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DISCOVERY OF CURCUMIN: MIRACULOUS ACTIVITY AS ANTICANCER

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ABSTRACT
Cancer is the second most life-threatening disease and one of the main public health problems worldwide now a day. Despite the great advances in cancer therapy, the incidence and mortality rates of cancer remain high. Therefore, the quest for more efficient and less toxic cancer treatment strategies is still at the forefront of current research. Curcumin, the active ingredient of the Curcuma longa plant, has received great attention over the past two decades as an anticancer agent, antioxidant and anti-inflammatory. Curcumin has been used either as a single agent or in combination with other agents. Modern science has shown that Curcumin modulates various signalling molecules, including inflammatory molecules, transcription factors, enzymes, protein kinase, protein reductase, carrier proteins, cell survival proteins, drug resistance proteins, adhesion molecules, growth factors, receptors, cell-cycle regulatory proteins, chemokine, DNA, RNA, and metal ions. In this review article, we discuss the discovery and key biological activities (specific as anticancer) of Curcumin, with a particular emphasis on its activities at the molecular, cellular, animal, and human levels. A summary of the medicinal chemistry and pharmacology of Curcumin and its derivatives in regard to anticancer activity and their main mechanisms of action is also described in this review.

KEYWORDS: Cancer, Curcumin, Anticancer, Antioxidant, Anti- inflammatory, Medicinal chemistry, Pharmacology.

INTRODUCTION[1-8]

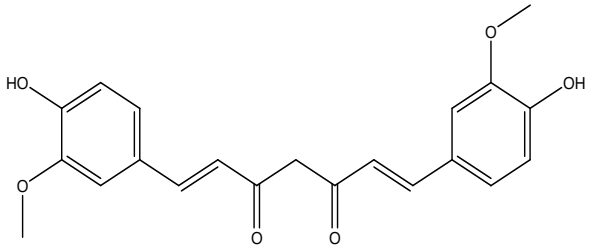
What is Cancer[1-4]

Cancer is the second most life-threatening disease and one of the main public health problems worldwide now a day. Cancer is one of the principal causes of mortality and morbidity around the globe and the numbers of cases are constantly increasing estimated to be 21 million by 2030. In 2019, there were around 11.57 lakhs new cases of cancer and more than 7.84 million deaths in the India alone. This uncontrolled proliferation of a normal cell which produces genetic instabilities and alterations accumulates within cells and tissues which transforms normal cell into a malignant cell. Despite the tangible advances in cancer therapy, the reported incidences of the disease and the mortality have not declined in the past 30 years. Understanding the molecular alterations that contribute to cancer development and progression is a key factor in cancer prevention and its treatment. There are several common treatments for targeting specific cancer cells to inhibit tumor development, progression, and metastasis without causing severe side effects. In addition to the chemically synthesized anticancer agents, several anticancer compounds with different modes of action have been extracted from plant sources, such as *Taxus brevifolia*, *Catharanthus roseus*, ***Curcuma longa,*** *Ocimum sanctum*, *Cephalotaxus* species, *Erythroxylum previllei*, and many others.

Curcumin[5-8]

Among them, Curcumin is the most important component of the rhizomes of *Curcuma longa* L. (turmeric) family (Zingiberaceae) and has been consumed for medicinal purposes for thousands of years. It was extracted from turmeric plant in a pure crystalline form for the first time in 1870. There are more than 9400 articles published on this **"magical molecule"** till date. Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-Dione) is also called diferuloylmethane. Curcumin is also known as "Natural yellw-3", that's why it is known as **Golden molecule**. Modern science has shown that Curcumin modulates various signalling molecules, including inflammatory molecules, transcription factors, enzymes, protein kinases, protein reductase, carrier proteins, cell survival proteins, drug resistance proteins, adhesion molecules, growth factors, receptors, cell-cycle regulatory proteins, chemokines, DNA, RNA, and metal ions. Curcumin and its derivatives have received immense attention in the past

two decades due to their bio functional properties such as anti-tumor, antioxidant, and anti-inflammatory activities. These properties are attributed to the key elements in the Curcumin structure. Therefore, a great deal of scientific work has shed light on the structure activity relationship (SAR) of Curcumin in an attempt to improve its physiochemical and biological properties. Due to the importance of cancer as a leading cause of death and the ongoing quest for more efficient and less toxic anticancer agents, this review has mainly focused on the anticancer activity of Curcumin.



