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AN INSIGHT INTO THE PHARMACOLOGICAL DEVELOPMENTS OF CURCUMIN: A COMPREHENSIVE REVIEW

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ABSTRACT

Turmeric, major source of Curcumin a perennial herbaceous plant native to South Asia, has garnered significant attention in recent years due to its diverse pharmacological properties. This review enlightens about current research on the anticancer, anti-inflammatory, and antioxidant properties of Curcumin. Numerous studies have demonstrated Curcumin's potential as a potent anticancer agent, attributed to its ability to modulate various molecular pathways involved in cancer development and progression. Additionally, Curcumin exhibits robust anti-inflammatory effects by inhibiting pro-inflammatory mediators and signaling pathways, offering promise for the treatment of inflammatory conditions such as arthritis, inflammatory bowel disease and other autoimmune diseases. Furthermore, the antioxidant properties of Curcumin contribute to its protective effects against oxidative stress-induced damage, thereby mitigating the risk of chronic diseases associated with oxidative damage. Low cost and easy availability of turmeric attracted the attention of many researchers. This review underscores the multifaceted therapeutic potential of Curcumin and highlights the need for further research to elucidate its mechanisms of action and optimize its clinical applications.

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INTRODUCTION

(Vasada.K at all, 2013) Indeed, the use of herbs and plant products for medicinal purposes has been deeply rooted in human history, with civilizations across the world harnessing the healing properties of various flora for millennia. The Indian subcontinent, in particular, boasts a rich diversity of aromatic and medicinal plants, which have play a important role in the traditional systems of medicine practiced in the region. [1].

(Louay.L at all, 2014) Turmeric, scientifically known as Curcuma longa, is indeed a herb belonging to the Zingiberaceae family, which also includes ginger. Widely cultivated in Asia, particularly in India and China, turmeric is renowned for its vibrant yellow-orange rhizomes, which are dried and ground to produce the powdered spice commonly used in cooking.

The use of turmeric spans diverse cultures and traditions, with the herb holding a prominent place in Asian cuisines for both its distinctive flavor and its ability to impart a rich golden hue to dishes. It is a key ingredient in curry powder, lending its characteristic color and subtle earthy taste to a variety of savory dishes. Turmeric has a plethora of names across different regions, reflecting its widespread use and cultural significance. In the Arab region, it is referred to as "Curcum," while in Sanskrit and Ayurvedic traditions, it is known as "Haridra." In Chinese, it is called "Jianghuang," which translates to "yellow ginger," and in Japanese, it is known as "Kyoo" or "Ukon."

Beyond its culinary uses, turmeric has a long history of medicinal use in traditional Chinese and Ayurvedic medicine. It is revered for its potent anti-inflammatory properties and is traditionally used to alleviate various inflammatory conditions, such as arthritis and joint pain. Additionally, turmeric is employed in the treatment of jaundice, menstrual difficulties, hematuria (blood in urine), hemorrhage, and gastrointestinal issues in these traditional medical systems. Modern scientific research has corroborated many of the traditional uses of turmeric, uncovering its bioactive compounds, such as curcuminoids, which exhibit antioxidant, anti-inflammatory, antimicrobial, and potential anti-cancer properties. These findings have led to the widespread popularity of turmeric as a natural remedy and dietary supplement for promoting overall health and well-being. In summary, turmeric's rich culinary heritage and medicinal virtues make it a prized herb in various cultural and medicinal traditions around the world. Its versatility, vibrant color, and potent health benefits continue to captivate the culinary and wellness industries, cementing its status as a beloved and revered botanical powerhouse [2].

(Vasada.K at all, 2013) Turmeric holds cultural and spiritual significance in Hindu rituals, with Hindu females applying it daily on their foreheads as a mark of auspiciousness. During Hindu wedding ceremonies, the application of turmeric paste to the bride is an essential ritual symbolizing purity and marital blessings. In Ayurveda, turmeric is revered for its therapeutic potential and is described as

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Dashemani Lekhaniya (emaciating), Kusthagna (anti-dermatosis), and Visaghna (anti-poisonous). It has been traditionally used to treat various health conditions, including inflammation, skin ailments, and infections [3]. (Louay.L at all, 2014) Turmeric's active constituents include flavonoid Curcuminoids, primarily comprising curcumin, monodexmethoxycurcumin, and bisdesmethoxycurcumin, with curcumin making up about 90% of the curcuminoid content. Other components include sugars, proteins, and resins. Curcumin, comprising 0.3-5.4% of raw turmeric, is the most extensively researched compound. Turmeric also contains volatile oils (tumerone, atlantone, and zingiberone). Curcumin is a lipophilic polyphenol insoluble in water but stable in the stomach's acidic pH [4].

(Verma kumar. R at all, 2018) Turmeric, is to have originated from India, has been utilized in the region for over 2500 years. Widely distributed in tropical and subtropical regions worldwide, the precise origin of the turmeric plant is uncertain, but it is thought to have originated in South-East Asia, possibly in India. Cultivated across India, the country is the primary producer of turmeric globally. Additionally, turmeric is cultivated in southern China, Taiwan, Japan, Burma, Indonesia, and throughout Africa. In Brazil, the use of turmeric has increased, primarily for its color-enhancing properties and ability to enhance food odor. In Europe, commercially available turmeric powder is predominantly sourced from India, with some also coming from other South-East Asian countries. Turmeric is most prevalent in southern Asia, especially in India, where it has a long history of cultural and culinary significance [5]. (Unlu. A at all) Curcumin, a polyphenol compound, exhibits diverse pharmacological effects on cytokines, kinases, enzymes, transcription factors, growth factors, and receptors. Studies have shown its antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, renoprotective, hepatoprotective, and hypoglycemic properties. Given its anti-inflammatory effects and the role of inflammation in cancer development, curcumin is being investigated for its potential in cancer prevention and treatment [6].

