Curcumin or curcumnoids – Industrial and medicinal potential

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Review

Curcumin or Curcumnoids : Industrial and Medicinal Potential

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Abstract

Turmeric (*Curcuma longa* L.) is a popular Indian spice that has been used for centuries in herbal medicines for the treatment of a variety of ailments such as rheumatism, diabetic ulcers, anorexia, cough and sinusitis. India is world's largest producer of turmeric, where it has been used as a home-remedy for several ailments for ages. The turmeric rhizomes contain 2.5–6.0 % curcuminoids which are responsible for the yellow colour. Curcuminoids comprise of Curcumin Ⅰ (Curcumin), Curcumin Ⅱ (Demethoxycurcumin) and Curcumin Ⅲ (Bisdemethoxycurcumin) which are found to be natural anti-oxidants. Curcumin (diferuloylmethane) the main curcuminoid present in turmeric and responsible for its yellow colour, has been found to possess many beneficial biological activities such as anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant, anti-diabetic, wound healing and anti-infective effects. The clinical use of curcumin is limited to some extent because of its poor water solubility and low bioavailability. Studies are in progress worldover to market the biological potential of this natural medicine.

Turmeric (*Curcuma longa* L.) is a popular Indian spice that has been used for centuries in herbal medicines for the treatment of a variety of ailments such as rheumatism, diabetic ulcers, anorexia, cough and sinusitis. It belongs to the genus *Curcuma*, which consists of several plant species with underground rhizomes and roots. About 40 species of the genus are indigenous to India, indicating the Indian origin[1]. It was originally used as a food additive to improve the palatability, storage and preservation of food. India is world's largest producer of turmeric, where it has been used as a home-remedy for several ailments for ages. The spice is cultivated in warm, rainy regions like India, China, Indonesia, Jamaica and Peru[2]. India is also the major exporter of turmeric at present, even though the crop is grown in several countries viz., Pakistan, Malaysia, Myanmar, Vietnam, Thailand, Philippines, Japan, China, Korea, Sri Lanka, Caribbean Islands and Central America. It is estimated that about 80 % of the world production of turmeric is from India alone. It is exported as raw material as well as its value added products, namely, turmeric powder and oleoresin.

Turmeric oleoresin is the solvent extract of turmeric and is added to food items as a spice and coloring agent. It is orange red in colour. The oleoresin yield ranges from 7.9 to 10.4 % Curcumin, the principal coloring matter forms one third of a good quality oleoresin. Curcumin or curcuminoids concentrate, for use as a food color, is not a regular article of commerce, because for most current uses the cheaper turmeric oleoresin has been found suitable. Curcumin gives a bright yellow color even at doses of 5-200 ppm. A variety of blends are available to suit the color of the product[3]. Curcumin is included in the list of colors with a restricted use because it has a low ADI (Acceptable Daily Intake) of 0-1.0 mg/kg body weight/day.

1. Curcuminoids

The turmeric rhizomes contain 2.5-6.0 % curcuminoids which are responsible for the yellow colour. Curcuminoids comprise of Curcumin I (Curcumin), Curcumin Ⅱ (Demethoxycurcumin) and Curcumin Ⅲ (Bisdemethoxycurcumin) which are found to be natural anti-oxidants[4].

2. Chemistry

Curcumin, $C_{21}H_{20}O_6$, m. p. 184 - 185 ℃ was isolated as early as 1815. It is insoluble in water but soluble in ethanol and acetone. The structure and synthesis of curcumin as diferuloylmethane was confirmed by the work of Lampe *et al*.[5] and also by Majeed *et al*.[6]. The main pigments in the rhizomes are curcumin [1, 7-bis-(4-hydroxy-3-methoxy prenyl)-1, 6-heptadiene-3, 5-dione] and two related demethoxy compounds, demethoxycurcumin and bisdemethoxycurcumin, which belong to the group of diarylheptanoids. Besides these three forms of curcuminoids, three minor constituents which are supposed to be geometrical isomers of curcumin have also been isolated[7]. One of these is assumed to be a cis-trans geometrical isomer of curcumin based on its UV spectrum, lower m.p. and lower stability when compared to curcumin which has a trans-trans configuration. Heller (1914) had isolated an isomer of curcumin, with a diketone structure. Cyclocurcumin having the same molecular formula as that of curcumin with cyclic structure was isolated from the nematocidally active fraction of turmeric[8]. The chemical structures of these components are given in Fig. 1. The fresh rhizomes also contain phenolics which possess anti-oxidant and anti-inflammatory activities.

