THE PHARMACOLOGICAL BASIS OF THE CURCUMIN NUTRACEUTICAL USES: AN UPDATE

D. Canistro[1,9], A. Chiavaroli[2,9], D. Cicia[3,9], F. Cimino[4,9], D. Currò[5,9], M. Dell'Agli[6,9], C. Ferrante[2,9], L. Giovannelli[7,9], S. Leone[2,9], G. Martinelli[6,9], L. Milella[8,9], E. Pagano[3,9], S. Piazza[6,9], M. Ponticelli[8,9], L. Recinella[2,9], S. Ristori[7,9], E. Sangiovanni[6,9], A. Smeriglio[4,9], A. Speciale[4,9], D. Trombetta[4,9], F. Vivarelli[1,9]

[1]Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy
[2]Department of Pharmacy, Medicinal Plant Unit (MPU), Giardino dei Semplici Botanic Garden, G. d'Annunzio University of Chieti-Pescara, Chieti, Italy
[3]Department of Pharmacy, Federico II Naples University, Naples, Italy
[4]Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy
[5]Department of Security and Bioethics, Pharmacology Section, Università Cattolica del Sacro Cuore, Rome, Italy
[6]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
[7]NEUROFARBA, University of Florence, Florence, Italy
[8]Department of Science, University of Basilicata, Potenza, Italy
[9]Working Group Pharmacognosy, Phytotherapy and nutraceuticals of the Italian Society of Pharmacology (SIF), Milan, Italy

E-mail: mario.dellagli@unimi.it
Doi: 10.36118/pharmadvances.2021.06

SUMMARY

Curcumin is the major phytoconstituent found in the rhizomes of *Curcuma longa* L. Preparations derived from the rhizome of the plant, referred as turmeric, have been used for centuries in the traditional Indian system of medicine. The recent literature has shown curcumin as one of the most interesting pleiotropic nutraceuticals capable of interacting with different molecular targets involved in chronic diseases. The present review summarizes and critically discusses the very recent literature published between 2018 and 2021. We focused on the preclinical pharmacological actions of curcumin in relation to its possible clinical application in several pathophysiological states and disturbances including inflammation and pain, as well as metabolic, cardiovascular, dermatological, and central nervous system diseases. The most relevant molecular targets of curcumin, such as transcription factors, pro-inflammatory mediators, enzymes, and protein kinase as well as pharmacokinetics in humans are also reviewed.

Key words
*Curcumin; nutraceutical; Pharmacology; botanicals, natural products.*

Impact statement
An update of the pharmacological and nutraceutical potential of curcumin emerging by preclinical and meta-analysis studies.

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INTRODUCTION

Turmeric (*Curcuma longa* L., Zingiberaceae Family) is native to India, the world's largest producer and exporter; however, it is currently also grown in Southeast Asia, Latin America, and China (1). The drug consists of turmeric rhizomes containing a percentage of curcuminoid ranging between 2-9% depending on the origin, soil conditions, and climate (2). Under the name of "curcuminoids" are grouped three diarylheptanoids (diferuloylmethane derivatives), which include curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BMC), and other less abundant secondary metabolites (3) (**figure 1**). In particular, curcumin is the major phytoconstituent found in the rhizomes of *Curcuma longa* L. since it accounts for 77%, while DMC and BMC for 17% and 3-6% approximately (1, 4); curcumin was extracted for the first time in a pure crystalline form in 1870 (5). Nonetheless, curcumin, DMC, and BMC have been isolated from various *Curcuma* spp., including *Curcuma amada* Roxb., *Curcuma manga* Val., *Costus speciosus* (J. Koenig) Sm., *Curcuma zedoaria* Rox., *Curcuma xanthorrhiza* Roxb. orth. var. (Javanese turmeric), *Curcuma hyneana* Val. & V. Zyp*., Curcuma soloensis* Val., *Curcuma wenyujin* H.Chen & C.Ling, *Curcuma oligantha* Trimen, *Curcuma aeruginosa* Roxb., *Curcuma phaeocaulis* Val., *Curcuma aromatica* Roxb. (wild turmeric), *Etlingera elatior* (Jack) R.M. Sm., *Zingiber cassumunar* Roxb., *Zingiber zerumbet* L. (6-9). Several pharmacological activities have been ascribed to curcumin as a pure compound, such as antioxidant, antimicrobial and anti-inflammatory properties (10-12). The recent literature has shown curcumin as one of the most interesting pleiotropic nutraceuticals capable of interacting with different molecular targets involved in inflammation and oxidative stress. Moreover, curcumin showed positive effects as vasculo- and neuro-protective agent (13-15), and beneficial properties in skin diseases (16).
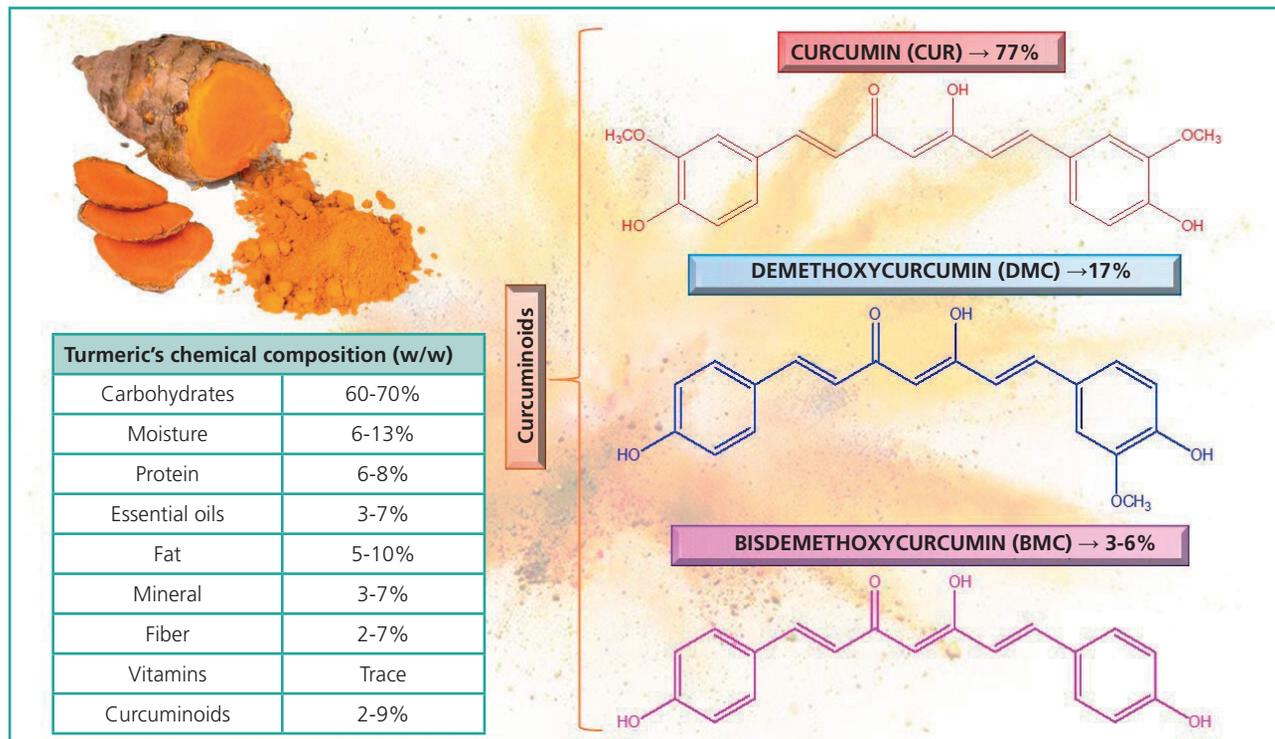
**Figure 1.** Representation of the major constituents of *Curcuma longa* L.
Curcumin (CUR), demetoxycurcumin (DMC), and bisdemethoxycurcumin (BMC) are generally grouped together under the name curcuminoid, which represents 2-9% of turmeric by weight. Among the curcuminoids, CUR, DMC, and BMC account approximately for 77%, 17%, and 3-6%, respectively.

The present review summarizes the very recent literature published between 2018 and 2021. We reviewed only the preclinical pharmacological actions for which extensive clinical investigation has been reported, mostly based on systematic review and meta-analyses of clinical trials (17). Curcumin chemistry, pharmacokinetic in humans and mode of action are also reviewed. The discussion of clinical data on its efficacy as well as the new pharmaceutical formulations developed to improve its oral absorption are outside the scope of this article.

CHEMISTRY

Thanks to its numerous health effects, curcumin has been extensively investigated from a chemical point of view. The IUPAC name of curcumin is (1*E*, 6*E*)–1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione, its chemical formula is $C_{21}H_{20}O_6$ and it possesses a molecular mass of 368.38 g/mol. Curcumin is a symmetric compound whose structure comprises three chemical units consisting of 2 aromatic ring systems containing *O*-methoxy phenolic groups linked through an α,β-unsaturated β-diketone moiety (**figure 2**) (18, 19).