HISTORY OF TURMERIC

(Kaur. A at all, 2019) Turmeric's exact origin remains unknown, but it has been integral to Ayurveda, an ancient Indian system of natural healing that translates to "science of life." Ayurvedic texts describe various medicinal uses for turmeric, including reducing congestion by inhaling its fumes and applying turmeric juice or paste to wounds, skin conditions, and diseases like smallpox and chickenpox. Turmeric holds significance in Indian tradition and worship, used to worship the Sun God during the solar period in India. Its common names, "haldi" in the north and "manjal" in the south, derive from Sanskrit and Tamil words, respectively. In Ayurvedic and Unani systems, turmeric has been extensively used for its medicinal properties, cited in Sanskrit medical treatises dating back to 250 B.C. Ayurvedic literature contains over 100 terms for turmeric, reflecting its diverse uses and attributes. It is revered as "jayanti," meaning "victorious over diseases," and "matrimanika," meaning "as beautiful

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as moonlight." Turmeric's historical use in India extends to worship and rituals, as mentioned in the Artharveda [7].

(Bhowmik. D at all, 2009) Turmeric (Curcuma longa) and other species of the Curcuma genus grow wild in Southern Asia, including India, Indonesia, Indochina, nearby Asian countries, and some Pacific Islands like Hawaii. These regions have a long history of traditional culinary and medicinal uses dating back to pre-history. In the Indian Ayurveda system, turmeric is considered strengthening and warming to the whole body. Traditional uses in India include improving digestion, intestinal flora, eliminating worms, relieving gas, cleansing and strengthening the liver and gallbladder, normalizing menstruation, alleviating arthritis and swelling, acting as a blood purifier, promoting proper metabolism, and providing relief for various conditions such as sprains, burns, cuts, bruises, insect bites, and itches. It's also used for soothing coughs and asthma, as an antibacterial and antifungal agent, and in cases of weakness or debility.

Turmeric is also utilized as a food colorant and dye for cloth, serving as a more affordable alternative to saffron. It has been and continues to be used in religious ceremonies and offerings, symbolizing life, purity, and prosperity. Interestingly, turmeric has had little mention in old European herbals. Marco Polo referred to it as "Indian saffron" primarily used for dying cloth. Although the ancient Greeks were aware of turmeric, it did not gain popularity in the West for culinary or medicinal purposes. However, it was utilized for making orange-yellow dyes [8]. (Vasada. K at all, 2013) Haridra, meaning "an efficacious drug for jaundice" in Sanskrit, is recognized as one of the oldest spices used in Western and Southern parts of India for thousands of years, playing a significant role in Ayurvedic medicine. It is often referred to as "Indian saffron" due to its deep cultural and medicinal connections with India. Originating in India, turmeric has a rich history of use and cultivation in the region. By 700 AD, it had spread to China, reaching East Africa by 800 AD and West Africa by 1200 AD. Turmeric's popularity continued to grow, and Arab traders introduced it to Europe in the 13th century, contributing to its global dissemination [9].

Family of Turmeric

(Bhowmik. D at all, 2009) Turmeric, scientifically known as Curcuma longa, belongs to the Zingiberaceae family, which is commonly referred to as the ginger family. The Zingiberaceae family is a large family of flowering plants, comprising approximately 53 genera and over 1,300 species distributed mainly in tropical and subtropical regions around the world [10].

Chemical Composition of Turmeric:

(Rathaur. P at all, 2012) Turmeric, also known as 'Haridra' or 'Haldi', is composed of protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%), and moisture (23.1%). Its essential oil (5-8%),

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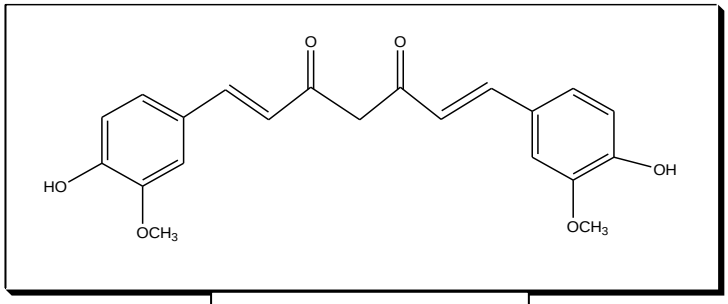
obtained through steam distillation of rhizomes, contains α-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%), and sesquiterpenes (53%).

Curcumin, the principal curcuminoid in turmeric, imparts the characteristic yellow color and is responsible for most of its therapeutic effects. It makes up an estimated 2-5% of turmeric. Alongside curcumin, desmethoxycurcumin and bisdesmethoxycurcumin are the other two major curcuminoids present. It was first isolated in 1815, with its structure elucidated as diferuloylmethane in 1910.



Structure of Curcumin

Curcumin is biphenolic compound which also possesses methoxy groups and ketonic groups. It has been reported that polyphenols has anti-cancer, anti-inflammatory and antioxidant properties [11].

