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CURCUMIN AND TEA TREE OIL: AN INCREDIBLE WONDERS OF NATURE

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ABSTRACT

Curcumin, a polyphenol found in turmeric, is effective in treating oxidative and inflammatory disorders, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. It can also manage exercise-induced inflammation and muscular pain, improving recovery and performance in active individuals. However, curcumin alone does not yield the expected health benefits due to its low bioavailability. Piperine, the main active constituent of black pepper, has shown the potential to enhance bioavailability by 2000% when complexed with curcumin. When paired with boosting substances, curcumin offers several health advantages. Metabolic disorders pose a significant threat to global human health, and curcumin, a natural polyphenolic chemical derived from the rhizomes of the plant Curcuma, has been used in clinical studies for the treatment of these disorders. Clinical data indicates that curcumin has significant therapeutic potential and few negative effects. However, further high-quality clinical trials are needed to validate its effectiveness and elucidate its biological processes and targets. Tea tree oil (TTEO) has traditionally been used for treating wounds, insect bites, boils, itching, and minor oral mucosal inflammation. However, most studies on its biological properties are in vitro, and there is often no correlation between chemical composition and observed properties. More robust studies with common procedures, formulations, and objectives, conducted in accredited laboratories worldwide, and using groups of individuals with well-defined acne, are needed to provide practical results. Nevertheless, further high-quality clinical trials are necessary in the future to validate its effectiveness and elucidate its biological processes and targets. This study aims to offer a concise summary of the extensive studies on the health effects of curcumin.

KEYWORDS: Curcumin; Turmeric; Tea Tree Oil; Melaleuca alternifolia (Tea Tree); Antioxidant; Anti-Inflammatory; Polyphenol; Clinical Evidence.

1. INTRODUCTION

Turmeric is a spice that has garnered significant attention from both the medical and scientific communities, as well as the culinary sector. Turmeric is a perennial herbaceous plant (Curcuma longa) belonging to the ginger family.[1] The therapeutic qualities of turmeric, the origin of curcumin, have been recognised for millennia; nevertheless, the capacity to elucidate the precise mechanisms of action and identify the bioactive constituents has only lately been explored.[2,3] Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (Figure 1), also known as diferuloylmethane, is the principal natural polyphenol present in the rhizome of Curcuma longa (turmeric) and other Curcuma species. The remaining two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. Curcuminoids are polyphenolic compounds that impart the yellow hue to turmeric. Curcumin can manifest in a minimum of two tautomeric forms: keto and enol. The enol form exhibits greater energy stability in both the solid state and in solution.[4, 5] Curcumin may be utilised for the measurement of boron in the curcumin technique. It interacts with boric acid to produce a red chemical known as rosocyanine. Curcumin is a vibrant yellow pigment that can serve as a food colouring agent. Its E number as a food additive is E100. Curcuma longa has been historically utilised in Asian nations as a medicinal plant owing to its antioxidant, anti-inflammatory, antimutagenic, antibacterial, and anticancer properties.[6,7]

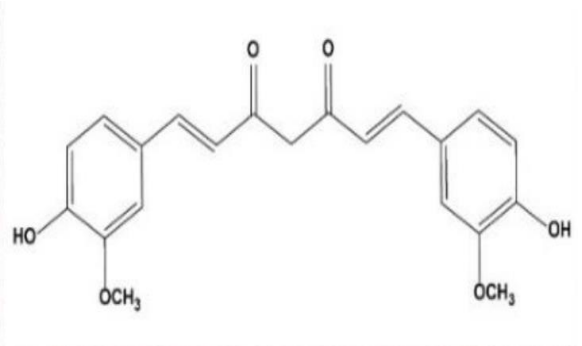

Figure 1: Curcumin (1, 7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione).

