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Curcumin in combination: Review of synergistic effects and mechanisms in the treatment of inflammation

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ABSTRACT

Inflammation has an important role in the pathology of various diseases, so it has become a therapeutic target for the development of new pharmacological treatments. Treatment of inflammation using non-steroidal anti-inflammatory drugs and steroids class of drugs is known to incur some side effects. Therefore, prevention of inflammation is key to preventing the severity level of the disease. One approach to bridge this problem is by synergistically combining two or more drugs to prevent inflammation. The anti-inflammatory effect of curcumin, a bioactive component especially in the Zingiberaceae family, which delivers a variety of health benefits, has been extensively researched in the last few decades. Curcumin combination has been reported to increase the anti-inflammatory activities. A literature review on researches regarding curcumin combination through some electronic databases, including PubMed and Google Scholar on the combined information, has been carried out. In this review, we summarize the pharmacological activity of curcumin in combination with other components, in particular on synergistic anti-inflammatory effects. To understand how combinations provide a synergistic effect, we present increased bioavailability, which increases the capacity of antioxidants to inhibit inflammatory mediators, receptors, and major signaling pathways. This review provides information and encourages more research in combining medicinal compounds to reduce inflammation.

INTRODUCTION

Inflammatory disease is known to have more than 200 types. The names of diseases ending with "itis" indicate the occurrence of inflammation. Acute inflammation is considered to be a defense mechanism because it helps with healing, but inflammation of chronic diseases such as cholangitis can lead to colon cancer. Inflammation if not treated will aggravate various chronic diseases, such as autoimmune, endocrine, neurodegenerative, and cardiovascular diseases, because it is involved in the development of these diseases (Chen *et al*., 2018). The molecular mechanisms that cause inflammation have been investigated, and various enzymes, cytokines, chemokines, and polypeptide hormones that can mediate inflammation have been identified. These include tumor necrosis factor (TNF), IL-1α, interleukin-1β (IL-1β), IL-6, interleukin-8 (IL-8), IL-18, chemokine, Matrix metallopeptidase 9 (MMP-9), vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX). Monocytes, neutrophils, eosinophils, and mast cells, if the numbers are not controlled, will recruit more immune cells to create more proinflammatory molecules. The consequence will be various types of chronic diseases because the process produces nitric oxide (NO) and reactive oxygen species (ROS), which are responsible for damage to the structure, function, integrity of lipids, proteins, and nucleic acids (Ben-Baruch, 2006).

The expression of this gene is highly regulated by the transcription factor of nucleus-κβ (NF-κβ) (Aggarwal *et al*., 2013). The NF-κβ pathway is responsible for chronic inflammation as it triggers the release of various types of cytokines, chemokines,

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adhesion molecules, and leukocyte recruitment, thereby weakening the NF-κβ pathway as a strategy for treating chronic inflammation (Lawrence, 2009). Anti-inflammatory drugs temporarily suppress the symptoms of inflammation, but the disease continues to develop over time and drugs, such as non-steroidal anti-inflammatory drugs, can increase the risk of adverse gastrointestinal, renal, and cardiovascular effects (Bacchi *et al*., 2012; Tai *et al*., 2018). Anti-inflammatory corticosteroid drugs have a strong therapeutic effect for various disorders, but long-term use also incurs side effects (Buchman, 2001; Oray *et al*., 2016).

Curcumin is a secondary metabolite found in many rhizomes of the Curcuma longa and Zingiberaceae family as a medicinal herb for antioxidant and anti-inflammatory properties (Lestari *et al*., 2014; Surh *et al*., 1998). There has been a widely spread use of curcumin as traditional medicine until now. Curcumin, 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione, and the yellow pigment in turmeric rhizome are used as medicine and there have been various studies developed to understand their use, especially in the Asian region (Noorafshan *et al*., 2013; Thakur *et al*., 1989). Curcumin has pharmacological effects on reducing inflammation because it interacts with many inflammatory pathways and mechanisms. Research reveals that curcumin has various health benefits, including activity to reduce inflammation, antioxidants, chemopreventive, and chemotherapy (Pulido-Moran *et al*., 2016). The pharmacological activity has been demonstrated in cultured cells, animal models, and human clinical trials (Hatcher *et al*., 2008). Compound combination studies provide opportunities for therapeutic problems of overcoming drug resistance and toxicity (Bulusu *et al*., 2016). A combination of drugs is used to treat severe and chronic diseases. This combination provides many advantages in treatment including achieving a synergistic therapeutic effect, reducing the dosage used so that toxicity will be reduced, and minimizing or delaying the induction of drug resistance (Chou, 2010).