IUPAC name: (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione

REPORTED BENEFITS OF CURCUMIN IN OUR DAILY LIFE:

(Bhowmik. D at all, 2009)

- It is a natural antiseptic and antibacterial agent, useful in disinfecting cuts and burns.
- When combined with cauliflower, it has shown to prevent prostate cancer and stop the growth
- of existing prostate cancer.
- Prevented breast cancer from spreading to the lungs in mice.
- May prevent melanoma and cause existing melanoma cells to commit suicide.
- Reduces the risk of childhood leukemia.
- Is a natural liver detoxifier.
- May prevent and slow the progression of Alzheimer's disease by removing amyloyd plaque
- buildup in the brain.
- May prevent metastases from occurring in many different forms of cancer.
- It is a potent natural anti-inflammatory that works as well as many anti-inflammatory drugs
- but without the side effects.
- Has shown promise in slowing the progression of multiple sclerosis in mice.
- Is a natural painkiller and cox-2 inhibitor.
- May aid in fat metabolism and help in weight management [12]

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Pharmacological Developments:

ANTI-CANCER PROPERTY OF TURMERIC

(Vasada.K at all, 2013) Curcumin exhibits anticancer activities by targeting various biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis, and metastasis. It exerts anti-proliferative effects in multiple cancers and inhibits the transcription factor NF-κB and downstream gene products such as c-myc, Bcl-2, COX2, NOS, Cyclin D1, TNF-α, interleukins, and MMP-9. Moreover, curcumin affects growth factor receptors and cell adhesion molecules involved in tumor growth, angiogenesis, and metastasis. In cancer cells, curcumin alters the deregulated cell cycle through cyclin-dependent, p53-dependent, and p53-independent pathways. Its efficacy in animal models highlights its potential as a multi-faceted tool against cancer. Curcumin's ability to interact with novel targets and synergize with chemotherapy makes it a promising candidate for cancer treatment. Furthermore, curcumin is well tolerated in humans, making it an attractive option for therapy. Targeting EGFR, miRNA, autophagy, and cancer stem cells in combination with curcumin presents promising mechanisms and targets for lung cancer therapy [13].

(Bhowmik. D at all, 2009) Recent scientific research supports turmeric's efficacy in treating various diseases and inhibiting the growth of different cancer types. It's particularly utilized for treating skin cancer and pre-cancerous skin conditions. Both topical and internal applications of turmeric are beneficial in this regard. Turmeric's active compound, curcumin, possesses anti-inflammatory and antioxidant properties, which contribute to its therapeutic effects. Further research is ongoing to understand its mechanisms and optimal usage [14]. (Gajanan. A at all, 2023) Curcumin demonstrates potent anti-tumor effects in cancer cells, making it a multifaceted weapon in the fight against cancer. Its success in animal models and its impact on key cell cycle signaling pathways highlight its therapeutic potential. Natural phytochemicals like curcumin can target new pathways and synergize with chemotherapy, offering promising avenues for cancer treatment. Curcumin's excellent tolerance in humans further supports its potential in cancer therapy. In the treatment of lung cancer, potential targets and procedures may involve EGFR-miRNA autophagy and cancer stem cell therapy in conjunction with curcumin.

Curcumin exerts its anticancer activity through various mechanisms, including interference with cellular pathways and modulation of cytokines, enzymes, and growth factors such as MAPK, EGF, NFκB, PKD1, COX-2, STAT3, TNFα, and IκKβ. Treatment with curcumin has been shown to simultaneously reduce anticancer drug IC50 and stem cell counts, suggesting its potential as an adjunct therapy in cancer treatment [15].

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Effect of Curcumin on Liver cancer : (Perrone. D at all, 2015) Curcumin has been shown to inhibit the formation of hepatic hyperplastic nodules, hypoproteinemia, and body weight loss in Wistar rats. In an animal experiment involving C3H/HeN mice injected intraperitoneally with N-nitrosodimethylamine (DENA), a potent hepatocarcinogen, one group of mice received a diet containing 0.2% curcumin starting four days before DENA injection until the end of the study. At 42 weeks of age, the curcumin-treated group demonstrated an 81% reduction in the multiplicity and a 62% reduction in the incidence of hepatocarcinoma compared to the non-treated group [16].

(Altaf S at all, 2012) CURCUMIN AND LIVER CANCER: IN VITRO STUDIES: Numerous studies conducted over the past several years have investigated the effects of curcumin and its analogs on both rodent and human hepatoma cells. In an initial study by Lin et al., curcumin was found to reduce the secretion of matrix metalloproteinase-9 (MMP-9), leading to inhibition of migration and invasion in SK-Hep-1 cells. Similar anti-invasive and antimigratory effects were observed in CBO140C12 cells in a study by Ohasi et al. Curcumin's reduction in MMP-9 secretion was accompanied by significant inhibition of adhesion and migration on fibronectin and laminin substrates.

Additionally, curcumin, like other dietary polyphenols, exhibits both antioxidant and pro-oxidant properties. Studies have shown that curcumin can increase reactive oxygen species (ROS) levels, demonstrating its dual role as an antioxidant and pro-oxidant agent.

