transducer and activator of transcription 3; TCF8, Zinc finger E-box-binding homeobox 1; TGF-β1, Transforming growth factor β; TLR4, Toll-like receptor 4; VEGF, vascular endothelial growth factor; WIF-1, Wnt inhibitory factor 1; ZEB1, Zinc Finger E-Box Binding Homeobox 1; ZEB2, zinc finger E-box binding homeobox 2; ↑ = curcumin activation/induction; ↓ = curcumin suppression/inhibition; **0** = without change.

[a] If a fraction was stated, the value was not explicitly stated in the article, but was subtracted from the presented graph.

[b] Unless other units are specified.

[c] Nature derivative of curcumin contained in turmeric extract.

nanoformulations probably were traditional applications of curcuminoids in Ayurvedic medicine in the form of golden milk (cow's milk, black pepper and honey). Milk constituents (e.g., lipids) strongly enhance curcumin solubility and stability [159]. Although, in the original recipe there was cow's milk, it can be easily replaced by other types, including plant ones. For example, Zheng et al. simply prepared a curcumin formulation with soy milk (~0.2 mg /mL) which had good stability (4 and 20 °C, 37 days) [160]. Microscopic analysis of the microstructures of soymilk curcumin loaded into small lipid nanoparticles (~ 400 nm) was performed.

Piperine, highly abundant in black pepper, strongly increases curcumin bioactivity [161]. Piperine inhibits and suppresses enzymes in metabolic transformation of curcumin [162,163]. Another study (Patil et al., 2016) suggests, that piperidine could directly interact with curcumin and suppress its aggregation [164]. A combination of curcumin and piperine (2:1) sometimes display an increase in the cytotoxicity against Caco-2 cells [165]. Shoba et al. reported, that in the healthy volunteer, co-application of piperine (20 mg) in combination with curcumin (2 g) resulted in an increase of curcumin biovailability by more than three orders of magnitude [166]. Nevertheless, results of another study were not convincing enough. [167] On the other hand, some in vivo studies suggest that piperine can have a strong potent protective effect on curcumin against carcinogens [168–171]. It cannot also be neglected that piperine suppresses the expression of IL-1β in gastric cancer cells induced by H. pylori and inflammation in pyloric mucosa of Mongolian gerbils after infection [172]. In short, we can say piperine most probably boosts therapeutic potential of curcumin by various mechanisms; however, further clinical studies are needed for a definitive assessment.

In the case of natural honey, numerous antitumoural effects were also observed [173]. In addition, however, its benefit could lie in

**Table 2**
Curcumin effects on tumours in animal models with emphasis on antimetastatic activity.

| Model | Experimental condition | Results |
|---|---|---|
| **Implanted** | | |
| **Melanoma** | | |
| C57BL/6 mice with B16F10 cells[127,132] | Orally; 200 nmol/kg in gum acacia; 10 alternate days. | ↓Serum sialic acid level (23%),<br>↓lung collagenhydroxyproline content (30%),<br>↓lung tumour nodule formation (10%) and<br>↑survival (+144%) |
| Mice with B16F10[129] | Orally; 3 and 6 mg/kg/day for 14 days | ↓lung metastasis (slight reduction) |
| **Bladder carcinoma** | | |
| Nude mice with MB49 [121] | Intravesical; (25 mg/kg and 50 mg/kg) in (23% DMSO and 30% propylene glycol in PBS) | ↑HO-1 protein expression in the lung tissue, lung nodule numbers (insignificant) |
| **Breast carcinoma** | | |
| Nude mice with MDA-MB-435LVB[133] | 2% curcumin in the diet; 5 days after tumour removal, and/or paclitaxel (i.p., 10 mg/kg, cremophor vehicle); 10, 17 and 24 days after tumour removal | **Lung metastasis** (<br>↓p65,<br>↓MMP 9 and<br>↓paclitaxel induced COX-2) |
| Nude mice with MDA-MB-231[80] | Intravenously (into fat); 25 and 50 mg/kg/ 2days for 21 days | Lytic bone lesion area (57% and 51%) bone-resorbing osteoclasts at the bone-tumour interface (48% and 53%) tumour mass (insignificant)<br>↑survival |
| Mice with 4T1[83] | IP; curcumin (50 mg) or curcumin and paclitaxel (25 and 25 mg) /daiy for 21 days | **Tumour** (<br>↓STAT3,<br>↓MMP2, 3 and 9,<br>↓cyclin D,<br>↓VEGF),<br>↓tumour volume and<br>↓neoplasticity (zero in the combination with paclitaxel) in mammary and hepatic tissues |
| Mice with 4T1[134] | Oral; (50 mg/kg) /2 day for 16 days | ↓Tumour volume,<br>↓pulmonary metastatic nodules |
| BALB/c mice with 4T1 [135] | IV; 30 mg/kg /day for 10 days | ↑OS (37 vs 28),<br>↓tumour volume and mass (1/2)<br>↑apoptosis index (2x) and<br>↓anogiogenesis (microvehicles per field 1/2), |
| Mice with bone implanted MDA-MB-231;[136] | IV; bortezomib (1 mg) and curcumin (1.337 mg) /kg, /7 day, 35 days | ↓number and mass of lung metastases (1/2)<br>**Bone**: (Slightly reduction in macraphage infiltration tumour volume) |
| **Liver carcinoma** | | |
| CBO140C12 Intrahepatic Metastasis the liver B6C3F1 mice[120] | Orally; 100 and 200 mg/kg/day for 20days | Number of intrahepatic metastases (1/3% and 5%)<br>Volume of primary tumour (1/4 and 1/6) |
| Phthalates induced Huh7 [118] | Intraperitoneal injection; curcumin (50 mg) and bis(2-ethylhexyl) phthalate (60 mg) /kg/2 day for month | ↓Tumour volume,<br>↓lung nodules |
| **Lung carcinoma** | | |
| C57BL/6 mice with LLC [137] s tumour removed after 10 days | Orally; 2% and 4% diet, 5 weeks before LLC implantation and 20 days after | **Plasma** (<br>↑angiogenin,<br>↑bFGF,<br>↑VEGF,<br>↑PDGF-BB,<br>↑IL-1β,<br>↑MCP-1)),<br>↑metastasis volume |
| **Prostrate carcinoma** | | |
| SCID mice with DU-145 [122] | Orally; 5 mg/kg in 0.5% methylcellulose and 0.1% Tween 80, three times per week for 10 weeks | Pulmonary metastasis (from 90% to 60%), No. of metastatic nodules (from 11.0 to 1.2), **tumour tissue** (<br>↓MMP2 and 9) |
| **Gastric carcinoma** | | |
| BALB/c nude mice with SGC-7901[138] | intraperitoneal injections; 40, 80, or 160 mg/kg/day for 8 weeks | **Lymphatic vessel** (**0**VEGFR-3, **0**Podoplanin, **0**Prox-1),<br>↓lymphatic vessel density,<br>↓**tumour volume and gastric tumour** (<br>↓VEGFR-3,<br>↓Podoplanin,<br>↓Prox-1,<br>↓LYVE-1) |
| **Colon carcinoma** | | |
| Chicken embryos with Rko [103] | Intravenously; 12th and 14th day | Liver and lung metastases (11% and 24%), **tumour** (<br>↓pre and miR-21) |
| Chicken embryos with HCT116[103] | Intravenously; 12th and 14th day | (Liver and lung metastases 55% and 53%), tumour (<br>↓pre and miR-21) |
| **Head neck carcinoma** | | |
| Mice with patient OSCC biopsy fragment[112] | injected around the tumour; 70 mg/kg /weak for 4 weeks | ↑Tumour differentiation,<br>↓inflammatory infiltrate |
| **Leukemie** | | |

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**Table 2** (*continued*)

| Model | Experimental condition | Results |
|---|---|---|
| BALB/cJGpt-Prkdcem$^{1Cd561}$/Gp mice with SHI-1[139] | Intraperitoneal injections; 15 and 30 mg /kg/day in olive oil for 15 days | **Tumour** (<br>↑p38,<br>↑JNK,<br>↓ERK and<br>↓NF-κB,<br>↓MMP 9 and 2),<br>↓tumour volume |
| **Induced** | | |
| Long-Evans Cinnamon rats [140] | 0.5% curcumin in the diet for life | ↓Median survival time (from 88.7 to 78.1 days),<br>↓Metastases (18% vs 0%) |
| MTX treated mice with MNNG/HOS/MTX[141] | Intraperitoneal; Curcumin (5 mg/ kg) and MTX (0.4 mg/ kg)/weakly for 4 weeks | P-gp expression (1/3), primary tumour volume (22%), cases of lung metastasis (from 3 to 0) |
| Viverrini infection and N-nitrosodimethylamine exposed golden hamsters[142] | Orally; 65 mg/day for 6 months | **Nuclear extract form liver** (<br>↓STAT-3,<br>↓c-fos,<br>↓p65,<br>↓TRAF-1 and<br>↓JAK2) **tumour** (<br>↓COX-2,<br>↓iNOS), Tumour volume and development, 5–6 month- no effect of curcumin on NF-κB activation |
| Tobacco smoke exposed BALB/c mice[143] | Orally; 50 or 100 mg/kg/day for 12 weeks | **Lung** (<br>↑E-cadherin,<br>↑ZO-1,<br>↓vimentin,<br>↓N-cadherin,<br>↓Jun,<br>↓FOS and<br>↓ERK 1/2) |

Akt, Protein kinase B; bFGF, Basic fibroblast growth factor; c-Fos, AP-1 transcription factor subunit; COX-2, Cyclooxygenase-2; Extracellular signal-regulated kinase 1/2; iNOS, Inducible nitric oxide synthase; HO-1, Heme oxygenase 1; IL-1β, Interleukin-1 beta; JAK2, Janus kinase 2, JNK, c-Jun N-terminal kinase; Jun, Fos-binding protein **p39;** GSK3β, Glycogen Synthase Kinase 3 Beta; LYVE 1, Lymphatic Vessel Endothelial Hyaluronan Receptor 1; MCP-1, Monocyte chemoattractant protein-1; MMP-2, Matrix metalloproteinase-2; MMP3, Matrix metalloproteinase-3; MMP-9, Matrix metalloproteinase-9; mTOR, Mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDGF-BB, Platelet-derived growth factor – two B subunits; PROX1, Prospero homeobox protein 1; STAT3, Signal transducer and activator of transcription 3; TRAF1, TNF Receptor Associated Factor 1; VEGF, vascular endothelial growth factor; VEGFR-3, Vascular endothelial growth factor receptor 3; ZO-1, Tight junction protein-1

↑ = curcumin activation/induction/enchant; ↓ = curcumin repression/inhibition; **0** = without change.

increasing the bioactivity of curcumin. Mor et al. reported that sucrose in the presence of piperine and high fat milk significantly increased the release of curcumin from its alginate deposit [159]. Honey has shown to have massive amounts of saccharides. There is an abundance of glucose and fructose and a smaller amount of sucrose in honey [174]. In this context, it is interesting that some curcumin formulations with enhanced bioactivity and bioavailability, such as Theracurmin and Neocurcumin, contain disaccharide maltase.

In accordance with the above, the application of solid lipid nanoparticles (similar nanostructure as milk) resulted in a significant increase of bioactivity of curcuminoids. In the case of Meriva (phytosomal formulation of curcuminoids), this formulation displayed an increase by more than an order of magnitude increase in maximum and total curcuminoid concentrations (0.2 and 1.3 μg/mL) in plasma of a healthy volunteer [175]. In oncological patients with solid tumours, Meriva applications lead to decreased levels of metastatic factors (interleukin 6 (IL-6), TGF-β, and tumour necrosis factor alpha (TNF-α)) [41]. Similarly, it was reported, that curcumin nanoformulaton sometimes lead to an increase in antimetastatic activity. [83,176] Promising pharmacokinetic results were also observed in other oral curcumin formulations (Table 3), for example after application of BCM-95 value of $c_{max}$ and $AUC_{0\text{-}inf}$ was 0.5 and 3 μg/mL (1.3 and 8.1 μM), respectively [177].

However, the question is to what extent the potential therapeutic efficacy of curcumin is caused by an increase of its concentration in the blood and how many other factors can increase curcumin concentration in the tumour tissue. Curcumin itself probably does not significantly accumulate in the tumour [146]. Nevertheless, nanoparticles (20–500 nm) and macromolecules (40 kDa and higher) accumulate strongly in tumour tissue due to the EPR effect (e.g., "enhanced permeability and retention'') [194]. They are too big for the diffusion through capillary walls and their half-life in plasma is higher compared to other small molecules (e.g., classical drugs and curcuminoids). On the other hand, a characteristic feature of tumour tissue is that it leaks through pores (100 nm to 1 μm, depending on the tumour type) or by fenestration and there is a limited functionality of the tumour lymphatic system. Nevertheless, larger nanoparticles (d>100 nm) can be transported by sinusoids in the spleen and fenestrae of the liver, which are approximately 150–200 nm in diameter [194].

The distribution of nanoparticles can also depend on protein interactions [195]. Numerous proteins can be bound to the surface of nanoparticles and their size can sometimes be larger [176]. Aggregates of proteins and nanoparticles are removed by macrophages from the circulation. [195] Minimizing protein binding (e.g., surface modification) is a necessary condition for the design of long circulating nanoparticles. Stealth polymers are mostly used for these purposes such as poly(ethylene glycol) (PEG), poly(2-oxazoline) (POx).

However, success may not be guaranteed. In the case of the glioblastoma patients treated with NovaSol (micellar curcuminoids formulation, 3 ×840 mg/day), it was found that curcumin serum and intratumoural concentration was 253 ng/mL (0.73 μM) and 56 pg/mg (0.15 μM), respectively. [196] Nevertheless, more optimistic results were reported by Gálvez et al. in breast cancer patients [193]. Although plasma concentration of free curcumin was 5.26 nmol/l. Its concentration in normal and malignant mammary tissue was approximately 1 and 0.2 mmol/l. However, authors did not test a single formulation of curcumin, but combined extracts (570 mg turmeric extract and ~ 350 mg other polyphenolic compounds per day). A negligible part of this formulation were flavonoids. In this context, it is interesting that some polyphenol compounds such as flavonoids can strongly enhance curcumin bioavailability and bioactivity [48,197–199].

