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A COMPREHENSIVE REVIEW OF *CURCUMA LONGA* (TURMERIC): CURCUMIN, PHARMACOLOGICAL ACTIVITIES, THERAPEUTIC POTENTIAL, AND SAFETY

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ABSTRACT

Turmeric (*Curcuma longa* L.), a member of the family Zingiberaceae, is widely used as a culinary spice and has a long history of application in traditional medicine. Its major bioactive constituents include curcuminoids, particularly curcumin, a polyphenolic compound extensively investigated for its potential pharmacological activities. Experimental studies have reported antioxidant, anti-inflammatory, antimicrobial, and other biological effects, attracting interest in its possible applications in inflammatory disorders, osteoarthritis, metabolic conditions, cardiovascular health, and cancer-related research. However, the strength of evidence varies across these therapeutic areas. This review provides a comprehensive overview of the historical background, botanical classification, morphology, and major chemical constituents of *Curcuma longa*, with particular emphasis on the chemical structure and pharmacological properties of curcumin. It also examines the traditional uses of turmeric, its contemporary therapeutic potential, marketed formulations, and associated safety concerns. Furthermore, the review discusses the possible mechanisms underlying curcumin's biological activities and highlights the importance of distinguishing experimental findings from evidence obtained through human clinical studies.

Despite its promising pharmacological profile, curcumin presents several challenges that may limit its clinical application, including poor water solubility, low oral bioavailability, and rapid metabolism. Various formulation approaches have been investigated to improve its absorption and systemic availability. Nevertheless, promising laboratory findings do not necessarily translate into established clinical benefits, and the long-term safety of some high-dose supplements requires further evaluation. Additional well-designed clinical trials are needed to establish its efficacy, appropriate dosage, safety profile, and potential interactions with medicines. Overall, turmeric and curcumin represent valuable subjects for pharmacological research, but their therapeutic applications should be guided by reliable clinical evidence rather than generalized claims.

KEYWORDS: *Curcuma longa*, Turmeric, Curcuminoids, Pharmacological Activities, Therapeutic Potential, Bioavailability, Formulations, Toxicity, Safety.

1 INTRODUCTION

Curcuma longa L., commonly referred to as turmeric, is a rhizome-bearing perennial herb belonging to the Zingiberaceae family and has been utilized for millennia across Asia as a culinary spice, natural colouring agent and traditional remedy. Its dried rhizome is recognized as an official drug in the Chinese Pharmacopoeia and is well established in Ayurveda and Traditional Chinese Medicine, where it has traditionally been used to address blood stasis, support circulation and alleviate pain. Curcumin in its purified crystalline form was first isolated in the nineteenth century, with systematic research into its health-related properties gaining prominence from the 1970s onward.[1,2,3]

Phytochemically, the rhizome of C. longa contains a mixture of curcuminoids, essential oils, carbohydrates and phytosterols, and reported analyses indicate that its curcuminoid content is generally greater than that found in the related drugs Curcumae Radix and Curcumae Rhizoma. The curcuminoid fraction primarily consists of curcumin (diferuloylmethane), demethoxycurcumin and bisdemethoxycurcumin, while additional metabolites such as β-elemene, curcumol and curdione also contribute to the overall pharmacological characteristics of the rhizome. Therefore, the medicinal importance of turmeric cannot be ascribed to curcumin alone. Variation in botanical origin and processing methods among related Curcuma drugs, together with the lack of systematic clinical guidance, has been associated with a risk of admixture and inappropriate use.[1,2,3]

Experimental studies have reported antioxidant, anti-inflammatory, antitumour and neuroprotective properties for both curcuminoid and essential oil constituents of the rhizome. Other documented activities include cardiovascular and cerebrovascular protection, immunomodulation, hepatoprotection, as well as analgesic, antiviral, antibacterial and hypoglycaemic effects. From a mechanistic viewpoint, curcumin is known to interact with multiple signalling molecules, with its antioxidant and anti-inflammatory activities considered to be central to the majority of its reported beneficial effects. At the signalling level, these actions are mediated through pathways involving NF-κB, MAPK and PI3K/AKT.[1,2,4]

Clinical investigations have evaluated curcumin in conditions associated with oxidative stress and inflammation, including metabolic syndrome, arthritis, anxiety, hyperlipidaemia and exercise-induced muscle soreness. A comprehensive meta-analysis encompassing 103 randomized controlled trials, involving 42 distinct outcomes and a total of 7216 participants, indicated that curcumin supplementation may influence fasting blood glucose, certain glycaemic parameters, lipid profile and biomarkers related to inflammation and oxidative stress. Nevertheless, the strength of evidence varies considerably across different therapeutic areas. In the field of oncology, a critical evaluation of available clinical trials failed to provide convincing evidence of a substantial therapeutic effect against cancer itself, with approximately half of the published trials focusing on the management of treatment-related adverse effects rather than on the malignancy per se.[4,5,6]

A major limitation for clinical translation is the unfavourable pharmacokinetic profile of curcumin. After standard oral administration, poor intestinal absorption coupled with rapid metabolism and systemic clearance leads to low concentrations in plasma and tissues. To address this issue, various approaches have been explored, including the use of bioavailability enhancers, molecular complexation, encapsulation technologies, specialized delivery formulations and nanoparticle-based systems, with co-administration of piperine reported to markedly increase systemic availability. Pharmacokinetic investigations in healthy volunteers have shown that bioavailability-enhanced formulations attain substantially higher relative absorption compared with unformulated curcuminoids, and reviews focusing on clinical trials have compared successive generations of formulations with respect to dosage, treatment duration, safety and efficacy. Some reviews have suggested that enhanced bioavailability is associated with improved therapeutic effects. However, the existing evidence remains

heterogeneous; in a survey of 165 randomized trials, bioavailability-enhancing strategies were used in 64% of studies, encompassing 25 different methods, yet only a small proportion (8.4%) directly compared more than one curcumin product. Furthermore, systematic reviews seldom consider variations in bioavailability between different formulations, and therefore their conclusions regarding orally administered curcumin should be interpreted cautiously.[4,7,8,9,10,11]

Safety represents an additional important aspect. Although turmeric has a long-standing history of consumption as a dietary spice, the safety profile, adverse effects and quality considerations of concentrated curcumin-containing products warrant independent evaluation. In the United States Drug-Induced Liver Injury Network registry, ten cases of liver injury attributed to turmeric were identified during the period 2004 to 2022. The pattern was predominantly hepatocellular, with an onset latency ranging from one to four months, a notable association with the HLA-B_35:01 allele, and one fatality due to acute liver failure. The authors noted that the apparent increase in such cases may be linked to evolving patterns of use or to the more frequent co-formulation of turmeric with black pepper. Since composition, dosage and formulation characteristics vary considerably across different products, safety data obtained for one preparation cannot be automatically extrapolated to others. In light of these factors, the present review provides an overview of _*Curcuma longa** with particular focus on its phytochemistry, the pharmacology of curcumin and its therapeutic potential. It further assesses the available clinical evidence, formulation approaches aimed at improving bioavailability and current safety data, with the objective of differentiating applications supported by robust evidence from claims that remain to be validated.[2,12]