CURCUMIN AND LIVER CANCER: IN VIVO STUDIES: Over the past decade, the effects of curcumin and its analogous compounds have been extensively studied in chemically-induced and xenograft preclinical rodent models of hepatocellular carcinoma (HCC). These investigations have documented the potential role of curcumin and its analogs in both the prevention and treatment of HCC [17].

Effect of Curcumin on respiratory disorder (lungs cancer): (Ahsan. R at all) Curcumin inhibits apoptosis by modulating miRNA pathways, crucial for inhibiting caspase-3 and the Pi3K/Akt pathway involved in cell survival. It also inhibits XIAP, contributing to its cytotoxic properties in non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) by increasing ROS and apoptosis. In NSCLC, curcumin inhibits cell proliferation via the JAK/STAT3 pathway, which is implicated in tumor recurrence and drug resistance. Additionally, it suppresses abnormal cell growth, migration, invasion, and angiogenesis in SCLC cells by inducing FOXO1, a transcription factor regulating cell proliferation and DNA repair. Curcumin's induction of FOXO1 upregulates p21 and p27, leading to cell cycle arrest and apoptosis. Further more, curcumin exerts epigenetic effects by reactivating silenced tumor suppressor genes, such as RARβ in NSCLC, through decreased promoter methylation, inhibiting tumor cell growth. It also downregulates early growth response protein 1 (EGR-1) in NSCLC patients, enhancing cell-cell adhesion and reducing cancer cell migration. Additionally, curcumin prevents the production and activity of matrix metalloproteinases (MMPs), key enzymes involved in

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cancer cell migration and invasion, through various mechanisms [18].

Therapeutic Activity of Curcumin in Head and Neck Squamous Cell Carcinoma:

(Wilken. R at all, 2011) Curcumin has shown promising results in various in vitro and in vivo models of head and neck squamous cell carcinoma (HNSCC), suggesting its utility as a potential treatment and chemopreventive agent.

In vitro studies have revealed that curcumin decreases cell growth and survival in HNSCC cell lines by affecting molecular pathways involved in cellular proliferation. It inhibits the activation of NF-κB, a key player in promoting cancer cell growth and survival, by suppressing its constitutive activation in multiple oral squamous cell carcinoma cell lines. Additionally, curcumin suppresses the IL-6 mediated phosphorylation and nuclear localization of STAT3, another signaling protein overexpressed in HNSCC. Furthermore, curcumin has been shown to suppress the growth of both immortalized oral mucosal epithelial cells and squamous cell carcinoma cells, while having minimal effects on normal oral epithelial cells.

In vivo studies using nude mouse xenograft models have demonstrated the growth suppressive effects of curcumin on HNSCC. However, the lipophilic nature and poor aqueous solubility of curcumin, along with its short half-life and low bioavailability following oral administration, have posed challenges in developing effective delivery systems for its use as a chemotherapeutic agent. To overcome these obstacles, various strategies are being explored, including the use of piperine as an adjuvant agent to enhance curcumin bioavailability, as well as the development of liposomal, phospholipid, and nanoparticulated formulations for intravenous administration. Liposomal formulations of curcumin have been studied in various cancers, such as pancreatic, colorectal, and prostate cancer, showing promising results in improving its bioavailability and efficacy. These advancements may pave the way for the successful clinical translation of curcumin as a therapeutic agent for HNSCC and other cancers [19].

ANTI -INFLAMMATORY ACTIVITY OF TURMERIC

(Julie. S at all, 2009) It is well-established that pro-inflammatory states are closely associated with tumor promotion. Therefore, phytochemicals like curcumin, which possess strong anti-inflammatory properties, are expected to exhibit chemopreventive activity. Preclinical cancer research involving curcumin has demonstrated its ability to inhibit carcinogenesis in various cancer types, including colorectal, pancreatic, gastric, prostate, hepatic, breast, oral cancers, leukemia, and at different stages of carcinogenesis. The anti-inflammatory mechanisms contributing to curcumin's anticarcinogenic potential include:

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- Inhibition of NF-κB and COX-2: Increased levels of COX-2 are linked to many cancer types, and curcumin inhibits their expression, thereby suppressing inflammation and tumorigenesis.
- Inhibition of arachidonic acid metabolism via lipoxygenase: Curcumin interferes with the metabolism of arachidonic acid, a key mediator of inflammation, through the lipoxygenase pathway, thereby reducing inflammation and cancer development.
- Scavenging of free radicals: Curcumin scavenges free radicals generated in the arachidonic acid pathway, preventing oxidative damage and inflammation.
- Decreased expression of inflammatory cytokines: Curcumin decreases the expression of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, leading to the inhibition of cancer cell growth.
- Downregulation of enzymes like protein kinase C: Curcumin downregulates enzymes involved in inflammation and tumor-cell proliferation, such as protein kinase C, further suppressing tumorigenesis.

These anti-inflammatory mechanisms collectively contribute to curcumin's potential as a chemopreventive agent against various types of cancer [20]. (Pernone. D at all, 2015) Molecular studies shows that curcumin blocks the activation of factors or enzymes involved in triggering the inflammatory response in human cells. For example, research by Such et al. demonstrated that curcumin inhibits the activity and expression of cyclooxygenase-2 (COX-2) in various cell lines and animal models. When topically applied, curcumin inhibits the lipopolysaccharide (LPS)-mediated induction of COX-2 expression. This effect, rather than directly inhibiting COX catalysis, contributes to the reduced formation of prostaglandin E2 (PGE2). Interestingly, in macrophages not stimulated by LPS, curcumin increases COX-2 levels.