The above suggests that the concentration of curcumin in plasma

**Table 3**
Pharmacokinetic parameters of curcumin and its formulations from clinical trials.

| (Dose Name; Subject) Lit. | Physiological curcuminoid concentration **Curcuminoid** ($c_{max}$ /ng/mL and AUC /ng.h/mL) |
|---|---|
| **Unformulated** | |
| (2 g; 8)[166] | **Free curcumin** ($c_{max}$ = 6) |
| (10 and 12 g; 1 and 1)[156]; | **Free curcumin** ($c_{max}$ = 50 and 51, respectively) |
| (1425 mg; 30 (33.6 ± 6.79 years)) [167] | **free curcumin** ($c_{max}$ = 18 and $AUC_{0–24\ h}$ = 56), **curcumin sulphate** ($c_{max}$ = 59.6 and $AUC_{0–24\ h}$ = 618), **curcumin glucuronide** ($c_{max}$ = 34 and $AUC_{0–24\ h}$ = 236), **Free DMC** ($c_{max}$ = 3.2 and $AUC_{0–24\ h}$ = 7.4), **free BDMC** ($c_{max}$ = 0.7 and $AUC_{0–24\ h}$ = 1.3), **THC glucuronide** ($c_{max}$ = 163 and $AUC_{0–24\ h}$ = 1230), **HHC glucuronide** ($c_{max}$ = 97.9 and $AUC_{0–24\ h}$ = 946), **THC sulphate** ($c_{max}$ = 59.5 and $AUC_{0–24\ h}$ = 317), **HHC sulphate** ($c_{max}$ = 128 and $AUC_{0–24\ h}$ = 1370), and **total curcuminoids** ($c_{max}$ = 445 and $AUC_{0–24\ h}$ = 5080) |
| (1295 mg curcumin, 396 mg **DMC**, and 108 mg BDMC; 3 (35 ± 10 years)) [175] | **Curcumin** ($c^{max}$ 9 ng/mL AUC = 122.5,), **DMC** ($c_{max}$ 4.2 ng/mL and AUC = 55.8) and **BDMC** ($c_{max}$ = 2.1 and AUC = 24.6) |
| (1800 mg; 15 (23.0 ± 2.4 years))[178] | **Curcumin** ($c_{max}$ = 2.3 and $AUC_{0–12\ h}$ = 10.8), **DMC** ($c_{max}$ = 1.7 and = $AUC_{0–12\ h}$ 18.4), **BDMC** ($c_{max}$ = 1.1 and $AUC_{0–12\ h}$ = 9.3), **THC** ($c_{max}$ = 1.1 and $AUC_{0–12\ h}$ = 1.1), and **total curcuminoids** ($c_{max}$ = 5.2 and $AUC_{0–12\ h}$ = 39.6) |
| (1500 mg; 7)[179] | **Free curcumin** ($c_{max}$ = 0.154.9 and $AUC_{0–24\ h}$ = 0.116), **total curcumin** ($c_{max}$ = 21 and $AUC_{0–24\ h}$ = 224), **DMC** ($c_{max}$ = 21 and $AUC_{0–24\ h}$ = 189), **BDMC** ($c_{max}$ = 8.8 and $AUC_{0–24\ h}$ = 51.6), **THC** ($c_{max}$ = 87 and $AUC_{0–24\ h}$ = 962), and **total curcuminoids** ($c_{max}$ = 48.4 and $AUC_{0–24\ h}$ = 470) |
| (500 mg; 12)[180] | **Curcumin** ($c_{max}$ = 43.1 and $AUC_{0–6\ h}$ = 165) |
| (90 mg; 7)[181] | **Curcumin** ($C_{max}$ = 1.8 and $AUC_{0–12\ h}$ = 5.75) |
| Curcumin powder (1800 mg; 24) [182]; | **Curcumin** ($c_{max}$ = 9.85 and $AUC_{0–6\ h}$ = 15.4), **DMC** ($c_{max}$ = 3.20 and $AUC_{0–6\ h}$ = 6.42), **BDMC** ($c_{max}$ = 2.15 and $AUC_{0-6\ h}$ = 4.89), **THC** ($c_{max}$ = 5.38 and $AUC_{6–h}$ = 7.88), and **total curcuminoids** ($c_{max}$ = 15.65 and $AUC_{0–6\ h}$ = 33.21) |
| (1.5 g, 3 g and 6 g; 11)[183] | **Curcumin** ($C_{max}$ = 41.63, 41.20 and 2.84, respectively); Negative correlation with antioxidative activity |
| (500 mg; 23)[184] | **Curcumin** ($c_{max}$ = 7.1 and $AUC_{0–24\ h}$ = 65.6 nM), **DMC** ($c_{max}$ = 1.3 and $AUC_{0–24\ h}$ = 10 nM), and **BDMC** ($c_{max}$ = 0.5 and $AUC_{0–24\ h}$ = 2.4 nM) |
| (2000 mg; 4)[177] | **Curcumin** ($c_{max}$ = 150 and $AUC_{0\text{-}inf}$ = 461) |
| **Piperine supplement** | |
| (2 g curcumin and piperine 20 mg; 8) [166] | **Free curcumin** ($c_{max}$ 180) |
| Curcumin C3 Complex® (1425 mg; with 14 mg piperine Sabinsa; 30) TEP [167] | **Free curcumin** ($c_{max}$= 12.9 and $AUC_{0–24\ h}$ = 54.1), **curcumin sulphate** ($c_{max}$ = 42.3 and $AUC_{0–24\ h}$ = 474), **curcumin glucuronide** ($c_{max}$ = 26 and $AUC_{0–24\ h}$ = 187), **Free DMC** ($c_{max}$ = 10.3 and $AUC_{0–24\ h}$ = 10.7), **free BDMC** ($c_{max}$ = 0.2 and $AUC_{0–24\ h}$ = 0.6), **THC glucuronide** ($c_{max}$ = 154 and $AUC_{0–24\ h}$ = 1230), **HHC glucuronide** ($c_{max}$ = 74 and $AUC_{0–24\ h}$ = 264), **THC sulphate** ($c_{max}$ = 59 $AUC_{0–24\ h}$ = 317), **HHC sulphate** ($c_{max}$ = 99 and $AUC_{0–24\ h}$ AUC24 = 1230), and **total curcuminoids** ($c_{max}$ = 373 and $AUC_{0–24\ h}$ = 4380) |
| (2000 mg; lecithin, piperine (Life Extension, USA); 4)[177] | **Curcumin** ($c_{max}$ = 344 and $AUC_{0\text{-}inf}$ = 624) |
| Silicon dioxide/triacetin/Panodan® Micronized powder | |
| (500 mg; 23)[184] | **Curcumin** ($c_{max}$ = 51 and $AUC_{0–24\ h}$ = 700 nM), **DMC** ($c_{max}$ = 34 AUC = 246 nM) and **BDMC** ($c_{max}$ = 5.1 and $AUC_{0–24\ h}$ = 27 nM) |
| **Liposomal and micellar system: Meriva (**lecithin curcuminoid formulation**)** | |
| (165 and 297 mg **curcumin**, 38 and 68 mg **DMC** and 6 and 11 mg **BDMC;** 3 and 3 (35 ± 10 years) [175] | **Curcumin** ($c_{max}$ = 24.2 and 50.3 and AUC = 272 and 538), **DMC** ($c_{max}$ = 39.1 and 134.6 and AUC = 297 and 655), and **BDMC** ($c_{max}$ = 8.8 and 24.9 and AUC = 70 and 142)) |
| (376 mg 15 (23.0 ± 2.4 years))[178] | **Curcumin** ($c_{max}$ = 2.8 and $AUC_{0–12\ h}$ = 28.7), **DMC** ($c_{max}$ = 5 and $AUC_{0–12\ h}$ = 28.7), **BDMC** ($c_{max}$ = 0.8 and $AUC_{0–12\ h}$ = 6.7), **THC** ($c_{max}$ = 0.1 and $AUC_{0–12\ h}$ = 1.1), and **total curcuminoids** ($c_{max}$ = 2.3 and $AUC_{0–12\ h}$ = 65.3) |
| (152 mg; 9)[185] | **Curcumin** ($C_{max}$ = 58.8) |
| (180–220 mg; 30) [167] | **Free Curcumin** ($c_{max}$ = 11.3 and $AUC_{0–24\ h}$ = 37.6), **curcumin sulphate** ($c_{max}$ = 27.1 and $AUC_{0–24\ h}$ = 291), and **curcumin glucuronide** ($c_{max}$ = 25.6 and $AUC_{0–24\ h}$ = 142), **free DMC** ($c_{max}$= 6.4 and $AUC_{0–24\ h}$ = 2.2), **BDMC** ($c_{max}$ = 0.2 and $AUC_{0–24\ h}$ = 0.2), **THC glucuronide** ($c_{max}$ = 72.7 and $AUC_{0–24\ h}$ = 628), **HHC** ($c_{max}$ = 31.7 and $AUC_{0–24\ h}$ = 323), **THC sulphate** ($c_{max}$ = 24 and $AUC_{0–24\ h}$ = 164), **HHC sulphate** ($c_{max}$ = 48 and $AUC_{0–24\ h}$ = 528), and **total curcuminoids** ($c_{max}$ = 209 and $AUC_{0–24\ h}$ = 2030) |
| **Liposomal and micellar system:** | |
| Doctor's Best Curcumin Phytosome (lecitin, 18% curcuminoids) | |
| (500 mg; 15)[186] | **Curcumin** ($c_{max}$ = 69 and $AUC_{0–24\ h}$ = 187) |
| Lipocurc™ (Lyposomal curcumin 80–400 mg/$m^2$; 50)[187] Intravenous | **Curcumin** ($C_{max}$ = 42–2358 ng/mL) and **THC** ($C_{max}$ = 41–265) |
| Liquid micellar preparation (NOV) c (60 mg; NovaSOL, | **Free curcumin** ($c_{max}$ = 9.1 and $AUC_{0–24\ h}$ = 25.2), **curcumin sulphate** ($c_{max}$ = 62.7 and $AUC_{0–24\ h}$ = 296), **curcumin glucuronide** ($c_{max}$ = 295 and $AUC_{0–24\ h}$ = 491), **free DMC** ($c_{max}$ = 1.3 and $AUC_{0–24\ h}$ = 2.6), **free BDMC** ($c_{max}$ = 0.2 and $AUC_{0–24\ h}$ = 0.1), **THC glucuronide** ($c_{max}$ = 711 and $AUC_{0–24\ h}$ = 3050) HHC ($c_{max}$ = 330 and $AUC_{0–24\ h}$ = 1790), **THC sulphate** ($c_{max}$=24 and $AUC_{0–24\ h}$ = 164), **HHC sulphate** ($c_{max}$ = 63 and $AUC_{0–24\ h}$ = 296), and **total curcuminoids** ($c_{max}$ =1760 and $AUC_{0–24\ h}$ =8540) |

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**Table 3** (*continued*)

| (Dose Name; Subject) Lit. | Physiological curcuminoid concentration **Curcuminoid** ($c_{max}$ /ng/mL and AUC /ng.h/mL) |
|---|---|
| AQUANOVA; 30) [167] | |
| BioCurc (lauryl macrogol-32 glycerides, polysorbate-20, DL-alpha-tocopherol) 400 mg | |
| BioCurc (76 mg, Boston BioPharm (Southlake, TX; 12)[188] | **Free curcumin** ($c_{max}$ = 2 ng/mL), **curcumin glucuronide** ($c_{max}$ 300 ng/mL), **curcumin sulphate** ($c_{max}$ = 20 ng/mL), and **total curcumin*** ($c_{max}$ = 277.24 ng/mL) |
| LipiSperse® (750 mg, Pharmako Biotechnologies, New South Wales; 5)[189] | **Curcumin** ($c_{max}$ = 691 and $AUC_{0–24\ h}$ = 1549)* , **DMC** ($c_{max}$ = 96.8 and $AUC_{0–24\ h}$ = 366), **BDMC** ($c_{max}$ = 24 and $AUC_{0–24\ h}$ = 128), and **total curcuminoids** ($c_{max}$ = 807 and $AUC_{0–24\ h}$ = 1898) |
| WDTE60N/ TurmXTRA®60 N (150 mg curcuminoids, Inventia Healthcare Ltd., India; 7)[179] | **Free curcumin** ($c_{max}$ = 0.438.9 and $AUC_{0–24\ h}$ = 0.807), **total curcumin** ($c_{max}$ = 435 and $AUC_{0–24\ h}$ = 232), **DMC** ($c_{max}$ = 36 and $AUC_{0–24\ h}$ = 171), **BDMC** ($c_{max}$ = 1.7 and $AUC_{0–24\ h}$ = 8.2), **THC** ($c_{max}$ = 0.141 and $AUC_{0–24\ h}$ = 1.130), and **total curcuminoids** ($c_{max}$ = 82.4 and $AUC_{0–24\ h}$ = 429.1) |
| Lipid formulation (500 mg; 23)[184] | **Curcumin** ($c_{max}$ = 3704 and $AUC_{0–24\ h}$ = 12147 nM), **DMC** ($c_{max}$ = 440 and $AUC_{0–24\ h}$ = 1224 nM) and **BDMC** ($c_{max}$ = 10.4 and $AUC_{0–24\ h}$ = 37 nM) |
| **Turmeric matrix formulation** | |
| Volatile oils of turmeric rhizome (376 mg, volatile oils of turmeric rhizome DolCas Biotech 15 (23.0 ± 2.4 years))[178] | **Curcumin** ($c_{max}$ = 0.5 and $AUC_{0–12\ h}$ = 5.8), **DMC** ($c_{max}$ = 0.2 and $AUC_{0–12\ h}$ = 2.2), **BDMC** ($c_{max}$ = 0.3 and $AUC_{0–12\ h}$ = 2.6), **THC** ($c_{max}$ = 0.0 and $AUC_{0–12\ h}$ = 0.3), and **total curcuminoids** ($c_{max}$ = 0.1 and $AUC_{0–12\ h}$ = 10.9) |
| BCM-95®CG (BiocurcumaxTM) | |
| Curcu-Gel Ultra/ BCM-95 (500 mg; Volatile oil formulation; 15) [186] | **Curcumin** ($c_{max}$ = 47.54 and $AUC_{0–24\ h}$ = 117) |
| BCM-95 (279 mg micronized with turmeric essential oils; 9)[185] | **Curcumin** ($C_{max}$ = 45.0) |
| (2000 mg; 8)[177] | **Curcumin** ($c_{max}$ = 553 and $AUC_{0\text{-}inf}$ = 3050) |
| Cureit™/Acumin (500 mg; Aurea Biolab C completely natural turmeric matrix formulation NTM formulation;15) [186] | **Curcumin** ($c_{max}$ = 170 and $AUC_{0–24\ h}$ = 824.9) |
| Cureit Capsules (500 mg; 12)[180] | **Curcumin** ($c_{max}$ = 434 and $AUC_{0–8\ h}$ = 904) |
| (376 mg, hydrophilic carrier, cellulosic derivatives and natural antioxidants; (lot number CU20DNS1–008/ 009 OmniActive Health Technologies; 15 (23.0 ± 2.4 years) [178] | **Curcumin** ($c_{max}$ = 273 and $AUC_{0–12\ h}$ = 307), **DMC** ($c_{max}$ = 5.4 and $AUC_{0–12\ h}$ = 54.4), **BDMC** ($c_{max}$ = 1.4 and $AUC_{0–12\ h}$ = 10.2), THC ($c_{max}$ = 0.7 and $AUC_{0–12\ h}$ = 7.7), and **total curcuminoids** ($c_{max}$ = 34.9 and $AUC_{0–12\ h}$ = 380) |
| Cavacurmin® γ-CD (348 mg curcumin, 21.6 mg DMC and 2.4 BDMC; 12) [190] | **Curcumin** ($c_{max}$ = 73 and $AUC_{0–12\ h}$ = 328), **DMC** ($c_{max}$ = 12 and $AUC_{0–12\ h}$ = 51), **BDMC** ($c_{max}$ = 1.4 and $AUC_{0–12\ h}$ = 9.4), and **total curcuminoids** ($c_{max}$ = 87 and $AUC_{0–12\ h}$ = 389) |
| **Theracurmin**® (Ghatti gum/glycerin/Lipids/hydroxymethyl, maltose) | |
| CR-033 P (90 mg, TOYO capsule, Shizuoka, Japan; 24)[181] | **Curcumin** ($C_{max}$ = 33.78 and $AUC_{0–12\ h}$ = 177.55) |

