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Natural Products

Curcumin—From Molecule to Biological Function

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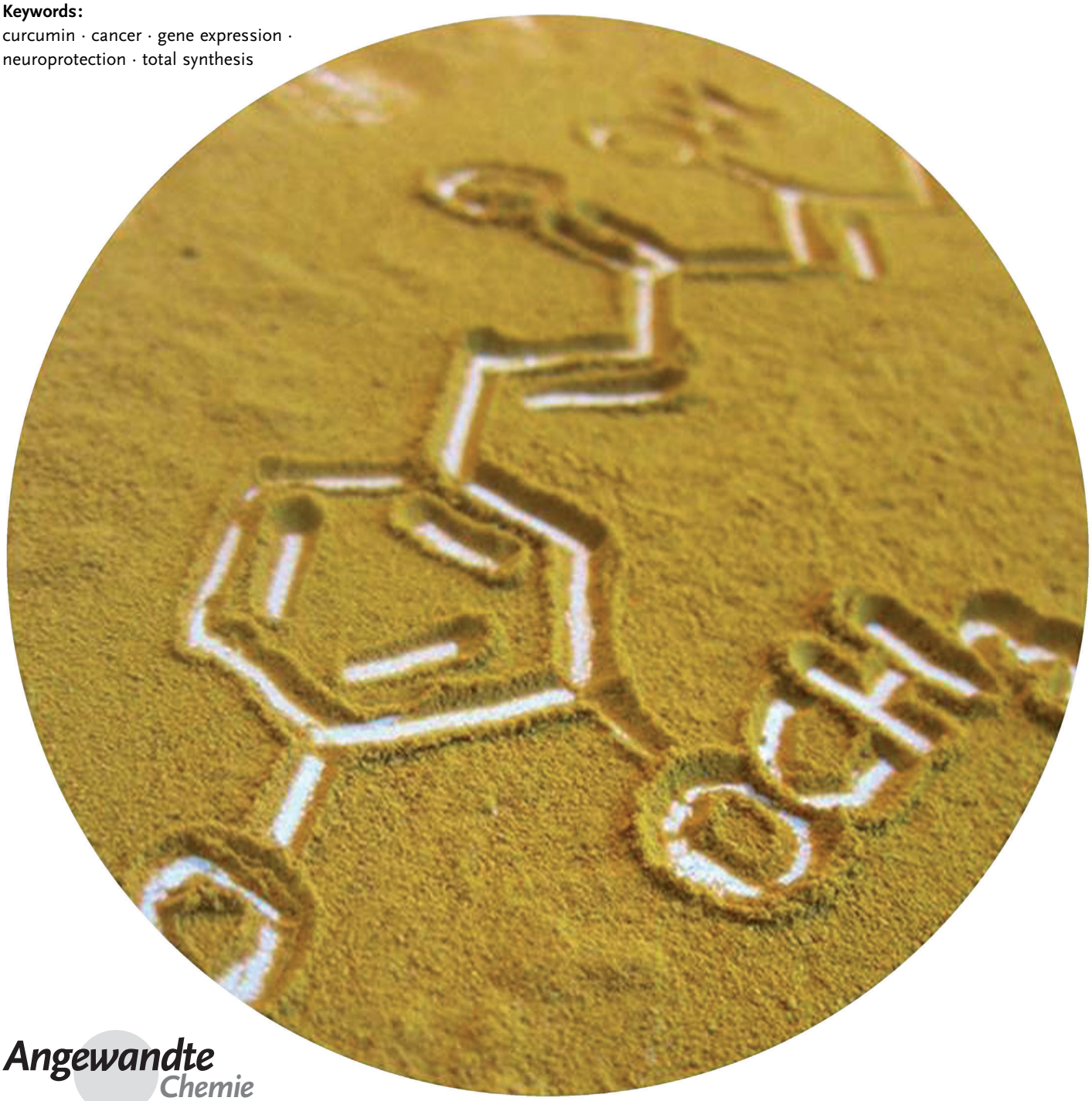
curcumin · cancer · gene expression · neuroprotection · total synthesis



Turmeric is traditionally used as a spice and coloring in foods. It is an important ingredient in curry and gives curry powder its characteristic yellow color. As a consequence of its intense yellow color, turmeric, or curcumin (food additive E100), is used as a food coloring (e.g. mustard). Turmeric contains the curcuminoids curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Recently, the health properties (neuroprotection, chemo-, and cancer prevention) of curcuminoids have gained increasing attention. Curcuminoids induce endogenous antioxidant defense mechanisms in the organism and have anti-inflammatory activity. Curcuminoids influence gene expression as well as epigenetic mechanisms. Synthetic curcumin analogues also exhibit biological activity. This Review describes the development of curcumin from a "traditional" spice and food coloring to a "modern" biological regulator.

From the Contents

1. History and Cultivation of Curcuma longa

Turmeric has long been known as a spice, remedy, and dye.[1] Marco Polo mentioned turmeric in his travel logs about China and India as early as 1280. In the 13th century, Arabian merchants brought turmeric to the European market from India. During the British rule of India in the 15th century, turmeric was combined with several other spices to form curry powder.[1]

The Latin name *Curcuma* is derived from the Arabic word, Kourkoum, which was the original name for saffron.[2] As a consequence of its golden color and taste, *Curcuma* became known as "Indian Saffron" in Europe (Figure 1).[1,3] *Curcuma longa* L. (German: Kurkuma, Gelbwurz(el), English: turmeric) is a member of the ginger family (Zingiberaceae), to which the genus *Zingiber*, ginger, also belongs. *Curcuma* is assigned as rhizomatous and is a monocotyledonous perennial herbaceous plant. It has an intense yellow-colored fleshy root tuber that is very similar in appearance to the branched finger-shaped ginger root. This herbaceous perennial plant bears 6–10 distichous, elliptical leaves that can grow up to one meter long. The 10–15 cm long yellow flowers bloom from late autumn to midsummer, and the petals are arranged in a spiral along a spikelike stalk. *Curcuma* does not bear fruit.

Curcuma has emerged from continuous crossbreeding and selection. Today there are some 120 known species of *Curcuma*. In addition to the most common *Curcuma longa* (syn. *C. domestica*), *C. aromatica* and *C. xanthorrhiza* are also relatively widespread.[4–6] *Curcuma* requires a hot, humid climate and a lot of water. It is, therefore, prevalent in tropical and subtropical regions, particularly in India, China, and South East Asia (Indonesia, Thailand, Vietnam, and the Philippines). The current major cultivation areas are in India, where *Curcuma* is also known as "*Haldi*".[2,4,7–9] India is the largest worldwide producer, consumer, and exporter *of Curcuma*. The production of *Curcuma* in India has grown by approximately 40% in the last ten years, and annual production in 2008–2009 was about 900000 tons.[10]

Figure 1. Turmeric at the Grand Bazaar in Istanbul.

2. Curcumin and Its Derivatives: Structure and Stability

Curcuma contains 3–5% curcuminoids (50–60% curcumin) and up to 5% essential oils and resins.[8,11] The curcuminoid content in turmeric can vary between 2 and 9%, depending on the geographical conditions.[8] Of the numerous types of *Curcuma* investigated, *Curcuma zedoaria* shows the highest curcuminoid content ($>100\ \mu g\,g^{-1}$) compared to *Curcuma longa* ($1–2\ \mu g\,g^{-1}$) and *Curcuma aromatica* ($\leq 0.1\ \mu g\,g^{-1}$).[12] Many studies have investigated the biosynthesis of curcuminoids in the plants.[13–18] These studies have

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shown that curcuminoid biosynthesis is a multistep process by which *p*-coumaroyl-CoA is produced from the amino acid L-phenylalanine, with cinnamic acid and *p*-coumaric acid being intermediates.[15] According to Kita et al., however, curcuminoid is preferentially biosynthesized from cinnamoyl-CoA.[18] The condensation reaction of *p*-coumaroyl-CoA with malonyl-CoA results in the formation of a diketide intermediate. The key enzyme at this point in the biosynthesis of curcuminoids is type III polyketide synthase. This enzyme produces bisdemethoxycurcumin from the diketide, which serves as a chain extender, and a further molecule of *p*-coumaroyl-CoA. In subsequent steps involving hydroxylases and *O*-methyltransferases, demethoxycurcumin is obtained from bisdemethoxycurcumin, and curcumin is produced from demethoxycurcumin. For the direct synthesis of demethoxycurcumin and curcumin from *p*-coumaroyl-CoA, feruloyl-CoA is first obtained over four steps. This then further reacts, as described above, with malonyl-CoA, and the resulting diketide then reacts with *p*-coumaroyl-CoA or an additional molecule of feruloyl-CoA.[15] The simplified biosynthesis pathway for curcuminoids, modified according to Ramirez-Ahumada et al. as well as Katsuyama et al., is illustrated in Scheme 1.[15,17]

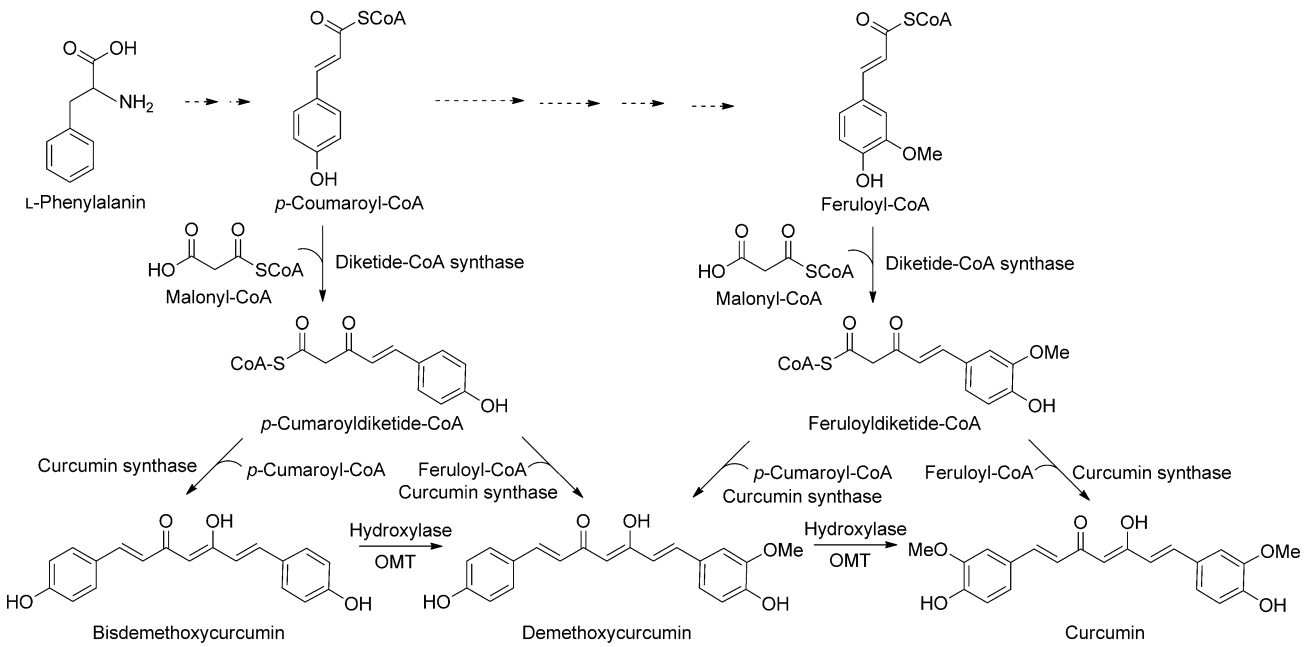
Turmeric owes its yellow color to curcumin, the main curcuminoid, demethoxycurcumin (4-hydroxycinnamoyl-(feruloyl)methane), and bisdemethoxycurcumin (bis(4-hydroxycinnamoyl)methane), which all belong to the diarylheptanoids. These pigments are obtained from the rhizome through solvent extraction and subsequent crystallization.[19] A newly discovered component of turmeric is cyclocurcumin.[20] The chemical structures of curcumin, demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin are illustrated in Scheme 2. As early as the 19th century, an orange–yellow crystalline powder was isolated from the dried rhizome of *Curcuma* and named curcumin and/or diferuloylmethane [IUPAC name (1*E*,6*E*)-1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione; CAS number: 458-37-7].[2,3,21–24] The molecular formula of curcumin is $C_{21}H_{20}O_6$ and it has a molecular weight of 368.39 g mol^{-1}. The melting point is about 170–175 °C.[25] The physicochemical characteristics of curcuminoids are summarized in Table 1. Commercially available curcumin is generally composed of about 77 % curcumin, 17 % demethoxycurcumin, and 3 % bisdemethoxycurcumin. Chemically, curcumin is a bis-α,β-unsaturated β-diketone of two ferulic acid units, connected through a methylene group, and is a typical Michael acceptor. As a Michael acceptor, curcumin is able to react with thiols (e.g. glutathione).[26,27] The Michael-acceptor function of curcumin appears to be of central importance for epigenetic regulation mechanisms (see Section 4.3).[26] In contrast to curcumin, the α,β-unsaturated β-diketone in the less familiar cyclocurcumin is substituted by an α,β-unsaturated dihydropyranone. Curcumin exists mostly in a hydrogen-bond-stabilized keto–enol state (keto–enol tautomerism; Scheme 3). Tautomeric equilibrium is partly dependent upon the polarity and the pH value of the solvent. In nonpolar solvents, curcumin exists in the enol form, because of intramolecular hydrogen bond formation, whereas in polar solvents it exists in the

Gerald Rimbach studied nutritional science at the Justus-Liebig-University in Giessen (Germany), where he received his PhD in 1993 and habilitated in nutrition physiology in 1998. He worked for two years at the Institute of Molecular and Cell Biology at the University of California, Berkeley (USA), and in 2000 was appointed as Lecturer of Molecular Nutrition at the University of Reading (UK). Since 2003 he has been Professor of Food Science at the Christian Albrechts University Kiel. His research focuses on the health effects of plant bioactives by using cell and molecular biological techniques.

Patricia Huebbe studied nutritional science at the Christian Albrechts University Kiel (Germany) and obtained her MSc in 2003. In 2007, she completed her PhD thesis entitled "The influence of apolipoproteins E genotype and vitamin E on neurodegeneration". Her research interests focus on the interaction of dietary and genetic factors within the context of healthy aging. Her work involves experiments with cultured cells and mouse models, as well as human trials.