Additionally, studies by Zhang et al. showed that curcumin suppresses COX-2 protein and mRNA expression, as well as TPA- or chenodeoxycholate-induced PGE2 production. Furthermore, curcumin reduces the expression of COX-2 and PGE2 synthase 1, both of which are involved in PGE2 formation, a key mediator of inflammation and tumor development. Curcumin also reversibly inhibits the conversion of prostaglandin H2 (PGH2) to PGE2 by microsomal PGE2 synthase 1 in A549 lung cancer cells stimulated with interleukin (IL)-1β. In human whole blood stimulated with LPS, curcumin inhibits PGE2 formation by COX-2 from arachidonic acid (AA), while the formation of other prostaglandins by COX-1 is suppressed at much higher concentrations. Studies have suggested that curcumin's deletion of microsomal PGE2 synthase 1 is crucial for its anti-inflammatory and anticancer activities [21].

(Labban. L at all, 2014) Curcuminoids exhibit a wide range of anti-inflammatory effects by inhibiting various enzymes and molecules involved in inflammation. They inhibit enzymes such as lipoxygenase (LOX), cyclooxygenase (COX), phospholipases, elastase, hyaluronidase, and collagenase.

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Additionally, curcuminoids decrease the formation of leukotrienes, prostaglandins, thromboxane, nitric oxide, and other inflammatory mediators like monocyte chemoattractant protein-1, interferon-inducible protein, TNF, and interleukin-12. Clinical research has investigated the effects of a combination of 480mg curcumin and 20mg quercetin on delayed graft rejection (DGR) in kidney transplant patients. The study found that the treatment groups experienced lower rates of DGR compared to the control group, with significantly improved early kidney function. This improvement is attributed to curcumin's potent anti-inflammatory and antioxidant properties. Potential mechanisms underlying the enhanced kidney function include the induction of the hemeoxygenase enzyme, suppression of pro inflammatory cytokines, and scavenging of free radicals associated with tissue damage. While the role of quercetin in this compound was minimal, the majority of the observed benefits are attributed to curcumin's actions [22].

(Bhowmik. D at all, 2009) Turmeric is renowned for its potential to reduce inflammation and alleviate pain. To incorporate it into your diet effectively, it's recommended to start with a small amount, such as ¼ teaspoon, and gradually increase it to 1 teaspoon over the course of a month. This can be achieved by adding turmeric powder to soups, incorporating it into cooked dishes, mixing it into scrambled eggs, or sprinkling it over salads. For enhanced effectiveness, some studies suggest combining turmeric with a dash of cayenne pepper. This combination may further enhance its anti-inflammatory properties. Moreover, turmeric is believed to have anti-inflammatory effects in the digestive tract. Many individuals have reported improved digestion and reduced bloating after adding turmeric to their meals. Additionally, consuming turmeric after overindulging may aid in digestion and alleviate discomfort [23].

ANTI-OXIDANT PROPERTY OF TURMERIC

(Labban. L at all, 2014) Both water and fat-soluble extracts of turmeric, as well as its active component curcumin, exhibit potent antioxidant activity, comparable to vitamins C and E. Studies have shown that curcumin pretreatment can mitigate ischemia-induced changes in the heart, suggesting a protective effect against ischemic damage.

In vitro studies on endothelial cells have demonstrated that curcumin enhances cellular resistance to oxidative damage by upregulating the expression of heme oxygenase-1, a stress protein involved in antioxidant defense mechanisms. Additionally, curcumin has been found to inhibit T-cell proliferation through blocking specific pathways involved in immune response. Furthermore, curcumin has shown protective effects against testicular damage caused by exposure to di-n-butylphthalate (DBP). It increases levels of glutathione (GSH) and testosterone while enhancing the activity of glucose-6-phosphate dehydrogenase (G6PD) and reducing levels of malondialdehyde (MDA), a marker of oxidative stress. These properties are attributed to the intrinsic antioxidative abilities of curcumin [24]. (Kumar. A at all, 2011) Curcumin's antioxidant properties have been recognized since 1975. It acts as

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a scavenger of oxygen free radicals and can protect hemoglobin from oxidation. In vitro studies have shown that curcumin significantly inhibits the generation of reactive oxygen species (ROS), such as superoxide anions, hydrogen peroxide (H2O2), and nitrite radicals, by activated macrophages, which are crucial in inflammation processes. Moreover, curcumin lowers ROS production in vivo. Its derivatives, demethoxycurcumin and bis-demethoxycurcumin, also exhibit antioxidant effects. Curcumin demonstrates a potent inhibitory effect against H2O2-induced damage in various cell types, including human keratinocytes, fibroblasts, and NG 108-15 cells [25].

(Jyotimayee. B at all) Chronic health issues, such as cardiovascular disease, inflammation, cataracts, and cancer, are associated with free radical damage. Antioxidants property play a important role in protecting tissues from such damage by inhibiting the synthesis of radicals, scavenging them, or accelerating their breakdown. Synthetic antioxidants, commonly used in food and pharmaceuticals, may pose health risks, leading to a growing interest in natural antioxidant sources. Turmeric extract loaded nanoliposomes (TEL) have shown significant antioxidant and inhibitory effects, surpassing those of free turmeric extract, offering potential benefits for health. Turmeric, torch ginger, curry leaf, and lemongrass are among the natural sources with high levels of antioxidants. Turmeric oil has also been suggested as an environmentally friendly method for removing silver nanoparticles. These were highlight the natural antioxidants and innovative approaches for health promotion and environmental sustainability [26].