2. Botanical Classification and Morphology of *Curcuma longa*

2.1 Botanical Classification

Curcuma longa L., commonly known as turmeric, is a perennial, rhizome-bearing herb classified under the family Zingiberaceae and genus Curcuma. The plant is extensively cultivated in India and other tropical and subtropical areas and is valued for its use as a culinary spice, natural pigment and traditional medicinal herb. The subterranean rhizome constitutes the main medicinal and commercial part of the plant and represents a major source of curcuminoids and volatile compounds explored for their pharmacological activities. Correct botanical nomenclature and taxonomic authentication of C. longa are essential to ensure the identity of plant material employed in pharmacognostic and pharmaceutical

investigations.[13,14,15] he taxonomic classification of C. longa comprises Kingdom Plantae, Order Zingiberales, Family Zingiberaceae, Genus Curcuma and Species *Curcuma longa* L. The plant is mainly propagated vegetatively via its underground rhizomes. Precise botanical identification is crucial, as other species within the Curcuma genus may exhibit differences in phytochemical composition and therapeutic properties. Hence, proper botanical authentication represents an essential initial step for quality control and standardization of turmeric-derived products.[14,16]

2.2 Morphological Characteristics

Curcuma longa is a herbaceous perennial plant that may attain a height of approximately 1 m under favourable growing conditions. Its underground stem consists of a central rhizome and several lateral branches. The rhizomes are generally ovoid, oblong, cylindrical, or irregularly branched, with a yellowish-brown external surface and a characteristic yellow to orange internal colour. They possess a distinctive aromatic odour and a pungent, slightly bitter taste. These macroscopic features are useful for the preliminary identification and pharmacognostic evaluation of turmeric rhizomes.[15,17]

The leaves are large, simple, and typically oblong to lanceolate in shape, characterized by a prominent midrib and parallel venation. The overlapping leaf sheaths give rise to a pseudostem. The inflorescence appears as a spike-like structure comprising overlapping bracts bearing pale-coloured flowers. The underground rhizomes also serve as the primary organs for vegetative propagation. While these morphological features assist in the identification of turmeric, they should be evaluated in conjunction with other diagnostic criteria, as closely related Curcuma species may display comparable external morphology.

From a pharmacognostic standpoint, the rhizome is of particular significance, as it contains parenchymatous tissue, starch grains, vascular bundles and oil-bearing cells. Both macroscopic and microscopic examinations can offer valuable diagnostic information concerning the identity and quality of crude turmeric material. Features such as shape, branching pattern, surface characteristics, internal colour, fracture behaviour, odour and microscopic anatomical traits together can aid in botanical authentication. However, morphological evaluation alone is insufficient to determine the complete chemical profile or to detect all types of adulteration. Consequently, analytical techniques including chemical profiling and chromatographic fingerprinting may be employed in combination with botanical assessment to enhance the authentication and standardization of turmeric preparations. Such

quality-control measures are important in curcumin research, as differences in botanical identity, quality of raw material and processing methods can affect the composition of the final product.[15,16,17]

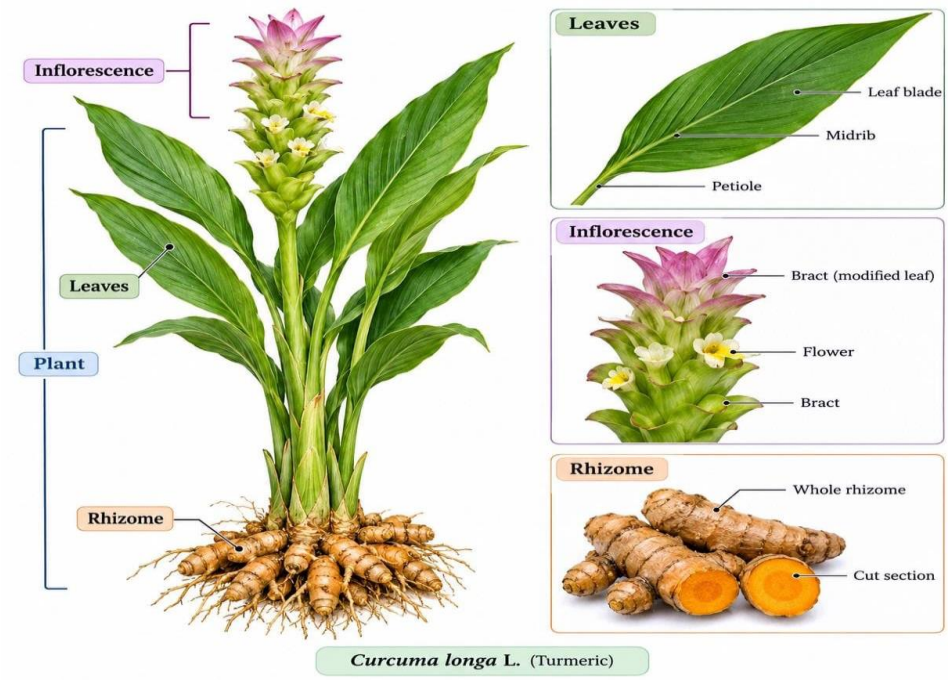


Figure 1: Botanical morphology of *Curcuma longa* L. (turmeric), illustrating the whole plant, leaves, inflorescence, and rhizome. The figure highlights the major morphological features of turmeric, including its broad green leaves, characteristic flowering spike, and underground rhizomes, which are the primary source of curcumin and other bioactive constituents.[15,16,17]

3. Phytochemistry and Chemical Constituents of *Curcuma longa*

3.1. Overview of Phytochemical Composition

The rhizome of *Curcuma longa* L. exhibits a complex phytochemical profile that underlies its characteristic colour, aroma, and diverse biological properties. Its major chemical constituents include curcuminoids, essential oils, terpenoids, polysaccharides, phytosterols and other phenolic compounds. Among these, curcuminoids have received considerable scientific attention owing to their antioxidant and anti-inflammatory potential, while the essential oil fraction, rich in sesquiterpenes such as ar-turmerone, α-turmerone and β-turmerone, contributes to the characteristic aroma and has also been investigated for its biological effects. The relative abundance of these constituents varies considerably depending on cultivar, geographical origin, edaphic and climatic factors, rhizome maturity, harvesting practices and post-harvest processing. Therefore, the chemical composition of turmeric

should be regarded as a multi-constituent phytochemical matrix rather than a single active principle. Although curcumin is the most extensively investigated compound, other curcuminoids (demethoxycurcumin and bisdemethoxycurcumin) and volatile constituents may act synergistically and contribute to the overall bioactivity of turmeric extracts.