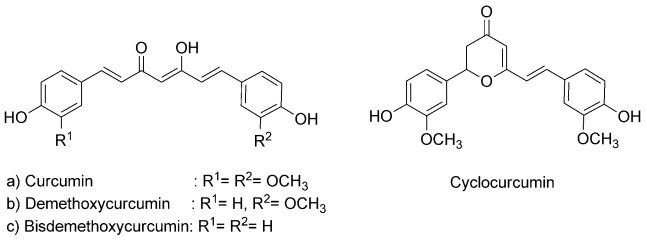
Tuba Esatbeyoglu studied food chemistry and, in 2010, obtained her PhD on the isolation and characterization of secondary plant metabolites and the synthesis of proanthocyanidins at the Technical University Braunschweig (Germany). Since 2010, she has been working as a postdoctoral fellow at the Institute of Human Nutrition and Food Science at the Christian Albrechts University Kiel (Germany). Her research focuses on the development of analytical detection methods for the quantification of plant bioactives, the identification of lead compounds, and the assessment of their possible role in health.

Insa M. A. Ernst studied nutritional science at the Christian Albrechts University Kiel (Germany) and at the Universidad Politécnica de Madrid (Spain). Since 2008, she has been working at the Institute of Human Nutrition and Food Science at the Christian Albrechts University Kiel, where she received her PhD in 2011. The specific focus of her research is the chemopreventative actions of plant bioactives.



Scheme 1. Biosynthesis pathways for curcuminoids.[15,17] Initially, the phenylpropanoid diketide intermediate is produced from the condensation of phenylpropanoid-CoA and malonyl-CoA in the presence of diketide-CoA synthase. The corresponding curcuminoids are obtained from this intermediate through reaction with a further molecule of phenylpropanoid-CoA catalyzed by the enzyme curcumin synthase. Hydroxylases and O-methyltransferases then transform bisdemethoxycurcumin into demethoxycurcumin and curcumin.

diketo form.[20,28,29] In acidic and neutral media, the keto form of curcumin dominates and acts as a proton donor, whereas at pH values above 8 the enol form predominates and serves as an electron donor.[30,31] This orange–yellow pigment is soluble in ethanol and concentrated acetic acid. Curcumin shows a weak green fluorescence in ethanol. Furthermore, curcumin is soluble in dichloromethane, chloroform, methanol, ethyl acetate, dimethyl sulfoxide, and acetone.[32] Curcumin is insoluble in water and diethyl ether. It is also light-sensitive and unstable in alkaline solutions.[8,22,33–35]



Scheme 2. Chemical structures of curcuminoids.

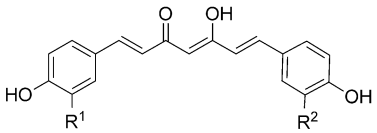
In addition to curcuminoids, turmeric also contains 1–5% essential oils, primarily including mono- and sesquiterpenes such as α- and β-turmerone (ca. 35%), ar-turmerone (ca. 12%), turmerol, zingiberene (ca. 25%), zingiberol, curcumol, β-curcumene, and xanthorrhizol (Scheme 4).[8,9,24,36] These essential oils in turmeric are used in aromatherapy and the perfume industry.[4]

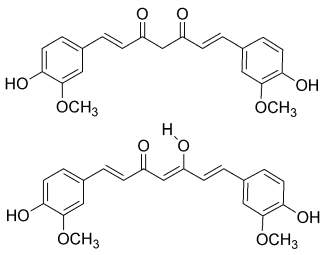
The two symmetrically arranged chromophores of the structural motif C=O−C=C and the conjugated double bond give curcumin its yellow color.[37] Curcumin displays its highest absorption in organic solvents, such as methanol, at 420 nm. This absorption is drastically reduced in more aqueous solutions.[38,39] Similarly, the absorption spectra of

Dawn Chin received her MSc in nutritional science in 2009 at the Christian Albrechts University Kiel (Germany). In the same year, she commenced her PhD within the research group of Professor Rimbach. Her work is focussed on the possible role of dietary factors in the prevention of age-related neurodegenerative diseases.

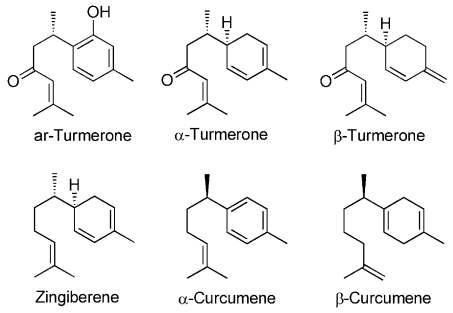
Anika E. Wagner studied nutritional science at the Justus-Liebig-University in Giessen (Germany) and the Robert Gordon University in Aberdeen (UK). She obtained her PhD in 2006 at the University of Lübeck (Germany) and then became a postdoctoral fellow at the Institute of Human Nutrition and Food Science at the Christian Albrechts University Kiel (Germany) from 2006–2009. In November 2009 she was appointed as Assistant Professor of Molecular Nutrition (Kiel). Her research interests focus on the anti-inflammatory and chemopreventative properties of plant bioactives.

Table 1: Characteristics of curcuminoids.[22,25]

chemical name	a) 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-dien-3,5-dione b) 1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-dien-3,5-dione c) 1,7-bis-(4-hydroxyphenyl)-hepta-1,6-dien-3,5-dione
C.A.S. number	a) 458-37-7 b) 33171-16-3 c) 33171-05-0
molecular formula, molecular weight [g mol^{-1}]	a) $C_{21}H_{20}O_6$, 368.39 b) $C_{20}H_{18}O_5$, 338.39 c) $C_{19}H_{16}O_4$, 308.39
chemical structure	 a) curcumin: $R^1 = R^2 = OCH_3$ b) demethoxycurcumin: $R^1 = H$, $R^2 = OCH_3$ c) bisdemethoxycurcumin: $R^1 = R^2 = H$
physical and chemical properties	
physical state	solid
color	orange-yellow (at neutral pH value)
odor	odorless
melting point	170–175 °C
flammability	nonflammable
light sensitivity	light sensitive
solubility	insoluble in water, diethyl ether soluble in ethanol, acetic acid



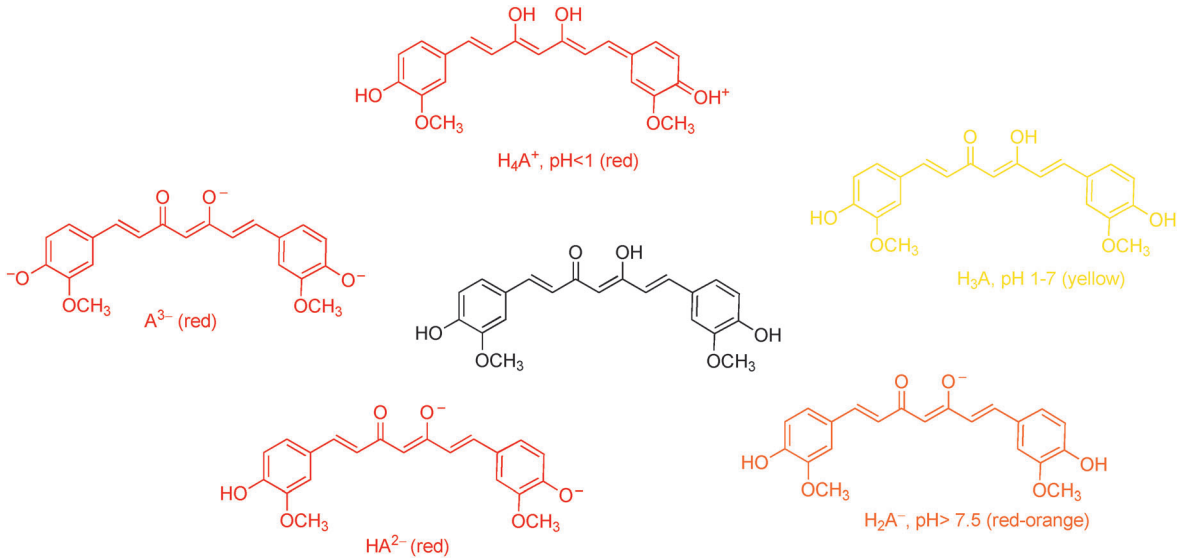
Scheme 3. Chemical structures of curcumin in the keto and enol form.



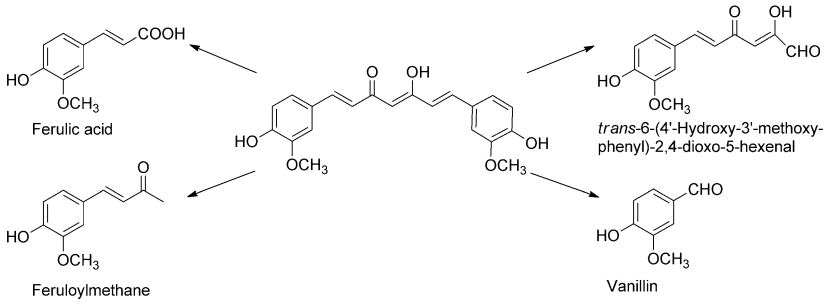
Scheme 4. Chemical structures of some sesquiterpenes from *Curcuma longa*.

curcumin show different profiles at different pH values, with the maximum absorption displaying a gradual hypsochromic shift. The maximum absorption in alkaline solutions is observed at 463 and 261 nm, with a shoulder at 360 nm. In acidic solutions, however, the maximum absorption is displaced from 463 to 422 nm, i.e. towards a shorter wavelength due to a hypsochromic shift. The absorption intensity also decreases with a decreasing pH value.[34,39] Curcumin has the properties of an acid–base indicator. At $pH < 1$ curcumin is in the protonated state and displays a red color, while at pH 1–7 it is bright yellow and exists in the neutral state. At $pH > 7$, deprotonated curcumin again exhibits a red color in solution.[23,24,34] The color transition point is between pH 8 and 9; therefore, turmeric extract can be used as a measure of alkalinity.[36] Scheme 5 illustrates the possible dissociation of curcumin in aqueous solution. The alcoholic extract from turmeric can also be used in turmeric paper for the detection of boric acid and borates. By using this method, alkaline solutions and oxalic acid display a characteristic green–black color whilst acidic solutions give an orange–red color.[2,22,32,35,36]

The stability of curcumin in aqueous solution is pH-dependent.[30] Curcumin is most stable at pH 1–6, for example, in the stomach or small intestine, where its degradation is very slow. However, its solubility in aqueous solution is poor in this pH range.[23,30] Curcumin is probably stable because of the undissociated form of the hydroxy groups in this pH range. Curcumin becomes unstable at $pH > 7$ and, as such, 90% of curcumin is degraded within 30 min in in vitro preparations under physiological pH conditions (0.1M phosphate buffer solution, 37 °C, pH 7.2).[23,30,40,41] Tetrahydrocurcumin, one of the main curcumin metabolites, is significantly more stable under physiological pH and temperature conditions.[42] The degradation of curcumin proceeds according to first-order kinetics.[30] Faster degradation has been observed in the pH 8.2–8.5 range.[23] Curcumin degrades mainly into *trans*-6-(4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexenal and to a lesser extent into vanillin, ferulic acid, and feruloylmethane.[30] The chemical structures of the degradation products are illustrated in Scheme 6. The rate of degradation is at a maximum at pH values of about 10.2. The degradation of bisdemethoxycurcumin proceeds considerably slower than that of curcumin and demethoxycurcumin. One possible reason for this could be the absence of the two methoxy groups. Owing to its increased heat stability and lower degradation rate in alkaline environments, bisdemethoxycurcumin is added to foods to improve color stability. Curcumin is only stable for 1 to 2 h in 0.1M sodium hydroxide, although its stability increases in aqueous solutions at $pH > 11.7$.[24,34] Besides lowering the pH value, curcumin degradation can be inhibited by antioxidants, such as ascorbic acid, *N*-acetyl-L-cysteine, and glutathione.[40] Similarly, the stability of curcumin in cell culture media, containing 10% fetal calf serum, and in blood (both pH 7.4) is improved compared to in alkaline environments. The degradation rate under such conditions is approximately 20% after one hour and increases to about 50% after eight hours.[30] As curcumin is rapidly degraded in alkaline solutions and is poorly soluble in acidic aqueous solutions and under physiological pH, the stabiliza-



Scheme 5. Possible dissociation of curcumin in aqueous solution.[23]



Scheme 6. Chemical structures of degradation products of curcumin (0.1 M phosphate buffer, pH 7.2, 37 °C).[30]

tion of curcumin with cyclodextrin has been proposed with a view to using a curcumin–cyclodextrin complex in food and pharmaceuticals in the future.[43] The stability of curcumin could also be enhanced by adding phospholipid liposomes or bovine serum albumin.[28]

2.1. Occurrence of Curcumin in Foods and as a Food Additive (E100)

Unlike in the USA and England, turmeric on its own is not a well known spice in most European countries (e.g. Germany). Nowadays, turmeric is an ingredient of spice blends, mainly curry powder, which generally consists of turmeric, clove, paprika, ginger, cardamom, coriander, cumin, mace, pepper, and cinnamon.[3,7,8,36]. Turmeric is also a widely used natural pigment in the cosmetic, textile, and food industries. The symmetrical packing of the chromophores in curcumin enables it to dye cotton.[35] Turmeric is commonly used as a food coloring in mustard, pastries, dairy products, and canned fish, and can serve as a substitute for the more expensive saffron. The intense yellow color is indeed similar to that of saffron, but turmeric has a different, somewhat tart, bitter taste and an aromatic, piquant scent. As a consequence, turmeric is not used to season desserts and cakes, but is used in rice, meat, and fish dishes.[2,7] It seems plausible, given its bitter taste, that curcumin acts as a defense against herbivores.

