REVIEW

# Improving therapeutic effects of curcumin – a review

**ZORKA STANIĆ**

**Summary**
Curcumin, a naturally occurring polyphenol isolated from the rhizomes of *Curcuma longa* and widely used as a colouring agent as well as spice in many food items, is well-known in the scientific community as a simple molecule exhibiting multiple therapeutic, anti-inflammatory and anticancer properties. Its ability to overcome multidrug resistance in different cancer cell types provides a starting point for its implementation as a therapeutic agent. The application of nanomaterials as drug carriers improves the solubility of this drug and its accumulation at tumour sites. This article reviews the pharmacology of curcumin with its general chemical and therapeutic features, and provides additional evidence to support the improvement of its pharmacological effects.

**Keywords**
curcumin; synergy; antioxidant; chemoprevention; anticancer

Turmeric, *Curcuma longa*, a popular Indian spice used in human nutrition for thousands of years and also used for centuries in herbal medicines against a variety of diseases, is permanently in the centre of interest of the world scientific community [1–4]. Consumed with a daily intake of approximately 3 g/70 kg [1], this spice is not only used in food preparation, but serves as a safe, natural medicament without any adverse or side effects in clinical trials [5]. Curcumin, as the main ingredient of turmeric, is the subject of intensive examination of various mutually intertwined scientific fields, such as chemistry, medicine or, pharmacy [6–9]. To summarize the relevance of curcumin, we classified scientific papers as follows (levels of importance are expressed as a percentage):

- medicinal chemistry, anticancer research, carcinogenesis, gastroenterology, phytomedicine, phytotherapy, tropical biomedicine, surgical research, nanomedicine (~ 60 %);
- biochemical, biophysical and analytical research, chemico-biological interactions, free radical biology, biomaterials, biomacromolecules (~ 20 %);
- pharmacology, immunopharmacology, ethnopharmacology (~ 10 %);
- food chemistry, nutritional biochemistry, agricultural chemistry, life sciences, chemical toxicology (~ 10 %).

Antioxidant, anti-inflammatory, antibacterial, anti-proliferative, anticarcinogenic, anti-amyloidogenic and antiviral (including anti-HIV) effects are just some of the numerous biological activities shown by curcumin (Tab. 1). However, its low water solubility and stability, rapid metabolism and consequently poor absorption or bioavailability are viewed as the 'weaknesses' of this justifiably popular compound. Given these features of curcumin, the main guidelines for further research may be established. Micellar nanocarriers, liposomes and phospholipid complexes offer a significant improvement with regard to stability and increased curcumin efficacy [6]. The aim of this review is to provide an update on the recent advances in nanoparticles-based curcumin delivery and pH-sensitive intracellular drug loading and release at the desired location, including the synergistic effects of curcumin with a number of chemotherapeutic agents.

## Natural polyphenols, their derivatives and synthetic analogues

As numerous clinical trials indicated, scientific circles seriously consider the undeniable value of chemoprevention in cancer preclusion. Chemoprevention, based on the use of synthetic, semi-synthetic and natural compounds, is principally employed to prevent, inhibit, adjourn or reverse carcinogenesis. Bioavailability, lack of cytotoxicity

**Zorka Stanić**, Department of Chemistry, Faculty of Science, University of Kragujevac, R. Domanović 12, P. O. Box 60, 34000 Kragujevac, Serbia. E-mail: zorkas@kg.ac.rs

**Tab. 1.** Activities of curcumin as dealt with in scientific publications.

| **Pharmacological activities** | |
|---|---|
| Anti-inflammatory | [10–12] |
| Antioxidant: | [13–18] |
| – direct effects | [19, 20] |
| – indirect – cytoprotective effects | [21–32] |
| Anti-tumor | [14, 33–37] |
| Anti-arthritic | [13, 38] |
| Immunoregulatory | [39–44] |
| Hepatoprotective | [45, 46] |
| Anti-ischemic | [47] |
| Cognition-enhancing | [45, 48] |
| Anti-pruritic | [49] |
| Anti-dyspeptic | [50] |
| Pulmonoprotective | [51] |
| Anti-anxiety | [52, 53] |
| Antidepressant | [52, 53] |
| Analgesic | [45] |
| Lipid-lowering properties | [54–60] |
| Anti-malarial | [61] |
| Anti-amyloid | [61] |
| Anti-hiv | [61] |
| Antidiabetic | [62] |
| Fungicidal | [63] |
| Bactericidal | [64–68] |
| Anti-protozoal | [69] |
| Anti-venom | [70] |
| Anti-proliferative | [71] |
| Anti-angiogenic | [72] |
| Anti-aging | [73] |

| **Pharmacological effects** | |
|---|---|
| Reduces lipid peroxidation | [74–76] |
| Increases the level of catalase | [21, 74–76] |
| Increases the level of glutathione peroxidase | [22, 74–76] |
| Increases the level of superoxide dismutase | [21, 74–76] |
| Scavenges reactive oxygen and nitrogen species: | [74–82] |
| – superoxide anion | [77, 78] |
| – hydroxyl radicals | [74] |
| – hydrogen peroxide | [74, 77] |
| – singlet oxygen | [79] |
| – nitric oxide | [80, 81] |
| – peroxyl radicals | [74] |
| – peroxynitrite | [82] |

| **Molecular targets associated with curcumin anticancer activity** [83] | |
|---|---|
| Inflammatory cytokines | Trascription factors |
| Kinases | Growth factors |
| Miscellaneous | Receptors |
| Enzymes | |