This review aims to investigate the combination of curcumin with two or more other drugs and how this combination can synergistically provide an anti-inflammatory effect rather than a single use. In this review, we summarize the anti-inflammatory effects that arise from the combination of various components with curcumin, especially the results of the synergistic anti-inflammatory effect. The benefits of this review provide scientific information regarding the combined effects when curcumin is combined with other components to suppress inflammation. The results of this review are expected to provide information on strategies for handling inflammation, with a synergistic effect between components, so as to provide effective treatment with minimal side effects.

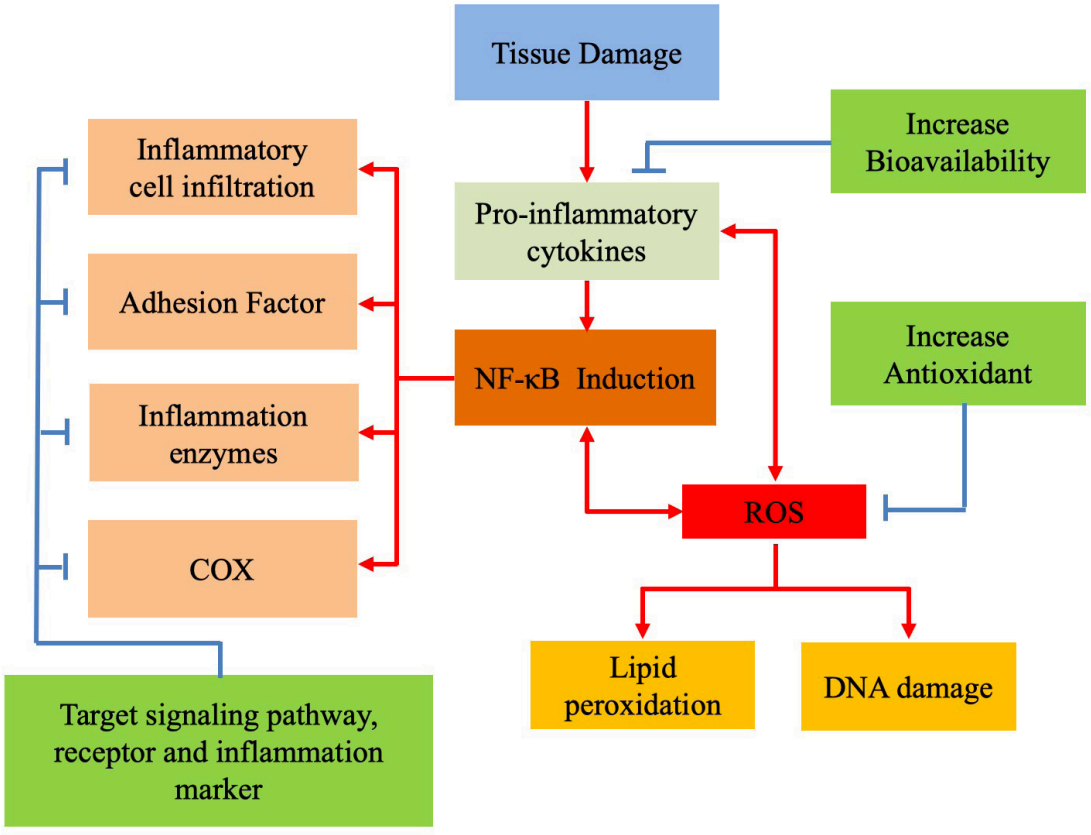

Figure 1. The mechanism of the combined synergistic anti-inflammatory effect of curcumin through various mechanisms increases bioavailability by regulating metabolism. The combination can directly increase antioxidants to fight ROS. Reduced ROS can attenuate the NF-κβ pathway and then regulate the transcription and translation of the proinflammatory marker. This altered molecule will suppress the proliferation and migration of immune cells and maintain the integrity of endothelial cells to further reduce the production of proinflammatory markers that ultimately inhibit inflammation (Zhang *et al*.,2019).