The Safe Dosage And Toxicology Of Curcumin

(Kocaadam. B at all, 2017) Curcumin has been deemed safe for consumption by the FDA, with no reported toxic effects. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) have established an adequate daily intake (ADI) value for curcumin ranging from 0 to 3 mg/kg. Studies have shown that intake of up to 12 grams of curcumin per day has not resulted in harmful effects in healthy individuals. However, there are concerns regarding potential interactions with enzymes involved in drug metabolism, DNA impairment, and iron chelation. Further research is needed to explore these potential relationships and ensure the safety of curcumin consumption [27].

Curcumin Enhances Immunity

(Akram. M at all) Curcumin has been found to aid the body in combating cancer by assisting in the elimination of cancerous cells that may evade apoptosis. Studies examining the intestinal lining post-curcumin ingestion have revealed an increase in the number of CD4+ T-helper and B-type immune cells. Additionally, curcumin has been shown to enhance overall immunity, as evidenced by increased antibody levels and immune activity observed in mice administered curcumin in research conducted in India [28].

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Turmeric as First Aid:

(Rathaur. P at all, 2012) Research has demonstrated that turmeric possesses hemostatic properties, enabling it to halt bleeding from wounds. Additionally, it acts as a vulnerary, aiding in wound healing because of its anti-inflammatory and antimicrobial properties. Turmeric powder has a healing effect on both aseptic (clean) and septic (infected) wounds in animal models such as rats and rabbits [29].

Curcumin on Health Promotion and Disease Prevention

(Sharifi Rad. J at all) Several biological effects promoting health and preventing disease have been attributed to curcumin and its derivatives. A bibliometric analysis conducted by Yeung et al. (2019) highlighted the significant contributions of the United States, China, India, Japan, and South Korea to scientific research on the bioactive effects of curcumin. These studies primarily focus on the anticancer, anti-inflammatory, and antioxidant properties of curcumin, as previously noted by Xu et al. (2018) [30].

Applications Of Curcumin In Food Processing

(Yang. T at all, 2023) Food preservation has been vital for human survival since ancient times, ensuring continuity of life amidst changing dietary habits and busy lifestyles. With the rise in demand for ready-to-eat foods and the need to extend shelf life while maintaining quality, the development of effective preservation methods has become essential. Seafood, in particular, presents unique challenges in preservation due to hygiene regulations, seasonal availability, waste management, and consumer convenience. Utilizing seafood processing has thus become increasingly important. The growing food industry, coupled with changes in consumption patterns, has led to the widespread use of food additives as a technological necessity. The demand for semi-finished or fully prepared foods has surged, driven by the lifestyle of individuals who lack time for food preparation at home. Consequently, the use of food additives has become inevitable to meet consumer needs and ensure product diversity and convenience [31].

ADVANTAGES OF TURMERIC

(Mary Eve. B at all)

- Inflammation
- Degenerative eye conditions
- Metabolic syndrome
- Arthritis
- Hyperlipidemia (cholesterol in the blood)

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- Anxiety
- Muscle soreness after exercise
- Kidney health [32]

DISADVANTAGES OF TURMERIC

(Radhakrishnan. R at all)

- Mild side effects include upset stomach, acid reflux, diarrhea, dizziness, and headaches.
- Consuming large doses of turmeric supplements can significantly increase urinary oxalate levels, increasing the risk of kidney stone formation.
- Since turmeric acts as a blood thinner, it should be avoided if you have a bleeding disorder.
- Turmeric can interact negatively with medications including blood thinners, antidepressants, antibiotics, antihistamines, cardiac drugs, and chemotherapy treatments. It can also interfere with diabetes medications and result in dangerously low blood sugar levels.
- Turmeric can aggravate stomach problems, such as acid reflux and gallstones.
- Since turmeric limits iron absorption, you shouldn't take it if you are on iron supplements.
- Women who are pregnant or breastfeeding can eat food that contains turmeric as a spice but should avoid taking turmeric supplements. These supplements may stimulate uterus contractions and cause complications [33].

Curcumin Bioavailability: From In Vivo Findings to Clinical Applications

(Sharifi Rad. J at all) The effectiveness of any therapeutic compound in vivo depends on its bioavailability, particularly its free (unbound) concentration, both in the bloodstream and at the therapeutic target site. Several studies have demonstrated minimal levels of unformulated curcumin in the serum and plasma of both rats and humans following various administration routes such as gavage, oral, intraperitoneal, and intravenous.

Interestingly, the data indicates that serum or plasma curcumin levels may not directly correlate between rodents and humans. Furthermore, the route of administration significantly impacts the achievable serum levels. For instance, higher concentrations of unformulated curcumin in the serum or plasma are observed with intravenous and intraperitoneal administration compared to oral or gavage administration [34].