Structure of Curcumin

DISCOVERY OF CURCUMIN[8, 9]

The discovery of Curcumin dates to around two centuries ago when Vogel and Pelletier reported the isolation of "yellow colouring-matter" from the rhizomes of *Curcuma longa* (turmeric) and named it Curcumin. Curcumin was first isolated in 1815 and formulated into its crystalline form in 1870. Later, this substance was found to be a mixture of resin and turmeric oil. In 1842, Vogel Jr. obtained a pure preparation of Curcumin but did not report its formula. In the decades that followed, several chemists reported possible structures of Curcumin. However, it was not until 1910 that Milobedzka and Lampe identified the chemical structure of Curcumin as diferuloylmethane, or 1, 6-heptadiene-3, 5-dione-1, 7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E). Further work by the same group in 1913 resulted in the synthesis of the compound. Subsequently, Srinivasan separated and quantified the components of Curcumin by chromatography. The first article published regarding the use of Curcumin in human disease was in 1937. This article found that healthy persons injected with an intravenous solution containing Curcumin had rapid emptying of the gallbladder, which demonstrated that Curcumin could treat sub acute, recurrent, or chronic cholecystitis.

Although turmeric, the major source of Curcumin, has been consumed as a dietary spice and a cure for human ailments for thousands of years in Asian countries, the biological characteristics of Curcumin were not scientifically identified until the mid-twentieth century. In a paper published in *Nature* in 1949, Schraufstatter and colleagues reported that curcumin is a biologically active compound that has anti-bacterial properties. The authors found that Curcumin was active against strains of *Staphylococcus aureus*, *Salmonella paratyphi*, *Trichophyton gypseum*, and *Mycobacterium tuberculosis*. Despite those findings, only five papers were published on Curcumin during the next two decades. In the 1970s, Curcumin became the subject of scientific investigation, and three independent groups discovered diverse characteristics of Curcumin, including cholesterol-lowering, anti-diabetic, anti-inflammatory, and anti-oxidant activities. Later, in the 1980s, Kuttan and colleagues demonstrated the anti-cancer activity of Curcumin in both *in vitro* and *in vivo* models. In 1995, our group was the first to demonstrate that Curcumin exhibits anti-inflammatory activity by suppressing the pro-inflammatory transcription factor nuclear factor (NF)-κB; we also delineated the molecular mechanism of the inhibition.

The interest in Curcumin research has increased dramatically over the years. As of June 2011, more than 4000 articles on Curcumin were listed in the National Institutes of Health PubMed database (www.ncbi.nlm.nih.gov/sites/entrez). We now know that Curcumin can modulate multiple signalling pathways in either a direct or indirect manner. This polyphenol has been shown to possess activities in animal models of many human diseases. In human clinical trials, Curcumin has been found to be safe and efficacious, and the U.S. Food and Drug.

BIOLOGICAL ACTIVITY OF CURCUMIN AS ANTICANCER[10-13]

Curcumin (diferuloylmethane) is the chief component of the spice turmeric. Turmeric contains a class of compounds known as the curcuminoids, comprised of Curcumin, demethoxycurcumin and bisdemethoxycurcumin. Curcumin is the principal curcuminoid and comprises approximately 2-5% of turmeric; it is responsible for the yellow colour of the spice as well as the majority of turmeric's therapeutic effects.

Aside from being employed as flavouring and colouring agent in food, turmeric has also been widely used in Ayurvedic medicine for its anti-oxidant, antiseptic, analgesic, antimalarial and anti-inflammatory properties. Curcumin has been consumed as a dietary supplement for centuries and is considered pharmacologically safe.