Curcumin, a polyphenolic compound, has been demonstrated to interact with many signalling molecules and exhibit cellular activity, hence substantiating its numerous health advantages.[8,9] It has been demonstrated to alleviate inflammatory illnesses[9], metabolic syndrome[10], pain[11], and to assist in the therapy of inflammatory and degenerative ocular disorders.[12, 13] Furthermore, it has been demonstrated to be advantageous for the kidneys.[14] Although several therapeutic advantages of curcumin supplementation exist, the majority of these benefits stem from its antioxidant and anti-inflammatory properties. Notwithstanding its purported advantages through anti-inflammatory and antioxidant pathways, a significant issue with the isolated consumption of curcumin is its low bioavailability, principally attributed to inadequate absorption, fast metabolism, and rapid excretion.[15] Multiple drugs have been evaluated to enhance the bioavailability of curcumin by targeting these distinct pathways. The majority have been designed to inhibit the metabolic route of curcumin to enhance its bioavailability.[16] Piperine, a recognised bioavailability enhancer and the principal active constituent of black pepper, is linked to a 2000% increase in the bioavailability of Curcumin.[18] Consequently, the challenge of inadequate bioavailability seems to be addressed by including compounds like piperine that augment bioavailability, so forming a curcumin complex.[19, 20]

We performed an extensive literature review utilising the ISI Web of Science, PubMed, Science Direct, and Google Scholar databases to gather information about the impact of curcumin on metabolic disorders. The data retrieval employed the following keywords: “curcumin” and (“metabolic disease”, “diabetes”, “obesity”, or “non-alcoholic fatty liver disease”) and (“clinical trials” or “human trials”). Furthermore, we utilised the website ClinicalTrials.gov to gather registered clinical trials about curcumin for metabolic illnesses. Subsequent to our search, we conducted a thorough analysis of the whole texts of the literature to ascertain eligibility for inclusion in this study. Editorials, conference papers, and research with inadequate or inaccessible data were removed.

2. Properties of Curcumin

Curcumin possesses antioxidant, anti-inflammatory, antiviral, and antifungal properties. Research indicates that curcumin is non-toxic to people.[21] Curcumin demonstrates anti-inflammatory effects by inhibiting many compounds that are crucial in the inflammatory process. Turmeric is efficacious in mitigating post-surgical inflammation. Turmeric aids in the prevention of atherosclerosis by diminishing the production of blood clots.[22] Curcumin suppresses the proliferation of Helicobacter pylori, a bacterium responsible for stomach ulcers and associated with gastric malignancies. Curcumin may chelate heavy metals like cadmium and lead, therefore mitigating their toxicity.[23] This characteristic of curcumin elucidates its neuroprotective effects. Curcumin functions as an inhibitor of cyclooxygenase, 5-lipoxygenase, and glutathione S-transferase.[24,25] It is a prevalent spice, primarily recognised for its use in Indian cuisine as a fundamental component in curries and many ethnic foods.[26] Turmeric has been utilised for ages in Ayurvedic medicine, which combines the therapeutic effects of plants with nutrition.[27] This remarkable plant has gained prominence in the West due to its extensive array of therapeutic advantages.[28] Turmeric is a powerful antioxidant. Curcumin, its principal active component, possesses antioxidant properties comparable to vitamins C, E, and Beta-Carotene, rendering turmeric a preferred option for cancer prevention, liver protection, and the mitigation of premature ageing.[29-31] Numerous published research indicate that turmeric suppresses the proliferation of various types of cancer cells. Moreover, turmeric serves as a potent anti-inflammatory, alleviating ailments such as bursitis, arthritis, and back pain.[32] The anti-inflammatory effects of turmeric are probably attributable to a combination of three distinct qualities. Turmeric diminishes the synthesis of inflammation-promoting histamine.[33] Secondly, it enhances and extends the effects of the body's endogenous anti-inflammatory adrenal hormone, cortisol. Additionally, turmeric augments circulation, facilitating the elimination of toxins from tiny joints where cellular waste and inflammatory substances are often sequestered.[34, 35] Studies have also validated the digestive advantages of turmeric. Turmeric functions as a cholagogue, enhancing bile production, therefore augmenting the body's capacity to digest fats, aiding digestion, and facilitating the elimination of toxins from the liver.[36-38]

