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An Updated Review of Curcumin in Health Applications: In-vivo Studies and Clinical Trials

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Turmeric (Curcuma longa) are known to contain curcumin, a lipophilic polyphenol from the curcuminoid group. Curcumin has been used for generations in traditional medicine, due to antioxidant, anti-inflammatory, hepatoprotective, cardio-protective, antimicrobial, nephroprotective, immunomodulatory, hypoglycemic, anti-rheumatic, anti-cancer, and anti-fibrotic properties. Therefore, this study aimed to determine pharmacological activity potential of curcumin using selected test parameters. Several journals were collected from PubMed, Scopus, and Science Direct for this review, limiting the time frame to the last 8 years. The findings are then presented in the form of figures and tables, followed by a full discussion based on the appropriate reference. The results showed that curcumin had antioxidant and anti-inflammatory effects. These effects contributed to various mechanisms of action in numerous diseases, including cardiovascular, anti-cancer, arthritis, brain injury, Alzheimer's, digestive disorders, anti-aging, and hepatoprotection. Several external factors that influenced test results included curcumin dosage, duration of administration, and pain- or disease-inducing ingredients. In long-term therapy with certain drugs, the administration of curcumin could be considered at the right dose to avoid dangerous side effects.

Keywords: Antioxidant; Anti-Inflammatory; Curcumin; Pharmacological Activity; Rhizomes.

Several medicinal plants, including rhizomes of turmeric (*Curcuma longa*), ginger (*Curcuma xanthorrhiza*), and red ginger (*Zingiber officinale* Var. Rubrum), are known to contain curcumin, also referred to as diferuloylmethane (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). This compound is a lipophilic polyphenol belonging to the

curcumionide group. Numerous in vitro and in vivo studies have demonstrated biological and pharmacological effects of curcumin, making it a viable alternative herbal medicine for diseases such as asthma and liver damage. The various functions can be attributed to antioxidant, anti-inflammatory, hepatoprotective, cardio-protective, antimicrobial, nephroprotective, immunomodulatory, hypoglycemic, anti-rheumatic, anti-cancer, and anti-fibrotic properties [1,2].

Studies on pharmacological effects of curcumin have produced both positive and negative results. Several tests related to curcumin activity have produced different effects [3]. The test group given low-dose curcumin showed positive results in all hepatoprotective test parameters. The amounts of SOD (superoxide dismutase) and MDA (malondialdehyde), which helped lower oxidative stress, did not change in the test group given high doses of curcumin. Some researchers report a study on a population of type 2 diabetes patients, and the results found no change in the hs-CRP (high-sensitivity C-reactive protein) test parameters [4]. Therefore, this study aimed to explore the therapeutic or placebo effects of curcumin on various diseases. This review was conducted on the latest literature on clinical trials and animal studies to provide updated information. Additionally, it talks about the outcomes of tests that don't support the hypothesis or samples that don't have significant effects.

MATERIALS AND METHODS

In this review, several journals were collected from PubMed, Scopus, and Science Direct with a maximum limit of the last 8 years. The keywords used include curcuminoid, hepatoprotective, liver, and curcumin health benefits. Furthermore, only English-language journals or publications offering open access were used. The inclusion criteria include (a) clinical studies that examined the role of curcuminoid in health benefits; (b) pharmacological activity of active curcuminoid compounds in living organisms; and (c) the possible pharmacological effects of active curcuminoid on hepatoprotective factors and health benefits. The findings are then presented in the form of figures and tables, followed by a full discussion based on the appropriate reference.

RESULTS AND DISCUSSION

Active Curcuminoid Compounds

Curcumin is a natural yellow hydrophobic polyphenolic pigment that is insoluble in water. This active compound is found in several medicinal