| **The most common disease targets of curcumin** [84] | |
|---|---|
| Metabolitic diseases | Esophaus |
| Diabetes | Kidney |
| Hypoglycemia | Leukemia |
| Hypothyroidism | Lung |
| Hyperlipidemia | Neck |
| Obesity | Pancreas |
| Autoimmune diseases | Prostate |
| Bowel disease | Skin |
| Eczema | Stomach |
| Multiple scierosis | Lung diseases |
| Sclerosis | Bronchitis |
| Rheumatoid arthritis | Cystic fibrosis |
| Scleroderm | Hyaline membrane disease |
| Neurological diseases | Other inflammatory diseases |
| Alzhemer's disease | Allergy |
| Depression | Arthritis |
| Epilepsy | Asthma |
| Lewy body disease | Colitis |
| Parkinson's disease | Gall stone |
| Cardiovascular diseases | Pancreatitis |
| Atherosclerosis | Sinusitis |
| Cardiomyopathy | Ulcer |
| Myocardial infarction | Others |
| Stroke | Antispasmodic sprains |
| Liver diseases | Cataract |
| Alcohol-induced liver disease | Fanconi anemia |
| Cirrhosis | Fatigue |
| Fibrosis | Fever |
| Jaundice | Hematuria |
| Cancer | Hemorrhage |
| Bladder | Osteoporosis |
| Bone | Scabies |
| Brain | Septic shock |
| Breast | Wound healing |
| Colong | |

and chemical stability are necessary initial conditions for consideration of the compounds undergoing further clinical investigation. In this context, natural polyphenols, their derivatives and synthetic analogues [6, 85–88] exhibit pleiotropic effects on cancer cells and, accordingly, they could be used in cancer prevention and therapy. "Deketene curcumin" (1,5-bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadiene-3-one), previously described as a synthetic curcumin analogue and formed in larger quantities as a consequence of pyrolysis during common household cooking, exhibits higher stability and stronger anticancer activity compared to curcumin [89].

In the review by LEWANDOWSKA [90], a detailed overview of covalent modification (hydroxylation, methylation, acylation, galloylation) of polyphenols was presented, with a special emphasis on improving cytotoxic, pro-oxidant, antiproliferative, proapoptotic, proautophagic and antimigratory activities of the covalently modified polyphenols as determined by in vitro and, in some cases, in vivo testing. For example, curcumin modified by the incorporation of two methyl groups proved to be a markedly stronger growth inhibitor of colon cancer cells and their apoptosis inducer in comparison with unmodified curcumin (Tab. 2). In addition to the improvements of pharmacological/pharmacokinetic properties of the covalently modified polyphenolic compounds in terms of enhancing their biological potential in vitro and their bioavailability in vivo (Tab. 2), positively affecting their anticancer potential specifically on the prevention/inhibition of carcinogenesis, the key questions still remain unanswered: what happens with other biological activities of the covalently modified compounds and what are the resulting changes in these compounds that could have negative effects on the human body?

### Principal chemical properties of curcumin

Rhizomes of *C. longa* contain the highest percentage of carbohydrates in comparison with other constituents and also have the highest proportions of proteins, essential and fixed oils, minerals and curcuminoids (pigments, 2–6% w/w) [1]. Commercial turmeric extract contains the following main curcuminoids: curcumin (Cur), demethoxycurcumin (DMCur) and bisdemethoxycurcumin (BDMCur) [6, 83, 108]. Along with curcumin, which is the subject of this study and hereinafter will be extensively discussed, DMCur and BDMCur are also potential antitumour substances. Briefly, for instance, a multifunctional cancer-targeting delivery system based on DMCur-carrying chitosan nanoparticles and modified with a bioactive shell is used to prevent premature drug release and guide the nanocarriers to their target [109]. Another research indicated that DMCur itself induced apoptosis of the human lung cancer cells through the mitochondrial-dependent pathway [110]. A recent investigation showed that BDMCur served as a therapeutic agent that markedly inhibited growth of ovarian cancer due to reducing cellular oxidative stress [111].

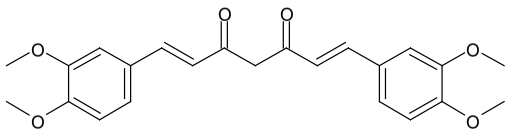
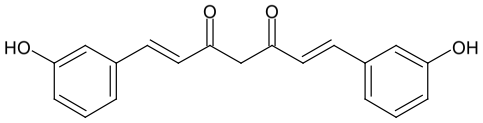
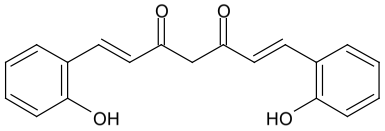
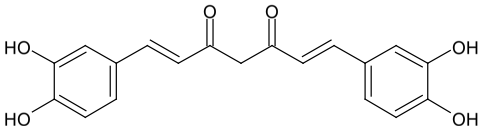
Curcumin, a bis-α,β-unsaturated β-diketone, exhibits keto-enol tautomerism with predominant keto form in acidic/neutral medium and enol form in alkaline medium [6, 108, 112]. Due to the enol form, curcumin is an ideal chelator of metal and metalloid ions [108]. Most published studies emphasize that curcumin has a poor aqueous solubility, diminished absorption, rapid metabolism, inactive metabolites, rapid clearance outside the body and, therefore, curcumin shows poor bioavailability in vivo and low levels in plasma as well as negligible tissue biodistribution (Tab. 3).

