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A COMPREHENSIVE STUDY OF RECENT ADVANCES IN CURCUMIN

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ABSTRACT

Curcumin, a low molecular weight , lipophilic major yellow natural polyphenolic and the most well known plant derivedcompound, is extracted from the rhizomes of the turmeric [curcuma longa] plant, belonging to Zingiberaceae.Curcumin and its analogues prevent oxidative damage and inhibit the binding of toxic metabolites to DNA. Its anti- inflammatory, anticancer and anti-oxidant properties of exploited efficiency may benefit mankind in colourful ways. It has a low toxic effect on the body, hence large doses can be given without any fear of toxicity that reflects its broad therapeutic index. It shows a wide spectrum of biological actions like anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anti-coagulant,antifertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, antiulcer, hypotensive, hypercholesterolaemia, antivenom activities.This review article mainly focuses on the properties, chemistry, pharmacological activities like antibacterial, antiviral, anti-inflammatory, antidiabetic, antioxidant, anti-HIV, antimicrobial, antifertility, anti-parkinsonism, antifungal, anticoagulant,cardioprotective, hepatoprotective and also effective in various types of cancers and also their toxicity studies.

KEYWORDS: Anti-inflammatory,Antioxidant,Curcuma longa,Curcumin extractionCurcumin

INTRODUCTION

Turmeric is an Indian rhizomatous herbal plant [Curcuma longa] of the ginger family [Zingiberaceae]of well-known medical benefits. The medical benefits of turmeric could be attributed to the presence of active principle called Curcuminoids.Curcumin,demethoxycurcumin [DMC] and bisdemethoxycurcumin [BDMC] are collectivelyknown as curcuminoids. These yellow coloured curcuminoids areisolated from curcuma longa [turmeric] rhizomes.It is a perennial herb that grows primarily in tropical and subtropical climates. The fat-soluble polyphenolic pigments also called curcuminoids are mainly responsible for the yellow colour of curcumin.Curcumin has been used in tradition as a medical herb due to its various advantages such as antioxidant, anti-inflammatory, anti-mutagenic, antimicrobial, and several therapeutic properties. Curcumin shows poor absorption, rapid metabolism, and rapid elimination. Several agents have been introduced to

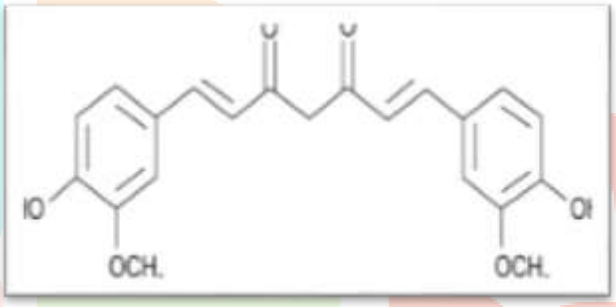
improve the bioavailability of curcumin. Most interesting one is piperine, it enhances curcumin bioavailability by blocking the metabolic pathways of curcumin.Curcumin is available in several forms including capsules, tablets and ointments. Curcuminoids have been approved by the US Food and Drug Administration [FDA] as 'Generally Recognised as Safe' [GRAS]. It is the purpose of this review to provide a brief overview of thepotential health of curcumin.

PROPERTIES OF CURCUMIN

- Curcumin [1,7-bis(hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] C21 H20 O6, is the mostimportant active ingredient responsible for the biological activity of turmeric.
- Curcumin is insoluble in water; but soluble in ethanol and acetone
- Naturally occurring ratio of curcuminoids in curcumin are about 5% bisdemethoxycurcumin. 15%demethoxycurcumin and 80% curcumin.(1)
- Curcumin is relatively unstable in phosphate buffer at ph 7.4 and the stability is strongly improved by either lowering the ph,or by adding
  glutathione;N-acetyl cysteine; ascorbic acid or rat liver microsomes (2)
- chemical synthesis of curcumin analogues has resulted in compounds with stronger antioxidant and cancer chemoprotective activities (3)
- The unique structure of curcumin, which has the phenolic hydroxyl group, heptadiene chain and diketone moiety (6)is responsible for all the therapeutic activities of curcumin such as anti- inflammatory,antitumor, anti-cancer,anti-HIV, antibacterial,antidiabetic, antioxidant,a wound healing agent, Alzheimer's disease and as an antidepressant agent
- First turmeric lowers the production of inflammation inducing histamine.
  Second, turmeric promotes circulation, pushing toxins out of small joints
  where cellular wastes and inflammatory substances are usually trapped,and it also boosts and prolongs the function of the body's natural anti-inflammatory adrenal hormone,cortisol.
- Turmeric is a cholagogue ,meaning it stimulates bile secretion,aiding digestion and removing toxins from the liver.
- Turmeric has a proven effect on cancer ie. Pancreatic cancer,prostrate cancer,multiple myeloma
- Turmeric can reduce insulin resistance and improves pancreatic cells functions
- Turmeric is more beneficial to type 2 diabetics and it can also reduce the intensity of type 1 diabetics
- It can reduce acne due to its antiseptic properties

