Chapter

Curcuminoids: The Novel Molecules of Nature

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Abstract

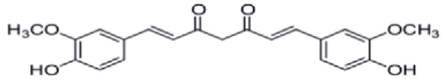
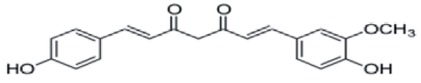
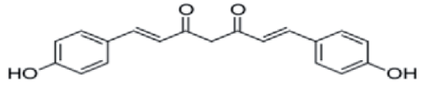
Curcuminoids inactivate Nuclear Factor-Kappa B (NF-κB), a key pro-inflammatory transcription factor which is involved in inflammation and immune response in diseases like cancer. NF-κB activation is necessary to determine tumor microenvironment which controls migration and metastatis of cancer cells through chemokines and their receptors and involvement of some cell adhesion molecules. Therefore inhibition of NF-κB by curcuminoids could be a new approach in treatment of cancer by immune modulation. Curcuminoids are not bioavailable and therefore there were problems in efficacy. Now by using bioavailable curcuminoid formulations the problem has been resolved to a great extent. Out of 49 placebo controlled double blind clinical trials using curcuminoids, 17 have been found to be successful. Therefore curcuminoids could be developed as an adjunct therapy for diseases like cancer to save human life.

Keywords: Curcuminoids, Inflammation, Immunomodulation, Human clinical trial

1. Introduction

Curcuminoids are natural polyphenolic compounds present in the rhizome of *Curcuma longa* plant which are responsible for the yellow color of turmeric and it's medicinal properties [1]. Turmeric has been used for centuries not only to make Indian curry spicy but also for healing wounds, reducing pain and as antibacterial agent in our traditional system of medicine [2]. No one knew what component of turmeric was responsible for these medicinal properties till Vogel Peletier isolated the pigment from it in 1815 [3]. No structural studies could be done as the isolated pigment was found to be a mixture of oleoresin and oil. Finally Vogel A Jr. isolated the pure pigment in 1842 but he did not determine its structure [4]. After unsuccessful attempts by many chemists, Milobedzka J and Lampe V determined the chemical structure of curcumin to be diferuloylmethane and named it as curcumin in 1910 almost hundred years after it was first isolated in 1815 [5]. Later the same group synthesized the molecule in 1913 which established its structure firmly [6]. Subsequently K R Srinivasan developed chromatographic methods to separate curcumin and showed it to have three components [7, 8].

Using diverse extraction techniques and chromatographic methods which are coupled with sensitive mass spectrometric detection system to identify the extracted molecules we now know that turmeric contains atleast 235 specialized secondary metabolites which include 109 sesquiterpene and 68 monoterpene molecules besides the three Curcuminoid molecules which are the subject of discussion here [9]. The three molecules viz. Curcumin (which is the major Curcuminoid), demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) which are

Name of compound	Structure & molecular weight (g/mol)	IUPAC name	Physical appearance	Molecular formula	Physical & chemical properties
Curcumin	 **M.W : 368.38**	1E,6E-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione	Bright orange yellow powder	$C_{21}H_{20}O_6$	Melting Point: 183°C Boling Point: 591.4°C at 760 mmHg Density: 1.3 ± 0.1 g/cm^3
Demethoxy Curcumin	 **M.W : 338.37**	1E,6E-1-(4Hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl) hepta-1-6-diene-3,5-dione	Orange colored powder	$C_{20}H_{18}O_5$	Melting Point: 178°C-180°C Boling Point: 573.4 ± 50.0 °C at 760 mmHg Density: 1.3 ± 0.1 g/cm^3
Bisdemethoxy Curcumin	 **M.W : 308.33**	(1E,6E)-1,7-Bis(4-hydroxyphenyl) hepta-1,6-diene-3,5-dione	Yellow colored powder	$C_{19}H_{16}O_4$	Melting Point: 226°C-231°C Boling Point: 551.3 ± 45.0°C at 760 mmHg Density: 1.3 ± 0.1 g/cm^3

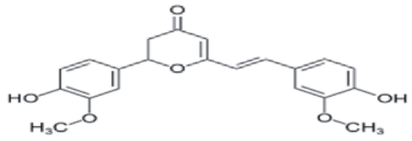
Name of compound	Structure & molecular weight (g/mol)	IUPAC name	Physical appearance	Molecular formula	Physical & chemical properties
Cyclocurcumin	 **M.W : 368.38**	2-(4-hydroxy-3-methoxyphenyl-6-[(E)-2-(4-hydroxy-3- methoxyphenyl) ethenyl]-2,3H-dihydropyran-4-one	Yellow colored powder	$C_{21}H_{20}O_6$	Melting Point: 179°C-226°C Boiling Point: 571.9 ± 50.0°C at 760 mmHg Density: 1.4 ± 0.1 g/cm^3

Table 1.
Structure and properties of curcuminoids present in turmeric.

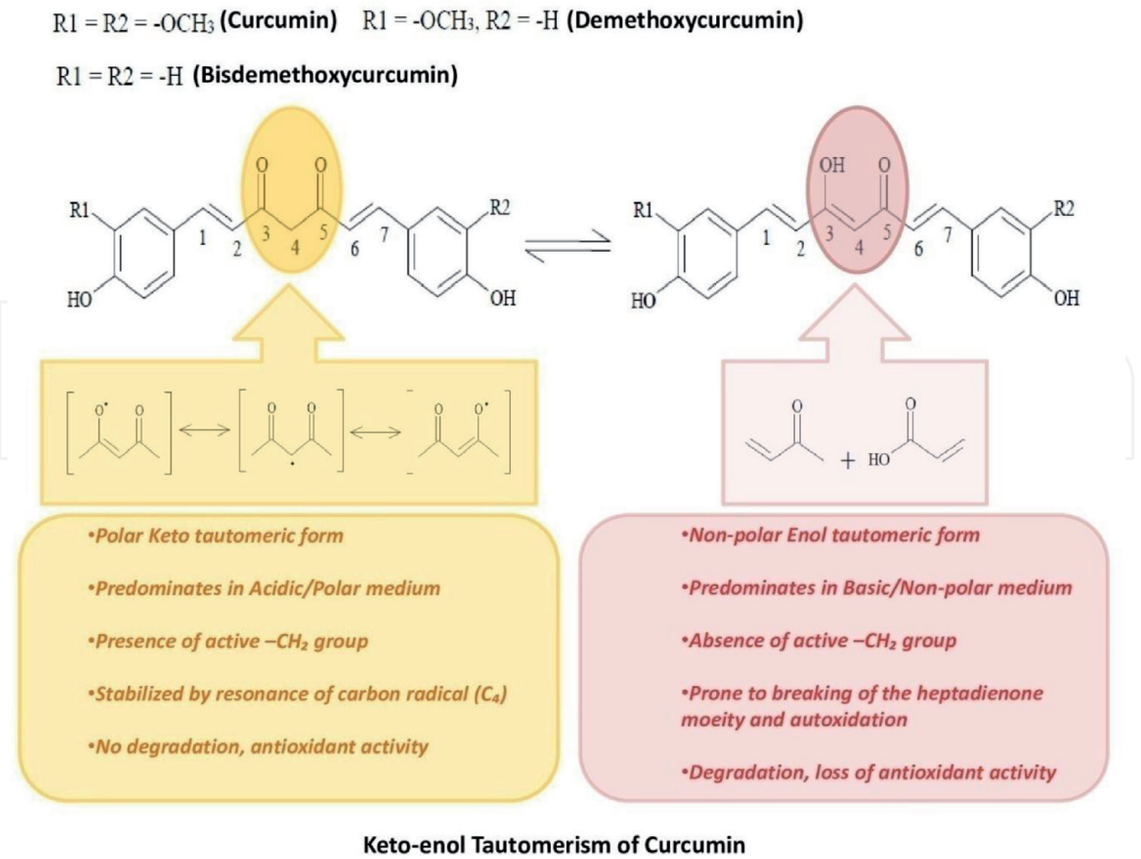


Figure 1.
Tautomeric forms of curcumin.

minor components of turmeric appear to have many medicinal properties. A fourth molecule called Cyclocurcumin which in the absence of α, β-unsaturated β-diketone motif is not considered as a Curcuminoid but an analog of Curcumin, has recently been identified to be present in the rhizome in much less concentration but with some interesting medicinal properties (**Table 1**) [10]. **Table 1** gives the structure of the four molecules and summarizes the chemical properties of the three curcuminoids and cyclocurcumin for comparison.