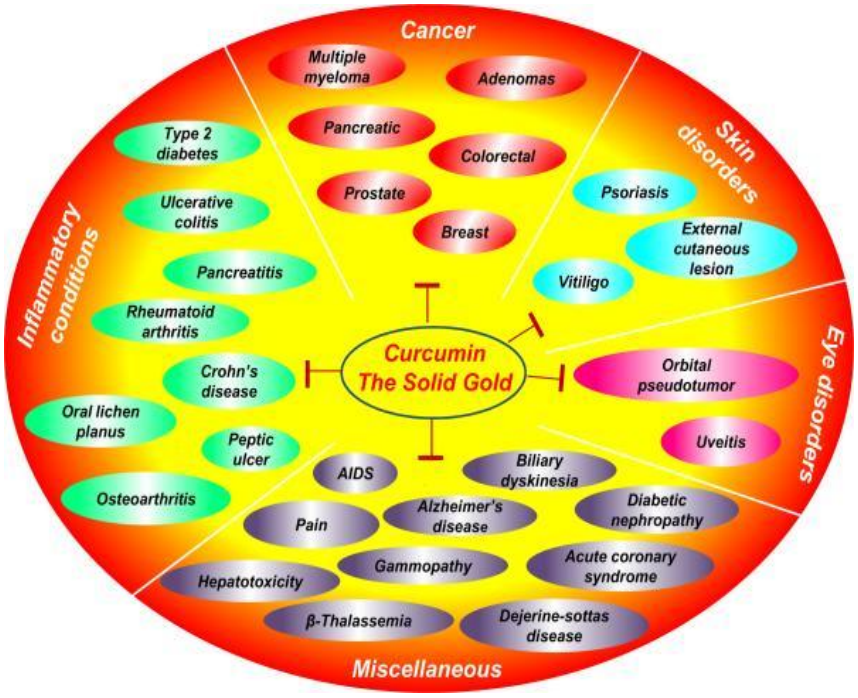


Fig. 2: The variety of human disorders against which curcumin's potential has been revealed by numerous clinical trials.

Curcumin has been studied in multiple human carcinomas including melanoma, head and neck, breast, colon, pancreatic, prostate and ovarian cancers. Epidemiological studies attribute the low incidence of colon cancer in India to the chemo preventive and antioxidant properties of diets rich in Curcumin. The mechanisms by which Curcumin exerts its anti-cancer effects are comprehensive and diverse, targeting many levels of regulation in the processes of cellular growth and apoptosis. Besides the vertical effects of Curcumin on various transcription factors, oncogenes and signalling proteins, it also acts at various temporal stages of carcinogenesis--from the initial insults leading to DNA mutations through the process of tumorigenesis, growth and metastasis. Because of the far-reaching effects and multiple targets of Curcumin on the cell growth regulatory processes, it holds much promise as a potential chemotherapeutic agent for many human cancers.

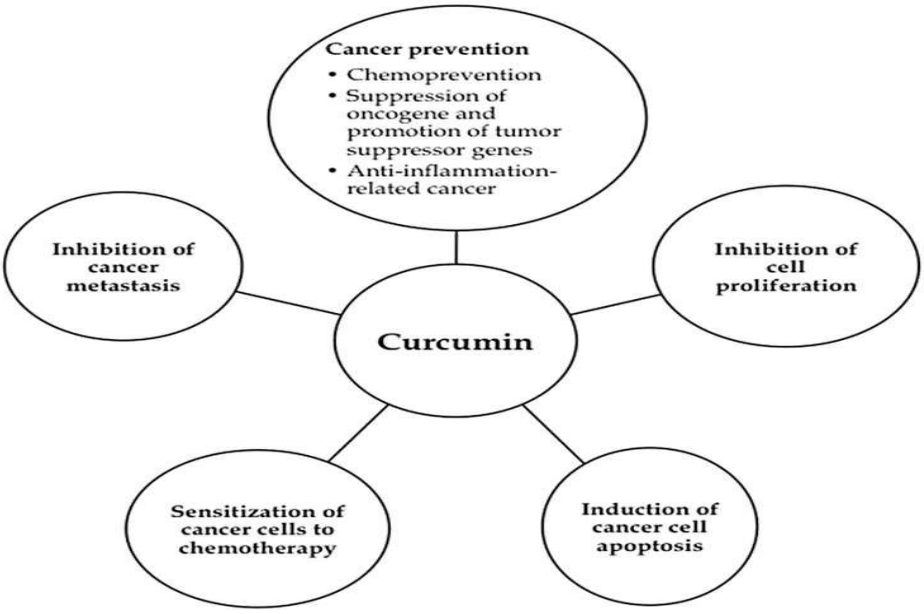


Fig. 3: Anticancer properties of Curcumin.