CHEMISTRY OF CURCUMIN

The chemical compound curcumin, also called diferuloyl methane, is symmetrical. Curcumin is known by the IUPAC nomenclature (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl).1,6-Heptadiene-3,5-Dione has a molecular weight of 368.38 and the chemical formula C21H20O6. Its structure consists of three chemical components: two aromatic ring systems with o-methoxy phenolic groups, linked together by a seven-carbon linker made up of an,-unsaturated -diketone moiety [3-6,33]. Scheme 2 provides curcumin's chemical structure.It is almost insoluble in water and readily soluble in polar solvents like DMSO, methanol, ethanol, acetonitrile,chloroform, ethylacetate, etc. It is sparingly soluble in hydrocarbon solvents like cyclohexane and hexane.curcuin has an alliphatic man chain that is unsaturated, and the aryl group can be substituted or not.the active constitunet of turmeric are flavonoid curcumin (diferuloyl methane)and various volatile oils including turmerone, at lantone,and zingiberene.other constituents include protein, sugars and resins.Curcumin which makes up 0.3-5.4 percent of raw turmeric, is the most well studied active compound.



EXTRACTION OFCURCUMIN FROM TURMERIC

Literature studies have shown that the extraction of curcumin from turmeric could be done in several different ways. The curcuminoids are not water-soluble and therefore extractions have to be made in nonpolar solvents. In previous studies hexane, acetone, ethylene dichloride and different alcohols have been used to extract the curcumin analogues. It has been shown that the best yield has been obtained from the attempts where the extraction is made by acetone.

One way to extract the compounds is to use a soxhlet apparatus and it implies that the extraction and filtration of the productis done in the same step. The powder of turmeric is put in a paper thimble in a glass container. The vapour of heated solvent is condensed when it reaches the glass container and fills it up. When the volume of the extract reaches a certain level, the filtrate will flow back by leverage to the round bottom flask containing the solvent. By observing when the filtrate becomes colourless, the extraction is stopped.

Another way to extract the curcuminoids is to suspend the turmeric powder in acetone and stir it for several hours. To get rid of the remaining unsolved material from the turmeric powder, the solution is filtered off. The quantity of the curcuminoids can be analyzed by using a HPLC with a suitable mobile phase. However, to separate the molecules in a larger amount, column chromatography has to be done with an appropriate mobile phase. The mobile phase is chosen by testing different solvents on TLC with UV-detection to get appropriate

Rf values, and an optimized separation of the curcuminoids. Further purification of purified and separated curcuminoids can be done by crystallization.

SOXHLET EXTRACTION

A large filter paper was used instead of a paper thimble. The paper was folded so that it could contain 20 g of turmeric powder and was then placed in the soxhlet apparatus. 200 ml acetone was heated and refluxed for extraction of the "filter paper thimble". The procedure was monitored until the yellow colour of the extractions faded after 5 h. An advantage with Soxhlet extraction was that no further filtration was needed before it was concentrated. The obtained extract gave a crude yield of 2,6 g, which was purified by column chromatography.

SEPARATION OF CURCUMIN

To distinguish curcumin and its equivalents, column chromatography was used to purify all extractions. A 100 mL mixture of silica gel and dichloromethane was used to pack the column. Using the Rf values from TLC, a suitable mobile phase to elute the compounds was selected.plates that detect UV light. The best separation between the three curcuminoids was achieved using the dichloromethane-methanol (97:3) elution method. The first column was created to clean the extract of any potentially unknown chemicals left behind from the turmeric powder. Through TLC analysis, the mobile phase dichloromethane/methanol (97:3) was used to regulate the fractions. The three analogues were not properly separated after the initial column chromatography, though. The same volumes of silica and dichloromethane were used to create a second column in an effort to achieve a better separation.

Unfortunately, the TLC analysis of the results did not reveal any improved separation. With the exception of a few fractions that contained pure curcumin (A), the majority of the fractions from the initial chromatography were essentially undissociated. Following many columns of the semi-separated pooled fractions, pure samples of each of the curcuminoids A–C were produced. The pure substances were examined The three analogues were not properly separated after the initial column chromatography, though. The same volumes of silica and dichloromethane were used to create a second column in an effort to achieve a better separation.Unfortunately, the TLC analysis of the results did not reveal any improved separation. With the exception of a few fractions

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Compound A: 1H NMR (CD3)2CO (300 MHz): 3.90 (6H,s), 5.93 (1H, s), 6.60 (2H,d),6.82 (2H,d), 7.10(2H, d), 7.18 (2H, s), 7.56 (2H, d)

PHARMACOLOGICAL ACTIVITIES

Curcuma longa has been proven to have a number of therapeutic properties. The majority of the plant's pharmacological properties are found in the rhizomes, which are also utilized as anti-diabetic, anti-inflammatory ,anti-diarrheal , hepatoprotective , and anti-asthmatic medications. Additionally, it is frequently found in cosmetics. The next paragraphs address the numerous pharmacological effects of turmeric.