METHOD

A systematic search was conducted to find all publications related to the topic up to August 2020 on PubMed and Google Scholar databases. "Curcumin, combination, and anti-inflammatory" were used as the keywords used to find the related articles. The inclusion criteria in this review were articles using a combination of curcumin components (drugs or phytochemicals) that can provide anti-inflammatory effects, comparing the effects of curcumin alone with a combination, and articles that produce anti-inflammatory effects that are synergistic or better than using curcumin alone. Some published articles in English were selected based on the criteria that these articles provide comparative data between the single use of curcumin and its combination. Articles were excluded from primary articles if they were conference articles, review articles, and thesis. All synthetic derivatives of curcumin are not mentioned in this review. Articles searched until August 2020 found 55 main articles and 36 types of components combined with curcumin (Table 1). These selected articles were written based on *in vitro* and *in vivo* experiments on curcumin and its combination. After selecting these articles, we conducted a review by mainly assessing the types of test animals, cells, the induction compound used, and the effects of these combinations.

Determination of the effects of a combination

The combination of more than one type of drug component is often used in medicine. A particular strategy does not always enhance its specific pharmacological effect; combinations involving two or more components can provide additive, synergistic, or antagonistic effects. The Chou-Talalay method has been used in combination with drug studies worldwide and evaluations of its effects. The combination index (CI), where CI = 1, indicates additive effect, CI < 1 synergism, and CI > 1 antagonism (Chou, 2006). Based on our exploration, this method is widely used for drug combination studies. Combination of index calculation was carried out using the following formula:

$$CI = \frac{(D)1}{(Dm)1} + \frac{(D)2}{(Dm)2}$$

$(D)1$ and $(D)2$ are the concentrations of components X and Y which are combined to produce a value of IC_{50}. $(Dm)1$ and $(Dm)2$ are the concentrations of components X and Y given singly and obtained the value of IC_{50}. Determination of the combined effect in test animals followed the same principle as that in CI. However, combination studies reveal that drugs have some limitations, such as being more expensive, more time-consuming, having limited group, and population limitations. In this review, we got to measure the combined effect of *in vitro* using a comparison between the combined effect of the drug with those uncombined. The effect was obtained by a simple formula of X + Y > X or X + Y > Y. In clinical trial research, if treatment using a drug combination gives a better pharmacological effect than monotherapy, it can be concluded that it has a synergistic effect (Chou, 2010). In this review, it is known that the CI method has been used in several *in vitro* studies. Studies using test animals obtained the synergy effect based on a comparison between combination and single use, and only the curcumin combination with a synergistic anti-inflammatory effect was discussed.

Effect of curcumin on anti-inflammation

Curcumin has been known to have various pharmacological activities, in particular as anti-inflammatory properties. Curcumin is known for its ability to suppress acute and chronic inflammation (Noorafshan *et al*., 2013). Curcumin can work through various mechanisms either singly or in combination. The mechanism of curcumin as an anti-inflammatory includes the inhibition of arachidonic acid metabolic processes, COX and LOX pathways, and decreases prostaglandin synthesis. Curcumin specifically inhibits COX-2 expression (Goel *et al*., 2001; Kunnumakkara *et al*., 2009; Zhang *et al*., 1999). Curcumin has more active activity against the COX-2 enzyme when compared to the COX-1 enzyme (Ramsewak *et al*., 2000). Curcumin can prevent anti-inflammatory responses in synovial fibroblasts by inhibiting prostaglandin E2 synthesis (PGE2) and suppressing COX-2 (Moon *et al*., 2010). The anti-inflammatory effect of curcumin is also seen in 5-LOX inhibition on rat peritoneal neutrophils and cyclooxygenase activity on human platelets (Ammon *et al*., 1993). The activity of curcumin as suppressing inflammation has been shown in in vitro and in vivo studies because it can reduce the production of proinflammatory cytokine IL-8, inflammatory protein monocyte-1, chemotactic protein monocyte-1 (MCP-1), IL-1β, and tumor necrosis factor-α (TNF-α) (Anthwal *et al*., 2014; Gupta *et al*., 2014; Hong *et al*., 2004).