As shown in Figure 2, in comparison to curry powder or mustard, turmeric powder has by far the highest content of curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin). Curcumin is the main curcuminoid in the foods analyzed. In 2009, approximately 100 ready-packed and 600 loose turmeric samples were analyzed in India for their curcumin content. The curcumin content of the packed samples was between 2.2 and 3.7%; in 18 of the samples the content was $\geq 3\%$. The loose samples contained less curcumin than the packed samples, at 0.2–2.7%.[44] A significantly lower curcuminoid level was found in curcumin-supplemented dressings,[12] drinks,[12] yogurts,[45] sweets,[38] pickled gherkins,[38] and tea.[12]

To date, various natural pigments, such as riboflavin (E101i-ii), carminic acid (cochineal, E120), chlorophyll and its

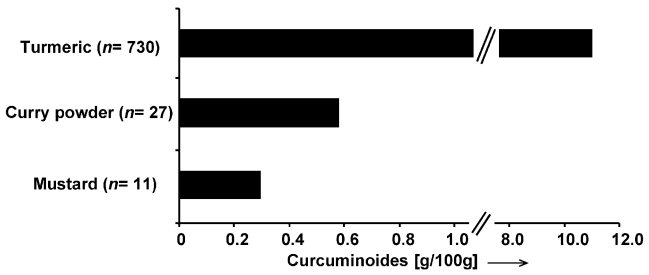
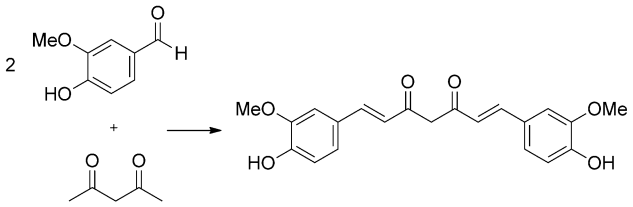


Figure 2. Curcuminoid content of turmeric (curcumin, demethoxycurcumin, bisdemethoxycurcumin),[12,21,44] curry powder,[21,38,39] and mustard;[38,39] *n*: number of analyzed samples.

copper-containing complexes, chlorophyllin (E140-141), caramel color (E150a-d), carotenoids (E160a-f, E161b, E161g), betanin (E162), and anthocyanins (E163), have been approved as food colorings, and curcumin (E100) belongs to this group.[46] Curcumin can only be added to certain foods because of its light sensitivity and instability in alkaline solutions (pH > 7). According to the German regulation on additives ("*Zusatzstoff-Zulassungsverordnung*"), appendix 1B (pigments approved for specific foods) and 1C (foods for which only certain pigments are approved), curcumin is permitted for use in defined amounts (20–500 mg kg^{-1}) in products such as drinks, smoked fish, processed cheese, sauces, and mustard, and at "quantum satis" levels in margarine.

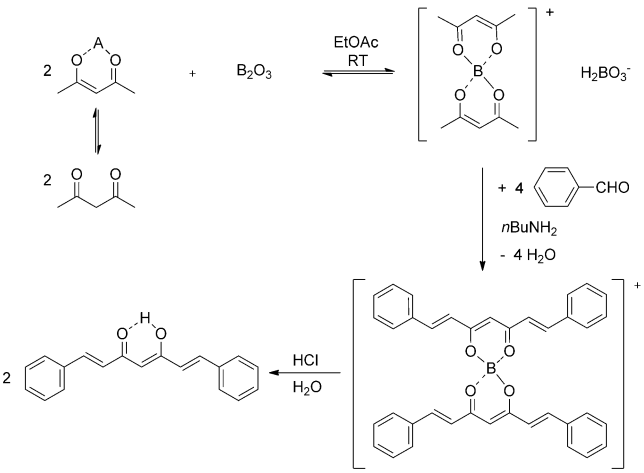
2.2. Synthesis of Curcuminoids and Their Synthetic Analogues

Isolating curcuminoids as standard compounds is time-consuming and this has resulted in the establishment of methods to synthesize curcumins and their analogues, demethoxy- and bisdemethoxycurcumin. Curcumin was first isolated in 1815 by Vogel and Pelletier.[35] In 1870, curcumin was successfully produced in its crystallized form.[32] The molecular formula $C_{21}H_{20}O_6$ was confirmed by Milobedzka et al. and in 1910 the structural formula of a diferuloylmethane was postulated.[37] In 1918, Lampe synthesized curcumin in five steps starting from ethyl acetoacetate and carbomethoxy feruloyl chloride (Scheme 7). After condensation and subsequent saponification and decarboxylation, the intermediate product was again exposed to carbomethoxy feruloyl chloride. The resulting condensation product, a carbomethoxy diferuloylacetone derivative, was then cleaved under hot acidic conditions. Curcumin was finally generated after saponification and decarboxylation. This pathway enabled the definitive structural formula for curcumin to be determined.[35] Pavolini synthesized curcumin in 1950 within 30 min by heating 2 parts vanillin and 1 part acetylacetone in the presence of boron trioxide. However, the yield of curcumin was only about 10% in this one-step reaction (Scheme 8).[47]

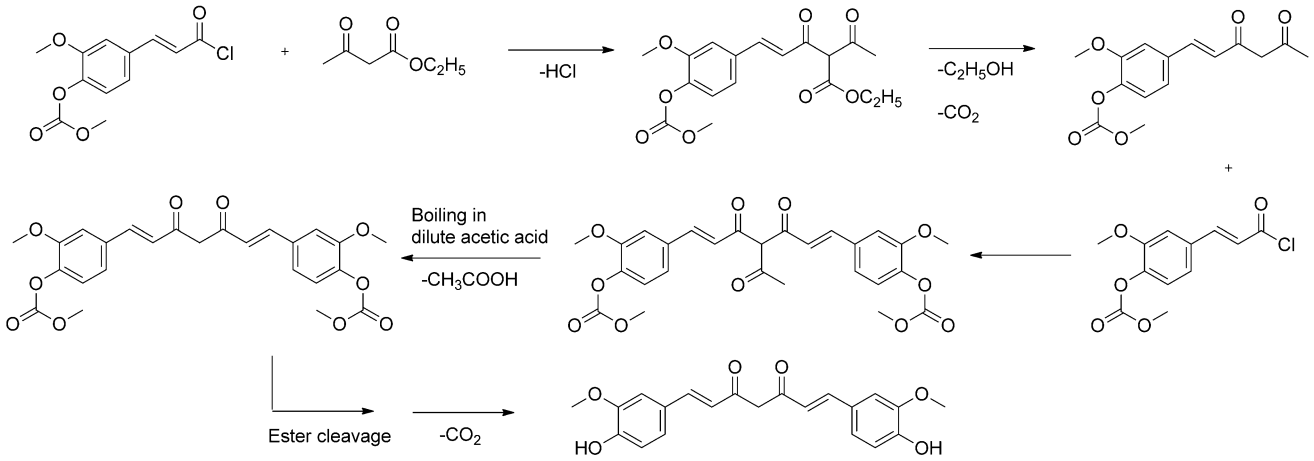


Scheme 8. Synthesis of curcumin according to Pavolini.[35]

In 1964, Pabon further developed this method and increased the yield of curcumin to 80% through the use of trialkyl borates and *n*-butylamine and omitting vanillin. A generalized synthesis pathway for curcuminoids is shown in Scheme 9. Pabon also obtained curcumin from the reactants vanillin (4-hydroxy-3-methoxybenzaldehyde) and acetylacetone (pentan-2,4-dione).[47] Acetylacetone was initially complexed with boron trioxide to protect the methylene groups from the Knoevenagel condensation. Then, a nucleophilic attack with benzaldehyde took place at both terminal methyl groups. Subsequently, a step-wise addition of *n*-butylamine



Scheme 9. Synthesis of curcuminoids according to Pabon.[47]



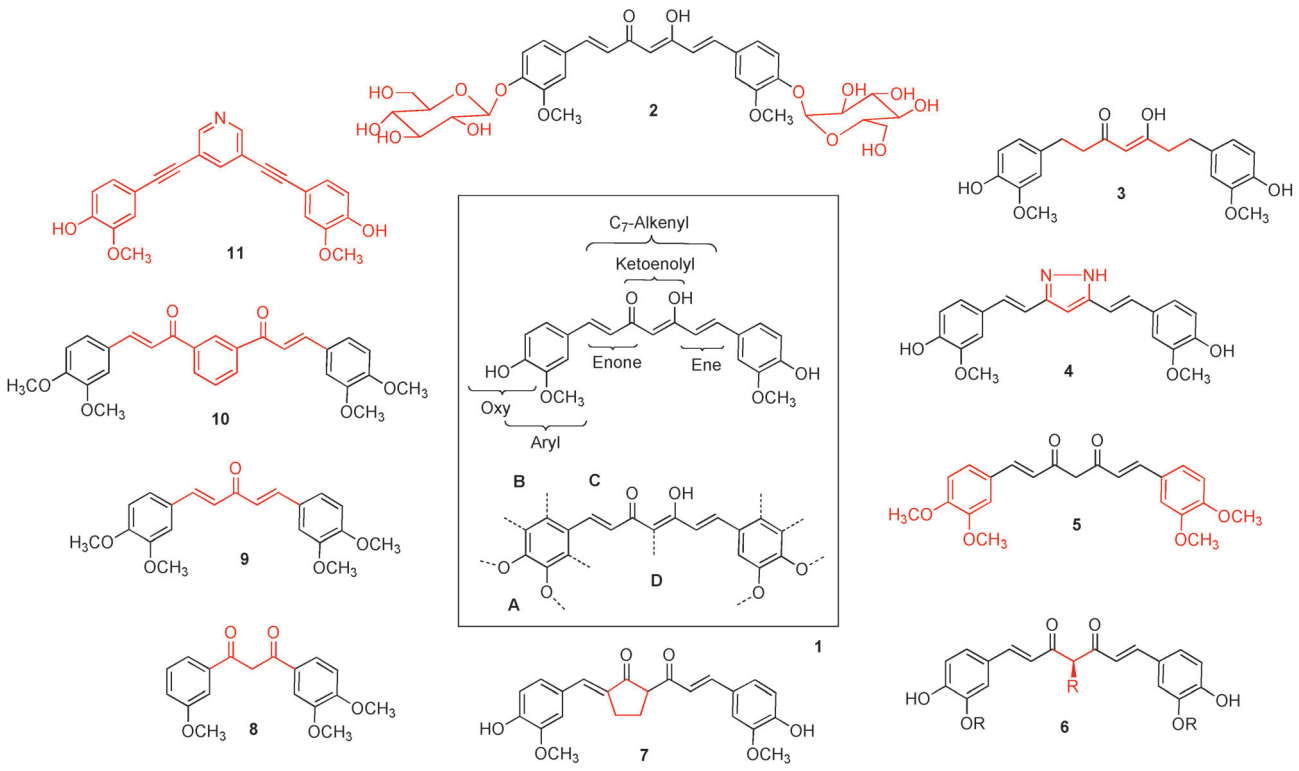
Scheme 7. Synthesis of curcumin according to Lampe.[35]

was carried out. The water resulting from the condensation of benzaldehyde and the boron complex was removed with *n*-tributyl borate. The boron complex dissociates in a slightly acidic environment into two equivalents of the corresponding curcuminoid. Synthetic dimethoxycurcumin is also produced in a similar manner. Pabon[47] also established the synthesis of other curcuminoid analogues. However, with this approach, asymmetric compounds, such as demethoxycurcumin, can only be isolated as a mixture of curcuminoids, which require subsequent purification.[47–49] The synthesis of demethoxycurcumin and other curcuminoids from pentan-2,4-dione and equimolar amounts of vanillin and 4-hydroxybenzaldehyde was established almost 20 years later.[50] The chemical structure of curcumin was confirmed by Roughley and Whiting in 1973.[13] The presence of curcumin in solution as a keto–enol tautomer was first demonstrated by Payton et al. in 2007 using NMR spectroscopy.[51] Pure curcumin is very rare and expensive. It is possible to separate the three curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) cost-effectively from a commercially available curcuminoid mixture from turmeric using crystallization and column chromatography.[52]

More than 700 curcumin analogues and their biological activities were described in a review article in 2010. Some of these analogues appear to be more potent in terms of biological activity than curcumin.[11] There are two options for modifying the structure of curcumin: it is possible to alter the substitution pattern on the aromatic rings, and it is also possible to vary the unit between the two aromatic rings, thus altering the chain length. Curcumin analogues have been divided into four main groups: the monophenyls, the heterocyclic compounds, the analogues with the various substitutions at the phenyl rings, and those with different linkages between the two phenyl rings. Examples include imide, pyrazole, and isoxazole analogues, as well as those with fluorine.[49,50,53] Some synthetic curcumin analogues are shown in Scheme 10.

3. Bioavailability and Safety of Curcumin

The primary prerequisite for the biological activity of curcumins in humans and animals is its availability. Bioavailability studies have characterized the rate and concentration at which curcumin is absorbed, appears in the plasma, and reaches its target site. The bioavailability of curcuminoids is primarily determined by their metabolism (particularly in the intestine and liver). In the following sections, absorption, metabolism, and tissue concentrations of curcuminoids will be described, and methods to increase their bioavailability discussed. Finally, the safety of curcumin will be assessed.



Scheme 10. Synthesis of curcumin analogues with possible sites (**1**) for structural modification of curcumin. **A**: Modification of the -OCH_3 and OH groups, elimination, or substitution of the -OCH_3 group; **B**: insertion and elimination of atoms or groups on the aromatic ring, replacement of the aromatic ring by heteroaromatic rings or "multirings"; **C**: Modification of the number of -C=C and -C=O bonds, including the -C=C bonds in the cyclic structures; **D**: substitution of the 1,3-diketone compound by a ketone, modification of the number of enone units, masking of the 1,3-diketone, conversion of the 1,3-diketone into cyclic structures, such as pyrazole or isoxazole. Curcumin derivative (**2**); reduced curcumin derivative (**3**); masking of the central 3-diketone (**4**); aryl analogue (**5**); substituted acetylacetone analogue (**6**); conformationally restrained analogue (**7**); C3-linked analogue (**8**); C5-linked analogues (**9**); C7-linked analogue (**10**); atypical analogues (**11**). Modified from Ref. [76].

3.1. Absorption, Metabolism, and Tissue Concentration

The bioavailability of curcumin has been studied in numerous investigations in laboratory rodents (mouse, rat) as well as in humans (Table 2).[42,54–65] The different studies are only partially comparable because, besides species differences, there are substantial variations in the concentration and duration of curcumin administered.

Generally, the oral bioavailability of curcumin is low due to a relatively low intestinal (small intestines) absorption[66] and rapid metabolism in the liver,[55] followed by elimination through the gall bladder.[67] It has been shown in Sprague Dawley rats that, following oral administration of curcumin (1 g kg^{-1} body weight), most of the curcumin is eliminated unchanged through the feces. The amount excreted in the urine is negligible.[66] Curcumin is, therefore, mainly removed by fecal excretion with minimal elimination in the urine.

Table 2: Plasma and tissue concentration of curcumin after administration in different species.

