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Health Benefits of Curcumin

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Chapter

Chemical and Physical Properties, Pharmacokinetics, and Pharmacodynamics of Curcumin Derivatives

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Abstract

Curcumin derivatives (Curcuminoids) are a highly intriguing class of phytochemical compounds, widely discussed due to their presence as active ingredients in various pharmaceutical formulations and food supplements. There are three main compounds in curcuminoids: curcumin, desmethoxycurcumin, and bisdemethoxycurcumin. These compounds exhibit distinct chemical structures, which significantly influence their chemical and physical properties, pharmacokinetic profiles, and pharmacodynamic characteristics. From a pharmacokinetic perspective, curcuminoid-based formulations present unique challenges due to their poor water solubility and low permeability in the gastrointestinal tract (GIT). In terms of pharmacodynamics, curcuminoids interact with multiple receptor targets and enzymes, contributing to a wide range of pharmacological effects, including anti-inflammatory, antioxidant, and anticancer activities, among others. Therefore, this book explores in depth the chemical and physical properties of curcumin derivatives and their impact on pharmacokinetic and pharmacodynamic profiles.

Keywords: curcuminoid, curcumin, desmethoxycurcumin, bisdemethoxycurcumin, chemical–physical properties, pharmacokinetics, pharmacodynamics

1. Introduction

Curcuminoids belong to a class of secondary metabolites/phytochemical compounds, similar to other phytochemical groups such as flavonoids, alkaloids, and terpenoids. The biosynthetic pathway of curcuminoid compounds in Curcuma sp. [1, 2] originates from the primary metabolite L-phenylalanine (1), which undergoes deamination to form cinnamic acid (2). Cinnamic acid (2) serves as the starting material for the synthesis of coumaric acid (3), caffeic acid (4), and ferulic acid (5). Ferulic acid is synthesized from coumaric acid through the intermediate product, caffeic acid

(4). Both coumaric acid (3) and ferulic acid (5) are the main precursors in the formation of the curcuminoid framework. Coumaric acid (3) is converted by the enzyme 4CL (4-coumarate-CoA ligase) into the more reactive compound coumaroyl-CoA (6). Similarly, ferulic acid (5) is converted by the same enzyme into feruloyl-CoA (7), which is also a more reactive compound. Coumaroyl-CoA (6) and feruloyl-CoA (7) then react with the acid group from malonyl-CoA to form coumaroyl-diketide-CoA (9) and feruloyl-diketide-CoA (10) with the assistance of the enzyme DSC (diketide-CoA synthase). Coumaroyl-diketide-CoA (9) reacts with ferulic acid (5) to form demethoxycurcumin (10) with the help of the CURs (curcumin synthases) enzyme. Similarly, feruloyl-diketide-CoA (10) reacts with coumaric acid (3) under the action of CURs to produce demethoxycurcumin (10). If coumaroyl-diketide-CoA (9) reacts with coumaric acid (3), it forms bisdemethoxycurcumin (11), while feruloyl-diketide-CoA (10) reacts with ferulic acid (5) results in the formation of curcumin. Thus, the biosynthetic pathway of curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) is illustrated in **Figure 1**.

Curcuminoids are phytochemical compounds widely found in Curcuma species, such as *Curcuma longa* (Turmeric), *Curcuma xanthorrhiza* (Javanese Ginger), *Curcuma heyneana* (Javanese Giring Ginger), *Curcuma zedoaria* (White Turmeric), etc. [3]. There are three main compounds classified as curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin, whose chemical structures are presented in **Figure 2**.

The curcuminoid content in Curcuma species can serve as both an identity marker and a pharmacological activity marker. For example, extraction using 90% ethanol as a solvent from *Curcuma longa* (Turmeric) and *Curcuma heyneana* (Javanese Giring Ginger) contains three curcuminoids: curcumin, demethoxycurcumin, and

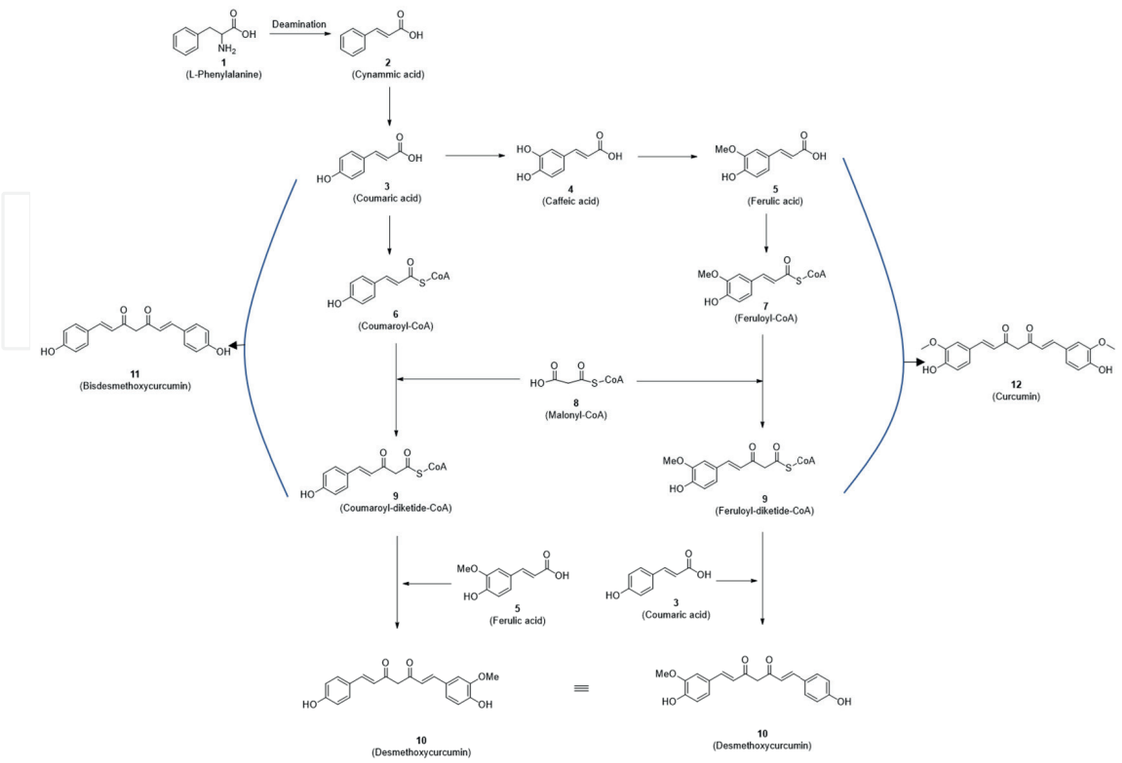

Figure 1.
Biosynthesis of curcuminoid (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) in Curcuma sp.

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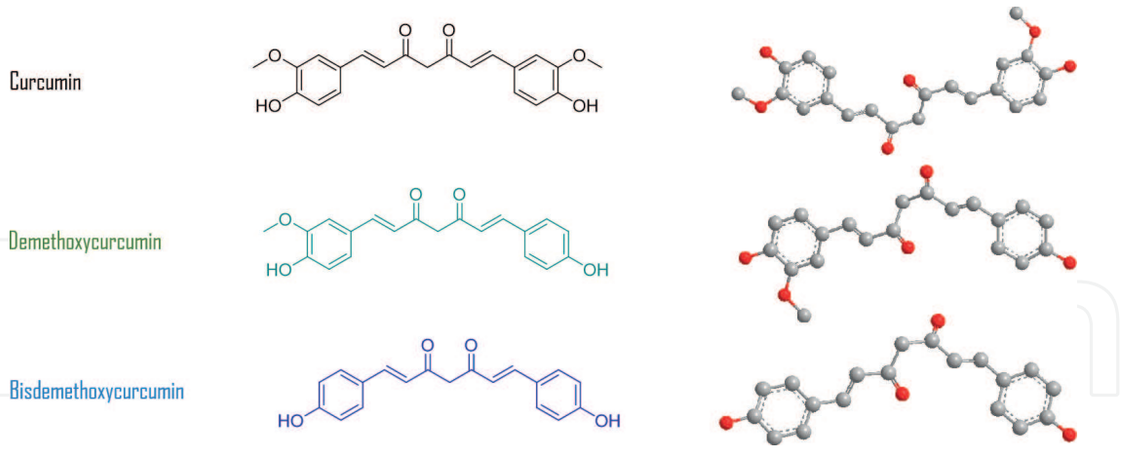


Figure 2.
2D and 3D chemical structure of curcuminoid (curcumin, demethoxycurcumin, and bisdemethoxycurcumin).