Analyses of labeled demethoxycurcumin (DMC), an unsymmetrical curcuminoid, by ^{13}C-NMR, revealed that one molecule of acetic acid or malonic acid and two molecules of phenylalanine or phenylpropanoids were incorporated into DMC. The incorporation efficiencies of the same precursors into DMC and curcumin were similar, and were in the order malonic acid > acetic acid and cinnamic acid > p-coumaric acid >>ferulic acid. These results suggested the possibility that the pathway to curcuminoids utilized two

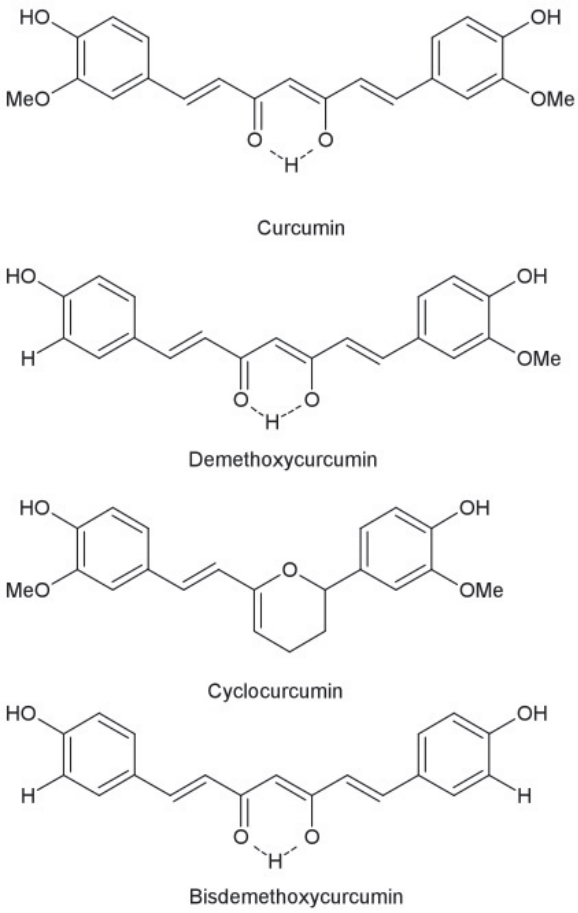

Fig.1. Chemical structures of curcuminoids in turmeric

cinnamoyl CoAs and one malonyl CoA, and that hydroxy- and methoxy- functional groups on the aromatic rings were introduced after the formation of the curcuminoid skeleton[9].

3. Extraction and detection

Depending on its origin and the soil conditions where it is grown, turmeric contains 2.5-6.0 % curcuminoids. The word "curcuminoids" indicates a group of compounds such as curcumin, demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin. Out of these, curcumin is the major component and cyclocurcumin is the minor component[10]. Although chlorinated solvents extract curcumin very efficiently from turmeric, they are not commonly employed due to their non-acceptability in the food industry. 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. Another commercially viable and efficient extraction method is by supercritical carbon dioxide. Being free from organic solvents, pilot plants based on supercritical carbon dioxide have been established in several countries for the extraction of curcumin from turmeric. There are also a few reports on enzyme-assisted extraction, where pretreatment of turmeric with enzymes like α-amylase and glucoamylase yielded significant increase in curcumin yield. However due to higher cost of extraction, this method is not commercially viable.

Curcumin can be separated from curcuminoids by column chromatography by adsorbing the mixture on silica gel using mixtures of solvents like dichloromethane/acetic acid or methanol/chloroform to yield three different fractions. The curcumin fraction is further purified on silica gel using chloroform/dichloromethane and ethanol/methanol mixtures as eluents.

High-efficient column chromatographic extraction (CCE) procedures were developed for the extraction of curcumin from turmeric. Turmeric powder was loaded into a column with 2-fold 80 % ethanol. The column was eluted with 80 % ethanol at room temperature. For quantitative analysis with a non-cyclic CCE, 8-fold eluent was collected as extraction solution. For large preparation with a cyclic CCE, only the first 2-fold of eluent was collected as extraction and other eluent was sequentially circulated to the next columns. More than 99 % extraction rates were obtained through both CCE procedures, compared to a 59 % extraction rate by the ultrasonic-assisted maceration extraction with 10-fold 80 % ethanol. The CCE procedures are high-efficient for the extraction of curcumin from turmeric with minimum use of solvent and high concentration of extraction solution[11].

