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CURCUMIN AS AN ANTICANCER AGENT

Shruti Santosh Gavali[*1], Sujata V. Lambe[*2]

[*1,2]SMBT College Of Pharmacy, India.

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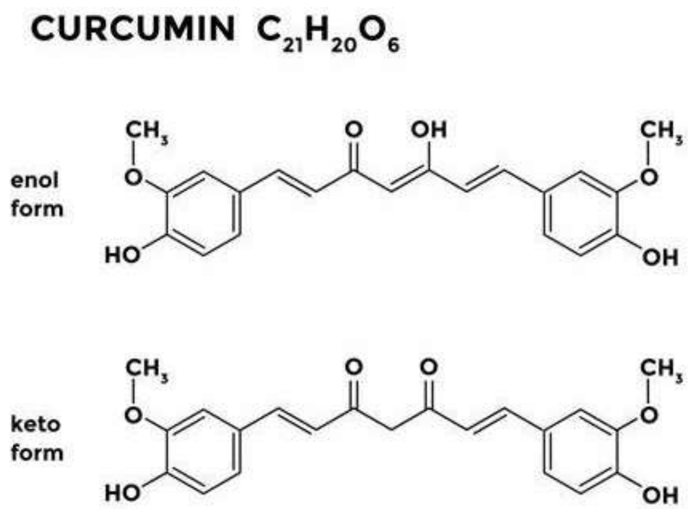
ABSTRACT

Curcuma longa, or turmeric, is a spice that has been used extensively for its therapeutic qualities in the ayurvedic medicine systems of South Asia, including China and India. Curcuma's primary constituent, curcuma, contains three curcumins, which give turmeric its various therapeutic and physical qualities. The current study examines the literature in a systematic manner about curcumin's anti-inflammatory properties in cancer therapy. Studies have revealed that curcumin is a very pleiotropic chemical that interacts with a wide range of molecular targets. According to a thorough review of the research, curcumin, turmeric's main active ingredient, has a major role in several forms of cancer. Curcumin's capacity to inhibit and/or activate several intercellular transcription factors, which control protein expression and development, is primarily responsible for its anticancer potential. In this overview, the mechanism of action and effects are briefly covered. Curcumin is a tautomeric molecule that occurs as an enolic form in organic solvents and as a keto form in water. Epidemiological evidence suggests that consuming turmeric may reduce the risk of some cancers and have other positive biological effects on humans, however the results are not definitive. Curcumin, the active element in turmeric, has been widely studied for its anti-inflammatory, anti-ulcer, anti-diabetic, antiviral, antioxidant, wound healing, and anti-cancer effects. These advantages have been related to the biological benefits of turmeric.

Keywords: Curcumin, Anti-Cancer, Anti-Inflammatory Properties.

I. INTRODUCTION

For thousands of years, people have utilized the rhizome of turmeric (Curcuma longa L.) in many regions of the world, especially in Asian nations, as a spice, culinary additive, coloring agent, and herbal medicine. Many ancient medical systems, such as Islamic, Chinese, and Ayurvedic, have employed it for a variety of ailments. It has been used mostly to treat digestive issues, as well as various inflammatory illnesses including arthritis, as well as to boost the immune system and act as a cardio-, hepato-, and neuroprotective agent. Turmeric contains a diarylheptanoid derivative called curcumin, which has anti-inflammatory, antioxidant, and anticancer qualities. It also regulates weight and metabolic issues and treats mood and cognitive difficulties. One of the most researched components is curcumin, which is generally thought to be the cause of turmeric's medicinal efficacy in treating a variety of conditions, including ulcerative colitis, inflammation, and edema8. pancreatitis, osteoarthritis, rheumatoid arthritis, retinal disorders, dyspepsia, gastric ulcers, and irritable bowel syndrome. These numerous in vivo investigations have demonstrated the medicinal potential of turmeric in Alzheimer's disease and offered supportive data.[1]



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Plant Profile

Synonyms of Curcuma Longa: -

- Sanskrit: Ameshta
- English: Indian saffron
- Hindi: Haldi
- Marathi: Halad

BIOLOGICAL SOURCE: - Turmeric consists of dried, as well as, fresh rhizomes of the plant known as Curcuma longa Linn (C. domestica), belonging to family **Zingiberoside**, it contains not less than 1.5 per cent of curcumin.[10]



Macroscopy:

Color: The vivid yellow color of curcumin is well-known. It appears as a vivid, bright yellow pigment when it is pure. This hue is frequently used in food coloring and natural dyes.