Tissue	Species	Dose, administration	Duration of treatment	Plasma/serum or tissue concentration [μmol L^{-1} and μmol kg^{-1}]	Ref.
plasma	mouse BALB/c	100 mg kg^{-1}, i.p.	once	6.1	[42]
plasma	mouse C57Bl/6J	100 mg kg^{-1}, i.p. [^{14}C]curcumin	once	25 ± 2	[258]
plasma, liver, brain	mouse NMRI	50 mg kg^{-1}, oral gavage	once	n.d.	[63]
brain	mouse BALB/c	100 mg kg^{-1}, i.p.	once	1.1 ± 0.03	[42]
brain	mouse C57Bl/6J	100 mg kg^{-1}, i.p. [^{14}C]curcumin	once	2.9 ± 0.4	[258]
brain	mouse B57BL/6	100 mg kg^{-1}, i.p.	once	13.6	[63]
heart	mouse C57Bl/6J	100 mg kg^{-1}, i.p. [^{14}C]curcumin	once	9.1 ± 1.1	[258]
lungs	mouse C57Bl/6J	100 mg kg^{-1}, i.p. [^{14}C]curcumin	once	16 ± 3	[258]
liver	mouse BALB/c	100 mg kg^{-1}, i.p.	once	73.0 ± 7	[42]
liver	mouse C57Bl/6J	2 g kg^{-1}, oral	1 week	0.119 ± 0.031	[258]
liver	mouse C57Bl/6J	100 mg kg^{-1}, i.p. [^{14}C]curcumin	once	73 ± 20	[258]
spleen	mouse BALB/c	100 mg kg^{-1}, i.p.	once	70.7 ± 2.9	[42]
kidneys	mouse BALB/c	100 mg kg^{-1}, i.p.	once	20.4 ± 0.2	[42]
kidneys	mouse C57Bl/6J	100 mg kg^{-1}, i.p. [^{14}C]curcumin	once	78 ± 3	[258]
intestines	mouse BALB/c	100 mg kg^{-1}, i.p.	once	480.6 ± 18.6	[42]
small intestine	mouse C57Bl/6J	1–5 g kg^{-1}, oral	1 week	39 ± 9-240 ± 69	[258]
large intestine mucosa	mouse C57Bl/6J	1–5 g kg^{-1}, oral	1 week	15 ± 9-715 ± 448	[258]
colon mucosa intestinal mucosa	mouse C57Bl/6J	100 mg kg^{-1}, i.p. [^{14}C]curcumin	once	200 ± 23	[258]
plasma	rat Sprague Dawley	100 mg kg^{-1}, gavage	once	trace	[62]
plasma	rat F344	2%, diet	14 days	n.d.	[259]
plasma	rat Sprague Dawley	1 g kg^{-1}, i.v.	once	≈27	[66]
plasma	rat F344	2%, diet	3 h	< 0.01	[259]
plasma	rat F344	500 mg kg^{-1}, i.g per gavage	once	0.03 ± 0.009	[259]
plasma	rat F344	2%, diet	7 days	0.012 ± 0.005	[259]
plasma	rat F344	500 mg kg^{-1}, i.g per gavage	7 days	0.065 ± 0.028	[259]
plasma	rat F344	40 mg kg^{-1}, i.v.	once	n.d.	[61]
plasma	rat F344	500 mg kg^{-1}, p.o. (gavage)	once	0.005	[61]
plasma	rat Sprague Dawley	10 mg kg^{-1} i.v.	once	0.98 ± 0.14	[67]
plasma	rat Sprague–Dawley	500 mg kg^{-1} p.o.	once	0.16 ± 0.03	[67]
plasma	rat Wistar	340 mg kg^{-1}, gavage	once	0.0065 ± 0.0045	[83]
serum	rat albino Wista	1 g kg^{-1} p.o.	7 days	1.36	[82]
serum	rat Albino Wistar	2 g kg^{-1}, oral	once	3.66 ± 0.62	[55]
serum	rat Albino Wistar	500 mg kg^{-1}	once	227.5 ± 14.82	[71]
blood	rat Albino Wistar	2.0–2.7 g kg^{-1}, gavage	once	n.d.	[68]
liver	rat Sprague–Dawley	1 g kg^{-1}, gavage	once	ca. 0.41	[66]
liver	rat F344	≈1.2 g kg^{-1}, diet	14 days	0.8 ± 0.3	[259]

Table 2: (Continued)

Tissue	Species	Dose, administration	Duration of treatment	Plasma/serum or tissue concentration [$\mu mol\,L^{-1}$ and $\mu mol\,kg^{-1}$]	Ref.
liver	rat Albino Wistar	2.0–2.7 $g\,kg^{-1}$, gavage	once	n.d.	[68]
liver	rat F344	2%, diet, 500 $mg\,kg^{-1}$, i.g per gavage	3 h, once or 7 days	ca. 0.1	[259]
gall bladder	rat Sprague Dawley	1 $g\,kg^{-1}$, gavage	once	ca. 2.7	[66]
kidneys	rat Sprague Dawley	1 $g\,kg^{-1}$, gavage	once	ca. 0.41	[66]
kidneys	rat Albino Wistar	2.0–2.7 $g\,kg^{-1}$, gavage	once	n.d.	[68]
colon mucosa	rat F344	$\approx$1.2 $g\,kg^{-1}$, diet	14 days	1800 ± 800	[259]
mucosa	rat F344	2%, diet	3 h	279 ± 295	[259]
mucosa	rat F344	500 $mg\,kg^{-1}$, i.g. per gavage	once	1.7 ± 0.9	[259]
mucosa	rat F344	2%, diet	7 days	482 ± 412	[259]
mucosa	rat F344	500 $mg\,kg^{-1}$, i.g. per gavage	7 days	18 ± 24	[259]
serum	human	2 $g\,kg^{-1}$, oral	once	0.016 ± 0.014	[55]
serum	human	4–8 g per day, oral	3 months	0.51 ± 0.11–1.77 ± 1.87	[54]
serum	human	10–12 g, oral	once	ca. 0.15	[58]
plasma	human	36–180 mg per day, p.o.	4 months	n.d.	[56]
plasma	human	450–3600 mg per day, p. o.	4 months	n.d.–0.011 ± 0.0006	[57]
plasma	human	10–12 g, oral	once	n.d.	[65]
Liver	human	450–3600 mg per day, oral	1 week	n.d.	[59]
colorectal	human	450–3600 mg per day, oral	1 week	0–19.6 ± 14.8	[60]

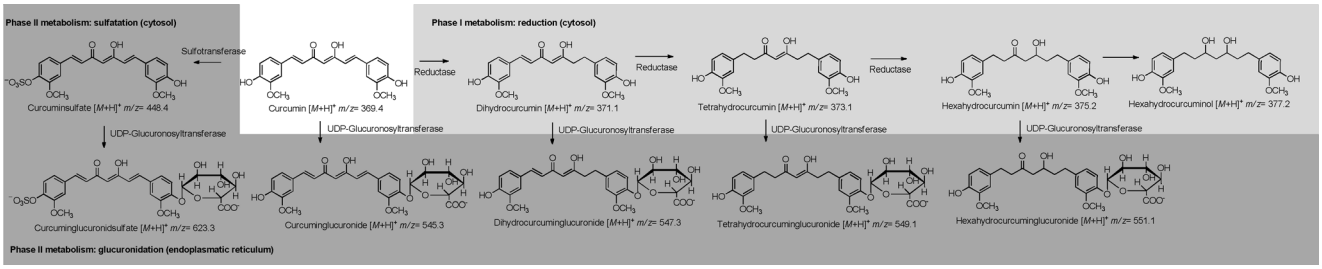
Other studies with laboratory rodents also confirm the low uptake of orally administered curcumin.[68,71]

In effect, it seems that significant amounts of curcumin are only detectable in human plasma after oral ingestion of high doses (in the gram range).[54,55,57,58,65] The plasma levels of curcumin in many bioavailability studies are often below 1 $\mu mol\,L^{-1}$. The highest plasma concentrations of curcumin were usually observed in the first 1–2 h after ingestion.[54] Table 2 summarizes plasma and tissue concentrations of curcumin in different species. Curcumin is metabolized by phase I and II enzymes. Curcumin is conjugated with glucuronic acid and sulfate in enterocytes and hepatocytes (phase II metabolism).[59,61,72,73] The phase I metabolites dihydro-, tetrahydro-, and hexahydrocurcumin, which are mainly produced by hepatic reductases, are present in free and conjugated forms (mainly as glucuronides).[42,61,63] Dihydroferulic acid and ferulic acid have also been identified as curcumin metabolites.[70] In addition, hexahydrocurcuminol (from the reduction of hexahydrocurcumin) is also a known curcumin metabolite.[61] Some important phase I and II metabolites of curcumin are presented in Scheme 11.

Curcumin conjugates are actively transported out of the enterocyte through the multidrug resistance-related proteins (MRP1 and MRP2), which accounts for the low bioavailability of curcumin.[74] MRPs are under the transcriptional control of the transcription factor Nrf2 (see Section 4.1), which is in turn activated by curcumin.[75]

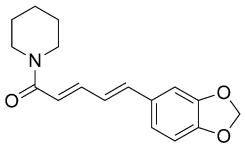
The highest concentrations of curcumin are found in the intestine. However, curcumin levels are very low and can fall below detection limits in the plasma and other tissues (e.g. kidneys, brain; Table 2).

Various methods have been proposed to improve the solubility of hydrophobic curcumin in aqueous solutions to enhance its bioavailability. The solubility of curcumin may be enhanced by the formation of complexes with metal ions, such as Zn^{2+}, Cu^{2+}, Mg^{2+}, and Se^{2+}, as well as with serum albumin.[6]



Scheme 11. Phase I and phase II metabolism of curcumin in laboratory rodents and humans.[42]

The bioavailability of curcumin can also be improved with piperine, nanoparticles, liposomes, and phospholipids, or by altering curcumin analogues structurally.[64,76] The glucuronidation of curcumin, and hence its phase II metabolism, is inhibited in the presence of piperine (an alkaloid from black pepper, 1-piperoylpiperidine; Scheme 12), and this may



Scheme 12. The chemical structure of piperine, the main alkaloid in black pepper.

increase its bioavailability.[55,71] However, increasing curcumin bioavailability by inhibiting phase II metabolism should be carefully scrutinized, since many xenobiotics are detoxified through this pathway.

Nanoencapsulation of curcumin using poly(lactic-*co*-glycolic acid) (PLGA) can also lead to enhanced bioavailability. Xie et al. showed that by using PLGA nanoparticles (particle size of ca. 200 nm) they are able to elevate the relative oral bioavailability of curcumin by five- to sixfold in rats.[77] Furthermore, other animal studies with curcumin–PLGA nanoparticles (158 nm) have reported a more than 20-fold increase in the relative bioavailability of oral curcumin .[78,79]

In another study, the encapsulation of curcumin in lecithin liposomes (particle size of ca. 220 nm) also led to increased curcumin bioavailability in rats.[80] In addition, the encapsulation of curcumin with cyclodextrin resulted in higher cellular concentrations in vitro.[81]

The application of curcumin–phospholipid complexes or curcumin–phosphatidylcholine complexes also increased the absorption of curcumin after oral administration in rats.[82–85] Curcumin levels in plasma and liver were increased by approximately fivefold compared to control animals.[83]

3.2. Toxicity

Curcumin has been assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the EU Scientific Committee for Food (SCF). The JECFA set an acceptable daily intake (ADI) value of 0–3 $mg\,kg^{-1}$ body weight per day for curcumin in 2004. The ADI value of 3 $mg\,kg^{-1}$ body weight per day was based on the NOAEL (no observed adverse effect level) of 250–320 $mg\,kg^{-1}$ body weight per day.[19] The SCF, on the other hand, has not made any specification for the ADI value of curcumin.[19,36] According to the directive 67/548/EWG, curcumin neither poses a threat to man nor the environment.[25] The JECFA evaluated four acute oral toxicity studies in mice and rats and found LD_{50} values of $2- > 10\ g\,kg^{-1}$ body weight for mice and $5- > 10\ g\,kg^{-1}$ body weight for rats.[19]

Turmeric is generally consumed daily in India and several other Asian countries. Indeed, the maximum daily intake of turmeric in Nepal is about 1.5 g (which corresponds to ca. 50 mg curcumin) and in India can be up to 2.0–2.5 g (which corresponds to a maximum of ca. 100 mg curcumin).[6,54,86] Clinical trials have used pharmacologically effective doses of curcumin that exceed normal dietary intake. In numerous phase I studies, adverse effects were not observed in humans taking up to 12 g of curcumin per day orally ($200\ mg\,kg^{-1}$ body weight) over a period of four months.[54–56,58] In 2 out of 15 subjects, however, the daily intake of curcumin led to diarrhea (grade 1—2), and in one subject to nausea (grade 2).[57] The safety of high curcumin doses (12 g per day) was also assessed in an investigation by Lao et al. They found that curcumin treatment caused diarrhea, skin rash, headaches (grade 1), and yellow-colored feces in 7 out of the 24 subjects included.[58]

It can thus be concluded that dietary curcumin has only very low or no toxicity. However, side effects caused by very high doses of curcumin, such as those used in clinical studies, cannot be completely ruled out. As such, the safety of adding curcumin to functional foods and dietary supplements should be rigorously assessed.

4. Biological Activity and Molecular Targets of Curcumin

Turmeric has been used as a medicinal plant for thousands of years. In traditional Indian (Ayurveda) and Chinese medicine, turmeric is prescribed for the treatment of inflammation.[87] The first scientific article on the treatment of biliary disorders with turmeric was published in 1937.[88] A search with the term "curcumin" in the medical database PubMed (http://www.ncbi.nlm.nih.gov/pubmed?term=curcumin, last accessed on 27.09.2011) resulted in 73 articles up to 1990. The number of publications on the topic "curcumin" has drastically increased in the last 20 years (4055 articles altogether, of which 402 are review articles, 2042 animal studies, 2116 human trials, and 59 clinical trials; Figure 3). For the year 2010 alone, 700 articles can be found in PubMed with the search term "curcumin". The number of completed clinical studies (phase I, II, and III) are, however, relatively low. On the website of the US National Institute of Health (http://www.clinicaltrials.gov/ct2/results?term=curcumin, last accessed on 20.10.2011) there are 62 reported phase I, II, and III studies to date.

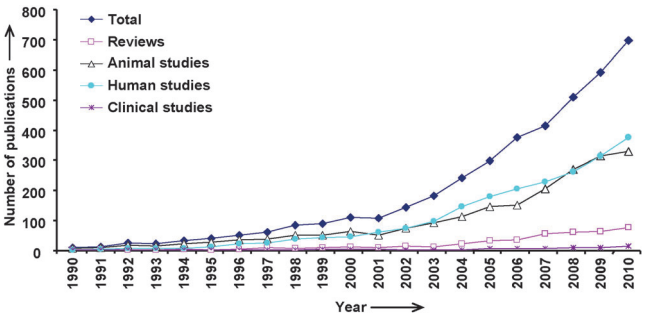


Figure 3. Number of publications (since 1990) retrieved with the search term "curcumin". Source: PubMed (http://www.ncbi.nlm.nih.gov/pubmed?term=curcumin, last accessed 27.09.2011).

Many health benefits, such as antioxidant, antibacterial, anti-inflammatory, analgesic, wound healing, and eupeptic properties, have been attributed to curcumin. Furthermore, anticarcinogenic and neuroprotective effects of curcumin are also being investigated.[1,8]

In the following sections, the free-radical-scavenging, antioxidant, anti-inflammatory, anticarcinogenic, and neuroprotective properties of curcumin will be discussed in detail.