Moreover, the extraction method and analytical technique employed significantly influence the recovery and quantification of these constituents. Hence, systematic phytochemical characterization and standardization using validated markers are essential for ensuring batch-to-batch consistency, enabling comparison of experimental findings, and evaluating the true pharmaceutical potential of turmeric-derived preparations.[18,19]

3.2. Curcuminoids

Curcuminoids are yellow-coloured polyphenolic compounds belonging to the diarylheptanoid class and represent the principal pigmenting constituents of *Curcuma longa* rhizomes. The three major curcuminoids are curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC). Curcumin is generally the most abundant, whereas DMC and BDMC differ in the number of methoxy substituents on their aromatic rings. These minor structural variations significantly influence their physicochemical properties, chemical stability, bioavailability and biological activities.Curcumin, chemically designated as diferuloylmethane [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], has been extensively investigated for its antioxidant, anti-inflammatory and pleiotropic pharmacological activities. DMC and BDMC possess closely related structures and have also demonstrated relevant biological effects in experimental models. Nevertheless, the activity of isolated curcuminoids should not be extrapolated directly to whole turmeric extracts, which contain a complex mixture of curcuminoids and essential oils that may exhibit synergistic or additive effects.Furthermore, the relative proportions of individual curcuminoids vary markedly among different cultivars, geographical sources and commercial formulations. Consequently, detailed compositional analysis and standardization of curcuminoid content are imperative for accurate interpretation, comparison and reproducibility of pharmacological research.[18,19]

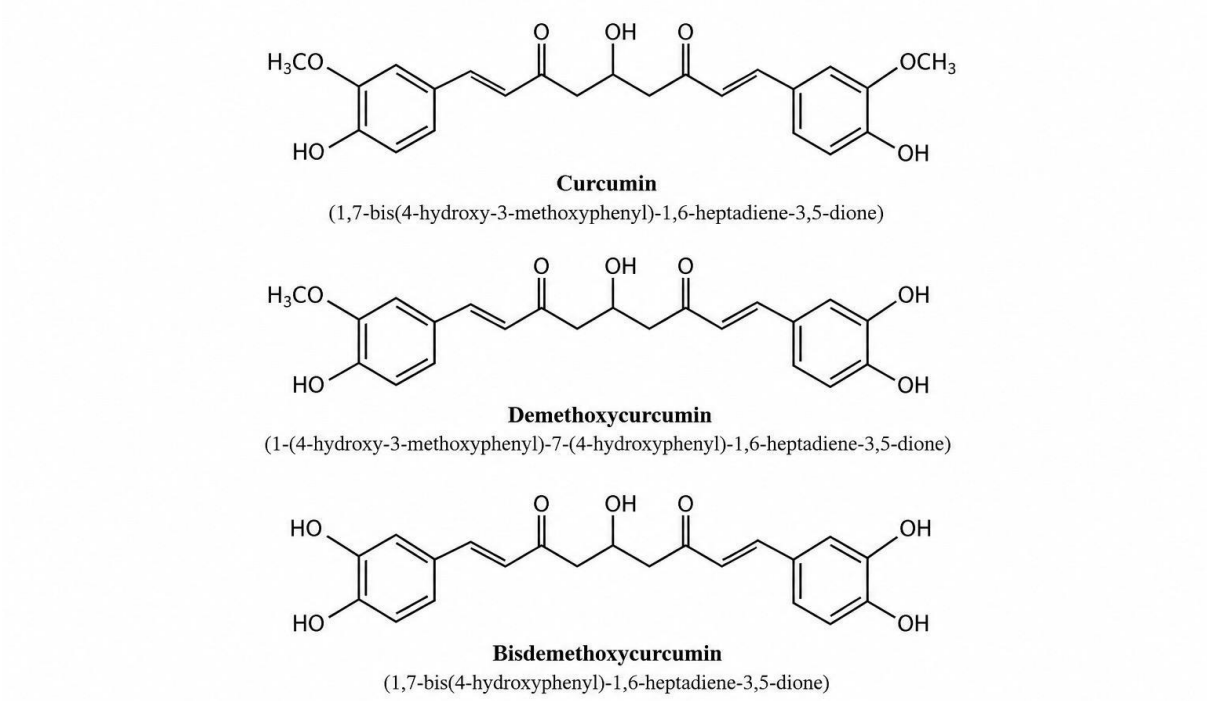


Figure 2: Chemical structures of the three major curcuminoids present in *Curcuma longa* L.: (A) curcumin, (B) demethoxycurcumin, and (C) bisdemethoxycurcumin. The compounds differ in the number of methoxy substituents on their aromatic rings. Source: Chemical structures based on PubChem compound records.[20]

3.3. Volatile Oils and Terpenoid Constituents

The volatile oil fraction is another important constituent of C. longa rhizomes and contributes substantially to the characteristic aroma of turmeric. Chemical analyses have identified numerous volatile constituents, predominantly sesquiterpenes and other terpenoids. The major components commonly reported in turmeric essential oil include ar-turmerone, α-turmerone, β-turmerone, curlone (β-turmerone) and zingiberene. Their relative concentrations vary considerably depending on geographical origin, cultivar, rhizome maturity, extraction technique and analytical conditions.Turmeric essential oils have demonstrated antioxidant, antimicrobial and anti-inflammatory activities in experimental models. Certain individual sesquiterpenes, such as ar-turmerone, have also been investigated for their potential neuroprotective, cytotoxic and anti-inflammatory effects. However, findings obtained from isolated terpenoids or concentrated essential oils cannot be directly extrapolated to conventional dietary consumption of turmeric or to established clinical practice.Importantly, the chemical composition and pharmacological profile of essential oil fractions differ markedly from those of curcuminoid-enriched extracts. Therefore, these fractions should be

distinctly characterized, standardized and evaluated separately when investigating the therapeutic potential of *C. longa* preparations.[19,20]

3.4. Other Phytochemical Constituents

In addition to curcuminoids and essential oils, *C. longa* contains polysaccharides (including ukonan A, B, C and D), phytosterols (β-sitosterol, campesterol, stigmasterol), organic acids and other phenolic constituents. These compounds contribute to the overall chemical complexity of the rhizome and may significantly influence the physicochemical properties, solubility and biological behaviour of crude extracts. Their abundance and distribution are dependent on botanical source, extraction solvent, processing conditions and analytical methods employed. The presence of multiple phytochemical classes underscores the importance of investigating turmeric as a complex botanical matrix rather than attributing all its biological effects solely to curcumin. While curcumin remains the most extensively studied constituent, emerging evidence suggests that polysaccharides may contribute to immunomodulatory activity, phytosterols to lipid-lowering effects, and non-curcuminoid phenolics to antioxidant capacity. Therefore, studies employing chemically well-characterized and standardized preparations are warranted to delineate the individual contributions of these constituents and to determine whether synergistic, additive or antagonistic interactions among them modulate the overall biological activity.[18,19,20]

Table 1: Major phytochemical constituents of *Curcuma longa* and their biological relevance.