## CURCUMIN – A NATURAL POLYPHENOL WITH THERAPEUTIC POTENTIAL

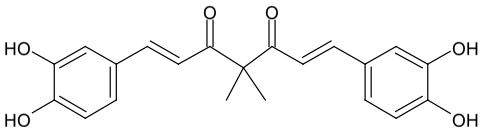
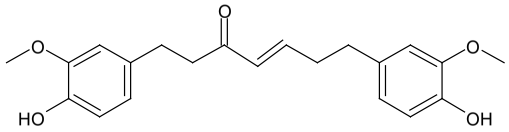
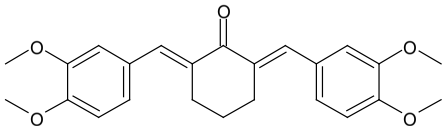
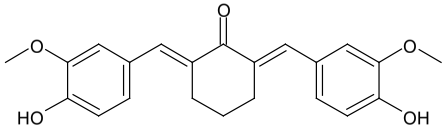
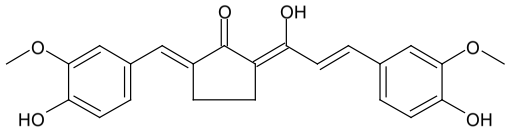
According to the US National Institutes of Health, there are currently 125 clinical trials evaluating the toxicity and efficacy of curcumin in the treatment of patients with different types of cancer, cardiovascular diseases, cognitive and psychiatric disorders, diabetes and other diseases [121]. A wide range of diseases targeted by curcumin is displayed in Tab. 1. Multi-target-oriented mechanisms of curcumin action enable achieving successful outcomes in the treatment of various types of cancer, including breast, uterine, colorectal, prostate and stomach cancer. Extensive researches showed that curcumin has an enormous potential against cancer in human blood, brain, lung and bladder. Curcumin intervenes at every stage of a complex development preceding the occurrence of cancer, its expansion and possible metastatic progression.

The morphological and biochemical features of paraptosis, which is a type of programmed cell death characterized by dilation of the endoplasmic reticulum and/or mitochondria, as a potential anticancer therapeutic strategy linked to various natural products, including curcumin, was reviewed by LEE [122]. Curcumin shows anticancer effects inducing paraptosis-associated cell death and selectively killing transformed cells, while normal cells are spared. As the authors concluded, the understanding of the mechanisms of paraptosis-inducing natural products and relationships between their

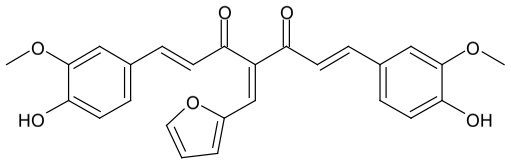
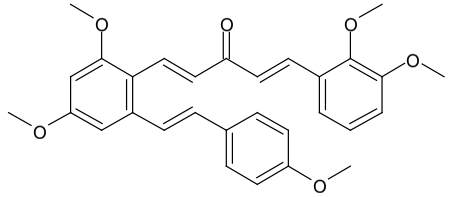
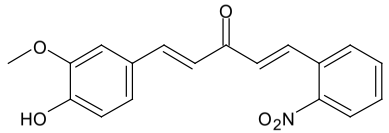
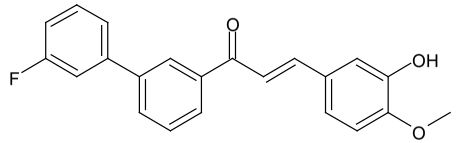
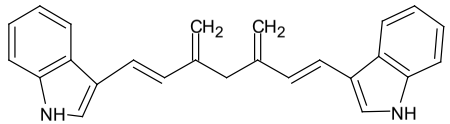
**Tab. 2.** Examples of curcumin analogues.

| Curcumin analogue | Effects | Comparison with curcumin | Ref. |
|---|---|---|---|
|  1,7-bis-(3,4-dimethoxyphenyl)-hepta-1,6-diene-3,5-dione | Anti-inflammatory activity in murine and human lymphocytes | Higher metabolic stability | [91] |
| | Inhibiting proliferation and inducing of apoptosis in human HCT116 colon cancer cells in vitro | More stable in cultured cells<br>More potent in the ability to kill cancer cells by apoptosis<br>Less extensively metabolized in microsomal systems<br>More stable in vivo | [92] |
| | In combination with radiation, significantly increases the apoptosis and mitotic death in A549 cells<br>Synergistically enhance the cancer cells killing when combined with radiation by targeting thioredoxin system | A very potent radiosensitizing effect | [93] |
| | Multi-drug resistant modulator inhibition of P-glycoprotein function in human leukemic cells line (K562/Adr) | – | [94] |
| | Efficiently induces gefitinib-insensitive epidermal growth factor receptor degradation; shows inhibitory effects on phosphorylation in two gefitinib-resistant lung adenocarcinoma cell lines, CL1-5 and H1975 | Equal | [87] |
|  1,7-bis(3-hydroxyphenyl)-hepta-1,6-diene-3,5-dione | Causes apoptosis in human liver hepatocellular carcinoma cells with the reactive oxygen species generation | Stronger cytotoxicity activity, reactive oxygen species-generating ability and apoptosis-inducing activity | [95] |
|  1,7-bis(2-hydroxyphenyl)-1,6-heptadiene-3,5-dione | Apoptotic induction in human breast cancer cell, MCF-7: significantly regulates PI3k/Akt, both intrinsic and extrinsic apoptotic pathways by inhibiting Bcl-2 and inducing p53, Bax, cytochrome c, Apaf-1, FasL, Caspases- 8, 9, 3 and PARP cleavage | Induces apoptosis more effectively | [96] |
|  1,7-bis-(3,4- dihydroxyphenyl)-hepta-1,6-diene-3,5-dione | Inhibits epidermal growth factor receptor phosphorylation in both CL1-5 and H1975 cells without induction of receptor degradation; reduces gefitinib-induced gastrointestinal damage in the non-transformed intestinal epithelial cell line, IEC-18 | Equal | [87] |