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**Table 3** (*continued*)

| (Dose Name; Subject) Lit. | Physiological curcuminoid concentration **Curcuminoid** ($c_{max}$ /ng/mL and AUC /ng.h/mL) |
|---|---|
| CR031P (30 mgx3, BIHOLON, Toyama, Japan; 24)x3[181] | **Curcumin** ($C_{max}$ = 30.75 $AUC_{0–12\ h}$ = 148) |
| (182 mg; 9)[185] | **Curcumin** ($C_{max}$ = 231.5 (2 h) 167 (6 h) and 66.4 (24 h)) |
| Drinkable formulation (30 mg/100 mL; 24 (23–32 years)) [191], | **Curcumin** ($C_{max}$ = 25.5 and $AUC_{0–8\ h}$ = 121) |
| Turmipure GOLD (90 mg; A dried colloidal suspension, TPG quillaja extract, sunflower oil, and acacia gum containing, Naturex; 30)[167] | **Free curcumin** ($c_{max}$ = 15.4 and $AUC_{0–24\ h}$ = 25.7), **curcumin sulphate** ($c_{max}$ = 63 and $AUC_{0–24\ h}$ = 575), **curcumin glucuronide** ($c_{max}$ = 42.5 and $AUC_{0–24\ h}$ = 226), **free DMC** ($c_{max}$ = 2.7 and $AUC_{0–24\ h}$ = 9.4), **free BDMC** ($c_{max}$ = 0.4 $AUC_{0–24\ h}$ = 0.6), **THC glucuronide** ($c_{max}$ = 277 and $AUC_{0–24\ h}$ = 2030), **HHC glucuronide** ($c_{max}$ = 165 and $AUC_{0–24\ h}$ = 1540), **THC sulphate** ($c_{max}$ = 61 and $AUC_{0–24\ h}$ = 211), **HHC sulphate** ($c_{max}$ = 197 and $AUC_{0–24\ h}$ = 1830), and **total curcuminoids** ($c_{max}$ = 678 and $AUC_{0–24\ h}$ = 6520) |
| Curcuwin Ultra+ OmniActive Health Technologies | |
| (50 mg, lot number CU20DNS3–096 (04)/069; 23) [182] | **Curcumin** ($c_{max}$ = 28.36 and $AUC_{0–6\ h}$ = 86), **DMC** ($c_{max}$ = 4.33 and $AUC_{0–6\ h}$ = 9.35), **BDMC** ($c_{max}$ = 1.05 and $AUC_{0–6\ h}$ = 0.49), **THC** ($c_{max}$ = 13.98 and $AUC_{0–6\ h}$ = 41), and **total curcuminoids** ($c_{max}$ = 43.83 and $AUC_{0–6\ h}$ = 133) |
| (100 mg, lot number CU20DNS3–096 (04)/073))[182] | **Curcumin** ($c_{max}$ = 54.1 and $AUC_{0–6\ h}$ = 162), **DMC** ($c_{max}$ = 7.98 and $AUC_{0–6\ h}$ = 20.28), **BDMC** ($c_{max}$ = 1.15 and $AUC_{0–6\ h}$ = 0.82), **THC** ($c_{max}$ = 26.24 and $AUC_{0–6\ h}$ = 81), and **total curcuminoids** ($c_{max}$ = 86.98 and $AUC_{0–6\ h}$ = 274) |
| **Patients** | |
| Micronized powder (National Cancer Institute); Smoker (≥ 50 years and ≥ 8 rectal ACF)[192] | |
| (2 g/day; 30 days; 20)[192] | **Plasma**: **curcumin** ($c_{max}$ = 7.3/3.8; pre/post treatment)<br>**Rectal mucosa**: **Curcumin** ($c_{max}$ = ND/4.21; pre/ post treatment) |
| (4 g/day, 30 days;) [192] | **Plasma**: **curcumin** ($c_{max}$ = 15.8/78.5 ng/mL; pre/post treatment), **Rectal mucosa**: **curcumin** ($c_{max}$ = 3.8/4.5; pre/ post treatment) |
| Capsule (Laboratorios Admira S.L. (Alcantarilla, Murcia, Spain; 65 mg transresveratrol 190 mg turmeric extract 125 mg flaxseed extract and 125 mg red clover extract; 296 mg phenolic compounds); Breast cancer patients)[193] | |
| (3 x capsule (121 mg curcumin, 15 mg BDMC and 43 mg DMC) / day from (diagnosis to surgery and 4–6 h before surgery); 39)[193] | **Plasma**: **free curcumin** = 5.26 nM, **BDMC** = 3.89 nM and **DMC** = 2.45 nmol<br>**Normal mammary tissue: free curcumin** = 198 pmol/g ~ 1 μM, **BDMC** = 8.78 pmol/g ~ 0.05 μM and **DMC** = 44 pmol/g 0.2 μM)<br>**Malignant tissue**: **free curcumin** = 109 pmol/g~ 0.2 μM, **BDMC** = 2.73 pmol/g~5 nM and **DMC** = 13 pmol/g~ 22 nM) |

could be comparative with its concentration in the tumour. In this case, it could be assumed that most effective clinically tested oral formulations could achieve a micromolar curcumin concentration in the tumour tissue. It cannot be neglected, that similar concentrations could also be expected in the normal healthy tissue. On the other hand, curcumin toxicity is low, and any side effects are tolerable. In addition, curcumin displayed a protective effect against some disorders associated with carcinogenesis and side effects of used anticancer therapies. It is implied, that its distribution in the normal tissue could be a part of its therapeutic effects. The question is whether if the curcumin intratumoural concentration is reached it may already display antimetastatic effects. As far as we can predict from in vitro studies (e.g., table 1), some suggest that this assumption is possible [69,88–92,94,97,99,102–104,109,111–113,117, 118,120,121]. However, to achieve full clinical potential of curcuminoids, it is sometimes necessary to increase their bioavailability and bioactivity. Therefore, other curcuminoid formulations such as nanoformulation for metastasis suppression are intensively developed.

Although the main goal in the formulation of curcuminoids is their accumulation in the tumour tissue. Some studies suggest, their benefit could also be achieved outside of the tumour tissue. For example, NANOCurc (lipid-polymer nanoparticles; d=177.3 ± 6.2 nm) significantly increases curcumin efficacy in the reduction of cancer cell adherence and TNF-α activation of endothelial cells [60]. NANOCur display significantly higher cellular uptake after TNF-α activation against free curcumin.

## 4. Curcuminoid administration: influence of curcumin administration route on its bioavailability and therapeutic effectivity

The curcuminoid levels in the blood, or tumour tissue and their clinical/biological effects are strongly dependent on the method of their administration. Intravenous administration is often used in biological studies, but not as often as in clinical studies. Transferability of results can be strongly limited. On the other hand, in the case of nanodrugs such as liposomal formulations, intravenous application is a common route [200]. It should be mentioned that intravenous formulation of the curcuminoid (Lipocurc™) was also studied in clinical trials [187]. The highest observed concentration of curcumin and tetrahydroxycurcumin in the blood was 2.3 and 0.265 μg/mL, respectively. This result suggests that proportions of metabolically transformed curcumin are sometimes lower than with oral application. It is important to note, that in the case of oral application, curcumin level was significantly lower ($c_{max}$ = 0.553 and $AUC_{0\text{-}inf}$ = 3050 ng/mL) [177].

Although oral application is more comfortable for the patients, the intravenous route could lead to microsomal concentration of curcumin in the blood (6.6 μM) and tumour tissue and thereby higher therapeutic efficiency. Nevertheless, curcumin blood level/therapeutic efficiency

could be significantly increased by its application in the form of metal complexes [201]. In the case of copper curcumin, its highest concentration was 125.8 μg/mL (349 μM). Considering these results obtained in the mice model with metastatic breast cancer to be transferable, application of copper curcumin noticeably slowed down tumour growth, delayed metastasis, and prolonged survival in mice. Nevertheless, it was not enough to fully eradicate the tumour. And it is hard to imagine that intravenously applied curcumin could reach even higher concentrations. Here it is necessary to note curcumin's possible toxicity. For example, Lipocurc was well tolerated when administered intravenously, but at dosages $\geq$ 120 mg/m$^2$, transient echinocyte formation in red blood cells was observed with a concomitant increase in mean cell volume [187]. Curcumin is also an inhibitor of the hERG K+ channel [202] and thereby possible cardiotoxicity cannot be neglected [203]. Ranjan et al. reported, that high curcumin doses, such as 6 μM (in the case of liposomal formulation) can decrease its activity by up to 30% [202]. The above suggests that increasing physiological concentration of curcumin can increase its effectivity, but cannot be excluded, that serious side effects, may occur at lower curcumin concentrations than full tumour eradication. And formulation methods and drug delivery systems can strongly increase curcumin bioavalibity and bioactivity, but not unlimited.

It also suggests that curcumin cannot treat cancer by itself. However, numerous high impact studies suggest that correctly applied curcumin could be a promising agent for the enhancement of anticancer treatments. For example, intraparental application of NanoCurc displayed maximal concentration 17 mg/mL (47 μM) in the mice model [204]. Nevertheless, its combination with gemcitabine resulted in strong effects against pancreatic carcinoma. Tumour growth was blocked and any micrometastases in lung, lymph nodes or peritoneum were not found. In the case of both single agents, micrometastases were found in the lymph nodes. This effect could be explained by higher intra-tumoural curcumin levels (>2.5 μg/g of tissue), which was enough for the potent inhibition of NF-κB binding to DNA after applying both agents. In contrast, only applying NanoCurc™ displayed ~4-fold lower intratumoural curcumin levels and both single applications did not display significant inhibition of NF-κB functionality.

The choice of the optimal route is not universal and strongly depends on the type of cancer. More detailed information about methods of curcumin administration (oral, inhalation and intratumoural) are provided in the next subchapters.

### 4.1. Oral administration

Oral administration has been the main method of drug administration for thousands of years, with strong advantages such as safety, good tolerance and compliance, low treatment costs, and convenience to the patients [205]. In this case, the relationship between curcuminoids and gut microflora should be considered. It could be explained by the paradox between curcuminoid limited bioavailability and observed anticancer effects.

After oral administration, curcumin can be metabolized by reduction (catalysed by enzymes of phase 1), conjugation (catalysed by enzymes of phase II), and microbial or non-enzymatic degradation (Fig. 4) [206].

During phase I metabolism, curcumin is mainly converted to tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin [207, 208]. During phase II, their glucuronide and sulfate O-conjugated metabolites are produced [207–209]. Nevertheless curcuminoids, glucuronide and sulfate conjugates are can be to simpler phenolic compounds such as ferulic acid and in the cecum and colon [207,208]. However, microbial transformation of natural curcuminoids can mean a loss of biological activity, but not necessarily [210]. In the case of tetrahydroxycurcumin and octahydrocurcumin, some high impact studies suggest, that their anticancer effectivity could be at least comparable with natural curcumin [211–214]. On the other hand, curcumin, unlike tetrahydrocurcumin, can directly interact with the STAT3 SH2 domain, suppress its dimerization and subsequent nuclear translocalization [215]. In the case of curcumin sulfate and glucuronide curcumin, their possible inhibitory effects against EGFR and NF-κB cannot be excluded [216] Nevertheless, glucuronide curcumin could have significantly lower cellular uptake compared to natural curcumin. Jamil et al. reported, that MDBA-231 human breast cancer cells can metabolize curcumin to curcumin sulphate and subsequently excrete it from the cells [217]. On the other hand, tumours can produce sulfatase [218], which can convert curcumin sulphate and glucuronide to natural curcumin [219]. Besides nanoparticles could protect transported curcuminoids against gut microbiota. Nevertheless, the possibility of crossing the intestinal barrier must be taken into account [220].

On the other hand, curcumin accumulated in the gastrointestinal tract displayed strong effects on intestestinal microflora (microbial richness, diversity and composition) [221–223]. During carcinogenesis, levels of Alistipes, Fusobacteria, Porphyromonadaceae, Staphylococcaceae, Coriobacteridae, Methanobacteriales and Akkermansia spp. are enhanced, while others are permanently reduced, such as Lactobacillus, Bifidobacterium, Ruminococcus, Roseburia, Faecalibacterium spp. and Treponema [224]. Curcumin application is associated with the increase in Lactobacillus, Bifidobacterium, and butyrate producing bacteria and the decrease in Prevotellaceae, Coriobacterales, Enterobacteria, and Enterococcus [221]. On the molecular level a decrease in production of amino acids and inflammatory factors and an increase in butyrate levels can be expected Dependent on the human condition, intestinal microflora can produce various different metabolites (reduced, demethylated form hydroxylated forms of curcumin). [208] Possible alternative mechanisms are shown in Fig. 5.

However, the question is whether all this is sufficient for effective antimetastatic therapy. Results obtained from the in vitro studies could suggest, that orally applied lipid formulations could be associated with potent antimetastatic effects, especially in combination with other therapeutic modalities. For example, in the case of the mice model with metastatic breast cancer, phospholipid nanoparticles containing curcumin and photothermal dyes reduce pulmonary nodules by more than an order of magnitude [134]. Applied curcumin dose was 50 mg/kg per 2 days (~3.5 g for human). In the clinical trials, the orally applied Meriva formulation was associated with the decrease in levels of some metastatic factors (e.g., IL-6, TNF-α and TGF-β). [41] Similarly it was reported that administration of BCM-95 (BIO-CURCUMIN®) in dose 500 mg/d can reduce NF-kB activity in PBMCs and blood levels TNF-α of in patients with none-alcoholic fatty liver disease [225]. In clinical trials, maximum micromolar concentration levels were achieved with oral administration of both curcuminoid preparations. Dhillon et al. reported, that anti-inflammatory effects of curcuminoids can be sometimes observed during lower plasma concentration (~tens of nanomoles/l) [226].

In the case of digestive tract cancers, oral curcumin administration could display a significant therapeutic impact [145,146,227]. For example, patients with colorectal cancer after curcumin administration (3.6 g/day, 7 days) displayed a significant decrease in 3-(2-deoxy--beta-di-erythro-pentafuranosyl)-pyr[1,2-alpha]-purin-10(3 H)-one (M (1)G; DNA oxidation product) and COX-2 protein level [146]. Combination of curcumin and triple therapy significantly reduce all scores of active, chronic and endoscopic inflammation in patients with chronic gastritis compared to the baseline and to the triple therapy group [145]. This effect was associated with a decrease in oxidative markers and DNA damage and an increase in the antioxidative capacity of gastric mucosa. Another significant benefit of oral curcumin formulations could be related to the prevention of oncological diseases, for example by reducing DNA damage and oxidative stress [144–146].

It implies, that micromolar blood levels of curcuminoids available in oral formulations could be sufficient to significantly reduce tumour inflammation, decrease cancer risk and inhibit some metastatic mechanisms. Relevant in vivo studies suggest that oral administration of suitably designed curcumin formulations in combination with other cancer agents could lead to a stronger antitumour and antimetastatic

effects.

### 4.2. Inhalation administration

The inhalation administration is a promising alternative strategy for the delivery of anticancer agents into lung tumours. Agents could bypass the intracellular and extracellular drug-metabolizing enzyme in the gastrointestinal tract and liver and their therapeutic index would be significantly higher. [228] On the other hand, inhalation administration may be limited by the toxicity of the injected substances to lung tissue, their rapid clearance and lipophilicity. Here it may be interesting to note, that curcumin inhalation formulation displays favourable toxicity to lung cells and tissue. In addition, it was reported that there may be a protective effect against chemo and radiotherapy [229,230].