S.No.	Phytochemical class	Representative constituents	Biological or pharmacological relevance
1	Curcuminoids	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Principal yellow pigments; investigated for antioxidant and anti-inflammatory activities
2	Sesquiterpenoids	Ar-turmerone, α-turmerone, β-turmerone, curlone	Major constituents of turmeric volatile oil; investigated for various biological activities
3	Other terpenoids	Zingiberene and other volatile terpenes	Contribute to the aroma and chemical profile of turmeric oil

4	Polysaccharides	Water-soluble polysaccharide fractions	Investigated for potential immunomodulatory and other biological effects
5	Sterols	Plant sterol constituents	Contribute to the overall phytochemical composition
6	Other phenolic compounds	Various reported phenolic constituents	May contribute to the chemical and biological properties of extracts

Table 1: Compiled from published reviews on turmeric phytochemistry and Curcuma essential oils The table provides a qualitative summary; constituent concentrations vary with botanical source and extraction method.[18,19,20,21]

4. Traditional and Modern Therapeutic Uses of *Curcuma longa*

4.1. Traditional Medicinal Uses and Ethnopharmacological Significance

Curcuma longa L., commonly known as turmeric and traditionally called Haridra in Ayurveda, has a long history of use in traditional Indian and other Asian medicinal systems. Its rhizome is valued as a culinary spice, natural colouring agent, and ingredient in traditional medicinal preparations. Ethnomedicinal literature describes its use in relation to digestive and respiratory complaints, skin conditions, and inflammatory symptoms. These historical applications have contributed to sustained scientific interest in turmeric as a botanical source of potentially bioactive compounds Traditional turmeric preparations include powders, pastes, decoctions, and topical formulations. Their composition may differ according to the plant material, preparation method, storage conditions, and route of administration. Consequently, traditional use of turmeric as a whole rhizome should not be considered equivalent to the use of a standardized extract or purified curcumin. Although traditional knowledge provides a valuable starting point for pharmacological investigation, it does not independently establish clinical efficacy or determine the appropriate dose for a particular medical condition.[21,22]

4.2. Phytochemical Basis of Modern Pharmacological Investigation

The pharmacological investigation of turmeric has focused particularly on curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin. The rhizome also contains volatile constituents and other phytochemicals that contribute to its overall chemical profile. Differences between whole-rhizome preparations, extracts, and purified compounds

are important when interpreting experimental findings because these materials do not provide identical chemical exposures Curcumin's chemical properties also influence its development as a potential therapeutic compound. Its limited aqueous solubility, chemical instability under certain conditions, metabolism, and relatively low systemic availability following conventional oral administration can complicate its pharmacological evaluation. Formulation strategies have therefore been investigated to improve its solubility, stability, and absorption. However, improved pharmacokinetic properties should not automatically be interpreted as evidence of superior clinical efficacy; each formulation requires evaluation using appropriate safety and clinical outcomes.[22,23,24]

4.3. Anti-Inflammatory and Antioxidant Activities

Anti-inflammatory and antioxidant activities are prominent areas of curcumin research. Experimental investigations have examined its effects on inflammatory mediators, cellular signalling pathways, and processes associated with oxidative stress. These observations provide possible mechanistic explanations for some of the biological effects reported in preclinical studies. Nevertheless, the magnitude and relevance of these effects depend on the experimental model, compound concentration, and biological endpoint. Findings from laboratory experiments cannot be directly translated into established therapeutic benefits in humans Human intervention studies have also evaluated whether turmeric or curcumin supplementation influences inflammatory and oxidative-stress biomarkers. A systematic review and dose–response meta-analysis of randomized controlled trials reported changes in selected markers, supporting continued investigation of these effects. However, the interpretation of such findings requires attention to study quality, heterogeneity, formulation, and certainty of evidence. A change in a biochemical marker does not necessarily demonstrate prevention of disease, improvement in clinical symptoms, or reduction in long-term complications.[22,23,25]

4.4. Digestive and Gastrointestinal Applications

Digestive complaints represent an important connection between traditional turmeric use and modern clinical investigation. The European Medicines Agency has assessed turmeric rhizome as a herbal medicinal material, providing a regulatory perspective on its traditional use and available evidence. Such assessments distinguish long-standing medicinal use from indications supported by sufficient clinical evidence for well-established efficacy A systematic review specifically examining turmeric for digestive disorders evaluated studies

involving conditions such as dyspepsia, irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease, and peptic ulcers. The review highlights the need to consider the evidence separately for each condition rather than treating digestive disorders as a single therapeutic category. Differences in study design, sample size, preparation, and measured outcomes limit the extent to which results can be generalized across indications Accordingly, turmeric's traditional use in digestive complaints should be described separately from demonstrated treatment efficacy. Further well-designed clinical studies are needed to clarify which preparations may provide clinically meaningful benefits, for which conditions, and under what circumstances.[26]

4.5. Metabolic and Hepatic Research

Curcumin has been evaluated for its possible impact on various metabolic parameters, including glycemic indices, lipid profile and inflammatory biomarkers. Since these outcomes relate to different aspects of metabolic health, they should be interpreted individually rather than being generalized as an overall improvement in all metabolic disorders. Heterogeneity in study populations, intervention period, curcumin formulation and methodological quality may account for inconsistencies observed across clinical studies.[27,28,29]

Non-alcoholic fatty liver disease (NAFLD), now increasingly referred to under the umbrella term metabolic dysfunction-associated steatotic liver disease (MASLD), has also been investigated in curcumin research. A recent GRADE-assessed systematic review and dose-response meta-analysis including 15 randomized controlled trials with 905 participants reported that curcumin supplementation significantly lowered alanine aminotransferase (ALT) and aspartate aminotransferase (AST), while no significant effect was observed on alkaline phosphatase (ALP), and curcumin plus piperine showed no significant effect on ALT and AST. Substantial heterogeneity was noted across studies. In another systematic review and meta-analysis focused specifically on aminotransferases in NAFLD patients (15 trials, n=835), curcumin did not significantly affect ALT but was associated with a reduction in AST, again with high heterogeneity. These variations highlight that changes in a single biochemical marker should not be interpreted as overall improvement in liver disease, prevention of progression, or long-term clinical benefit.[30,31]

4.6. Other Investigated Pharmacological Activities

Turmeric and its active constituents have been investigated across multiple biological domains, including antimicrobial, anticancer-related, neuroprotective, hepatoprotective and

other pharmacological activities. Research in this area has focused on cellular responses, modulation of inflammatory pathways, oxidative stress regulation and other molecular mechanisms. Such studies may assist in identifying potential therapeutic targets and in guiding future investigations. However, demonstration of activity in an experimental model does not by itself establish clinical effectiveness. Particular caution is required when interpreting anticancer and antimicrobial findings, as laboratory studies often utilize concentrations or exposure conditions that are markedly different from those attainable in humans. In addition, results obtained with purified curcumin cannot be directly extrapolated to whole turmeric preparations. Therefore, these biological activities should be described as investigational unless adequate clinical evidence supports a specific therapeutic use, and turmeric should not be presented as a substitute for established treatments for serious diseases.[32,33,34]