Texture: Curcumin can have a variety of natural forms, including powder and crystalline structures. Depending on how it's processed and the form it takes, the texture can change.

Form: Curcumin can be found as powder, flakes, or solid crystals, among other forms. These forms may differ based on variables like storage conditions, processing techniques, and purity.

Odor: Curcumin itself usually doesn't smell very strong, but it can smell a little spicy or earthy, kind of like turmeric.

Purity: Superior curcumin has a consistent, vivid hue[10]

II. REVIEW OF LITERATURE

1. Rohan, K., Swapnil, H., Akshay, A., Hrishikesh, J., Ankita, P.: Turmeric : Curcuma longa stated that Turmeric (Curcuma longa) and its active constituent, curcumin, have been used for their therapeutic properties for a long time. Here are some key points from their review:

a. Anti-Inflammatory Effects: Most of the medicinal impacts of turmeric and curcumin are attributed to their anti-inflammatory properties. They can help mitigate inflammation in conditions such as arthritis, inflammatory bowel diseases, osteoarthritis, psoriasis, and dermatitis.

b. Antinociceptive Properties: Turmeric and curcumin also exhibit antinociceptive effects, which means they can help alleviate pain. This includes different types of pain, including neuropathic pain.

c. Antioxidant Benefits: The antioxidant effects of turmeric and curcumin contribute to their overall health benefits.

d. Patents and Clinical Applications: Several patents and documents highlight the significance of turmeric and curcumin in various therapeutic and pharmaceutical fields. However, more high-quality clinical trials are needed to firmly establish their clinical efficacy.

2. Oglah, M.K., Mustafa, Y.F., Bashir, M.K., Jasim, M.H.: Curcumin and its derivatives: A review of their biological activities stated that in summary, turmeric and curcumin hold promise as supplementary therapies in phytotherapy, especially for inflammatory disorders and pain management.

Focus and Scope:

- The review concentrates on currently available animal and clinical studies that shed light on the potential pharmacological effects of curcumin and its derivatives.
- It aims to uncover the diverse biological activities associated with these compounds.
- Antioxidant Activity:

- Curcumin exerts antioxidant activity through various mechanisms:
- Direct chemical reaction with free radicals
- Chelation with metal ions, leading to oxidative stress
- Regulation of antioxidant-related enzyme activity and gene expression
- Other Notable Findings:
- The paper discusses curcumin derivatives with potential antifungal activity and analogues showing anti-trichomoniasis activity.

3. Tanvir, E.M., Hossen, M.S., Hossain, M.F., Afroz, R., Gan, S.H., Khalil, M.I., Karim, N.: Antioxidant properties of popular turmeric (Curcuma longa) varieties from Bangladesh. J stated that The study aimed to assess their antioxid, Anti-Inflammatory properties, Pharmacologyant properties and determine the content of polyphenols, flavonoids, tannins, and ascorbic acid.

Here are the key findings:

A. Antioxidant Activity:

- The antioxidant activity was evaluated using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical-scavenging activity and ferric reducing antioxidant power (FRAP) valu
- The ethanolic extract of Chittagong's *mura* exhibited the highest concentrations of:
- Polyphenols (16.07%)
- Flavonoids (9.66%)
- Ascorbic acid (0.09 mg/100 g)
- *Chora* from Chittagong resulted in high yields (17.39%).
- The ethanolic extract of Khulna's *mura* demonstrated a higher DPPH radical-scavenging activity with the lowest 50% inhibitory concentration (IC50) (1.08 µg/mL).
- Khulna's *chora* had the highest FRAP value (µM Fe per 100 g).