Several HPLC methods are available for detecting/quantifying curcumnoids. Liquid chromatography-coupled mass spectrometry has been another versatile tool for detecting curcumin. Of all these the most sensitive method for detection of curcumin (up to 1 ng/mL) is by fluorescence, by exciting in the 400 to 450 nm region. Li *et al*.[12] studied stability of three curcuminoids and simultaneous determination of curcuminoids in turmeric by HPLC using ternary gradient system.

4. Synthesis

A century after its isolation from turmeric, the first paper on synthesis of curcumin was reported by Lampe in 1910[5]. The method involved five steps starting from carbomethoxyferuloyl chloride and ethyl acetoacetate. Later Pabon[13] reported a simple 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 and with slight modifications the method by Pabon has been adopted by several research groups for all subsequent curcumin syntheses.

5. Therapeutical properties

Curcumin (diferuloylmethane) the main curcuminoid present in turmeric and responsible for its yellow colour, has been found to possess many beneficial biological activities such as anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant and anti-infective effects[14]. Many bacterial strains display multidrug resistance and active anti-biotics available are limited. Curcumin is reported to be an effective anti-biotic against Methicillin-resistant *Staphylococcus aureus* (MRSA), a major human pathogen and has the potential of reducing the use of existing anti-biotics[15].

6. Anti-oxidant potential

Curcumin is an excellent scavenger of most reactive oxygen species (ROS), a property that bestows curcumin with anti-oxidant activity in normal cells. The reaction of peroxyl radicals with curcumin produces curcumin phenoxyl radicals, which are less reactive than the peroxyl radicals and thereby protecting from ROS-induced oxidative stress. Bhuller *et al*.[16] studied anti-oxidant and

biological activities of 15 curcumin analogues. The results revealed that compounds with specific functional groups and carbon skeleton had specific biological profiles. Among the compounds tested, the derivatives (*E*)-2-(3,4-dimethoxybenzylidene)-5-((*E*)-3-(3,4-dimethoxyphenyl) acryloyl)cyclopentanone, and (*E*)-2-(4-hydroxy-3-methoxybenzylidene)-5-((*E*)-3-(4-hydroxy-3-methoxyphenyl) acryloyl)-cyclopentanone and the parent compound curcumin exhibited the strongest free radical scavenging and anti-oxidant capacity.(*E*)-2-(4-hydroxy-3-methoxybenzylidene)-5-((*E*)-3-(4-hydroxy-3-methoxyphenyl)- acryloyl) cyclopentanone was the most potent angiotensin converting enzyme (ACE) inhibitor, while the derivatives, (*E*)-2-(4-hydroxybenzylidene)-6-((*E*)-3-(4-hydroxyphenyl)acryloyl) cyclohexanone, (*E*)-2-(3,4-dimethoxybenzylidene)-6-((*E*)-3-(3,4-dimethoxyphenyl) acryloyl)cyclohexanone and (*E*)-2-(3,4-dimethoxybenzylidene)-5-((*E*)-3-(3,4-dimethoxyphenyl) acryloyl)cyclopentanone exhibited strong tyrosinase inhibition. Moreover, (*E*)-2-(3,4-dimethoxybenzylidene)-6-((*E*)-3-(3,4-dimethoxyphenyl)-acryloyl) cyclohexanone was also found to be the strongest human HIV-1 protease inhibitor *in vitro* among the tested compounds. These curcumin analogs were not toxic against normal human lung cells[16].

7. Curcumin in wound healing

Curcumin has also been shown to have modulating effects on wound healing. The wound healing potential of curcumin is attributed to its biochemical effects such as its anti-inflammatory, anti-infectious and anti-oxidant activities. Curcumin has also been found to enhance cutaneous wound healing through involvement in tissue remodeling, granulation tissue formation, and collagen deposition. Various studies have shown that application of curcumin on wound also enhances epithelial regeneration and increases fibroblast proliferation and vascular density. Curcumin has the ability to enhance granulation tissue formation, collagen deposition, tissue remodeling and wound contraction. It has become evident that optimizing the topical application of curcumin through altering its formulation is essential to ensure the maximum therapeutical effects of curcumin on skin wounds[14].