This structure led to an extended conjugation due to the electron cloud spanning along the molecule. For this reason, in the solution, curcumin can exist in *cis-trans* isomers where the *trans*-form is slightly more stable than the *cis*-form for the presence of the 2 phenolic-methoxy groups in the opposite sides of curcumin backbone (20). Furthermore, the diketone moiety, for the intramolecular hydrogen atom transfection, is subjected to keto-enol tautomerism, and this tautomeric form can even exist in several *cis-trans* forms. Thus, depending on different factors like polarity of the solvent, temperature, and substitution on the aromatic rings, curcumin can exist in different types of conformers (19). In particular, when curcumin is in the crystal state, it appears in a cis-enol configuration stabilized by resonance; in this case, the structure consists of 3 planar groups interconnected by 2 double bonds (20). Generally, the keto-enol tautomerism of curcumin depends on the solution's pH: the enol-form dominates under alkaline conditions while the keto-form under neutral and/or acidic conditions (21) (**figure 3**). This presence of the enol form into the alkaline condition can be rationalized by forming the intramolecular hydro-
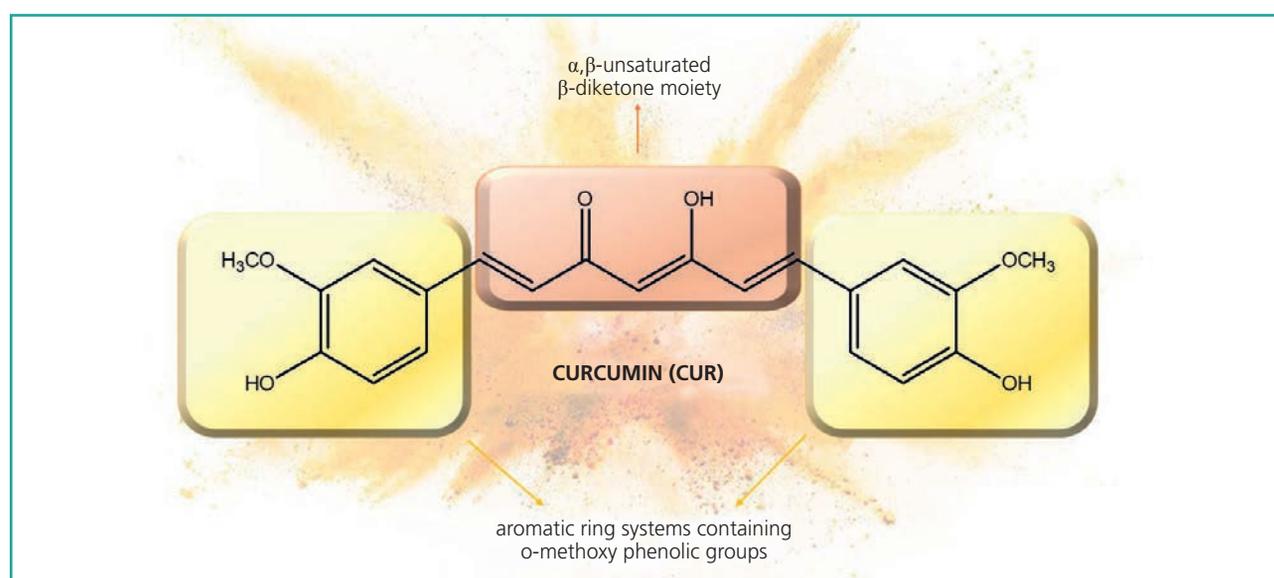
Figure 2. Representation of curcumin chemical structure. The symmetric structure of curcumin comprises three chemical units consisting of 2 aromatic ring systems containing O-methoxy phenolic groups linked through an α,β-unsaturated β–diketone moiety.
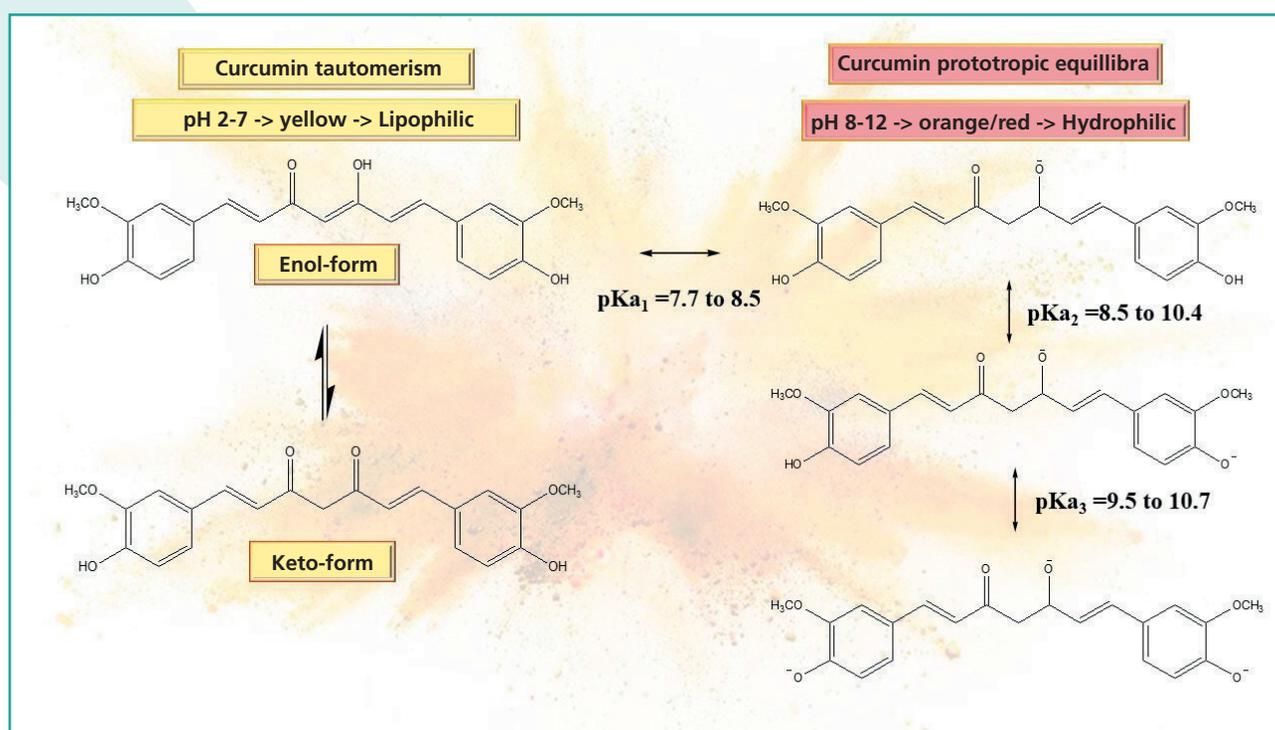
Figure 3. Representation of curcumin tautomerism and prototropic equilibria. The keto-enol tautomerism of curcumin depends on the solution's pH: the enol-form dominates under alkaline conditions while the keto-form under neutral and/or acidic conditions.

gen bond, which is generated when curcumin exists in the enolic form (1).

Curcumin is insoluble in aqueous solution at either neutral or acidic pH; however, for its lipophilic nature (logP3.0) it is soluble in organic solvents like ethanol, methanol, dimethyl sulfoxide, and acetone. The solubility of curcumin in an aqueous solution rises under alkaline conditions, although it should be considered that curcumin rapidly degrades under both alkaline and neutral condition (1).

The enol-form of curcumin possesses three ionizable protons represented by the enolic group and two phenolic groups (4). Thus, in this form, curcumin is a weak Brönsted acid with three prototropic equilibria at three different pK_as. The first pK_a (pH range of 7.5 to 8.5) changes the colour of curcumin from yellow to red. Furthermore, in the basic pH range, the anionic curcumin solubility in water is greater than the neutral form (20).

Regarding curcumin's biological activities, it was seen that they are related to the presence of 3 reactive sites: Michael acceptor, hydrogen atom donor, and metal chelator. In particular, the α,β-unsaturated β-diketone moiety acts as a metal chelator and also as a Michael acceptor in a nucleophilic addition reaction. Furthermore, all 3 active curcumin sites (the 2 aromatic ring systems containing o-methoxy phenolic groups and an α,β-unsaturated β-diketone moiety) can undergo oxidation by the transfection of electrons and the abstraction of hydrogen. All these pharmacophoric sites are strictly related to the anti-inflammatory, antioxidant, anticancer, and neurotrophic activity of curcumin. In the following section of the review, the main biological activities of curcumin will be analyzed.

MOLECULAR TARGETS OF CURCUMIN

Curcumin exerts pharmacological actions by interacting, directly or not, with a number of molecular targets, including transcription factors (22-24), inflammatory mediators (25), protein kinases (26), and enzymes (27) (for review see (28)).

Curcumin reduces nuclear factor kappa-B (NF-κB) activation and its Nuclear translocation by inhibiting phosphorylation of p65 subunit and degradation of NF-κB inhibitor alpha (IκBα) (22, 25, 29-31). NF-κB is a transcription factor that regulates the genic expression of the main pro-inflammatory cytokines (*e.g.* interleukin (IL)-1, IL-2, and interferon-γ (IFNγ)) involved in pathways associated with inflammation, pain and tumorigenesis (32).

Curcumin is also a potent inhibitor of 5-lipoxygenase (LOX, that may contribute to its anti-inflammatory effect) (27), and activates the mitogen-activated protein kinases (MAPKs)/Akt signaling pathways, which are mainly involved in mitosis, differentiation, cell proliferation, and cell survival/apoptosis (33, 34). Specifically, it has been reported that curcumin: (i) inhibits the IRS-1/AKT/PRAS40/Raptor/mTOR signaling cascade by inducing the proteasomal degradation of IRS-1 in colorectal cancer cells (35); (ii) reduces human aortic valve interstitial cells differentiation by suppressing the phosphorylation of extracellular signal-regulated kinases (ERK), IκBα and Akt (26); (iii) increases the nuclear factor-E2-related factor (NRF2) through an increase of the brain-derived neurotropic factor (BDNF) and ERK1/2 activation (36); (iv) increases PTEN expression and consequently decreases (via a selective packaging of miR-21 in exosomes) Akt phosphorylation, resulting in leukemic cell growth (37).

Also, curcumin protects against the development of neuropathic pain mainly through its inhibitory action on NF-κB, ERK and c-Jun N-terminal kinase (JNK) in pain models associated with peripheral nerve injury (38).

More recently, curcumin has been shown to reduce the proliferation of melanoma cells through the downregulation of Wnt/β-caten-
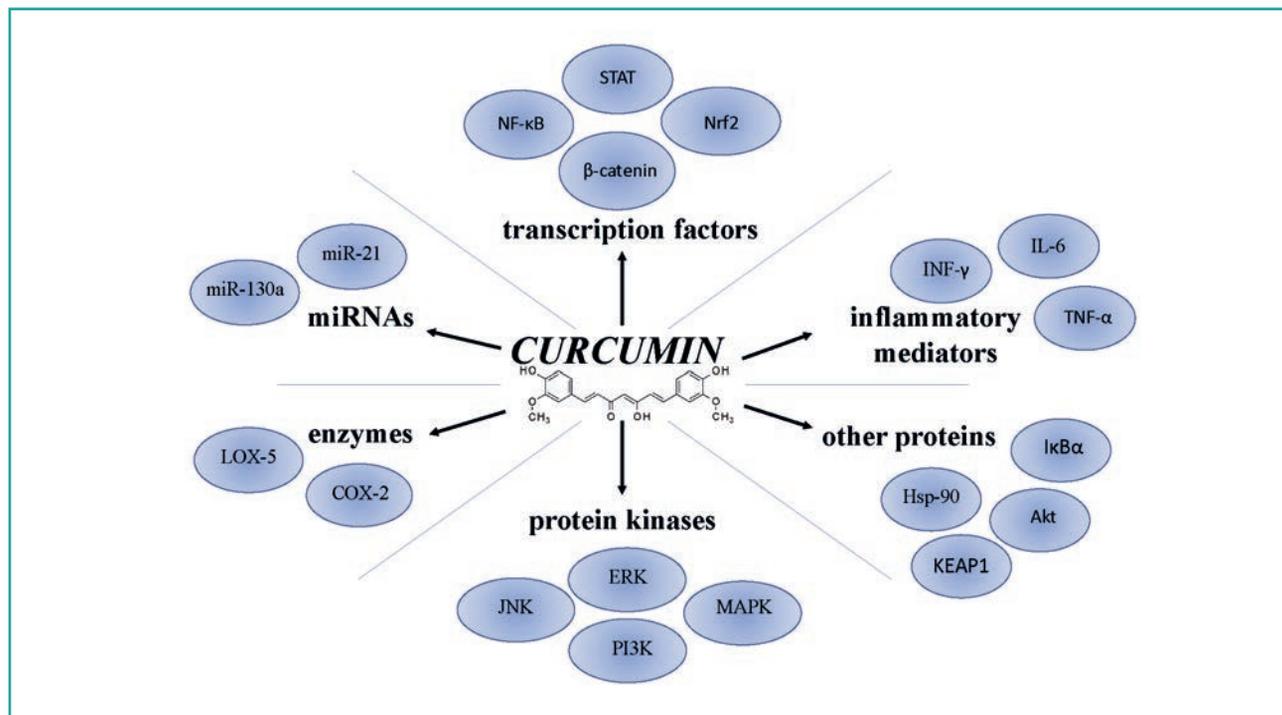
Figure 4. Schematic representation of the main molecular targets of curcumin.
The pharmacological effects of curcumin might be explained by the interactions with several targets which include transcription factors, pro-inflammatory mediators, enzymes, and protein kinases.
5-lipoxygenase (LOX); c-Jun N-terminal kinase (JNK); cyclooxygenase-2 (COX-2); extracellular signal-regulated kinases (ERK); heat shock protein 90 (Hsp90); interferon-γ (IFNγ); interleukin (IL)-1, IL-2; Kelch-like ECH-associated protein 1 (KEAP1); miR-130a; miR-21; mitogen-activated protein kinases (MAPKs); NF-κB inhibitor alpha (IκBα); Nuclear factor kappa-B (NF-κB); nuclear factor-E2-related factor (NRF2); signal transducer and activation transcription (STAT); β-catenin.

in signaling pathway proteins DVL2, β-catenin, cyclin D1, COX-2, and Axin2 (24). Also, curcumin suppresses the Wnt/β-catenin pathway via miR-130a (an inhibitor of the negative regulator Nkd2) in colon cancer cells SW480 (39). Additionally, curcumin has been reported as a modulator of the signal transducer and activation transcription (STAT) proteins. Specifically, curcumin inhibits i) IL-6-induced STAT3 phosphorylation and its consequent nuclear translocation and ii) IFN-γ-induced STAT1 phosphorylation. Both nuclear factors are involved in promoting inflammation, cells proliferation and angiogenesis (30, 31, 40, 41).

Finally, the antioxidant effect of curcumin is mainly correlated to KEAP1-NRF2-ARE pathway (42, 43). Curcumin induces NRF2 upregulation, mainly by binding to Kelch-like ECH-associated protein 1 (KEAP1), resulting in oxidative stress reduction (31, 44, 45). Nonetheless, it has been reported that curcumin exerts a neuroprotective effect by reverting the increased expression of heat shock protein 90 (Hsp90) in models of neurotoxicity (46).

In summary, the diverse and various pharmacological effects of curcumin might be explained by the interactions with several targets, the most relevant of which include transcription factors, pro-inflammatory mediators, enzymes, and protein kinase (**figure 4**).