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Safety and Toxicity

(Ahmad shabir. R at all, 2020) Turmeric and its constituents have undergone extensive safety evaluations through various research methods including in vitro studies, animal studies, and clinical trials. According to a comprehensive review, standardized powder or extract of turmeric and curcumin administered orally showed no significant side effects or toxicities in animals. Cell culture studies indicated that curcumin has an antiproliferative effect on normal cells and can reduce cell viability, but no reports of mutagenicity or genotoxicity were found. The oral use of turmeric in humans are to be safe, even at high doses, with only a small proportion of cases reporting mild side effects such as itching, tongue redness, tachycardia, and gastrointestinal complaints like flatulence, diarrhea, nausea, and constipation. However, there are challenges regarding the bioavailability of oral curcumin, with intravenous formulations showing greater absorption. Therefore, intravenous curcumin should be administered at lower doses compared to oral use [35].

NUTRITIONAL CONTENT OF TURMERIC

(Guneri. N at all, 2020)

Nutritional Ingredient	Content (per 100g)
Water	12.85g
Energy	312.00 kcal
Protein	9.68g
Total fat	3.25g
Carbohydrate	67.14g
Total fiber	3.25g
Total sugar	3.21g
Sucrose	2.38g
Dextrose	0.38g
Fructose	0.45g
FATS	
- Total fatty acid saturated	1.838g
- Total fatty acid monounsaturated	0.449g
- Total fatty acid polyunsaturated	0.756g
- Total fatty acid trans fatty	0.58g
Cholesterol	0.00
Vitamins	

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Nutritional Ingredient	Content (per 100g)
- Vitamin C, total ascorbic acid	0.70mg
- B1, thiamine	0.058mg
- B2, riboflavin	0.150mg
- B3, niacin	1.360mg
- B6, pyridoxine	0.107mg
- B9, folic acid	0.00
- B12	0.00
- Vitamin D	0.00
- Vitamin A, IU	0.00
- Vitamin E, (α tocopherol)	4.43mg
- Vitamin K	13.40µg
Minerals	
- Calcium, Ca	168mg
- Iron, Fe	55.00mg
- Magnesium, Mg	208mg
- Phosphor, P	299mg
- Potassium, K	2080mg
- Sodium, Na	27mg
- Zinc, Zn	4.5mg
- Copper, Cu	1.300mg
- Manganese, Mn	19.800mg
- Selenium, Se	6.2µg
Others	
- Caffeine	0.00 [36]

Dermatological uses of Curcumin

(Gopinath. H at all, 2018) Curcumin has shown promise in treating inflammatory and neoplastic skin disorders. In a randomized double-blind placebo-controlled trial involving 20 patients with oral lichen planus, high-dose curcuminoids (6 g per day) improved signs and symptoms. This treatment was well-tolerated, with diarrhea being the most common adverse effect. Additionally, a topical gel preparation containing 1% curcumin inhibited phosphorylase kinase and improved lesions in chronic plaque psoriasis. Furthermore, curcumin may promote healing and prevent scarring in acute injuries such as

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burns [37].

Turmeric as healing properties

(Bhowmik. D at all, 2009) Besides flavoring food, to purify the blood and skin conditions problems is probably the most common use of Turmeric.

Turmeric, a spice derived from the Curcuma longa plant, has a long history of use in Ayurvedic medicine for its various health benefits. Here's a summary of its uses and properties:

Organ Treatment: Turmeric is used to treat skin conditions, support heart health, aid liver function, and assist in respiratory health by expelling excess Kapha.

Activities: It exhibits a wide range of activities, including being an alterative (blood purifier), analgesic (pain reliever), antibacterial, anti-inflammatory, anti-tumor, anti-allergic, antioxidant, antiseptic, antispasmodic, appetizer, astringent, cardiovascular tonic, carminative (relieves gas), cholagogue (promotes bile flow), digestive, diuretic, stimulant, and vulnerary (promotes healing of wounds).

Therapeutic Uses: Turmeric is used in treating anemia, cancer, diabetes, digestion issues, food poisoning, gallstones, indigestion, irritable bowel syndrome (IBS), parasites, poor circulation, staph infections, and wounds.

Reproductive System: It helps regulate the female reproductive system, purifying the uterus and breast milk. In men, it purifies and enhances semen, despite its pungent and bitter taste.

Other Uses: Turmeric is used to reduce fevers, diarrhea, urinary disorders, insanity, poisoning, coughs, and lactation problems. It's also effective for external ulcers and helps remove mucus in the throat, watery discharges like leucorrhea, and pus in the eyes, ears, or wounds.

Ayurvedic Cooking: Turmeric is a staple in Ayurvedic cuisine, where it is used to detoxify the liver, balance cholesterol levels, fight allergies, stimulate digestion, boost immunity, and enhance complexion [38].

Present scenario of cultivation and usages of Turmeric

(Kaur. A at all, 2018) Indian spices, particularly turmeric, have experienced significant export growth over the past five years, with a compound annual growth rate of 14% in rupee terms. The country contributes about 80% of world turmeric production and 60% of global exports. Major turmeric-producing states in India include Andhra Pradesh, Tamil Nadu, Orissa, Maharashtra, Assam, Kerala, Karnataka, and West Bengal, with Andhra Pradesh alone accounting for 60% of total production.

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While turmeric is also cultivated in countries like China, Myanmar, Nigeria, and Bangladesh, India dominates with 82% of the cultivated area. Turmeric from India is highly regarded worldwide, and the US FDA has deemed curcuminoids, its active compounds, as generally safe. Clinical trials have demonstrated the safety of curcuminoids even at high doses, showcasing its wide range of biological actions, including anti-inflammatory, antioxidant, anticarcinogenic, and antidiabetic properties, among others [39].