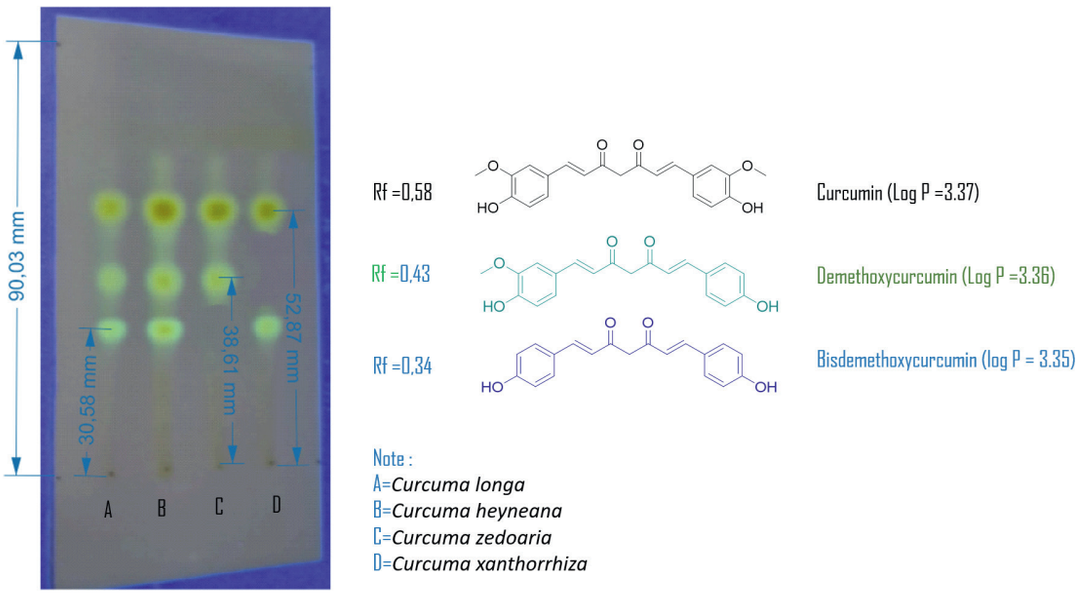


Figure 3.
TLC Profile of Curcuminoid under UV light at 366 nm, using a stationary phase of Silica Gel 60 GF 256 and a mobile phase of chloroform: ethanol: glacial acetic acid (94:5:1).

bisdemethoxycurcumin. However, extraction with 90% ethanol from *Curcuma xanthorrhiza* (Javanese Ginger) contains only two curcuminoids, there are curcumin and demethoxycurcumin. Similarly, *Curcuma zedoaria* (White Turmeric) also contains only two curcuminoids: curcumin and desmethoxycurcumin. These differences can be observed through Thin Layer Chromatography (TLC) under UV light at 366 nm, using a stationary phase of Silica Gel 60 GF 256 and a mobile phase of chloroform: ethanol: glacial acetic acid (94:5:1), as illustrated in **Figure 3** [4].

2. Chemical and physical properties of curcuminoids

The major phytochemicals of curcuminoids are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. The distinguishing factor among them is the presence or absence of methoxy groups. Methoxy groups are auxochromes that are nonpolar and

act as electron-donating groups, which can activate the benzene ring. The presence of methoxy groups significantly influences the chemical and physical properties of curcuminoids, including lipophilicity, solubility, melting point, antioxidant activity, and acidity [5–7].

2.1 Lipophilicity of curcuminoids (Log P)

The loss of one or two methoxy groups in curcumin results in distinct chemical and physical properties, which in turn lead to different pharmacokinetic and pharmacodynamic profiles. A simple example is the separation of curcumin (Log P = 3.369), demethoxycurcumin (Log P = 3.361), and bisdemethoxycurcumin (Log P = 3.353) using Thin Layer Chromatography (TLC) with a polar stationary phase, Silica Gel 60 GF 256, and a nonpolar mobile phase consisting of chloroform: ethanol: acetic glacial (94:5:1) due to their significantly different polarities [4, 8].

Methoxy groups are nonpolar, so the loss of methoxy groups increases polarity, leading to a lower Log P and a higher Log S compared to curcumin. As a result, the polarity ranking is bisdemethoxycurcumin > demethoxycurcumin > curcumin, whereas their lipophilicity follows the opposite trend: curcumin > demethoxycurcumin > bisdemethoxycurcumin [9].

This phenomenon causes bisdemethoxycurcumin to have the smallest Rf value (0.34) among the three, as its higher polarity allows stronger interactions with the stationary phase (silica gel), which contains silanol groups, as shown in **Figure 4**. In contrast, curcumin is more eluted by the nonpolar mobile phase, giving it the highest Rf value (0.58). This occurs because curcumin dissolves better in the nonpolar mobile phase due to the presence of two methoxy groups. Additionally, these two methoxy groups create steric hindrance between the silanol groups of the silica gel and the phenolic alcohol or beta-diketone groups in curcumin, weakening hydrogen bond interactions compared to bisdemethoxycurcumin (**Figure 4**).

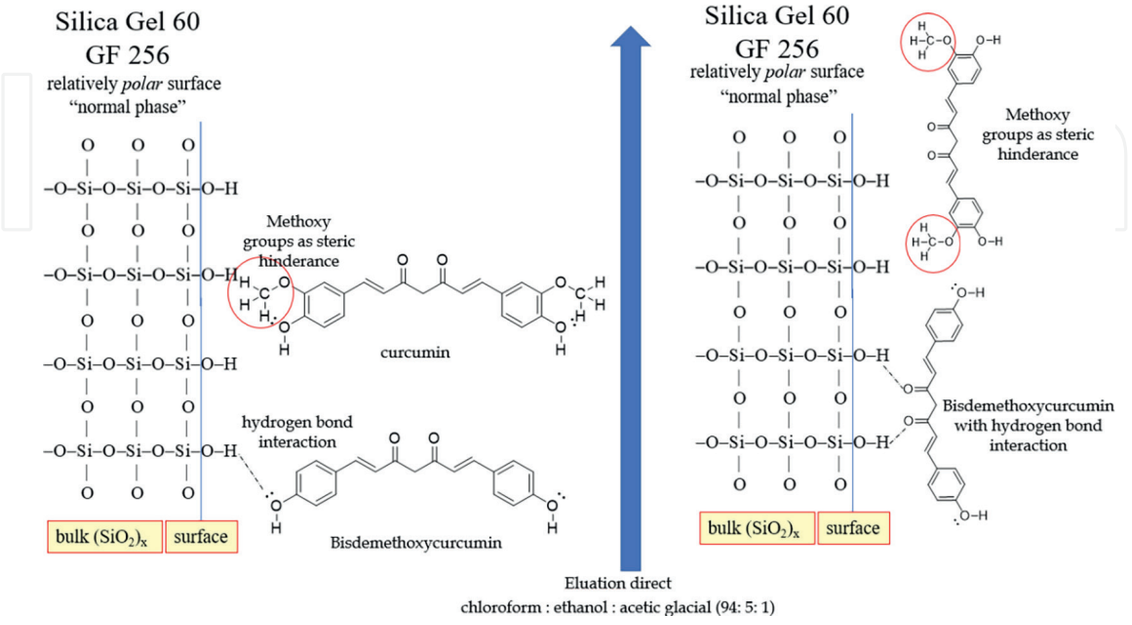


Figure 4.
Chemical bond interaction between curcuminoids with the stationary phase of Silica Gel 60 GF 256 and a mobile phase of chloroform: ethanol: glacial acetic acid (94:5:1).

2.2 Solubility of curcuminoids (Log S)

The solubility of curcuminoids in water falls under the classification of practically insoluble (<0.1 mg/mL). However, in terms of their relative solubility in water, bisdemethoxycurcumin (0.015 mg/mL) > demethoxycurcumin (6.56×10^{-3} mg/mL) > curcumin (3.5×10^{-3} mg/mL) [8]. The loss of two nonpolar (-OMe) groups allows bisdemethoxycurcumin to interact more easily with water molecules through hydrogen bonding compared to curcumin. The presence of nonpolar methoxy groups hinders water molecules from forming hydrogen bonds with the phenolic groups of curcumin due to steric hindrance, resulting in a solubility of approximately 3.5×10^{-3} mg/mL in water for curcumin, whereas bisdemethoxycurcumin has a solubility of about 0.015 mg/mL. This phenomenon is illustrated in **Figure 5**.

The presence or absence of methoxy groups also affects the Log S values of curcuminoids. Log S represents the logarithm of a compound's partition coefficient in water/octanol, indicating its solubility behavior: the higher the Log S (+) value, the more soluble the compound is in polar solvents (water) [10–12]. Conversely, a lower Log S (−) value indicates reduced solubility in polar solvents (water). The Log S values of bisdemethoxycurcumin (Log S = −4.23) > demethoxycurcumin (Log S = −4.34) > curcumin (Log S = −4.45), as bisdemethoxycurcumin can interact more readily with water molecules through hydrogen bonding compared to curcumin [11, 12].