PHARMACOKINETIC OF CURCUMIN IN HUMANS

Curcumin is poorly absorbed after oral administration, due to a very low water solubility, to the spontaneous degradation (particularly at ph > 7) into ferulic acid, feruloylmethane, vanillin, hexanal and bicyclopentadione derivatives; it is also metabolized in the intestinal mucosa and liver, and by enzymes produced by the intestinal microbiota (47, 48). Data from studies on rats and mice indicate that the oral bioavailability of curcumin is as low as approximately 1% and most of the orally administered curcumin is eliminated in the feces (47). The portion of curcumin that is not eliminat-ed through the fecal route is extensively metabolized. Curcumin is subjected to both conjugation reactions that give rise to curcumin glucuronide and curcumin sulfate, and to reduction reactions that give rise mainly to tetrahydro-curcumin and hexahydro-curcumin and to a lesser extent to dihydro-curcumin and octahydro-curcumin (also named hexahydrocurcuminol), which are then conjugated with glucuronic acid and sulfuric acid (47). Intestinal and hepatic alcohol dehydrogenases and a NAPDH-dependent curcumin/dihydrocurcumin reductase produced by strains of *Escherichia coli* contribute to the synthesis of the reduced metabolites of curcumin (48, 49).

Several papers are available in the literature reporting data from pharmacokinetic studies on curcumin in humans. In some of them, however, the plasma samples were subjected to pre-treatment with β-glucuronidase, with or without sulfatase, before the quantification of curcumin concentrations, so that they do not really study the pharmacokinetics of curcumin. Consequently, these studies were not considered. In addition, we have focused on the studies conducted using rhizome extracts of *Curcuma longa* L., most of which have used the product called "Curcumin C3 Complex" or "C3 Complex" or "C3" produced by Sabinsa Corporation (East Windsor, NJ, USA).

To date, no studies have investigated the pharmacokinetic parameters (oral bioavailability, distribution volume and systemic clearance) of curcumin, demethoxy-curcumin and bisdemethoxy-curcumin, the other two main curcuminoids contained in the rhizome extracts of *Curcuma longa* L., in humans. In most clinical studies, the plasma concentrations of curcumin were measured at various times after administration of products containing curcuminoids. These studies only allow an estimate of the oral absorption of these molecules.

Sharma *et al.* (2001) administered 2 to 10 capsules per day of the product P54FP, each of which contains 18 mg of curcumin and 4 mg of demethoxy-curcumin in 200 mg of essential oil obtained from *Curcuma* spp., correspond-

ing to curcumin doses of 36-180 mg, to 15 patients with intractable colorectal adenocarcinoma (50). In this study, no quantifiable levels of curcumin or its metabolites in either plasma or urine were detected. However, in these patients' feces, important levels of curcumin were found, up to about 388 μg/g of dried feces in patients who had taken the highest dose of the product.

Sharma *et al.* (2004) administered higher single daily doses of curcuminoids (500 mg-4 g) as the "C3" product, each capsule of which contained 450 mg of curcumin, 40 mg of demethoxy-curcumin and 10 mg of bisdemethoxy-curcumin, to patients with colorectal cancer no longer treatable with conventional therapies, until disease progression or withdrawal of consent (up to four months) (51). Curcumin was detected in plasma in only 3 of 6 patients treated with 4 g of curcuminoids, at mean levels of 11.1 nM half an hour or one hour after administration on days 1, 2, 8 and 29. Curcumin sulfate and curcumin glucuronide were detected in the plasma of all 6 patients taking this dose, at mean levels of 8.9 nM and 15.8 nM, respectively. Authors found both curcumin and its conjugated metabolites in the urine and high levels of curcumin in the stools of these 6 patients, up to about 43 μg/g of dried stool.

Garcea *et al.* (2004) found very low levels of curcumin, curcumin glucuronide, and curcumin sulfate, close to the limit of detection (3 nM) of the assay method, in the portal blood collected during surgery from 4 patients with liver metastases from colorectal adenocarcinoma, seven hours after taking a dose of 4 g of curcuminoids (52). They administered to patients the "Curcumin C3 Complex" product, which contained 450 mg of curcumin, 30 mg of demethoxy-curcumin and 20 mg of bisdemethoxy-curcumin in each 500 mg capsule. Patients had taken this dose every day for the 7 days before surgery. At levels not reported in the paper, curcumin was also found in the systemic circulation of two of these patients one hour after taking the dose. Curcumin and conjugated metabolites were not detected in either the portal or peripheral blood of patients treated with doses of 500 mg and 2 g. The same group published a year later a study again conducted on patients with colorectal cancer, with the same product ("Curcumin C3 Complex"), at the same doses (0.5-4 g), and for the same period of administration (7 days; (53)). Curcumin was detectable at levels above the limit of detection of the assay method (0.3 nM), but below the limit of quantification (3 nM), in the systemic circulation of only one patient, one hour after taking the dose of 4 g. No metabolites of curcumin were detectable in plasma.

Similar results were obtained in a study conducted on 24 healthy volunteers receiving doses of curcuminoids in the range 500 mg-12 g as the "C3 Complex" product containing a minimum 95% of curcumin, demethoxy-curcumin and bisdemethoxy-curcumin (54). Measurable plasma concentrations were observed in only two subjects taking 10 g or 12 g of the product, with C_{max} of 50.5 ng/mL at 4 hours and 57.6 ng/mL at 2 hours, respectively. The same group then published a work conducted on 12 healthy volunteers divided into two treatment groups, who received the product "C3 Complex" at doses of 10 g and 12 g of curcuminoids, respectively. Each 250 mg capsule of "C3 Complex" contained 187 mg of curcumin, 58 mg of demethoxy-curcumin and 5 mg of bisdemethoxy-curcumin (55). Measurable plasma concentrations of curcumin were observed in only one subject, half an hour after taking the 10 g dose. Pretreatment of plasma with glucuronidase and sulfatase allowed, on the other hand, detecting C_{max} of curcumin around values of 0.9-2 μM. Similarly, in two other studies in which 4 g (56) or 12 g (57) doses of curcuminoids were administered to 12 and 10 healthy volunteers, respectively, no curcumin was detected in plasma in any of the enrolled subjects (limit of quantification of the assay method: 2 ng/mL and 1 ng/mL, respectively). Also in these studies, the "Curcumin C3 Complex" product was used.

Pharmacokinetic studies with the product "Curcumin C3 Complex" have also been con-

ducted in patients with Alzheimer's disease (58). This product, at doses of 2 g/day and 4 g/day, and a placebo were administered in parallel to 36 patients (12 patients per arm) for 24 weeks. At the visit programmed at week 24, patients underwent blood sampling before taking the 4 g dose and at various times after taking the dose. The levels of curcumin and tetrahydro-curcumin were measured by liquid chromatography/tandem mass spectrometry in the plasma before taking the dose and 3 hours after taking the dose. Mean baseline levels of curcumin and tetrahydro-curcumin were approximately 2.7 ng/mL and 6.9 ng/mL, respectively. Three hours after taking the dose, the levels of these two molecules were approximately 7.8 ng/mL and 3.7 ng/mL, respectively. Pretreatment of the plasma samples with β-glucuronidase allowed to detect much higher levels of the glucuronidated metabolites of these two substances, ranging between about 96 and 298 ng/mL (58).

In conclusion, the analysis of the available literature allows only to state that the oral absorption of curcumin, administered by rhizome extracts of *Curcuma longa* L., is very low, with plasma levels that are in the low nanomolar range after taking doses of the extract of 4-12 g. No information is yet available on pharmacokinetic parameters of curcumin in humans.

INFLAMMATION AND PAIN

There is some evidence that curcumin-containing supplements may exert anti-inflammatory and analgesic actions in patients with arthritis-related diseases and inflammatory bowel disease (59). Detailed experimental information on the analgesic, antiarthritic and gut anti-inflammatory effects of curcumin, is reported below.

Antiarthritic actions

Arthritis derives from the Greek language and is composed of arthro-, meaning "joint" and -itis, meaning "inflammation". Arthritis represents a group of pathologies principally characterized by articular and structural damage, inflammation and pain (60). More than one hundred different types of arthritis have been described: the most prevalent forms are osteoarthritis (OA), rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), crystal-induced arthritis, and related autoimmune diseases. Although these diseases arise from different causes, they exhibit similar symptoms and treatments (61). Current drug therapy for arthritis includes analgesics, disease-modifying antirheumatic drugs (DMARDs) in combination with corticoids, and non- steroidal anti-inflammatory drugs (NSAIDs) to reduce both severe pain and inflammation (62). Despite NSAIDs represent conventional first-line treatment, they are associated with gastrointestinal and cardiovascular adverse events, mainly due to long-term use and high dosages (63). Therefore, plant-derived products with anti-inflammatory properties and minimal side effects are gaining interest in the treatment of arthritis (64). Multiple studies proved curcumin therapeutic effects against several inflammatory, neuronal, cardiovascular, gastrointestinal, endocrine, and metabolic diseases, including diabetes, arthritis, obesity, and cancer (65). It is well known that curcumin acts on different signaling pathways, in particular inhibiting the production and activity of nuclear factor kappa-B (NF-κB), toll-like receptor 4 (TRL4), mitogen-activated protein kinase pathways (MAPKs), cyclooxygenase-2 (COX-2) and inflammation-associated markers including the main cytokines involved in the inflammatory cascade of arthritis, such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) (66-69).

Several groups proved curcumin therapeutic effect against the progression of arthritis. Two recent studies showed the *in vitro* and *in vivo* efficacy of curcumin in monosodium urate (MSU)-induced gouty arthritis. Li *et al.* (2019) observed that curcumin exerted a significant reduction in MSU-induced NLR family pyrin domain containing 3 (NLRP3) inflammasome expression, possibly through inhibition of

the TLR4/NF-κB signaling pathway in macrophages (70). These results were supported by an *in vivo* experiment showing that curcumin, 200 mg/kg, could protect rats from MSU-induced gouty arthritis. In line with the previous study, Chen *et al.* (2019) found that curcumin treatment improved MUS-induced inflammation by suppressing IkBα degradation, NF-κB signaling and NLRP3 inflammasome activation (71). Another research explored the protective effect of curcumin on monosodium iodoacetate (MIA)-induced knee osteoarthritis (OA). Intravenous injection with curcumin (200 mg/kg) inhibits TLR4/NF-κB signaling pathway and reduces inflammation, improving knee function in an OA rat model (72). Curcumin also showed therapeutic effects on rat anterior cruciate ligament transection (ACLT) osteoarthritis, by interfering with oxidative stress, which plays a crucial role in the development of OA through activation of endoplasmic reticulum (ER) stress and chondrocyte apoptosis. Curcumin significantly attenuated ER stress both *in vitro* and *in vivo,* by suppressing the Protein Kinase R-like ER Kinase (PERK)-phosphorylation of eukaryotic initiation factor-2alpha (eIF2α)-activating transcription factor 4 (ATF4)-C/EBP homologous protein (CHOP) signaling pathway and reducing CHOP expression, a biomarker of ER stress and apoptotic activation in chondrocytes (73). Furthermore, curcumin increased the expression of silent information regulator factor 2-related enzyme 1 (SIRT1) in a dose-dependent manner, and in previous studies SIRT-1 has been shown to play a key role in the regulation of ER stress-related chondrocyte apoptosis (74). These findings could suggest the activation of SIRT-1 and inhibition of ER stress as potential mechanisms underlying effects of curcumin in ACLT rat OA model (73). Moreover, curcumin has been shown to relieve inflammation, synovial hyperplasia and other symptoms in a rat rheumatoid arthritis model by suppressing Akt/mammalian target of rapamycin (mTOR) pathway and decreasing IL-1β, TNF-α, matrix metalloproteinases (MMP)-1, and MMP-3 lev-

els (75). A further study investigated the possible correlations between cartilage protection exerted by curcumin in OA and autophagy promotion. Curcumin decreased apoptosis and enhanced autophagy, playing a protective role on cartilage degradation and chondrocyte apoptosis, in both age-related and surgically induced mice OA, through inhibition of Akt/mTOR signaling pathway, as indicated by increased autophagy key regulators light chain 3 (LC3) and Beclin 1. These results were supported by a study involving an OA cell model that validated curcumin efficacy by modulating inflammatory cytokines and autophagy inhibitors; curcumin treatment improved autophagy reduction, cell viability decrease, and apoptosis (76). Recently, Chen *et al.* (2020) confirmed the protective effects of curcumin on IL-1β-induced chondrocyte apoptosis through activating autophagy and inhibiting NF-κB pathway (77). Overall, increasing *in vitro* and *in vivo* evidence suggests that curcumin could be a promising treatment for different types of arthritis through its potent anti-inflammatory effects. Promising pre-clinical and pilot clinical trial data showed beneficial and safe results of curcumin in knee OA, as compared to conventional drug treatment, with similar benefits and a reduction of adverse effects (78-80). In conclusion, further studies are required to fully investigate the efficacy and bioavailability of curcumin as a long-term arthritis therapy.