Each of the three curcuminoid molecules contains two aromatic o-methoxy phenolic groups, except BDMC which has only phenolic groups joined linearly through a seven carbon chain linker contain**ing** α, β-unsaturated β-diketone groups. The presence of this linker chain with the α, β-unsaturated β-diketone groups, a unique feature of curcuminoid molecules, allows the curcuminoids to remain either in the keto or enol form depending upon the ambient pH and exhibit biological activities (**Figure 1**) [11].

Every year more than 10 thousand papers are published worldwide describing the biological activity and therapeutic potential of Curcumin. Here we will discuss some of the properties of curcumin and will introduce the *Curcuma longa* plant. *Curcuma longa* has been cultivated in India and other south eastern countries with suitable weather and soil conditions for centuries [12]. Significant efforts have been made to understand the biosynthesis of these molecules in the rhizome and purify them from turmeric to study their chemistry. Efforts have been made to synthesize them in heterologous systems like E.coli and so that novel curcuminoids could be made and tested for their activities. We will also discuss how there has been concerted efforts to discredit curcumin as a lead molecule due to it's poor ADMET (absorption, distribution, metabolism, excretion, and toxicology) properties inspite of credibility of successful traditional usage to emerge as new neutraceutical drugs against diseases [13].

2. The *Curcuma longa* plant

Curcuma longa belongs to Zingiberaceae family which includes *Zingiber officinalis*, the source of ginger another very useful herb [14]. *Curcuma longa* grows to a height of 1 m as an upright, perennial plant displaying bright foliage and colored flowers. The plant is sterile as it produces seeds which are not viable but *Curcuma longa* can be vigorously propagated by using the rhizomes of the plant [15]. It does not grow in the wild and is thought to have arisen by selection and vegetative propagation of a hybrid between wild plant *Curcuma aromatica* which is, native to India and some other closely related species [16]. It is estimated that the genus *Curcuma* contains between 80 and 117 species, the majority of which are found in Southeast Asia, but some of which can also be found in the Himalayas, Southern China, Australia, and the Pacific Islands [16, 17]. Carolus Linnaeus, the famous Swedish taxonomist, coined the name Curcuma for the genus and included it in his book Species Plantarum, which was published in the year 1753. The plant derives its name "curcuma" from the Arabic word Kurkum, in reference to the yellowish color of its root [17].

To thrive, *Curcuma longa* requires temperatures ranging from 20^0Celsius to 35^0 Celsius, and significant rainfall during the monsoon season when it is cultivated [18]. Turmeric is best known for its culinary applications as a major component of curry powder, for which it has been dubbed "Indian saffron" as a cheaper alternative to the far more expensive saffron spice. Turmeric is also used in cosmetics and toiletries. Its active ingredient has a distinct earthy, slightly bitter, slightly hot peppery flavor and a mustardy smell. The genus *Curcuma* also contains a number of economically important species, such as *C. angustifolia* (short-leaved turmeric), *C. zedoaria* (also known as zedoary) and *C. amada* which is a slang term for "amazing" (mango ginger). Curcuma plants such as *C ornata*, which has beautiful green leaves and pinecone-like flowers of light pink color that lasts for a month, *C elata,* which can withstand cold climate conditions and produces extremely brilliant yellow flowers, and *C petiolata* 'Emperor' from Thailand, which produces pink colored flowers, are few examples which can be grown as house plants.

Erode, a city in the Indian state of Tamil Nadu, with suitable weather conditions and rainfall is the world's largest producer of turmeric and the world's most important trading center for the spice, earning it the nickname "Turmeric City" in addition to Sangli, a town in the Indian state of Maharashtra, which too is another significant trading center for turmeric throughout Asia. In a year, India produces 600,000 tons of turmeric, which accounts for 75% of the world's total annual production of 800,000 tons. The rhizomes, which are underground stems that look like roots and have a brown surface with bright orange or yellow interior flesh, are processed to produce a lemon yellow powder known as turmeric.

3. Extraction of curcuminoids from turmeric and it's synthesis in the laboratory

The extraction of curcumin from turmeric has become of immense commercial interest due to health benefitting medicinal properties of curcumin. For the process to be commercially viable it should be efficient, simple and the end product should be suitable for human consumption. Since India is one of the largest producers of turmeric, quite naturally there are a lot of activities with respect to extraction of curcuminoids from turmeric on a commercial scale. Typically, the content of curcuminoids in turmeric ranges from 2%-9% of the total dry weight depending upon origin of the plant and the conditions of the soil where it is grown. Even

though Curcumin was first isolated as a pigment in the impure form by Vogel in the year 1815, the methods of curcuminoids extraction are being standardized till very recently. The most commonly used method for extracting curcumin from turmeric has been the employment of solvent extraction followed by column chromatography for separating curcuminoids from other molecules that are extracted. Soxhlet extraction, ultrasonic extraction, microwave, zone-refining and dipping methods have been tried, and among these the Soxhlet, ultrasonic and microwave extractions are the most commonly employed methods [19]. Recently, it has been reported that pulse ultrasonic and microwave-assisted extraction methods are superior to continuous extraction methods. As there is an increase in the use of curcumin in dietary supplements, researchers are continually developing newer extraction methods in order to increase the yield and quality of the end product. Green bio based methods which do not use surfactants or solvent are also being developed. When compared with the conventional ethanol/water based extraction methods, the surfactant free microemulsion (SFME) methods have been found to be more efficient in extracting curcuminoids [20]. Some of the newer methods use food grade molecules like triacylglycerol which can solubilize curcumin in the presence of water for achieving higher yield and use of supercritical carbon dioxide makes it a method free of any organic solvents [21]. Pilot plants based on supercritical carbon dioxide have been established in several countries for the extraction of curcumin from turmeric with the purpose of making the extraction process of curcumin a commercially viable one.

Column chromatography can separate curcumin from curcumin mix (a mixture of curcumin, demethoxycurcumin, and bisdemethoxycurcumin) by adsorbing the mixture on silica gel and then eluting with solvent mixtures such as dichloromethane/acetic acid or methanol/chloroform to yield three different fractions. The curcumin fraction is then purified further on silica gel using eluents such as chloroform/dichloromethane and ethanol/methanol mixtures. The high performance liquid chromatography (HPLC) technique has been used extensively in the detection and estimation of curcumin in different fractions. In general, reverse phase C18 columns are used as the stationary phase, with various gradients of solvents containing acetonitrile/water or chloroform/methanol used as the mobile phase [22]. Curcumin detection is simple and can be done by using absorption detectors in the visible range of 350 to 450 nm or in the UV region using a common detection wavelength in the range of 250 to 270 nm. Several researchers have also used HPLC-diode array and fluorescence detection methods. Another versatile tool for detecting curcumin is liquid chromatography-coupled mass spectrometry [23].