Curcuminoids, which fall under the category of practically insoluble in water, require the use of solvents with higher solubility for the extraction process from Curcuma species. Researchers commonly use ethanol, acetone, or DMSO as extraction solvents due to their superior solubility properties. Curcuminoids exhibit solubility in 96% ethanol and acetone at approximately 33–100 mg/mL and are highly soluble in DMSO at concentrations >1000 mg/mL. This is because DMSO is a polar aprotic solvent known for its ability to effectively dissolve many organic compounds [13].

2.3 Melting point of curcuminoids

Curcumin has a melting point of 183°C, whereas bisdemethoxycurcumin has a melting point of 233°C [14–16]. The higher melting point of bisdemethoxycurcumin compared to curcumin is due to the absence of two methoxy groups, which facilitates the formation of stronger intramolecular hydrogen bonds. As a result, a higher amount of thermal energy is required to break these bonds and transition from the solid to the liquid phase. In contrast, curcumin has difficulty forming intramolecular

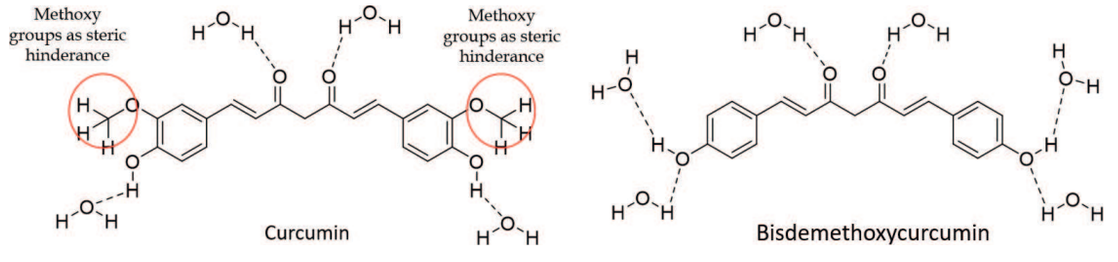


Figure 5.
Hydrogen bond interaction between curcuminoid and water.

hydrogen bonds due to the presence of two methoxy groups, which introduce steric hindrance, as illustrated in **Figure 6**. When ranked by melting point values, the order is: Bisdemethoxycurcumin > Demethoxycurcumin > Curcumin.

2.4 Antioxidant activity of curcuminoids

The antioxidant mechanism to counteract reactive oxygen species (ROS) consists of primary and secondary antioxidants [3, 17–18]. Primary antioxidants function to stop the formation of free radicals or capture free radicals before they cause further damage. The main mechanism of primary antioxidants is to scavenge free radicals and stabilize them by donating electrons without becoming reactive free radicals themselves or inhibiting the free radical chain reaction by converting free radicals into a less reactive form.

Secondary antioxidants work by supporting the function of primary antioxidants or deactivating free radical products that have already formed. Secondary antioxidants do not directly scavenge free radicals but inhibit oxidative reactions through various mechanisms. The main mechanisms of secondary antioxidants include chelating heavy metal transitions such as Cu^{2+}, Pb^{2+}, and Ni^{2+}, or regenerating primary antioxidants and breaking down ROS [3, 17–19].

Curcuminoid compounds exhibit both primary and secondary antioxidant activities. The primary antioxidant activity of curcuminoids occurs through free radical scavenging and stabilization via the resonance system present in their structure. Curcumin has the best resonance stability compared to bisdemethoxycurcumin and demethoxycurcumin because it possesses two methoxy groups, which act as Electron-Donating Groups (EDGs) that donate electrons to the conjugated system or aromatic ring [5–7]. The presence of two methoxy groups activates the aromatic ring, making it more ∂^- (partially negative), which aligns with the resonance system, thereby facilitating the release of hydrogen atoms from its two phenolic groups to neutralize ROS, as illustrated in **Figure 7**.

Additionally, the presence of two methoxy groups induces a latent polarity system (**Figure 8**) that aligns with the resonance system, allowing for more effective neutralization of ROS compared to bisdemethoxycurcumin and demethoxycurcumin [20, 21].

For this reason, curcumin exhibits a higher potential as an antioxidant compared to bisdemethoxycurcumin and demethoxycurcumin. When ranked by antioxidant potential, the order is as follows: Curcumin > Demethoxycurcumin > Bisdemethoxycurcumin.

Based on in vitro antioxidant activity assays using the DPPH method, it has been reported that the IC_{50} values are 4.7 μM for curcumin, 5.2 μM for

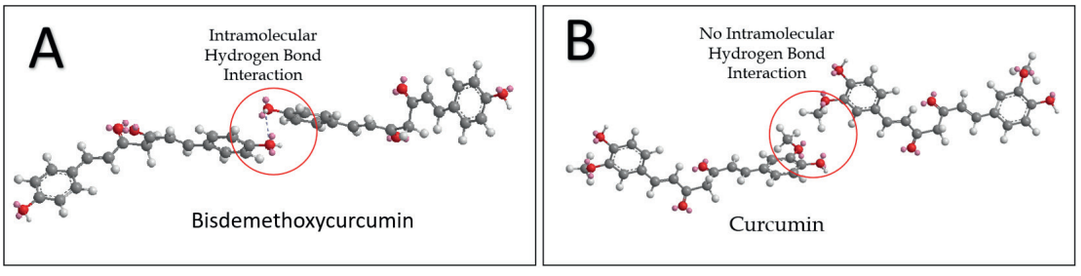


Figure 6.
Intramolecular hydrogen bond interaction: A. Bisdemethoxycurcumin; B. Curcumin.

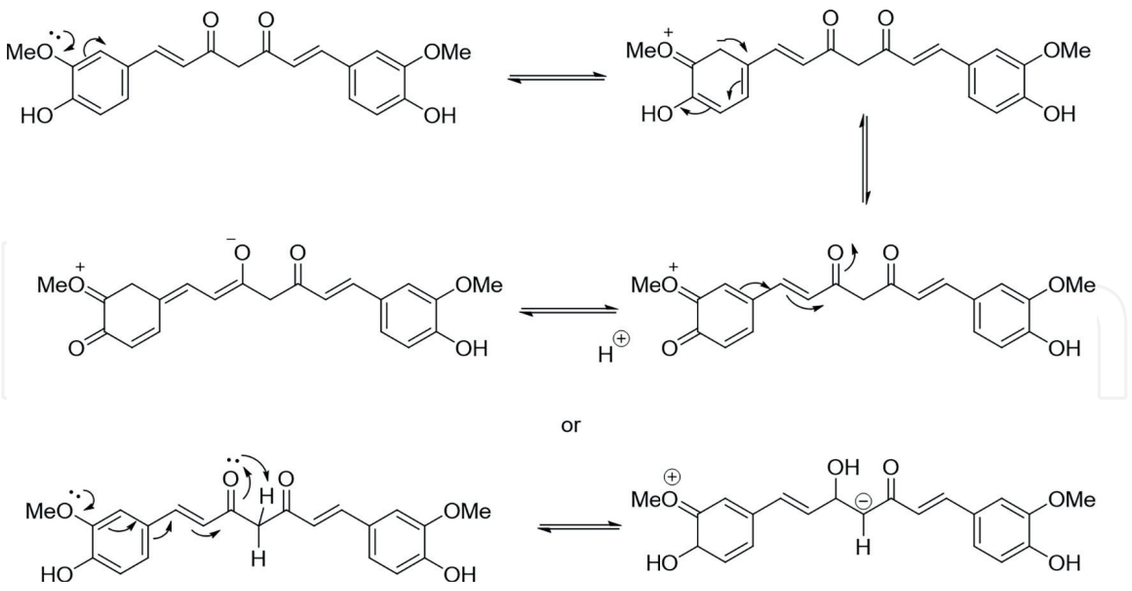


Figure 7.
Resonance system in the chemical structure of curcuminoid.

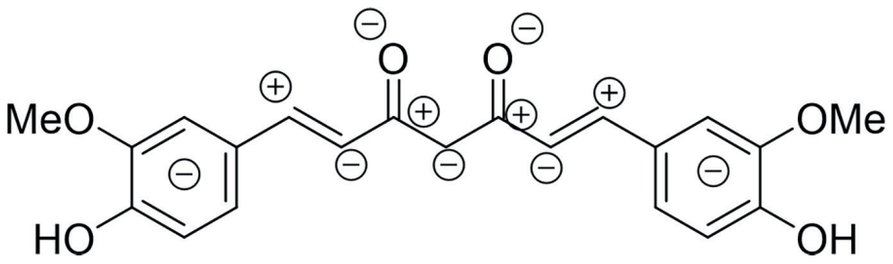


Figure 8.
Latent polarity in the curcuminoid system.

demethoxycurcumin, and 7.0 μM for bisdemethoxycurcumin [3, 17–19]. The process of free radical stabilization by curcumin is illustrated in **Figure 9**.

The secondary antioxidant activity of curcuminoids has been widely reported for their ability to chelate several heavy metal transition ions, such as Hg^{2+}, Pb^{2+}, Cu^{2+}, Ni^{2+}, etc. [19]. The presence of methoxy groups in curcumin induces a repulsion effect, creating space for chelating heavy metal transition ions, making the chelation process more stable compared to bisdemethoxycurcumin and demethoxycurcumin, as illustrated in **Figure 10**.