4. Kaur, N., Kumar, M., Dhiman, S., Kaur, J., Devi, M.: Journal of Chemical and Pharmaceutical Research , 2016 , 8 (2): 301-318 Review Article Curcumin and its derivatives as chemotherapeutic agents stated that Drug Delivery Systems:

- The review also highlights recent advancements in drug delivery systems specifically designed for efficient curcumin delivery to cancer cell

Importance of Curcumin:

Cancer remains a major global health challenge, and despite advances in therapy, incidence and mortality rates persist.

Curcumin's potential as an anticancer agent offers hope for more effective and less toxic treatment strategies.

5. Raut, V.V., Navsupe, N., Pathak, V., Bhandari, S. V, Patil, S., Student: Comprehensive Review on Versatile Nature of Curcumin and it's Pharmacological Activities stated that it provides valuable insights into the multifaceted properties of curcumin, a bioactive compound found in *Curcuma longa* (turmeric). Let's delve into the details:

A. Curcumin Overview:

- Curcumin, also known as diferuloylmethane, is a naturally occurring polyphenolic molecule derived from the rhizomes of *Curcuma longa L.* and related species.
- It imparts the characteristic yellow color to turmeric roots (family Zingiberaceae).
- Curcumin is highly lipophilic, phenolic, and water-insoluble.
- Approximately 4% of turmeric's dry weight consists of curcumin.

B. Chemical Properties:

- Curcumin exists in tautomeric forms:
- In organic solvents, it appears as an enolic form.
- In water, it adopts a keto form.
- Its fragrance is faintly orange and ginger-like, with a bitter taste.

C. Pharmacological Activities:

- Curcumin has been extensively studied for its various health benefits:
- Anti-inflammatory: Curcumin exhibits potent anti-inflammatory effects.
- Anti-ulcer: It helps protect against gastric ulcers.
- Anti-diabetic: Curcumin shows promise in managing diabetes.
- Antiviral: It may combat viral infections.
- Antioxidant: Curcumin scavenges free radicals.
- Wound Healing: It aids in tissue repair.
- Anti-cancer: Curcumin's potential in cancer prevention has been explore

D. Bioavailability Challenges:

- Curcumin's poor water solubility poses challenges for its effective delivery.
- Researchers have explored various strategies, including micelles, nanoparticles, liposomes, and phospholipid complexes, to enhance its bioavailability.

III. MICROSCOPIC CHARACTERSTICS

Microscopy: Using free hands, a transverse piece of the rhizome was cut, placed in water, and examined under a microscope. The rhizome that had been dried and cured was ground into a powder, which was then suspended in water and examined under a microscope. Fluorescence analysis: The powder was exposed to visible, short- and long-wavelength UV light after being treated with various reagents. HPLC examination: One of the seven components of the ayurvedic remedy known as Pathyashadangam kwath, which is mentioned in the Sharngadhara Samhita, is the rhizome of Curcuma longa. The aerial portion of Andrographis paniculata, stem of Tinospora cordifolia, stem bark of Azadirachta indica, and dried fruit pericarps of Terminalia chebula, Terminalia Billerica, and Phyllanthus emblica are the other ingredients. A kasha yam was made without any of the Pathyashadangam kasha yam's constituents except Curcuma longa, and it was also put through an HPLC test. The SPD-M10A vp photo diode array detector (PDA), Shimadzu LC-10 AT vp binary gradient pump, and Luna 5u C18 analytical column (250 x 4.6 mm) were used in the HPLC study. Acetonitrile (60%) was the mobile phase utilized in A. B: 50 mM potassium dihydrogen orthophosphate (40%), with orthophosphoric acid added to bring the pH down to 3.5.14. The overall flow rate was 0.8 ml/min, with an injection volume of 20 µL. There was an isocratic elution. The column oven was set to 250o C, the detection wavelength was 450 nm, and the total run time was 12 minutes. [10]

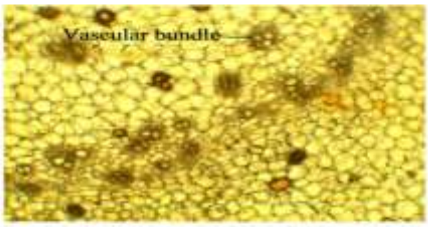


Figure 1: A portion of TS of rhizome.