ANTI INFLAMMATORY ACTIVITY	Examples of certain chemicals that are inhibited by curcumin include phospholipase, lipoxygenase, COX-2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, and hyaluronidase,Interferon- inducible protein, tumour necrosis factor, and interleukin-12 are other examples. The molecule in turmeric has been shown to have a stronger anti- inflammatory effect.Curcumin seems to have an anti-inflammatory impact by inhibition of cytokines that are pro-inflammatory.
ANTI-DIABETIC	Researchers have discovered that combining turmeric with amla and honey can help treat diabetes.The use of turmeric revealed an increase in postprandial blood insulin levels while having no effect on blood glucose levels, indicating that turmeric may have triggered insulin secretion. By preserving the vital enzymes needed for it, the curcuminoid in turmeric prevents lipid peroxidation. A scientific study has demonstrated the effectiveness of turmeric powder as a diabetes treatment.Additionally, the acetone extract lowers blood glucose levels.

CARDIOVASCULAR DISEASES	Unlike other antioxidants, turmeric has a variety of antioxidants that do not degrade when heated.These antioxidants in turmeric assist prevent atherosclerosis by preventing cholesterol from degrading.Similar to vitamin E and C, these antioxidants demonstrate that free radical reaction is prevented. An animal study demonstrates that the antioxidants in turmeric reduce the levels of cholesterol and other triglycerides, which are known to cause a number of cardiovascular problems.In a study carried out in America, two groups of mice were chosen, and both groups were fed the typical American diet, with the exception of one group that also received turmeric along with the meal.After a four-month investigation, it was discovered that the mice that had been fed turmeric had 20 percent less blocked arteries than the control group. Rabbits were also subjected to this impact.
HEPATOPROTECTIVE EFFECT	Turmeric powder works well to treat jaundice. Jaundice is treated using a tri- mixture of turmeric, amla, and gairika. Due to its capacity to scavenge free radicals, the anti-inflammatory action of curcumin found in turmeric extract has hepatoprotective effect.It demonstrates improved hepatocyte repair by reducing inflammation inside them.Oral administration of the ethanolic extract demonstrated a dose-dependent hepatoprotective effect. In addition to these, it contains volatile oils that haveanti-inflammatoryproperties.
NEUROPROTECTIVE EFFECT	By lowering oxidative stress, the volatile oil included in turmeric exhibits neuroprotective effects in ischemia. The turmeric oil is demonstrated to considerably lessen the mitochondrial failure observed in ischemia. This demonstrates that turmeric's volatile oil may have neuroprotective properties.
ALZHEIMER'SDISEASE	When curcumin is given to old mice who have plaque buildup, it greatly reduces the plaque deposition found in Alzheimer's disease.Additionally, it lessens the quantity of cells subjected to oxidative stress. The amazing anti-inflammatory and antioxidant properties of curcumin are the cause of its therapeutic effect.

CHEMOPROTECTIVE ACTIVITY	Curcumin has the ability to activate DDR (DNA Damage Response), which can be employed and applied in the treatment of prostate cancer, making it suitable for usage in nutraceuticals. Cells that have been exposed to bile acid for a longer period of time can be healed by curcumin. These effects of curcumin have been demonstrated and examined in both animal and human cell cultures.
ANTI CANCER ACTIVITY	Curcumin, the primary component of turmeric, inhibits mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis, and metastasis among other cancer-related processes. It also exhibits anti- proliferative properties in a variety of cancer types. In addition to these, it also inhibits a significant number of growth factor receptors and other molecules involved in the development of tumours.Curcumin confers anti-cancer efficacy via changing the tumour cell's cell cycle. Curcumin has the ability to demonstrate cancer chemotherapy, and it is widely known that curcumin is well tolerated in people. Utilising curcumin for lung cancer.
ANTI-ALLERGICEFFECT	Rat stomach mast cells are likewise deregulated by curcumin, which also lowers or suppresses histamine release. In vitro compound 48/80- induced systemic anaphylaxis was reduced by curcumin, while in vivo passive cutaneous anaphylaxis was mediated by anti-DNP immunoglobulin E (IgE). Thus, it was demonstrated that it can stop mast cell-dependent allergic reactions
ANTIDERMATOPHYTIC ACTIVITY:	Curcumin's antimutagen, antioxidant, free radical scavenging, anti- inflammatory, and anti-carcinogenic qualities enable it to shield human skin from damaging UV radiation. In addition, the plant's leaves have demonstrated encouraging antifungal action against fungi found on human skin.