2.5 Acidity of curcuminoid (pKa)

The presence or absence of methoxy groups in curcuminoids leads to differences in pKa values. A lower pKa value indicates that a compound is more prone to protonation or the release of H+, meaning it exhibits stronger acidity [5–7]. The influence of methoxy groups on acidity can be observed in **Table 1**. Methoxy groups, classified as Electron Donating Groups (EDG), activate the aromatic ring, making the hydrogen atom on the phenolic group more easily dissociable [22]. This is evident in curcumin, where the presence of methoxy groups results in a phenolic hydrogen pKa value of 9.4, whereas in the absence of methoxy groups, the pKa value

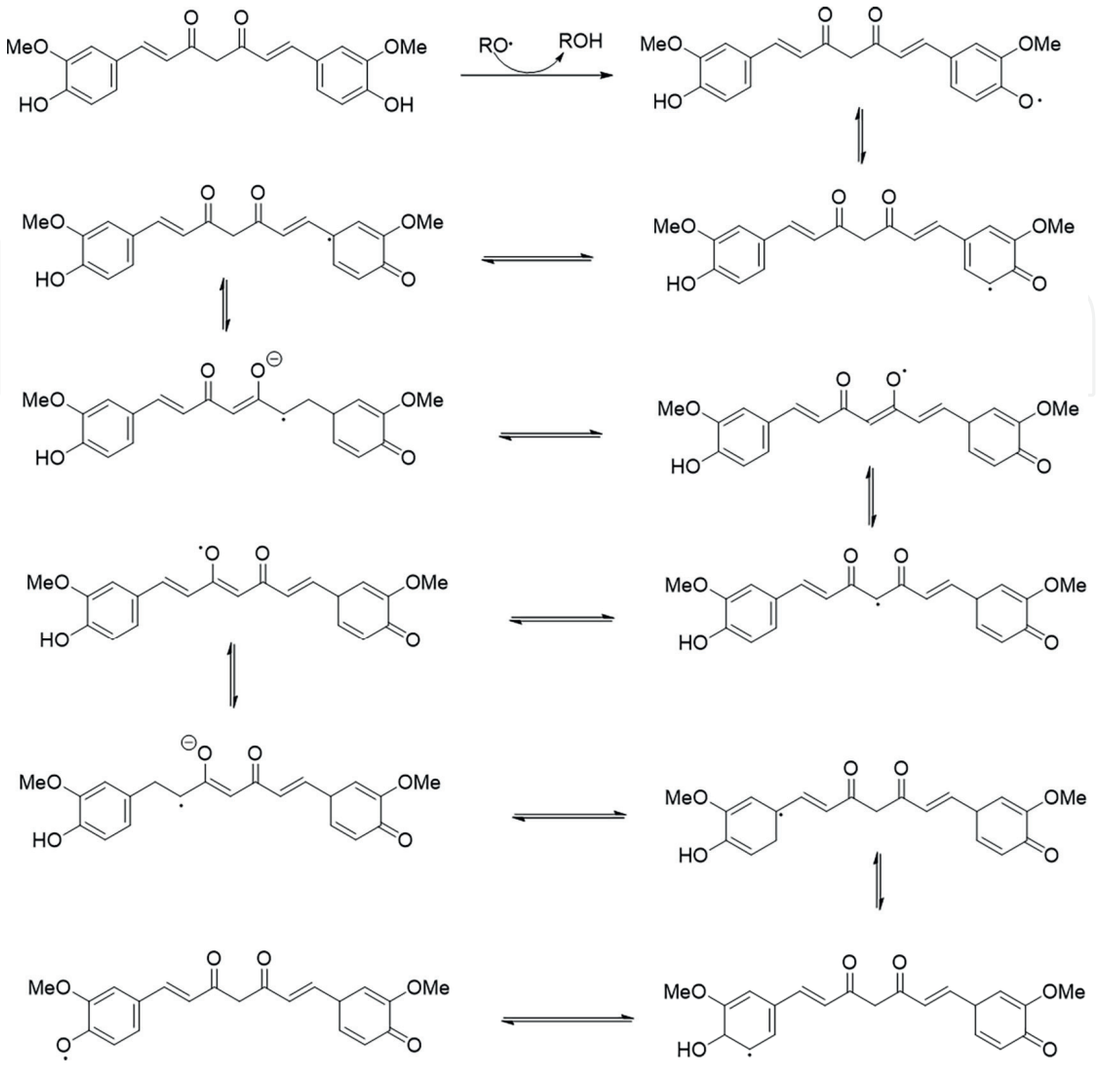


Figure 9.
Mechanism of Radical Oxygen Species (ROS) neutralization in the chemical structure of curcumin.

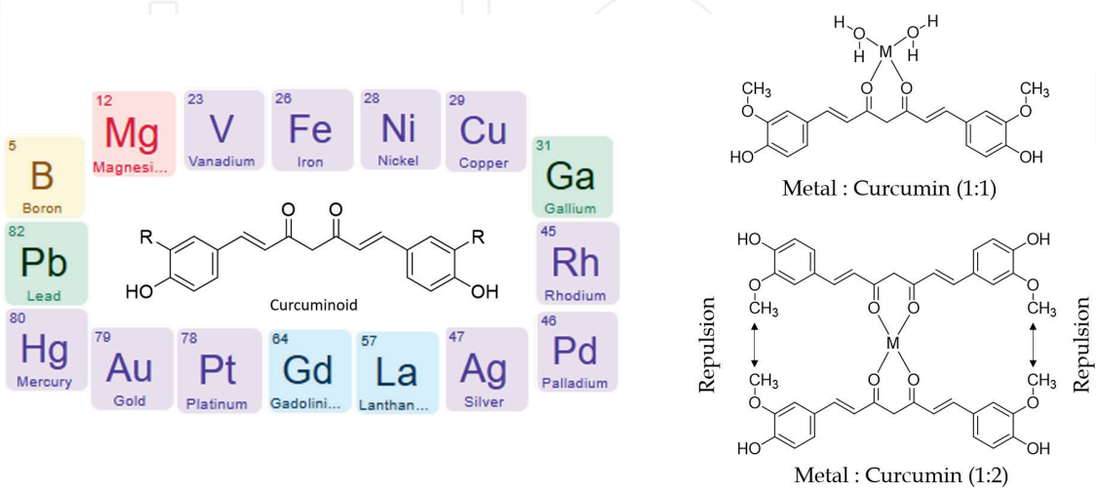


Figure 10.
Chelation process of curcumin with various metal elements.

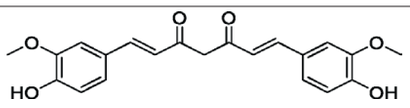
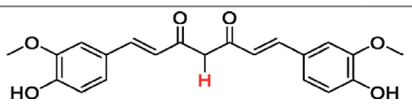
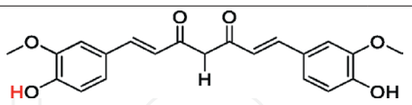
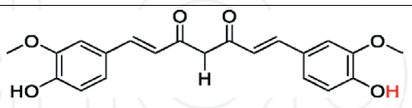
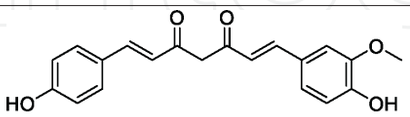
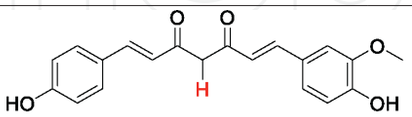
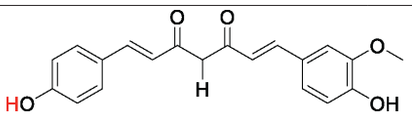
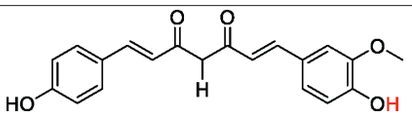
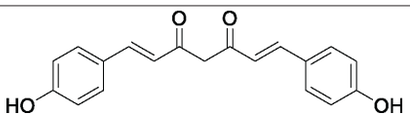
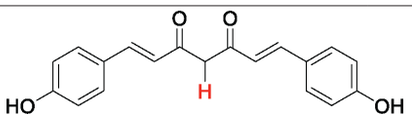
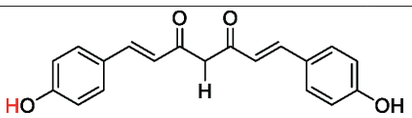
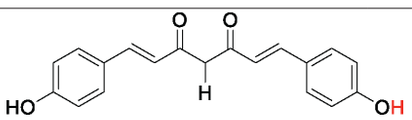
Compounds	H atoms position	pKa
 Curcumin		8.1
		9.4
		9.4
 Demethoxycurcumin		8.2
		9.6
		9.4
 Bisdemethoxycurcumin		8.3
		9.6
		9.6

Table 1.
pKa values of acidic hydrogen atoms.

of the phenolic hydrogen remains 9.4 [22]. The methoxy groups not only activate the benzene ring but also contribute to resonance effects within the diketone system, facilitating the dissociation of the α-hydrogen. This is reflected in the pKa values of curcumin (8.1), demethoxycurcumin (8.2), and bisdemethoxycurcumin (8.3). The overall resonance effects influenced by methoxy groups are illustrated in **Figure** 7.