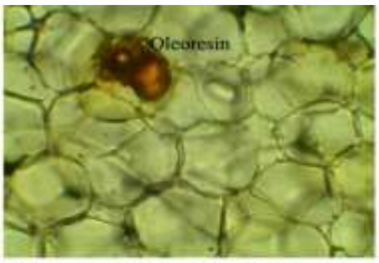


Figure 2: An enlarged portion showing cell with oleoresin.

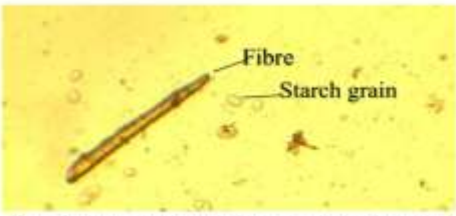
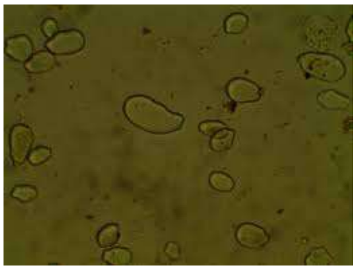


Figure 3: Fibre and starch grain (Low power view).



IV. CHEMICAL CONSTITUENTS

About 5% of turmeric is made up of resin, zingiberene starch grains in abundance, volatile oil, and curcuminoids, which are compounds that give turmeric its yellow color. Curcumin is the main ingredient of curcuminoids. The remaining ingredients in turmeric oil are borneol, zingiberene, caprylic acid, and turmericone. It has been found that curcumin has anti-inflammatory and anti-microbial properties.[10]

PYSIOCHEMICAL CONSTITUENTS: -

Ash value: -

A compound such as curcumin can have its ash value determined using the following formula:

Value of ash (%) = Ash value (%) = Weight of sample/Weight of ash*100%

Ash's weight = Weight of the sample: 100%

Ash value (%) = Sample weight Content of ash *100%

Within this formula:

"Weight of ash" describes the mass of the residue that remains after the sample has been completely burned. "Weight of sample" describes the sample's initial weight prior to burning.

The ash value is represented as a percentage and may be obtained by dividing the weight of the ash by the weight of the sample and multiplying the result by 100%. The amount of inorganic material in the sample is shown by this percentage. [10]

Moisture content: -

There are several ways to find curcumin's moisture content, but the loss on drying (LOD) approach is the most often used. Here's how to use this approach to find curcumin's moisture content:

Weighing the Sample: Using a digital balance, precisely weigh a specified quantity of curcumin (often 1 to 5 grams). Note the sample's original weight.

Sample Drying: Put the weighted sample in an oven that has been preheated to a certain temperature (typically between 105°C and 110°C) and leave it there for a certain amount of time (usually two to four hours).[3]

Weighing Once More: To avoid the sample absorbing moisture from the surroundings, take it out of the oven after the allotted drying period and let it cool in a desiccator. To get the final weight of the dried sample, weigh it once again.

Calculating Moisture Content: The following formula may be used to determine the moisture content: **Moisture Content (%)=(Initial weight of sampleInitial weight of sample−Final weight of sample)×100%**

Extraction Process: -

Raw Material Preparation: After being gathered and cleansed to get rid of dirt and other contaminants, turmeric rhizomes are used. To improve the extraction surface area, they can also be dried and powdered into a fine powder.

Choice of Solvent: Ethanol, methanol, acetone, and ethyl acetate are among the solvents that may be used to extract curcumin. A number of variables, including the required level of curcumin purity, regulatory restrictions, and environmental concerns, influence the choice of solvent.