Extrapulmonary distribution is dependent on the aerodynamic diameter and on the patients breathing pattern [228]. Large particles (d$>$ 5 μm) are filtered by inertial impaction in the upper airways (mouth, trachea and main bronchi). Medium-sized particles (d = 1–5 μm) are gravitationally distributed to the central and distal tracts. Small particles (d = 0.1 −1 μm) are mostly exhaled. Ultra-small particles are moved (d $<$ 100 nm) by random Brownian motion to alveolar regions, while particles that are 10 nm and smaller stay in the tracheo-bronchial region due to their high diffusion coefficients [231]. Aerodynamic characteristic of curcumin powder (MMAD 3.81 μm) implies its absorption into the lung tissue [232]. A problem could be its absorption through the lung epithelial barrier. Drug absorption in the lung epithelia is primarily dependent on their molecular weight and lipophilicity [228,233]. In general, absorption of small hydrophobic molecules takes minutes, while in the case of large hydrophilic molecules it takes hours. Particles bigger than 200 nm are usually captured by macrophages in the lung tissue. Formulations of curcuminoids can significantly improve distribution and control their uptake into the bloodstream/tumour tissue [232]. Some studies imply that this strategy could lead to a significant improvement in curcumin pharmaceutical efficiency (Table 4). Nevertheless, other clinical trials are requested for validation.

Results obtained from relevant in vivo studies suggest that there is high potential in this strategy [229,237,239,241]. In primary lung cancer models (rats exposed to 3-methylcholanthrene and diethylnitrosamine), the inhalation of curcumin nanoparticles (liposomal curcumin dry powder) sometimes resulted in decreased levels of MDA, TNF-α and VEGF and activation of caspase-3 [239]. Its antitumour effectivity was significantly higher than in the case of curcumin powder and gemcitabine. This approach could also be used for the treatment of lung metastases. Su et al. reported that silica nanoparticles modified curcumin significantly and suppressed the formation of lung metastases in the melanoma bearing mice [237]. This effect was associated with the reduction of Il-6 and IL-8 in the lung tissue. However, the decrease in TNF-α levels was significantly higher than in the case of curcumin powder. It is probably caused by higher phagocytosis of curcumin nanoparticles compared to curcumin powder. In addition, the inhalation administration with a suitable curcumin formulation displayed potent protective effects on the non-tumour tissue lung tissue, for example alleviation of inflammation, or radiation pneumonitis [229].

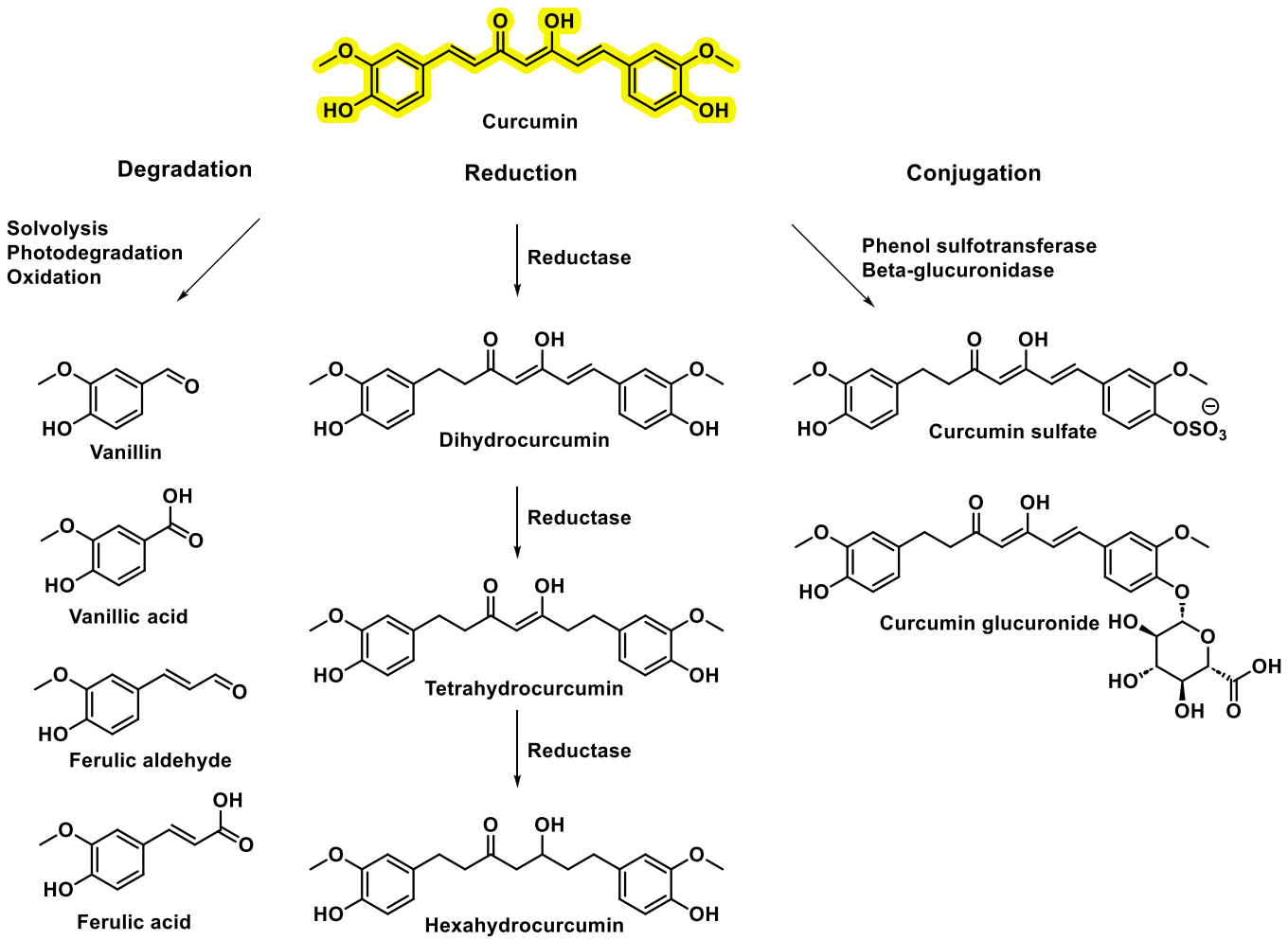


**Fig. 4.** Metabolic transformation of curcumin (classical schema).

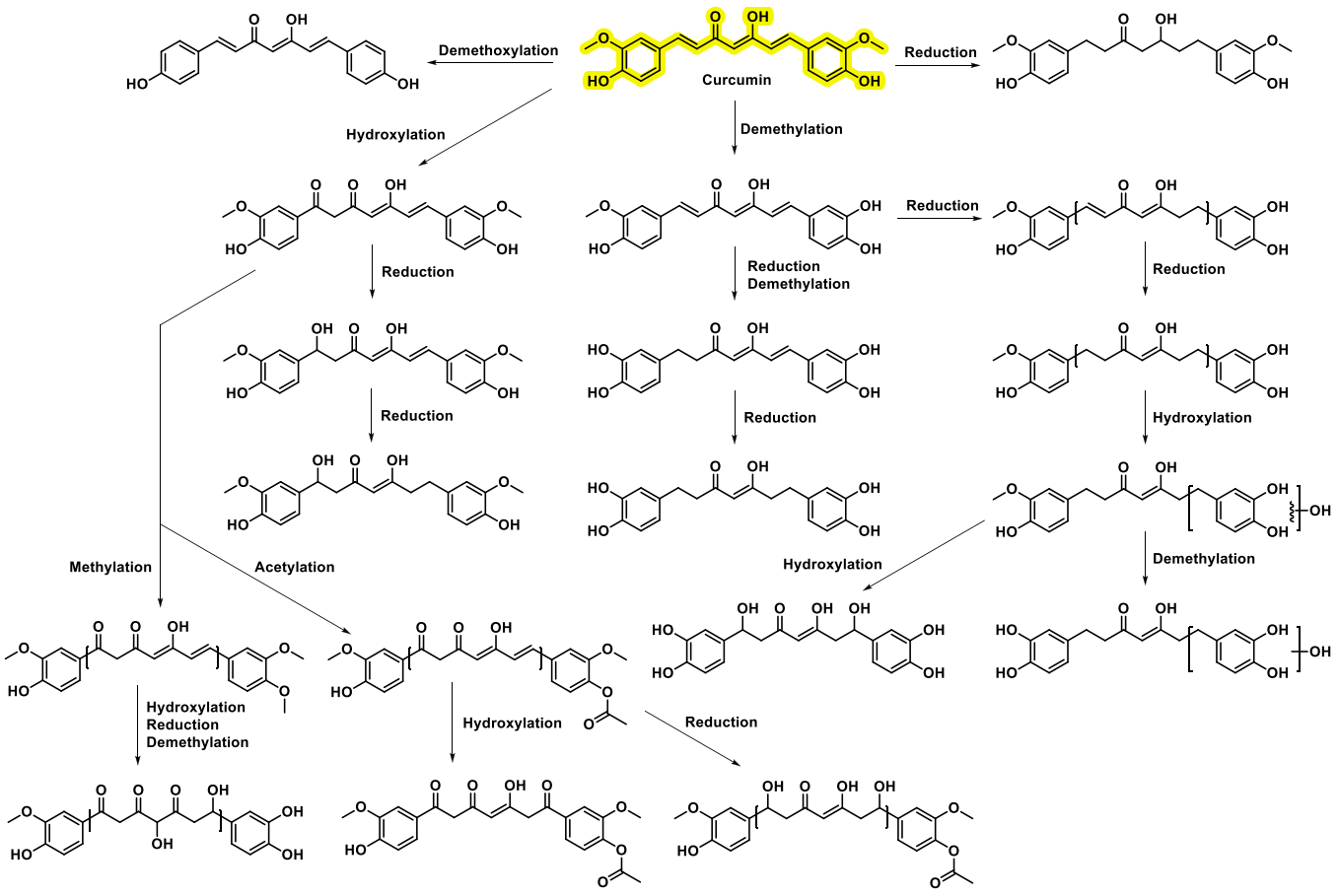


**Fig. 5.** Alternative models of curcumin transformation by gut microflora.

### 4.3. *Intratumoural therapy*

Effective methods of antimetastatic treatment could be based on curcumin intratumoural therapy. The first successful intratumoural therapy was based on bacterial toxins which were administered over 100 years ago, by Dr. William Coley [242,243]. In the present time IT therapy is a intensively studied therapeutic method [244]. One key factor, which controls effectivity of IT therapy is drug distribution in correspondence with the molecular size, charge, and other properties in the tumour and the surrounding tissues. Agents must target the tumour tissue whole and avoid clearance by lymphatic drainage and cell absorption. Compared to proteins, small molecules displayed high potency and improved tissue penetration. Nevertheless, their tumour retention can be significantly improved by suitable formulation (e.g., liposomal carriers, polymeric and hydrogels) [245–247].

Some high impact studies suggest, that suitably designed intratumoural formulations of curcumin could significantly improve its intratumoural concentration and thus its therapeutic efficacy [247–250]. For example, curcumin intratumoural administration (20 mg/kg; mice with H22 tumour) doubles apoptosis rates in the tumour tissue [250]. Nevertheless, in the case of liposomal nanoformulations, curcumin apoptotic effectivity (25–30%) increased fivefold against baseline and blank liposomes. Similarly, these formulations increase Caspase-3 overexpression and decrease VEGF levels. Gao et al. reported, that peritumoural/intratumoural injections of mesoporous silica nanoparticles modified by pegylated lipid bilayer containing curcumin and paclitaxel displayed significantly higher reduction of 4T1 tumours than the corresponding intravenous application in the mice model. [251] Pharmacokinetic study (Sprague-Dawley rats; 18 mg curcumin and 3 mg paclitaxel/kg) showed that the peritumoural route is associated with significantly better curcumin pharmacokinetic parameters such as $C_{max}$ (6.2 (16.8 μM) vs 4.3 μg/mL) and $AUC_{0–8\,h}$ (89 vs 59 μg.h/mL) compared to intravenous administration. In connection to this, it should be noted, that intraparental application of NanoCurc displayed maximal plasma concentrations of 17 mg/mL (47 μM) in the mice model with pancreatic cancer [204].

Intratumoural application of TriCurin (combination of curcumin, epicatechins, and resveratrol) induced large necrotic areas in the human papillomavirus-positive head and neck squamous cell carcinoma in the mice model [249]. Based on in vitro studies, it can be assumed that the intratumoural levels of used substances can be in the micromolar range. On the other hand, TriCurin application (liposomal formulation of curcumin with resveratrol and epicatechin gallate) is also associated with repolarization of the TAM phenotype (from M2 to M1) and activation of NK cells, resveratrol and epicatechin gallate can also directly kill tumour cells [46], and sublethal TriCurin doses can repolarize the TAM phenotype [252]. However, we cannot expect, that the intratumoural route will always lead to a better therapeutic effect compared to the intravenous application. For example, Chang et al. reported, that intratumoural curcumin application (unformulated and liposomal formulation) displayed a significantly higher decrease in tumour volume compared to the intravenous administration [253]. However, no significant difference was observed in the case of the tumour mass.

An interesting variation of this strategy could be tumour excision and subsequent curcumin application into the tumour site. In the melanoma mice model, curcumin oil nanoemulsions with prolonged retention applied this way resulted in very strong suppression of tumour recurrence and metastatic activity [128]. The effect of natural unmodified curcumin was significantly lower.