3. Pharmacokinetics of curcuminoids

The differences in the chemical and physical properties of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, resulting from variations in their chemical structures, also impact their pharmacokinetic aspects, including absorption, distribution, metabolism, and excretion. These differences are discussed in detail one by one.

3.1 Absorption of curcuminoids

To determine how well curcuminoids are absorbed through the gastrointestinal tract (GIT), it is necessary to compare their water solubility and permeability data [10, 23]. Both of these factors play a crucial role in determining the Biopharmaceutical Classification System (BCS) category to which they belong. The water solubility and permeability data of curcuminoids are presented in **Table 2**.

Curcumin has poor water solubility (low solubility) and falls into the category of practically insoluble, with a solubility of <0.1 mg/mL. Its permeability is 4.87×10^{-6} cm/s, which is classified as low permeability since it is $<9.0 \times 10^{-6}$ cm/s [8, 24, 25]. Curcumin belongs to BCS Class IV because it has both low solubility and low permeability (**Figure 11**) [10]. BCS Class IV compounds exhibit very poor bioavailability when absorbed through the gastrointestinal tract (GIT). Several in vivo studies have shown that oral administration of a single 2 g dose of curcumin in Mus musculus resulted in plasma concentrations of less than 5 μg/mL, indicating poor absorption in the GIT [26].

The removal of one methoxy group from curcumin results in demethoxycurcumin. Since the methoxy group is nonpolar, its absence slightly increases water solubility to 6.56×10^{-3} mg/mL. However, the solubility of demethoxycurcumin is still classified as low solubility and remains in the practically insoluble category (<0.1 mg/mL) [10, 23]. The loss of one methoxy group significantly affects the permeability of demethoxycurcumin, which has a permeability value of 12.53×10^{-6} cm/s, classifying it as high permeability since it is $>9.0 \times 10^{-6}$ cm/s [8, 24, 25]. Demethoxycurcumin falls into BCS Class II due to its low solubility and high permeability (**Figure 11**). BCS Class II compounds exhibit slightly higher bioavailability compared to curcumin.

The removal of two methoxy groups from curcumin results in bisdemethoxycurcumin. Since methoxy groups are nonpolar, their absence slightly increases water solubility to 0.015 mg/mL. However, bisdemethoxycurcumin still falls into the low

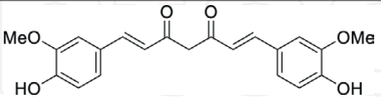
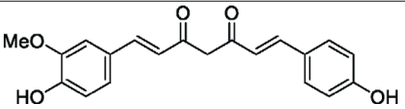
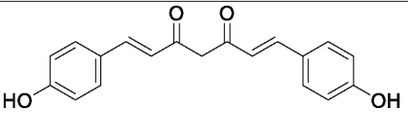
Compounds	Water solubility (mg/ml)	Coca2 permeability (cm/s)	BCS class
 Curcumin	3.5×10^{-3} Practically insoluble	4.87×10^{-6} Low permeability	IV
 Demethoxycurcumin	6.56×10^{-3} Practically insoluble	12.53×10^{-6} High permeability	II
 Bisdemethoxycurcumin	0.015 Practically insoluble	12.56×10^{-6} High permeability	II

Table 2.
Data on water solubility, permeability, and BCS of curcuminoids.

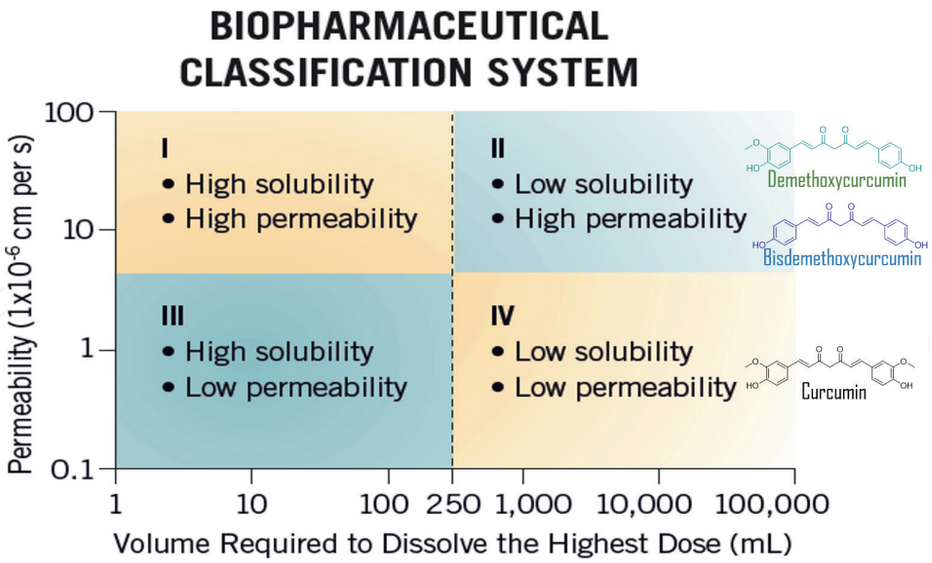


Figure 11.
Biopharmaceuticals classification system quadrant of curcuminoids.

solubility category and remains classified as practically insoluble (<0.1 mg/mL) [10, 23]. The loss of two methoxy groups significantly influences the permeability of bisdemethoxycurcumin, which has a permeability value of 12.56×10^{-6} cm/s, classifying it as high permeability ($>9.0 \times 10^{-6}$ cm/s) [8, 24, 25]. Bisdemethoxycurcumin belongs to BCS Class II due to its low solubility and high permeability (**Figure 11**). Among curcumin and its derivatives, bisdemethoxycurcumin has the highest bioavailability. Therefore, in terms of bioavailability, the ranking from highest to lowest is as follows: Bisdemethoxycurcumin > Demethoxycurcumin > Curcumin.

3.2 Distribution of curcuminoids

Curcuminoids are natural compounds classified as weak acids [13]. Weakly acidic compounds tend to bind to albumin proteins, whereas weakly basic compounds are more likely to interact with P-glycoprotein [27–29]. Curcumin contains methoxy groups that act as Electron Donating Groups (EDG), activating the benzene ring and making the alpha hydrogen in the diketone system more prone to releasing H+, thereby generating a negative charge on the curcumin molecule. This negative charge facilitates its binding to albumin proteins (**Figure 12**).

Several studies have reported that curcumin binds to plasma albumin proteins at a rate of more than 95% [30–32]. When curcumin interacts with albumin, it has a longer half-life, takes more time to be metabolized, and requires a longer duration for excretion from the body [27]. However, it is also important to consider its interactions with other drugs that bind to albumin, as curcumin may displace them, leading to an increase in free drug concentration in the blood [27–29]. As of now, moderate interactions between curcumin and 132 drugs have been documented on the website www.drugs.com, which is widely used by clinicians to identify drug–drug interactions when medications are administered concurrently [33, 34]. Based on the binding affinity of curcuminoids to plasma albumin proteins, the order is as follows: curcumin > demethoxycurcumin > bisdemethoxycurcumin.

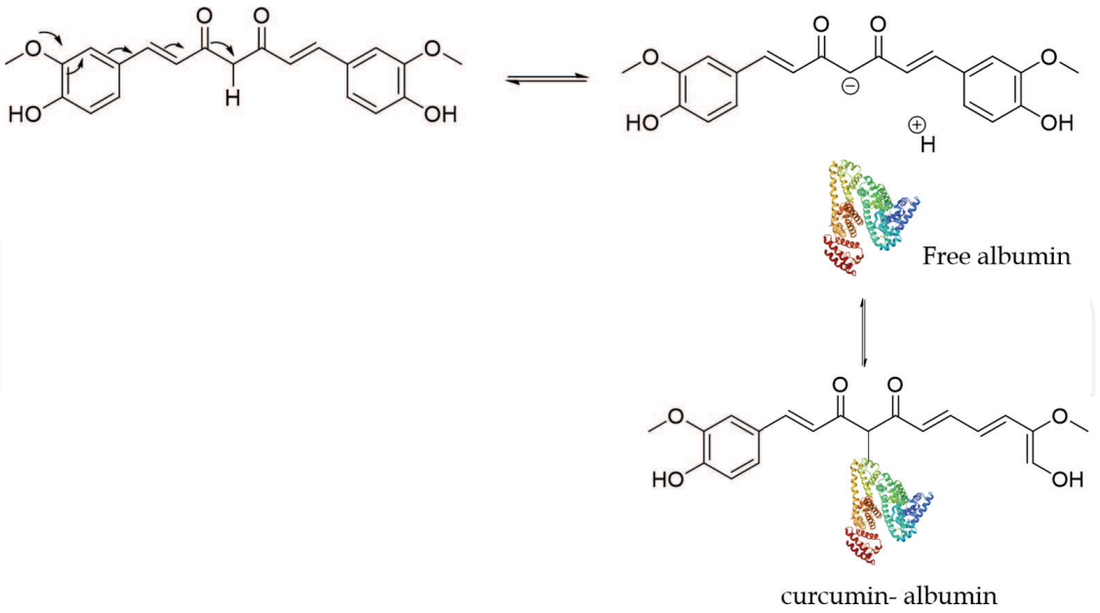


Figure 12.
Curcumin-albumin chemical bonding interaction.