Inflammatory bowel disease

Inflammatory bowel diseases (IBD) represent a set of immune-mediated gastro-intestinal disorders mainly represented by ulcerative colitis (UC) and Chron's disease (CD) (59). The etiology of IBD is still unknown, but it is believed to involve the overstimulation and the excessive response of the intestinal mucosal immune system to resident luminal microorganisms. According to the recent epidemiological studies, countries such as the United States, the United Kingdom, and the Northern Europe have a higher incidence rate of IBD comparing to the developing countries. However, recent-

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ly, it has been recorded in an increase of incidence and prevalence of IBD also in developing countries with a higher frequency for UC with respect to the CD (81). There are many pharmacological approaches available to treat IBD (cyclosporine, corticosteroids, 5-aminosalicylic acid, mercaptopurines, anti-TNF-α, and azathioprine). Despite this, many of them have prohibitive costs and can cause serious adverse effects, as well as manifesting a limited effectiveness and specificity (82).

Considering this, researchers are increasingly interested in natural bioactive compounds, which possess strong anti-inflammatory and antioxidant activities, as new promising strategies to treat the IBD (81). The most investigated bioactive compound from this point of view is curcumin.

Different preclinical studies carried out on rodents have highlighted how curcumin shows anti-apoptotic, antioxidant, and anti-inflammatory properties (81) modulating many transcription factors such as NF-κB, β-catenin, activator protein 1, peroxisome proliferator-activated receptorγ (PPARγ), different signal transduction pathways such as the p38-mitogen-activated protein kinase as well as by inhibiting enzymes involved in the onset of inflammation such as COX-2 and the inducible isoform of NO synthase (iNOS). Moreover, the down-regulation of pro-inflammatory cytokines such as interferon (IFN)-γ, TNF-α, interleukin (IL)-1β, IL-12 IL-15, IL-17, and IL-23, and the up-regulation of IL-4 and IL-10 have been observed in histological samples following administration of curcumin to murine models with induced colitis (83).

In inflamed intestine, curcumin can interact with transient potential vanilloid receptor 1 (TRPV1) improving the visceral hyperalgesia and colitis in mice (81). These results corroborate previous observations, which showed the curcumin ability to suppress the membrane TRPV1 upregulation induced by phorbol myristate acetate in the HEK293 cell line (81). Moreover, curcumin has a strong suppressive role in NLRP3 inflammasome activation in mice, down-regulating the dextran sulfate so-

dium (DSS)-induced K$^+$ efflux, intracellular ROS formation and cathepsin B release (81).

Beyond the clear inflammatory event, recently it has been shown that mutation in autophagy-related genes is associated with development of IBD and, also in this case, curcumin can play a pivotal role. Indeed, it has been demonstrated that its administration remarkably reduces the expression of autophagy target genes such as Beclin-1, autophagy-related gene 5 (ATG5) and LC3II, leading to improvement in colitis (81). Furthermore, curcumin was able to reduce autophagosome formation in intestinal epithelial cells in a mouse model of DSS-induced colitis (81).

IBD can lead to the onset of concomitant diseases such as a recurrent anaemia due to a poor iron absorption. Curcumin is able to modulate iron metabolism proteins, reducing the iron stores and restoring its physiological hematic level (81). Despite the description of clinical studies are beyond the scope of the present review, it should be noted that, to date, few clinical studies have been conducted to evaluate the clinical efficacy of curcumin (59, 84).

One of the main problems in evaluating the clinical efficacy of curcumin is that commercial formulations are often an impure blend consisting of ~75% curcumin, 17% demethoxy curcumin, 3% bisdemethoxycurcumin and 5%-0% cyclocurcumin. Another limitation to the clinical application of curcumin as a therapeutic agent is its weak bioavailability, mainly due to its poor solubility in water (~11 ng/mL), followed by a rapid metabolism and excretion (85). Moreover, curcumin is unstable in both basic and neutral environment. For this purpose, various strategies have been adopted to improve the pharmacokinetics of this molecule such as nanotechnologies. Considering this, further controlled and randomized clinical trials are needed to better define the role of curcumin in the treatment of IBD.

Analgesic effects
Pain and inflammation are the main pathological conditions underlying the chronic use of

analgesic treatments. Despite many effective analgesic drugs belonging to different classes, including non-steroidal, opioid, non-opioid and others, their use is often limited by severe multi-organ adverse effects, and addiction. Therefore, the search for effective and safer alternative therapeutic options is an actual matter of debate. There is a growing interest in alternative medications, including herbal extracts that have long been used by folk populations in the conventional forms of infusions and decoctions. These traditional remedies could not only be effective and safe, towards chronic conditions such as pain, but also represent, in some cases, innovative strategies for implementing local botanical chain productions. In this regard, it is sensitive to highlight the potential use of *Curcuma* species extracts and natural compounds for treating pain. Turmeric (*Curcuma longa*) has a long traditional use in the Ayurvedic medicine for counteracting musculoskeletal pain (86). In the last decade, multiple studies were conducted on both *Curcuma* extracts and the main curcuminoid curcumin; in natural formulas it is also possible to find turmeric extracts mostly con-

stituted by curcumin (87, 88). In preclinical experimental paradigms of nociception, namely tail-flick and acetic acid-induced writhing tests, the administration of curcumin 15-120 mg/kg determined a dose-dependent pain relief effect (89). The antinociceptive efficacy of curcumin was compared to that of pregabalin. Specifically, curcumin was as potent as pregabalin, whereas the pharmacological association of the two compounds led to synergistic effects probably related to multiple concomitant mechanisms.

The efficacy of the sole curcumin as analgesic is consistent with the downregulation of different pro-inflammatory pathways (17, 90, 91). Direct interactions of curcumin with target proteins involved in the inflammatory response are also predicted by the bioinformatics platform STITCH (http://stitch.embl.de/) (**figure 5**). In this regard, the results of the components-targets analysis confirmed a high probability (> 70%) of peroxisome proliferator-activated receptor-γ (PPARγ, PPARG) activation and cyclooxygenase-2 (COX-2, PGTS2) inhibition induced by curcumin, as well. Recently, the efficacy of propofol in counteract-
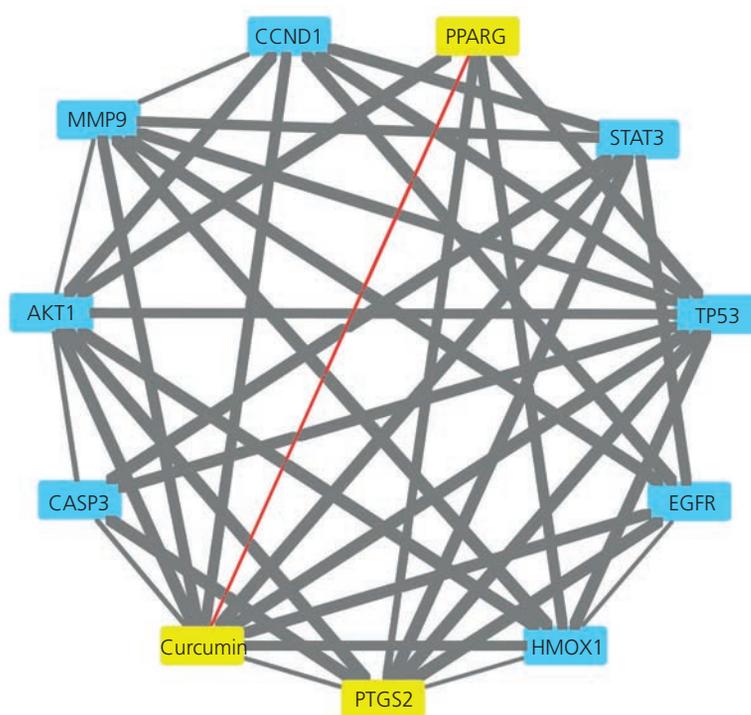
Figure 5. Components-targets analysis conducted on the bioinformatics platform STITCH (http://stitch.embl. de/) underlying putative interactions of curcumin with receptors and enzymes involved in the inflammatory response. Of noteworthy interest for the analgesic properties demonstrated by curcumin are the putative interactions with type cyclooxygenase-2 (COX-2, PGTS2) and peroxisome proliferator-activated receptor-γ (PPARγ, PPARG).

ing the neuropathic pain has been related to the PPARγ stimulation, as well (92).

The mechanism of action of curcumin as analgesic was also investigated in a new trigeminal neuralgia rat model induced by the injection of the cobra venom in the infraorbital nerve (93). The intra-gastric administration of curcumin was able to revert the cobra venom-induced mechanical allodynia, and this effect was also mirrored by the reduction of pain-induced depression, in rats. The same authors showed alterations on ether lipid and glycerophospholipid metabolism, as well. These findings also add to modulatory effects induced by curcumin on the activity of neurotransmitters and neuropeptides, such as monoamines and neurotrophic factors, regulating the neurogenesis and hypothalamic-pituitary axis, and possibly mediating the tight relationships occurring between depression and chronic pain (94-99). Recently, multiple studies also demonstrated the analgesic effect of curcumin in neuropathic pain. In the mouse chronic constriction injury model, an experimental paradigm mimicking neuropathic pain, curcumin exerted an analgesic effect that was related, albeit partially, to the inhibition of pro-inflammatory cytokines in both the sciatic nerve and the spinal cord (100). Similar results were also observed following the administration of nanocurcumin, whose efficacy in neuropathic pain was paralleled by decreased production of cytokines, in the rat hippocampus, with concomitant improvements of cognitive functions (101). The efficacy of curcumin towards neuropathic pain was demonstrated in streptozotocin-induced diabetic rats, as well. In this context, the analgesic effect was related to curcumin capability to induce the expression of the phosphorylated form of c-Jun N-terminal kinase (pJNK) located in the neurons and astrocytes of the dorsal root ganglion (DRG) (102).

The aforementioned preclinical results pointed to the efficacy of curcumin as analgesic, thus supporting the clinical use. However, concerns remain about the dosage regimen because of different factors, including the low bioavailability of curcumin and variability in the preparation of the formulations used in the studies (103, 104). Nevertheless, the oral administration of nano-micelle curcumin (40 mg twice a day) was effective in reducing pain in 36 patients suffering from knee osteoarthritis (105). The efficacy as analgesic was also observed when curcumin was topically administered (106). In this regard, a clinical trial demonstrated the efficacy of curcumin in patients suffering from recurrent minor apthous ulcers. The treatment was effective in reducing ulcer size, pain, healing, and recurrence, thus strongly supporting the clinical relevance of this natural compound.

Collectively, pre-clinical and clinical findings seem to corroborate the analgesic efficacy of curcumin that is related, at least in part, to inhibitory effects on multiple pro-inflammatory pathways.

METABOLIC EFFECTS

Effects on body weight and obesity

Obesity is a rapidly increasing chronic disease due to a long-term imbalance between energy intake and energy expenditure (107). Obesity is considered a risk factor for developing a number of chronic diseases, such as cardiovascular diseases, type 2 diabetes mellitus, and some types of cancer (108). A growing body of evidence suggested that curcumin could exert beneficial properties on obesity and obesity-related metabolic diseases (109, 110). In this regard, curcumin has been reported to decrease body weight gain in both animals and human subjects (111-113). A study in mice showed that a very high-fat diet (VHFD) supplemented with curcumin (0.7% *w/w*) for 13 weeks led to a reduction in body weight gain and body fat, along with an increase in lean body mass (114). However, in disagreement with other studies (115), the same authors did not find any effect of curcumin on adipocyte cell size (114). On the other hand, other studies reported no effects of dietary curcumin on body weight and adiposity, in mice (116).