Highlighted products of Curcumin longa with their appearance, chemical constituents and their uses:

(Fuloria. S at all, 2022)

Product Name	Appearance	Chemical Constituents	Uses
Whole rhizome (dried form)	Orange-brown, red-yellow, or pale yellow	3%–15% curcuminoids, and 1.5%–5% essential oils	Medicinal purposes
Ground C. longa	Yellow or red-yellow	Curcuminoids and essential oils may be reduced during processing	Used as a condiment, dye, medicine, and dietary supplement
C. longa oil	Yellow to brown oil	Monoterpenes in leaves, sesquiterpenes in rhizomes	Used as a spice, medicine, and dietary supplement
C. longa oleoresins	Dark yellow, reddish-brown viscous fluid	25% of essential oil, 37%–55% curcuminoids	Used as a food dye, medicine, and dietary supplement
Curcumin	Yellow to orange-red crystalline powder	Curcumin, bisdemethoxy, and demethoxy derivatives	Used as a spice, medicine, and dietary supplement [40]

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Effect Of Turmeric On Pain

(Razavi marjan. B at all, 2021) Turmeric exhibit pain-alleviating effects attributed to their anti-inflammatory, antioxidant, and antiapoptotic properties. Additionally, curcumin's antinociceptive effect may involve activating opioid mechanisms. Clinical trials and animal studies have confirmed their efficacy in various pain models, including acetic acid–induced visceral pain, formalin-induced orofacial nociception, diabetic neuropathic pain, neuropathic pain due to chronic constriction injury, and postoperative pain [41].

Nano formulations and its Green Synthesis of Curcumin Longa with its Related Compounds:

(Fuloria. S at all, 2022) The usage of nano formulation antibiotics has indeed gained significant attention in recent years due to their potential to enhance therapeutic outcomes compared to traditional antibiotic formulations. Nanomedicine, which integrates principles from nanotechnology and pharmaceutical sciences, offers promising avenues for improving drug delivery, targeting specific tissues or cells, reducing side effects, and overcoming challenges such as antibiotic resistance.

Nanoformulations of antibiotics can improve their bioavailability, stability, and efficacy by encapsulating them within nanoparticles or modifying their surface properties. These nanostructures can protect the antibiotics from degradation, facilitate their transport across biological barriers, and enable controlled release at the desired site of action. Moreover, nanotechnology enables the design of multifunctional platforms that can combine antibiotics with imaging agents or targeting ligands for enhanced diagnostic and therapeutic capabilities.

The rapid expansion of nanomedicine reflects the growing interest in harnessing nanotechnology to address various healthcare challenges, including infectious diseases. However, it's essential to continue research into the safety, efficacy, and scalability of nanoformulation antibiotics to ensure their successful translation into clinical practice [42].

Future Directions

(Fuloria. S at all, 2022) Curcuma longa (turmeric) and its active compound curcumin have attracted significant interest in both traditional medicine and modern research due to their diverse pharmacological properties, including anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory effects. The potential of curcumin to modulate cytokine storms, which are implicated in the severe stages of COVID-19, has garnered attention as a potential therapeutic strategy. Extensive research and development efforts have been directed towards elucidating the medicinal value of turmeric and curcumin, exploring their mechanisms of action, and investigating their clinical applications. Studies have suggested that curcumin may help mitigate cytokine storms by suppressing

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the excessive production of pro-inflammatory cytokines, thereby attenuating the inflammatory response associated with severe COVID-19 cases. However, for the rational utilization of curcumin in the management in human diseases, including COVID-19, it is crucial to have accurate knowledge regarding their effective doses, safety profiles, and modes of action. Clinical trials and further research are needed to determine the optimal dosing regimens, assess potential side effects, and establish the efficacy of turmeric based therapies in different patient population [43].

(Singletary at all) In trials, different bioavailable curcuminoid forms were used without data supporting improved absorption/distribution. High variability in pharmacokinetics and nonlinear dose dependency were observed for one novel formulation. Serum or urine levels of curcuminoids and metabolites should be measured in trials to assess bioavailability, compliance, and efficacy. The influence of comedications on curcuminoid efficacy needs clarification. Combining curcuminoids with NSAIDs and hypoglycemic drugs may enhance efficacy, reduce doses, and lower adverse effects, requiring further study [44].

CONCLUSION

Based on the comprehensive review of literature regarding curcumin's therapeutic effects, particularly its potential in pain management, it is evident that curcumin possesses multifaceted properties that contribute to its efficacy in alleviating pain. Through its anti-inflammatory, antioxidant, antiapoptotic mechanisms, and possible activation of opioid pathways, curcumin has demonstrated promising results in both clinical trials and animal models across various pain conditions, including visceral pain, orofacial nociception, diabetic neuropathy, neuropathic pain, and postoperative pain.

These findings underscore the potential of curcumin as a valuable therapeutic agent in pain management. However, further research is necessary to elucidate the precise mechanisms of action, optimize dosage regimens, and evaluate long-term safety and efficacy in diverse patient populations. Additionally, exploring the synergistic effects of curcumin with other medications, such as NSAIDs or opioids, warrants attention to enhance therapeutic outcomes while minimizing adverse effects.

In conclusion, the accumulated evidence supports the therapeutic effect of curcumin in pain management, offering a promising avenue for the development of novel and effective treatment strategies.

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