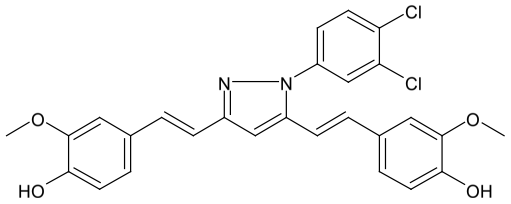
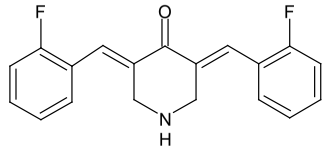
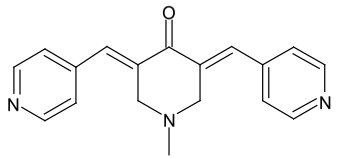
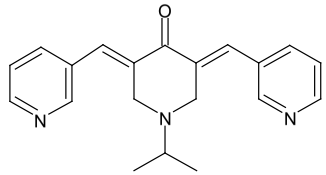
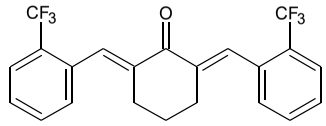
**Tab. 2.** *continued*

| Curcumin analogue | Effects | Comparison with curcumin | Ref. |
|---|---|---|---|
|  1,7-bis(3,4-dihydroxyphenyl)-4,4-dimethyl hepta-1,6-diene-3,5-dione | Excellent Nrf2-dependent cytoprotection | Increased stability | [97] |
|  1,7-bis(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one | Used against protozoa of the *Trypanosoma* and *Leishmania* species | Displays a much-enhanced activity against kinetoplastid parasites that causes human and veterinary disease, without any toxicity against a human cell line | [69] |
|  2,6-bis-(3,4-dimethoxy-benzylidene)-cyclohexanone | Multi-drug resistant modulator inhibition of both P- glycoprotein function and expression in human leukemic cell line (K562/Adr) | – | [94] |
|  2,6-bis((3-methoxy-4-hydroxyphenyl) methylene)-cyclohexanone | Inhibits human equilibrative nucleoside transporter 1, ENT1, in pancreatic cancer cells | Equal | [98] |
|  2-(4-hydroxy-3-methoxybenzylidene)-5-(-3-(4-hydroxy-3-methoxyphenyl) acryloyl) cyclopentanone | Modulates genes involved in multiple apoptosis pathways in human hepatocellular carcinoma cells (HepG2) – completely inhibits the tumor cell proliferation | Better anti-proliferation activity | [99] |

**Tab. 2.** *continued*

| Curcumin analogue | Effects | Comparison with curcumin | Ref. |
|---|---|---|---|
|  <br>4-((furan-2-yl) methylene)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione, MHMD | Induces A549 lung cancer cells death through apoptosis and necrosis | Bioavailability of MHMD is about 10-fold higher | [100] |
|  <br>1-{2,4-dimethoxy- 6-[4-methoxystyryl] phenyl}-5-(2,3-dimethoxyphenyl) penta-1,4-dien-3-one | Anti-inflammatory activities: significantly protected against lipopolysaccharide-induced acute lung injury in the in vivo mouse model | Greater stability | [101] |
|  <br>1-(4-Hydroxy-3-methoxyphenyl)-5-(2-nitrophenyl) penta-1,4-dien-3-one | Exhibits significant protection against lipopolysaccharide-induced death in septic mice | Shows intense anti-inflammatory activities | [88] |
|  <br>1-(3'-fluoro-[1,1'-biphenyl]-3-yl)-3-(3-hydroxy-4-methoxyphenyl) (prop-2-en-1-one) | The potent growth inhibitory activity in human colorectal cancer cells;<br>Inhibites the intracellular microtubule assembly, alters the expression of cyclin-dependent kinase 1 (CDK1), and ultimately induces G2/M cell cycle arrest. | Better cytotoxicity | [102] |
|  <br>1, 7-di (1H-indol-3-yl) hepta-1, 6-diene-3, 5-dione), ICA | Significantly inhibits the proliferation of various cancer cell lines and induces apoptosis by intrinsic and extrinsic pathway: induces the activation of caspase 3, 8 and 9, followed by down regulation of cyclin D1;<br>Hold promise as an anti-cancer agent for colon cancer | Better anti-proliferation activity | [103] |

**Tab. 2.** *continued*

| Curcumin analogue | Effects | Comparison with curcumin | Ref. |
|---|---|---|---|
|  4,4'-2,2'-(1-(3,4-dichlorophenyl)-1H-pyrazole-3,5-diyl) bis(ethene-2,1-diyl) bis(2-methoxyphenol), CDPP | Potential drug candidate against adipogenesis and dyslipidemia | Enhanced gastrointestinal stability and bioavailability | [104] |
|  3,5-bis[(2-fluorophenyl) methylene]-4-piperidinone | Exhibits anticancer effects on colorectal cancer cells by inducing reactive oxygen species generation and subsequent mitochondrial dysfunction, deregulation of cell cycle, and apoptosis | Greater anti-tumor efficacy and metabolic stability | [105, 106] |
|  1-methyl-3,5-bis[(4-pyridyl) methylidene]-4-piperidone | Induces the aryl hydrocarbon receptor in colon adenocarcinoma cells | Better anti-tumor agent | [107] |
|  1-isopropyl-3,5-bis[(pyridine-3-yl) methylene] piperidin-4-one | Induces the aryl hydrocarbon receptor in colon adenocarcinoma cells | Better antitumor agent | [107] |
|  2,6-bis(2-(trifluoromethyl)benzylidene) cyclohexanone | Reduces high glucose-induced inflammation profiles both in vitro and in vivo, and then prevents renal injury in experimental diabetic rats via its anti-inflammatory actions | Stronger inhibition against high glucose-induced TNF-$\alpha$ expression | [21] |

**Tab. 3.** Main advantages and disadvantages of curcumin applications.

| **Application** [113–116] |
|---|
| Functional food |
| Supplements |
| Pharmaceuticals |
| Food preservative |
| Natural colorant in food products |

| **Main advantages** [6] |
|---|
| From natural source |
| Highly functional compound |
| Nontoxic up to high dosages (12 g per day) |
| Toxic to cancerous cells |
| Cytoprotective to healthy cells |
| A large variety of biological targets |
| A large variety of interactions |

| **Main disadvantages** [6, 117–120] |
|---|
| Low bioavailability: |
| – low intestinal absorption |
| – rapid metabolism rate (in the liver/plasma) |
| – rapid systematic clearance |
| Poor water solubility (11 ng·ml$^{-1}$) |
| Prone to degradation (in non-aqueous solvents and alkaline solutions) |
| Light sensitivity |

structure and activities could be very useful for facilitating the design of novel therapeutic agents with improved ability to induce paraptosis.