Extraction: Turmeric may have curcumin extracted using a number of techniques, such as:

Traditional Soxhlet Extraction: In this technique, a Soxhlet extractor is used to cycle a solvent through the turmeric powder many times. Curcumin and other chemicals are dissolved in the solvent and collected in a separate flask.

Liquid-Liquid Extraction: In this technique, a solvent and turmeric powder are combined in a vessel, and the solvent phase is used to extract the curcumin. Curcumin is then obtained by separating and evaporating the solvent phase.

Supercritical Fluid Extraction (SFE): SFE is the process of extracting curcumin by employing supercritical fluids, such as carbon dioxide (CO2). In certain temperature and pressure ranges, CO2 transforms into a supercritical fluid, with characteristics of both a gas and a liquid. It can dissolve curcumin rather well, and once extracted, the CO2 is easily extracted, leaving behind a pure extract of curcumin.

Purification: Other chemicals and contaminants may be present in the crude curcumin extract that is produced during the extraction procedure. Methods of purification like chromatography (e.g., high-performance liquid chromatography, column chromatography)

Drying: To get rid of any remaining solvent and water after purification, the curcumin extract is usually dried. To produce dry curcumin powder, a variety of drying techniques such as vacuum drying, spray drying, or freeze-drying can be employed.

Quality Control: To guarantee the safety and effectiveness of the curcumin extract for use in a variety of applications, quality control procedures include examining the extract's purity, potency, and composition are crucial.[3]

Cold Maceration

Using a magnetic stirrer , cold maceration was done at ambient temperature and 450–500 rpm. In a nutshell, 150 mL of ethanol was used to extract 25.00 g of material. The solution was filtered (MN-751) to remove the solid material from the extract solution after three hours of stirring. Rotavapor was used to evaporate the extract solution at 40 °C. Equation (1) was used to compute the extraction yield. Until the spectrophotometric and HPLC-MS/MS tests were completed, the extract was kept in a freezer.

Microcapsule densities and flow characteristics of curcumin

Pbulk, or bulk density, was calculated using ASTM standard D7481-18. Bulk density was computed using the sample mass and volume after the powder was weighed after being loaded into a 250 mL graduated glass cylinder. Using a tapped density tester (model: Thermonik, Campbell Electronics, Mumbai, India), the volume of curcumin microcapsules after 500 taps was used to calculate the tapped density (ρtapped). Eight replications were used to get the mean values of densities.

Equations 2 and 3 demonstrate how the static flowability of microencapsulated powder was represented in terms of Carr's Index (CI) and Hausner's Ratio (HR).

Carr′sIndex(%)=ρ bulkρ tapped\ tapped

Ratio Hausner′s = ρ tapped ρbulk [3]

PHYTOCHEMICAL STUDY: -

Initial phytochemical analysis of the crude extract

By employing widely used precipitation and coloration reactions documented in standard reference books, the presence of several phytoconstituents including carbohydrates, proteins, alkaloids, glycosides, terpenes, steroids, flavanoids, tannins, and saponins was assessed in the crude extract.

carbs: After dissolving the extract in ten milliliters of distilled water and filtering the filtrate using Whatmann No. 1 filter paper, tests are run to determine the amount of carbs present.

a) Molish test:

A test tube containing 2 ml of solution was used. Molish Reagent was added in one drop. The test tube's sides were used to add 2 milliliters of concentrated HCL.A voilet ring was observed to form in the test tube. Carbohydrates are present when there is a Voilet ring at the intersection of the two liquids.

c) Protein:

After dissolving the extract in 10 milliliters of distilled water, the filtrate was filtered using Whatmann No. 1 filter paper, and its protein and amino acid content was examined.

Biuret test: A drop of 2% copper sulphate solution was added to an aliquot containing two milliliters of filtrate. This was then mixed with 1 milliliter (or 95% ethanol) and an excess of potassium from potassium hydroxide pellets. The presence of proteins was shown by the pink color in the ethanol layer.