The effects of high glucose and secretion of IL-6, IL-8, MCP-1, and TNF-α are inhibited by curcumin in cultured monocytes (Jain *et al*., 2009). Another study using curcumin has shown its activity as a powerful asthma reliever. This effect is due to the mechanism of inhibiting the production of IL-2, IL-4, and IL-5 and reducing immunoglobulin E2 (Chung *et al*., 2012; Kobayashi *et al*., 1997). Curcumin also has anti-inflammatory activity in pancreatitis rats by regulating the expression of NF-κβ, activator protein 1, inducible nitric oxide synthase (iNOS), TNF-α, and IL-6 (Gulcubuk *et al*., 2013). The ability of curcumin to inhibit the mitogen-activated protein kinase (MAPK) and NF-κβ pathways was shown in the in vitro test; curcumin also inhibits IL-6 and TNF-α in BV2 microglia cells stimulated with lipopolysaccharide (Cho *et al*., 2007; Jin *et al*., 2007).

Curcumin activity can reduce inflammation by reducing the formation of ROS and increasing enzymatic activity, such as methionine sulfoxide reductase A expression. It also increases enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Dai *et al*., 2015; Meshkibaf *et al*., 2019). The use of curcumin in thallium acetate-induced rats at a dose of 200 mg/kg can contribute to increasing SOD activity, CAT, and total liver antioxidant capacity (Abdel-Daim *et al*., 2015). Curcumin has antioxidant activity so it can act as an NO scavenger and as an oxidative DNA cleaving agent (Ahsan *et al*., 1999; Nilani *et al*., 2009). The expression of the iNOS gene in BALB/c mice isolated from peritoneal macrophages and livers of mice injected with lipopolysaccharide (LPS) is also inhibited after receiving curcumin (Chan *et al*., 1998). Curcumin can inhibit NO production, iNOS, and messenger ribonucleic acid (mRNA) protein expression in RAW 264.7 cells stimulated with lipopolysaccharide or interferon-γ (Fu *et al*., 2016). Curcumin has been shown to have activity in inhibiting lipid peroxidation, a process that is found in rat liver microsomes (Reddy *et al*., 1992). Similarly, in rat brain homogenates, curcuminoids show antioxidant activity (Sreejayan *et al*., 1994).

Table 1. Synergistic effect of combining curcumin as anti-inflammatory.