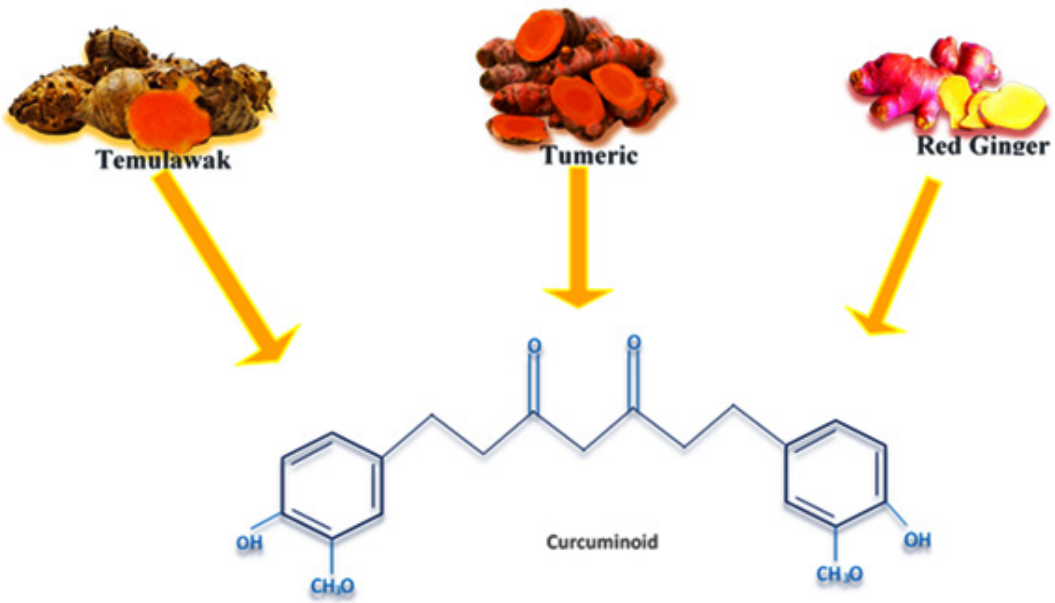

Fig. 1. Medicinal plants containing active curcuminoid compounds

plants used in traditional medicines [Figure 1]. Studies have showed pharmacological effects of curcumin, manifesting as antioxidants and anti-inflammatory agents, through mechanisms including alterations in gene expression and cellular signaling [5]. Turmeric, or kencur [Figure 1], is a plant native to India and widely cultivated in areas with temperatures between 20æ%C-35æ%C and high rainfall, such as Indonesia [6,7].

Rhizomatous roots are specifically collected at the end of the vegetative phase when the plant can produce therapeutic effects. For decades, several chemical compounds found in ginger have been studied, including oxygenated sesquiterpenes, monoterpenes, and curcuminoid derivative compounds such as curcumin, bisdemethoxycurcumin, and demethoxycurcumin [6,8].

Pharmacological Activity of Curcuminoid Compounds for Health

Studies on the active compound curcumin have increased in the last few decades due to the therapeutic potential, which spans almost all parts of the human body. Other functions include antioxidant, anti-inflammatory, human immune regulatory system, antidiates, nervous system protector, cardiovascular system protector, anticancer [9–11], arthritis, brain injury, Alzheimer's, anti-aging, and hepatoprotective effects [12,13,14,15,16]. Pharmacological activities reported in the reviewed studies are shown in [Figure 2].

Recent clinical and in vivo tests have been carried out to show the emergence of pharmacological effects of curcumin. Specifically, studies have tested curcumin under predetermined protocols with a wide variety of doses, populations, and groups of animals. Empirical studies assert that plants contain curcumin, a compound with the potential to cure all diseases. This result became the basis for studies developing the effects of curcumin in almost every part of the human body, with varying degrees of success. Furthermore, numerous in vivo investigations and clinical trials have been conducted. Tables 1 and 2 show the numerous in vivo studies and clinical trials in sick populations.

Antioxidant Effect

Antioxidant activity of curcumin is one of the several protective mechanisms. Oxidative stress is a supporting factor for damage to important organs in the body [42]. All cells, both animal and human, require oxygen for normal function to form ATP, which the body then converts into energy through metabolic processes. However, reactive oxygen species, which play a role in liver damage, can transfer oxygen into toxic compounds. During the aerobic respiration process, the production of free radicals potentially causes aging and cell death [43].