The above clearly indicates that the intratumoural route can

**Table 4**
Examples of tested inhalation curcumin formulations.

| Formulation | Model | d/da | Exp. condition | Effect |
|---|---|---|---|---|
| Core–shell microparticles[234] | A549 | 3.8 μm | (0–200 μg/mL; 24–72 h) | Slow cytotoxic activity, strong antibacterial activity |
| Chitosan microspheres with 2-HP-β-CD and doxorubicin[235] | A549 | 2.58/3.8 μm | (0–20 μM; 24–72 h; in solvent) | $IC_{50}$ (11.3, 9.2 and 6.5 μM, 24, 48, and 72 h, respectively) |
| Chitosan microspheres with 2-HP-b-CD and doxorubicin and elastin[235] | A549 | 4.3/4.9 μm | (0–20 μM; 24–72 h, in solvent) | $IC_{50}$ (8.5, 5.2 and 3.4 μM; 24 h, 48 h and 72 h), ↑cytotoxicity |
| Pectin-PVP microparticles[236] | fertilized chicken eggs | $D_{50/90}$ 0.99/ 2.74 μm | 7 mg; 13 days/ in calf serum | ↑angiogenesis activity |
| | A549 | | 2.5–250 μg/mL; 24 h; in solvent | ↑cytotoxicity |
| Pluronic modified silica particles [237] | mice with lung metastasis of B16F10 melanoma | 7.59 nm/ 1–3 μm | 12 mg; 7 d; aerosol inhalation | ↓**Inflammation** ( ↓IL-6 and ↓IL-8; approximately half of cytokines level) and ↑TNF-α (slightly), ↑higher weight |
| Curcumin in physiological solution[238] | LPS-stimulated A549 cells | - | under air-liquid interface (0–100 μM; aresol) and submerged conditions (0–20 M; in the medium) | Lower IL-6 and IL-8 production; higher curcumin effectivity under air-liquid interface |
| Proliposomes with HPβCD[232] | A549 | 126 and 150 nm /2.10 and 3.18 μm* | 0–200 mg/mL | ↑cytotoxicity, ↓IL-6, ↓IL-8 and ↓TNF-α |
| | Albino rats | | curcumin 1 mg; intratracheally and endotracheal; 24 h | **Lung tissue** ( ↓$T_{max}$ (from 2 to 1 h), ↑$C_{max}$ (from 1.2 to 5.0 and 3.3 μg/mL), ↑$AUC_{0-24}$ (from 6.9 to 12.5 and 9.9 μg/mL), ↑$AUC_{inf}$ (from 7.2 to 19.8 and 12.3 μg/mL), ↑MRT (from 4.8 to 7.5 and 7.3 h) |
| Liposomal curcumin Dry powder[239] | A549 and BEAS-2B cells | 94 nm/5.81 μm* | 0–100 μm; I medium; 24 h | ↑cytotoxicity and ↑cytoselectivity for cancer cells |
| | Sprague–Dawley rat with MCA and DEN induced lung cancer | | curcumin 1 mg; dry powder inhalation; 4 d | Tumour factor ( ↓VEGF ↓BCL-2, ↓TNF-α) and oxidative stress ( ↓MDA), stimulated apoptotic signalling ( ↑Caspase-3) and ↓tumour nodules |
| Mesoporous polydopamine nanoparticles[229] | BEAS-2B cells | | 0–125 μm | ↓apoptosis |
| | Sprague-Dawley rats with single dose of 15 Gy | 290 nm/5.17 μm * | curcumin 1 mg; 1xpre-irradiation dose and 1/week post-irradiation dose/4 weeks; sprayed the drug formulations | Reduction of haemorrhaging and pulmonary fibrosis, tumour factors (TNF-α, IL-6, IL-1β and TGF-β1) and oxidative stress (MDA) induction of SOD |
| Milled formulation (curcumin and paclitaxel 3:1)[230] | A549 and Calu-3 cells | $d_{50}$ = 2.2 μm /3.12 μm * | 0–100 μM; 72 h; In medium | $IC_{50}$ (18.9 and 22.9 μM), |
| | Beas-2B | | | n.d. |

(*continued on next page*)

**Table 4** (*continued*)

| Formulation | Model | d/da | Exp. condition | Effect |
|---|---|---|---|---|
| Microrods with TNF-α siRNA [240] | dTHP-1 and A549 | 2.85 μm | 0–100 μg/mL-20% curcumin loading capacity | Slow cytotoxicity, strong reduction of TNF-α |
| Curcumin RBP exosomes[241] | LPS-activated RAW264.7 cells | - | 5 μg; 4 h; in medium | cytokine level (<br>↓TNF-α,<br>↓IL-6 and<br>↓IL-1β, and<br>↓RAGE downregulation curcumin cellular uptake |
| | Mice with LPS intratracheal administration | | 5 μg; 24 h; intratracheally | **Lung tissue and BAl fluids** (T<br>↓NF-α and<br>↓IL-1β) |

d = mean particle da = aerodynamic diameter; Mass median aerodynamic diameter (MMAD).

significantly improve curcumin bioactivity and prolong its effect and enhance its activity against primary tumours, including its metastatic activity. However, can intratumoular administration of curcumin directly target micro and metastases? Besides the suppression of cell migration and invasiveness of the primary tumour, long-term exposition to curcumin micromolar concentrations could also hack tumour exosomes and induce formation of exosomes with antitumour activity targeted in part at (pre)metastatic sites. Another step could represent direct intratumoral application curcumin.

## 5. Limitations of curcumin applications

Despite very promising results from in vitro and in vivo studies (Tables 1 and 2), curcumin displays significant limitations for its wide clinical use in the anticancer treatment [152]. For example, after oral application of 12 g of curcumin extract, serum level of curcumin was only 57.6 ng/mL. [156] Curcumin most probably had no significant selectivity for tumour tissue [193]. This strongly suggests that oral application of curcumin cannot have a direct effect on tumour tissues/cells and its antitumour effect is mostly caused by modulation of the gut microbiota. A direct effect (cytostatic, even migrastatic) on cancer cells can be observed at least at micromolar concentrations of curcumin. Hence, some limitations of the use of curcumin in the anticancer treatment should be considered (see overview in the Table 5).

Low curcumin bioactivity is mostly caused by its low solubility (456 μg/L) [154,155] and biostability. Currently, pharmaceutically approved excipients (cyclodextrins, oligosaccharides, polymers) can be used, which can significantly improve the solubility of curcumin [159, 254,255]. Lipid nano and microparticles are another available option for improving the efficacy of curcumin. Clinical trials have shown that their applications are associated with significantly increased curcumin blood level versus unformulated curcumin extracts (Table 3). Golden milk can be easily prepared at home and lipidic curcumin formulations such as Meriva formulation are commercially available. In this context, it should be mentioned that nanoparticles with suitable size display significantly higher bioviability than low molecular compounds (Fig. 6) [256].

Recently, some advanced nanoparticles system with excellent anticancer/antimetastatic efficacy have been developed and tested (in biological studies; **table XXX**), such as gold nanoparticles containing curcumin and paclitaxel, or phospholipids nanoparticles for the transport combination of curcumin and IR780 (photothermal dyes) [134, 257]. However, their approval for clinical practice cannot be expected in the near future. Because, therapeutic usability and safety of gold nanoparticles and IR780 will need to be validated be clinical trials.

Higher curcumin efficacy can also be achieved by changing the method of administration. Oral administration of Lipocurc™ displays

**Table 5**
Limitations of the use of curcumin and their possible solution.

| Limitation | Importance | Solution | Applicability |
|---|---|---|---|
| Low solubility<br>Low stability | High<br>High | Drug delivery systems/ formulations | Cyclodextrin - available<br>lipidic formulation -available<br>oligosaccharides -available |
| Insufficient bioactivity against tumour cells | Medium | Combination with other agents/ therapy | Polyphenols - available<br>Piperidine - available |
| Low distribution into cancer tissue | High | Drug delivery systems | Lyposomes - available<br>Solid nanoparticles -experimental<br>Modified lipidic nanoparticles -experimental |
| | | Alternative route | Intravenous - clinical trial<br>Inhalation -experimental<br>Intratumoural - experimental |
| Toxicity | Low | Drug delivery system/ nanoparticles | Too little knowledge to make decisions |
| Loss of therapeutic efficiency | Low | Combination with other agents/ therapy | Too little knowledge to make decisions |

value of blood $c_{max}$ 0.553 ng/mL [177]. In this case of an intravenous formulation, the highest concentration observed was 2.3 μg/mL [187]. In a mouse model of lung cancer, inhalation administration significantly increases therapeutic effectivity [237]. Another step could be direct intratumoural application of curcumin. Intraparental administration of nanoformulated curcumin (Sprague-Dawley rats) displays a higher value of $c_{max}$ than intravenous administration (6.2 vs 4.3 μg/mL) [251]. The results of the studies presented in the Table 1 suggest that archival concentrations could be associated with important anti-tumour/antimetastatic effects.

On the other hand, an important benefit of curcumin could be to reduce the risk of cancer or its recurrence. Clinical studies have shown that curcumin can significantly decrease the effect of various carcinogens, or alleviate various pathologies associated with carcinogenesis [144–146,192,258,259]. This suggests its application as protective agents for the subjects at risk. For this purpose, oral and inhalation administration are suitable due to the ease of application. However,

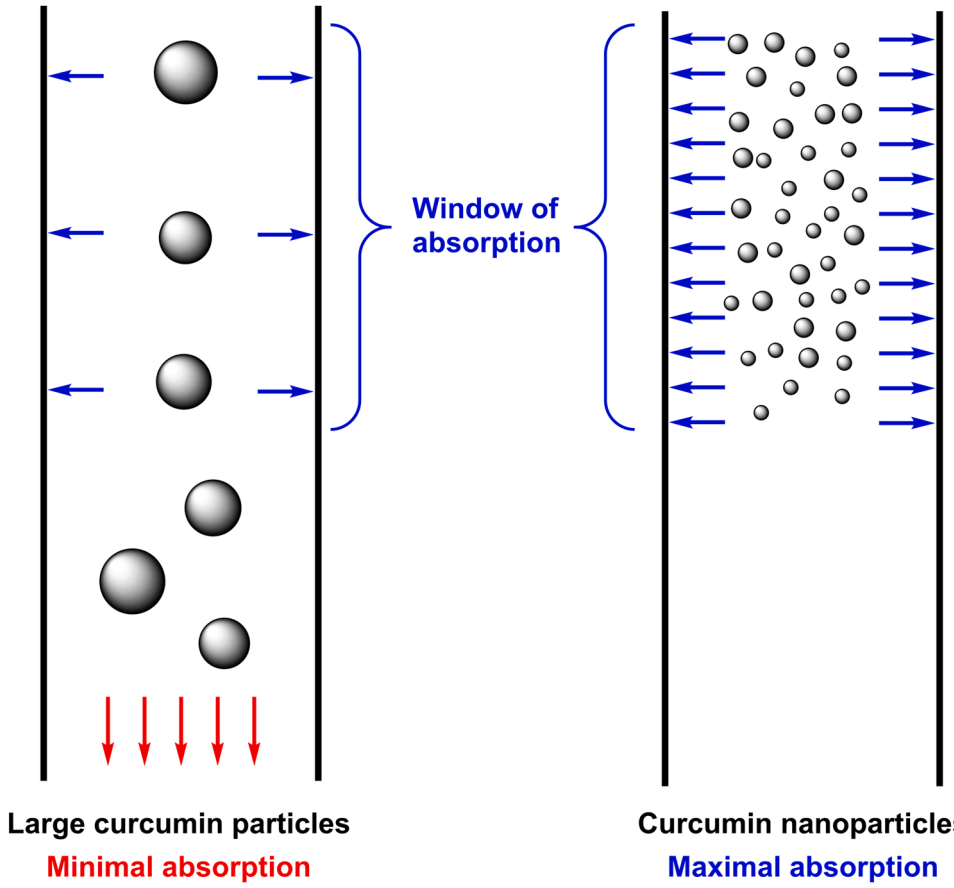


**Fig. 6.** Influence of curcumin nanoformulations on its bioaviability. Bulky particles of curcumin powder are poorly soluble and thus the bioabsorption/bioavability curcumin is severely limited. On the other hand, nanoformulated curcumin can be easily dissolved and effectively absorbed in the gut.

commercially available formulations of curcumin are intended only for the oral administration.

It follows from the foregoing that even efficacy of curcumin formulation is likely to be limited. A possible solution could be its application with other nature compounds such as piperidine (as constituent of black pepper, which is part of golden milk) or polyphenols. For example, the combination of curcumin with two compounds, resveratrol and epicatechin gallate (food-derived natural polyphenols; 4:1:12.5, molar ratio) exhibited microsomal values of $IC_{50}$ against head and neck cancer cell lines and potent anticancer effects in mice model of head and neck cancer [249].

Possible limitations of curcumin, especially in the long-term applications, may also be curcumin toxicity or loss of therapy sensitivity. Although curcumin does not show significant selectivity for tumour tissue, it has potent cytoselectivity for tumour cells [197]. In this case, normal cells/tissues display protective effects (decrease of oxidative stress, or protection of tissues from hypoxia) [257,260]. Nevertheless, Storka et al. reported possible toxic effect of curcumin in lipidic formulations against red blood cells (in vitro) [187]. However, no serious problem was not observed in a clinical study (healthy subjects). On the other hand, some patients with locally advanced or metastatic cancer have shown hematological adverse effects after intravenous administration of lyposomal curcumin (300 mg/$m^2$ over 6 h) [261].

Curcumin is a direct inhibitor of NF-κB signalling and decreases the activity and expression of P-glycoprotein (drug efflux pump) [262]. Curcumin is therefore well known as a promising substance for suppressing of multidrug resistance. However, in this case of a cholangiocarcinoma model (golden hamster exposed by nitrosamine), loss of inhibition activity against NF-κB was observed (six-month application) [142]. This suggests that although the risk of resistance is low, it cannot be completely excluded.

## 6. Future direction

Numerous studies strongly imply, that curcumin is a promising antimetastatic agents. High impact studies and clinical trials suggest that curcumin application could enhance clinically used therapies, for example by reducing side effects of the main therapy. Curcumin formulations, especially in combinations with other polyphenols, piperine, represent promising agents for reducing the risk of cancer and its recurrence. Nevertheless, its therapeutic effectivity is severely limited by its bioactivity and biostability.

Nanoparticles are a well-studied system for drug transport, especially for anticancer agents with a high therapeutic impact [263–267]. In the case of curcumin, nanoformulations can significantly increase its stability and physiological concentration and thereby its anticancer effect [158]. However, nanoparticle accumulation in the tumour tissue can significantly improve their modification by tumour selective ligands such as RR-11a (synthetic enzyme inhibitor of Legumain, an asparaginyl endopeptidase) [268]. To increase therapeutic effectivity, nanoparticles together with curcuminoids can transport other anticancer agents such as anticancer peptides [115], photothermal dyes [134], cytostatic drugs (e.g., paclitaxel) [83]. Examples of studied curcumin nanoformulations and other antimetastatic systems are shown in Table 6.

Newly developed curcumin nanoparticle systems displayed high potential in the improvement of curcumin therapeutic effectivity. For example, curcumin formulated with double hydroxide nanoparticles displayed strong antimetastatic activity against A172 cells. [125] The nanoparticles represented submicromolar concentrations of curcumin (0.27 μM) and decreased cell migration and invasiveness by

approximately one-third, while the effects of unformulated curcumin were negligible. In combination with used anticancer groups, the nanoparticles can also significantly boost curcumin's anticancer effectivity. Application of nanofibrous microspheres containing curcumin and docetaxel (8 g/kg; 1:1) increase in mean overall survival (OS; 48 days vs 18 days) compared to the control in the mice model with colon cancer [288]. In the case of free drugs, formulated and free docetaxel OS was 42, 39 and 29 days. A similar trend was observed in the reduction of abdominal metastases. A combination of the bortezomib and curcumin (1 and 1.337 mg/kg, respectively) transported by alendronate coated with poly-lactic-co-glycolic acid nanoparticles displayed strong therapeutic potential in the model of breast and bone metastases (mice with bone-implanted MDA-MB-231) [136]. Nanoparticles application sometimes decreases macrophage infiltration in bone metastases. Beside classically used drugs, curcumin formulation could be used for the enhancement of the novel therapeutic modalities such as photothermal therapy. Microemulsifying nanoformulations of curcumin and IR780 (photothermal dyes) decrease the number of metastatic nodules in the lung compared to single agents by more than two orders of magnitude compared to the control [134].

In clinical practice, other routes of administration, such as intravenous, pulmonary, and especially intratumoural administration, can significantly enhance the efficacy of curcumin. The question is whether improving the concentration of curcumin in the tumour could give any therapeutic quality. Beside significantly reducing tumour mass, and cell migration, another promising effect of curcumin could also be that it could target tumour microflora. It is well known that *Helicobacter pylori* is strongly associated with the induction and development of gastric tumours, which includes metastatic activity [291,292]. It was reported that curcumin displayed potent activity against various strains of *Helicobacter pylori* (MIC ~ 5–50 μg/mL) [293,294].

In the case of other tumour types, it was also observed, that its specific microflora supports their development [295–298]. Interestingly, metastases have a different proportion of microflora compared to the primary tumour. Curcumin and especially its nanoformulations are effective against certain pathogenic microorganisms such as *Staphylococcus aureus*, *Escherichia coli* and *Mycoplasma*, which have been identified as representatives of the tumour microflora (Table 7) [299].