4.1. Free-Radical Scavenging and Antioxidant Characteristics through Induction of the Nrf2 Signaling Pathway

The presence of the phenolic, β-diketone, as well as the methoxy groups contribute to the free-radical-scavenging activity of curcumin. Some authors have postulated that the radical-scavenging properties of curcumin mainly derive from its phenolic structure.[89,90] The highest radical-scavenging activity has been observed with compounds in which the phenolic hydroxy groups are restrained by electron donors, such as two methoxy groups, in the *ortho* positions.[5,91–93] This is why curcumin is a stronger radical scavenger than demethoxycurcumin and bisdemethoxycurcumin.[91,94] In contrast, electron acceptors, such as nitro groups, reduce the radical-scavenging activity.[5] The radical-scavenging properties of curcumin are largely attributable to it being in the enol form in aqueous solutions.[24] In the keto form, the methylene substitutents on the β-diketone (heptadienone) group account for the radical-scavenging properties of curcumin.[31] The β-diketone groups render curcumin analogues potent superoxide and DPPH (1,1′-diphenyl-2-picrylhydrazyl) radical scavengers.[95] The sole presence of the β-diketone is, however, insufficient for the radical-scavenging activity.[96] According to Jovanovic et al. as well as Litwinienko and Ingold, the central hydrogen atoms of the methylene and phenolic hydroxy groups are involved in the formation of phenoxyl radicals.[96,97] Youssef et al. also showed that the radical-scavenging activity of curcumin increases when methylene and hydroxy groups are present in the *para* position.[93] In addition, the radical-scavenging activity can be enhanced with the number and the substitution pattern of the hydroxy groups on the benzene ring.[95] Furthermore, it has been shown that the phenolic analogues of curcumin are more potent inhibitors of lipid peroxidation, and exhibit an improved free-radical-scavenging activity in DPPH and $ABTS^{+\bullet}$ (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) assays compared to non-phenolic analogues.[92]

Radical-scavenging properties have also been determined for synthetic curcumin analogues, where the two aromatic rings are bridged by seven carbon atoms (such as curcumin), or those with three and five carbon atoms, by using the $ABTS^{+\bullet}$ and FRAP (ferric reducing antioxidant power) assay. The influence of different substituents on the benzene ring and the presence of the central methylene hydrogen atoms on the scavenging ability of these compounds were investigated. The reduced form of curcumin, tetrahydrocurcumin, displayed by far the strongest free-radical-scavenging activity in the $ABTS^{+\bullet}$ assay. This suggests that the presence of enones or dienones is not essential for free-radical-scavenging activity. Analogues without methoxy groups and curcumin isomers also possess free-radical-scavenging activity. Some curcumin analogues bridged by three or five carbon atoms show a higher free-radical-scavenging activity than the reference compound trolox (a vitamin E derivative). Curcuminoids that possess an unsubstituted benzene ring, a dienone structure, or those in which the central methylene groups have been substituted with an alkyl residue also possess free-radical-scavenging activity. However, compounds substituted with two alkyl residues are inactive. Compounds that possess neither an unsubstituted benzene ring nor a central methylene group with an alkyl residue are also inactive.[98]

Curcumin is composed of two monomers of ferulic acid, and the monomer has also been studied for its free-radical-scavenging properties.[99] TEAC (trolox equivalent antioxidant capacity), FRAP, and ORAC (oxygen radical absorbance capacity) assays were used as test systems. Interestingly, according to the TEAC, FRAP, and ORAC assays, the free-radical-scavenging properties of curcumin are lower than that of its monomer, ferulic acid. These results are summarized in Table 3. In our cell culture studies, however, the antioxidant effects of curcumin were considerably higher than those of ferulic acid. These results suggest that curcumin induces endogenous antioxidant defense mechanisms (e.g. through gene regulatory mechanisms). The redox-regulated transcription factor Nrf2 (nuclear factor (erythroid-derived 2)-like 2) plays a key role in this process. The Nrf2 signal transduction cascade and the potential sites of action of curcumin are presented schematically in Figure 4.

Table 3: Radical scavenging properties of curcumin and ferulic acid as determined by TEAC (compared with trolox), FRAP (compared with vitamin C), and ORAC assays (compared with trolox).

	Curcumin [mM mg^{-1}]	Ferulic acid [mM mg^{-1}]	*P* value
TEAC	1.46 ± 0.02	9.91 ± 0.16	0.001
FRAP	2.67 ± 0.01	6.68 ± 0.34	0.004
ORAC	13.8 ± 3.10	782 ± 146	0.002

Nrf2 is a redox-sensitive transcription factor which, under basal conditions, is bound to its inhibitor Keap1 in the cytoplasm.[100] The activation of Nrf2, which causes it to translocate to the nucleus and bind as a heterodimer to the antioxidant responsive element (ARE) in DNA to initiate target gene expression, can be triggered through various pathways.[101] Electrophiles can modify the cysteine residues of Keap1, thereby releasing Nrf2 and allowing it to translocate into the nucleus.[102,103] Furthermore, Nrf2 can be released from the Nrf2–Keap1 complex through various kinase signaling pathways, such as p38, ERK (extracellular signal-regulated kinases), or JNK (cJun NH2 terminal kinase).[104–106] Balogun et al. showed that the induction of heme oxygenase 1 (HO1) in curcumin-treated renal epithelial cells is mediated by the activation of Nrf2.[107] HO1 is a ubiquitously expressed enzyme with antioxidant activity which catalyzes the degradation of heme to carbon monoxide, iron, and biliverdin.[108] Balstad et al.[109] reported a time- and dose-dependent induction of Nrf2 by curcumin in HepG2

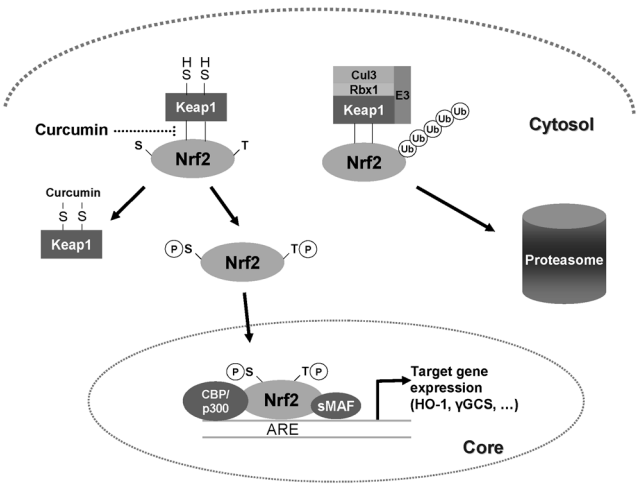


Figure 4. Schematic illustration of the Keap1–Nrf2 signaling pathway. Nrf2 is a transcription factor that regulates the gene expression of antioxidant and phase II enzymes. In the basal form, Nrf2 is bound to its repressor Keap1 in the cytoplasm. The proteasomal degradation of the protein is initiated through the polyubiquitination of Nrf2 mediated by a Cul3/Rbx1/E3 ubiquitin ligase complex. In response to an inducer, such as curcumin, the binding between Keap1 and Nrf2 is disrupted, and the reactive cysteine in Keap1 is altered either by oxidation or covalent modification. Thereby, Nrf2 can translocate into the cell nucleus where it forms a heterodimer with the small Maf proteins and, together with the cofactor CBP/p300, binds to the ARE on DNA to induce expression of the target gene, such as HO-1. Moreover, the phosphorylation of Nrf2 at serine (S) and threonine (T) by various kinases, such as PI3K, PKC, JNK, and ERK, can facilitate the release of Nrf2 from Keap1. Modified from Refs. [250, 251].

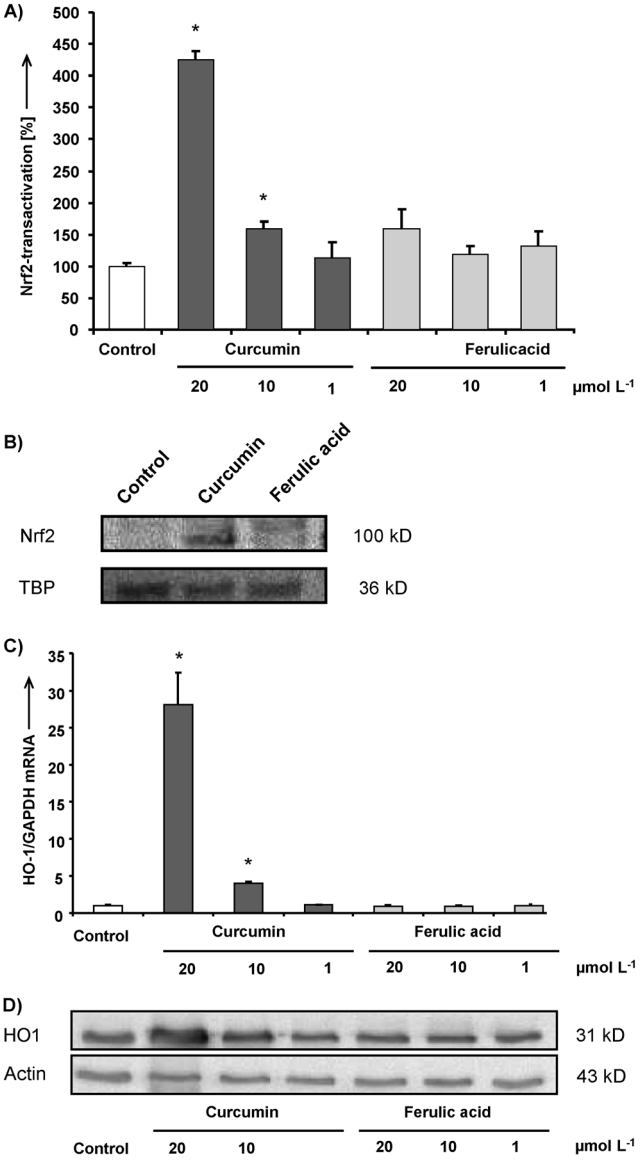


Figure 5. A) Nrf2 transactivation following 24 h incubation of transiently transfected NIH3T3 fibroblasts with curcumin (20, 10, and 1 μmol L^{-1}) and ferulic acid (20, 10, and 1 μmol L^{-1}) (mean + S.E.M.; two passages in triplicate, for the method, see Ref. [252]; $*p \leq 0.05$; Mann–Whitney U test). B) Nuclear Nrf2 protein levels in NIH3T3 fibroblasts following 6 h treatment with curcumin (20 μmol L^{-1}) and ferulic acid (20 μmol L^{-1}) as determined by Western blot analysis (for the method, see Ref. [253]). TATA-binding protein (TBP) was used as a loading control. C) HO1 gene, and D) protein expression following 12 h and 24 h incubation of NIH3T3 fibroblasts with curcumin (20, 10, and 1 μmol L^{-1}) and ferulic acid (20, 10, and 1 μmol L^{-1}) as determined by real-time PCR and Western blot analysis (mean + S.E.M.; two passages in duplicate, for the method see Ref. [252]; $*p \leq 0.05$; Mann–Whitney U test). Actin was used as the loading control in the Western blots.

hepatocytes in vitro. Moreover, in a transgenic mouse model that expresses luciferase in response to the activation of ARE, the authors demonstrated a time-dependent increase in Nrf2 transactivation after an intraperitoneal injection of curcumin.[109] Our studies with murine NIH3T3 fibroblasts also suggest that curcumin can activate Nrf2. In our experiments, the ability of curcumin and its monomer, ferulic acid, to induce Nrf2 activation was compared.[99] NIH3T3 cells were first transfected with an Nrf2-dependent luciferase plasmid. Subsequently, the cells were treated with different concentrations of curcumin (1, 10, 20 μmol L^{-1}) and ferulic acid (1, 10, 20 μmol L^{-1}). Curcumin led to a significant dose-dependent increase in Nrf2 transactivation compared to untreated cells. In comparison, ferulic acid treatment did not induce Nrf2 transactivation (Figure 5A).[99] These findings have been confirmed at the protein level. Curcumin led to a considerable increase in nuclear Nrf2 protein levels. Ferulic acid, on the other hand, did not change Nrf2 protein levels in the nucleus (Figure 5B).[99] In addition, the influence of curcumin and ferulic acid on the Nrf2 target gene HO1 was investigated. NIH3T3 fibroblasts were again treated with different concentrations of curcumin and ferulic acid. Curcumin treatment led to a significant dose-dependent increase in HO1 mRNA levels compared to untreated cells (Figure 5C).[99] The increase in HO1 mRNA results in a higher protein concentration of HO1 as shown in the corresponding Western blot (Figure 5D).[99] Conversely, treatment with ferulic acid did not induce HO1 mRNA or protein levels (Figure 5C,D).[99] Our data suggest that the cellular antioxidant effects of curcumin are not mediated by its monomer, ferulic acid. It appears that the biological effects are only exerted by the curcumin molecule form, that is, as a dimer of ferulic acid.

As well as inducing HO1, curcumin also induces the antioxidant enzyme paraoxonase 1 (PON1). PON1 is primarily synthesized in the liver and circulates in the blood bound to HDL.[110] PON1 prevents or slows down the oxidation of LDL and thus mediates anti-atherogenic effects.[111] The oxidation of LDL is considered to be a key event in atherogenesis. Principal substrates of PON1 are paraoxon and phenylacetate, which are used in enzyme activity assays. Figure 6 shows that curcumin dose-dependently mediated the induction of PON1 transactivation in Huh7 hepatocytes. Again, in contrast to curcumin, ferulic acid did not induce PON1.[99]

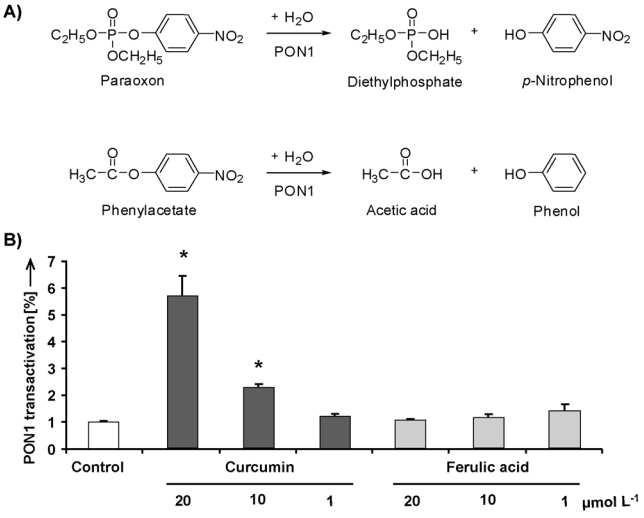


Figure 6. A) Hydrolysis of paraoxon and phenylacetate by paraoxonase 1. B) Dose-dependent induction of paraoxonase 1 transactivation in stably transfected human Huh 7 hepatocytes following incubation with curcumin (20, 10, and 1 μmol L^{-1}) and ferulic acid (20, 10, and 1 μmol L^{-1}; mean + S.E.M.; $n = 3$; $*p \leq 0.05$; ANOVA).