Lampe published the first paper on the synthesis of curcumin in 1918, a century after its isolation from turmeric. The procedure consisted of five steps, beginning with carbomethoxyferuloyl chloride and ending with ethyl acetoacetate. Later, Pabon reported a simpler method for the synthesis of curcumin in high yields using acetyl acetone and substituted aromatic aldehydes in the presence of boron trioxide (B_2O_3), trialkyl borate, and n-butylamine (**Figure 2**). This method was adopted by several research groups for all subsequent synthesis of curcumin with minor modifications. The primary step in all of these methods is the reaction of 2,4-diketones with appropriately substituted aromatic aldehydes. To prevent the participation of diketone in Knoevenagel condensations, it is complexed with boron. These reactions are best performed in anhydrous conditions and polar aprotic solvents, where curcumin can be easily separated from reaction mixtures. Primary and secondary amines are used as catalysts to provide the basicity required to deprotonate the diketone's alkyl groups. Scavengers such as alkyl borates are used to remove the water produced during the condensation reaction. Water, if not removed, can react with the diketone complex, reducing the curcumin yield. Under slightly acidic

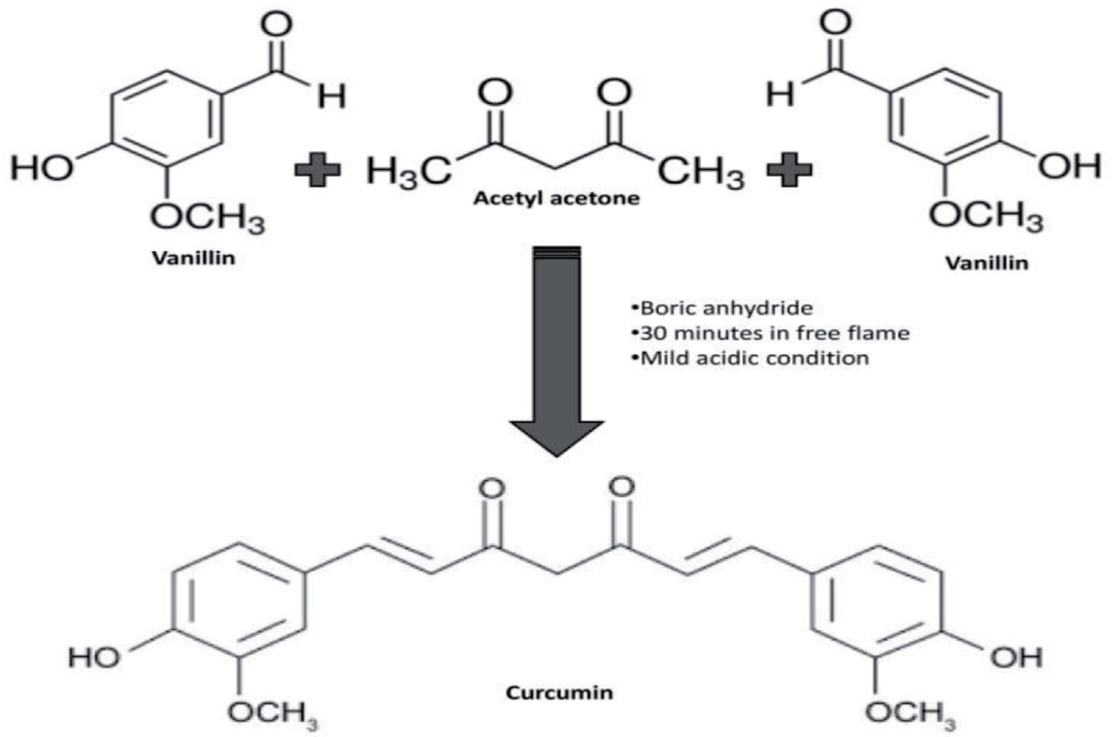


Figure 2.
Laboratory synthesis of curcumin.

conditions, the boron complex dissociates into curcumin. Washing and repeated precipitation followed by column chromatography can then be used to separate curcumin from this reaction mixture [24].

4. Chemistry of curcuminoids

The relative concentrations of the three curcuminoids in the turmeric vary depending upon the source of the rhizome used for propagation and the climatic conditions as well as fertility of the soil in which it is grown. Typically it varies between the following ranges: curcumin (70-80%), demethoxy curcumin (10-20%), and bisdemethoxy curcumin (3-6%) [25]. Because curcumin is the primary curcuminoid found in turmeric, it could be playing a significant role in the control of the medicinal properties of the mixture. It is equally important that we should investigate how the other two molecules contribute to curcuminoids' health benefitting effects like anti-inflammatory, anti-oxidant, and immunomodulatory properties [24].

Because the methylene group in curcumin contains two active hydrogen atoms and is flanked by two keto groups, the hydrogen atom attached to the carbon atom can migrate to the oxygen atom of the keto group, resulting in the keto-enol tautomeric forms (**Figure 1**) Extensive research over the last few decades have established the role of these distinct functional domains in curcumin's observed biological activities.

When the pH is between 3 and 7, it is the keto form that is predominantly found embedded in the lipid bilayer of membranes, while the enol form is found around pH 8. Curcumin's physicochemical and antioxidant properties are determined by this keto-enol-enol equilibrium. It is worth noting that when curcumin is present in the enol form, both aromatic rings at either end of the molecule can interact through extensive electron delocalization via the pi orbitals of the C=C bonds in the

heptadiene linker. Due to these structural constraints, the aromatic rings at either end of the molecule must be in the same plane, transforming the whole molecule into a planar structure.

The two aromatic rings with hydroxyl and O-methyl groups can exist in separate planes and interact with other molecules independently. The keto form exhibits distinct physiological properties, whereas the enol form, which must be planar, degrades rapidly [26]. When curcumin is administered orally or via intraperitoneal injection, it is rapidly eliminated through the feces due to its low solubility, which results in decreased absorption and extensive systemic clearance due to its degradation or metabolic conversion to more water-soluble forms that are rapidly secreted out. In the gut, curcumin is converted enzymatically to more soluble forms such as glucuronide and sulphate conjugates or reduced to tetrahydrocurcumin and hexahydrocurcuminglucuronides [27].

Curcumin's fundamental antioxidant activity is entirely dependent on the presence of hydrogen on the phenolic or central methylene groups. By losing a proton, a phenoxy-radical can be generated from the curcumin molecule's phenolic groups, and similar reactions can generate a carbon radical from the central methylene group. Although the phenoxy radical is more stable than the carbon radical, experimental data from study of curcumin indicate that both phenoxy and carbon radicals contribute to curcumin's biological activity. The phenoxy or carbon radicals produced by curcumin molecules are resonance stabilized by extensive conjugation via the heptadiene linker. As a result, curcumin acts as a potent scavenger of various reactive oxygen species (ROS), including hydroxyl radicals, hydrogen peroxide, singlet oxygen, and superoxide anion, thereby preventing damage to macromolecules in circulation or present in tissue. As a result, the phenolic groups or active methylene groups are a critical component of the curcumin molecule which contribute to its bioactivity [28].

As with curcumin, the other two curcuminoids (demethoxycurcumin and bisdemethoxycurcumin) also contain phenolic hydroxyl groups, a heptadiene chain, and a diketone moiety, which contribute to their diverse therapeutic properties, including antioxidant, anti-inflammatory, and anticancer properties. Curcumin has the highest antioxidant capacity, followed by demethoxycurcumin and bisdemethoxycurcumin. This observation holds true only when curcuminoids are not degraded, as is the case when an acidic or polar medium is used. On the other hand, under basic or non-polar conditions, bisdemethoxycurcumin is more stable than demethoxycurcumin, which in turn is more stable than curcumin. Apart from pH or the nature of the medium the structure of the phenolic compounds has an effect on the stability of curcuminoids. The electron donating group like OH or OMe groups on the benzene rings has a preference for the enol tautomer. Thus, among the three curcuminoids, the equilibrium shifting toward formation of the enol tautomer is greatest for curcumin and least for bisdemethoxycurcumin due to the presence of two methoxy groups. Bisdemethoxycurcumin, on the other hand, is less susceptible to degradation than demethoxycurcumin, which is less susceptible to degradation than curcumin. In basic or non-polar solvents, the rate of degradation is as follows: curcumin >demethoxycurcumin> bisdemethoxycurcumin (**Figure 3**).