3.3 Metabolism of curcuminoids

The primary purpose of curcuminoid metabolism in the liver is to convert lipophilic curcuminoids into hydrophilic compounds, allowing them to be excreted through the kidneys [27]. The metabolism of curcuminoids transforms active compounds into inactive metabolites. There are two phases in curcuminoid metabolism: phase 1 and phase 2 [27–29]. Phase 1 begins with the metabolism of curcuminoids into slightly more polar compounds [27]. Several studies have reported that curcuminoids undergo demethylation and reduction reactions during phase 1 metabolism [3, 18, 35].

Curcumin undergoes phase 1 metabolism through demethylation and reduction processes. The demethylation process converts curcumin into demethylcurcumin. Since curcumin contains two methoxy groups, further demethylation leads to the formation of bisdemethylcurcumin [3]. During the reduction process, curcumin is converted into tetrahydrocurcumin, followed by hexahydrocurcumin, and then further reduced to hexahydrocurcuminol (**Figure 13**).

In phase 1 metabolism, curcumin is transformed into slightly polar metabolites. As a result, these metabolites are rarely found in urine but are more commonly excreted in feces alongside bile salts [14]. These metabolites participate in the enterohepatic cycle, which plays a role in dissolving gallstones in cases of cholestasis [14].

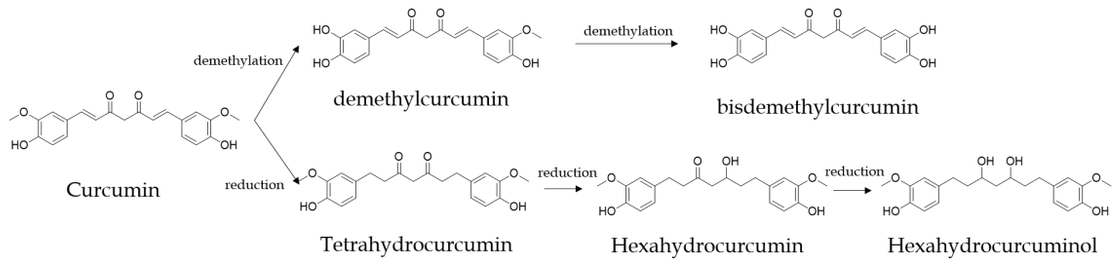


Figure 13.
Phase 1 metabolism of curcumin.

Demethoxycurcumin also undergoes phase 1 metabolism through methylation and reduction processes [3]. However, due to the loss of one methoxy group, the methylation process occurs in only one step, resulting in demethyldemethoxycurcumin. Meanwhile, the reduction process remains the same, producing three major metabolites: tetrahydrodemethoxycurcumin, hexahydrodemethoxycurcumin, and hexahydrodemethoxycurcuminol (**Figure 14**).

During phase 1 metabolism, demethoxycurcumin is converted into slightly polar metabolites. As a result, these metabolites are rarely found in urine but are more commonly excreted in feces along with bile salts. These metabolites participate in the enterohepatic cycle, which plays a role in dissolving gallstones in cases of cholestasis.

Bisdemethoxycurcumin undergoes phase 1 metabolism exclusively through the reduction process without methylation, as it lacks methoxy groups entirely, as shown in **Figure 14**. Bisdemethoxycurcumin is reduced into three major metabolites: tetrahydrobisdemethoxycurcumin, hexahydrobisdemethoxycurcumin, and hexahydrobisdemethoxycurcuminol (**Figure 15**) [3].

During phase 1 metabolism, bisdemethoxycurcumin is converted into slightly polar metabolites. As a result, these metabolites are rarely found in urine but are more commonly excreted in feces along with bile salts. These metabolites participate in the enterohepatic cycle, which plays a role in dissolving gallstones in cases of cholestasis [14].

Phase 2 metabolism of curcuminoids occurs through sulfate conjugation and glucuronic acid conjugation, as illustrated in **Figure 16**. In this phase, curcumin is converted into curcumin sulfate and curcumin glucuronide [3, 18, 35]. The sulfate and glucuronic conjugation processes in curcumin are more challenging due to the presence of two methoxy groups, which create steric hindrance. This steric effect slows down the metabolism compared to bisdemethoxycurcumin, which lacks methoxy groups [5–7].

For demethoxycurcumin, the sulfate and glucuronic conjugation processes produce demethoxycurcumin sulfate and demethoxycurcumin glucuronide. These reactions occur faster than in curcumin because the absence of one methoxy group reduces steric hindrance, facilitating the attachment of sulfate and glucuronic acid groups. In contrast, bisdemethoxycurcumin undergoes sulfate and glucuronic

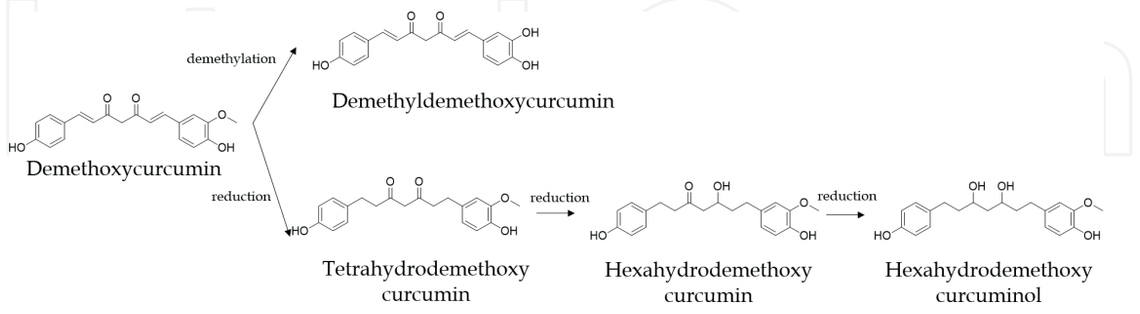


Figure 14.
Phase 1 metabolism of demethoxycurcumin.

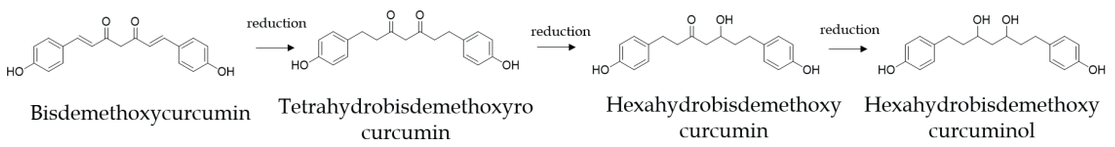


Figure 15.
Phase 1 metabolism of bisdemethoxycurcumin.