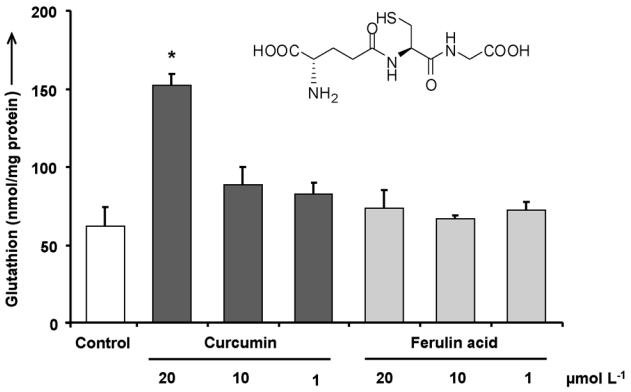


Figure 7. Glutathione concentration in Huh 7 hepatocytes following 24 h treatment with curcumin (20, 10, and 1 μmol L^{-1}) and ferulic acid (20, 10, and 1 μmol L^{-1}) (mean + S.E.M.; one passage in duplicate or triplicate; for the method, see Ref. [254]; $*p \leq 0.05$; univariate ANOVA after transformation (sqrt), Dunett post-hoc test).

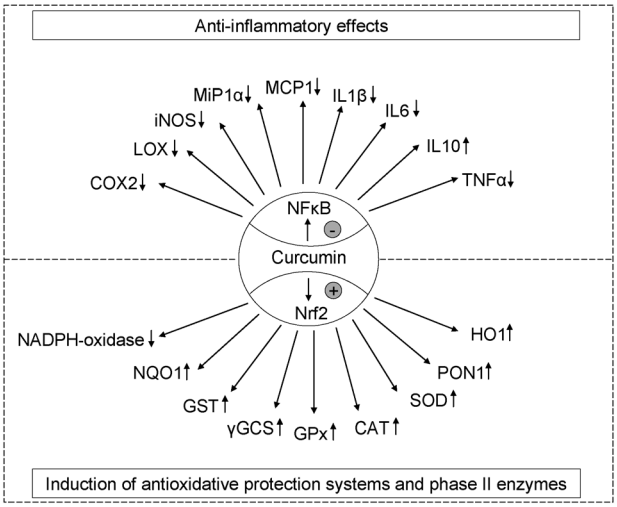


Figure 8. Biological activity of curcumin. The anti-inflammatory effects of curcumin are partly mediated through the inhibition of the transcription factor NFκB. The induction of antioxidant defense mechanisms and phase II enzymes is achieved by curcumin-mediated induction of Nrf2 signaling pathways.

Glutathione (GSH) is a tripeptide composed of glutamic acid, cysteine, and glycine, and is the most important cytosolic antioxidant.[112] The key enzyme in GSH biosynthesis is γ-glutamylcysteine synthetase (γGCS), which is in turn under the transcriptional control of Nrf2.[113,114] Similar to HO1[107] and PON1,[110] GSH is induced by curcumin,[115] but not by ferulic acid (Figure 7).[99] Besides the induction of antioxidant defense mechanisms, including HO1, PON1, and GSH as well as phase II enzymes[116] through Nrf2-dependent signaling pathways, curcumin also appears to mediate anti-inflammatory effects (Figure 8). The transcription factor NFκB plays a key role in curcumin-mediated anti-inflammatory effects.[117]

4.2. Nuclear Factor κB (NFκB) and the Anti-inflammatory Effects of Curcumin

Nuclear factor κB (NFκB) is a ubiquitously expressed eukaryotic transcription factor that is responsible for the regulation of numerous genes.[118] Five subunits have been described for NFκB: p50 (NFκB1), p52 (NFκB2), p55 (RelB), p65 (RelA), and c-Rel (Rel).[117] When NFκB is activated by stimuli such as bacterial lipopolysaccharides (LPS) or pro-inflammatory cytokines, it translocates to the cell nucleus and initiates the expression of a variety of target genes, such as TNFα and IL1β.[117] These pro-inflammatory molecules are partly involved in cell proliferation and tumorigenesis.[119,120] Cell culture studies have reported the inhibition of the transcription factor NFκB by curcumin.[121–127] Mackenzie et al. demonstrated that curcumin is taken up by H-RS cells (Hodgkin and Reed-Sternberg cell line) and inhibits the NFκB–DNA interaction as well as the expression of NFκB target genes.[127] The classical NFκB signaling pathway is shown in Figure 9.

Curcumin is a traditional remedy for inflammatory diseases.[128] The anti-inflammatory effects of curcumin have

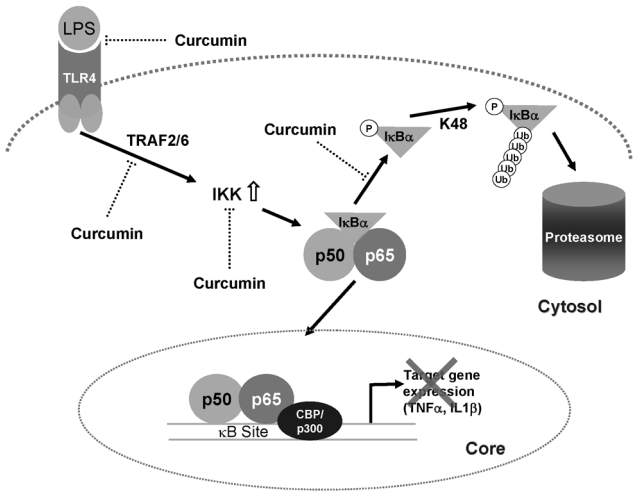


Figure 9. Schematic illustration of the classical NFκB signaling pathway. The classical NFκB signaling pathway can be activated by various stimuli, such as LPS. First, the adaptor proteins TRAF2 and TRAF6 are activated through which IKK is then activated. This consists of two catalytic subunits, IKKα and IKKβ, as well as the regulatory subunit, IKKγ/NEMO. Upon activation, IKK phosphorylates IκBα protein, which retains the p50/p65 heterodimer in the cytoplasm. While the p50/p65 NFκB dimer is released, the phosphorylated IκBα protein is polyubiquitinated on K48 and marked for proteaosomal degradation. The p50/p65 heterodimer then translocates to the nucleus where, together with the CBP/p300 cofactor, it binds to the κB site on the DNA and induces expression of target genes, such as TNFα and IL1β. The NFκB signaling pathway can be modulated at various points (dotted lines) by curcumin, causing a suppression of target gene expression. Modified from Ref. [255–257].

been postulated on the basis of a number of in vitro and in vivo studies.[6,129] Jancinova et al.[130] observed that curcumin dose-dependently increased the number of pre-apoptotic and apoptotic cells in PMA (phorbol myristate acetate) stimulated, isolated, human neutrophilic granulocytes (these constitute ca. 50–65% of white blood cells and play a central role in inflammation). Furthermore, curcumin dose-dependently increased caspase 3 activity. The authors also showed in a rat model of arthritis (an inflammatory arthropathy) that the application of curcumin significantly inhibited the activity of neutrophilic granulocytes, thus confirming curcumin's anti-inflammatory properties in vivo. Anti-inflammatory effects of curcumin have also been reported in the kidney. A curcumin injection in mice prior to an intraperitoneal LPS administration led to an inhibition of the LPS-induced increase in renal MCP-1 (monocyte chemoattractant protein 1) mRNA levels.[131] Mechanistic cell culture studies using the human renal epithelial cell line HK-2 showed that LPS-induced mRNA and protein levels of MCP-1 and interleukin 8 (IL8) were reduced by curcumin treatment. Furthermore, curcumin prevented LPS-induced NFκB–DNA binding. The authors therefore concluded that the anti-inflammatory effects of curcumin are partially mediated by the inhibition of NFκB–DNA binding, thereby decreasing MCP-1 gene expression.[131]

The Gram-negative bacterium *Helicobacter pylori* infects the stomach and is partly responsible for many gastroduodenal diseases, such as gastritis, gastric ulcers, and stomach cancer. The International Agency for Research on Cancer has classified *H. pylori* as a class I carcinogen.[132,133] Curcumin inhibits bacterial growth in both cultured cells[134,135] and in mice infected with *H. pylori*.[132,135] Possible explanations for this are reduced NFκB–DNA binding;[134] inhibition of the pro-inflammatory molecules MMP-3 (matrix metalloprotease 3) and MMP-9 (matrix metalloprotease 9); reduction in the levels of pro-inflammatory cytokines, such as TNFα (tumor necrosis factor 1α), IL1β (interleukin 1β), and IL8; or a reduction in iNOS (inducible nitric oxide synthase).[135] However, the bacteriostatic effect of curcumin could not be confirmed in humans.[136]

Bereswill et al.[137] showed that curcumin is potentially anti-inflammatory in a mouse model of ileitis (inflammation of the ileum). Studies by Murphy et al.[138] and Villegas et al.[139] reported similar findings. Acute ileitis was induced in mice by infection with *Toxoplasma gondii*. Subsequently, mice received 100 mg kg^{-1} body weight curcumin, per os (oral application), for up to 8 days after initial infection. In comparison with the placebo-treated animals, curcumin administration increased the number of regulatory T cells and reduced T lymphocytes and neutrophilic granulocytes in the ileum. Moreover, treatment with curcumin led to an increase in the anti-inflammatory cytokine interleukin 10 (IL10) and a decrease in the pro-inflammatory cytokines IL-23p19 (interleukin-23p19), IFNγ (interferon γ), TNFα, IL6, and MCP-1 in the mucosa of the ileum.[137] These findings are in accordance with those of Villegas et al.,[139] who showed that supplementation with 0.6% curcumin for 5 weeks in a mouse model of chronic colon inflammation reduced inflammation-associated colon carcinogenesis. The curcumin-supplemented mice also demonstrated reduced levels of the anti-inflammatory cytokines TNFα, IFNγ, cyclooxygenase 2 (*COX-2*), and iNOS.

Our own experiments with the murine monocyte cell line RAW264.7 confirm the anti-inflammatory effects of curcumin.[99] The cells were first stimulated with LPS to make them pro-inflammatory before being treated with different concentrations of curcumin and ferulic acid. Compared to LPS-stimulated controls, curcumin led to a dose-dependent reduction in the gene expression of the pro-inflammatory cytokine IL1β (Figure 10).[99] Conversely, ferulic acid, the monomer of curcumin, did not cause a reduction in IL1β mRNA levels compared to LPS-stimulated control cells. These results once again suggest that the anti-inflammatory effects of curcumin require it to be in its dimeric form and are not attributable to its monomer, ferulic acid.

4.3. Modulation of Epigenetic Mechanisms with Curcumin

Despite its relatively low bioavailability, curcumin may mediate health effects.[140] One possible explanation is, as a result of its hydrophobicity, curcumin accumulates intracellularly when ingested regularly. Another possibility is that curcumin influences epigenetic regulation of gene expression[142] which may occur at very low curcumin concentrations.[143] The term "epigenetic" describes an inheritable alteration in gene expression that does not arise from a modification in the DNA sequence.[144,145] Epigenetic

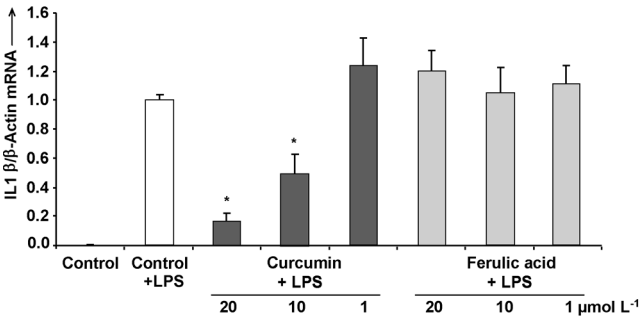


Figure 10. IL1β mRNA expression in lipopolysaccharide (LPS, 100 ng mL^{-1}) stimulated murine RAW264.7 macrophages following 6 h incubation with curcumin (20, 10, and 1 μmol L^{-1}) and ferulic acid (20, 10, and 1 μmol L^{-1}). The relative mRNA concentrations were determined using real-time qRT-PCR with respect to the β-actin mRNA concentration. The vehicle control (0.1% dimethylsulfoxide) plus LPS was set as 1. (Mean + S.E.M.; $n = 3$; $*p \leq 0.05$ compared with the control with LPS; ANOVA.)

modifications comprise changes in DNA methylation, histone modification, and microRNA expression, as illustrated in Figure 11.[144,146,147,158]

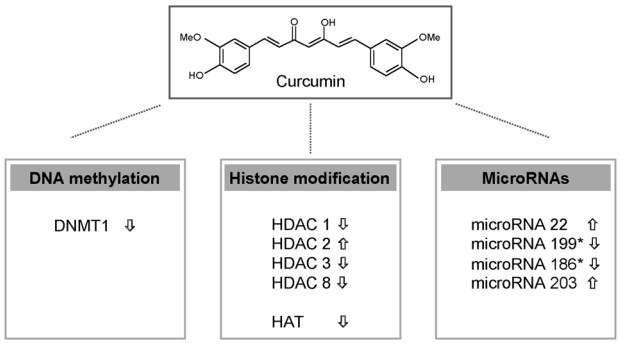


Figure 11. Curcumin as a putative epigenetic regulator. Curcumin modulates DNA methylation (through DNMT1), histone modification (through HDAC1, HDAC2, HDAC3, HDAC8, and HAT), and microRNAs (through microRNA 22, microRNA 199*, microRNA 186*, microRNA 203). Modified from Ref. [158].