8. Curcumin and cancer

The usefulness of curcumin in the treatment of several types of cancer has been well established. Thyroid cancer is the most common malignancy of endocrine organs, and its incidence rates have steadily increased over recent decades. Although the most indolent tumours can be effectively managed, metastatic tumours at distant secondary sites behave aggressively and currently there is no effective form of treatment. Zhang *et al*.[17] reported that curcumin might be an effective tumouristatic agent for the treatment of aggressive papillary thyroid carcinomas. It was reported that curcumin inhibited multiple metastasis steps of K1 papillary thyroid cancer cells and suppressed viability of K1 cells as well as its cell attachment, spreading, migration and invasion abilities in a dose-dependent manner. Curcumin could also down-regulate the expression and activity of matrix metalloproteinase-9 (MMP-9). The studies by Dahmke *et al*.[18] revealed that the anticancer effect of curcumin was increased during heating. During household cooking "deketene curcumin" which is formed as a result of pyrolysis, was shown to have stronger anti-cancer effect compared to curcumin and had higher toxicity on B78H1 melanoma cells[18]. Curcumin (0.5 %) significantly inhibited the production of aflatoxins (> 96 %)[19]. Curcumin and its metabolite, tetrahydrocurcumin have been extensively investigated as anti-inflammatory and anti-cancer molecules. Tetrahydrocurcumin was observed to be more effective than curcumin in preventing azoxymethane-induced colon carcinogenesis[20, 21].

9. Curcumin as anti-inflammatory agent

Curcumin has been used widely in traditional therapies for various diseases, especially as an anti-inflammatory agent[22]. The combination of curcumin with non-steroidal

anti-inflammatory drugs increased antinociceptive activity in rats. Antinociception was assessed using the formalin test. Diluted formalin was injected subcutaneously into the dorsal surface of the right hind paw. Nociceptive behavior was quantified as the number of flinches of the injected paw during 60 min after injection, and a reduction in formalin-induced flinching was interpreted as an antinociceptive response. Rats were treated with oral diclofenac (1–31 mg/kg), curcumin (3.1–100 mg/kg) or the diclofenac–curcumin combination (2.4–38.4 mg/kg). The oral bioavailability of diclofenac (10 mg/kg) was studied in presence and absence of curcumin (31 mg/kg). Diclofenac, curcumin, or diclofenac–curcumin combination produced an antinociceptive effect on the formalin test. The study indicated synergistic effect of curcumin and diclofenac as evidenced by the reduced experimental ED_{30} value (9.8 mg/kg) against the theoretical ED_{30} value of 19.2 mg/kg. The diclofenac–curcumin combination can interact at the systemic level and may have therapeutic advantages for the clinical treatment of inflammatory pain[22].

10. Curcuminoids in neuroprotection

Turmeric is used in traditional medicine as a neuroprotective agent. It protects the brain against neurotoxic insults and neurodegeneration. Multiple pathways including oxidative stress and mitochondrial damage are implicated in neurodegenerative diseases such as Parkinson's disease. Currently the drugs used in the treatment provide only symptomatic relief and have limitations in terms of adverse effects and inability to prevent neurodegeneration. Dietary supplementation of mice with 0.5 % and 1 % turmeric suspensions in drinking water for 3 months resulted in increase in GSH levels which was mediated through an increase in g-GCL activity[23]. To demonstrate neuroprotection by curcumin, several mechanisms have been put forth by various investigators. Curcumin and its analogues show inhibition of the Ca^{2+} -dependent and Ca^{2+} -independent activities of CaMKII *in vitro*. CaMKII is a downstream component of the neuronal glutamate signaling pathway and is involved in the glutamate-induced excitotoxicity. Hence acute inhibition of CaMKII may be a potential strategy for providing neuroprotection as shown by two independent groups using the CaMKII inhibitor tat-CN21 peptide. Pyrazole-curcumin is a better inhibitor of CaMKII, than the parent curcumin I[24].

Alzheimer's disease is another neurodegenerative disease with progressive loss in memory which is characterized by the deposition of the senile plaques mainly composed of β-amyloid fragment and neurofibrillary tangles. Acetylcholinesterase inhibitors are the major class of drugs approved for Alzheimer's disease, providing symptomatic relief and resulting in improvement in cognitive function. Ahamed and Gilani[25] used *in-vitro* and *ex-vivo* models of acetylcholinesterase inhibitory activity along with Morris water maze test to study the effect on memory in rats. Curcuminoids inhibited Acetylcholinesterase in the *in-vitro* assay with IC_{50} value of 19.67, bisdemethoxycurcumin 16.84, demethoxycurcumin 33.14 and curcumin 67.69 μM. In the *ex-vivo* acetylcholinesterase assay, curcuminoids and its individual components except curcumin showed dose-dependent (3–10 mg/kg) inhibition in frontal cortex and hippocampus. This indicated that total curcuminoids, curcumin, bisdemethoxycurcumin and demethoxycurcumin inhibited acetylcholinesterase *in-vitro* and *in-vivo* and curcumin the major component had relatively weak activity. At a fixed dose of 10 mg/kg, all compounds showed comparable effect in scopolamine-induced amnesia.