The activity of Curcuminoids is strongly influenced by the methoxy group. The antioxidant activity of curcuminoids is primarily due to the active methylene group; however, the presence of an electron-donating methoxy groups ortho to the phenolic hydroxyl group also contributes to the molecule's antioxidant activity via an inductive effect on the hydroxyl group. Curcumin has the highest antioxidant activity of the three curcuminoids due to the presence of two methoxy groups.

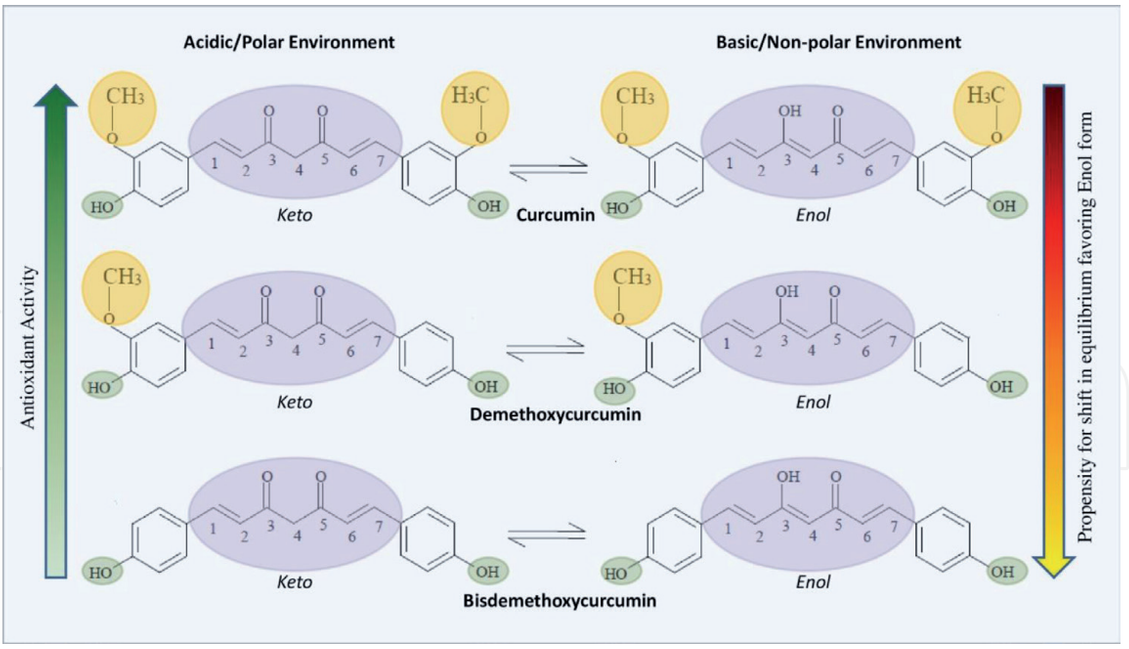


Figure 3.
Structure–function relationship of Curcuminoids.

Demethoxycurcumin has greater antioxidant activity than bisdemethoxycurcumin, which lacks a methoxy group.

5. Pharmacology of curcumin: role of degradation products

Curcumin is poorly bioavailable and fairly unstable in tissue under normal physiologic conditions. As a result, it is very likely that the metabolically transformed curcumin products, which are relatively more water-soluble, are responsible for the observed health benefits of curcumin. It has been shown that 90% of curcumin degrades within 30 minutes in phosphate buffer (pH 7.4) into various products such as, trans-6-(4hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexanal, ferulic aldehyde, ferulic acid, feruloyl methane, vanillin, and a few others [29]. Degradation occurs in basic medium via nucleophilic attack of the basic -hydroxide ion. The alkaline hydrolysis of curcumin produces feruloylmethane and ferulic acid. Further hydrolysis of the feruloylmethane results in the formation of vanillin and acetone. Thus, under basic conditions, the heptadienone moiety is broken, resulting in the disappearance of the active methylene group that contributes tothe majority of curcumin's antioxidant activity. Depending on the conditions it is subjected to, Curcumin can also undergo autoxidation or photooxidation to give rise to different degradation products (**Figure 4**).

Furthermore, it is unclear how curcumin exerts its inhibitory effects on such a large number of different enzymes whose binding pockets are unable to bind curcumin specifically. By comparing the biological activities of curcumin and its degradation products against diseases such as Alzheimer's and cancer, as well as their preferential inhibition of certain enzymes, it appears as though the bioactive degradation products may play a significant role in contributing to curcumin's observed pharmacological effects [30]. On the other hand, when curcumin enters the bloodstream, it forms complexes with proteins such as Albumin etc. and gets stabilized [31]. As a result, the rapid degradation of curcumin

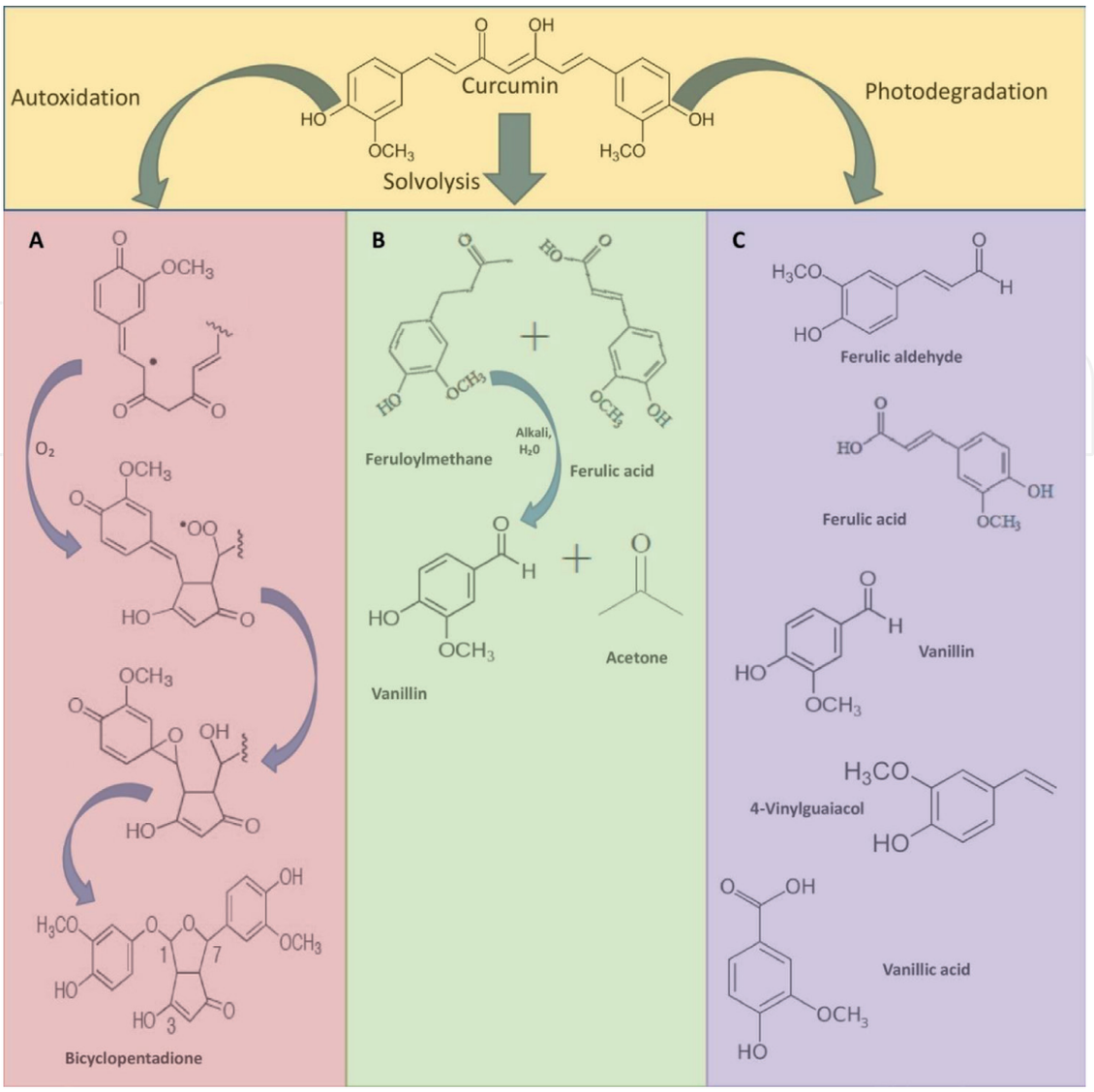


Figure 4.
Different paths for degradation of curcumin.

observed in the absence of proteins may not be occurring to the same extent in the tissue. This possibility should be investigated further in order to understand curcumin's pharmacokinetics and beneficial effects in the treatment of various diseases.