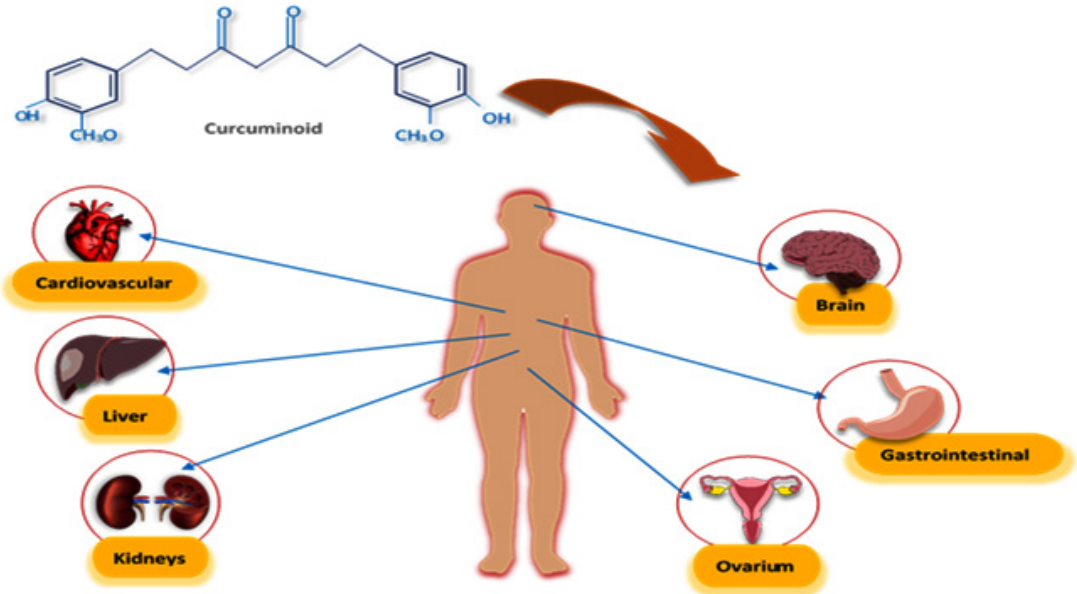

Fig. 2. The role of curcuminoid in health for all parts of the human body

Table 1. *In vivo* studies on active curcuminoid compounds

Active Compounds	Test Animal Group	Dose	Measured parameters	Reference
Curcumin	32 adult male Wistar rats (200-250 gr)	100 mg/kg/day for 28 days orally.	↓ALP, ↓ASP, ↓ALT	17
Curcumin and the Curcumin Phytosome	50 male mice (25-30 g)	100-200 mg/kg body weight orally.	Groups III and IV ↑MDA, ↓SOD, ↓CAT and ↓GPx. Group V ↓MDA, ↑SOD, ↑CAT and ↑GPx	18
Curcumin + dimethylnitrosamine	32 Adult male Wistar rats (260~280 g).	100 mg/kg body weight orally.	Group III ↓AST, ↓ALT, and ↓ALB Group IV ↓AST, ↓ALT, and ↓ALB	19
Curcumin	66 Adult male Wistar rats (180-200 g).	100-200 mg/kg body weight orally.	Group III ↓ALT, ↓AST, ↓AFP, ↓albumin concentration, ↓MDA and ↑SOD Group IV ↓ALT, ↓AST, ↓AFP, ↑albumin concentration, ↔ MDA and ↔SOD, ↑hepatic lobule physique	20
Curcumin + BPA	42 Adult male Wistar rats (250–300 g)	100-130 mg/kg body weight orally.	Group III ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST Group IV ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST Group V ↑MDA, ↓SOD, ↓CAT, ↓GPx and ↓GST	21

			Group VI ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST Group VII ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST	
Curcumin + Paraquat (PQ)	36 Adult male Wistar rats (220–250 g)	100 mg/kg body weight orally.	Group V ↓ALT, ↓AST, ↓ALP and ↓MDA Group VI ↓ALT, ↓AST, ↓ALP and ↓MDA	22
Curcumin	24 adult male Wistar rats	Curcumin 50 mg/kg body weight for 12 weeks orally.	Group IV (first phase) and Group III (second phase) ↓fibrosis, ↓liver biomarkers, ↑CAT, ↑SOD, ↑GSH, ↑electrolyte homeostasis	23
Curcumin	25 adult male Wistar rats (250-280 grams)	10-50 mg/kg body weight, intraperitoneally for 5 weeks.	↓NLRP3, IL-1β, IL-6, IL-18, TNF-α ↑BDNF/TrkB, PI3K/Akt signaling pathways	24
Curcumin	30 adult male Wistar rats (180-200 grams)	300 mg/kg body weight orally for 4 weeks.	↓Serum creatinine, ↓urine albumen, and ↓urea nitrogen enhanced E-cadherin, ↓LC3 proteins expression, ↓p62, ↓hosphorylated levels of Akt, ↓mTOR, and ↓P13K levels	25
Curcumin	30 adult male Wistar rats (200-220 grams)	15-60 mg/kg body weight, through oral gavage.	↓Inflammation via up-regulating miR-200a-mediated TXNIP and ↓NLRP3 inflammasome pathway	26
Curcumin	48 adult male Wistar rats (230-250 grams)	200 mg/kg body weight orally.	↓Inflammation by downregulation of ↓TNFa, ↓IL1b, and ↓IL 6 Blocked TLR4 /MyD88/NFkB signal pathways	27

↓ *significantly decreased,* ↑ *significantly increased,* ↔ *showed no effect (still)*