11. Curcumin and hepatoprotective action

The therapeutic potential of curcumin for treating hepatic disorders is well known. The molecular mechanism of the hepatoprotective action of curcumin is due to its anti-oxidant properties and inhibitory activity against nuclear factor (NF)-κB that regulates different proinflammatory and profibrotic cytokines. A systematic discussion of the hepatoprotective activity of curcumin

and its possible mechanisms of actions is discussed by Nabavi *et al*.[26]

12. Curcumin and diabetes

Curcumin, has renoprotective effects on diabetic nephropathy (DN) by down regulating sphingosinekinase 1-sphingosine 1-phosphate (SphK1-S1P) signaling pathway in diabetic rat kidneys and glomerular mesangial cells (GMCs) exposed to high glucose (HG)[27]. SphK1-S1P-mediated fibronectin (FN) and transforming growth factor-beta 1 (TGF-b1)over production were inhibited. In addition, curcumin dose dependently reduced SphK1 expression and activity in GMCs transfected with SphKWT and significantly suppressed the increase in SphK1-mediated FN levels. Furthermore, curcumin inhibited the DNA-binding activity of activator protein 1 (AP-1), and c-Jun small interference RNA (c-Jun-siRNA) reversed the HG-induced up-regulation of SphK1. These findings suggested that down-regulation of the SphK1-S1P pathway is probably a novel mechanism by which curcumin improves the progression of DN. Inhibiting AP-1 activation is one of the therapeutic targets of curcumin to modulate the SphK1-S1P signaling pathway, thereby preventing diabetic renal fibrosis.

A 9-month curcumin intervention in a prediabetic population significantly lowered the number of prediabetic individuals who eventually developed T2DM. In addition, the curcumin treatment appeared to improve overall function of b-cells, with very minor adverse effects. Therefore, this study demonstrated that the curcumin intervention in a prediabetic population is beneficial.

In a study, workers confirmed that CUR-G is the major metabolite of CUR found in the plasma after oral administration of CUR in rats. They compared the effects of CUR and CUR-G in HepG2 cells, and found that there were less effects of CUR-G compared to CUR, which was related to the absorption rates of these two compounds[28].

Susana *et al*.[29] studied therapeutic targets for curcumin in diabetes as well as the structural characteristics and targets of its analogues and observed that shortening of the central seven-carbon chain of curcumin gave rise to compounds without glucose-lowering effects but potentially useful for the treatment of diabetes complications; whereas preserving this chain retained the glucose-lowering properties.

13. Toxicity studies

Curcumin is found to have very low toxicity. The LD_{50} of oral administration of curcumin in rats as well as in mice is greater than 2000 mg/kg body weight with no adverse-effect or changes in clinical observations[30]. Reproductive toxicity of curcumin, was evaluated in Wistar rat by Ganiger *et al*.[31] for two successive generations. In this study curcumin, mixed at the concentrations of 1500, 3000 and 10,000 ppm was fed to three groups of rats, i.e., low, mid and high dose groups. Control group received experimental diet without the curcumin mixture. No treatment-related adverse toxicological effects were observed in the parental animals. None of the reproductive parameters were affected and there were no effects on the offspring other than a small reduction in pre-weaning body weight gain of the F2 pups at the highest dose level. It was concluded that the observed adverse effect level for reproductive toxicity of curcumin, fed in the diet for two successive generations to rats in this study was 10,000 ppm, which was equivalent to 847 and 959 mg/kg bodyweight per day for male rats and 1043 and 1076 for females for F0 and F1 generations, respectively. This toxicology study on curcumin was reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at the 61st Meeting, 2003. The JECFA group considered that the small body weight reduction in the F2 pups of the highest dose group prevented this from being regarded as a no adverse effect level, and so allocated an ADI for curcumin of 0–3 mg/kg bw based on the intake of 250–320 mg/kg bw in the mid-dose group as the NOEL[31].