4.3.1. *DNA Methylation*

DNA methylation is involved in the regulation of gene activity and forms the basis of chromatin structure. Compared to nontransformed cells, cancer cells often show an altered DNA methylation pattern in CpG islands.[148,158] Cancer cells may display genome-wide hypomethylation, promoter hypermethylation, or both.[146,158] Various DNA methyltransferases (DNMT1, DNMT3a, DNMT3b) are involved in the regulation of DNA methylation.[149,158] In 2009, Liu et al. demonstrated for the first time that curcumin can inhibit a DNMT1 analogue.[150,158] Curcumin has been identified as a competitive inhibitor of the catalytic center of DNMT1 in computer-based modeling studies.[151] However, in an earlier study, Medina-Franco et al. postulated that curcumin may only exhibit a weak DNMT1 inhibitory activity, if any.[152,158]

Using TRAMP mice, a model for prostate cancer, Barve et al. showed that dietary supplementation with 2% curcumin over 10 or 16 weeks led to a significant reduction in the development of tumors.[153] TRAMP mice express low mRNA and protein levels for the transcription factor Nrf2, which plays a central role in cellular antioxidant defense mechanisms.[154,155] In the tumorigenic cell line TRAMP-C1, Yu et al.[155] found five methylated CpG sites in a CpG island in the promoter region of the Nrf2 gene, while no methylation was observed in these sites in the non-tumorigenic cell line TRAMP-C3. The authors demonstrated that the methylation of this CpG island caused inhibition of the transcriptional activity of Nrf2. The hypermethylation of this CpG site in TRAMP-C1 cells was significantly reduced following treatment with curcumin.[156]

4.3.2. *Histone Modification*

Post-translational histone modification is also a mechanism of epigenetic modification and is neutrally involved in gene regulation as well as carcinogenesis.[157,158] Histones are components of chromatin. Chromatin is made up of nucleosomes, which are histones with a DNA strand wrapped around them. Some histones are also known as core histones. Histone modifications usually occur at the N terminus and either allow or prevent the binding of DNA-repair proteins and transcription factors on DNA.[158] Core histones can be post-translationally modified by acetylation, deacetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP ribosylation, and biotinylation.[157,158] Acetylation mediated by histone acetyl transferases leads to gene activation, whereas deacetylation by histone deacetylases results in the inhibition of gene expression.[159,160]

4.3.2.1. *Histone Deacetylases (HDACs)*

As a consequence of their sequence homology to yeast deacetylases, the 18 currently known human HDACs are classified into four groups.[158,161,162] HDAC1, -2, -3, and -8 belong to class I, while HDAC4, -5, -7, and -9 to class IIa. HDAC6 and -10 have been assigned to class IIb. Class III represents sirtuins 1–7, and class IV HDAC 11.[161,163] Various studies have shown that HDACS are dysregulated in cancer cells.[157,164] Thus, HDAC inhibitors are currently being investigated in various clinical studies for their application in cancer therapy.[165–167] Although curcumin did not inhibit HDAC activity in one in vitro study,[168] various other studies have identified it as an HDAC inhibitor.[169–172] Bora-Tatar et al. showed that curcumin treatment leads to a stronger HDAC inhibition in HeLa cells (epithelial cells from a cervical carcinoma) compared to the currently known HDAC inhibitors, valproic acid and sodium butyrate.[158,169] Liu et al. reported the inhibition of various class I HDAC proteins (HDAC 1, -3, -8) in Raji cells (B lymphocytes isolated from Burkitt's lymphoma) incubated with curcumin, which led to an increased acetylation of histone 4.[158,170] Chen et al. also demonstrated that curcumin dose-dependently inhibited HDAC1 and HDAC3 in Raji cells. HDAC2 plays a central role in the anti-inflammatory effects of corticosteroids.[158,171]

Patients with chronic obstructive pulmonary disease (COPD) have reduced HDAC2 activity, and this loss in activity correlates with the severity of the disease.[173] In a human monocyte cell line in which HDAC2 activity has been inhibited with cigarette smoke and oxidative stressors, enzyme activity could be restored by incubation with curcumin.[158,173] This shows that depending on the type of HDAC, curcumin can either exert inhibitory or stimulatory effects.

4.3.2.2 Histone Acetyltransferases (HATs)

HATs acetylate lysine residues on histones by transferring acetyl groups from acetyl-CoA onto lysine.[158] To date, numerous nuclear HATs have been identified. On the basis of their primary sequence homology, they have been assigned to four main families: Gcn5/PCAF (general control nonrepressed protein 5 and p300 associated and CBP-associated factor), MYST (which stands for the founding members of this class: MOZ, Ybf2/Sas3, Sas2, and Tip60), p300/CBP (300 kDa protein and CREB-binding protein), and Rtt109 (regulator of Ty1 transposition gene product 109).[174] Many studies have described curcumin as a potent HAT inhibitor.[26,158,168,175,176] Balasubramanyam et al. showed in in vivo and in cell culture studies with HeLa cells that curcumin can specifically inhibit p300/CBP HAT activity.[175] Morimoto et al. also demonstrated that curcumin inhibits p300/CBP HAT activity in rat primary cardiomyocytes. In addition, the authors observed that curcumin (50 mg kg^{-1} per day over 6 weeks) protected against heart failure in rats by acting as a specific inhibitor of p300/CBP HAT.[158,176] In Hep3B hepatocytes, curcumin treatment led to a dose- and time-dependent reduction in histone acetylation. In vitro assays have also indicated that curcumin inhibits HAT activity directly.[168]

4.3.3. MicroRNAs

MicroRNAs are evolutionarily conserved small noncoding RNAs that are approximately 22 nucleotides long. They can modulate the expression of many target genes post-transcriptionally and are thus involved in numerous cellular processes.[177–179] MicroRNAs are involved in the regulation of the cell cycle, apoptosis, cell differentiation, carcinogenesis, metastasis, and angiogenesis.[180] It is thought that approximately 50% of the protein-coding genes are under the influence of microRNAs. Approximately 800 microRNAs are expressed in humans, which is similar to the number of known transcription factors and RNA-binding proteins.[181]

Sun et al. showed, using microarray analysis, that curcumin treatment can lead to the up-regulation of microRNA 22 and down-regulation of microRNA 199* in human pancreatic carcinoma cells.[158,182] A genome-wide search using biotransformatics tools identified estrogen receptor 1 (ESR1) and the transcription factor SP1 as putative targets of microRNA 22. Through antisense experiments, the authors found that the inhibitory effect of curcumin on ESR1 and SP1 is mediated through microRNA 22. Curcumin treatment of A549/DDP multidrug-resistant human lung adenocarcinoma cells promoted apoptosis. Zhang et al. showed that this curcumin-induced apoptosis is mediated through microRNA 186* dependent signaling pathways. Curcumin caused a significant down-regulation of microRNA 186*.[158,183] Sani et al. observed that curcumin treatment induced the tumor suppressive microRNA 203 in bladder cancer cells. It has been suggested that the specific inhibition of microRNAs by curcumin may be a potential therapeutic approach for the treatment of cancers.[158]

4.4. Anticarcinogenic Effects of Curcumin

Several studies have described anticarcinogenic and chemopreventive effects of curcumin. These anticarcinogenic and chemopreventive effects are attributed directly or indirectly to curcumin-regulated signal transduction pathways. It has been shown that curcumin exerts its potential anticarcinogenic effects by influencing the cell cycle,[184] p53 (tumor suppressor gene), and various transcription factors (such as Nrf2 and NFκB); by modulating inflammatory signaling cascades; and by inducing apoptosis.[185] Interestingly, evidence suggests that the metabolite of curcumin, tetrahydrocurcumin, also possesses anticarcinogenic properties.[186]

4.4.1. p53-Dependent Signaling Pathways

The tumor suppressor protein p53 acts as a transcription factor and regulates numerous target genes, for example, *p21Cip1* and *Bax*,[184,187,188] as well as microRNAs, such as miR-34, miR-192, and miR-145,[189]under cellular stress. As a consequence of its central role in the regulation of the cell cycle, p53 is an important tumor suppressor protein.[184,190] In response to DNA damage, p53 can arrest the cell cycle and/or induce apoptosis.[190] Choudhuri et al. showed that curcumin induces apoptosis in the human breast carcinoma cell line MCF-7 by a p53-mediated increase in Bax protein expression.[184,191] In another study, Choudhuri et al. demonstrated that treatment of tumor cells with curcumin led to an increase in p53 levels in the G2 phase of the cell cycle.[158,192] The elevated p53 levels in turn led to the increased expression of pro-apoptotic Bax. This caused the release of cytochrome c (Cyt C) from mitochondria, which is necessary for apoptosis. Experiments with p53-null, dominant negative cancer cells transfected with wild-type p53 have confirmed that curcumin induces apoptosis through a p53-dependent pathway. However, treatment of normal epithelial cells with curcumin led to cell-cycle arrest in the G0 phase. This was probably caused by an increase in a cell-cycle arresting protein (p21Waf-1) and the simultaneous decline in cyclin D1 which together might have protected epithelial cells from a curcumin-induced apoptosis that normally occurs in the G2 phase.[184,192]

4.4.2. p53-Independent Signaling Pathways

Bharti et al. treated human multiple myeloma (bone marrow cancer) cells with curcumin.[123,184] NFκB is constitutively active in multiple myeloma cells. Treatment with

curcumin reduced NFκB–DNA binding and prevented nuclear retention of p65. Curcumin was found to down-regulate IκB kinase, which led to the inhibition of the phosphorylation of NFκB inhibitor α (IκBα). Moreover, the authors observed that curcumin treatment was associated with an inhibition in the expression of the NFκB target genes IκBα, B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xl), cyclin D1, and interleukin 6 (IL6). This led to the suppression of proliferation and a cell-cycle arrest at the G1/S phase. Curcumin treatment also activated the expression of caspases 7 and 9, thus indicating a possible induction of apoptosis. Further indication that apoptosis was triggered by curcumin was the increased cleavage of poly(ADP-ribose) polymerase (PARP) following curcumin treatment. All these factors made the multiple myeloma cells more sensitive to chemotherapeutic agents.[123,184] Treatment of the immature B-lymphoma cell line BKS-2 with curcumin suppressed proliferation, but this was not observed in healthy B lymphocytes treated with curcumin. Furthermore, there was a time- and dose-dependent increase in the rate of apoptosis in the BKS-2 cells.[193] Curcumin treatment of these cells resulted in a marked reduction in the mRNA levels of the survival genes egr-1, c-myc, and bcl-xl, as well as the tumor suppressor gene p53.[193] The authors showed that curcumin also significantly reduced NFκB–DNA binding in BKS-2 cells. In addition, by using B lymphoma cells, Shishodia et al. showed that active NFκB and IκB kinase are constitutively expressed in these malignant cells, thereby causing the over-expression of NFκB target genes, such as IκBα, bcl-2, bcl-xl, COX2, and cyclin D1. Down-regulation of the constitutively active NFκB, inhibition of the phosphorylation of IκBα, and reduction in IκB kinase activity were observed after incubation of various B-lymphoma cell lines with curcumin. Additionally, curcumin suppressed phosphorylation of the p65 subunit of NFκB, thus preventing its translocation into the nucleus. The NFκB target genes IκBα, Bcl-2, Bcl-xl, COX2, and cyclin D1 were also down-regulated at the mRNA level.[125,184] Anto et al.[194] as well as Mukhopadhyay et al.[195] showed that curcumin induced apoptosis in the HL-60 human leukemia cell line and in DU145 and LNCaP human prostate cancer cells through the activation of caspases 3 and 8. Shishodia et al. also demonstrated a curcumin-induced activation of caspases 3, 7, and 9 in B-lymphoma cells.[125,184] Moreover, incubation of these cells with curcumin led to the induction of PARP, a protein family that recognizes DNA strand breaks and is involved in various cellular processes such as DNA repair and the maintenance of genetic integrity.[196]

4.5. Curcumin and Neuroprotection: Molecular Mechanisms and Experimental Data

4.5.1. Availability in the Brain

Potential health benefits of curcumin are possibly limited because of its relatively low oral bioavailability. However, by virtue of its lipophilicity, curcumin is able to permeate the blood–brain barrier and may, therefore, reach brain tissue in biologically effective concentrations. The maximum curcumin concentration in the brain occurs 20–60 minutes after either intraperitoneal or intravenous administration (100 mg kg^{-1} body weight) in laboratory rodents.[42,63] As a result of its rapid metabolization, curcumin is no longer detectable after 2 h.[197] Short-term administration of a high dose of curcumin to laboratory mice in the diet (100 mg kg^{-1} diet) did not lead to a significant enrichment of curcumin in brain tissue.[63] In another study, a curcumin concentration of approximately 1.5 μmol kg^{-1} could be detected in the brain of mice after long-term (four months) curcumin supplementation (500 and 2000 mg kg^{-1}).[198] Therefore, it is possible that curcumin can, to some extent, be enriched in the brain by long-term supplementation to exert potential neuroprotective effects.

4.5.2. Neuroinflammation

In addition to neurons, the brain is also comprised of glial cells, which are subdivided into micro- and macroglia (e.g. astrocytes). Microglia are macrophages and the primary immune cells in the brain. Astrocytes are responsible for a balanced electrolyte and neurotransmitter milieu in the vicinity of neurons, supplying the neurons with energy and supporting neuronal functions. Latent microglia can be activated and the inflammation cascade triggered, particularly through the NFκB pathway, in response to various stimuli (e.g. bacterial and viral infections, hypoxia/ischaemia resulting from infarctions, and neurodegenerative diseases, such as Alzheimer's dementia). The release of pro-inflammatory cytokines, such as TNFα and IL1β, is thought to facilitate astrogliosis, during which astrocytes are also activated and the inflammatory response in the brain aggravated.[199–201] Chronic inflammation results in permanent alterations in neuronal metabolism (energy balance, neurotransmitter production, cytoskeletal structure), thereby triggering neurodegeneration.[202] The term neuroinflammation describes the activation of microglia and astrocytes that can lead to increased neuronal death. The dysregulated interaction of activated glial cells and neurons plays a central role in the pathogenesis of Alzheimer's dementia (AD), which is why many cell culture studies and animal experiments have been carried out to examine the effect of curcumin on neuroinflammation in AD relevant models.