However, although we consider these readings to be transferable, they are usually too high (approximately hundreds of micromoles) with exceptions for oral and possibly intravenous administration. In comparison, the cytotoxicity of curcumin against tumour cells (represent by $IC_{50}$) is orders of magnitude higher. It could be strongly suggested that curcumin doses, which can effectively target intratumoural microbiota, but most probably tumour cells will die first.

There are three points against these claims. Firstly, the value of curcumin $IC_{50}$ for the tumour microflora such as *S. mutans* (10.2 μM) could be more comparable with $IC_{50}$ than minimal inhibition concentration (MIC; 175 μg/mL) [319]. Besides, in the case of *A. baumannii* (ATCC 19606) curcumin combination with other agents such as EGCG display significantly antimicrobial effectivity (MIC = 4 μg/mL) [324]. It could be implied, that the therapeutic effect of above discussed Tricurin (curcumin formulation with resveratrol and epicatechin gallate) could also be associated with the reduction of tumour microbiota.

Secondly, significantly lower curcumin concentrations than MIC can still display potent effects against tumour microbiota (e.g., reduction biofilm formation, protease secretion) [303,329].

Thirdly, the above discussed MIC values were mostly obtained by using normal unformulated curcumin. At such concentrations, the curcumin used can be expected to be highly aggregated and its therapeutic ability could be severely reduced. In line with this hypothesis, the MIC value of curcumin quantum dots against *P. gingivalis* (ATCC 33277)was 1.1 μM [329]. This suggests that curcumin may act against the intratumoural microflora approximately as effectively as against cancer cells, and its antimicrobial toxicity is an integral part of the anticancer effect.

The above clearly shows the therapeutic potential of curcumin in

**Table 6**
Curcumin anticancer systems with the emphasis on antimetastatic activity.

| **Model and experimental conditions (route and dose)** | **Curcumin effect**<br>**Assay** (value of tested effect in the curcumin presence/ original value of tested effect[a]; dose / time |
|---|---|
| **Solid core system** | |
| Double hydroxide (d = 119 nm)[125] | |
| A172[125] | **Cell** ( |
| | ↓PI3K, |
| | ↓AKT and |
| | ↓mTOR), **Apoptosis** (4.85% and 6.59%; 0.1 and 0.5 μg/mL/24 h), **Sratch** (1/2 and 1/3; 0.1 and 0.5 μg/mL/24), **Migration** (68% and 59%; 0.1 and 0.5 μg/mL/18 h), and **Invasion** (69% and 64%;0.1 and 0.5 μg/mL/24 h) |
| Gold nanoparticles (d= 101/152; water/serum containing medium)[83] | |
| MDA-MB 231 an 4T1 | **Cell** ( |
| | ↑E-Cadherin, |
| | ↓STAT3, |
| | ↓VEGF), **Proliferation** (2/3 and ½; 10 μg/mL/24 h), **Sratch** (1/2 and ½; 10 μg/mL/36 h), and **Migration** (1/5 and 1/3; 10 mg/mL/24 h) |
| Mice with 4T1; IP, 50 mg/kg/d for 21 days | **Tumour** ( |
| | ↓STAT3, |
| | ↓MMP2, 3 and 9, |
| | ↓cyclin D, |
| | ↓VEGF), |
| | ↓tumour volume and zero neoplasticity in both mammary and hepatic tissues |
| Gold nanoparticles (d= 128/166 nm; water/serum containing medium) modified by curcumin and paclitaxel; 1:1, mass ratio[83] | |
| MDA-MB 231 and 4T1 | **Cell** ( |
| | ↑E-Cadherin, |
| | ↓STAT3, |
| | ↓VEGF), **Proliferation** (½ and ½; 10/24 h), **Sratch** (1/3 and 1/3/24; 5 mg/mL/24 h), and **Migration** (1/10 and 1/6; 5 mg/mL/24 h) |
| Mice with 4T1; IP 25 and 25 mg (curcumin and paclitaxel)/kg /d for 21 days | **Tumour** (Paclitaxel induced |
| | ↓STAT3, |
| | ↓MMP 2 and 3, |
| | ↓cyclin D, |
| | ↓VEGF), tumour volume and zero neoplasticity in mammary and hepatic tissues |
| Graphene Oxide (d =123 nm)[269] | |
| A549 and MDA-MB-231 | **Cell** ( |
| | ↑ROS and |
| | ↓ΔΨm) and **Proliferation** ($IC_{50}$; 17.8 and 49 μg/mL/48 h) |
| Graphene Oxide (d = 139 nm) curcumin and paclitaxel[269] | |

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**Table 6** (*continued*)

| Model and experimental conditions (route and dose) | Curcumin effect<br>**Assay** (value of tested effect in the curcumin presence/ original value of tested effect[a]; dose / time |
|---|---|
| A549 and MDA-MB-231 | **Cell** (<br>↑ROS and<br>↓ ΔΨm) |
| Superparamagnetic iron oxide nanoparticles modified with β-cyclodextrin and Pluronic (curcumin) and a free drug (gemcitabine)[270] | |
| Panc-1 and HPAF-II | **Panc-1** (CXCL12 activated (<br>↓CXCR4, NF-κB<br>↓, SHH) gemcitabine activated α-SMA<br>**Cell** (<br>↓RRM1 and<br>↓RRM2,<br>↑DCK,<br>↑hCNT<br>↓miR-21 and<br>↑miR-200a), **Proliferation** (>1/10; 15 +0.2 μM/48 h),<br>↓secondary tumourspheres,<br>↓cell migration) |
| Mice with HPAF-II; IP, Curcumin (100 μg) and gemcitabine (300 μg) twice a week, 7 weeks | **Tumour** (<br>↓Smo, E-cadherin,<br>↓N-cadherin,<br>↑Sufu,<br>↓Gli-1 and 2,<br>↓α-Sma, SHH),<br>↓Tumour mass,<br>↑elasticity tumour tissue<br>↓Intestine, Liver, Lungs and Brain metastasis |
| Zeolitic imidazolate framework-8 nanoparticles modified with hyaluronic acid (d = 184/217; solid/hydrodynamic)[271] | |
| 4T1 tumour-bearing BALB/c mice, 25 mg/kg (whole nanoparticles) /3 days for 15 days | ↓Tumour mass and<br>↓lung metastasis |
| Pegylated nanodiamant (d = 19/95/128 nm; water/DMEM/RPMI); (curcumin and irinotecan)[272] | |
| in LSL-KrasG12D/+ ; Trp53loxP/loxP mice with Ca5Cre adenovirus; IP,15 and/ or 5 mg/kg (curcumin and/ or irinotecan) | ↓Tumour volume, **tumour** (<br>↓Ki67, IL-10 and TAM M2 markers (<br>↓Ym1 and<br>↓Ly6G)), and **serum** (<br>↓IL-9,<br>↓IL-10,<br>↓INF-γ) |

**Table 6** (*continued*)

| Model and experimental conditions (route and dose) | Curcumin effect<br>**Assay** (value of tested effect in the curcumin presence/ original value of tested effect[a]; dose / time |
|---|---|
| **Lipid nanoparticles** | |
| Lipid nanoparticles (d=20 nm) modified with PEG and α-NTP (synthetic inhibitor of asparaginyl endopeptidase)[115] | |
| 5–8 F cells | **Proliferation** (41%; 50 μM/24 h)<br>**Scratch** (1/2 *; 50 μM/24 h) |
| Mice with 5–8 F; IV, 125 nmol 13th, 15th, 17th, 19th, and 21th day | ↓tumour volume (sometimes), delayed lung metastasis and<br>↑OS |
| Lipid nanoparticles (d=20 nm) modified with PEG and α-NTP-(d=150 nm[273]); Hydrazinocurcumin (curcumin synthetic analogue)[268] | |
| Coculture 4T1 with RAW264.7 | **4T1 Apoptosis** (0; RAW264.7/12 h; Pretreatment 18 μM/12 h), **Macrophage** (IL-10$^{high}$, IL-12$^{low}$ and TGF-β$^{high}$;<br>↓STAT3<br>↓MMP9,<br>↓MMP2,<br>↓VEGF and **0**CD206) **4T1**(<br>↓STAT3<br>↓MMP9,<br>↓MMP2 and<br>↓VEGF), **4T1 Migration** (1/3; RAW264.7/12 h; Pretreatment 18 μM/12 h), and **4T1 Invasion** (1/4; RAW264.7/12 h; Pretreatment 18 μM/12 h) |
| Mice with 4T1 and E-RAW264.7; IV, (1 mM) 10th, 13th, 16th, 19th, 22th, 25th day | **Metastase** (<br>↓STAT3,<br>↓Ki-67<br>↓,<br>↓CD31-positive microvessel density)<br>↓Tumour volume and<br>↑OS |
| Phospholipid nanoparticles (38 nm) containg curcumin and IR780 (photothermal dyes)[134] | |
| 4T1 | **Cell** (<br>↑ROS), **Proliferation** (~50%;9–12 μg/mL curcumin/12 h), **Invasion** (49%; 6 and 3 μg/mL (curcumin and IR780)/24 h; 12 h pretreatment), **Migration** (12.1%; 6 and 3 μg/mL (curcumin and IR780)/24 h; 12 h pretreatment) |
| 4T1 under photothermal therapy | **Proliferation** (~50%; /6–9 μg/mL (curcumin and IR780; 2:1, mass ratio) /12 h), **Invasion** (6.1%; 6 and 3 μg/mL (curcumin and IR780)/24 h; 12 h pretreatment), and **Migration** (12.1%; 6 and 3 μg/mL (curcumin and IR780)/24 h; 12 h pretreatment) |
| Mice with 4T1 under photothermal therapy; Oral (50 and 5 mg (curcumin and IR780)/ kg /2 days for 16 days | ↓Tumour volume,<br>↓pulmonary metastatic nodules (more than an order of magnitude) |

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**Table 6** (*continued*)

| Model and experimental conditions (route and dose) | Curcumin effect<br>**Assay** (value of tested effect in the curcumin presence/ original value of tested effect[a]; dose / time |
|---|---|
| Lyposome decored TN (fusion peptide of cell-penetrating peptide and cell NF-κB essential modulator -binding domain peptide; inhibitor of NF-κB) and hyaluronic acid (d = 127 nm); curcumin and celecoxib, ~1:1 molar ratio[274] | |
| 4T1, RAW264.7 and HUVEC | **Cell** (<br>↓NF-κB,<br>↓IL-6 and<br>↓TNF-α), **Proliferation** ($IC_{50}$; 12.3, 9.2 and 270 μM/24 h), **Macrophage migration** (<5; 20 μM/6 h; 4T1 induced), and **Mamosphera volume** (50%; 20 μM/9 d) |
| Mice with 4T1; IV, 20 mg (curcumin and celecoxib)/ 5 kg, 9th, 12th, 15th, 18th, 21th day | **Tumour** (<br>↑IKB-α,<br>↓TNF-α,<br>↓IL-6),<br>↑OS,<br>↓tumour volume,<br>↓lung and bone metastasis |
| Lyposome decored TN (fusion peptide of cell-penetrating peptide and cell NF-κB essential modulator -binding domain peptide; inhibitor of NF-κB) and hyaluronic acid (d = 127 nm); curcumin and celecoxib, ~1:1 molar ratio and doxorubicin lyposomes (d = 110 nm)[275] | |
| Mice with 4T1; IV, 21 (curcumin and celecoxib; 1:1, mass ratio) and 2.1 mg (doxorubicin)/ kg 9th, 15th, 21th, 27th day | ↓Lung metastasis, OS,<br>↓MDSC infiltration in the lung tissue, |
| Liposomes modified with glycyrrhetinic acid and galactose (d = 139 nm); capsaicin and curcumin[276] | |
| HepG2 and HepG2/LX-2 cells | **Cell** (<br>↓P-gp,<br>↓Vimentin<br>↑E-Cadherin), **Proliferation** ($IC_{50;}$ 7.25 μM and 11.36 μM /24 h), and<br>↓Cell migration |
| Mice with H22 and H22/HSC[276]; IV, 5 mg/kg/2 days for 2 weeks | **HSC** (<br>↓α-SMA,<br>↓CD31),<br>↓Tumour volume,<br>↓number of pulmonary nodules |
| Liposomes modified with glycyrrhetinic acid and galactose (d = 154; curcumin and combretastatin A-4 phosphate (CA4P)[277] | |
| BEL7402 and BEL7402/HUVEC) | **BEL7402** (<br>↓VEGF)<br>↓Cell adhesivity and<br>↓Cell migration |
| BALB/c mice with H22; IV 5 mg/kg and/or 5 mg (curcumin and/or CA4P)/ 2 days for 2 weeks | ↓VEGF,<br>↓VEGFR2 and<br>↓lung metastasis |
| Pegylated liposomes (d=190 nm) modified with RGDK-lipopeptide (α5β1 integrin receptor-targeting)[278] | |
| HUVEC and B16F10 | **Cell** (<br>↓TGFβ1,<br>↓TGfBR2,<br>↓Smad 2,<br>↓Smad 3,<br>↓Smad 4 and<br>↑Smad 7), **Proliferation** (~40% and 40%; 20/24), **Migration** (1/2 and ½; 12 μM /24 h) and **Invasion** (1/2 and ½;12 μM /24 h) |
| C57BL/6 J mice with B16F10[278]; IV, 12 mg, 14th, 16th, 19th, 21th, 24th day | ↓OS,<br>↓tumour volume (more than an order of magnitude),<br>↓Microvessel densities around tumours |
| Pegylated liposomes (d = 208 nm) modified with RGDK-lipopeptide (α5β1 integrin receptor-targeting); curcumin and doxorubicin; 6:1, molar ratio[278] | |
| B16F10 and HUVEC | **Cell** (<br>↓TGFβ1,<br>↓TGfBR2,<br>↓Smad 2,<br>↓Smad 3,<br>↓Smad 4 and<br>↑Smad 7), **Proliferation** (~30% and 30%; 1 μM /10 h), **Migration** (1/5 and 1/10; 7 μM /24 h; 8 h pretreatment), **Invasion** (1/4 and 1/6; 7 μM /24 h; 8 h pretreatment) |
| | ↓OS,<br>↓tumour volume (half against double dose single agents),<br>↓Microvessel densities around tumours |
| Lyposomes (d=168 nm) Zn-Curcumin[201] | |
| 4T1 | **Proliferation** ($IC_{50}$; 5.5 μg /48 h),<br>↓Cell invasion and migration |
| Mice with 4T1; IV, 20 mg/kg (Zn-curcumin), 2th 5th 8th 11th day | **Tumour** (apoptotic,<br>↓Ki67,<br>↓CD31),<br>↑OS<br>↓tumour volume,<br>↓number of lung metastatic foci, |
| Lyposomes (d=168 nm) Cu-curcumin[201] | |

(*continued on next page*)