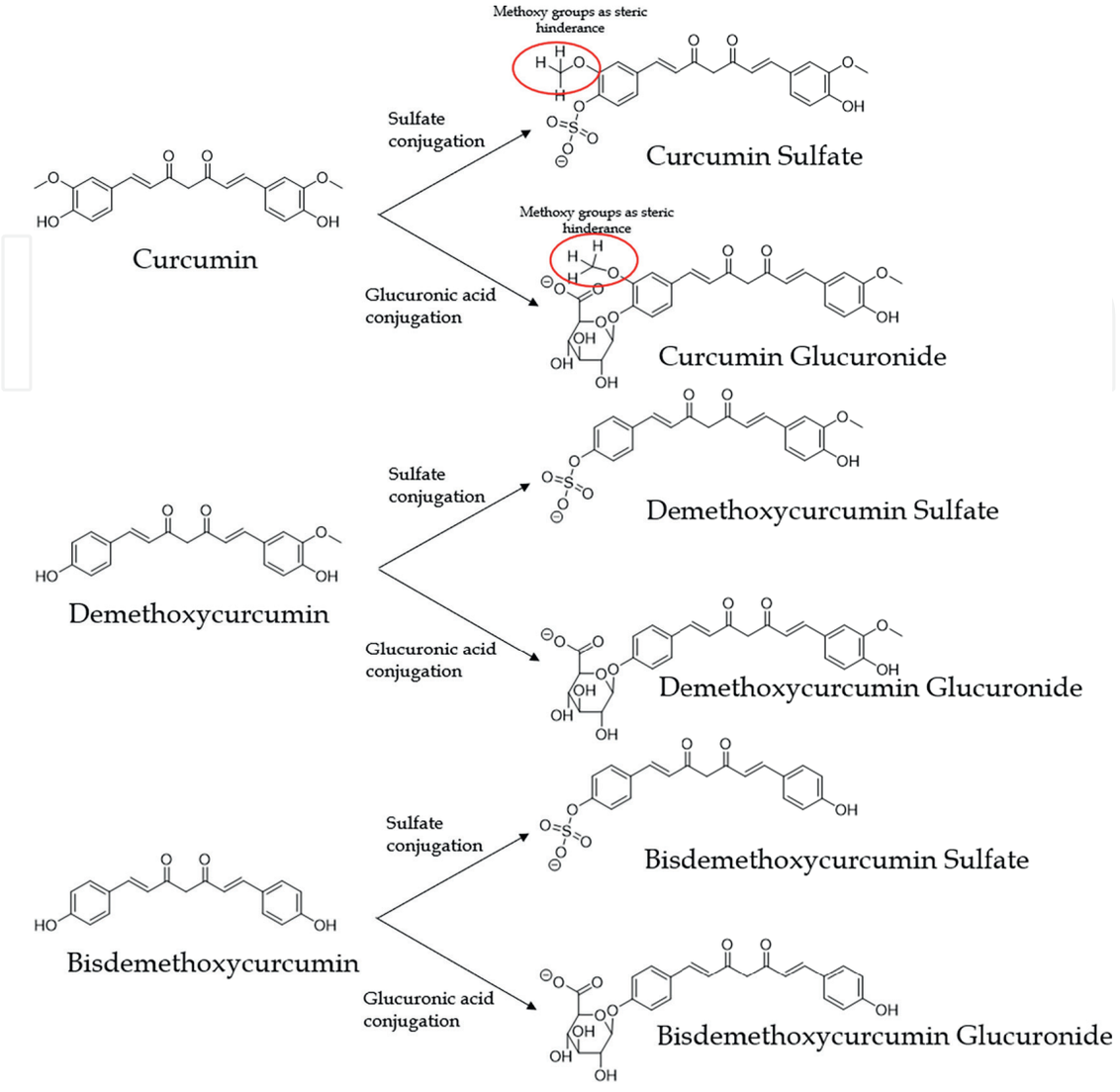


Figure 16.
Phase 2 metabolism of curcuminoids.

conjugation even more rapidly, producing bisdemethoxycurcumin sulfate and bisdemethoxycurcumin glucuronide.

The complete absence of methoxy groups allows easier attachment of sulfate and glucuronic acid, increasing the likelihood of conjugation. Sulfate and glucuronic acid groups are highly polar due to their anionic charges, making them highly water-soluble [5–7]. Consequently, the phase 2 metabolism of curcuminoids produces very polar metabolites that can be easily excreted through the kidneys in urine [14].

The metabolic rate of curcuminoids ranked from the slowest to the fastest, is as follows: Curcumin > Demethoxycurcumin > Bisdemethoxycurcumin. The presence of two methoxy groups in curcumin not only enhances its binding to albumin, prolonging its metabolism but also introduces steric hindrance, delaying sulfate and glucuronic acid conjugation.

3.4 Excretion of curcuminoids

Curcuminoids are eliminated from the body through two organs: the liver and kidneys [27]. The majority of phase 1 curcuminoid metabolites are excreted via the liver

[14, 27]. More than 90% of curcumin is excreted in feces through the enterohepatic cycle, while a smaller portion is excreted in urine [14, 27]. This phenomenon occurs because the presence of two methoxy groups in curcumin facilitates its metabolism via phase 1 through methylation and reduction, producing slightly polar metabolites that are stored in bile salts, secreted into the gastrointestinal tract, and eliminated with feces. The high concentration of curcumin in bile makes it more effective in dissolving gallstones in cholestasis cases compared to demethoxycurcumin and bisdemethoxycurcumin.

A small portion of curcumin undergoes phase 2 metabolism through sulfate conjugation and glucuronic conjugation. However, the presence of two methoxy groups creates significant steric hindrance, which interferes with these processes, resulting in fewer metabolites and consequently lower urinary excretion of curcumin. Some studies report that curcumin has a half-life ($t_1/_2$) of 6.77 ± 0.83 hours [35], while others report a half-life of 7–8 hours [36]. Curcumin's half-life falls within the intermediate half-life category (4–12 hours), with a recommended administration of 1–2 times per day.

Compared to curcumin, demethoxycurcumin, and bisdemethoxycurcumin have shorter half-lives due to the absence of methoxy groups, which accelerate phase 1 and phase 2 metabolism. Bisdemethoxycurcumin is more easily excreted in urine by the kidneys. The lack of methoxy groups allows bisdemethoxycurcumin to undergo phase 2 metabolism more rapidly through sulfate conjugation and glucuronic conjugation, producing highly polar metabolites that are easily dissolved in urine. This phenomenon results in bisdemethoxycurcumin having a shorter excretion half-life ($t_1/_2$) compared to demethoxycurcumin and curcumin. The ranking of half-life values ($t_1/_2$) from highest to lowest is as follows: curcumin > demethoxycurcumin > bisdemethoxycurcumin.

4. Pharmacodynamics of curcuminoids

Differences in the chemical and physical properties of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, resulting from variations in their chemical structures, also impact their pharmacodynamic aspects. These differences influence interactions with various receptors and enzymes, leading to pharmacological effects such as anti-inflammatory, antioxidant, anticancer, and chelating agent activities. The methoxy group in curcuminoids serves as a pharmacophore that plays a crucial role in enhancing pharmacological activities, including anti-inflammatory, antioxidant, anticancer, and chelating agent effects, as illustrated in **Figure 17** on the Qualitative Structure–Activity Relationship (QSAR) [19, 37]. From a pharmacodynamic perspective, the pharmacological response follows a potency ranking from strongest to weakest as follows: Curcumin > demethoxycurcumin > bisdemethoxycurcumin.

4.1 Antiinflammation activity of curcuminoids

One of the main mechanisms for inhibiting the inflammatory response is the inhibition of COX-2 (Cyclooxygenase-2). All types of pain and inflammation trigger the release of COX-2 mediators, as the breakdown of cell membranes containing phospholipid bilayers leads to the conversion of these components by COX-2 into various other inflammatory mediators. Curcuminoids exhibit COX-2 inhibitory activity due to their structural similarity to celecoxib, the first prototype of selective

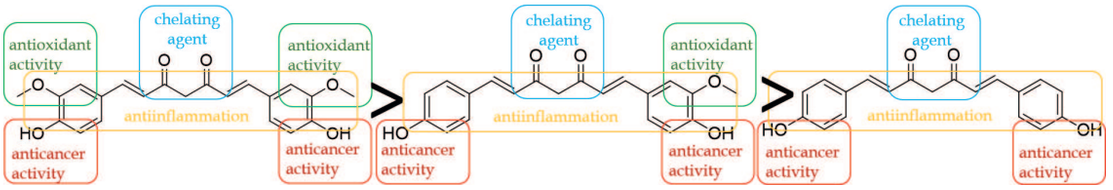


Figure 17.
Qualitative structure–activity relationship of curcuminoids.

COX-2 anti-inflammatory drugs, as well as newer-generation drugs such as etoricoxib, as shown in **Figure 18**. Curcuminoids selectively inhibit COX-2 because they possess the same pharmacophore as selective COX-2 inhibitors, including a V-shape structure, two benzoic rings, a hydrogen bond acceptor (HBA), and a hydrogen bond donor (HBD) [38, 39].

Inflammatory mediators in various diseases follow different regulatory pathways; however, COX-2 is a common pathway present in most inflammatory cases. One of the advantages of curcumin is its ability to inhibit not only the COX-2 pathway but also other inflammatory pathways, such as the Interleukin family (IL), Tumor Necrosis Factor-alpha (TNF-α), Inducible Nitric Oxide Synthase (iNOS), Macrophage Migration Inhibitory Factor (MIF), and others. For example, in Inflammatory Bowel Disease (IBD), key inflammatory mediators include the Interleukin family (IL-1, IL-6, IL-8) and Tumor Necrosis Factor-alpha (TNF-α) [40]. A comprehensive illustration of inflammatory mediators involved in specific diseases that can be inhibited by curcuminoids is presented in **Figure 19**.

The anti-inflammatory activity of curcumin is stronger compared to bisdemethoxycurcumin. The loss of two methoxy groups reduces the number of hydrogen bond acceptors, as the oxygen atom in the methoxy group acts as a hydrogen bond acceptor. This feature is one of the pharmacophores involved in inhibiting inflammatory mediators such as COX-2 [6].