Besides its modulatory effects on several molecular targets, such as NF-κB , IL-6, TNF-α, IL-1β, monocyte chemoattractant protein-1, and NLRP3 inflammasome (117), curcumin could also play a key role in adipogenesis. In this context, curcumin treatment inhibited the differentiation of murine 3T3-L1 preadipocyte cell line (118). Stimulation of white adipose tissue (WAT) lipolysis was also reported following daily curcumin (50 mg/kg) administration for 8 weeks, in high fat diet (HFD)-induced obese mice (113). Moreover, it has been observed that curcumin could significantly suppress adipogenic differentiation of human bone marrow mesenchymal stem cells, in a concentration-dependent manner, by decreasing mRNA and protein expression levels of Kruppel-like factor 15 (119). Promotion of brown adipose tissue (BAT)-mediated thermogenesis has been proposed as a possible therapeutic strategy against obesity (120). Recently, Song and collaborators (2018) reported that in HFD fed mice dietary curcumin supplementation increased energy expenditure and thermogenesis after cold exposure. Moreover, *in vivo* and *ex vivo* studies showed that curcumin decreased WAT inflammation and promoted uncoupling protein-1 (UCP-1) expression in BAT, possibly through PPARα and PPARγ-dependent and independent mechanisms (121). More recently, curcumin also enhanced the browning process as well as mitochondrial respiratory function in 3T3-L1 cells. These effects have been suggested to be related to stimulatory effects on PPARγ, UCP-1, PR domain protein 16 (PRDM16), and PPARγ coactivator-1α (PGC-1α) expression levels (115).

Despite its beneficial properties on obesity, curcumin possesses low oral bioavailability related to low intestinal absorption and rapid elimination (122). Nishikawa and collaborators (2018) reported that, differently from native curcumin, oral administration of low dose highly dispersible and bioavailable curcumin formulation for 4 weeks was able to stimulate the formation of brown-like adipocytes in inguinal WAT and increase energy expenditure, in mice (123).

Further studies are necessary to better define the therapeutic potential of curcumin in the prevention and management of obesity.

Effects on blood lipids

Turmeric and curcuminoids, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin, have been described for their lipid-lowering effects in several preclinical and clinical studies (124-134). Curcumin is able to improve the metabolic status, decreasing serum triglycerides (TG) levels in streptozotocin (STZ)-induced diabetic mice (124, 125). Recently, Xia and collaborators (2020) also reported that pre-treatment with curcumin (300 mg/kg body weight) for 12 weeks could prevent hyperglycaemia and hyperlipidaemia induced by high-fat diet combined with STZ treatment in rats, as well as liver damage, mainly through antioxidant and anti-apoptotic mechanisms. In particular, curcumin reduced fasting blood glucose (FBG), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (AST), and aspartate transaminase (ALT) levels (135). On the other hand, several studies have reported disappointing results on plasma HDL-C levels after curcumin treatment (136). The beneficial effects of curcumin on plasma lipid profile have also been compared with statins, a well-established treatment in hyperlipidaemia (137). Curcumin seems more effective in reducing TG, while statins in lowering LDL-C. On the other hand, despite curcumin was suggested in dyslipidemia treatment (138), recent works did not find any beneficial effects of curcumin on lipid and glucose profile, in mice fed a high-fat diet (114, 139). In particular, a high-fat diet supplemented with curcumin (0,1% of curcumin and 0,01% pepper) for 4 weeks did not reduce serum levels of cholesterol, TG and glucose (139). Similarly, curcumin supplemented diet (0.7% w/w) did not modify serum TG levels in mice fed with a very high-fat diet for 13 weeks (114). The limitations of these studies could be related to dose of curcumin administered, duration of the study and method of supplemen-

tation. The molecular mechanisms underlying the hypolipidemic effects of curcumin could involve oxidative and lipid-mediated stress in the vascular system (140). Curcumin could modulate the activity of specific transcription factors controlling the expression of genes involved in free radical scavenging and lipid homeostasis (137, 140, 141). On the other hand, curcumin was found to decrease the expression of lipogenic enzymes and transcription factors, such as ATP-citrate lyase, Acetyl-CoA carboxylase and Fatty acid synthase in rats fed with a high-fructose diet (142). Different curcumin formulations with improved bioavailability have been studied for their effects on lipid metabolism (143, 144). A recent report examined the comparative effects of curcumin versus nano-curcumin on insulin resistance, serum levels of apelin and lipid profile in type 2 diabetic rats (145). Oral administration of curcumin and nano-curcumin (100 and 200 mg/kg) for 28 days improved serum lipid profile, in diabetic rats. In addition, the effects of nano-curcumin were more effective than curcumin, possibly due to increased solubility and bioavailability (145). Then it is desirable to improve the bioavailability of various curcumin formulations to examine its actual effects on lipid metabolism and HDL function (143, 144).

Antidiabetic actions

According to The World Health Organization, diabetes mellitus (DM) is going to be one of the leading causes of death worldwide (146), and type 2 diabetes mellitus (T2DM) represents the most prevalent form with a remarkable impact on public health. T2DM is mainly characterized by insulin resistance that leads to hyperglycemia and its relative long-term complications including macrovascular and microvascular damage, retinopathy, neuropathy, and nephropathy (147). The leading hypothesized mechanisms to explain insulin resistance and β-cells impairment have been oxidative stress, deregulation of lipid deposition in several organs which in turn lead to inflammatory responses (148). Since T2DM to date cannot be cured, the current approach is focused on the control of disease progression by the use of lifelong anti-diabetes drugs (149), although, limiting the number of T2DM new occurrences should be the key strategy to counteract its health impact. Due to the burgeoning healthcare costs and the pharmacological side effects that negatively impact on the compliance, the scientific community has shown a growing interest in new effective therapeutic agents from medicinal plants (150).

Accumulating evidence suggests that curcumin could be a promising agent against T2DM improving some key aspects related to T2DM pathogenesis such as β-cells function, insulin resistance and mitigating oxidative stress and inflammation (151). Results from streptozotocin (STZ)-induced diabetic rat models showed how curcumin supplementation at a dose ranging from 30 to 100 mg/kg b.w. per os effectively counteracts hyperglycemia improving insulin response (152), and there is compelling evidence that curcumin reduces oxidative stress and lipid peroxidation, inducing antioxidant enzyme activities as recently reviewed (147). Curcumin administered for 21 days as diet supplementation (1% weight ratio) decreased circulating malondialdehyde (MDA) levels, while SOD and insulin levels were increased in a STZ-induced diabetic rat model (153). Benefits against renal dysfunction and oxidative stress were also raised from the study by Lima and colleagues (154) that showed how STZ-induced diabetic rats treated orally with curcumin (90 mg/kg b.w./day, for 45 days) showed lower glycaemia levels and a marked decrement of advanced glycation biomarkers and oxidative stress in the plasma, liver, and kidney (154). In the last decade, the antioxidant effects of curcumin were investigated in-depth and promising results also come from alloxan-induced diabetes models where curcumin (0.08 mg/kg b.w./day orally for 21 days) significantly decreased serum glucose and glycated hemoglobin concentration, as well as liver and serum MDA whereas glutathione level and GPx activity were increased (147). Con-

sistently, data from genetic and diet-induced diabetes models (high-fat diet and high-sucrose diet) confirmed that curcumin orally administered at dosage of 90 mg/kg b.w. for 9 weeks ameliorated insulin resistance, glucose intolerance, inflammation, and it boosted the enzymatic antioxidant machinery (155).

Along with oxidative stress, inflammation also plays a key role in diabetes progression and its complications occurrence. Several studies indicated that curcumin administration ameliorates inflammatory response inhibiting the expression of NF-κB target genes such as IL-6, TNF-α, MCP-1 as well as 8-hydroxy-2'- deoxyguanosine (8-oxo-dG) (149, 156).

These aspects are of great interest since TNFα and IL-6 are known to promote insulin resistance (157). Furthermore, curcumin counteracts the glucose-induced over-expression of TNF-α IL-1β and IL-6 (158). Intriguingly, the inhibition of IL-1 system by curcumin expression is of particular interest considering that it contributes to both β-cells impairment and apoptosis (159).

Obesity is a relevant causal factor in the etiology of insulin resistance (160). Adipose tissue contributes to chronic inflammation by activating protein kinases related and TNF-α receptors, such as the inhibitor of kappa B kinase (IKK) and JNK, which phosphorylates IRS-1 reducing its interaction with the insulin receptor leading to a decrease in insulin signaling transduction (161). The JNK signaling pathway seems to be one of the most important mechanisms connecting insulin resistance in obese patients (162), noteworthy, JNK knockout mice show lower adiposity, enhanced sensitivity to insulin and an increased capacity for insulin receptor signaling even under the lipid-rich regimen (160). Hence, the inhibiting effects of curcumin on this pathway achieve a considerable relevance (159).

Furthermore, curcumin diet supplementation reduces the gene expression of transcription factors involved in hepatic lipogenesis, such as the sterol regulatory element-binding protein 1c (SREBP1c), which promotes cholesterol synthesis and it can restore the expression of PPARγ, a key regulator of glucose/lipid metabolism in adipose tissue, skeletal muscle, heart, and liver which is down-regulated in diabetic mice (151); this could be a further beneficial effect of curcumin, in line with other drugs like thiazolidinediones that target the PPARγ expression.

Overall, promising results from both, preclinical and clinical studies, although the mechanisms by which curcumin exerts its effects are still not fully understood, suggest that curcumin can target key mediators of inflammation, improving β-cells function, antioxidant status and lipid metabolism, hence the interest of the scientific community for curcumin as a potential candidate against T2DM and its complications. Results from clinical trials seem to some extend confirm what emerged from *in vivo* studies; however, to date, further studies are mandatory to better draw the efficacy and the safety profile of curcumin and its specific dosage in T2DM patients (currently, FDA and EFSA maximum recommend 3 mg/kg/day). Interestingly, although currently the medical practice guidelines do not recommend using curcumin during pregnancy, some investigations indicate a putative benefit effect on glycemic control in gestational diabetes mice (163, 164). This represents, beyond doubts, an intriguing aspect that deserves further investigations. The putative curcumin-drug interactions need to be better explored, as recently reviewed by Bahramsoltani *et al.*: some studies reported significant pharmacokinetic alterations such as changes in C_{max} and AUC when co-administered with cardiovascular drugs, antidepressants, anticoagulants, antibiotics, and chemotherapeutic agents probably due to the inhibition of cytochrome P450 isoforms by curcumin (165). These should not surprise since it is known that numerous vegetables as well as their derivatives, especially when they are rich in polyphenols, can strongly affect the activity of xenobiotic metabolizing enzymes, therefore caution is mandatory in patients on polytherapy (166, 167).

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In conclusion, although further studies are needed, the encouraging results reassumed above makes curcumin as a prime candidate for clinical use against insulin resistance and T2DM.

CARDIOVASCULAR EFFECTS

The effects of curcumin against cardiovascular diseases have been indicated in several studies. Systematic reviews and meta-analyses of clinical trials have suggested that curcumin may improve endothelial function and blood pressure (13, 168).

Blood pressure

An increasing number of evidence shows that curcumin possesses cardioprotective efficacy in several animal models, and this effect seems mainly due to its vascular effects. In an *in vivo* animal model of Pb- and Cd-induced hypertension accompanied by hemodynamic disturbances, orally administered curcumin (100 mg/kg/day for the last 4 week of the Pb- or Cd- 16 week exposure) significantly reduced by 50% the metal-induced increase in systolic blood pressure (SBP) induced by the metals (169). In addition, treatment with curcumin improved the hemodynamic status of metal exposed rats by lowering arterial blood pressure, decreasing heart rate (HR), and increasing hindlimb blood flow, thereby reducing peripheral vascular resistance. The effects of curcumin on HR may be related to the observed decrease in blood pressure with a subsequently restored baroreflex. Furthermore, Pb and Cd attenuated acetylcholine (Ach)-induced nitric oxide (NO)-dependent vasodilation and this effect was restored by curcumin (169). The amelioration in blood pressure values was then associated with the modulation of NO and endothelial nitric oxide synthase (eNOS), that were partially restored by curcumin. The effects on blood pressure were also confirmed also in a high-fat diet-fed rat model of hypertension since curcumin (orally administered at a dose of 100 mg/kg/day for the final eight weeks of the 16 weeks study) restored SBP to the controls (170).