Curcumin induces cell death in numerous animal and human cell lines, including leukaemia, melanoma, and carcinomas of the breast, lung, colon, kidney, ovaries and liver. It appears to function by caspase-dependent

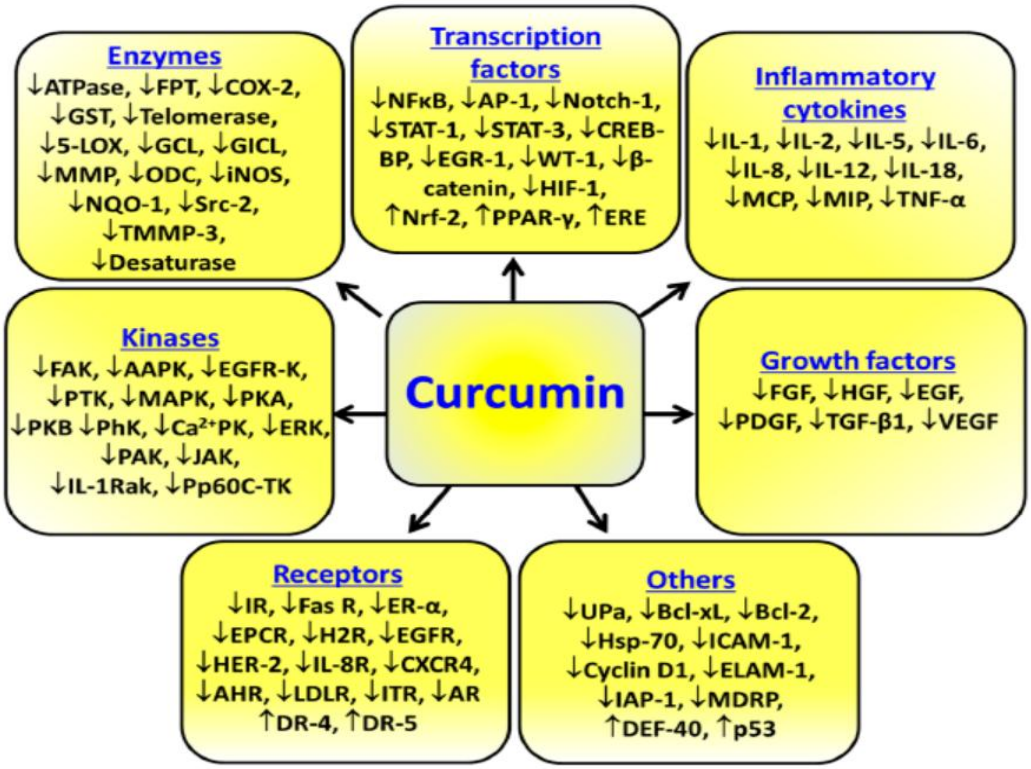
and independent (mitochondrial) mechanisms, which are associated with the presence and absence of p53. Certain data have demonstrated that Curcumin exhibits a biphasic action, which acts on the proteasome, with an activation at lower doses and with inhibition at higher doses. As the inhibition of the proteasome leads to apoptosis, and its stimulation leads to cell survival, it is possible that Curcumin results in apoptosis or survival depending on the dosage used. In addition, turmeric at different doses may also affect the type of cell death: Low doses lead to oxidative stress and apoptosis, while higher doses lead to reduced production of reactive oxygen species, reduction of ATP and necrotic cell death.

Mechanism of action of Curcumin[9, 14-16]

The main mechanisms of action by which Curcumin exhibits its unique anticancer activity include inducing apoptosis and inhibiting proliferation and invasion of tumors by suppressing a variety of cellular signalling pathways. Several studies reported curcumin's antitumor activity on breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumors, showing its capability to target multiple cancer cell lines.

Curcumin is a highly pleiotropic molecule with numerous targets and mechanisms of action, including altering the activity of enzymes, growth factor receptors, cofactors, and other molecules. The wide range of action of Curcumin can be demonstrated by its activity in inhibiting lipoxygenase by binding lipoxygenase itself or binding to phosphatidylcholine micelles. Curcumin also inhibits tumor invasion and angiogenesis by irreversibly binding CD13/ amino peptidase. It has also shown both in-vitro and in-vivo to block aggregation and fibril formation by directly binding small β- amyloid species.

In spite of all the above mentioned advantages, curcumin's applications are limited due to its low water solubility which results in poor oral bioavailability and also low chemical stability. Another obstacle is the low cellular uptake of Curcumin. Due to its hydrophobicity, the Curcumin molecule tends to penetrate into the cell membrane and bind to the fatty acyl chains of membrane lipids through hydrogen binding and hydrophobic interactions, resulting in low availability of Curcumin inside the cytoplasm. To overcome these obstacles and improve the overall anticancer activity of Curcumin, several structural modifications have been suggested to enhance selective toxicity towards specific cancer cells, increase bioavailability, or enhance stability. Another approach is to use different delivery systems to improve curcumin's physiochemical properties and anticancer activity. This review focuses on the SAR of Curcumin and its analogues and their anticancer activity in different cancer cell lines, animal models, and human clinical trials as well as different types of Curcumin delivery systems that have been used for cancer therapy.