**Nanoencapsulation of curcumin – its bioavailability enhancement and supporting role in disease treatment**

Cancer patients, suffering from a degenerative disease that leads to uncontrolled tumour cells proliferation, usually undergo different treatments such as chemotherapy, radiation therapy and immunotherapy applied before or after surgery. Chemotherapy, although being the principal treatment of cancer, has limited efficacy and, even worse, most chemotherapy regimens applied induce side effects. The solution is in the novel, more effective and non-toxic natural products used as therapeutic agents. The effectiveness of drugs (e.g. curcumin) could be improved by using catanionic lipid nanocarriers [123], mixed micelles [124], organically modified silica nanoparticle-curcumin complex conjugated with hyaluronic acid [125] or curcumin-cyclodextrin/cellulose nanocrystals complex (used for encapsulation of curcumin) [126], which is finally manifested through enhanced absorption, accumulation and reduced clearance of curcumin (Tab. 4, 5). As a result of increased bioavailability of curcumin, cytotoxicity against tumour cells is much improved [123, 126]. For effective non-surgical therapies, such as systematic chemotherapy, curcumin could be used as a supplement inhibiting tumorigenesis and metastasis. In combination with traditional chemotherapeutic drugs, curcumin could reduce their concentration and/or side effects, and enhance the impact on applied substances action through inhibiting cell growth, proliferation and migration [141].

*Opisthorchis viverrini* is currently a major health problem, particularly in north-eastern Thailand, where six million people have been infected with this parasite [142]. The latest investigation confirmed that curcumin is a promising chemopreventive agent in reducing cholangiocarcinoma, which can develop after infection with *O. viverrini* [142]. Namely, the effects of the combination of praziquantel (the usual drug with a constellation of undesirable side effects) and nano-encapsulated curcumin for the treatment of *O. viverrini*-infected hamsters are clearly manifested in reduced periductal fibrosis and attenuated abnormality of bile canaliculi in an animal model. Due to curcumin-loaded polymeric nanocarriers, the results, very promising for the future treatment of this widespread disease, were classified as being of "potential clinical significance" [142].

Bioavailability and medical value of curcumin could be much more improved by using curcumin lipid nanoemulsion with a particle size of approximately 100 nm [143]. The effect of particle size on the physiological activities of curcumin-loaded lipid nanoemulsion was confirmed by the investigation of the inhibitory effects of nanoemulsions against in vitro and in vivo inflammatory and allergic activities [143]. Nanogels, with particles usually of few hundred nanometres in diameter, are very suitable for targeted drug delivery and biosensing, and are used for therapeutic purposes. As an example, chitin, easily fabricated into nanogels without cross-linking, has considerable potential in drug delivery and nanotherapeutics [144]. Chitin nanogels, a relatively new class of natural polymeric nanomaterials, can be blended, incorporated, loaded or labelled with a wide range of drugs and molecules. Curcumin-loaded chitin nanogels were found to be more effective against melanoma in comparison to control curcumin solution [144].

**Delivering to the desirable location**

Glioblastoma multiforme (GBM) is the most common form of brain tumour, accounting for 77 % of the malignant brain tumours. Conventional approaches, such as radiation therapy, chemotherapy and surgery, are usually combined in the treatment of GBM. Unfortunately, the combined treatment effects show an average survival shorter than one year. Although the efficiency of the treatment could increase to some extent, unwanted side effects of the therapy are also remarkable. It is well known that the effectiveness of this tumour treatment is directly related to the possibility of drug delivery to the central nervous system. The critical problem arising during drug is the crossing of the blood-brain barrier (BBB). Nanotechnology then appears to be a great tool in clinical application. Using nanoparticles for drug delivery through the BBB represents one of the new promising approaches to solving the problem of the treatment of patients suffering from GBM [145]. The applicability of nanoparticles in the treatment of GBM is reflected in their outstanding characteristics such as small size, biocompatibility, easy encapsulation, tumour-specific targeting, self-assembly and other already mentioned features [6], with a strong effect on loading, release and stability of therapeutic agents in targeted drug delivery. Curcumin-loaded magnetic nanoparticles used for drug delivery exhibited cytotoxic effects due to the suppression of GBM tumour cell, opening a new horizon in the treatment of these progressive and fatal diseases [145, 146]. Curcumin exerts effects on serine/threonine protein kinase, mitogen-activated protein kinase, activator of transcription 3, nuclear factor kappa β, insulin-like growth factor and, consequently, on malignant brain-tumours through all of these pathways [147]. A non-invasive therapeutic approach based on the rapid delivery of exosome encapsulated curcumin significantly delayed the brain tumour growth and inflammatory-related brain diseases, such as glioblastoma [148]. Development and investigation of drugs are primarily directed towards their delivery to the desired location, inflammatory cells in this case, without harming normal tissues. Using exosome as a delivery vehicle seems an excellent solution for this purpose, because exosomes significantly increase solubility, stability, bioavailability and anti-inflammatory activity of the encapsulated curcumin and show efficacy in the treatment of multi-drug resistant cancer cells [149, 150].