3. Chemical Properties of Curcumin

Curcumin was initially extracted from the rhizomes of Curcuma longa L. in 1815. Curcuma longa is a perennial plant characterised by its fleshy, orange, tuberous rhizomes and is extensively cultivated in India, China, and Indonesia.[39, 40] The curcumin level in Curcuma longa typically ranges from 1.2% to 9.1%.[41] Curcuma wenyujin, Curcuma phaeocaulis, and Curcuma kwangsiensis are indigenous to the Sichuan, Guangxi, and Zhejiang regions of China, respectively.[42, 43] The curcumin level in the rhizomes of the three medicinal plants varies from 0.071 to 1.717 mg/g.[13–15] The price of curcumin is around 6.96 USD per gram.[45] Curcumin is a diketone with the IUPAC designation (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione.[46] The chemical formula is $C_{21}H_{20}O_6$, and the molecular weight is 370.40 g/mol. Curcumin is an orange-yellow crystalline powder with a somewhat bitter taste.[47] It is insoluble in water and readily soluble in polar solvents.[48, 49] Numerous techniques exist for the extraction of curcumin. Alongside solvent extraction, acid-base extraction, and enzyme extraction, other methods such as microwave-assisted extraction, supercritical fluid extraction, and emulsification liquid–

liquid microextraction can also be employed to extract curcumin from plant sources.[50-52]

4. Pharmacological Application

4.1 Anti-Inflammatory Activity

Oxidative stress is associated with several chronic illnesses, and its pathogenic mechanisms are intricately linked to inflammation, since one may readily provoke the other. It is established that inflammatory cells release various reactive species at the inflammation site, resulting in oxidative stress, hence illustrating the connection between oxidative stress and inflammation.[53] Moreover, certain reactive oxygen and nitrogen species can trigger an intracellular signalling cascade that amplifies pro-inflammatory gene expression. Inflammation has been recognised as a contributing factor in the progression of several chronic illnesses and disorders.[54-56] The diseases encompass Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, cerebral injury, cardiovascular disease, metabolic syndrome, cancer, allergies, asthma, bronchitis, colitis, arthritis, renal ischaemia, psoriasis, diabetes, obesity, depression, fatigue, and acquired immune deficiency syndrome. AIDS.[57, 58] Tumour necrosis factor α (TNF-α) serves as a principal mediator of inflammation in several disorders, with its effects controlled by the activation of the transcription factor nuclear factor (NF)-κB.[59] While TNF-α is regarded as the most powerful activator of NF-κB, its expression is concurrently controlled by NF-κB. Besides TNF-α, NF-κB is activated by numerous inflammatory cytokines, gram-negative bacteria, various pathogenic viruses, environmental pollutants, and factors such as chemical, physical, mechanical, and psychological stress, elevated glucose levels, fatty acids, ultraviolet radiation, cigarette smoke, and other pathogenic agents.[60, 61] Consequently, medicines that inhibit NF-κB and its controlled gene products may have therapeutic benefit against many illnesses.[62] Curcumin has demonstrated the ability to inhibit NF-κB activation induced by several inflammatory triggers.[63] Curcumin has demonstrated the ability to inhibit inflammation via many pathways not included in this study, therefore reinforcing its role as a possible anti-inflammatory drug.[64]