Table 2. *Clinical Trial* of active curcuminoid compounds

Active Compounds	Test Group	Dose	Tested Parameters	Reference
Curcumin	19 people with inflammatory disease (osteoarthritis)	1.5 kg curcumin every day for 6 weeks and placebo group	↑SOD,↑GSH, ↓MDA	28
Nanocurcumin	84 obese people with non-alcoholic fatty disease	40 mg nano-curcumin twice daily for 3 months and placebo group	↓TNF-α, ↓IL-6, ↓hs-CRP	29
Curcumin	100 people with type 2 diabetes	Curcumin 500 mg daily, piperine 5 mg daily, and placebo group for 3 months	↔hs-CRP	30
Curcumin	72 PCOS women (18-49 years)	Curcumin 1500 mg a day (500 mg a third a day) and maintain a normal lifestyle and the placebo group with the same dose	↓FPG, ↔LH, FSH, FI, HOMA-IR, QUICKI, BMI, WC	31
Curcumin	16 people with type 2 diabetes	180 mg curcumin daily for 12 weeks and placebo group	↓IR (Insulin resistance), ↓TG (Triglycerides)	32
Curcumin	44 people with type 2 diabetes	1.5 kg curcumin every day for 10 weeks and placebo group	↓TG (Triglycerides), ↓hs-CRP, ↓Adiponectin	33
Curcumin	118 people with type 2 diabetes	1 kg curcumin every day for 8 weeks and placebo group	↑SOD, ↓MDA	30
Curcumin	12 people with inflammatory disease (rheumatoid arthritis)	250 and 500 mg/kg curcumin twice daily for 3 months and placebo group	↑CRP, ↑ESR, ↑VAS, ↑DAS28, ↑RF responses	34
Curcumin	43 people with non-alcoholic fatty liver disease	1 kg of curcumin every day for 8 weeks	↓TC, ↓TG, ↓LDL-C, ↑HDL-C	35
Curcumin	19 people with inflammatory diseases	1.5 kg curcumin every day for 6 weeks and placebo group	↓TNF-α, ↓TGF-β	36
Curcumin	20 men with prostate cancer	3 kg curcumin every day for 3 months and placebo group	↑SOD, ↓TAC	37
Curcumin	33 people with coronary artery disease	500 mg curcumin daily for 8 weeks and placebo group	↓TG, ↓LDL-C, ↓VLDL-C	38
Curcumin	123 people with Neurodegenerative diseases	500 and 1000 mg curcumin daily for 8 weeks and placebo groups	↓Depressive and ↓Anxiolytic symptoms	39
Curcumin	31 people with traumatic b rain injury	Curcuminoid 500 mg/day + biopterin 5 mg/day every day for 4 weeks and placebo group	↓IL-6, ↓TNF-α, ↓MCP-1, ↓CRP, ↔GPx, ↔SOD, ↑APACHE II, ↑NUTRIC	40
Curcumin formulation	43 people with gastrointestinal symptoms (mostly women with an average age of 50 years)	2 people: 0 gr/day 13 people: 5 gr/day 28 people: 10 gr/day for 4 weeks	↓Frequency and severity of GI symptoms, ↑Physical functioning, ↑Intestinal permeability, ↑Proton pump	41

↓ *significantly decreased,* ↑ *significantly increased,* ↔ *showed no effect (still)*