14. Enhancing bioavailability

Curcumin is found to be safe to treat various ailments

either singly or in combination with other drugs. However, the clinical use of curcumin is limited to some extent because of its poor water solubility and low bioavailability. Hence studies are under way to enhance the bioavailability of curcumin and make use of this wonder molecule to the maximum level. Water-soluble turmeric extract using polyglycolized glycerides like Gelucire 44/14 has strong ROS scavenging potential than the methanolic turmeric extract, as Gelucire 44/14 extracts the rich amount of curcuminoids from turmeric. The antioxidant activity is mainly attributed to curcuminoids[32]. Spray drying technique has been found to be successful to preparare microparticles and the solubility of turmeric extract can be improved 100-fold by preparing microparticles by spray drying[33]. Derivatives of curcumin with alkyl-substituted amino acids, such as alanine, valine, serine and cysteine, exhibited lower IC_{50} values than did curcumin in antioxidant assays. With respect to anti-mutagenicity against *Salmonella typhimurium* TA 98 and TA 1531, the derivatives had better or similar effect to that of curcumin[34].

Krishnakumar *et al*.[35] evaluated the performance of impregnated curcumin. It was observed that curcumin impregnated with soluble fibre from fenugreek had enhanced bioavailability and slow release of stable colloidal curcumin. Oral administration of BR213 curcuma galactomannoside, curcumin-impregnated soluble fibre, dispersions enhanced the bioavailability 20 times at 250 mg/kg dosage in animals. Human hepatic bioavailability improved 12.9 times at a dose of 250 mg (equivalent to 100 mg curcumin) and 15.8 times at 1500 mg (equivalent to 600 mg curcumin) as compared to unformulated curcumin dosage of 1000 mg[35]. Ultrasound was found to be a novel tool for the particle size reduction and homogeneous distribution of colloidal curcumin in the fibre solution.

15. Conclusion

Curcumin possesses a blend of anti-carcinogenic, proapoptotic, anti-angiogenic, anti-metastatic, immunomodulatory and anti-oxidant activities. The molecular mechanisms underlying the activities of curcumin are diverse and involve combinations of cell signaling pathways at multiple levels of tumorigenesis. With the ongoing problems of drug resistance, toxicity, and high treatment cost associated with the current FDA-approved anti-cancer drugs, it would be most advantageous to look into curcumin as an anti-cancer agent, to be administered alone or in combination with available anticancer drugs; such explorations may demonstrate that curcumin offers not only efficacy but also affordability. Extensive clinical trials and mechanism of action have to be clearly understood to market it as a product.

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〔日本語訳（要旨）〕

クルクミン（クルクミノイド）―産業および医療における可能性

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ターメリック（*Curcuma longa* L.）は、リウマチ、糖尿病性潰瘍、食欲不振、咳、副鼻腔炎など様々な病気の治療のために、数世紀にわたって生薬に使用されてきたインドの一般的なスパイスである。インドは様々な病気に対する家庭薬として長年使用されているターメリックの世界最大の産地である。ターメリックの根茎には、黄色の基となるクルクミノイド類が2.5～6.0％含まれる。クルクミノイド類にはクルクミンⅠ（クルクミン）、クルクミンⅡ（ジメトキシクルクミン）、およびクルクミンⅢ（ビスジメトキシクルクミン）があり、これらは天然の抗酸化物質であることが分かっている。ターメリックに含まれ、その黄色の源である主要クルクミノイドのクルクミン（ディフェルロイルメタン）は、抗炎症、抗酸化、抗癌、抗変異原性、抗凝固、抗糖尿病、創傷治癒、および抗感染効果など多くの有益な生物活性を有することが確認されている。クルクミンは水への溶解度が低く、生物学的利用能も低いため、クルクミンの臨床用途はある程度の範囲で制限されている。この天然薬物の生物学的可能性を製品化するため世界中で研究が進められている。

PROFILE

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Functioning as Head Division of Crop Production and Post Harvest Technology in ICAR- Indian Institute of Spices Research. Joined Indian Council of Agricultural Research as Agriculture Scientist since 1985. Main area of research includes oil, oleoresin and pungent/colour principles of black pepper, ginger, turmeric and cardamom. Thirty years experience in the field of spice oils and oleoresin. Edited Book Chemistry of Spices. Published 52 research articles.

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Presently working as Principal scientist in the Division of Crop production and PHT, Indian Institute of Spices Research, Kozhikode. Has more than 29 years research experience in quality evaluation of spices, medicinal and aromatic crops and their bioactive principles. Major areas of interest include characterization of flavour and bioactive constituents of spices, namely, cardamom, ginger, turmeric, cinnamon, nutmeg, clove and allspice.