ANTI-DRUG RESISTANT ACTIVITY	Curcumin is a powerful inhibitor of drug resistance. It demonstrates a new capacity to stop P-glycoprotein and its mRNA from being upregulated as a result of Adriamycin (ADM). The increased intracellular drug accumulation and concurrently increased ADM cytotoxicity are functionally related to thepreventive capacity.

CURCUMIN DELIVERY

1. **Oral delivery**

Curcumin has often been administered orally in research, whether the subjects are people or animals. This curcumin, when taken orally, showed a number of biological benefits, including antioxidant, anti-inflammatory, anti-cancer, and antidiabetic.

Recently, it was demonstrated that curcumin (3 mg) given orally to mice attenuated oxidative stress following muscle injury brought on by downhill jogging. The oxidative stress brought on by exercise in people has also been linked to curcumin. In a trial, 90 mg of curcumin or a placebo were given orally two hours before and right after exercise. By raising blood antioxidant capacity, curcumin administration reduced exercise-induced oxidative damage.In mice, curcumin given orally decreased

inflammatory cytokines including TNF, cyclooxygenase (COX)-2, and inducible nitric oxide synthase, indicating that it has anti-inflammatory properties. It also further suppressed colon carcinogenesis brought on by dextran sodium sulphate. Curcumin used orally has been demonstrated in clinical trials to inhibit inflammatory molecules.

2. **Subcutaneous administration**

Curcumin has been administered subcutaneously to animals to produce efficient and long-lasting tissue concentrations. Curcumin is formed because sustained release of unformulated curcumin subcutaneously administered in animals is probably not possible. Mice's liver continued to contain curcumin for over a month after receiving a single subcutaneous dosage of microparticles. Additionally, it has been demonstrated that when MDA-MB-231 xenografts were implanted into naked mice, the curcumin microparticle formulation significantly outperformed controls in terms of its anticancer effectiveness.

3.Delivery Intravenously

Numerous studies have demonstrated that curcumin intravenously injected displays anticancer properties in animal models. Curcumin has been proven by Kim et al. to have anticancer effects in a mouse xenograft model of colorectal cancer.

Additionally, they have demonstrated that human serum albumin (HSA) nanoparticles loaded with curcumin have a better therapeutic impact than curcumin without producing toxicity. Numerous other research showed that liposomal curcumin prevented the development of various tumour types in mice models.

4.Topical delivery

A topical therapy is a drug that is used to cure illnesses by applying it to bodily surfaces like the skin or mucous membranes. To explore the effects of curcumin on inflammation in target organs, wound healing, skin cancer, and other conditions, it

has been applied topically. According to a study, topical application of a curcumin gel formulation significantly reduced imiquimod-induced psoriasis-like inflammation in the ears of BALB/c mice. It reduced the mRNA levels of the cytokines IL-17A, IL-17F, IL-22, IL-1, IL-6, and TNF- in the skin of the ear.Curcumin applied topically has also been reported to speed up the recovery of skin wounds caused by CO2 lasers.

5. Nasal delivery

Nasal administration of curcumin has been utilised to improve its bioavailability and facilitate direct medication delivery from the nose to the brain. According to a study, the absolute bioavailability of curcumin in an in situ ion-sensitive gelling system based on microemulsions was 55.82% after intranasal delivery. Additionally, following intranasal administration, there was a larger concentration of curcumin in the brain compared to the blood than there was after intravenous administration.

CURCUMIN BIOAVILABILITY

Evidence from multiple academic publications showed that curcumin had poor bioavailability, biodistribution, metabolism, and absorption. Therefore, ongoing research on curcumin has shown some potential solutions to these issues. Several formulations, including nanoparticles, liposomes, micelles, and phospholipid complexes, have been developed to improve the bioavailability, longer circulation,

improved permeability, and resistance to metabolic processes of curcumin.

CONCLUSION

Curcumin has attracted interest from all over the world due to its many health benefits. These benefits appear to be primarily mediated by its anti-inflammatory and anti-oxidant activities. The most effective approach to obtain these benefits from curcumin is to mix it with ingredients that dramatically increase its bioavailability. According to study, curcumin may help treat oxidative and inflammatory disorders, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. Additionally, it could help physically active individuals recover more quickly and perform better in the future by reducing inflammation and muscle soreness brought on by exercise. Additionally, a relatively small dose may be beneficial even for people who have no recognised medical conditions.

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CONFLICT OF INTEREST

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