4.7. Formulation Variability and Safety Considerations

Evaluation of the therapeutic potential of turmeric requires clear differentiation between culinary turmeric, powdered rhizome, standardized extracts, purified curcumin, and formulations developed for enhanced absorption. These product types can differ markedly in curcuminoid concentration, overall chemical profile, bioavailability and systemic exposure. As a result, findings obtained with one specific formulation cannot be automatically extrapolated to other products. Precise reporting of product composition, dosage, duration of treatment and formulation characteristics is therefore essential for accurate interpretation of clinical outcomes. Safety should be assessed in parallel with potential benefits. The European Medicines Agency revised its monograph on *Curcuma longa* rhizoma to include a warning against use in cases of biliary obstruction, cholangitis, liver disease, gallstones and other biliary disorders, following pharmacovigilance reports. Such reports merit attention but should not be interpreted as indicating that every turmeric preparation causes hepatic injury. Risk assessment must take into account the specific product, dose, exposure duration, individual susceptibility, concomitant medications and overall quality of evidence. The distinction between normal dietary use and concentrated supplementation is particularly relevant. Data on culinary exposure cannot be assumed to establish the safety of high-dose or enhanced-bioavailability extracts. A balanced evaluation thus requires both efficacy evidence and systematic monitoring of adverse events, especially for products intended for long-term use.[35,36]

4.8. Critical Comparison of Traditional Uses and Modern Scientific Evidence

The existing literature illustrates how traditional medicinal use can inform phytochemical investigation, experimental research, and subsequent clinical evaluation. Historical applications of C. longa provide context for its traditional use, while pharmacological studies explore potential mechanisms of action and identify bioactive constituents. Clinical trials and systematic reviews are required to assess whether laboratory observations translate into clinically meaningful benefits for specific conditions. The quality and strength of evidence differ across indications, and encouraging results from preclinical studies should not be regarded as proof of therapeutic efficacy in humans. Future studies should focus on standardized botanical preparations, reproducible extraction methods, full disclosure of chemical composition, and rigorously designed clinical trials. It is also important to differentiate between changes in surrogate biochemical markers and patient-relevant outcomes, with adequate safety monitoring and appropriate duration of follow-up. Such an approach would help to clarify the therapeutic relevance of traditional uses and reduce uncertainty resulting from variation in products and study methodologies. Overall, C. longa remains a valuable subject for pharmacological research, but its clinical applications should be judged on the basis of the quality, consistency, and clinical relevance of the available evidence.[37,38,39]

5. Pharmacological Activities and Therapeutic Potential of *Curcuma longa*

5.1 Anti-Inflammatory, Antioxidant and Immunomodulatory Potential

The pharmacological potential of *Curcuma longa* is linked to its diverse phytochemical profile, notably curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin. Curcumin has been widely studied for its influence on inflammatory signaling, oxidative stress and cellular defense. Experimental data indicate that it can interfere with pathways such as NF-κB and MAPK signaling, regulating inflammatory responses via suppression of HMGB1/TLR4/NF-κB axis and reduction of NF-κB p65 nuclear translocation. This modulation affects mediators including TNF-α, IL-6 and COX-2. Curcumin also activates Nrf2-associated antioxidant responses and upregulates endogenous enzymes such as SOD, catalase and GPx. However, these effects depend on concentration, formulation and biological context; therefore preclinical findings should not be interpreted as proof of equivalent clinical benefits.[40,41,42,43]

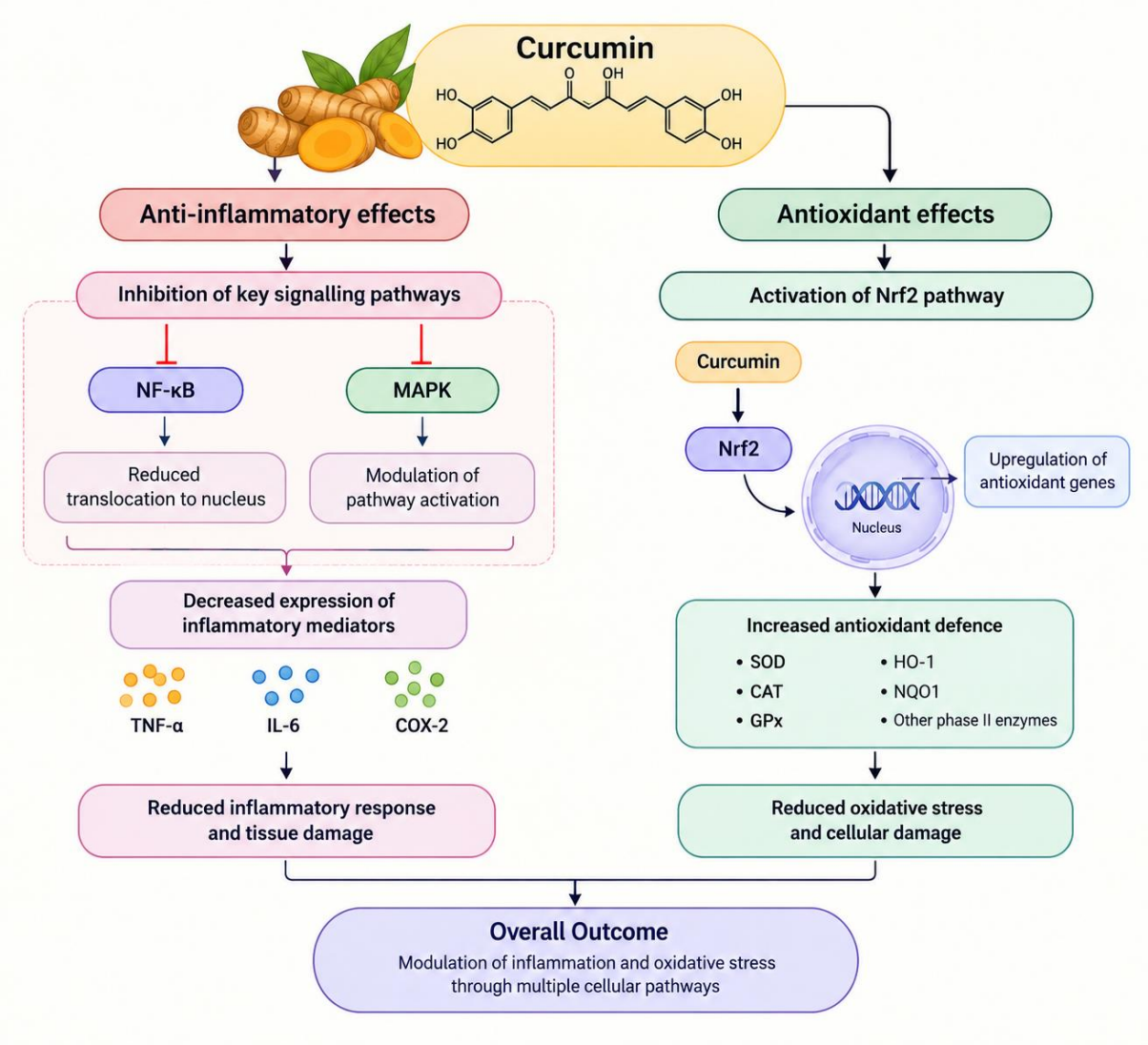


Figure 3: Proposed anti-inflammatory and antioxidant mechanisms of curcumin, illustrating the modulation of NF-κB and MAPK signalling pathways, regulation of inflammatory mediators, and activation of Nrf2-associated antioxidant defence. Source: Prepared by the author based on published literature.[40,41,42,43]