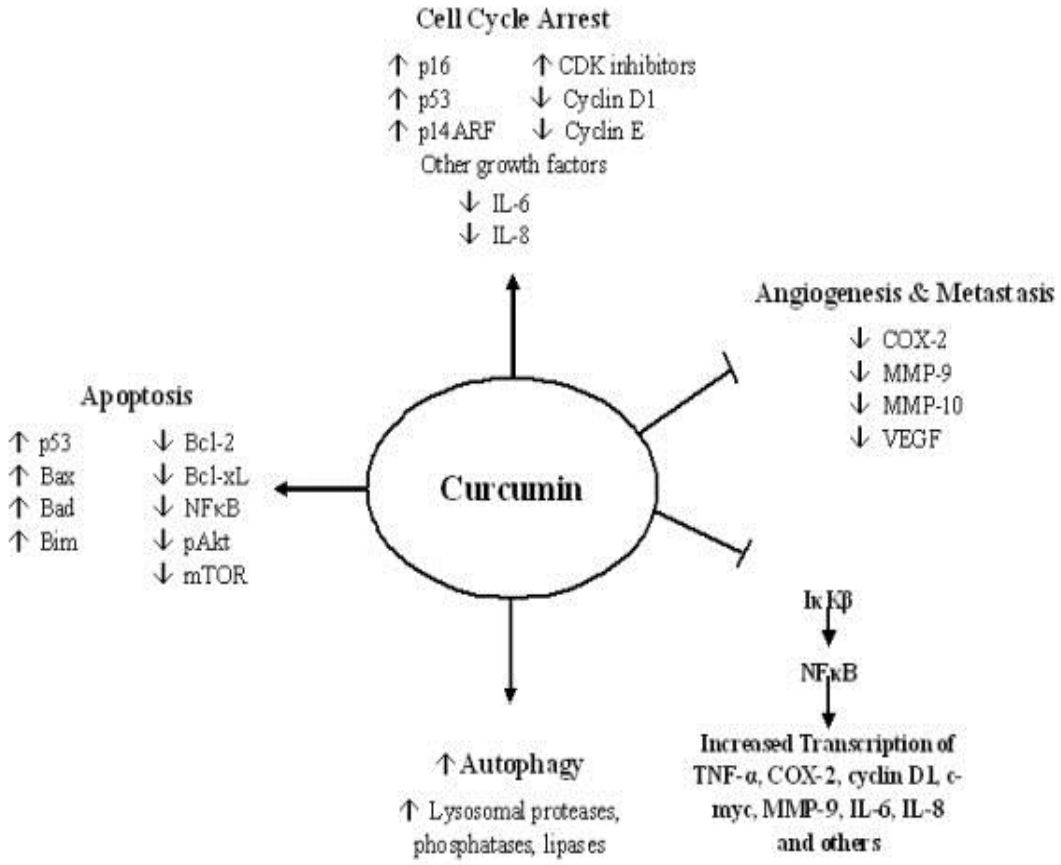


Fig. 1: Curcumin as tumor suppressor and it's mechanism of action

Structure activity relationship of Curcumin and its derivatives[17-21]