4.2 Antioxidant Activity

Curcumin's benefits on numerous illnesses are mostly due to its antioxidant and anti-inflammatory characteristics.[65, 66] Systemic oxidative stress indicators improve with curcumin.[67] Research suggests that it can boost antioxidant activity, including superoxide dismutase (SOD).[68-70] A meta-analysis of randomised control trials found that supplementing with purified curcuminoids significantly improved oxidative stress parameters, including SOD and catalase activities, GSH levels, and lipid peroxides.[71] The meta-analysis found that all trials used a formulation to address bioavailability issues, with four out of six using piperine. Curcumin's impact on free radicals involves many methods. It can scavenge reactive oxygen and nitrogen species (ROS and RNS)[72], modulate GSH, catalase, and SOD enzyme activity[73], and inhibit ROS-generating enzymes like lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase.[74] Additionally, curcumin, a lipophilic molecule, effectively scavenges peroxyl radicals, making it a chain-breaking antioxidant like vitamin E.[75]

4.3 Metabolic Syndrome

Curcumin has been shown to attenuate systemic inflammation, which is associated with many conditions affecting various systems, including Metabolic syndrome (MetS), which includes insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein cholesterol (HDL-C), elevated low-density lipoprotein cholesterol (LDL-C), elevated triglyceride levels, and obesity.[76] Curcumin has been shown to improve insulin sensitivity, suppress adipogenesis, reduce elevated blood pressure, inflammation, and oxidative stress. It also modulates the expression of genes and enzymes involved in lipoprotein metabolism, leading to a reduction in plasma triglycerides and cholesterol and an elevation of HDL-C concentrations.[77-79] Both overweight and obesity are linked to chronic low-grade inflammation, which is thought to be at the core of complications associated with diabetes and cardiovascular disease.[80] Addressing inflammation is important. In a randomized double-blind placebo-controlled trial, 117 subjects with MetS received either 1 g curcumin plus 10 mg piperine to increase absorption or a placebo plus 10 mg piperine for eight weeks.[81] Within-group analysis revealed significant reductions in serum concentrations of TNF-α, IL-6, transforming growth factor beta (TGF-b), and monocyte chemoattractant protein-1 following curcumin supplementation.[82,83] The study found that curcuminoids were more effective than the placebo in reducing serum LDL-C, non-HDL-C, total cholesterol, triglycerides, and lipoprotein a (Lp(a)), in addition to elevating HDL-C concentrations. The effects of curcuminoids on triglycerides, non-HDL-C, total cholesterol, and Lp(a) remained significant after adjustment for baseline values of lipids and body mass index.[84-86]

5. Side Effects

Curcumin has a well-established safety record, with the Allowable Daily Intake (ADI) value being 0.1-3.5 mg/kg body weight. Several trials on healthy subjects have confirmed its safety and efficacy. However, some negative side effects have been reported, such as diarrhea, headache, rash, and yellow stool in seven subjects receiving 501-12,002 mg in a dose response study.[87, 88] Additionally, some subjects receiving 0.451 to 3.06 g/day curcumin for one to four months reported nausea and diarrhea, as well as an increase in serum alkaline phosphatase and lactate dehydrogenase contents.[89] Curcumin, a natural product with potential for treating Type 2 Diabetes, Obesity, and Non-Alcohol-Deficit Lipoproteinemia (NAFLD), has been found to cause mild gastrointestinal reactions in patients.[90] These

reactions include constipation, nausea, diarrhea, stomach pain, and flatulence. However, these adverse events are only experienced in individual patients and are not serious. In a clinical trial involving 109 patients with T2DM, curcumin intervention resulted in a few mild adverse events.[91] A double-blind, randomized, placebo-controlled trial found almost no side effects after 3 months of nanocurcumin intervention. Some studies have shown curcumin has no side effects even at doses as high as 1515 mg/d.[92] These results suggest curcumin is a safe natural product with mild and sporadic side effects, which has led to its approval as "Generally Recognized as Safe" by the US Food and Drug Administration.[93-95]

6. Tea Tree Oil

Melaleuca alternifolia (tea tree) is a small tree of the family Myrtaceae native to Australia. The tea tree essential oil (TTEO) produced from its leaves can be classified into three major chemotypes: terpinen-4-ol, terpinolene, and 1,8-cineole.[96] Other chemotypes are a combination of dominant and nondominant constituents, with various compositions. The terpinen-4-ol chemotype is dominant and also medicinally more interesting. In medicine, TTEO is used against acne, reduces contact dermatitis, and improves wound healing.[97-98]