5.2 Metabolic, Hepatic and Other Therapeutic Applications

The metabolic effects of *C. longa* have attracted considerable research attention because inflammation, oxidative stress, and dysregulation of glucose and lipid metabolism contribute to several chronic disorders. Curcumin supplementation has been investigated for its potential effects on fasting blood glucose, insulin resistance indices, circulating lipids and inflammatory markers. Evidence from randomized controlled trials suggests improvement in some parameters, but the strength of evidence varies across outcomes. Variability in participant characteristics, baseline health status, dose, duration and product composition makes cross-study comparisons difficult. Moreover, findings obtained with concentrated

extracts or bioavailability-enhanced formulations cannot be automatically extrapolated to turmeric consumed as a culinary ingredient. Hepatic health is another important area. Curcumin has been studied in individuals with non-alcoholic fatty liver disease (NAFLD) and related metabolic conditions, with trials assessing liver enzymes and other metabolic indicators. However, changes in individual biochemical markers do not by themselves demonstrate resolution of liver inflammation, reversal of fibrosis or prevention of long-term complications, which require evaluation in appropriately designed studies using clinical and diagnostic endpoints. Curcumin has also been explored in gastrointestinal and musculoskeletal disorders and as a complementary approach in oncology. Systematic reviews have examined its possible role in supportive cancer care, but results must be interpreted in relation to specific cancer type, intervention, setting and outcome. Investigation of a complementary role does not establish curcumin as a standalone anticancer therapy or a substitute for standard care.[44,45,46,47]

5.3 Bioavailability, Formulation Challenges, Safety and Future Directions

Despite extensive pharmacological investigation, the clinical translation of curcumin remains limited by its unfavourable physicochemical and pharmacokinetic properties. Curcumin exhibits poor aqueous solubility, limited intestinal permeability and undergoes extensive first-pass metabolism via glucuronidation and sulfation, resulting in low systemic exposure following conventional oral administration. Consequently, various formulation strategies including lipid-based delivery systems, micelles, phospholipid complexes, nanoemulsions and amorphous solid dispersions have been investigated to enhance its solubility, absorption and systemic exposure. Pharmacokinetic studies in healthy volunteers have demonstrated that these formulations can produce markedly varying degrees of bioavailability enhancement compared to unformulated curcumin. However, heterogeneity in formulation composition, dose, analytical methods and pharmacokinetic endpoints makes direct inter-formulation comparisons challenging. Importantly, increased systemic exposure should not be automatically equated with improved therapeutic efficacy or long-term safety, which requires independent clinical validation.[48,49,50]

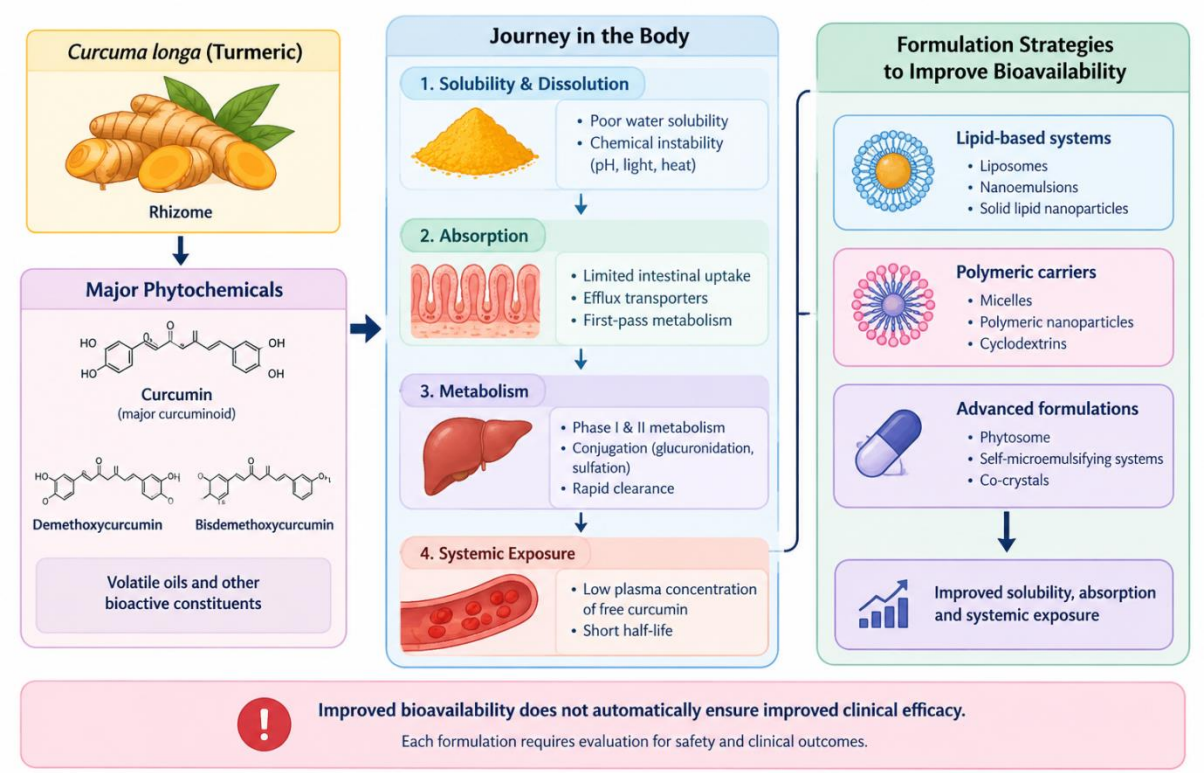


Figure 4: Schematic representation of factors limiting curcumin bioavailability, including poor solubility, limited intestinal absorption, extensive first-pass metabolism and rapid systemic clearance, along with formulation strategies investigated to improve bioavailability. Source: Prepared by the author based on published literature.[48,49,50]

Safety is an essential consideration in the evaluation of turmeric and curcumin-derived products. Although turmeric has a long history of culinary use as a spice, concentrated dietary supplements differ considerably in chemical composition, daily dose and systemic exposure. Commonly reported adverse effects include mild gastrointestinal symptoms such as nausea, dyspepsia and diarrhoea. In addition, rare but clinically significant cases of herb-induced liver injury (HILI) associated with turmeric-containing supplements have been documented. A case series from the United States Drug-Induced Liver Injury Network (US-DILIN) described ten cases of turmeric-associated liver injury, several of which involved formulations co-formulated with piperine as a bioavailability enhancer, suggesting a potential role of increased systemic exposure in susceptibility. While this report does not establish the incidence or causality of liver injury among all users, it underscores that the safety of concentrated and bioavailability-enhanced formulations cannot be inferred from traditional culinary use and warrants careful, formulation-specific assessment. Product quality, presence of adulterants, individual susceptibility (including genetic polymorphisms), concomitant

hepatotoxic medications and duration of exposure should therefore be considered when interpreting safety data. Future research should prioritize botanical authentication, comprehensive chemical standardization using validated markers (curcuminoids and essential oils), reproducible manufacturing under Good Manufacturing Practice (GMP), formulation-specific pharmacokinetic evaluation, and systematic pharmacovigilance with standardized adverse event reporting. Clinical trials should explicitly describe the tested preparation (whole rhizome powder vs. standardized extract vs. isolated curcumin vs. combination product), exact dose and curcuminoid content, duration of intervention, participant characteristics, concomitant medications and pre-specified outcomes. Investigators should refrain from considering these preparations as pharmacologically interchangeable. Such a rigorous, evidence-based approach will help delineate which applications have reproducible clinical benefits, which formulations offer meaningful pharmacokinetic advantages without compromising safety, and where current evidence remains insufficient to support therapeutic recommendations.[51,52]