**pH-Responsive controlled curcumin release**

A pH-sensitive polymer-drug conjugate based on the conjugation between *cis*-aconitic anhydride (Cis) and F68 polymer (poly (ethylene oxide)-co-poly (propylene oxide)-co-(polyethylene oxide) triblock copolymer, PEO-PPO-PEO) in the first step, and covalent linkage of curcumin to the hydrophilic segment in the second step (F68-Cis-Cur conjugate), represents a novel and interesting way of intracellular drug loading and release [151]. Owing to the conjugation properties, the amount of curcumin leaching out of the micelles in blood at pH 7.4 is minimized and, oppositely, intracellular drug release in tumour cells in mildly acid environment is very rapid due to pH-sensitive cleavage of *cis*-aconitic anhydride linkers. This is facilitated

**Tab. 4.** Improving bioavailability and stability of curcumin.

| **Bioavailability (maximum plasma level)** | | |
|---|---|---|
| Oral | 0.06±0.01 $\mu g \cdot ml^{-1}$ | [127] |
| Intravenously | 0.36±0.05 $\mu g \cdot ml^{-1}$ | [127] |
| Oral administration (1 $g \cdot kg^{-1}$) to mice | 0.22 $\mu g \cdot ml^{-1}$ | [128] |
| Intraperitoneal administration (0.1 $g \cdot kg^{-1}$) to mice | 2.25 $\mu g \cdot ml^{-1}$ | [128] |
| Oral administration (12 $g \cdot d^{-1}$) to human | 0.051 $\mu g \cdot ml^{-1}$ | [129] |

| **Improving bioavailability and stability by using some formulations** [6, 62, 130–137] |
|---|
| Phospholipid complexes |
| Liposomes |
| Piperine |
| Polymeric micelles |
| Encapsulation in hydrogel beads based on: |
| – proteins |
| – polysaccharides |
| – protein-polysaccharide |
| Solid lipid nanoparticles |
| Curcumin-metal chelates |
| Modification of skeleton |
| **Other ways of improving bioavailability** [138–140] |
| Increasing water dispersion |
| Increasing water solubility |

| **Key points of the formulations application** [62, 136] |
|---|
| Increase permeability |
| Increase retention coefficients |
| Enhance delivery of curcumin |
| Increase cellular uptake |
| Sustain release |
| Control release |

**Tab. 5.** Examples of improving bioavailability of curcumin.

| Formulations | Administration | Species/ Cell line | Dose | Effects | Ref. |
|---|---|---|---|---|---|
| Chitosan-based polyelectrolyte complexes | Oral | Rat | 200 $mg \cdot kg^{-1}$ | Retention status as well as bioactivities and chemotherapeutic effectiveness of curcumin are improved via nanoencapsulation in chitosan-based complexes. | [62] |
| Improving bioavailability by using unusually high dose of curcumin | Oral | Human | 0.5–12 $g \cdot d^{-1}$ | Improvement is observed in 7 out of 25 patients with various high-risk and pre-malignant lesions. The study demonstrated that curcumin is not toxic to humans up to 8 000 mg per day, when taken by mouth for 3 months.<br>Note: Biochemical analyses suggested that curcumin is biotransformed in dihydrocurcumin and tetrahydrocurcumin, which are later converted to mono-glucuronide conjugates. Very high dose of curcumin is important, because some of these metabolites may retain the pharmacologic properties of curcumin. Therefore, the relatively low serum concentration of curcumin in the patient, may not necessarily reflect the total beneficial, biological activity of oral curcumin usage. | [131] |
| Curcumin lecithin formulation | Oral | Human | 165–297 $mg \cdot d^{-1}$ | The improved absorption, and a better plasma curcuminoid profile, might underlie the clinical efficacy of curcumin-lecithin formulation at doses significantly lower than unformulated curcuminoid mixtures. | [132] |
| Hydrogel beads used to encapsulate and protect curcumin | – | Simulated gastro-intestinal tract | – | Retention and release can be engineered by controlling the pore size of the hydrogel beads – by using different types or concentrations of biopolymers and cross-linking agents or by varying environmental conditions such as pH, ionic strength and temperature.<br>Alternatively, retention and release can be controlled by engineering the nature of the attractive and repulsive interactions between the nutraceutical and the biopolymer molecules that make up the hydrogel network inside the beads. | [134] |
| *N*-carboxymethyl chitosan coated curcumin-loaded solid lipid nanoparticles | – | MCF-7 | 1–10 $\mu mol \cdot l^{-1}$ | The formulation exhibited suppressed burst release in simulated gastric fluid while sustained release is observed in simulated intestinal fluid. It exhibited increased cytotoxicity and cellular uptake on MCF-7 cells. The lymphatic uptake and oral bioavailability of the formulation are found to be 6.3-fold and 9.5-fold higher than that of curcumin solution, respectively. The formulation could be an efficient oral delivery system for curcumin. | [136] |
| | Oral | Rat | 50 $mg \cdot kg^{-1}$ | | |
| Metal complexes of curcumin | Intra-peritoneal injection | Mice | 10 $mg \cdot kg^{-1}$ | Various metals have advantageous properties that can be used to mitigate the inherent disadvantages of curcumin, such as higher stability under physiological conditions and ease of detection in vivo. For example, Zn-curcumin complex induced conformation change in p53-R175H and p53-R273H mutant proteins. Zn-curcumin localized inside glioblastoma tissues suggesting its ability to cross the blood-tumor barrier. | [137] |
| Nanoparticles of curcumin | – | Microbes | 75–350 $\mu g \cdot ml^{-1}$ | The aqueous dispersion of nanocurcumin is much more effective than curcumin against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Penicillium notatum*, and *Aspergillus niger*.<br>The water solubility and antimicrobial activity of curcumin are markedly improved by particle size reduction up to the nano range. | [138] |
| Sub-micrometer dispersion of curcumin | – | – | – | High-pressure homogenization is proven to be a mature method to create readily dispersible curcumin powders with high water dispersity, which is of vital importance for the enhancement of the oral bioavailability of curcumin. | [139] |
| Matrix encapsulation of curcumin in gelatin | – | Microbes | 1–100 $mg \cdot ml^{-1}$ | The water solubility of curcumin increased 38.6-fold after it had been encapsulated in gelatin microparticles. Encapsulation of curcumin in gelatin particles by electrohydrodynamic atomization greatly improved its antioxidant and antimicrobial properties. | [140] |