No.	Component	Pharmacology model	Induction/treatment	Result	Reference
1	Piperine	Male Swiss albino mice	LPS	Suppresses proinflammatory cytokines (IL-1β and TNF-α)	(Jangra *et al*., 2016)
		Male Wistar mouse	Olfactory bulbectomy model	Lower brain TNF-α and caspase 3 levels	(Rinwa *et al*., 2013)
		Male C57BL/6J mice	High fat	Downregulates proinflammatory cytokines (IL-6 and TNFα)	(Neyrinck *et al*., 2013)
		Epithelial cells HT-29	TNF-α	Inhibits TNF-α and COX-2	(Kaur *et al*., 2018)
		Albino Wistar Rat	-	Increases bioavailability	(Shoba *et al*., 1998)
		Male C57BL/6 mice	High fat	Suppresses proinflammatory cytokines IL-1β	(Miyazawa *et al*., 2018)
		Male Wistar rats	Haloperidol	Inhibits NO, TNF-α, and NF-κβ	(Bishnoi *et al*., 2011)
		RAW 264.7	RANKL	Inhibit osteoclastogenesis	(Martins *et al*., 2015)
2	Resveratrol	Male Wistar rats	Fipronil	Increases glutathione (GSH), GPx, SOD, and CAT; malondialdehid (MDA) and NO decrease	(Al Basher *et al*., 2020)
		Chondrocyte	IL-1β	Inhibits expression IL-1β, COX-2, MMP-3, MMP-9, and VEGF	(Csaki *et al*., 2009)
		Colon cancer HCT-116	-	Reduces proliferation and stimulation of apoptosis accompanied by attenuation of NF-κβ activity	(Majumdar *et al*., 2009)
		HO radical	-	Resveratrol is able to protect curcumin from degradation	(Coradini *et al*., 2014)
		Male rat Wistar	complete Freund's adjuvant (CFA)	Reduces paw thickness and arthritis score	(Coradini *et al*., 2015)
		Male Laka mice	Benzo[a]pyrene	Brings down the enzyme activity of COX-2, significantly improved protein expressions of p21	(Malhotra *et al*., 2011)
		Weaned piglets	-	Inhibits IL-1β and TNF-α	(Gan *et al*., 2019)
		Male Wistar rats	Cotton ligature	Inhibits IL-1β and IL-4	(Corrêa *et al*., 2017)
		Male adult Wistar	Aluminum chloride	Inhibits COX-2 and increase SOD, GSH, CAT, and glutathione S-transferase	(Zaky *et al*., 2017)
3	Quercetin	Male albino rats	Carrageenan	Increases GSH levels and HO-1 mRNA expression, reducing paw thickness, induced elevation in MDA, NO, and TNF-α	(Heeba *et al*., 2014)
		Albino rat	Diazinon	Increases antioxidant parameters (GSH and GPx SOD, and CAT)	(Abdel-Diam *et al*., 2019)
		K562 cells	-	Inhibits total NO, NF-κβ, and COX-2	(Güran *et al*., 2019)
4	Puerarin	Male Sprague Dawley rat	LPS	Reduces IL-1 and MMP-9; increases IL-10	(Singh *et al*., 2013)
5	Turmeron	Male rats	dimethylhydrazine	Reduces expression of iNOS and COX-2, decreasing NF-κβ transcription activity	(Murakami *et al*., 2013)
6	Fish oil	Mice	dextran sulfate sodium (DSS)	NF-κβ activity and inflammatory score in the colonic mucosa	(Jia *et al*., 2011)
7	Rhizoma Paridis saponins	Male Sprague Dawley rat	-	Reduces COX-2, IL-1β, NF-κβ, enhancement of HO-1, GSH, SOD, and Nrf2 activities	(Man *et al*., 2016)
8	Hydrolyzed collagen and green tea extract	Osteoarthritic human chondrocytes	IL-1β	Reduces NO, MMP-3, and IL-6	(Comblain *et al*., 2015)
9	Emu oil	Male Sprague Dawley rat	Carrageenan and CFA	Inhibits paw volume, reduces TNF-α, IL-6, and IL-1β	(Jeengar *et al*., 2014)
10	Vitamin E	Mice	High calorie	Increases activity (GPx) and Nrf-1 and reduces lobular inflammatory score and numeric analog scale score	(Heritage *et al*., 2017)
11	Vitamin B2, carnitine, and N-acetyl-cysteine	16HBE cell	Cigarette smoke extract	Decreases the inflammatory cytokine gene IL-1β, IL- 6, TNFα, and NOS	(Vanella *et al*., 2017)
12	Berberine	Male Sprague Dawley rats	High calorie	Decreases expression of Sterol regulatory element-binding transcription factor 1, protein extracellular signal-regulated kinase, TNF-α, and protein c-Jun N-terminal kinase	(Feng *et al*., 2018)
13	Vitamin D3	Adult female Wistar rats	High calorie	Reduces arthritis score and myeloperoxidase activity	(da Silva *et al*., 2019)
14	Ursodeoxycholic acid	Rat	NAFLD	Increases total antioxidant capacity, GSH, GPx, and SOD; decreases MDA levels and iNOS expression	(Gheibi *et al*., 2019)
15	Ursolic acid	Female ICR mice	tissue plasminogen activator (TPA)	Inhibits the expression of IL-1β, IL-6, IL-19, IL-22, cemokine ligand 2 (CXCL2), COX-2, and VEGFA	(Tremmel *et al*., 2019)