Chemical structure modification does not only affect the receptor binding and pharmacological activity of a drug molecule but also alters its pharmacokinetics and physiochemical properties. Determining the essential pharmacophores within a drug molecule requires a thorough study of its natural and synthetic analogues. The chemical structure of Curcumin is depicted in Figure 4. As can be observed, it consists of two phenyl rings and each ring substituted with hydroxyl group at C4 and methoxyl group at C3 and connected via a seven carbon keto- enol linker (C7). While Curcumin is naturally derived, its derivatives are generally produced by a chemical reaction between aryl-aldehydes and acetyl acetone. This assembly method can yield multiple chemical analogues, such as compounds with alkyl substituents on the middle carbon of the linker (C7 moiety). A SAR study of Curcumin derivatives demonstrates that the presence of a coplanar hydrogen donor group and a β-diketone moiety is essential for the antiandrogenic activity for the treatment of prostate cancer. In addition, scanning 50 Curcumin analogues showed that shortening the linker from seven carbon atoms (C7) to five carbon atoms (C5) improves the antiandrogenic activity. As a result of introducing a methyl group at both C2 and C6 positions, a new Curcumin derivative has been produced (Figure 4b). This derivative exhibited a steric hindrance effect toward metabolizing enzymes, such as alcohol dehydrogenase, and demonstrated significantly higher activity than Curcumin in inhibiting endothelial cell proliferation and invasion both in vitro and in vivo. Dimethylcurcumin or ASC-J9 (5-hydroxy-1, 7-bis (3, 4-dimethoxyphenyl)-1, 4, 6-heptatrien-3-one) is a newly developed Curcumin analogue which enhances androgen receptor degradation and has been used for treatment of prostate cancer. Moreover, it has also shown a significant antiproliferative effect against estrogen-dependent breast cancer cells. Although methylation has enhanced the targetability and activity of the molecule, it has also increased its hydrophobicity massively compared to Curcumin, which has limited its administrable dose in cancer therapy.

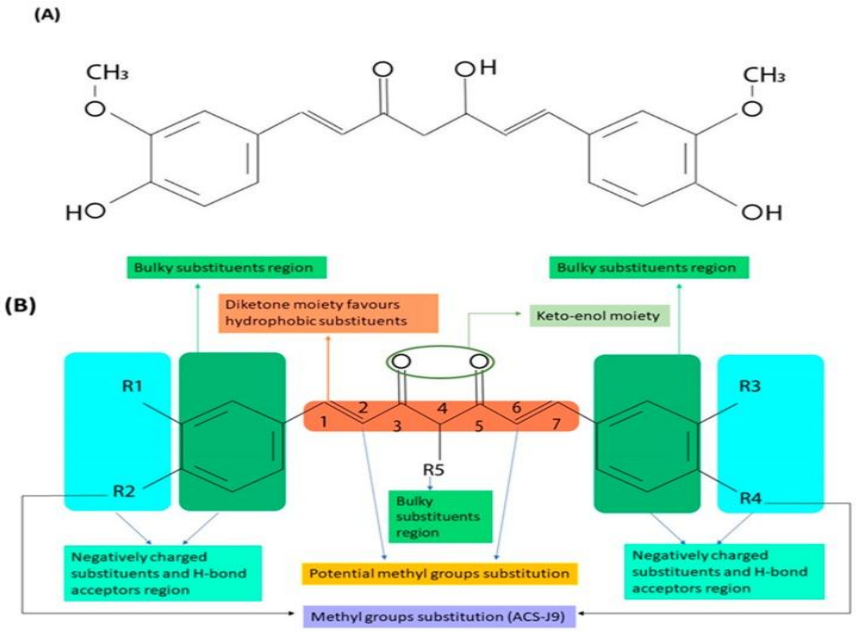


Fig 4 (A) Chemical structure of Curcumin. (B) The main pharmacophores and potential substitution positions.

Furthermore, studies on the kinetic stability of synthetic Curcumin derivatives have pointed out that glycosylation of the Pharmacophore aromatic ring improves the compound's water solubility, which enhances its kinetic stability and leads to a better overall therapeutic response. During phase I and phase II metabolism, the main routes of converting Curcumin into a higher extractable form are oxidation, reduction, and conjugation (glucuronidation and sulfurylation). The conjugation reactions occur on the hydroxyl groups (4-OH) attached to the phenyl rings of Curcumin. Thus, curcumin's kinetic stability can be enhanced by masking the 4-OH groups. Another study has revealed a correlation between the hydrophobic property of the benzyl rings and androgen receptor affinity. The benzyl rings are also crucial for inhibiting tumor growth, and adding hydrophobic substituent, such as CH_3 groups, on them (R1, R2, R3, R4 in Figure 4B) have been linked to the increased antitumor activity of Curcumin derivatives. O-methoxy substitution was found to be more effective in suppressing nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), but this modification has also affected the lipophilicity of Curcumin. A summary of the potential sites of modification on the Curcumin molecule is illustrated in Figure 4B.