6. Biosynthesis of curcuminoids in the rhizome

Three polyketide synthases (PKS) isoforms, CURS1, CURS2, and CURS3, found in the leaves and rhizomes of *Curcuma longa* are involved in catalyzing the synthesis of various curcuminoids using various feruloyldiketide-CoAs as starter substrates [32]. The Curcuminoid Biosynthetic Pathway in *Curcuma longa* rhizome was investigated using 13C-labeled precursors and the enzyme involved in the process. It has been demonstrated that CURS1 exclusively utilizes feruloyl-CoA as a starting substrate and converts feruloyldiketide-CoA esters to curcumin. Similarly, CURS2 produces both curcumin and demethoxycurcumin using feruloyl-CoA as a starter substrate, whereas CURS3 produces all three curcuminoids, curcumin, demethoxycurcumin, and bisdemethoxycurcumin, using either feruloyl-CoA or 4-coumaroyl-CoA as the starter substrate [32].

Heterologous production of Curcuminoids has been attempted in *E. coli* and *Saccharomyces cerevisiae*. Katsuyama et al. prepared an *E. coli* strain with artificial biosynthetic pathway by combining enzyme-encoding genes such as 4-coumarate-CoA ligase (4CL) from *Lithospermumerythrorhizon* (Le4CL1), curcuminoid synthase (CUS)from *O. sativa* and Acetyl-CoA carboxylase (ACC) from *Corynebacterium glutamicum* which generated a new set of gene clusters which produced curcuminoids [33]. Using this approach and by adding two different unnatural carboxylic acids, 9 new curcuminoids which are not found in nature could also be produced [34]. This precursor-driven biosynthetic approach allowed the production of unnatural novel polyketides. This way of producing unnatural curcuminoids may provide novel drug candidates.

The production of curcumin and its derivatives by CURS may be an adaptive mechanism employed by the *Curcuma longa* plant to both protect against and respond to a variety of threats. Curcumin is a potent antioxidant that acts as a scavenger of free radicals, removing them from the plant's cells. Curcumin's bitter taste may also serve as a deterrent to herbivores.

7. Can curcuminoids be lead molecules to be a drug?

In a spirited article Kathryn *M. nelson* et al. have pointed out that "curcuminods which constitute about ~5% of turmeric has been classified as pan-assay interference (PAINS) compounds as well as invalid metabolic panaceas (IMPS) candidate [35]. Further curcuminoids are nonbioavailable, unstable and reactive compounds. Therefore they arehighly improbable lead for development of any drug. They pointed out and I quote "To our knowledge, compound 1 has never been shown to be conclusively effective in a randomized, placebo-controlled clinical trial for any indication. Curcumin is best typified, therefore, as a missile that continually blows up on the launch pad, never reaching the atmosphere or its intended target (s). These results have given curcumin the label of pharmacodynamically fierce (hits many targets) yet pharmacokinetically feeble (does not get to its targets). While these failures would normally end further research on its use as a therapeutic, they apparently have not deterred researchers interested in its development."

Responding to this paper by Nelson et al., Padmanaban G. and Nagaraj V. wrote a paper entitled "Curcumin May Defy Medicinal Chemists" to remind Dr. Nelson that just taking 4 clinical trials on curcuminoids into consideration it is not proper to suggest that all research on Curcuminoids should be suspended [36]. They wrote and I quote ". With over 10,000 papers published and 120 clinical trials under various stages of progress using curcumin, the review is a huge dampener, considering the projected potential of curcumin and other natural products as a panacea. Even if 1% of the papers published make sense, it would still be a sizable number to warrant against passing a negative verdict on the whole field. The review has picked four clinical trials and concluded that given its low systemic bioavailability, it is doubtful whether oral curcumin would ever be effective in human clinical trials."

After this paper by Padmanaban et al. was published, Nelson et al. responded without realizing that their arguments are based on wrong interpretation of data generated by others [37]. Soon another paper was published pointing out that while some of the arguments about curcuminoids are true, many of the conclusions drawn by Nelson et al. on the basis of referred papers are hard to accept as they were never made by the authors of these referred papers. The issue of curcuminoids being PAINS compounds was insignificant unless it actually interferes

with the high-throughput screening employed. What actually matters at the end of the human clinical trials and case studies is whether human life could be saved for which nature has designed these molecules [38]. In a recent letter to editor of Nature Michal Heger writes not to discount all the curcumin trial data. He points out that out of 49 clinical trials conducted recently 17 have shown efficacy. Therefore the molecular targets and the mechanisms of action of curcumin should be examined further [39]. Curcuminoids are wonderful molecules and can be developed to play significant role as adjunct therapy against inflammatory diseases. The pace of research on curcumin has not slowed down in spite of the two papers by Nelson et al.

It has been demonstrated that when curcumin was bound to chitosan nano particles and delivered orally to mice infected with *Plasmodium yoelii* parasite, the treated mice survived longer than the infected untreated mice [40]. Curcumin alone could not do so. When it was adsorbed on to chitosan nano particles and fed orally it's bioavailability increased and it entered into infected RBC and prevented hemozoin synthesis which killed the parasite.

In another experiment it was demonstrated that when nano curcumin alone was given orally to *Mycobacterium tuberculosis* infected mice it did not kill the *Mycobacteria* and the infected animals did not survive. But when it was administered in the presence if INH it helped to cure the infected mice in five weeks while INH alone could cure only in 8 weeks [41]. Therefore the combination of nano curcumin with INH was more effective than INH alone.

In a third experiment it has been shown that nano curcumin when administered orally to mice can modulate memory T cells and induced immune response against BCG in a manner which does not happen in the absence of nano curcumin [42]. These papers showed that curcumin can modulate immune memory mechanisms which was effective in prevention of death.

8. Human clinical trials with curcumin demonstrating efficacy of treatment

8.1 Curcumin for the prevention of colorectal neoplasia

Inhibition of the procarcinogenic eicosanoids prostaglandin E2 (PGE2) and 5-hydroxyeicosatetraenoic acid (5-HETE) has been shown in rodent models to have the potential to suppress carcinogenesis. In a nonrandomized, open-label clinical trial involving 44 patients, Robert E. et al. evaluated the effects of oral curcumin administration (2 g or 4 g per day for 30 days) on PGE2 within aberrant crypt foci (ACF), 5-HETE, ACF number, and proliferation [43]. To be eligible, men and women had to be at least 40 years old, a current smoker with a smoking history of more than three pack-years, and have at least eight rectal ACF detected using magnification chromoendoscopy. Subjects were excluded if they used nonsteroidal antiinflammatory drugs (NSAIDs), such as acetylsalicylic acid (ASA, or aspirin), for more than 10 days per month, unless they completed a 30-day washout period, or if they had a history of chronic inflammatory bowel disease, prior pelvic irradiation, or a history of endoscopically confirmed peptic ulcer disease within 5 years of enrollment. Neither dose of curcumin reduced PGE2 or 5-HETE in ACF or normal mucosa, nor did it reduce Ki-67 in normal mucosa, but the group receiving 4 g oral curcumin experienced a significant decrease in the number of ACF. After treatment, the reduction in ACF in this group was associated with a fivefold increase in serum curcumin or curcumin conjugates levels.