No.	Component	Pharmacology model	Induction/treatment	Result	Reference
16	Boswellic acids	Rat	CFA	Reduces paw volume, but does not significantly reduce TNF-α and IL-6	(Khayyal *et al*., 2018)
17	Salidroside	Rat	LPS	Reduce in the IL-6 and TNF-α	(Vasileva *et al*., 2018)
18	Silymarin	Male Wistar albino rat	Gamma radiation	Decreases the level of IL-18, TNF-α, C-reactive protein, Bax, factor-related apoptosis, and the activity of Casp-3	(Abdel-Magied *et al*., 2019)
19	Prednisolone	Rat	Adjuvant-induced arthritis	Reduces TNF-α, IL-1β, and IL-6 and increase IL-10	(Yan *et al*., 2019)
		RAW 264.7	LPS	Reduce TNF-α, IL-1β, and IL-6 and increases IL-10	
20	Thymoquinone	Sprague Dawley rats	Cisplatin	Reduces TNF-α, IL-6, and MCP-1	(Al Fayi *et al*., 2020)
21	Flavocoxid	Chondrocytes	LPS	Reduces IL-1β of NF-κβ and sgnal transducer and activator of transcription 3 mRNA expression	(D'Ascola *et al*., 2019)
22	Tolfenamic acid	Female BALB/c mice	TPA	Reduces levels of COX-2 and inhibition of IKK and NF-κβ	(Zhou *et al*., 2020)
23	Luteolin	Male C57BL/6 mice	TNF-α	Reduces TNF-α vascular inflammation	(Lijuan *et al*., 2019)
24	Polyunsaturated fatty acid	RAW 264.7 cells	LPS	Suppresses iNOS, COX-2, 5-lipoxygenase, and cytosolic phospholipase A2	(Saw *et al*., 2010)
25	Sulforaphane	RAW 264.7 cells	LPS	Reduces TNF-α, IL-1, NO, and PGE2	(Cheung *et al*., 2009)
26	Augmentin	Mice	K. Pneumoniae	Decreases TNF-α, NO, MPO, and MDA	(Bansal *et al*., 2010)
27	Saikosaponin A	Male Sprague Dawley rats	CCl_4	Decreases interferon-γ, TNF-α, IL-1β, and IL-6, by the inhibition of NF-κβ activation	(Wu *et al*., 2010)
28	Essential turmeric oils	Male mice	DSS cholangitis	Increases anti-inflammatory cytokines IL-10 and IL-11	(Toden *et al*., 2017)
29	Erythromycin	Rat	Osteomyelitis model	Reduces levels TNF-α and IL-6, suppress bone lesions, and decreases the histopathological score	(Zhou *et al*., 2017)
30	Metformin	Male Wistar rat	Gentamicin	Reduces MDA and NO and an increase in the levels of SOD, CAT, GSH, and GPx	(Cao *et al*., 2019)
31	Salsalate	Mice	High fat	Reduce IL-1β and IL-6	(Wu *et al*., 2017)
32	Capsaicin	Male Wistar rats	Carrageenan	Reduces paw inflammation and 5-lipoxygenase	(Manjunatha *et al*., 2006)
		Male Wistar rats	Acetic acid	Inhibition of vascular permeability and inhibition of leukocyte mobilization	(Kumar *et al*., 2017)
33	Selenium	Male albino Wistar	LPS	Reduces IL-6	(Al-dossari *et al*., 2020)
34	Irbesartan	Male albino rats	Streptozotocin	Reduces serum levels of IL-6 and TNF-α	(Khaled *et al*., 2010)
35	Acetylsalicylic acid	Wistar albino rats	Carrageenan	Decreases in paw edema and MDA and increases GSH and SOD	(Mohapatra *et al*., 2019)
36	Hyaluronic acid	Male Wistar rat	CFA	Reduce paw edema levels of the TNF-α, IL-1, and VEGF	(Fan *et al*., 2018)

The presence of oxidative stress causes chronic inflammation, which exerts a strong influence leading to modulation of the expression of the nucleus-κβ (NF-κβ) factor pathways and TNF-α pathways that amplify the infºlammatory response (Reuter *et al*., 2010; Sethi *et al*., 2008). Curcumin inhibits constitutive NF-κβ and IκB kinase (IKK). The suppression of proliferation, cell cycle arrest, and apoptosis induction caused by inhibition of several expression pathways of gene products are regulated by NF-κβ (Jobin *et al*., 1999; Shishodia *et al*., 2005).