**Table 6** (*continued*)

| Model and experimental conditions (route and dose) | Curcumin effect<br>**Assay** (value of tested effect in the curcumin presence/ original value of tested effect[a]; dose / time |
|---|---|
| 4T1 | **Proliferation** ($IC_{50}$; 5.6 μg/48 h), |
| | ↓Cell invasion and migration |
| Mice with 4T1; IV, 20 mg/kg (Cu-Curcumin), 2th, 5th, 8th, 11th day | **Tumour** (apoptotic, |
| | ↓Ki67, |
| | ↓CD31), |
| | ↑OS |
| | ↓tumour volume, |
| | ↓number of lung metastatic foci, |
| Lipid nanoparticle with polymeric core (poly(lactic-co-glycolic acid)) and modified PEG (d= 171/177 nm, water/ PBS)[60] | |
| MDA-MB-231 | **Proliferation** ($IC_{50}$; 30 μM /72 h), **HUVEC** ( |
| | ↓ICAM-1) and **Vascular adhesion** (30%; 10 μM /24 h; to TNF-α activated HUVEC) |
| Oil nanoemulsion (d ≈ 200 nm)[128] | |
| B16F10 cells | **Proliferation** ($IC_{50}$; 46 μM/24 h), **Cell** ( |
| | ↑ROS), **Migration** (1/2; 12.5 μM/24 h) and **Invasion** (1/5; 12.5 μM/24 h) |
| C57BL/6 mice with B16F10, were administered after excising the tumour and before suturing the wound 1500 μM; 14 days | ↓Tumour recurrence and metastasis (more than an order of magnitude) |
| Micelles (d = 53.5 nm),[279] | |
| A549 | **Cell** ( |
| | ↓VM channels |
| | ↓MMP-2 and |
| | ↓HIF-1α), **Proliferation** (89.9%; 62.5/24) and **Cell adhesion assessments** (67;8/ 12) |
| Nanomicellar-curcumin (10 nm, Exir Nano Sina Company (Tehran, Iran)[280] | |
| The B16F10 cell line | **Proliferation** (1/8; 20/24) |
| C57BL/6 mice with B16; IP, 20 mg/kg, 4X/week, 3 weeks | ↑OS, |
| | ↓lung metastasis, **lung** ( |
| | ↓Treg and |
| | ↑activated T cells + **serum** ( |
| | ↑CXCL10 and |
| | ↑IFN-γ) |
| **Polymeric system** | |
| Monomethyl poly(ethylene glycol)-poly(ε-caprolactone) copolymer (MPEG-PCL) micelles (28.2)[135] | |
| 4T1 | **Proliferation** (~50; 20 μg/48 h) |
| BALB/c mice with 4T1, IV, 30 mg/kg /day for 10 days | ↑OS (42 vs 28 days), |
| | ↓tumour volume and mass (1/4) |
| | ↑apoptosis index (4x) and |
| | ↓angiogenesis (microvehicles per field 1/ 3), |
| | ↓number and mass of lung metastases (1/ 4) |

**Table 6** (*continued*)

| Model and experimental conditions (route and dose) | Curcumin effect<br>**Assay** (value of tested effect in the curcumin presence/ original value of tested effect[a]; dose / time |
|---|---|
| Poly(2-ethyl-2-oxazoline)-poly(D,L-lactide) conjugate with curcumin and doxorubicin (d=104 nm); 5:1, mass ratio[281] | |
| MDA-MB-231 | **Proliferation** ($IC_{50}$; 0.66 and 0.13 μg/mL (curcumin and doxorubicin) /48 h), **Cell adhesion assay** (60%; 0.21 and 0.04 13 μg/mL (curcumin and doxorubicin)/ 48 h), **Scratch** (52%; 0.86 and 0.17 μg/mL (curcumin and doxorubicin)/ 48 h), **Transendothelial migration** (100%; 0.86 and 0.17 μg/mL (curcumin and doxorubicin) /48 h) and **Invasion** (60%; 0.86 and 0.1713 μg/mL (curcumin and doxorubicin)/ 48 h), |
| BALB/c nude mice with MDA-MB-231; Intravenously 4 and 20 mg/g doxorubicin and curumin/2, 14 | **Lung tissue** (**0**MMP-9, **0**E-Cadherin), |
| | ↓reduction of lung metastasis. |
| Polymeric nanoparticle (50 nm)[282] | |
| BXPC-3, MiaPaCa and PBMC | Cancer cells ( |
| | ↓NF-κB) PBMC ( |
| | ↓LPS induced IL-6, IL-8 and TNF-α production) |
| Polymeric nanoparticle (50 nm)[282]; curcumin (NFC) and free drug sorafenib[283] | |
| Huh7 | **Cell** ( |
| | ↓ ERK 1/2, |
| | ↓MMP-9, |
| | ↓p65 (nukleus), |
| | ↓CD133 and |
| | ↑TIMP-1), **Proliferation** ($IC_{50}$; 35 μM/ 48 h), **Invasion** (1/4; 40 μM/24 h) and **Invasion** (1/5; 40 μM /24 h; in the combination of 10 μM sorafenib) |
| MHCCLM3 | **Cell** ( |
| | ↓ERK1/2, |
| | ↓MMP-9, |
| | ↓p65 (nukleus), |
| | ↓CD133 and |
| | ↑ TIMP-1), **Proliferation** ($IC_{50}$; 5 μM /48 h), **Invasion** (6/10; 40 μM/24 h), and **Invasion** (1/3; 40 μM/24 h; in the combination of 10 μM sorafenib) |
| Mice with MHCCLM3;NFC (1.56 g/kg/ daily, IP) and or sorafenib (30 mg/ kg/ daily, oral) | ↓CD133, |
| | ↓tumour mass, |
| | ↓Pulmonary metastasis |
| | synergy |
| Alendronate coated poly-lactic-co-glycolic acid 235 nm curcumin and bortezomib [136] | |
| Mice with bone implanted MDA-MB-231; IV,1 and 1.337 mg (bortezomib and curcumin) /kg /7 day, 35 day | **Bone**: (Sometimes reduction in macrophage infiltration of tumour mass) |
| PLGA–curcumin NPs (188 nm)[284] | |
| MDA-MBA-231 | **Proliferation** (73%; 2.5 μg/mL /24), **Scratch** (80%; 2.5 μg/mL /24) and **Invasion** (80% and 56%; 7.5 μg/mL/24 h and 48 h) |
| NanoCurc[204] | |

(*continued on next page*)

**Table 6** (*continued*)

| Model and experimental conditions (route and dose) | Curcumin effect<br>**Assay** (value of tested effect in the curcumin presence/ original value of tested effect[a]; dose / time |
|---|---|
| Mice with Pa03C; IP, NanoCurc (25 mg/kg) and or gemcitabine (20 mg/kg) twice, daily, 2weaks | ↓Tumour mass,<br>↓Micrometastasis in lungs, lymph nodes, and peritoneum -strong synergic effect<br>**tumour** ( |
| | ↓NF-KB, |
| | ↓cyclin D1 and |
| | ↓MMP-9) |
| Dextran Nanobubles (dextran sulfate-shell and perfluoropentane core, d = 348 nm) [285] | |
| PC-3 and DU-145 | **Proliferation** (86% and 91%; 5 μM/24 h)<br>**adhesion** (1/3 and ½; 5 μM /18 h; TNF-α activated, 30 min pretreatment) and migration (1/3 and 1/3; 5 μM /18 h; TNF-α activated and normal) |
| Chitosan-Coated Polycaprolactone Nanoparticles 189 nm[129] | |
| B16F10 | |
| Mice with B16F10; orally 3 and 6 mg/day for 14 days | ↓Lung metastases (formation tumour nodules 44% and 36%) |
| BSA nanoparticles 130 nm, curcumin and doxorubicin[286] | |
| Mice with B16F10 | ↓Lung metastases (weight 1/4) |
| Hyaluronic acid (HA)-functionalized regenerated silk fibroin-based nanoparticles (210 nm) fluoruracil and curcumin (1:4)[287] | |
| 4T1 | **Proliferation** ($IC_{50}$; 37 and 1.2 μM /24 and 48 h) and **Scrath** (37% (total drug); 16 mg/24) |
| BALB/c nude mice with 4T1; IV, 5 mg/kg total day 27 day | ↓Tumour mass,<br>↑OS, **tumour tissue** (<br>↓Ki67), apoptosis cell,<br>↓numbers of lung metastasis nodules |
| Nanofibrous microspheres (PLA-PEO-PPO-PEO-PLA); doxorubicin and curcumin, 1:1 [288] | |
| CT26 mice, IP; 8 mg/kg | **Tumour tissue** (<br>↓Ki-67),<br>↑OS,<br>↓abdominal metastases (1/4),<br>↓microvesell density (1/5) |
| **Cell and cell derived systems** | |
| B16F10 derived nanovesicle[289] | |
| B16F10/spleen T cells | ↑CD8 + and<br>↑CD4 + T cells |
| Biotin chitosan naporticles (hydrodynamic size = 377 nm), biotin mesenchymal stem cells and streptavidin[290] | |
| Mice with mice melanoma B16F10; IV | ↓lung metastases |

α-SMA, Alpha smooth muscle actin; ΔΨm, Mitochondrial membrane potential; Akt, Protein kinase B; CXCL10, C-X-C motif chemokine ligand 10; CXCL12 C-X-C motif chemokine ligand 12; CXCR-4, C-X-C chemokine receptor type 4; DCK, Deoxycytidine kinase, PI3K, Fosfatidylinositol-3-kináza; hCNTs, Homology Modeling of Human Concentrative Nucleoside Transporters; HIF-1α, Hypoxia-inducible factor 1-alpha; GLI1, GLI Family Zinc Finger 1; GLI1, GLI2 Family Zinc Finger 2; ICAM-1, Intercellular Adhesion Molecule 1; IkB-α, Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IL-6, Interleukin 6I; L-9, Interleukin 9; IL-10, Interleukin 10;; IL-12, Interleukin 12; INF-γ, Interferon gama; mTOR, Ly6G, Lymphocyte antigen 6 complex locus G6D; Mammalian target of rapamycin; MMP-2, Matrix metalloproteinase-2; MMP3, Matrix metalloproteinase-3; MMP-9, Matrix metalloproteinase-9; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; Pgp, P-glycoprotein 1; ROS, Reactive oxygen species; RRM1, Ribonucleoside-diphosphate reductase large subunit; RRM2, Ribonucleotide reductase small subunit; SHH, Sonic Hedgehog; SMO, Smoothened, Seven Transmembrane Spanning Receptor; Sufu, Suppressor of fused homolog; STAT3, Signal transducer and activator of transcription 3; TGF-β, Transforming growth factor β; TGF-β1, Transforming growth factor β1; TGfBR2, Transforming growth factor beta receptor II; TIMP1, TIMP Metallopeptidase Inhibitor 1; TNF-α Tumour necrosis factor alpha; VEGF, Vascular endothelial growth factor; VEGFR-2, Vascular endothelial growth factor receptor 2; vascular mimicry (VM); Ym1, known as chitinase-like protein 3;

5–8 F, Human nasopharyngeal cancer; A172; Human glioblastoma A549, Human lung adenocarcinoma; B16, Murine melanoma cell line; B16F10, Highly metastatic murine melanoma cell line; BEL7402, Human hepatocellular carcinoma; BXPC-3, Human pancreatic adenocarcinomas; CT26, Mouse colon adenocarcinoma; DU-145, Human prostatic carcinoma; H22, Mouse hepatocellular carcinoma; HPAF-II, Human pancreatic adenocarcinoma; HepG2, Human liver cancer cell line; HSC, Mouse hepatic stellate cell; Huh7, Human hepatoma; HUVEC, Human umbilical vein endothelial cells; LX-2, Human hepatic stellate cell; MDA-MB 231, Triple negative human breast adenocarcinoma; MiaPaCa, Human pancreatic ductal adenocarcinoma; MHCCLM3, Human hepatocellular carcinoma; PBMC, Peripheral blood mononuclear cells; Pa03C, Human pancreatic cancer; PC-3, Human prostate cancer; Panc-1, Human pancreatic cancer; RAW264.7, Mice macrophage cell line; 4T1, Mice mammary tumour

↑ = curcumin activation/induction/enhance; ↓ = curcumin suppression/inhibition; **0** = without change.

[a] If a fraction was stated, the value was not explicitly stated in the article, but was subtracted from the presented graph.

anticancer therapy, especially as an antimetastatic. Nevertheless, it cannot be ruled out that in some cases it may not be sufficient. In medical research, curcumin analogues and synthetic derivatives are intensively studied in anti-cancer therapy. Possible synthetic approaches to the modification of curcumin chemical structures are shown in the Fig. 7.

The most used strategy is the elimination of β-diketone moiety from the curcuminoid structure motif. The enolic proton of the curcumin also plays a critical role in its aggregation [333]. Breaking of intermolecular hydrogen bonds between the formed layers primarily through the acidic enolic proton exchange can lead to significantly increase curcumin solubility [333]. On the other hand, α,β-unsaturated diketone moiety can represent a Michael reaction acceptor, which belongs to the major class of phase-II enzyme inducers [334]. It can be possible, that this structure motif may be responsible for inducing HO-1 and STAT3 inhibition [215,335]. In addition, some studies suggest that synthetic curcuminoids with a β-diketone moiety are promising anticancer agents [336]. Examples of curcumin derivatives are shown on Fig. 8.

For example, dimethylcurcumin (ASC-J9) induces degradation of the androgen receptors, including AR-V7 and AR-F876L, which are strongly associated with lacking sensitivity to therapy and metastasis during pancreatic cancer [337]. Its application sometimes decreases invasiveness of pancreatic cancer cells (Du145 and C4–2 cells), whereas this effect was significantly higher for AR-F876L positive cells [338]. Similarly, non-toxic doses of curcumin reduced AR expression and activity in LNCaP Similarly, non-toxic doses of curcumin reduced AR expression and activity in LNCaP Similarly, non-toxic doses of curcumin reduced AR expression and activity in LNCaP (prostate cancer cells) [339].

Various polar groups such as fluorine have also been studied to improve the solubility and biological efficacy of curcuminoids. For example, EF24 (1 μM) completely suppressed the migration of melanoma cells (A375 and Lu1205) [340]. Similarly, CDF (0.125 μM) displayed strong cytotoxicity (~ 50% viability), the decrease in CSC self-renewal capacity and potent antimetastatic effects (decrease in the cell invasiveness, migration, and angiogenesis) against pancreatic cancer cells (AsPC-1 and MiaPaCa-2) in hypoxia conditions [341]. This effect was associated with the decrease in IL-6 and VEGF protein levels.