8.2 Effects of curcumin supplementation in patients with polycystic ovary syndrome

Heshmati et al. investigated the effect of curcumin supplementation on fasting blood glucose, insulin resistance, and androgen levels in patients with polycystic ovary syndrome [44]. In a randomized double-blind placebo-controlled trial, 72 women with polycystic ovary were enrolled. The study included women with PCOS aged 18–49 years (considered to be of reproductive age) who had a definitive diagnosis of PCOS for at least two years (made by a specialist physician during the mild to moderate phase), had impaired glucose tolerance (IGT), were a user of only one of the metformin or clomiphene drug groups, and had a body mass index (BMI) greater than 25 but less than 30. Patients were excluded if they had any of the following: a) Other hormonal diseases/disorders, autoimmune diseases, cancer, inflammatory disease, infections, pregnancy, or lactation, b) use of multivitamin-mineral, omega3, polyphenolic, or antioxidant supplements, as well as anticoagulants such as heparin and warfarin or aspirin, blood cholesterol-lowering drugs (statins), or non-steroidal anti-inflammatory drugs (NSAIDs). Curcumin capsules containing 500 mg curcumin powder were given to the intervention group, while maltodextrin capsules containing 500 mg maltodextrin were given to the placebo group. For 12 weeks, participants took three capsules daily (1500 mg total). The trial's primary outcomes were changes in fasting plasma glucose (FPG), fasting insulin (FI), sex hormones (Estradiol, Dehydroepiandrosterone (DHEA), Follicle-Stimulating Hormone (FSH), and Luteinizing Hormone (LH), and the modified Ferriman-Gallwey (mFG) hirsutism questionnaire. Changes in waist circumference (WC), weight, and body mass index were secondary outcomes of this study (BMI). At the conclusion of the study, it was observed that FPG and Dehydroepiandrosterone levels had decreased significantly, whereas Estradiol levels had increased statistically non-significantly in the intervention group following oral curcumin administration, in comparison to the placebo control group. At the end of the study, the authors concluded that curcumin is a safe and useful supplement for the treatment of PCOS-associated symptoms.

8.3 Curcumin in radiation dermatitis

One of the most common side effects experienced by patients suffering from cancers of sarcoma, breast, lung, and head and neck cancer and receiving radiotherapy (RT) is radiation dermatitis. Because the skin is a highly proliferative and self-renewing organ, it is particularly susceptible to damage from ionizing radiation, and as a result, the majority of patients undergoing radiotherapy develop radiation-induced skin reactions. Following dose- and time-dependent standard fractionation regimens in conventional radiotherapy, an accumulation of basal keratinocyte loss and impairment of the epidermal skin barrier occurs. The severity of radiation dermatitis varies from mild to severe erythema to dry or moist desquamation and ulceration. The current clinical guidelines for radiation-induced skin reactions include the following: 1) washing with lukewarm water and a mild soap; 2) applying unscented, lanolin-free, water-based moisturizers; and 3) IMRT. There is, however, no consensus regarding an agent capable of effectively reducing or preventing radiation dermatitis. Due to the fact that curcumin is a potent antioxidant and anti-inflammatory agent that has long been used to treat skin conditions and wound healing, Ryan et al. conducted a randomized, double-blind, placebo-controlled clinical trial to evaluate curcumin's ability to reduce the severity of radiation dermatitis in 30 breast cancer patients [45]. Individuals over the age of 18 years who have been diagnosed with noninflammatory breast cancer or carcinoma in situ

and have been prescribed RT without concurrent chemotherapy were included in the study. Patients were excluded if they had bilateral breast cancer; had received prior radiation to the chest or breast area; had undergone breast reconstruction and/or expanders prior to RT; were on anticoagulant (warfarin, coumadin, or heparin) or anti-epidermal growth factor receptor (EGFR) therapy; or had received partial breast irradiations. All patients received standard fractionated radiotherapy (1.8–2.4 Gy per session) for four to seven weeks, with or without boost, for a total dose of 42 Gy. The intervention group received four 500 mg curcumin capsules (Curcumin C3 complex, Sabsina) three times daily during the course of RT prescribed. The control group received identical placebo capsules containing dicalcium phosphate 500 mg, excipients, and a yellow food coloring. Curcumin treatment was found to be more effective than placebo at reducing Radiation Dermatitis Severity (RDS) at the conclusion of treatment.

8.4 Curcumin in oral leukoplakia

Oral leukoplakia is a potentially malignant lesion of the oral cavity, for which no effective treatment is available. Kuriakose et al. conducted a Phase IIB Randomized Double-Blind Placebo-Controlled Trial to determine the efficacy of Curcumin in the treatment of Oral Leukoplakia [46]. After establishing eligibility and performing a baseline clinical examination, all subjects underwent lesion incision biopsy using a 5 mm punch biopsy. Subjects with a clinical and histologic diagnosis of leukoplakia, as well as other inclusion/exclusion criteria, were randomly assigned to receive either placebo or curcumin (three 600 mg capsules) twice daily after food for six months. At the conclusion of the study, physical examinations and laboratory tests, including complete blood count, serum biochemistry, and urine analysis, were performed at baseline, six months after randomization, and twelve months after randomization, respectively. The study concluded at the conclusion of the study period that curcumin was well tolerated, with combined clinical and histologic response assessments indicating a significantly better response with curcumin treatment compared to placebo.

8.5 Efficacy of curcumin in cancer patients

Saghatelyanet al. conducted a randomized, double-blind, placebo-controlled, parallel-group clinical trial to determine the efficacy and safety of an intravenous infusion of curcumin in combination with paclitaxel in patients with metastatic or advanced breast cancer [47]. The eligible patients were randomly assigned to one of two study groups: curcumin + paclitaxel (curcumin group) or paclitaxel + placebo (placebo group). Paclitaxel (80 mg/m2) plus curcumin (CUC-1*, 300 mg solution, once weekly) were administered intravenously to the curcumin group for 12 weeks with a 3-month follow-up. For the same period, the placebo group received paclitaxel plus a solution of riboflavin (200 mg in 20 ml). The study concluded that curcumin treatment had a significantly higher Objective Response Rate than placebo at four weeks of follow-up and was even better for patients who completed the treatment. Curcumin had a superior effect over placebo in both patients who completed the treatment and 3 months later. There were no other significant differences between the curcumin and placebo groups except that patients self-reported significantly greater physical performance with curcumin than with placebo during treatment and at the end of the follow-up, implying improved Paclitaxel tolerance in the curcumin group.

Choi et al. conducted a randomized, double-blind, placebo-controlled trial to determine the effect of curcumin on the duration of the first off-treatment, the

change in PSA and testosterone levels, the rate of PSA progression, and health-related quality of life scores in patients with prostate cancer receiving intermittent androgen deprivation (IAD) [48]. The study included patients with prostate cancer who were treated with IAD for I biochemical recurrence (BCR) following localized therapy (eg, radical prostatectomy, radiation therapy, and high intensity focused ultrasound) or (ii) metastatic prostate cancer at initial diagnosis. All participants in this study received at least six months of treatment with an LHRH agonist and anti-androgens and entered the ADT withdrawal (off-treatment) period after a minimum of three months of maintaining a stable PSA nadir level. Exclusion criteria included prior use of an IAD for prostate cancer, hypersensitivity to curcumin, prior use of dietary supplements containing curcumin or turmeric to treat or prevent prostate cancer within the preceding six months of enrollment, and serious medical or psychological conditions (including impaired liver, kidney, cardiac, or hematopoietic functions) other than prostate cancer. The patients were randomly assigned to receive either a placebo or curcumin (240 mg of curcuminoid powder in capsule form), which was administered as two capsules three times daily (1440 mg/day) for six months following the cessation of ADT. The study concluded that during the six-month active treatment period, the proportion of patients with PSA progression was significantly lower in the Curcumin treatment group than in the placebo treatment group. The change in PSA, testosterone levels, and HRQOL scores after six months were comparable between the curcumin and placebo groups, but adverse events were more prevalent in the placebo group than in the curcumin group.