6. Marketed Curcumin Formulations: Commercial Products, Delivery Systems and Clinical Evidence



Curcumin-based formulations have attracted considerable interest in pharmaceutical research because conventional oral curcumin exhibits poor aqueous solubility, limited intestinal permeability and extensive first-pass metabolism, resulting in low systemic exposure. To overcome these limitations, several proprietary formulations have been developed using distinct delivery technologies, including phospholipid complexes, colloidal dispersions, micellar systems, amorphous solid dispersions and solid-lipid particles. Well-characterized commercial examples include Meriva® (curcumin-phosphatidylcholine complex), Theracurmin® (colloidal nanoparticle dispersion), NovaSOL® (micellar solubilization) and Longvida® (solid-lipid particle technology).These products should not be considered

pharmacologically interchangeable, as they differ substantially in formulation composition, total curcuminoid content, ratio of curcumin to demethoxycurcumin and bisdemethoxycurcumin, manufacturing process, and resulting pharmacokinetic parameters (Cmax, Tmax, AUC and half-life). Furthermore, their commercial availability and claimed bioavailability advantages do not independently establish therapeutic efficacy for any specific indication. Therefore, each formulation warrants independent evaluation through product-specific pharmacokinetic studies, rigorously designed clinical trials with clinically relevant endpoints, and systematic safety assessment.[53,54,55,56]

Overall, marketed curcumin formulations illustrate how pharmaceutical formulation science can modify the delivery and pharmacokinetic behaviour of a natural compound. However, evidence of improved absorption represents only one stage in therapeutic development. Reliable conclusions require reproducible manufacturing, accurate characterization of the formulation, appropriately powered clinical trials, evaluation of clinically meaningful outcomes and continued safety monitoring. Future research should prioritize direct comparisons between formulations, standardized pharmacokinetic endpoints and independent clinical replication. Such an approach would help distinguish genuine clinical benefits from improvements in drug delivery alone and provide a stronger scientific basis for evaluating the therapeutic potential of commercial curcumin products.

7. Toxicity and Side Effects of *Curcuma longa* and Curcumin

Despite extensive investigation of *Curcuma longa* and its principal bioactive compound curcumin for therapeutic potential, its safety profile requires careful, formulation-specific evaluation. The safety of turmeric preparations depends on multiple factors, including dose, duration of administration, chemical composition, formulation technology, systemic exposure and individual susceptibility. Turmeric consumed in customary dietary amounts as a culinary spice should be clearly distinguished from concentrated extracts and bioavailability-enhanced supplements designed to markedly increase curcumin absorption. While many clinical trials have reported acceptable short-term tolerability, emerging clinical evidence and post-marketing pharmacovigilance data indicate that certain concentrated preparations may be associated with adverse effects, including rare but clinically significant herb-induced liver injury (HILI). Therefore, the safety of turmeric should be assessed on the basis of the specific preparation, dose and exposure pattern rather than its natural origin alone.[57]

7.1 Gastrointestinal Adverse Effects

Gastrointestinal disturbances are among the most commonly reported adverse effects associated with oral turmeric and curcumin supplementation. These may include nausea, dyspepsia, abdominal pain, acid reflux, bloating, diarrhoea and constipation. The incidence, severity and frequency of these symptoms may vary according to dose, formulation technology, duration of use and individual tolerance. Although such effects are generally mild to moderate and self-limiting, persistent gastrointestinal discomfort may reduce adherence and lead to discontinuation of supplementation. Furthermore, clinical studies have been heterogeneous with respect to the products investigated, curcuminoid dose, concomitant excipients and methods used for adverse event ascertainment and reporting, making direct comparisons of tolerability between formulations difficult. Consequently, tolerability findings from one specific preparation should not be automatically extrapolated to all commercially available turmeric and curcumin supplements.[58,59]

7.2 Potential Hepatotoxicity

One of the most significant safety concerns associated with concentrated turmeric and curcumin products is the rare but clinically relevant occurrence of herb-induced liver injury (HILI). A clinicopathological case series from the US Drug-Induced Liver Injury Network (DILIN) involving ten patients described liver injury associated with turmeric supplements, with most cases demonstrating a predominantly hepatocellular pattern of injury. Some patients presented with symptoms such as malaise, fatigue or jaundice, whereas others were identified incidentally through abnormal liver function tests. These observations support turmeric as a potential causative agent for drug-induced liver injury, although case series data alone cannot establish incidence among all supplement users.The Australian Therapeutic Goods Administration (TGA) has also issued a safety advisory concerning liver injury associated with medicinal products containing *Curcuma longa* or curcumin. In its 2023 advisory, the TGA reported approximately 20 cases in Australia with varying severity, including cases requiring hospitalization, and noted that some involved products containing additional ingredients (e.g., piperine) that could have contributed to the injury. Regulatory evidence suggests that the risk is rare but potentially serious and may be greater with high-dose or enhanced-bioavailability preparations. However, available evidence does not establish that all turmeric-containing products carry an equivalent level of risk.[60,61]

7.3 Clinical Case Reports and Individual Susceptibility

Published case reports provide additional evidence concerning the possible relationship between turmeric supplementation and liver injury. Individual case reports have described patients developing marked hepatocellular injury, with elevated serum aminotransferases and bilirubin and clinical symptoms of acute hepatitis after using turmeric-containing products, with biochemical improvement (positive dechallenge) following discontinuation in several cases. Some reports also documented recurrence upon re-exposure (positive rechallenge). Such observations are important for pharmacovigilance and identification of safety signals, but they cannot independently establish causality because confounding factors such as concomitant hepatotoxic medicines, other herbal supplements, alcohol use, underlying liver disease and individual susceptibility may influence the outcome. An additional consideration is the possible role of genetic susceptibility. A genome-wide association study of turmeric-associated liver injury identified a strong association with the human leukocyte antigen (HLA) allele HLA-B_35:01, which was present in 7 of 10 affected individuals compared to a low background prevalence. This finding suggests that adaptive immune-mediated mechanisms may contribute to injury in genetically susceptible patients. Nevertheless, HLA-B_35:01 is not deterministic; its presence does not mean that every carrier will develop liver injury, nor does its absence exclude risk. Furthermore, routine HLA screening is not currently recommended as a predictive tool for supplement users. Further studies are required to clarify the immunological mechanisms and clinical utility of this association.[62,63]