Curcumin inhibits the release of pro-inflammatory cytokines and prostaglandins in stimulated astrocytes and microglia in vitro. The mRNA levels of COX2 and iNOS as well as the activation of transcription factors, such as NFκB, were significantly reduced after incubation with curcumin.[203,204] Curcumin supplementation was also shown to significantly attenuate mRNA and protein levels of IL1β and iNOS in laboratory mice, leading to a striking improvement in cortical brain structure and a reduction in the characteristic features of AD pathology.[198,205] Furthmore, LPS-induced activation of microglia and subsequent expression of iNOS and NADPH oxidase (NOX) have been shown to be inhibited in vivo by curcumin. Neuronal axon damage, associated with microglial activation in the brain, has also been reduced by curcumin treatment.[206]

Nonsteroidal anti-inflammatory drugs (NSAID), such as ibuprofen, which act against neuroinflammation,[207] suppress prostaglandin synthesis by the nonspecific inhibition of COX1

and COX2 enzymes. Similarly, curcumin appears to reduce the production of prostaglandins by limiting the availability of their precursor, arachidonic acid, through the reduced phosphorylation of cytosolic phospholipase A2 (cPLA2).[208] The exact mechanisms of the anti-inflammatory effects of curcumin in the brain remain elusive. However, altered phosphorylation patterns and activation of particular kinases, such as the MAP kinases, ERK and MEKK1–JNK or JAK–STAT, have been discussed.[208,209] Reduced phosphorylation of IκB also appears to play a central role in the anti-inflammatory effects of curcumin in the brain.[121] Furthermore, there is evidence suggesting that curcumin stimulates the transcription factor PPARγ (peroxisome proliferators activated receptor γ) to counteract inflammation in glial cells.[203]

4.5.3. *Excitotoxicity*

There are various receptors for the neurotransmitter glutamate in the brain, one of them being the *N*-methyl-D-aspartate (NMDA) receptor. Activation of the NMDA receptor results in the transmission of excitatory signals between neurons. One important consequence of this is the opening of voltage-dependent calcium channels such that intracellular calcium concentrations in neurons are elevated. Excessive activation (overstimulation) of the NMDA receptor leads to excitotoxic effects which are associated with the neurodegenerative alterations in AD, epilepsy, and stroke. During excitotoxicity, there is a massive increase in intracellular Ca^{2+} concentration and increased activation of calcium-dependent enzymes, such as protein kinases, phospholipases, and calpains.[210,211] This results in the depolarization of the mitochondrial membrane, the accumulation of toxic radicals, and the activation of caspases.[212,213] Numerous in vitro studies have shown that curcumin represses NMDA receptor-mediated Ca^{2+} overload and protects neurons from excitotoxicity.[214–217] Curcumin modulates protein kinase C activity, thus reducing NMDA receptor phosphorylation and activation.[216,218] Curcumin has also been shown to reduce the calcium-dependent activation of caspases.[218] Excitotoxic activation of neuronal NOS (nNOS) results in increased intracellular NO levels and production of reactive nitrogen species, such as peroxynitrite ($ONOO^-$).[211,219] Curcumin prevents nNOS induction[214] and protects against peroxynitrite-induced neuronal death in vitro.[220] In addition, our own studies have shown that curcumin prevents hydrogen peroxide induced neurotoxiciy in Neuro2-A cells (Figure 12).[99] However, it should be taken into account that the curcumin concentrations applied in cell culture studies (up to 20 μmol L^{-1}) are supraphysiological compared to those found in the brain. Neuroprotective effects could not be observed at lower curcumin concentrations.[216–218] As a result of its low bioavailability, the possible neuroprotective effects of curcumin in vivo are questionable and require further clarification.

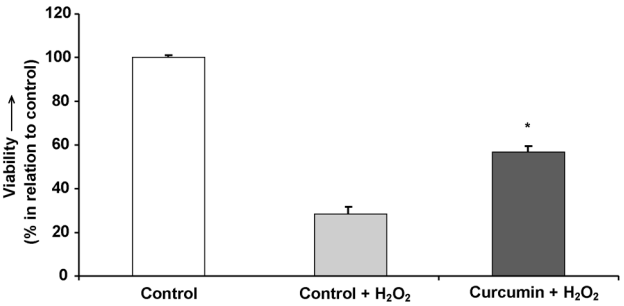


Figure 12. Neuroprotective effects of curcumin in terms of hydrogen peroxide induced cytotoxicity. Preincubation (24 h) of a neuronal cell line (Neuro-2a) with curcumin (20 μmol L^{-1}) in the presence of hydrogen peroxide (700 μmol L^{-1}) increases cell viability compared with cells only treated with hydrogen peroxide. The viability of the Neuro-2a cells was analyzed by using the Neutral Red assay following 2 h incubation with the agonists. The results are expressed as % absorption ($\lambda = 540$ nm) of the control cells (untreated). (Mean + S.E.M.; $n = 6$; $^*p \leq 0.05$ compared with the H_2O_2 treated control; t test.)

4.5.4 *Mitochondrial Dysfunction and Oxidative Damage*

Intracellular Ca^{2+} overload following excitotoxic signals is associated with mitochondrial dysfunction in neurons. The rapid rise in intracellular Ca^{2+} permeates into the mitochondria, where it inhibits complexes of the respiratory pathway, reduces ATP generation, and increases the production of reactive oxygen species. The depolarization of the mitochondrial membranes leads to the destabilization and release of mitochondrial proteins, such as Cyt c, into the cytosol. Curcumin reduces oxidative mitochondrial damage and prevents the release of Cyt c in primary neurons.[221] It has been shown in animal models that curcumin stabilizes the mitochondrial membrane potential and thus enhances membrane integrity. The stress-induced loss of activity in complexes I–IV of the respiratory chain and reduced ATP production are normalized by curcumin.[222–224] Oxidative damage can likewise contribute to mitochondrial dysfunction. It has been shown that curcumin may protect the brain against lipid peroxidation and the depletion of glutathione levels. Moreover, application of curcumin increases the activity of antioxidant enzymes (catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx)).[222–224]

4.5.5. *Ischaemia/Hypoxia*

Neuronal energy metabolism is oxygen- and glucose-dependent, and can not cope with hypoxic or hypoglycemic periods. A drop in either the oxygen or glucose concentrations in the brain inevitably leads to loss of neuronal function. Ischaemia results from a deficiency in the blood supply to the brain, or areas of the brain, as occurs in stroke. The consequences of ischaemia are excessive mitochondrial production of reactive oxygen species, a rise in intracellular Ca^{2+} levels through the activation of the NMDA receptor, stimulation of astrocytes, and neuronal death.[225,226] Evidence from animal models suggests that curcumin can protect against ischaemic damage. Besides containment of the injured area in the brain, curcumin can reduce oxidative damage and

mitochondrial dysfunction, as well as inhibit neuronal apoptosis and microglial activation.[222,227–229] During and after ischaemia, more leukotrienes and other inflammatory agents, such as cytokines, are produced which facilitate the infiltration of leukocytes. Proteolytic enzymes from the recruited leukocytes disintegrate the blood–brain barrier, and this results in edema in the damaged brain tissue.[225] The administration of curcumin to laboratory rodents may counteract edema and maintain the integrity of the blood–brain barrier.[230,231] In addition, in behavioral experiments, a significant improvement in cognitive performance has been observed in curcumin-treated animals compared to untreated ischaemic controls.[222,231,232] Interestingly, curcumin is able to provide significant protection from the harmful effects of ischaemia, irrespective of the route of its administration (intraperitoneal injection, gavage, or dietary supplementation).[232,233]

Despite the breadth of data available on the potential anti-ischaemic effects of curcumin in animal models, studies in humans are scarce. In fact, a possible therapeutic application of curcumin in stroke and ischaemia cases is under controversial discussion. On one hand, curcumin and its synthetic derivatives (CNB-001) are regarded as potential neuroprotectants on the basis of epidemiological observations and preclinical data.[234,235] However, a daily intake of high concentrations of curcumin would be required to achieve comparable levels to those used in animal models.[235]

4.5.6. *Alzheimer's Dementia*

Alzheimer's dementia (AD) is a multifactorial neurodegenerative illness that involves substantial neuronal loss. The central histological traits of AD are extracellular deposits of amyloid β peptide (Aβ plaques) and intracellular neurofibrilary tangles of hyperphosphorylated Tau protein.[236,237] AD is also associated with chronic inflammation, excitotoxicity, oxidative damage, and mitochondrial dysfunction.[238,239] As a consequence of its potential anti-oxidative, anti-inflammatory, and anti-excitotoxic effects, curcumin may be considered a promising therapeutic agent in the treatment of AD. Animal models show that curcumin not only reduces the extent of inflammation and oxidative damage, but also reduces the density of Aβ plaques and Aβ concentrations in the brain.[205,240,241] Curcumin appears to prevent the aggregation of Aβ peptide in vitro and assist in the clearance of existing aggregates.[242–244] NMR spectroscopic studies suggest that the aromatic carbon atoms adjacent to the hydroxy and methoxy groups of curcumin interact with the carbon atoms of the Aβ peptide.[245] It is also possible that curcumin inhibits the maturation of amyloid precursor protein and thereby prevents the production of Aβ in vitro.[246] However, the results of a placebo-controlled clinical trial involving patients with mild to intermediate AD are less clear-cut. The daily intake of curcumin (1–4 g per day over 6 months) had no significant effects on the serum concentrations of either amyloid β or F2 isoprostanes (surrogate marker for oxidative stress). However, the authors found a trend towards increased serum Aβ levels, which they interpreted as a possible clearance of Aβ plaques from the brain.[247] Improvements in cognitive performance were not observed during the six month long trial. The discrepancies between the studies likely arise, at least in part, from the different effective concentrations of curcumin employed. Curcumin concentrations in humans were up to 1000-times lower than those used in cell culture or animal studies.

Figure 13 illustrates a summary of the potential neuroprotective effects of curcumin based on cell culture studies and animal experiments.

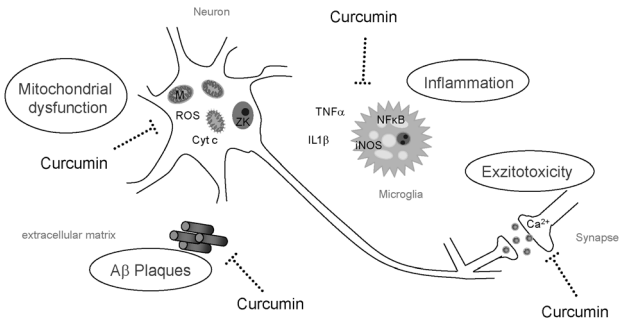


Figure 13. Summary of the potential neuroprotective effects of curcumin according to cell culture and animal model studies. Curcumin is an antioxidant and can protect neurons from increased reactive oxygen species (ROS) production, as occurs with mitochondrial dysfunction in ischemia. Curcumin protects against the loss of mitochondrial membrane integrity, and thus prevents the release of cytochrome c (Cyt c) into the cytosol and counteracts apoptosis. The extracellular aggregation of amyloid β (Aβ) is inhibited by curcumin, and the Aβ plaque density reduced. Excitotoxic effects are alleviated by curcumin through, for example, the inhibition of intracellular Ca^{2+} overload. Curcumin prevents the activation of microglia, by inhibiting the transcription factor NFκB. The expression of pro-inflammatory proteins, such as the inducible nitric oxide synthase (iNOS), is reduced by curcumin, and production of pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα) or interleukin 1β (IL1β), is lower. M: mitochondria; N: nucleus.

5. *Summary/Outlook*

Turmeric, or curcumin, has, to date, been utilized primarily as a spice and dye. In recent years, there has been mounting interest in the potential health benefits of curcumin. Many studies reporting the effects of curcumin have been carried out in cultured cells. The curcumin concentrations applied in cell culture studies are much higher than those found physiologically in vivo.

An important molecular switch through which curcumin may mediate its health benefits is the transcription factor Nrf2. Nrf2 orchestrates the expression of genes that encode antioxidant and phase II enzymes and also antagonizes NFκB, therefore also having an anti-inflammatory function. The induction of antioxidant defense mechanisms and phase II enzymes as well as the anti-inflammatory effects of curcumin probably play a central role in its neuroprotective, chemopreventive, and anticarcinogenic properties. Interestingly, Nrf2-dependent gene expression is repressed with age.[248,249] It would, therefore, be interesting to investigate systemati-

cally the possible role of curcumin in the context of healthy aging and the prevention of age-related diseases.

As curcuminoids generally have poor bioavailability, methods to increase their bioavailability have been established. In addition, there are attempts to supplement functional foods with curcumin. Curcumin itself has no or only very low toxicity. The intensive metabolism of curcumin in the intestines and by the liver, however, suggests that the organism strives to eliminate it efficiently. Therefore, it should be examined critically whether increasing the bioavailability of curcumin in foods or supplementing curcumin in high concentrations is indeed advisable.

The pharmacological effects of curcumin have been postulated on the basis of cell culture experiments and animal studies. As a result of the lack of clinical trial data, the efficacy of curcumoids as pharmaceuticals remains unclear. Recently, several phase II studies (intestinal, pancreatic, breast, rectal cancer) and one phase III study (pancreatic cancer) regarding the anticancerous effects of curcumin have begun in the USA. These studies are, however, far from completion (http://www.clinicaltrials.gov/ct2/results?term=curcumin, last accessed on 20.10.2011).

As for synthetic curcumin analogues, it remains to be seen if and to what extent these differ from natural curcuminoids with respect to their bioavailability and their pharmacological/toxicological effects.

Abbreviations

$ABTS^{+\bullet}$	2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)
AD	Alzheimer's dementia
ADI value	acceptable daily intake
ARE	antioxidant responsive elements
Bcl-2	B-cell lymphoma 2
Bcl-xl	B-cell lymphoma extra large
BW	body weight
CAT	catalase
CBP	CREB-binding protein
COPD	chronic obstructive pulmonary disease
COX2	cyclooxygenase 2
cPLA2	cytosolic phospholipase A2
Cul3/Rbx1	Cullin3-RING box1
Cyt c	cytochrom c
DNMT	DNA methyltransferase
DPPH	1,1′-diphenyl-2-picrylhydrazyl
ERK	extracellular signal-regulated kinase
ESR1	estrogen receptor 1
FRAP	ferric reducing antioxidant power
GPx	glutathione peroxidase
GSH	glutathione
GST	glutatione-*S*-transferase
γGCS	γ-glutamylcysteine synthetase
HAT	histone acetyl transferase
HDAC	histone deacetylase
HO1	hemeoxygenase 1
H-RS-Zellen	Hodgkin and Reed–Sternberg cells
i.v.	intravenous
i.g.	intragastric
i.p.	intraperitoneal
IFNγ	interferon-γ
IKK	IκB kinase complex
IL	interleukin
iNOS	inducible nitric oxide synthase
IκBα	NFκB inhibitor α
IκB	inhibitor of κB
JNK	c-Jun N-terminal kinases
Keap1	Kelch-like ECH associated protein 1
LOX	lipoxygenase
LPS	lipopolysaccharide
MCP-1	monocyte chemotactic protein 1
MIP1α	macrophage inflammatory protein 1α
MMP-3	matrix metalloprotease 3
MMP-9	matrix metalloprotease 9
MRP	multidrug resistance-related protein
n.d.	not determined
NEMO	NFκB essential modulator
NFκB	nuclear factor κB
NMDA	*N*-methyl-D-aspartate
nNOS	neuronal NOS
NOAEL	no observed adverse effect level
NQO1	NAD(P)H quinone oxidoreductase-1
NSAID	nonsteroidal anti-inflammatory drugs
ORAC	oxygen radical absorbance capacity
p300/CBP	300 kDa protein and CREB-binding protein
PI3K	phosphatidylinositol 3 kinase
PKC	protein kinase C
PLGA	poly(lactic-*co*-glycolic acid)
PMA	phorbol-12-myristate-13-acetate
PON1	paraoxonase 1
PPARγ	peroxisome proliferator activated receptor γ
Rtt109	regulator of Ty1 transposition gene product 109
SCF	scientific committee for food
SOD	superoxide dismutase
TBP	TATA-binding protein
TEAC	trolox-equivalent antioxidant capacity
TNFα	tumor necrosis factor α
TRAF	TNFα receptor associated factor

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