7. Components of Tea Tree Oil (TTO)

Melaleuca alternifolia (Maiden & Betch) Cheel is an evergreen Australian native tree and belongs to the Myrtaceae family. The leaves and branches of this species are rich in EOs, which along with other *Melaleuca* species (*M. dissitiflora* Smith, *M. linariifolia* F. Mueller, and *M. uncinata* R. Br.), EOs are known as tea tree oil (TTO). This TTO is used in the pharmaceutical, cosmetic, and food industries due to its antimicrobial, antioxidant, anti-inflammatory, and antineoplastic properties.[99] Adulteration of TTO happens, which may be related to confusion with the common name (tea tree) of some species in the genus *Leptospermum*, and species in the genera *Kunzea* and *Baeckea* from Australia and New Zealand, which also have the same common name. Nevertheless, the financial gain can be the most important factor in the adulteration of TTO[100], through the addition of lower-cost byproducts derived from *Eucalyptus* essential oil or even through the addition of pure chemical compounds obtained by chemical synthesis or fermentation (101). The Australian tea tree industry exports 90% of its production to international markets, around 900 metric tonnes of oil per annum. The production is mainly based on genetically improved populations resulting from a long-term breeding program (102). There are six oil chemotypes in *M. alternifolia* identified by the presence of distinct percentages of terpinen-4-ol, 1,8-cineole, and terpinelone: terpinen-4-ol chemotype containing 30 to 40% of this monoterpenoid (used in commercial TTO production); terpinolene chemotype; 1,8-cineole chemotype; and three chemotypes all dominated by 1,8-cineole but differing in either terpinen-4-ol or terpinolene content (103-105) According to the International Standard Organization (ISO 4730:2017) (106), TTO must have a minimum terpinen-4-ol content of 35% and a maximum 1,8-cineole content of 10%, nevertheless market prefers a TTO with the highest terpinen-4-ol (higher than 38%) and the lowest 1,8-cineole content (less than 3%) possible.[108] Ten monoterpene/monoterpenoids and five sesquiterpene/sesquiterpenoids can be found in TTO (Figure 2).

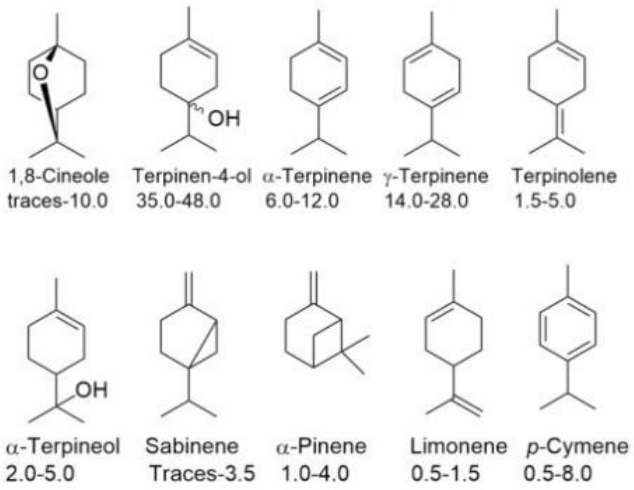

Figure 2: Chemical Compounds present in the TTO.