In another *in vivo* experimental model of hypertension and kidney dysfunction induced by the eNOS antagonist L-NAME (L-N^G-Nitro arginine methyl ester) in adult male Albino rats, curcumin (oral 100 mg/kg/day for 10 weeks) showed a significant decrease in mean arterial blood pressure beginning from the second week in comparison to the group receiving L-NAME alone (171). Interestingly blood pressure was totally restored by curcumin at the end of the experimental period. Furthermore, treatment of L-NAME rats with curcumin significantly restored the plasma nitrate/nitrite levels, and reduced oxidative stress and replenished antioxidant glutathione in renal tissue with partial restoration of normal redox status (171). Since persistent oxidative stress renders eNOS dysfunctional so that it no longer produces NO but O2$^{\bullet-}$ (172), the effects on cellular redox balance support an antioxidative mechanism for curcumin. In addition, it has been demonstrated that curcumin exerted a protective effect in nephrectomy-induced hypertension by enhancing the adaptive antioxidant response modulated by Nrf2 (173).

In addition, curcumin was able to prevent L-NAME- or Angiotensin II-induced hypertension in the rat by lowering the expression of angiotensin II receptor type 1 (AT1R) in arteries so resulting in vasodilation and increase of vascular compliance (171, 174). Interestingly, the regulation of curcumin on AT1R protein expression seemed to occur at the transcriptional level as demonstrated in embryonic thoracic aortic smooth muscle cells (174). Involvement of renin-angiotensin axis was further confirmed in ICR mice since treatment with curcumin (50 mg/kg body weight for 4 weeks) was significantly effective in reducing the blood pressure and inhibiting angiotensin-converting enzyme (ACE) activation and ACE mRNA expression when compared to untreated control mice (175).

However, different strategies based on drug delivery systems, including adjuvants (i.e. piperine), liposomes, micronization and nanosystems), have been developed in order to increase CUR bioavailability and absorption

(176). As to the hypertensive effect of curcumin, the pure compound encapsulated in Poly Lactic-co-Glycolic Acid (PLGA) nanoparticles at 5 mg/kg/day produced improvements in systolic blood pressure and left ventricular function similar to those of a free curcumin 100 mg/kg/day in rats withy high-fat diet-induced hypertension (170).

Similarly, in male, hypertensive, heterozygous TGR(m-Ren2)27 rats, a transgenic model of the severe renin-angiotensin system (RAS)-dependent hypertension, a low dose of curcumin (4.5 mg/kg) administrated in hyaluronic acid-based nanocapsules, resulted in mild hypotensive effects, while the same dose of curcumin given as oil solution at the same dose was ineffective (177). One has to note that free curcumin up to the dose of 100 mg/kg/day for 4 weeks appeared unable to decrease in a statistically significant way arterial pressure values in stroke-prone spontaneously hypertensive rats, although it delayed the onset of stroke and increased the survival (178).

These findings all suggest that supplementation of curcumin in the daily diet may be useful for the prevention of hypertension and support its use as a valuable adjunct to conventional antihypertensive drugs.
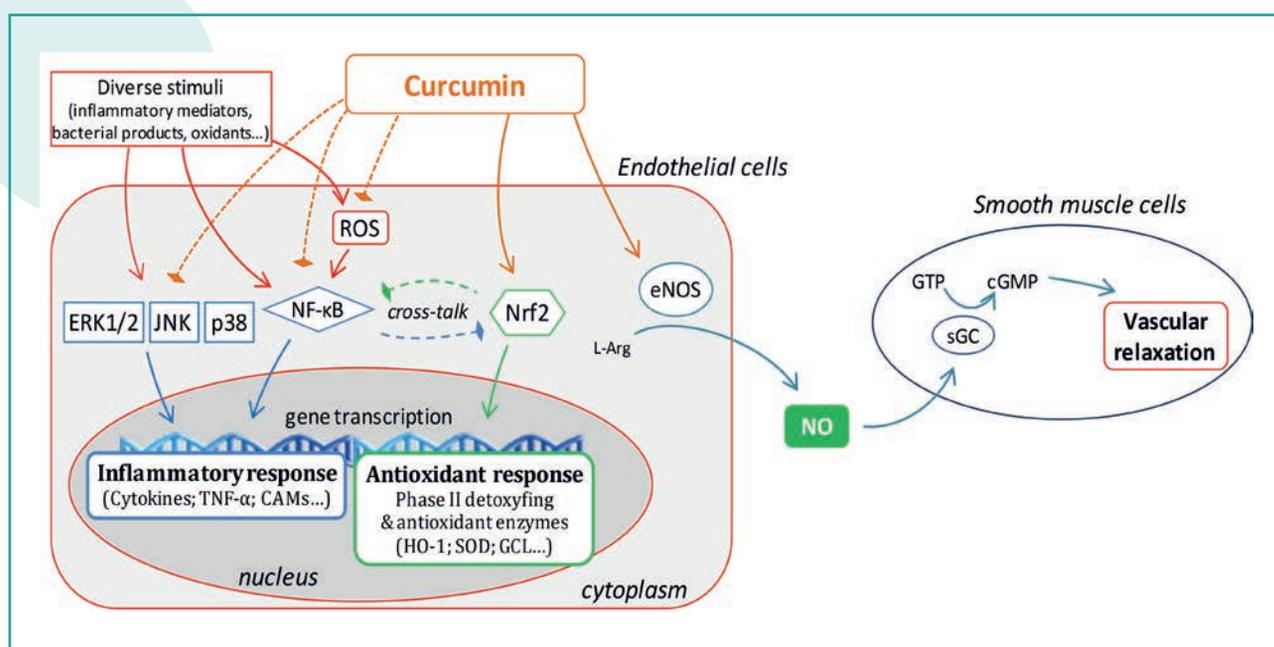
Endothelial function

The endothelium is a single layer of cells providing the inner layer of blood vessels in the entire circulatory system. It plays a pivotal role in maintaining cardiovascular homeostasis, attenuating vascular inflammation, and in regulating blood pressure, cellular trafficking, and coagulation (179). Disruption of endothelial function, characterized by pro-coagulative, pro-inflammatory, and pro-vasoconstrictive features, is an early event in many pathologies including atherosclerosis, hypertension, diabetes, and hyperlipidemia (179, 180). Moreover, angiogenesis, consisting of the development of new blood vessels, is essential not only for embryonic growth but also later for physiological repair processes such as wound healing, post-ischemic tissue restoration, and the endometrial changes of the menstrual cycle (181). The equilibrium between angiogenesis and vascular regression is crucial for preserving the microvascular network in heart, brain, and other tissues. Further, it is thought that endothelial dysfunction and impaired nitric oxide (NO) bioavailability play a critical role in angiogenic incompetence (182).

Scientific evidence supports the therapeutic use of curcumin in cardiovascular diseases as it may improve endothelial function mainly by its anti-inflammatory and antioxidant properties, and the capability to alter NO bioavailability (183, 184).

The anti-inflammatory effects of curcumin have been attributed mainly to its ability to modulate NF-κB pathway in endothelial cells, as well as the MAP kinases JNK, ERK1/2, and p38, leading to a decrease in the expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, and thus reducing trans-endothelial monocyte migration (67) (**figure 6**). In particular, NF-κB pathway is a reactive oxygen species (ROS)-dependent cell signaling pathway whose activation is tightly regulated in order to protect the organism, and its over-activation seems to be often implicated in many diseases including inflammation, immune disorders, and cancer (185).

Recently, Chen *et al.* (186), using a model of human aortic endothelial cells (HAECs), have shown that curcumin protects from endothelial dysfunction and inflammation caused by degradation of poly-L-lactic acid (PLLA), used in the clinic to produce biodegradable coronary artery stents. Curcumin, in fact, reduced NF-κB and consequently VCAM-1 levels increased by PLLA exposure, and increased endothelial nitric oxide synthase (eNOS) levels. Previously, Lu *et al.* (187) prepared and administrated intravenously twice a week curcumin loaded nanoparticles in pigs after stent implantation. Curcumin nanoparticles accelerated endothelial cells restoration and endothelium function recovery, and thus the authors

Figure 6. Effects of curcumin on endothelial dysfunction. Curcumin inhibits the pro-inflammatory ROS-dependent NF-κB pathway and the MAPKs pathway, and to activates the Nrf2 pathway, thus inducing the expression of genes encoding for antioxidant and detoxification enzymes. Moreover, curcumin induces the endothelial formation of NO, and thus vascular relaxation. ARE, antioxidant responsive element; CAMs, cell adhesion molecules; cGMP, cyclic guanosine monophosphate; eNOS, endothelial NO synthase; ERK, Extracellular signal-regulated kinases; GCL, glutamate cysteine ligase; GTP, guanosine-50-triphosphate; JNK, c-Jun N-terminal kinases; HO-1, heme oxygenase-1; LPS, lipopolysaccharides; NO, nitric oxide; Nrf2, nuclear factor erythroid-2 (NF-E2)-related factor 2; p38 MAPK, p38 mitogen-activated protein kinases; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase; SOD, superoxide dismutase; TNF-α, tumor necrosis factor α.

suggest they may potentially be an effective therapeutic alternative to reduce adverse events for drug-eluting stents. Furthermore, curcumin is a promising combined agent for the rescue of drug-eluting stents induced re-endothelialization delay; in fact, it significantly reversed the detrimental effects of the anti-smooth muscle proliferation drug rapamycin in rat aortic endothelial cells through upregulating eNOS (188).

Zhang and Li (189) demonstrated curcumin anti-inflammatory activity in a high glucose-induced inflammatory injury model in rat thoracic aorta endothelial cells. Treatment with 10 µM curcumin for 12 h inhibited high glucose-induced PI3K/Akt and NF-κB signaling pathway through inhibition of ROS, leading to a decrease in the protein expression of the proinflammatory cytokines IL-1β, IL-6, and TNF-α.

Moreover, Li *et al*. (190) reported the synergistic effect of curcumin and atorvastatin against endothelial dysfunction. In this model, liposomes modified using a targeting ligand (E-selectin-binding peptide) were used to co-deliver atorvastatin and curcumin to dysfunctional HAECs exposed to lipopolysaccharides (LPS) and overexpressing E-selectin. The treatment resulted in the suppression of E-selectin and ICAM-1. Furthermore, these findings were confirmed in an *in vivo* model since the administration of liposomes co-loaded with atorvastatin and curcumin in ApoE knockout (ApoE$^{-/-}$) mice reduced foam cell formation and secretion of inflammatory factors (IL-6 and MCP-1) by blocking monocyte migration into the intima.

The possible mechanism of action underlying the protective activity of curcumin against en-

dothelial dysfunction seems to be related to its antioxidant properties and, in particular, to its ability to induce nuclear factor erythroid 2-related factor 2/antioxidant responsive element (Nrf2/ARE) signaling pathway (183, 191) (**figure 6**). Nrf2 pathway regulates both the basal homeostatic as well as the inducible expression of many genes encoding for antioxidant and detoxification enzymes, such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutamate cysteine ligase (GCL), a key enzyme in GSH biosynthesis, and plays a key role in protecting cells upon oxidative stress conditions (192, 193). Nrf2 pathway, in particular, has been reported to protect against oxidative stress-induced endothelial dysfunction and atherosclerosis (194, 195). Moreover, various phytochemicals, including curcumin, are able to suppress NF-κB and activate Nrf2 pathway (196-198), supporting the hypothesis of a putative crosstalk between these signaling pathways (**figure 6**). In this context, Ouyang *et al*. (199) reported that curcumin protects human umbilical vein endothelial cells (HUVECs) from H_2O_2-induced oxidative stress. Cells pretreatment with curcumin (40 and 50 μM) for 12 h enhanced SOD and GSH levels and reduced those of ROS and malondialdehyde, supporting the role of curcumin in regulating oxidative homeostasis in HUVECs by stimulating antioxidant enzymes.

In view of a possible use of curcumin for actively supporting the survival and function of corneal endothelial cells (CECs) monolayers after transplantation, Li *et al*. (200) showed that curcumin-loaded lipid-poly(lactic-co-glycolic acid) (PLGA) hybrid microparticles are capable of protecting CECs from oxidative stress-induced cell death via modulating Nrf2 pathway and suppressing the secretion of pro-inflammatory cytokines by macrophages. The delivery system used in this study allowed overtaking the poor aqueous stability of curcumin and its short curcumin persistence, significantly ameliorating its therapeutic efficiency.

Furthermore, Lan *et al*. (178) have reported the preventive effect of curcumin (100 mg/kg/day for 4 weeks) on stroke in stroke-prone spontaneously hypertensive rats, by improving endothelial-dependent relaxation of carotid arteries and attenuating oxidative stress, as demonstrated also measuring ROS and NO levels in plasma and basilary arteries.