Enhancing the bioavailability of curcumin

There have been many studies conducted to determine the bioavailability of oral curcumin using experimental rats' amount to around 1% (Yang *et al*., 2007). Combinations of drugs can produce potent or reductive pharmacokinetic effects that may increase or decrease the therapeutic activity of one drug by the other drug through the regulation of absorption, distribution, metabolism, and excretion (Chou, 2006). Curcumin exhibits poor water solubility, chemical instability, and a low pharmacokinetic profile. Thus, the potential therapeutic activity provided by curcumin is debated because of the relatively poor bioavailability in humans regardless of its efficacy and safety (Dei Cas *et al*., 2019).

In this review, we found that the administration of piperine synergistically inhibits inflammation as compared to its single use. As a strong bioavailability enhancer, piperine can boost the bioavailability of curcumin (Jangra *et al*., 2016). Curcumin taken together with piperine in rats can increase the bioavailability of curcumin, as well as in humans, while it also leads to half-time elimination and significantly decreases the maximum time and clearance (Shoba *et al*., 1998). Curcumin absorption multiplies because piperine reduces the activity of the glucuronidase enzyme (Panahi *et al*., 2015). The additional mechanism of piperine enhances the bioavailability of curcumin by amplifying intestinal perfusion and enterocyte permeability (Atal *et al*., 1985; Shoba *et al*., 1998). Male Wistar rats treated with curcumin of 50 mg/kg and

piperine of 2.5 mg/kg for 21 days orally reduced their inflammatory mediator parameters, such as NO, TNF-α, and NF-κβ. Piperine has the activity of inhibiting glucuronidation of the small intestine, which causes increased absorption of curcumin. Piperine can also slow down the transit of curcumin in the digestive tract which results in increasing the remaining time in the intestine and allows for a higher absorption process (Bishnoi *et al*., 2011).

Curcumin is metabolized by intestinal microbiota, such as Escherichia coli and Blautia sp. These microbials are found to be active by an NADPH-dependent reductase in a two-step reduction pathway from curcumin to the intermediate product, dihydrocurcumin, and the end product, tetrahydrocurcumin (Hassaninasab *et al*., 2011). Similarly, a combination of piperine enables microbial metabolism in the digestive tract to convert curcumin into tetrahydrocurcumin. As a result, this metabolite can reach the adipose tissue (Neyrinck *et al*., 2013). Curcumin is reported to be a newly effective treatment for wound healing (Mohanty *et al*., 2017), since the addition of curcumin with emu oil may boost the flux by 1.84 and 4.25 times through the mouse skin, which can reduce the expression of proinflammatory mediators IL-1 β, IL-6, and TNF-α (Jeengar *et al*., 2016). In this review, increasing the bioavailability of curcumin can be done in combination with oral or topical use.

Increasing antioxidant

The structure of curcumin has many functional groups, including carbon–carbon double bonds; curcumin also contains β-diketone groups and phenyl rings containing hydroxyl and methoxy substituents. The presence of phenolic OH in the curcumin structure plays a major role in curcumin's activity (Priyadarsini *et al*., 2003; Wright, 2002). The combination of components may provide a synergistic effect, which will increase its efficacy at low doses to inhibit or eliminate tissue damage due to the initiation of oxidative stress. The combination of antioxidants can play a protective role in the development of oxidative stress and inflammation, by regulating key genes due to oxidative stress and also inhibiting the formation of cytokines that are responsible for inflammatory pathways (Vanella *et al*., 2017). Oxidative stimulation, proinflammatory cytokines, viruses, and LPS may activate NF-κβ, which eventually directs proteasomal degradation and phosphorylation of IkBα. This process will result in translocation that continues on the binding of NF-κβ to the gene promoter region located in the nucleus so that it encodes the production of proinflammatory mediators, such as cytokines, COX-2, and iNOS (Wu *et al*., 2014).