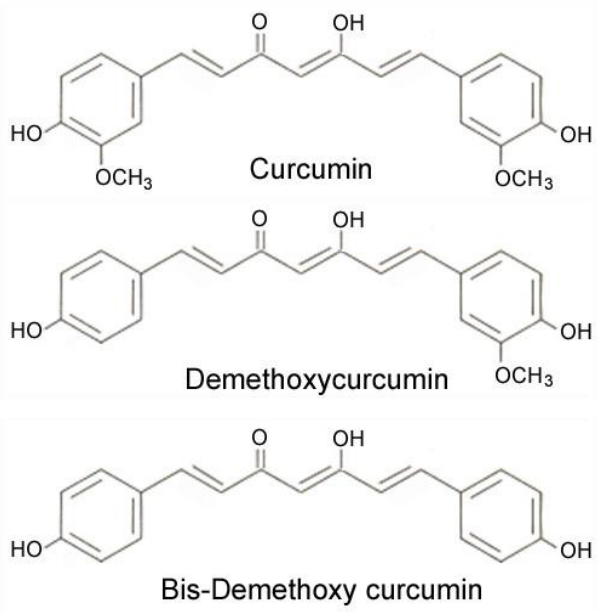


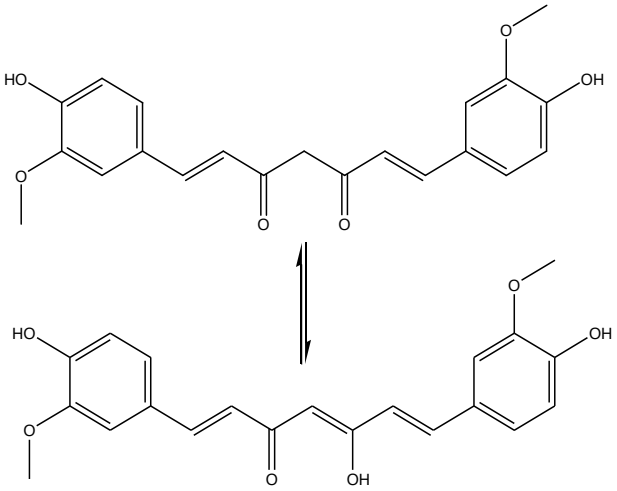
Fig. 5: Structure of the curcuminoids curcumin, demethoxycurcumin and bisdemethoxycurcumin

Some of the modified curcuminoids exhibit enhanced anticancer and anti-inflammatory activities compared to Curcumin due to the low level of hydrogenation, high level of methoxylation, and unsaturation of the diketone moiety. Ortho-methoxy substitution of the essential radical of curcuminoid alters the heptadiene moiety and the hydrogenation level. A comparative study on Curcumin and its derivatives revealed stronger antioxidant activity for several hydrogenated Curcumin derivatives compared to the original Curcumin compound. For example, tetrahydrocurcumin (THC) exhibited higher antioxidant activity than dihydrocurcumin (DHC) and unmodified Curcumin. Unlike Curcumin, THC, which is a non-electrophilic

derivative, failed to suppress the signal transducer and activator of transcription 3 (STAT3) signalling pathway and induce apoptosis. This suggests that the electrophilic nature of Curcumin is essential for inhibiting the STAT3 signaling pathway during anticancer therapy. Metallo-curcumin-conjugated DNA complexes have been constructed using Cu^{2+}/Ni^{2+}/Zn^{2+} metal ions to improve Curcumin solubility and enhance DNA-binding ability. These complexes also showed a better antibacterial activity and significant toxicity to several prostate cancer cell lines.

In addition to anticancer and anti-inflammatory properties, curcuminoids exert antioxidant activity mainly through the chelating effect of the diketone moiety. The presence of metals such as Cu^{2+}, Fe^{2+}, and Pb^{2+} boost the chelating power of curcumin derivatives. The unsaturated diketone group in curcumin root is a Michael reaction acceptor, part of phase II enzyme inducers, which can be responsible for NF-κB suppression in cancer cells. However, an investigation on 72 different Curcumin derivatives did not find a direct correlation between the inhibition of tumor growth through NF-κB and antioxidant activity. *O*-methoxy substitution resulted in increased antioxidant activity of Curcumin only when the methoxy group was not linked to the proton acceptor β-diketone moiety through conjugation. The equilibrium between the keto and enol forms of Curcumin relies on environmental factors such as pH. The keto form is dominant at acidic or neutral pH, while the enol form is more common in basic pH. This unique property has been exploited in the discovery of new Curcumin nanoassemblies with a buffering capacity that exhibit the "proton sponge effect" in endosomes and lysosomes.