As reported by Wang and Chen (201) in a recent review, curcumin shows dual effects on angiogenesis, showing anti- as well as pro-angiogenic activity, and it has been speculated it may depend on the different microenvironments and on curcumin dosage, with pro-angiogenic effects at a lower doses and anti-angiogenic at higher doses.

Various studies on different *in vitro* and *in vivo* animal models reported the potential anti-angiogenic role of curcumin in different types of pathologies, in particular cancer (183, 201, 202), but also endometriosis, liver fibrosis (202), and hemophilic arthropathy (203).

However, a proangiogenic activity of curcumin has also been reported. In particular, various studies reported curcumin wound healing properties, due to its capability to stimulate angiogenesis through increasing the expression of vascular endothelium growth factor (VEGF) (204) and also favored by its good anti-inflammatory, antibacterial, and antioxidant activity (201, 205). Curcumin employment in wound healing may be ameliorated through the development of innovative materials (206), such as mesoporous silica particles, heparin-grafted aligned PLGA nanofibers, chitosan nanoparticles, human epidermal growth factor-curcumin bandage bioconjugate loaded with mesenchymal stem cells, chitosan nanoparticles, nanostructured lipid carriers containing epidermal growth factor. These studies have been developed by means of *in vitro* cell-based models (HUVEC endothelial cells, NIH 3T3 fibroblasts, HaCaT keratinocytes) and *in vivo* experimental models on health and diabetic rodents (119, 207-212).

All these data support curcumin nutraceutical use for improving endothelial function thanks to its anti-inflammatory and antioxidant properties mainly through the regulation of the cross-

talk between Nrf2 and NF-κB pathways, and to its ability to increase nitric oxide availability (**figure 6**). Finally, curcumin shows dual effects on angiogenesis, showing both anti-angiogenic activities in different types of cancer, as well as pro-angiogenic effects giving curcumin a high potential in improving wound healing.

CENTRAL NERVOUS SYSTEM

The neurological effects of curcumin have been extensively investigated at the central nervous system (CNS) level. Curcumin has been clinically evaluated in patients with depression as well as in patients with neurodegenerative diseases such as Alzheimer's diseases (213, 214). However, the evidence of efficacy is far from being compelling.

This chapter collects the molecular mechanisms and preclinical studies of curcumin in the main pathologies of CNS, summarizing recent reviews and describing the most recent experimental evidence.

Stress and depression

Depression is a multifactorial disease that combines genetic predisposition with environmental factors, among which chronic stress plays an important role. Ramaholimihaso *et al.* extensively reviewed the different potential mechanism of action of curcumin in major depressive disorders (215) and their major findings are reported in brief. One of the main molecular causes of the disease has been hypothesized the deficiency of monoamines (dopamine, serotonin, noradrenalin), currently the basis of the major antidepressant therapies. *In vitro* and animal studies showed that curcumin enhances monoamines in the central nervous system, inhibiting monoamine oxidase (MAO) and increasing the expression of serotonin receptors. Curcumin reduced the inflammation-induced by overexpression of indoleamine 2,3 dioxygenase, an enzyme linked to tryptophan depletion which influences the availability of this precursor for the synthesis of serotonin. In addition, curcumin inhibit-

ed glutamate release, probably acting on the GluN2B subunit of NDMA receptors and consequently increasing BDNF levels. Curcumin showed neuroprotective effects by increasing the production of different neurotrophic factors, in particular BDNF (216).

The inflammatory state plays a role in depressive pathology and curcumin treatment reduced depressive behaviors in animals treated with LPS, thanks to the previously reported anti-inflammatory properties, creating a link with intestinal hyperpermeability (brain-gut axis). Similar effects in inflammatory markers were seen by de Gomes *et al.* (217). The contribution of the anti-inflammatory activity was also observed in animal models of chronic stress thanks to the reduction of NLRP3 inflammasome activation, resulting in lowering of nitric oxide (NO) and IL-1β levels. NLPR3 activation is also influenced by reduced intracellular potassium levels, mediated by P2X7 purinergic receptors and curcumin suppressed their activation. Furthermore, curcumin limited depressive symptoms in cortisol-treated animals and reduced the size of the adrenal gland in rats, one of the glandular symptoms of depression. Finally, curcumin's ability to relieve insulin resistance appears to be linked to decreased depressive-like symptoms *in vivo*.

Another possible mechanism involved in depression, not discussed in the described review, is the reduction of oxidative stress by the activation of NRF-2 signaling pathway by curcumin (218, 219). Curcumin also reduced depressive-like symptoms in animal treated with rotenone, a toxin associated to Parkinson's disease (220), and mercuric chloride (221).

Neurodegenerative diseases

Alzheimer's disease

The molecular basis for the neuroprotective role of curcumin in Alzheimer disease (AD) have been widely investigated and revised. The most characterized properties of curcumin are the direct interaction with β-amyloid and tau fibrils aggregation, and the acetylcholin-

esterase (AchE) inhibition (222). Not surprisingly for these targets, curcumin nowadays represents a scaffold for novel drugs design (223-225). During the last years, curcumin and its derivatives reached even greater attention for additional neuroprotective effects, potentially useful in the multitarget approach for AD treatment. Several authors demonstrated that curcumin may counteract oxidative stress and neuroinflammation in AD models by inducing autophagy: a fundamental mechanism was identified in the enhancement of AMPK activity (226-230). Moreover, curcumin may promotes autophagic proteins and their retrograde axonal transport (231).

The effect on AMPK, along with PPARγ agonism and BACE-1 inhibition, may explain how curcumin activates the transcription factor NRF-2, involved in neuroprotection and antioxidant defense (232-237). Again, the same targets are clearly included in the anti-inflammatory mechanism of curcumin, which showed to impair the activity of NF-κB and the inflammasome machinery leading to cytokines reduction (238-243). In analogy, curcumin favors SIRT-1 activity and the related post-transcriptional modifications, thus enhancing cell metabolism and reducing inflammation at the central level (226, 244). The inhibition of miR-146a and miR-155 has been suggested as further post-transcriptional effect of curcumin with anti-inflammatory consequences (245, 246). According to recent studies, the JAK/STAT signal inhibition in microglia represents another potential anti-inflammatory target (242).

AMPK/SIRT-1 activation by curcumin is also involved in the prevention of β-amyloid production through the activity of α-secretase; however, curcumin impairs also the β-secretase activity, thus reducing the levels of β-amyloid precursor (APP) (226, 247). Another important target of curcumin is GSK-3β, involved in fibrils deposition and the consequent cytotoxic events. Curcumin counteracted GSK-3β by activating Akt/PI3K pathway at the upstream level, which, as known, modulates the AMPK/NRF-2 pathway (248-250). GSK-3β inhibition

accounts for the activation of Wnt/β-catenin pathway, thus explaining the effect of curcumin on hippocampal neurogenesis and cognitive function (251, 252). The modulation of Akt is also correlated with the positive effect of curcumin on BDNF levels (253, 254), neuronal proliferation and differentiation (255, 256), and dendritic spines preservation (257, 258).

As revised by Pluta *et al.* (259) the biological activity of curcumin protects brain injury in ischemia-reperfusion models of AD. In addition, the beneficial effect of curcumin on memory deficit and cognitive impairment may involve metabolic effects such as the enhancement of glucose uptake and lactate levels in brain (260, 261). Finally, Sun et al reported that curcumin and microbiota were bidirectionally influenced in AD mice models (262).

Parkinson disease

In recent years many reviews have summarized the curcumin's beneficial effects on Parkinson's disease (PD) (226, 263). The neuroprotective role of curcumin on dopaminergic neurons is widely studied in various models of PD, showing an improvement of oxidative stress and neuroinflammation.

A great number of studies showed that curcumin increased the tyrosine hydroxylase and dopamine levels, the number of surviving dopamine neurons, the level of Bcl-2 and the protein expression of TFEB, LAMP2A, and LC3-II, while reduced nitric oxide synthase, Bax, α-Syn, and caspase 3 expression (253, 264-266). Others neuroprotective pathways modulated by curcumin are: the cholinergic system via an α7-nicotinic acetylcholine receptor (α7-nAChR)-mediated mechanism (267); the histone acetylation by targeting of histone acetyltransferases (HATs), resulting in the reduction of severity of L-DOPA-induced dyskinesia (268); the up-regulation of HSP90 studied in SH-SY5Y cells (46); and the correction of Akt/GSK-3β signaling (269).

Two recent *in vivo* studies on neurotoxic metal elements, revealed the beneficial effects of curcumin on dopaminergic and astroglial alterations

caused by chronic Cu or Al exposition in rats, which reinstated both tyrosine hydroxylase expression and locomotor performance (270, 271). *In vitro*, arsenic induces toxicity decreasing cell survival rate and enhancing the loss of mitochondrial membrane potential. Pre-treatment with curcumin significantly decreased arsenic effects, probably by antioxidant and anti-apoptotic mechanisms (272).

A new potential protective effect of curcumin on dopamine neurons is the regulation of autophagy, by decreasing the BAX/BCL2 ratio and increasing of LC3 and ATG10 expression (two factors involved in the formation of autophagosome) (273), by regulation of TFEB export signaling via inhibition of glycogen synthase kinase-3b (GSK-3b) (234), and by activation of autophagy in an ROS-dependent manner (255).

Some authors demonstrated a key role of curcumin in reducing oxidative stress, for example lowering the level of ROS (274) and oxidized proteins (275), and through modulation of the NRF-2/HO-1 pathway (234).

Furthermore, curcumin prevented the LPS-induced upregulation of the protein activity of NF-κB, proinflammatory cytokines (TNF-α, IL-1β, and IL-1α), and inducible nitric oxide synthase (iNOS). As already reported in other studies curcumin regulates molecules of the intrinsic apoptotic pathway (Bax, Bcl-2, caspase 3, and caspase 9), improves the glutathione system, and prevents the formation of α-synuclein aggregates in the dopaminergic neurons (276). In a LPS-induced BV-2 microglial cells, the administration of curcumin increased the production of the anti-inflammatory cytokines, IL-4 and IL-10, and regulated neuroinflammatory reactions by eliciting anti-inflammatory responses in microglia through JAK/STAT/SOCS signaling pathway (242). Moreover, curcumin enhanced microglia polarization by activating the AMP-activated protein kinase (AMPK) signaling pathway (277).

One of the more interesting, but still relatively unknown, mechanisms of curcumin is related to α-synuclein aggregation/disaggregation and oligomer-induced toxicity in dopaminergic neurons, which may prevent Lewy Bodies accumulation. Curcumin inhibited the α-synuclein aggregation in rodents treated with LPS or rotenone, through inhibition of oxidative stress generation, replenishing GSH levels, as well as preventing the inflammatory response (276, 278). Curcumin efficiently prevented mitochondrial Type 1 Hexokinase (HKI) and ROS enhancement induced by α-synuclein fibrillation products (279). In addition, curcumin induced the degradation of amyloidogenic proteins, including β-amyloid precursor protein and α -synuclein, through the TFEB-autophagy/lysosomal pathway, the inhibition of GSK-3b, and the increase of antioxidant genes (234). Moreover a molecular dynamics method showed that curcumin binds the Non-Amyloid-Component (NAC) domain of α-synuclein, reducing protein aggregation (280). Finally, Doythchinova *et al*. demonstrated the inhibitory activity of curcumin on Aβ aggregation at atomic level: the molecule intercalates among the Aβ chains, making peptides less flexible and more disordered, and reducing non-native contacts and H-bonds (281).

Huntington disease

Differently from AD, the evidence on curcumin in Huntington disease (HD) is less documented. However, the bioactivity of curcumin referring to autophagy induction, anti-inflammatory effect, and antioxidant defense at central level was suggested as plausibly useful against HD (228, 282-290). Despite the scarcity of *in vivo* demonstrations, curcumin was reported to impair the misfolding of huntingtin protein, in analogy with the well-established effect on β-amyloid (289, 291-295). Moreover, Pepe *et al*. recently demonstrated that nano-sized curcumin prevented huntingtin-mediated apoptosis in striatal derived cells (296). Elifani and Gharaibeh reported an ameliorated phenotype in HD murine models after oral administration of curcumin: in line with the scientific literature, both the authors observed the activation of pathways involved in BDNF expression, such

as TrkB, Erk, and Akt (292, 297). Moreover, the authors investigated the impact of curcumin on gastrointestinal disturbs resembled in the R6/2 mice model of HD, which cause weight loss and cachexia: the authors observed a recovery in body weight and intestinal function. On the other side, Khyati et al. suggested a possible beneficial effect of curcumin on disturbed circadian rhythm occurring in HD (298). In *Drosophila*, the dietary administration of curcumin led to the normalization of the transcriptional pattern and the recovery of the locomotion ability and exclusion behavior, similarly to melatonin. Such epigenetic effect of curcumin on the biological clock was already reported in aging rats with suprachiasmatic nuclei lesions and may correlate with SIRT-1 activation (299).