Millers test

Add a few drops of Millon's reagent to 2 milliliters of filtrate. The outcome was noted. The presence of proteins was shown by a white precipitate.

b) Wagner's test:

A few drops of Wagner's reagent are added by the test tube's edge to one milliliter of filtrate. It was noticed that the hue changed. A reddish-brown precipitate indicates a positive test result.

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c) Dragendorff's test:

Two milliliters of the reagent are applied to one milliliter of filtrate, and the outcome is closely monitored. A noticeable yellow precipitate indicates a positive test result.

d) Glycosides

a) Borntrager's Test:

The extract was heated to a boil with diluted sulfuric acid, then filtered. Chloroform was then added to the filtrate and thoroughly shaken. After the organic layer was separated, ammonia was gradually added. The ammonical layer becomes pink or red when gylcoside is present.

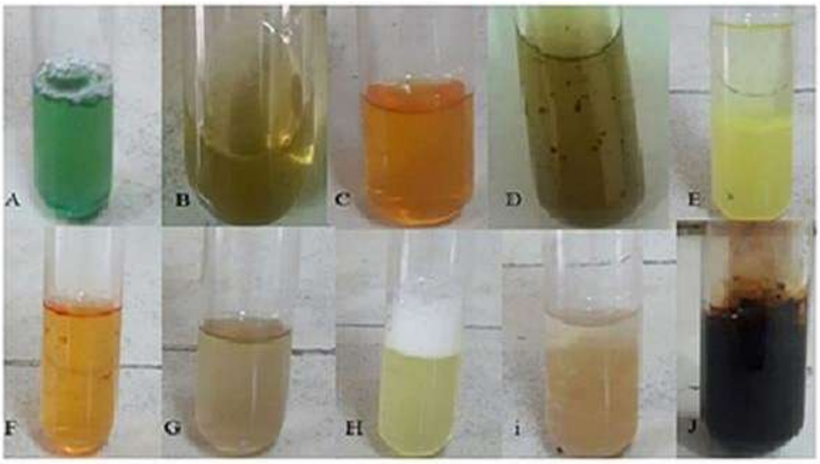
Terpenoid and steroid: Four milligrams of extract was treated with 0.5 ml of acetic anhydride and 0.5 ml of chloroform. Then concentrated solution of sulphuric acid was added slowly and red violet color was observed for terpenoid and green bluish color for steroids [28

Flavonoid: Four millilitres of extract solution was treated with 1.5 ml of 50% methanol solution. The solution was warmed and metal magnesium was added. To this solution, 5-6 drops of concentrated hydrochloric acid was added and red color was observed for flavonoids and orange color for flavones.

Tannins: To 0.5 ml of extract solution 1 ml of water and 1-2 drops of ferric chloride solution was added. Blue color was observed for gallic tannins and green black for catecholic tannins

Saponins: About 0.2 g of the extract was shaken with 5 ml of distilled water and then heated to boil. Frothing (appearance of creamy miss of small bubbles) shows the presence of saponins

Phytochemical	Test	*Curcuma longa* (L.)		*Curcuma aromatica* (Salib.)	
		Ethanol	Methanol	Ethanol	Methanol
Alkaloids	Dragendroff test	+	+	+	+
	Mayer's test	+	+	+	+
	Wagner's test	+	-	+	+
Flavonoids	Lead acetate test	+	+	+	-
	H_2SO_4 test	-	+	+	+
	Alkaline reagent test	-	-	+	+
	Zinc hydrochloride test	-	-	-	-
	Pew test	-	-	-	-
Phenol	Ferric chloride test	-	-	-	-
Saponins	Frothing test	-	-	-	-
Tannins	Lead acetate test	+	+	-	-



Phytochemical Analysis of Turmeric

- The green color indicated that the turmeric aqueous extract tested positive for carbs.
- The lack of yellow color verified that the turmeric aqueous extract tested negative for proteins.
- The presence of a strong yellow color indicated that the turmeric aqueous extract tested positive for flavonoids.
- The absence of blue violet color verified that the turmeric aqueous extract tested negative for anthocyanins.