4.2 Anticancer activity of curcuminoid

Curcuminoids exhibit anticancer activity at various stages of cancer cell growth inhibition. It begins with normal cells experiencing DNA damage due to exposure to physical, chemical, and biological agents, which have the potential to transform into cancer cells. At the preventive stage, curcuminoids inhibit cell growth and induce cell cycle arrest to facilitate DNA repair by increasing the activity of guardian genes such

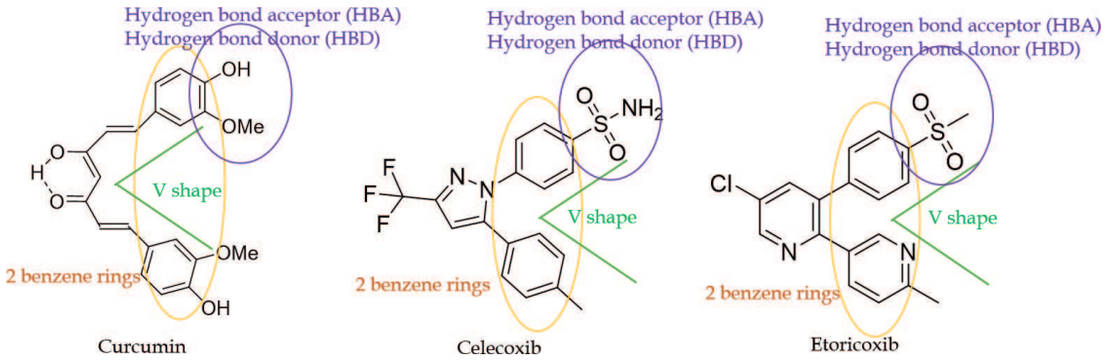


Figure 18.
Structural similarity of curcumin with COX-2 selective inhibitor drugs.

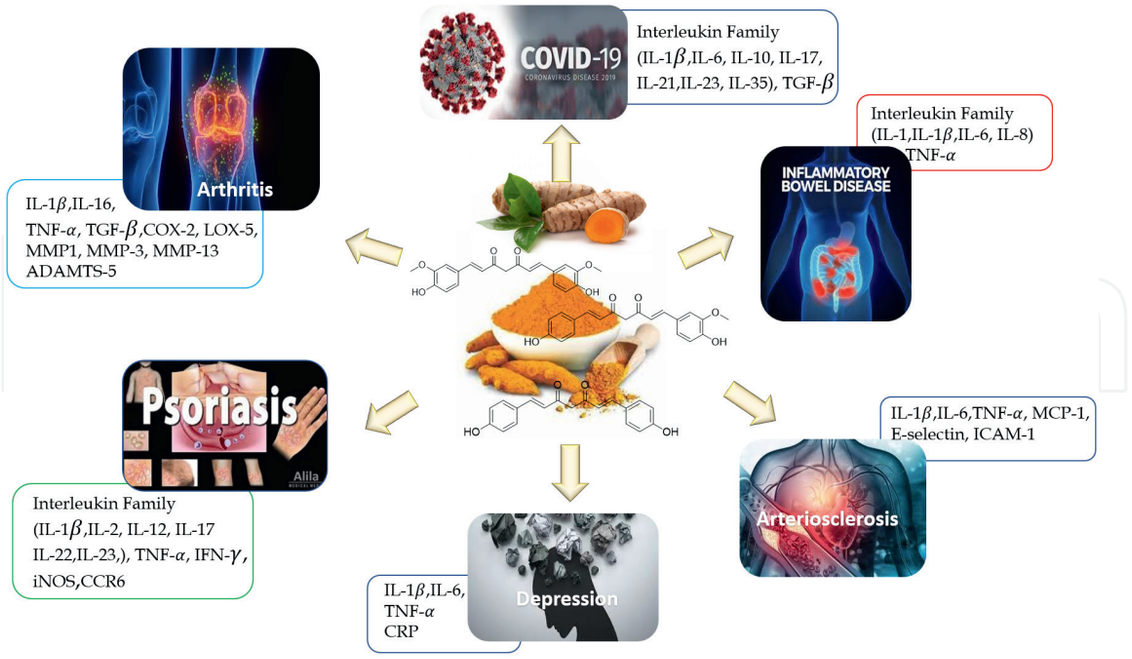


Figure 19.
Effect of curcuminoids on inflammatory bowel disease, arthritis, psoriasis, depression, and atherosclerosis.

as p53, p21, and p16, while decreasing the activity of Cyclin D1 and Cyclin E [3, 41]. If the DNA damage is too severe and cannot be repaired, curcuminoids enhance pro-apoptotic mediators such as BAX and BAK while reducing anti-apoptotic mediators such as BCL-2, BCL-xL, NF-κB, P-Akt, and mTOR [3, 41].

Apoptosis is a programmed cell death process that does not generate inflammatory mediators; if the damaged cells are not eliminated, they may continue to grow as cancer cells. Additionally, curcuminoids enhance autophagy to accelerate apoptosis by

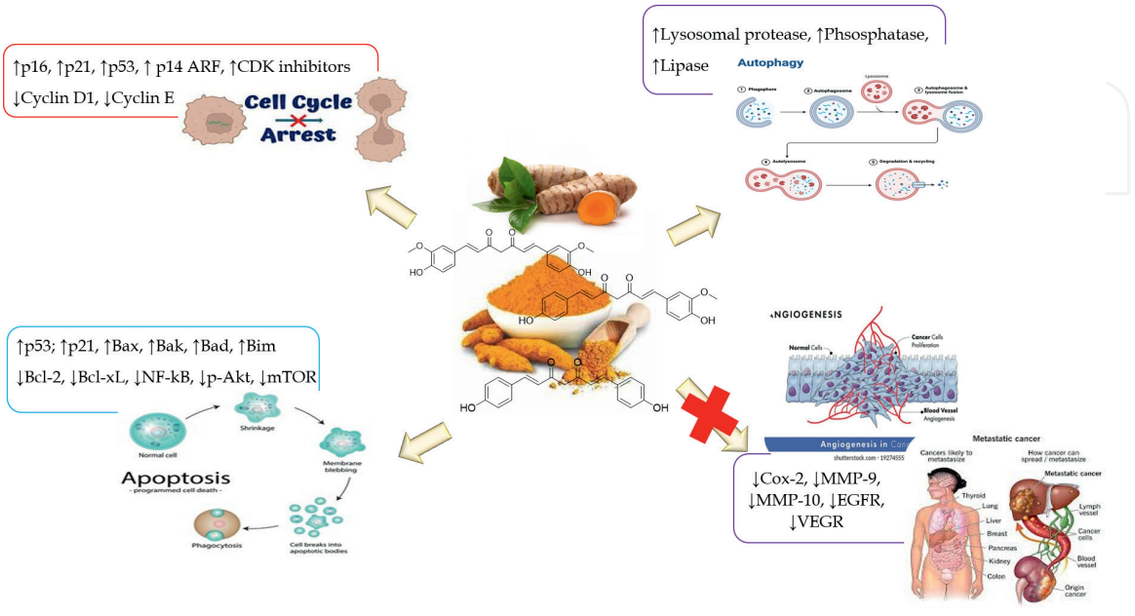


Figure 20.
Anticancer activity of curcuminoid.

increasing lysosomal proteases and proteolytic enzymes such as caspases through intrinsic (Caspase-9, Caspase-3, Caspase-6, Caspase-7) and extrinsic (Caspase-8) pathways.

At the curative stage, curcuminoids exhibit anti-angiogenesis and anti-metastasis activities. Angiogenesis is the process of forming new blood vessels from pre-existing ones, enabling cancer cells to grow more massively and aggressively due to increased nutrient and oxygen supply. Metastasis refers to the spread of cancer cells from the primary tumor to other parts of the body via the bloodstream (hematogenous), lymphatic system, or direct invasion into surrounding tissues. The mechanism by which curcuminoids inhibit angiogenesis and metastasis involves suppressing mediators such as COX-2, MMP-9, MMP-10, and VEGF [3, 41]. The anticancer activity of curcuminoids is further illustrated in **Figure 20**.

All curcuminoids contain phenolic OH groups, making them inherently active as anticancer agents. However, the anticancer activity of curcumin, both in the preventive and curative stages, is stronger due to the presence of methoxy groups, which enhance its antioxidant and chelating agent properties.

5. Conclusion

Curcuminoids are major phytochemicals widely isolated from various species of Curcuma sp. The variation in curcuminoid content among different Curcuma sp. species results in differing therapeutic effects, as curcuminoids consist of three main compounds: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. The presence or absence of methoxy groups in curcuminoids alters their chemical and physical properties, which in turn affects their pharmacokinetic and pharmacodynamic profiles. The methoxy group plays a crucial role in enhancing antioxidant, anticancer, anti-inflammatory, and chelating activities. However, its presence negatively impacts pharmacokinetic properties, such as reducing gastrointestinal (GIT) absorption due to classification in BCS Class IV. Therefore, when formulating curcumin, careful consideration must be given to the drug delivery system to enhance its solubility, and permeability enhancers should be added to improve its bioavailability.

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Conflict of interest

Authors declare no conflict of interest.

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