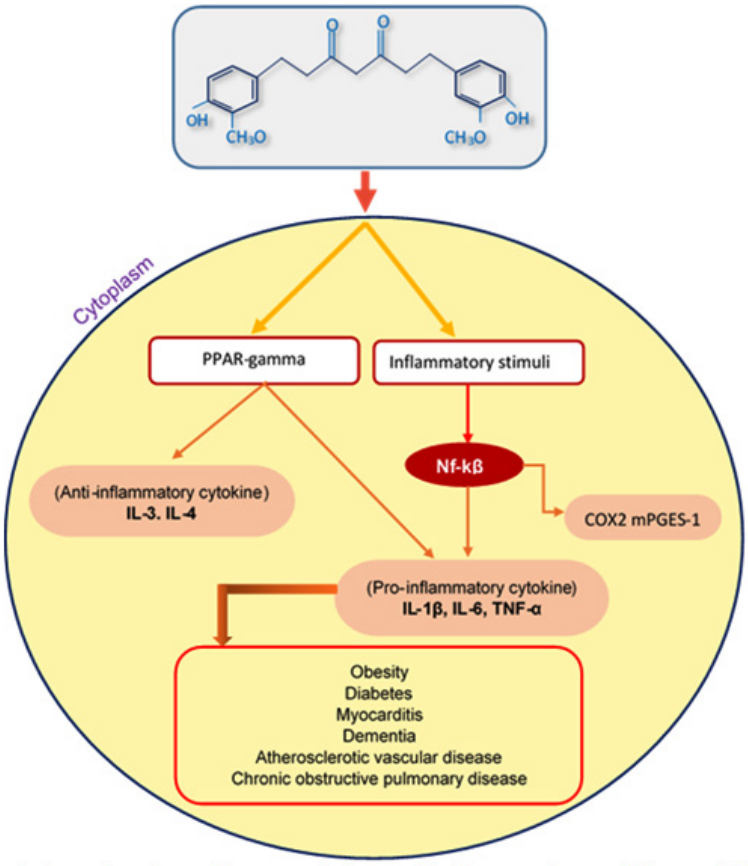

Fig. 3. Potential mechanism of curcumin in anti-inflammation activity and lifestyle-related conditions (*COX2 = cyclooxygenase-2; mPGES-1 = microsomal prostaglandin E synthase-1*) [55].

Mitochondria reduce oxygen molecules to produce superoxide or peroxide ions (H2O2), a free radical [44]. Superoxide and peroxide then react with metal ions and produce hydroxyl radicals. Subsequently, hydroxyl radicals react with cell components, including DNA and proteins, which can induce damage to the liver [45]. The therapeutic potential of polyphenols in curcumin is often associated with antioxidant properties, which are able to capture free radicals such as superoxide or peroxide ions (H2O2). According to a study, curcumin contains 10 times more antioxidants than vitamin E [43].

The active curcumin compound, with antioxidant effect, effectively binds free radicals and provides hydrogen atoms. Based on chemical structure, the phenolic hydroxyl group (an electron-donating group) is the main part that makes curcumin an antioxidant [11,46]. In hyperlipidemia disorders, the administration of curcumin can reduce the incidence of cardiovascular complications [47,48].

Anti-inflammatory Agent

During tissue damage from oxidative stress or other factors, inflammation is a response that starts a chain of events leading to repair processes, such as extracellular matrix reform and fibrosis [49]. Chronic inflammation is defined as macrophage inflammation through tissue invasion and can last for several months to years [50]. However, curcumin can turn on PPAR-gamma (Peroxisome Proliferator-Activated Receptor-gamma) and stop the production of pro-inflammatory cytokines such as TNF-alpha and interleukin-1â by blocking signaling pathways including Nf-kâ (Factor Nuclear kappa-â) [Figure 3] [51]. The invasion process of curcumin triggers the expression of inflammatory cytokines or growth factors, closely associated with the pathophysiology of various

diseases and lifestyles such as cardiovascular disease, obesity, diabetes, myocarditis, dementia, atherosclerotic, chronic obstructive pulmonary disease, and other conditions [49,52,53]. In type 2 diabetes patients, curcumin potentially raises lipid metabolism with a decrease in leptin and an increase in adiponectin levels in the blood [30,54,55]. The findings of this research provide more thorough data on the relationship between curcumin dosages and many blood biochemical markers, inflammation, and antioxidants. Research on humans and experimental animals yields almost identical results, however other investigations showed no significant impacts. In previous studies, there was not much discussion of the parameters that were affected by the use of curcumin.

CONCLUSION

In conclusion, various studies, both in vivo and clinical, on the test populations in this review showed that curcumin had pharmacological activity in various diseases. The polyphenolic compound had therapeutic potential attributed to the antioxidant properties that could capture free radicals. In hypercholesterolemia conditions, antioxidant activity reduced enzymes, which had a major effect on oxidative stress in the liver. Additionally, studies demonstrated anti-inflammatory activity of curcumin, which contributed to the mechanism of action in various diseases. The future prospectives of curcumin in health applications can be developed in various pharmaceutical preparations, such as nanoparticles, which have the potential to provide higher effects. Comprehensive clinical trials and the potential for drug interactions with other substances molecularly need further research.

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Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Author Contributions

Heru Sasongko : Conceptualization, Methodology, Supervision; Aulia Hanundita Maharani : Data Collection, Writing – Original Draft; Joshua Arianto Hutasoit : Data Collection, Analysis; Darmawan Lahru Riatma : Editing; Hardian Ningsih : Project Administration; Sritrusta Sukaridhoto : Supervision; Mohammad Robihul Mufid : Editing; MH. Ramdhani Ismar : Project Administration; Ardian Prima Atmaja : Editing; Alfi Tranggono Agus Salim: Visualization; Ronny Martien : Supervision

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