because extracellular pH in normal tissues is kept constant at pH 7.2–7.6, while pH of tumour tissues is typically by 0.5 lower) [152]. F86-Cis-Cur conjugation enhances intracellular curcumin delivery in cancer therapy. It was confirmed that F86-Cis-Cur micelles induced higher cytotoxicity compared to free curcumin [151]. Consequently, the effectiveness of pH-responsive controlled curcumin release is enhanced, which makes this method attractive for curcumin administration in cancer patients. Compared to their synthetic counterparts, clinically feasible and pH-sensitive naturally derived therapeutic compounds exhibit negligible deleterious effects on normal cells [153]. Conjugation of curcumin to the hydrophilic backbone of dextran, producing curcumin-dextran micelles, represents a promising candidate for safe and efficient cancer therapy. These micelles exhibit a rapid rate of curcumin release at a specific acidic environment in tumour cells with increased local concentration, resulting in profound cytotoxicity to cancer cells [153].

**Synergistic effect**

Scientific studies also include considerations for the implementation of curcumin in combination with other substances in order to increase their efficacy (Tab. 6). The presence of other substances is important primarily for curcumin solubility. It should be borne in mind that pure forms of each drug have different properties than multicomponent solids, such as co-crystals (according to the US Food and Drug Administration, co-crystals are defined as 'dissociable multi-component solid crystalline supramolecular complexes composed of two or more components within the same crystal lattice wherein the components are in neutral state and interact via nonionic interactions') [157]. Essentially, the investigation of multi-combined drugs requires simultaneous consideration of several factors including their administration with possible pharmacological outcomes, differential solubility, each compound stability, new-generation impurities as a result of incompatibility between the compounds, drug-inorganic salt, drug-nutraceuticals and drug-drug interactions. Computational predictive models for combined drugs exerting desired therapeutic effects have a crucial role in the rapidity of development of multidrug-based commercial products with enhanced physico-chemical and biopharmaceutical performance. This could lead to new platforms for developing effective therapeutics with reduced adverse effects. Nevertheless, despite the impressive developments in the field of pharmaceutical preparations, the commercial application of drugs based on co-crystals is still awaited [156]. Besides combining curcumin with other substances in order to enhance their efficacy, studies so far indicate that natural product curcumin exhibits synergistic effects with a great number of chemotherapeutic agents and reduces the unwanted side effects induced by anticancer drugs [158]. The synergistic effect of doxorubicin (DOX) and curcumin co-delivery by lipid nanoparticles (DOX/Cur-NPs) on apoptosis, proliferation and angiogenesis of hepatocellular carcinoma (HCC) in mice was examined and a decrease of the liver damage assessed by serum alanine aminotransferase and aspartate aminotransferase levels, liver/body weight ratio and histopathological analysis (Tab. 6) [141]. The inhibitory effect of a chemotherapeutic DOX/Cur agent and chemosensitizer using nanocarriers on diethylnitrosamine-induced HCC in mice was confirmed and the findings indicates a promising potential for cancer treatment. The synergistic effect achieved by the combination therapy improved target selectivity, inhibited the development of cancer drug resistance (as one of the major obstacles in curing cancer) and offered unprecedented opportunities for effective cancer treatment. Curcumin, as an essential ingredient in functional food products, when combined with radiotherapy, chemotherapy and immunological agents, demonstrated its synergistic effects, inducing multi-molecular targeting of all signalling pathways included in the process of cancer onset and progression [147].

**Curcumin in clinical trials**

The paper of Gupta et al. [159] deals with curcumin applications in the treatment of numerous diseases in humans. Large-scale clinical trials included irrefutable evidence and outcomes of curcumin's effects on various human diseases (Tab. 1), such as cancer, cardiovascular disease, arthritis, uveitis, ulcerative proctitis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, tropical pancreatitis, peptic ulcer, gastric ulcer, idiopathic orbital inflammatory pseudotumor, oral lichen planus, gastric inflammation, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, diabetic nephropathy, diabetic microangiopathy, lupus nephritis, renal conditions, acquired immunodeficiency syndrome, β-thalassemia, biliary dyskinesia, Dejerine-Sottas disease, cholecystitis and chronic bacterial prostatitis [159, 160]. Clinical efficacy of this fascinating molecule is circumstantially explained through detailed data reported in the literature and ongoing clinical trials with curcumin. Curcumin is highly effective and favorable outcomes related to its