8. Biological Properties of Tea Tree Oil (TTO)

TTO has been used for various medical conditions, including perionychia, empyema, gynecological conditions, epidermophyton infections, impetigo contagiosum, pediculosis, ringworm, tinea, throat, psoriasis, and mouth conditions.[109] A systematic review of preclinical and clinical studies found its efficacy against ectoparasites, justifying its use in pharmacotherapy of ectoparasitic infections. In Australian traditional medicine, M. alternifolia was used to treat bruises, insect bites, and skin infections. During World War II, TTO was used as an insect repellant to

reduce infection rates.[110-112] However, its use declined due to unreliable supply and variable quality. The International Organization for Standardization (ISO) has established limits for volatile constituents in TTO products to prevent variability. Ethnopharmacological studies reveal TTO's antimicrobial, antioxidant, and anti-inflammatory activities.[113-115]

The antimicrobial activity of the M. alternifolia plant (Tea Tree) has been a topic of interest since its traditional use by the Bundjalung Aborigines of northern New South Wales. The plant's crushed leaves were used to treat coughs, colds, and wounds, and the oil was used as a therapeutic agent. The first reports of TTO's antimicrobial activity were published by Penfold in the 1920s and 1930s. TTO's activity was compared to the disinfectant carbolic acid or phenol, and was rated as 11 times more active.[116-118] The RW coefficients of several TTO components were also reported, leading to TTO being promoted as a therapeutic agent. However, the evidence for TTO's medicinal properties is limited, as the data provided is mostly anecdotal. Contemporary data shows that TTO has broad spectrum activity, including antibacterial, antifungal, antiviral, and antiprotozoal activities. However, the antimicrobial activity of TTO has been impeded by its physical properties, which limit its miscibility in test media. Strategies to counteract this problem include adding surfactants to broth and agar test media, and occasionally using dyes as visual indicators of the MIC.[119-125]

6. CONCLUSIONS

Turmeric, a spice known for its therapeutic properties, is the primary source of curcumin, a polyphenol found in curcumin. Curcumin is effective in treating oxidative and inflammatory disorders, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. It can also manage exercise-induced inflammation and muscular pain, improving recovery and performance in active individuals. However, curcumin alone does not yield the expected health benefits due to its low bioavailability. Piperine, the main active constituent of black pepper, has shown the potential to enhance bioavailability by 2000% when complexed with curcumin. When paired with boosting substances, curcumin offers several health advantages. Metabolic disorders pose a significant threat to global human health, and curcumin, a natural polyphenolic chemical derived from the rhizomes of the plant Curcuma, has been used in clinical studies for the treatment of these disorders. Clinical data indicates that curcumin has significant therapeutic potential and few negative effects. It can decrease blood glucose and cholesterol levels, enhance insulin sensitivity, and mitigate inflammation and oxidative stress. However, further high-quality clinical trials are needed to validate its effectiveness and elucidate its biological processes and targets. Tea tree oil has traditionally been used for treating wounds, insect bites, boils, itching, and minor oral mucosal inflammation. However, most studies on its biological properties are in vitro, and there is often no correlation between chemical composition and observed properties. Some studies attribute TTO activities to synergism among essential oil constituents or mixtures of diverse origins. Despite studies focusing on anti-inflammatory and antioxidant activities, few reported effects on acne vulgaris. Clinical studies show heterogenic results due to the use of diverse formulations and objectives. This diversity and lack of consistent clinical studies make it difficult to establish a relationship between TTO and anti-acne effects through anti-inflammatory and antioxidant attributes. More robust studies with common procedures, formulations, and objectives, conducted in accredited laboratories worldwide, and using groups of individuals with well-defined acne, are needed to provide practical results. The biological activity and chemical composition of TTEO was evaluated. The TTEO was a terpinen-4-ol chemotype that also contained γ-terpinene, 1,8-cineole, and p-cymene. This TTEO can be used as a potential antioxidant. The best antimicrobial activity was observed against E. faecalis, and the minimum inhibitory concentration C. albicans showed better susceptibility to G+ and G− bacteria than yeast and biofilm-forming bacteria. The TTEO was also effective against P. fluorescens biofilm formation, while S. enterica biofilm needs to be tested with higher concentrations of TTEO. The TTEO from the Slovak Republic generally has good biological activity, which gives the potential for use in the food industry and medicine to prevent oxidation, inhibit the growth of bacteria, and inhibit the formation of biofilm.

7. Conflict of Interest

None.

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