An interesting strategy is the combination of curcumin and piperidine structure motif [342–345]. For example, Das et al. reported, that $IC_{50}$ of 3,5-bis(arylidene)− 4-piperidone dimers for colon cancer cell

**Table 7**
Curcumin effect on the intratumoural microbiota.

| Microflora | Cancer type | Variant | Toxicity |
|---|---|---|---|
| *Pseudomonas* [300] | Breast | *P. aeruginosa* | 50–2500 μg/mL (MIC)[197,301–306] |
| *Porphyromonas* [300,307] | Breast, Head and Neck | *P. gingivalis (ATCC 33277)* | 62.5 μg/mL (MIC) [308] |
| *Proteus*[300] | Breast | *P. mirabilis* | 192–300 μg/mL (MIC)[197,301] |
| *Enterotoxigenic Bacteroides* [309] | Colorecteral | *B. fragilis* | > 128, 32, 64 and 128 μg/mL (MIC) curcumin BDMC and DMC tetrahydroxy, respectively[310] |
| *Bacteroides*[311] | Colorectal | *B. dorei* | > 128, 128, 128 and > 128 μg/mL (MIC) curcumin BDMC and DMC tetrahydroxy, respectively[310] |
| *Prevotella*[311] | Colorectal | *P. intermedia* | 10 μg/mL (MIC)[312] |
| *Fusobacterium* [313–315] | Breast, Colorectal | *F. nucleatum* | 10 μg/mL (MIC) (27 μM)[312] |
| *Esterichia*[316] | Colorectal | *E. coli* | 192–1500 μg/mL (MIC)[197,301,302,317] |
| *Streptococcus* [318] | Lung | *S. pyogenes* | 31.25 μg/mL (MIC) [197] |
| | | *S. mutans* | 128–175 μM (MIC) 10.2 (IC50)[319,320] |
| *Aggregatibacter* [321] | Pancreatic | *A. actinomycetem* | 0.2 μg/mL (MIC) (0.54 μM)[322] |
| *Acinetobacter* [323] | Ovarian | *A. lwoffii* | 250 μg/mL[197] |
| | | *A. baumannii* | > 5000 μg/mL (MIC) [197] |
| | | *A. baumannii (ATCC 19606;* MDR*)* | > 256 μg/mL (MIC), Synergy EGCG[324] |
| *Mycoplasma* [325] | Ovarian | *M. hominis, capricolum, genitalium, pneumonie* | 50 μg/mL (MIC)[326] |
| | | *M. mycoides subsp. capri* | 100 μg/mL (MIC) [326] |
| *Klebsiella*[325] | Ovarian | *K. pneumonia* | 216–2000 μg/mL (MIC)[197,302,317] |
| *Staphylococcus* [327] | Non-melanoma skin cancer | *S. aureus* | 187–600 mg/mL (MIC) |
| | | *S. aureus (MSSA)* | 219 μg/mL (MIC) [302] |
| | | *S. aureus (MRSA)* | 217 μg/mL (MIC) [302] |
| | | *S. epidermidis* | 100 μg/mL (MIC) [197] |
| | | *S. epidermidis (ATCC 14990)* | 46.9 μg/mL (MIC) [328] |

MIC = minimal inhibition concentration.

lines (HCT116 and HT29) can vary in the range 0.01–0.1 μM [342]. In the case of 5-floururacil, these values were approximately hundred times higher. In addition to higher cytotoxicity in vitro, these compounds could exhibit higher bioactivity in vivo compared to curcumin.

PAC (Fig. 8 3,5-Bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidone) intraperitoneal application (100 mg/kg) showed $c_{max}$ 35 μg/mL (~320 μM) in the mice plasma, nevertheless in this curcumin application $c_{max}$ was only 10.3 μg/mL [344]. Since PAC sometimes exhibited cytotoxicity against MDA-MB-231 cells (55% vs ~5%; 10 μM, 72 h), PAC could represent a suitable structural motif for the treatment of triple negative breast cancer compared to single curcumin [345]. PAC (10 μM, 24 h) also displayed strong antimetastatic effects against MDA-MB-231 (reduction of cell migration and invasiveness by less than 5%) [344]. In the mice model with the MDA-MB231 tumour, PAC (100 mg/kg) sometimes decreased the expression of NF-κB, c-Myc and Cyclin D1 in the tumour tissue [344,345].

In the case of xenografts of colon and pancreatic cancer cells, lower levels of NF-κB, HIF-1α, VEGF and TGF-β proteins were sometimes observed after treatment with synthetic curcuminoids (EF31 and especially UBS109) compared to control and natural curcumin [346,347]. In accordance with UBS109 (15 mg/kg/weak, i.p.) strongly suppress metastatic activity MDA-MB-231 in the mice lung [348]. This effect was associated with high cytotoxic activity against MDA-MB231 ($IC_{50}$ =1.33 μM) and plasma concentration (618 ng/mL). In the case of oral application (50 mg/kg), UBS109 suppression of breast cancer induced bone destruction and bone metastasis. This effect was probably caused by the strong increase in bone mineralization and the decrease of osteoclast formation [349].

Since curcumin and other polyphenols are strong chelators, their use with highly soluble metal ions (e.g., $Zn^{2+}$, $Cu^{2+}$, $Mg^{2+}$ and $Se^{2+}$) leads to significant improvements of solubility and stability in aqueous systems [350]. Because labile β-diketone moiety of curcuminoids significantly participated in their instability [155], chelated metal ions can protect the curcumin moiety and improve its lifetime [350]. Metal–curcumin complexes display potent effectivity against various oncological diseases [351]. These biological properties are associated with the targeting of inflammatory and transcription factors, protein kinases, antiapoptotic proteins, and antioxidant enzymes. In addition, some of them (e.g., $Cu^{2+}$, VO, La) display sometimes higher light toxicity than original curcumin, comparable with Photofrin. [352] In combination with structure motif of the curcumin and ruthenium complexes, this could lead to an increase in curcumin therapeutic effectivity [353–356]. In this case, $IC_{50}$ value for Ru(cym)(bdcurc)(PTA)]$PF_6$ (Fig. 8) against A2780 was 0.14 μM (24 h), value for cisplatin was 1.5 μM. [354] Srivastava et al., reported that derivatives of [$Ru(NN)_2$(cur)]($PF_6$) [NN = bpy (1), phen (2)] display strong activity (MIC = 1 μg/mL) against methicillin and vancomycin-resistant *S. aureus* strains (intratumoural microbiota) [357]. Some of them are potent inhibitors of NF-κB [339], which might suggest their usefulness in the treatment of metastatic and drug-resistant tumours.

As implied above, suitable curcumin designed synthetic analogues can sometimes display higher in vitro and in vivo therapeutic potential compared to natural curcumin. For example, UBS109 (Fig. 8) displays higher plasma $c_{max}$ than $IC_{50}$ for MDA-BA231. Improving pharmaceutical properties of synthetic curcuminoids by finding the most suitable method of administration and formulation could lead to the preparation of highly effective antimetastatic agents. Nevertheless, numerous preclinical and clinical trials are requested for the final validation of this hypothesis and for the design of suitable therapeutic regiments.

## 7. Conclusion

Curcumin represents a promising structural motif for the independently multitargeting of various metastatic mechanisms. Nevertheless, its therapeutic abilities are strongly limited by its solubility and bioactivity. This review described various curcumin micro and nanoformulations used and studied for the improvement of therapeutic effectivity of curcumin. Also, the influence of various routes of application of curcumin on its therapeutic effectivity was considered. Finally, curcumin's possible effect on the tumour microbiota and some promising curcumin synthetic derivatives were also presented and discussed.

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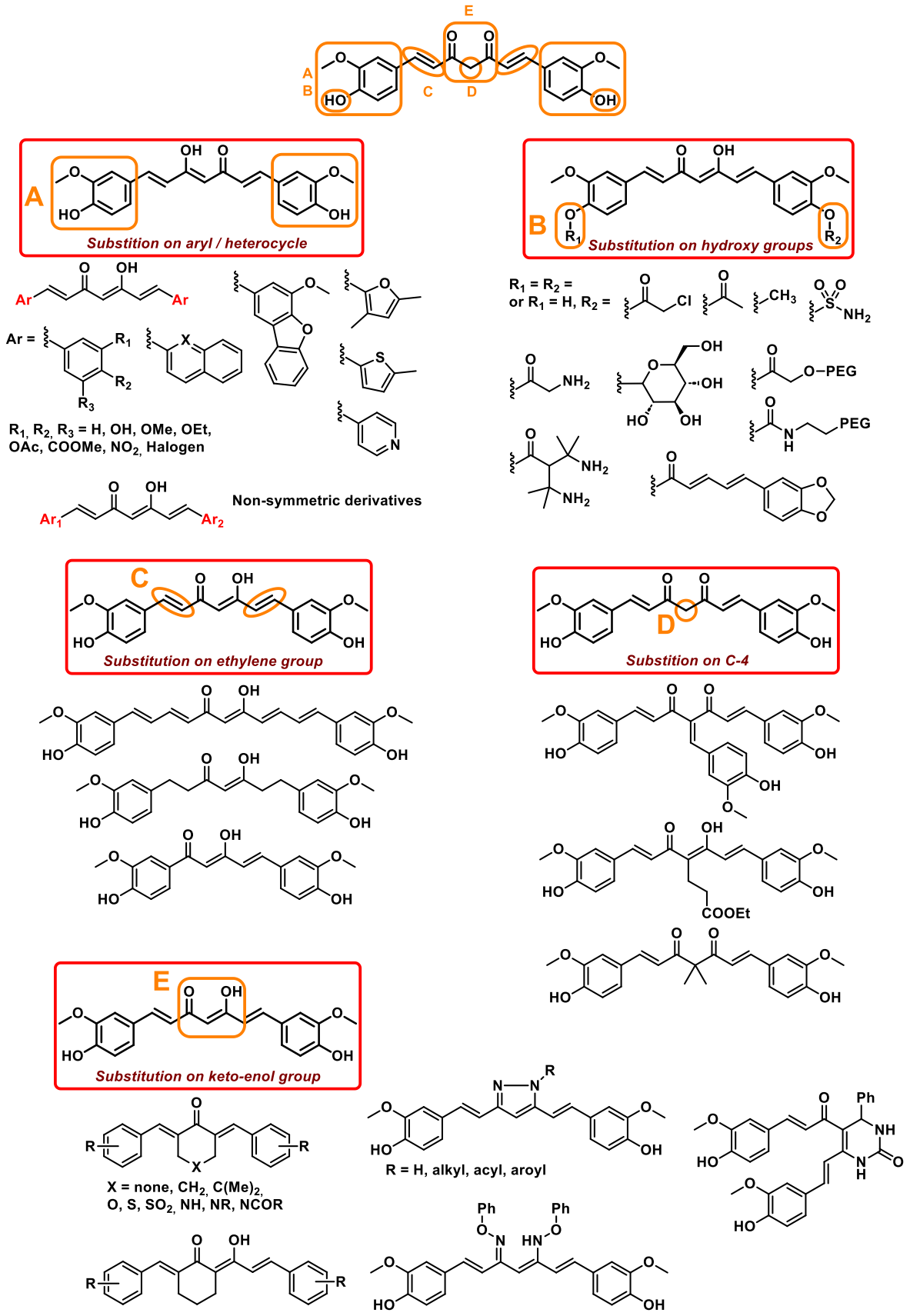


**Fig. 7.** Various approaches in the synthetic modification of curcumin more detailed described in the cited works [330–332], A, B - 2-methoxy-2-hydroxyphenyl moiety: substitution at hydroxy group, other substituents at phenyl core/heterocycle; C - ethylene moiety: reduced form ($CH_2CH_2$), omitting or extending by ethylene unit; D - substitution at C-4: substitution by alkyl, aryl or arylidene; E – diketo or keto-enol group: keto-enol tautomerism, heterocycle (especially pyrazole and isoxazole derivatives), Schiff bases and oximes, substitution for keto group (acetone or cyclic ketone derivatives).

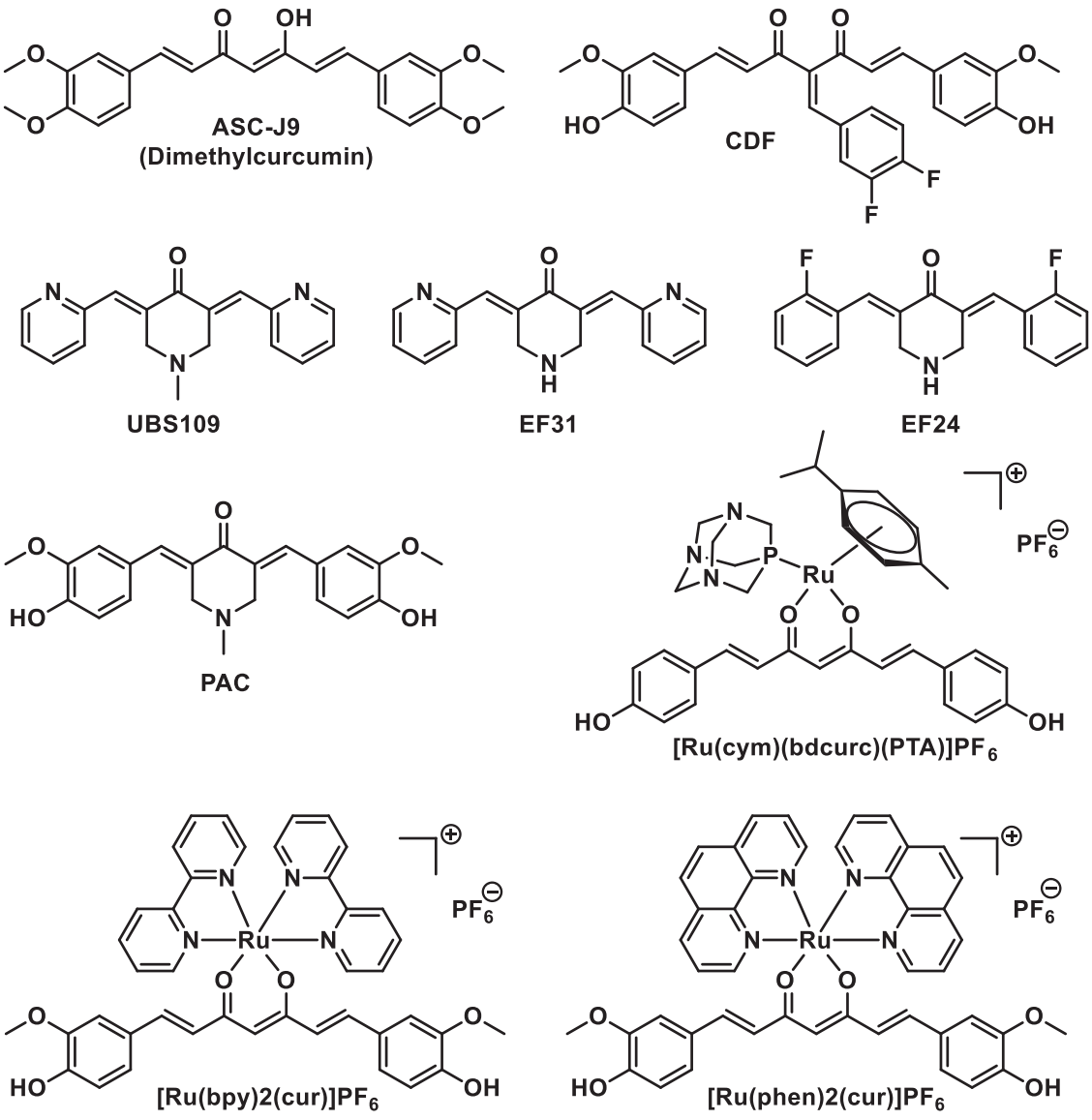


**Fig. 8.** Examples of tested curcumin derivatives.

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## CRediT authorship contribution statement

Petr Dytrych participate in writing and supervision of manuscript, he also integrates individual author contributions. Zdeněk Kejík participate in writing and supervision of manuscript, design of figures and table preparations. Jan Hajduch participate in writing and supervision of manuscript. Robert Kaplánek participate in supervision of manuscript and design of figures. Kateřina Veselá and Kateřina Kučnirová participate in writing manuscript and table preparation. Markéta Skaličková and Anna Venhauerová participate design of figures and preparing tables. David Hoskovec participate in writing and supervision of manuscript. Milan Jakubek and Pavel Martásek design concept of manuscript and participate in manuscript supervision.

## Conflict of interest statement

Petr Dytrych did not have any conflict of interest. Zdeněk Kejík did not have any conflict of interest. Jan Hajduch did not have any conflict of interest. Robert Kaplánek did not have any conflict of interest. Kateřina Veselá did not have any conflict of interest. Kateřina Kučnirová did not have any conflict of interest. Markéta Skaličková did not have any conflict of interest. Anna Venhauerová did not have any conflict of interest. David Hoskovec did not have any conflict of interest. Pavel Martásek did not have any conflict of interest. Milan Jakubek did not have any conflict of interest.

## Data availability

No data was used for the research described in the article.

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