7.4 Influence of Formulation and Bioavailability

The formulation and bioavailability of curcumin are important determinants in safety assessment. Conventional oral curcumin has poor aqueous solubility and limited systemic absorption due to rapid phase II metabolism and intestinal efflux. To overcome this, many commercial preparations employ specialised delivery systems (e.g., phytosomal, liposomal, micellar, nanoparticulate formulations) or absorption-enhancing ingredients such as piperine (black pepper extract) to increase systemic exposure by 20-fold or more. Although improved bioavailability may be desirable for therapeutic efficacy, a higher systemic Cmax and AUC also necessitates formulation-specific safety evaluation, as toxicokinetics may differ from traditional turmeric. Products containing piperine have been of particular regulatory interest, as piperine not only inhibits UGT and CYP3A4-mediated curcumin glucuronidation but also modulates hepatic drug transporters. A published case report and literature review described severe acute hepatocellular injury associated with combined turmeric and piperine use, with

rapid onset and positive dechallenge, highlighting the need for careful evaluation of enhanced-bioavailability products. However, this single report does not establish piperine as the sole or necessary cause of every case of turmeric-associated liver injury, as injury has also been reported with piperine-free formulations.[64,65]

7.5 Dose-Related and Preclinical Toxicity

Experimental toxicology studies have investigated the safety profile of turmeric and curcumin across different exposure levels. Sub-chronic and chronic toxicity studies in rodents have generally reported a low order of toxicity, with high oral LD50 values (>5 g/kg). However, certain animal studies conducted under exaggerated high-dose conditions (e.g., ≥1,000 mg/kg/day curcuminoids for 90 days) have reported adverse biochemical alterations (elevated ALT/ALP) or histopathological findings including hepatocellular hypertrophy, hepatic necrosis and forestomach ulceration. Similarly, in vitro laboratory studies have explored potential cellular, pro-oxidant and genotoxic effects at supraphysiological concentrations (>25 µM). These findings are relevant for hazard identification and for defining a no-observed-adverse-effect level (NOAEL), but they must be interpreted within the inherent limitations of the experimental models. The concentrations and doses employed in such studies, particularly in vitro IC50 experiments, often exceed by several orders of magnitude the systemic exposure achievable through customary dietary consumption (2-4 g turmeric ≈ 40-80 mg curcumin) or standard supplement use in humans. Therefore, preclinical high-dose findings should not be extrapolated as direct proof of toxicity or liver injury risk at ordinary dietary levels.[66,67]

7.6 Clinical Precautions and Risk Management

Appropriate risk minimization measures are necessary when concentrated turmeric or curcumin supplements are used, particularly with high-dose or enhanced-bioavailability formulations. Individuals who develop signs or symptoms suggestive of liver injury during supplementation — including yellowing of the skin or eyes (jaundice), dark urine, pale stools, unusual fatigue, persistent nausea, vomiting, pruritus or right upper quadrant abdominal discomfort — should promptly discontinue the suspected product and seek immediate medical assessment with liver function testing. People with current or previous liver disease, biliary obstruction, or concomitant use of potentially hepatotoxic medicines should consult a healthcare professional before initiating concentrated turmeric preparations. Furthermore, healthcare professionals should routinely include herbal and dietary supplements in

medication reconciliation when evaluating unexplained elevations in liver biochemistry, as patients often do not disclose these products, perceiving them as natural and therefore safe.[68]

7.7 Limitations of Current Safety Evidence

Interpretation of turmeric safety evidence is complicated by substantial heterogeneity in product composition, curcuminoid content (ranging from <3% to >95%), dose, duration of use, bioavailability-enhancing technologies and methods of adverse-event ascertainment and reporting. Clinical trials can provide useful information on short-term tolerability under controlled conditions, but their limited sample sizes (often n<100), short duration (typically 4-12 weeks) and exclusion of patients with hepatic comorbidities render them insufficiently powered to detect rare, idiosyncratic or delayed adverse effects such as drug-induced liver injury (DILI), which may have an incidence of <1 in 10,000. Conversely, spontaneous pharmacovigilance reports (e.g., FAERS, CAERS) and individual case reports are valuable for signal detection and hypothesis generation but are subject to under-reporting, incomplete documentation and confounding, and therefore cannot determine population incidence or establish definitive causality on their own. The presence of multiple ingredients, including piperine, catechins or other herbal extracts in multi-constituent formulations, further complicates causal attribution to curcumin alone and necessitates the application of structured causality assessment tools such as RUCAM.[69]

7.8 Overall Safety Assessment

Overall, turmeric and curcumin should neither be considered universally safe nor characterised as inherently hepatotoxic. The totality of available evidence suggests that customary dietary use and many standardised preparations are well tolerated in studied populations and settings, with a low incidence of adverse events. However, predominantly mild gastrointestinal disturbances (dyspepsia, nausea, diarrhoea) and rare but clinically significant cases of acute idiosyncratic drug-induced liver injury (DILI), including cases requiring hospitalisation and transplantation, warrant ongoing pharmacovigilance attention. A nuanced, risk-based safety assessment should distinguish between: (i) customary culinary use (2-4 g/day turmeric as spice), (ii) standardised oral supplements, and (iii) high-dose, bioavailability-enhanced concentrated formulations. Such assessment must integrate the specific product characterisation (curcuminoid content), formulation type, dose, duration of exposure, concomitant potentially hepatotoxic medicines or herbs, alcohol use, pre-existing hepatobiliary disease, and individual genetic susceptibility factors such as HLA-B*35:01.

Further well-designed prospective clinical studies with systematic liver biochemistry monitoring, consistent product characterisation according to Good Manufacturing Practice (GMP), and strengthened post-marketing adverse-event surveillance through formal causality assessment (RUCAM) are required to clarify the long-term safety profile of different turmeric preparations and to identify subpopulations who may be more susceptible to adverse effects.[70]

8. CONCLUSION

Curcuma longa L. is a chemically complex botanical containing curcuminoids, volatile oils and terpenoids, and should not be regarded as curcumin alone. Botanical authentication and standardized chemical characterization are essential for reproducible research. Curcumin exhibits antioxidant, anti-inflammatory and immunomodulatory activities via multiple signaling pathways and has been investigated in osteoarthritis, metabolic and cardiovascular disorders. However, evidence quality varies, and promising preclinical findings do not necessarily translate into clinical efficacy. Clinical trials report benefits for selected outcomes, but heterogeneity in design, dose, formulation and population limits generalizability. Poor solubility and rapid metabolism limit conventional curcumin bioavailability, prompting development of enhanced formulations (e.g., Meriva®, Theracurmin®, NovaSOL®, Longvida®). Improved pharmacokinetics should not be equated with superior therapeutic efficacy without formulation-specific clinical evidence. Safety assessment must differentiate culinary use (2-4 g/day) from concentrated supplementation. While generally tolerated with mild gastrointestinal effects, rare idiosyncratic drug-induced liver injury, including cases linked to high-dose and bioavailability-enhanced products and association with HLA-B*35:01, warrants pharmacovigilance. Dose, duration, formulation quality, comedications and individual susceptibility influence risk. Future research should prioritize well-designed trials using GMP-characterized, formulation-specific preparations with clinically relevant endpoints, comparative pharmacokinetic studies, and systematic long-term safety monitoring with RUCAM-based causality assessment to translate traditional use into evidence-based applications.

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