- The absence of the upper red layer supported the leuco-anthocyanin test result for the turmeric aqueous extract being negative.
- The presence of yellow color verified that the turmeric aqueous extract tested positive for coumarins. The following observations supported the results of the test:
- an upper red layer and a lower greenish layer indicated that the turmeric extract was positive for steroids;
- persistent foam indicated that the extract was positive for saponins;
- the presence of yellow precipitates indicated that the extract was positive for tannins; and
- the presence of blackish color indicated that the extract was positive for phenols.[4]

V. PHARMACOLOGICAL PROPERTIES

Antioxidant function

Herbs with antioxidant properties have a role in managing health by neutralizing free radical species. Curcumin has been found to be an excellent scavenger of reactive oxygen species (ROS) and reactive nitrogen species in vitro. In another study, the antioxidant activity of curcumin was demonstrated by inhibiting the controlled beginning of styrene oxidation. Curcumin's potent anticancer properties are ascribed to its antioxidant properties, which regulate DNA damage and lipid peroxidation driven by free radicals.

Additionally, it has a strong inhibitory impact on human keratinocytes and fibroblasts that are damaged by hydrogen peroxide. Furthermore, the primary component of turmeric, curcumin, has been shown to enhance the actions of detoxification enzymes like glutathione-S-transferase (GST).According to a previous study, curcumin effectively reduces intracellular amyloid toxicity at low[3]

Antidiabetic properties

An investigation into the effects of curcumin revealed that it increased the activity of every antioxidant enzyme when administered. Moreover, compared to groups such as nondiabetic and diabetic untreated rats, rats treated with curcumin had a notable rise in the expression of genes such as insulin-like growth factor-1, B-cell lymphoma 2, superoxide dismutase, and GST. Another study using rats shown that after isolated Langerhans islets were treated with curcumin, there was a substantial increase in insulin production, heme oxygenase (HO)-1 gene expression, and HO activity.[5]

Anti-inflammatory properties

The most widely used medications in the world for treating inflammation are nonsteroidal anti-inflammatory medicines (NSAIDs), which are also licensed for use on wounds and orthopedic ailments. These medications, however, have negative side effects and might result in stomach ulcers. Through the modification or blockage of several molecular pathways, curcumin has demonstrated a critical role in the prevention of the inflammatory process [Figure 1 and Table 1]. Curcumin, the main component of turmeric, was shown in an animal model research to suppress arachidonic acid metabolism and inflammation in the skin epidermis by downregulating the pathways of cyclooxygenase and lipoxygenase. Additional studies have also revealed that curcumin has anti-inflammatory properties.[4]

Antibacterial properties

Drug resistance to microorganisms is becoming more commonplace globally, and one of the primary reasons why treatments don't work is resistance to antimicrobial medicines. To solve these kinds of issues, a natural solution that is both secure and efficient is required. It has been established that curcumin, the main component of turmeric, possesses antiviral, antibacterial, and antifungal properties.[8] Curcumin demonstrated inhibitory action against methicillin-resistant strains of Staphylococcus aureus, with a minimum inhibitory concentration value of 125–250 μg/Ml, according to research results.[58] One of turmeric's main constituents, curcumin, has been shown to have a role in inhibiting the development of all Helicobacter pylori strains that have been isolated from individuals with gastrointestinal problems and infections in vitro.[4]

Anti-tumor action

Several plant-based items, including seeds, flowers, leaves, and stems, have demonstrated their ability to prevent tumors. It has been demonstrated that the main component of turmeric, curcumin, inhibits the activity of the enzymes that metabolize drugs (cytochrome p450 and p450 reductase). Several investigations using animal models discovered that dietary curcumin inhibited peroxisome proliferator-activated receptor δ in colon cancer cells, downregulating vascular endothelial growth factor and increasing the activity of Phase II enzymes such GSTs.A study's findings revealed a significant drop in cell viability in curcumin-treated cells, which was linked to NF-κB and Notch-1 downregulation and consistent with the triggering of apoptosis.according to a study, curcumin can stop melanoma cells from proliferating and cause them to undergo apoptosis.[6]

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