Although Curcumin has low water solubility and poor bioavailability, it enjoys a strong pharmacological effect in clinical applications. A novel study attempted to explain this unique property of Curcumin by testing the pharmacological effect of curcumin's metabolites resulting from physiological degradation. The parallel docking calculations of Curcumin degradation products were found to be similar to those of Curcumin because they share with the original compound the same binding pockets required for inhibiting several enzymes.



Keto- enol tautomerisam in Curcumin.

SUMMARY

1. Curcumin is the active ingredient of the dietary spice turmeric and has been consumed for medicinal purposes for thousands of years. Modern science has shown that Curcumin modulates various signalling molecules, including inflammatory molecules, transcription factors, enzymes, protein kinase, protein reductases, carrier proteins, cell survival proteins, drug resistance proteins, adhesion molecules, growth factors, receptors, cell-cycle regulatory proteins, chemokine, DNA, RNA, and metal ions.
2. Because of this polyphenol's potential to modulate multiple signalling molecules, it has been reported to possess pleiotropic activities. First shown to have anti-bacterial activity in 1949, Curcumin has since been shown to have anti-inflammatory, anti-oxidant, pro-apoptotic, chemo preventive, chemotherapeutic, anti-proliferative, wound healing, anti-nociceptive, anti-parasitic, and anti-malarial properties as well. Animal studies have suggested that Curcumin may be active against a wide range of human diseases, including diabetes, obesity, neurologic and psychiatric disorders, and cancer, as well as chronic illnesses affecting the eyes, lungs, liver, kidneys, and gastrointestinal and cardiovascular systems.
3. In this article, we discuss the discovery and key biological activities of Curcumin, with a particular emphasis on its activities at the molecular, cellular, animal, and human levels.

CONCLUSION AND FUTURE PERSPECTIVE

Curcumin, the active ingredient of the *Curcuma longa* extract, has been studied widely over the past few decades for its anti-inflammatory, antioxidant, anticancer, and ant androgenic effects. Curcumin has shown considerable anticancer effects against several different types of cancer, including prostate cancer, breast cancer, colorectal cancer, pancreatic cancer, and head and neck cancer both in vitro and in vivo. Recently, a number of studies have indicated the anticancer activities of Curcumin by investigating its effect on a variety of biological pathways involved in mutagenesis,

apoptosis, tumorigenesis, cell cycle regulation and metastasis.

Furthermore, its efficacy and safety in cancer patients either alone or in combination with other anticancer agents has been proven in several clinical studies with human subjects. However, the anticancer application of Curcumin has been limited mainly due to its low water solubility, which results in low cellular uptake and poor oral bioavailability, as well as low chemical stability. In spite of the tremendous effort to improve the physicochemical and biological properties of Curcumin, there are still several issues to be addressed in regard to its bioavailability, potency, and specificity for the target tissue. The medicinal chemistry approaches to improving the pharmacological properties of Curcumin have not managed to increase its potency significantly, and the Curcumin derivatives are not more potent than Curcumin itself. The key pharmacophores contributing to the biological activity of Curcumin are known to be the hydrogen donor group, the β- diketone moiety, the phenyl rings, and the substituent groups on them. Chemical modification of these moieties has led to Curcumin derivatives with higher efficacy and/or enhanced water solubility or stability.

Due to the low potency of Curcumin and its derivatives, higher doses are required to see a therapeutic response, which increases the adverse effects and reduces the patient compliance. Another drawback of the structural modification is that it is difficult to achieve a balance between efficacy and solubility, and in most cases, one has been sacrificed in favour of the other. Most of the structural modifications that improve Curcumin efficacy make the molecule more hydrophobic and reduce its solubility. Therefore, more work has to be done in this regard to overcome this problem.

These benefits are best achieved when Curcumin is combined with agents such as Piperine, which increase its bioavailability significantly. Research suggests that Curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and Hyperlipidemia. It may also help in the management of exercise-induced inflammation and muscle soreness, thus enhancing recovery and subsequent performance in active people. In addition, a relatively low dose can provide health benefits for people that do not have diagnosed health conditions.

In light of the long and established experience with Curcumin as a foodstuff and as a natural medicine in humans, its low cost, its proven chemo preventive and therapeutic potential, and its pharmacological safety, Curcumin is moving rapidly from the kitchen shelf toward the clinic.

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