Multiple sclerosis

Multiple sclerosis is an autoimmune disease of the central nervous system, characterized by a chronic inflammatory condition. CD4$^+$ T cells, especially Th17 lymphocytes, play a crucial role in the pathophysiology of multiple sclerosis and participate in the disruption of the blood brain barrier, demyelination, and neuronal damages. A recent review collected the main molecular targets modulated by curcumin in experimental model of the disease (300). The described effects of curcumin included a reduction in proinflammatory cytokines (such as IFN-γ, IL-1β, IL-6, IL-12, IL-17, IL-23, and TGF-β), caused by limited activation of NF-κB, MAPK, and JAK-STAT pathways, and a reduced infiltration of inflammatory cells in the central nervous system (decreasing CXCL1 and CXCL2). In turn, the reduction of inflammation prevents the disruption of the blood-brain barrier (modulating ZO-1 and reducing ROS). In addition, curcumin protected oligodendrocytes from apoptosis, by inhibiting intrinsic apoptotic pathway and mitochondrial stress, and axon degeneration reducing JNK phosphorylation and NO release (300). Recent studies investigated the effects of curcumin in experimental models of encephalo-

myelitis. Curcumin reduced the expression levels of pro-inflammatory cytokines and enhanced the activity of anti-oxidant enzymes in the corpus callosum of mice (301) and influenced AKT/mTOR signaling pathway inducing autophagy (302), a mechanism that, if altered, can lead to neuronal damage. Another study supported the protection of oligodendrocytes by intraperitoneal administration of dendrosomal nano-curcumin in cuprizone treated mice, preserving myelin content in the corpus callosum (303) and this formulation also enhanced oligodendrogenesis in vitro (304).

Furthermore, *in vitro* curcumin reduced the activation of CD4$^+$ T cells (Th1, Th17, and Treg) and influenced their proliferation promoting apoptosis (305).

Ischemic stroke

Curcumin is involved in the treatment of post-ischemic neurodegeneration and in the prevention of neurodegenerative changes development after cerebral ischemia (306).

Curcumin promotes neuron survival in *in vivo* and *in vitro* models of cerebral ischemia reperfusion (I/R) injury, exerting neuroprotective effects against ischemia injury. It was demonstrated that curcumin inhibits ischemia-induced mitochondrial apoptosis via restricting Bax and caspase-3 activation and increasing Bcl-2 protein levels (307, 308). Curcumin improved nerve damage symptoms and infarct volume, reduced brain water content, relieved neuronal apoptosis acting in the MEK/ERK/cREB pathway, induced the expression of p-MEK, p-ERK, p-cREB, Bcl-2, and reduced Bax levels (309). Moreover curcumin exhibited a protective function through PKS-q signaling by reducing blood-brain barrier dysfunction (310). Other studies demonstrated that curcumin protected cells by inhibiting apoptosis, balancing the Bax/Bacl2 protein expression, and attenuating autophagic activities mediating PI3K/AKT pathway activation (311). Curcumin suppressed inflammatory reactions and oxidative stress by regulating the TLR4/p38/MAPK pathway, downregulating LC3-II/LC3-I, IL-1,

TLR4, p-38, p-p38 (312), IL-6, NF-kB, Mcp-1, and F2IsoP (313). Other mechanisms involved in curcumin neuroprotection are the novel flotllin-1 and the ERK1/2 pathway (314).

Curcumin showed positive effects in the post-stroke depression (PSD), attenuating behavioral disorders associated with the disease. The Ca^{2+} accumulation and the inflammatory response associated with PSD were blocked by curcumin, inhibiting the activity of the P2X2 receptor, which then deactivated Ca^{2+} channel-mediated inflammatory response associated with PSD progression (315). Furthermore, curcumin enhanced the growth arrest-specific transcript 5 (GAS5), which contributed to the activation of the BDNF/Trkβ signaling pathway, promoting the expression of synaptic-related proteins. These results revealed a novel mechanism of curcumin on PSD through the GAS5/miR-10b/BDNF regulatory axis (316).

Amyotrophic lateral sclerosis

The potential interest of curcumin for amyotrophic lateral sclerosis (ALS) was recently revised by Buratti *et al.* (317). The author remarked that ALS was considered a proteinopathy after the important discovery of TAR DNA binding protein-43 (TDP-43) aggregates in ALS patients. Consequently, several studies were conducted on curcumin as neurotoxic protein aggregates inhibitor. Curcumin counteracted TDP-43 aggregation and the related cytotoxicity in several *in vitro* models. Moreover, dimethoxy-curcumin prevented the TDP-43-induced abnormalities in action potentials in motor neuron cell lines. Once again, the main suggested mechanisms were the induction NRF-2 activity and the inhibition of protein aggregation in motor neurons models (318). Despite curcumin may act through different neuroprotective mechanisms, the research on ALS gives only few results, thus underlining the necessity of more pre-clinical studies.

Epilepsy

Epilepsy is a neurological disorder characterized by recurrent and spontaneous seizures, often associated with cognitive and neurobiological consequences. A prolonged state of seizures can induce the activation of an inflammatory state that induces a greater predisposition and lead to neuronal death. In fact, oxidative stress and inflammatory state are the two main factors involved in epilepsy. As reviewed by Dhir *et al.* (319), curcumin thanks to its anti-inflammatory and antioxidant activities showed protective and therapeutic effects in this field.

In acute animal model of seizures, curcumin was found to elevate the seizure threshold in current electroshock test mice, similarly to phenytoin. Curcumin showed anticonvulsant effect in rats challenged with pilocarpine, by reducing oxidative markers (also in chronic models). The antioxidant mechanisms are also the basis of curcumin protection from kainic acid-induced seizures in rats, where a reduced percentage of convulsion and an increased latency to convulsions onset were found.

In chronic models, curcumin prevented seizures in rats induced by $FeCl_3$, a model mimicking human post-traumatic epilepsy, probably due to anti-inflammatory properties and by increased expression of voltage-activated Na^+ channel subtypes (320). Curcumin also increased the expression of ion–channel protein mutations CACNA1A (presynaptic CA^{2+} channel) and GABRD (post-synaptic Cl^- channel), channels mutations associated with epilepsy, in which related protein expressions are reduced during $FeCl_3$ treatment (321).

In addition, curcumin protected animals challenged with repeated chemical (pentylenetetrazol) and electrical insults, eventually protecting from cognitive decline, by a mechanism involving antioxidant effects and, in the case of pentylenetetrazol, by L-arginine nitric oxide pathway. A recent study showed a reduction of TNF-α by curcumin in pentylenetetrazol-treated mice, and upregulation of klotho and erythropoietin as neuroprotective factors (322).

In a kainic acid rat model, curcumin prevented activation of astrocytes and neuronal death, and a recent study showed a mechanism in-

volving the Bcl2 family and P38 MAPK pathways (323). The anti-epileptic effects were probably associated, according to the authors, to lower IL10RB, CXCL17, and nicastrin levels. Other possible mechanisms involved in the antiepileptic effects of curcumin are the regulation of calcium and aquaporin-4 channels, the increase of GABA inhibitory neurotransmitter, and the inhibition of mTOR pathway (324) and glutamate, as previously described. Recent studies also showed an anti-seizure effect of curcumin in pentylenetetrazol treated zebrafish (325).

SKIN

Clinical data suggest that curcumin may play a role in skin health management and might be beneficial in a number of skin diseases such as alopecia, atopic dermatitis (eczema), acne, androgenetic facial photo-ageing, oral liken planus, pruritus, psoriasis, vitiligo, and radiodermatitis (17).

Curcumin has been studied for its beneficial effects in various skin diseases upon topical and oral administration, mainly based on its antibacterial, anti-inflammatory, and antioxidant/scavenging activity, with *in vitro* active concentrations in the micromolar range (326). As low aqueous solubility, poor tissue absorption, rapid metabolism, and short plasma half-life limit its topical delivery, recent research has focused on developing new technologies to increase skin absorption.

Experimental *in vitro* and animal model studies indicate beneficial effects of curcumin in psoriasis, a chronically relapsing inflammatory skin disease: modulation of inflammatory mediator release from T cells and improvement of skin lesions have been repeatedly shown. Recently, the use of cellulose nanofiber film hybridized with curcumin-loaded lipid nanocarriers (327), a nanohydrogel system (328), curcumin-loaded silica particles (329), were reported to increase skin delivery and significantly improve psoriasis-like lesions in imiquimod-treated mice.

The efficacy of curcumin has also been shown in wound healing models. Bacterial growth,

inflammation and oxidative stress all interfere with the healing process, potentially causing a wound to become chronic. The addition of curcumin to different types of polymer-based dressings or nanofibers has been investigated in preclinical studies, showing improved effects in facilitating healing and preventing/reducing bacterial invasion (205, 206). Beneficial effects of curcumin preparations have been reported in animal models of diabetes-associated wounds (212, 330, 331). Among these, pre-treatment with curcumin has been proposed to improve the healing activity of stem cells on diabetic rat wounds (210, 332). Evidence obtained in humans indicate that curcumin's vasal activity on peripheral arterioles might be beneficial in reducing face redness and photodamage (16), and indeed curcumin has been proposed for the treatment of rosacea and acne (333). A liposomal gel preparation containing curcumin and lauric acid has been shown to reduce bacterial growth of *P. acnes* and to reduce comedone counts and cytokines in a rat ear model of acne (334). The antimicrobial activity coupled with the inhibition of several inflammatory pathways associated with hyper keratinization make curcumin a possible candidate for new plant-based treatments of acne (335).

In vitro antileishmanial activities have also been reported for curcumin-loaded Self-Emulsifying Drug Delivery System (SEDDS), laying the basis for the investigation of curcumin use in cutaneous and muco-cutaneous leishmaniasis (336).

Vitiligo is another oxidative stress-related skin condition, where the use of antioxidants has been proposed to protect melanocytes from becoming dysfunctional. In this context, curcumin has been shown to be effective in protecting human perilesional keratinocytes from oxidative stress *in vitro* (337).

Photodamage is a growingly relevant issue in dermatology, in view of raising incidence of skin cancer and photoaging in humans. Curcumin nanoparticles have been shown to reduce erythema, scale and local cytokine release

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in UVB-irradiated mice (338). Protective effects have also been reported *in vitro* towards UVA irradiation cellular effects in human dermal fibroblasts (339).

In conclusion, much research work is currently devoted to evaluating the efficacy of curcumin in skin disorders. The use of advanced delivery techniques for topical use has the potential to re-juvenate the traditional use of turmeric for dermatological diseases.

CONCLUSIONS

Curcumin has been tested in a multitude of preclinical studies, showing beneficial effects in several pathological conditions. Among the most promising pharmacological properties, anti-inflammatory and antioxidant effects cover a relevant position; the effect may be due to the modulation, at the molecular levels, of several inflammatory mediators which include NF-κB and Nrf2 whereas beneficial effects against metabolic syndromes seems to be linked to PPARγ modulation. However, the overall mode of action is multitarget since curcumin interacts with a variety of nuclear factors, enzymes, and growth factors. Despite beneficial effects demonstrated in different diseases, the avail-

able literature states that the oral absorption of curcumin, administered as component of turmeric extracts, is poor, with plasma levels that are in the low nanomolar range after taking doses of the extract of 4-12 g. These findings suggest that the main metabolites of curcumin previously detected in human plasma, which include the sulfate and glucuronide derivatives, may contribute to the health effects following curcumin intake.

However, different drug delivery methods have been set up to improve curcumin bioavailability, including inclusion in phytosomes, liposomes, and nanoparticles. Taken together, these methods have improved plasmatic levels of curcumin, and should be considered for future clinical studies.

ACKNOWLEDGMENTS

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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