**Tab. 6.** Synergistic effect of the interaction between curcumin and some compounds.

| Interacting compounds | Administration | Species/ Cell line | Dose (curcumin + compound) | Remarks | Ref. |
|---|---|---|---|---|---|
| **Antibiotics** | | | | | |
| Ampicillin | – | Microbes (ATCC 33591) | 125 $\mu g \cdot ml^{-1}$ + 15.6 $\mu g \cdot ml^{-1}$ | Curcumin reduces the minimal inhibitory concentration of the antibiotics used against methicillin-resistant *Staphylococcus aureus* infection; the bacterial counts below the lowest detectable limit after 24 h, when treated by combination of curcumin and oxacillin. | [67] |
| Ciprofloxacin | | | 62.5 $\mu g \cdot ml^{-1}$ + 7.8 $\mu g \cdot ml^{-1}$ | | |
| Norfloxacin | | | 62.5 $\mu g \cdot ml^{-1}$ + 16.6 $\mu g \cdot ml^{-1}$ | | |
| Oxacillin | | | 125 $\mu g \cdot ml^{-1}$ + 62.5 $\mu g \cdot ml^{-1}$ | | |
| **Chemotherapeutics** | | | | | |
| Cisplatin | – | U138MG | 10 $\mu mol \cdot ml^{-1}$ + 5 $\mu mol \cdot ml^{-1}$ | Curcumin synergized with cisplatin is enhancing glioblastoma cells death; it potentiated the effect of cisplatin to produce cellular injury in U87MG and U138MG cells. | [147] |
| | | C6 | 25 $\mu mol \cdot ml^{-1}$ + 5 $\mu mol \cdot ml^{-1}$ | | |
| Diclofenac | Oral | Rats | 31 $mg \cdot kg^{-1}$ + 10 $mg \cdot kg^{-1}$ | Diclofenac is non-steroidal anti-inflammatory and anti-pyretic drug, effective in treating a variety of acute and chronic pains.<br>The association diclofenac with curcumin can increase antinociceptive activity, permitting the use of lower doses and thus limiting side effects. | [154] |
| Doxorubicin | Oral | Mice | 2 $mg \cdot kg^{-1}$ | Doxorubicin is anthracycline antibiotic, one of the most efficacious drug in the treatment of hepatocellular carcinoma.<br>Enhancement of its inhibitory effect on diethylnitrosamine-induced hepatocellular carcinoma in mice. | [141] |
| Etoposide | Curcumin oral; etoposide intraperitoneal | Rats | 200 $mg \cdot kg^{-1}$ + 50 $mg \cdot kg^{-1}$ | Etoposide is a topoactive drug; the myelotoxic and leukemogenic action of etoposide makes it difficult to use a sufficiently high dose.<br>Curcumin can increase the antileukemic effect of etoposide through reactive oxygen species in sensitive myeloid leukemia cells, and it is harmless to normal human cells. | [155] |
| Paclitaxel | – | HBTSC<br>LN18<br>U138MG | 20 $\mu mol \cdot ml^{-1}$ + 10 $nmol \cdot ml^{-1}$ | Paclitaxel is a highly effective anti-cancer drug that stoichiometrically binds to microtubule and stabilizes microtubule structure.<br>Combined therapy acted synergistically to control the growth of human brain tumor stem cells (HBTSC), LN18, and U138MG cells by inhibiting survival, invasive and angiogenic signaling pathways, increasing apoptosis via activation of proteolytic activities of calpain and caspase-3. | [147] |
| Piperine | Oral | Human | 1 $g \cdot d^{-1}$ + 10 $mg \cdot d^{-1}$ | Piperine inhibits the action of xenobiotic metabolizing enzymes and exhibits antioxidant action via free radical quenching effect and by preventing reduced glutathione depletion; a strong inhibitor of hepatic and intestinal aryl hydrocarbon hydroxylation and glucuronidation.<br>This combination significantly improves superoxide dismutase activities, reduced concentration of malondialdehyde and C-reactive protein, and in that way, improves inflammatory status in patient with metabolic syndrome. | [15] |
| Pyrogallol | – | – | – | Pyrogallol exhibits anticancer activity.<br>In interaction with curcumin it improves physicochemical properties; dissolution rate 12 times faster than for curcumin alone. | [156] |
| Resorcinol | – | – | – | Resorcinol is conformer molecule, a safe chemical for human consumption.<br>In interaction with curcumin it improves physico-chemical properties; dissolution rate 5 times faster than for curcumin alone. | [156] |

therapeutic potential suggest further clinical investigation of its mechanisms of action. Although the pathways of its actions have not been fully clarified and specified from medical, chemical and biochemical aspects, the efficacy of curcumin against the diseases is evident [159]. Hence, curcumin delivery and its satisfactory loading concentration throughout entire tumour remain to be a serious scientific challenge.

## CONCLUSIONS AND FUTURE PERSPECTIVE

The low aqueous solubility of curcumin, its rapid metabolism and elimination from the body and, accordingly, poor bioavailability, constitute major obstacles for its medical applications. The investigations mentioned above were aimed to overcome these limitations and, hereby, improve the solubility, stability and bioavailability of curcumin. The efficacy of curcumin depends on its ability to enter the tumour cells and, therefore, nanoparticle-based carriers have a great potential because, for example, they could help curcumin enter the cell and reach the tumour site passing through the brain-blood barrier. The latter is particularly important for treatment of high-grade gliomas, including the most aggressive and lethal types of brain tumor, HGGs, and all these considerations together reasonably deserve further research efforts [161]. Enhancement of chemotherapeutic efficacy in cancer treatment is directly connected with overcoming the multidrug resistance in cancer cells where nanoparticle-based carriers and curcumin, as a nutraceutical ingredient, offer a great opportunity [162]. In this context, targeting tumour micro-environment, nanoparticles ensure a new problem-solving platform connected with tumour cell proliferation, metastasis and drug resistance [162].

Besides the above mentioned information [1, 6–9, 86], natural polyphenol curcumin has a further wide spectrum of activities, namely, a potential to prevent sexually transmitted viral infections caused by human immunodeficiency virus (HIV), herpes simplex virus (HSV) and human papilloma virus (HPV). Hitherto, investigations verified the complete functioning and, in some cases, even the mechanism of action and efficacy of natural polyphenols, including curcumin, in these diseases in vitro [163]. Unfortunately, scarce data of animal studies in vivo regarding the prevention of the mentioned infections using natural polyphenols have been reported. In the years to come, it is necessary to conduct systematic investigation and evaluation of the efficacy of natural polyphenols in vitro, ex vivo and in vivo, particularly for HIV, HSV and HPV. Here it is also necessary to emphasize the importance of multidisciplinary approach, such as in the case of pharmacological preparations, where the potential of nanocarriers for improving delivery of natural polyphenols was studied [163], and the same subject was discussed in a review from the point of view of food chemistry [6].

The implementation of safe, beneficial and highly functional compounds from natural sources in therapy brought about some modifications in order to achieve their multi-functionality, improve their bioavailability and delivery strategies, and reduce potentially negative side effects, with the general aim to enhance their effectiveness. Guidelines for the pursuit of future research all over the world have been provided. In this regard, improvement of aqueous solubility of curcumin, its delivery and investigation of its activity at tumour site should be thoroughly studied.

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