8.6 Effect of curcumin treatment in arthritis

Amalraj et al. conducted a randomized, double-blind, placebo-controlled, three-arm, parallel-group study to compare the efficacy of two different doses of curcumin to that of a placebo in patients with active rheumatoid arthritis (RA) [49]. For 90 days, twelve patients in each group received a placebo, 250 or 500 mg of the curcumin product, respectively. The American College of Rheumatology (ACR) response, visual analogue scale (VAS), C-reactive protein (CRP), Disease Activity Score 28 (DAS28), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) values were used to assess the patients' responses. At the conclusion of the study, RA patients who received the curcumin product at low and high doses reported statistically significant improvements in their clinical symptoms. Significant changes in ESR, CPR, and RF values were observed in patients receiving the study product when compared to baseline and placebo. The results indicate that this novel curcumin in a turmeric matrix acts as an analgesic and anti-inflammatory agent in the treatment of rheumatoid arthritis at a dose as low as 250 mg twice daily, as demonstrated by significant improvement in ESR, CRP, VAS, RF, DAS28, and ACR responses when compared to placebo. Both doses of the study product were well tolerated and were associated without any adverse events.

Fifty patients with Kellgren–Lawrence grade II or III knee osteoarthritis and a minimum age of 40 years were enrolled in a prospective, randomized, double-blind, placebo-controlled clinical study [50]. For eight weeks, either a placebo or Theracurmin containing 180 mg/day of curcumin was administered orally. Blood biochemistry analyses were performed before and after each intervention for the purpose of monitoring adverse events. The Japanese Knee Osteoarthritis Measure, the knee pain visual analogue scale (VAS), the Japanese Orthopedic Association's knee scoring system, and the need for nonsteroidal anti-inflammatory drugs were used to evaluate the patients' knee symptoms at 0, 2, 4, 6, and 8 weeks. At 8 weeks after treatment initiation, theracurmin-treated patients had significantly lower VAS scores for knee

pain than placebo-treated patients, except for those with initial VAS scores of 0.15 or less. Theracurmin significantly reduced celecoxib dependence compared to placebo. There were no significant adverse effects associated with Theracurmin treatment.

Osteoarthritis (OA) is a degenerative joint disease that is characterized by chronic and acute inflammation. Numerous studies have demonstrated curcumin's anti-arthritic properties in humans with OA and rheumatoid arthritis (RA). In a six-week randomized double-blind placebo-controlled trial, 40 subjects with mild-to-moderate knee OA were randomly assigned to receive either curcuminoid (500 mg/day in three divided doses, n = 19) with 5 mg piperine added to each 500-mg dose or a matched placebo (n = 21) [51]. Additionally, there was a reduction in systemic oxidative stress in subjects receiving the treatment compared to those receiving the placebo, as measured by serum SOD activity and concentrations of reduced GSH and malonedialdehyde (MDA). In a longer-term (eight months) randomized control trial, 50 subjects diagnosed with OA were randomly assigned to receive standard treatment plus two 500-mg tablets (Meriva®) daily containing a natural curcuminoid mixture (20%), phosphatidyl-choline (40%) and microcrystalline cellulose (40%) [52]. When comparing baseline to follow-up, the treatment group demonstrated significant decreases in all inflammation markers (soluble CD40 ligand (sCD40L), interleukin 1 beta (IL-1), interleukin 6 (IL-6), soluble vascular cell adhesion molecule 1 (sVCAM-1), and erythrocyte sedimentation rate (ESR), whereas the control group did not.

8.7 Effect of curcumin on inflammatory and metabolic disorders

Chronic low-grade inflammation is associated with the release of pro-inflammatory cytokines, which results in Metabolic syndrome (MetS), which is defined by insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein cholesterol (HDL-C), elevated low-density lipoprotein cholesterol (LDL-C), elevated triglyceride levels, and obesity, particularly visceral obesity. These cytokines are thought to be at the root of diabetes and cardiovascular disease complications. For eight weeks, 117 subjects with MetS received either 1 g curcumin plus 10 mg piperine to increase absorption or a placebo plus 10 mg piperine in a randomized double-blind placebo-controlled trial with a parallel-group design. Following curcumin supplementation, serum concentrations of TNF- α, IL-6, transforming growth factor beta (TGF-b), and monocyte chemoattractant protein-1 (MCP-1) were significantly decreased. TGF-b serum levels were decreased in the placebo group, but not those of IL-6, TNF- α, or MCP-1. Between-group comparisons indicated that the curcumin group significantly reduced serum concentrations of TNF- α, IL-6, TGF-b, and MCP-1. Curcuminoids were found to be more effective than a placebo at lowering serum LDL-C, non-HDL-C, total cholesterol, triglycerides, and lipoprotein a (Lp (a)), as well as elevating HDL-C concentrations. Additionally, there was a significant improvement in serum SOD activity, reduced MDA, and C-reactive protein (CRP) concentrations in the group receiving curcumin with piperine compared to the placebo group, and the authors concluded that short-term supplementation with a curcuminoid-piperine combination significantly improves oxidative and inflammatory status [53–55].

A double-blind, randomized pilot study was conducted on 31 hemodialysis HD patients and divided them into two groups: the curcumin group (receiving 100 mL of orange juice with 12 g of carrot and 2.5 g of turmeric after each dialysis session/week for three months) and the control group (receiving the same juice without curcumin). After three months of supplementation, the curcumin group demonstrated a significant decrease in NF-kB mRNA expression (AU) and plasma high sensitivity C-reactive protein (hsCRP) levels [56].

Cicero et al. conducted a randomized double-blind placebo-controlled trial in which 80 overweight subjects with suboptimal fasting plasma glucose were randomly assigned to receive 2 capsules of 800 mg phytosomal curcumin (Curserin®: 200 mg) [57]. The study included individuals aged 18 to 70 years, with a body mass index (BMI) of between 25 and 30 kg/m2, and FPG levels of between 100 and 125 mg/dL. Subjects were excluded if they had a personal history of cardiovascular disease or a risk factor for coronary heart disease, were taking glucose-lowering medications (oral antidiabetics, insulins), lipid-lowering medications (statins, fbrates, ezetimibe, omega-3 polyunsaturated fatty acids), or were taking drugs that affect lipid metabolism (i.e., full-dose thiazides, corticosteroids, or immunosuppressants), or After 56 days of treatment, it was observed that the curcumin-treated group had a significant improvement in fasting plasma insulin (FPI), HOMA index, waist circumference, blood pressure, triglycerides (TG), HDL-C, liver transaminases, gamma-GT, index of liver steatosis, and serum cortisol, when compared to the baseline. Additionally, FPI, TG, liver transaminases, fatty liver index, and serum cortisol levels improved significantly when compared to the placebo-treated group. In comparison to the baseline, the placebo group improved only in FPG and TG at the study's conclusion. In conclusion, the trial demonstrated that supplementation with a phytosomal curcumin preparation containing phosphatidylserine and piperine could improve glycemic factors, hepatic function, and serum cortisol levels in overweight subjects with impaired fasting glucose.

Satoskar et al. investigated the effect of curcumin on spermatic cord edoema following surgery. Forty-five patients (ages 15–68) received 400 mg curcumin (Group A), 250 mg lactose powder placebo (Group B), or 100 mg phenylbutazone (Group C) thrice daily for six days following inguinal hernia or hydrocele repair [58]. The spermatic cord edoema, spermatic cord tenderness, operative site pain, and operative site tenderness were all recorded and graded on a scale of 0-3 (0, absent, 1, mild, 2, moderate, 3, severe). The overall effect of treatment was determined by calculating the intensity score (TIS) for each group ranging from 0 to 12. Curcumin treatment resulted in an 84.2% reduction in TIS. TIS was reduced by 61.8% and 86%, respectively, with placebo and phenylbutazone treatments. Although phenylbutazone treatment reduced TIS to a comparable extent on day 6, it did not alleviate tenderness at the operative site. In comparison, Curcumin treatment was superior because it resulted in a decrease in all four inflammatory parameters.

Holt et al. studied ten patients aged 28 to 54 years to determine curcumin's therapeutic effect in the treatment of inflammatory bowel disease (IBD) [59]. Crohn's disease (CD) and ulcerative colitis (UC) are the two most common types of inflammatory bowel disease (IBD). Both are characterized by abdominal pain, vomiting, diarrhea, bloody stools, and weight loss, as well as secondary complications such as arthritis, pyoderma gangrenosum, and primary sclerosing cholangitis. Five patients with rectal UC were given 550 mg curcumin twice daily for one month and then three times daily for another month. The remaining five Crohn's disease patients received 360 mg curcumin three times daily for one month and then four times daily for an additional month. At baseline and at the end of the study period, hematological and biochemical blood analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), sigmoidoscopy, and biopsy were performed on the first group of patients. The second group of patients had their Crohn's Disease Activity Index (CDAI), CRP, ESR, hematological blood analysis, and kidney function evaluated. All five patients in the first group improved by the end of the study period, as measured by a global score, and all five subjects had normal ESR, CRP, and serologic indices of inflammation after two months of curcumin treatment. CDAI scores decreased by an average of 55 points in the CD group, and CRP and

ESR levels decreased in four of five patients. CDAI scores decreased by an average of 55 points in the second group, while CRP and ESR levels decreased in four of five patients.

8.8 Efficacy of curcumin in the treatment of neurological and brain disorders

For an 18-month period, forty subjects (aged 51–84 years) were randomly assigned to receive a bioavailable form of curcumin [Theracurmin® containing 90 mg of curcumin twice daily (N = 21)] or a placebo (N = 19). Verbal (Buschke Selective Reminding Test [SRT]) and visual (Brief Visual Memory Test-Revised [BVMT-R]) memory were used as primary outcomes, while attention (Trail Making A) was used as a secondary outcome to evaluate the efficacy and progress of treatment. FDDNP-PET signals in the amygdala, hypothalamus, medial and lateral temporal lobes, posterior cingulate, parietal, frontal, and motor regions were determined to measure the treatment outcomes and it was observed that in non-dementia adults, daily oral Theracurmin improves memory and attention. The FDDNP-PET results indicated that symptom improvement was associated with decreases in amyloid and tau accumulation in brain regions associated with mood and memory [60].

Numerous studies have confirmed curcumin's antidepressant properties in patients with major depressive disorder. In one study, for 12 weeks, 123 individuals with major depressive disorder were randomly assigned to one of four treatment conditions: placebo, low-dose curcumin extract (250 mg), high-dose curcumin extract (500 mg), or a combination of low-dose curcumin extract and saffron (15 mg). Depressive symptoms were assessed for changes or improvements in comparison to placebo. The active drug treatments (when used in combination) were associated with significantly greater improvements in depressive symptoms and superior improvements in Spielberger State–Trait Anxiety Inventory STAI-state and STAI-trait scores compared to placebo. Active drug treatments were also more effective in people with atypical depression than in the general population. The study concluded that active drug treatments containing varying doses of curcumin and a combination of curcumin were effective at alleviating depressive and anxiolytic symptoms in people with major depressive disorder, with no significant differences observed between the varying curcumin doses [61].

Another study enrolled forty patients who had just experienced their first episode of depression in a 5-week, double-blind, randomized, placebo-controlled clinical trial. Subjects received either 500 mg/d curcumin or a placebo in combination with antidepressants (escitalopram or venlafaxine). The Clinical Global Impression—Severity Scale, Hamilton Depression Rating Scale, and Montgomery-Asberg Depression Rating Scale were used as outcome measures. The analysis of variance revealed that both groups experienced significant positive changes in all scales of measurement from baseline to the end of the study. These changes became noticeable following the first visit following seven days of treatment. There was no statistically significant difference between curcumin and a placebo. However, patients in the curcumin group experienced a trend toward a faster resolution of depressive symptoms than those in the placebo group [62].

In a population of community-dwelling older adults, a 12-month, randomized, placebo-controlled, double-blind study was conducted to determine the ability of a curcumin formulation to prevent cognitive decline. For 12 months, participants (n 96) were randomly assigned to receive placebo or 1500 mg/d BiocurcumaxTM. At baseline and at the 6-month and 12-month follow-up assessments, a battery of clinical and cognitive measures was administered. Although no differences in clinical or cognitive measures were observed between the groups, a significant time treatment

group interaction was observed for the Montreal Cognitive Assessment (repeated measures analysis), which revealed a decline in function in the placebo group at 6 months that was not observed in the curcumin treatment group [63].

A 24-week, double-blind, randomized, placebo-controlled study with thirty-eight patients with chronic schizophrenia was conducted [64]. Subjects received either 3000 mg/d curcumin or a placebo in combination with antipsychotics. Positive and Negative Symptoms Scale (PANSS) and Calgary Depression Scale for Schizophrenia were used as outcome measures. The analysis of variance revealed that both groups experienced significant improvements in all scales of measurement from the baseline period to the study's conclusion. Within six months, curcumin produced a significant improvement in the total PANSS and the negative symptoms subscale. There were no differences between the treatment and placebo groups in terms of the positive and general PANSS subscales, as well as the Calgary Depression Scale for Schizophrenia scores.

A study examining the efficacy of curcumin oral supplementation in Amyotrophic Lateral Sclerosis randomly assigned patients to one of two groups: one that received a placebo for three months, followed by three months of curcumin oral supplementation (600 mg/day, Brainoil); and the second group that received curcumin oral supplementation (600 mg/day, Brainoil) for six months [65]. The evaluations were conducted at baseline (T0), three months after receiving either Brainoil or a placebo, and three months after the open-label phase. During an incremental forearm exercise test, clinical evaluations and measurement of oxidative stress biomarkers such as oxidative protein products (AOPPs), ferric reducing ability (FRAP), total thiols (T-SH), and lactate were compared to a control group and the study found that the ALS-FRS-r score in the first group decreased, whereas the second group maintained a stable ALS-FRS-r score. Additionally, while FRAP exercise values remained stable in the second group, they decreased in the first group without treatment, after 3 months into the study. The entire ALS population demonstrated increased oxidative stress when compared to controls, with those treated with curcumin in the second group exhibiting decreased exercise AOPPs with values comparable to controls.

9. Conclusion

Turmeric has been used in our traditional system of medicine for centuries in treating some of the common health related problems in children and elderly individuals. For example when children catch cold and cough and get fever thousands of mothers and grandmothers have given them a tea spoon full of turmeric suspended in milk to drink in the night before going to bed and invariably most of the children recover overnight. This has become an age old practice in Indian house hold for hundreds of years and there is no record how many children and elderly persons have benefited by this. At that time no one knew how turmeric worked and the modern medicine which the medicinal chemists think is their contribution was not even born. But since it had worked, even today a mother in an Indian village would prefer to give turmeric rather than an antibiotic to their children to control fever and cold. When children get infested with worms and their health deteriorates, mothers again give them turmeric orally for few days and children get cured and remain healthy. The modern medicinal chemistry has provided medicines like Albindazole which of course works but is toxic and children tend to get reinfected. Turmeric modulates the immune system and provides protection against reinfection. When children get wounded while playing mothers apply a paste of turmeric in some oil to the wound and it heals the wound very efficiently. Now modern

science has to give us answers to how this works rather than dismissing all these observations just because curcumin is unstable and cannot be a lead candidate. Even clinical trials, several of which have worked under double blind and placebo controlled conditions illustrate that curcuminoids, inspite of being unstable, can alleviate inflammatory conditions in several chronic disease conditions in humans. Therefore there is an intensive need to study Curcuminoids further and develop formulations which will help humans to combat severe overwhelming diseases.

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