Resveratrol and curcumin relieve and synergistically reverse tissue oxidative injury by increasing antioxidant defense through free radical scavenging. Resveratrol protects curcumin compounds by acting as an antioxidant that enables both substances to protect one another (Al Basher *et al*., 2020; Coradini *et al*., 2014). The ability of anti-inflammatory and antioxidant activity produced by curcumin at a dose of 50 mg/kg can be synergistically enhanced by combining it with quercetin of 50 mg/kg (Heeba *et al*., 2014). Administration of quercetin of 100 mg/kg and curcumin of 5 ml/kg should be carried out for 4 weeks. Diazinon-induced rats have a synergistic protective effect by reducing excessive MDA production, maintaining tissue antioxidant capacity, and improving liver enzymatic activity (Abdel-Diam *et al*., 2019). The enhanced anti-inflammatory effect of the combination of berberine of 50 mg/kg and curcumin of 50 mg/kg may decrease oxidative stress, liver inflammation, and lipid metabolism (Feng *et al*., 2018). Berberine combination treatment also has a synergistic effect on reducing inflammatory and oxidative stress responses in the cortex and hippocampus of rats (Lin *et al*., 2020).

The addition of vitamins E increases the antioxidant capacity. Vitamin E 1.5 mg/g and 1 mg/g curcumin increases β oxidation of fatty acids, increases CAT activity, and upregulates mitochondrial biogenesis. The combination decreases the percentage of hepatic steatosis and lobular inflammation (Heritage *et al*., 2017). The antioxidant effects decrease inflammation by vitamin B2 because it induces antioxidant genes like heme oxygenase 1 (HO-1), nuclear transcription factor erythroid 2 (Nrf2), and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (Vanella *et al*., 2017). The addition of curcumin to drugs, such as acetylsalicylic acid, Rhizoma Paridis saponins, and metformin, can prevent damage to the liver because curcumin is a strong antioxidant and increases SOD, GSH, HO-1, and CAT (Cao *et al*., 2019; Man *et al*., 2016; Mohapatra *et al*., 2019). The anti-inflammatory and antioxidant activity of curcumin can be synergistically enhanced by combining it with polyunsaturated fatty acid, docosahexaenoic acid, or eicosapentaenoic acid (Saw *et al*., 2010). Patients with chronic gastritis who are given curcumin are treated with triple therapy regimes, which indicate antioxidant effects, inhibit oxidative damage to DNA cells, and ultimately reduce chronic inflammation rate (Judaki *et al*., 2017).

Many compounds are reported to have antioxidant capacities to directly scavenge ROS, to temper the mitochondrial respiratory chain and metal chelating agents, and to increase endogenous antioxidant enzymes, such as SOD, CAT, and glutathione peroxidase (Wolfe *et al*., 2008; Yahfoufi *et al*., 2018). An increase in antioxidant activity is due to certain mechanisms, such as the self-protecting mechanism because the combined compound is capable of simultaneously detecting multiple antioxidant functions and scavenging of some physiological radical species, inhibition of the prooxidant apoenzyme, and iron ion reducing and chelating activities (Soccio *et al*., 2018). These components act in a variety of antioxidant mechanisms enabling them to protect one another from oxidative agents (Becker *et al*., 2007). Differences in the orientation of the components at the water or lipid interface facilitate synergistic antioxidant interactions (Liang *et al*., 2009).

Inhibiting inflammatory mediators, receptors, and major signaling pathways

Chemical constituents have interactions on inflammatory marker cells and signaling pathways for which these interactions are very specific. The critical point of the combined delivery method is to reach the threshold level of pathway activation, while the individual components cannot reach this level (Zhang, *et al.*, 2019). Resveratrol (Dull *et al*., 2019), quercetin (Li *et al*., 2016), puerarin (Wei *et al*., 2014), luteolin (Aziz *et al*., 2018), and thymoquinone (Shaterzadeh-Yazdi *et al.*, 2018) are reported to inhibit proinflammatory molecules, such as TNF-α, IL-1β, IL-6, and NO. Quercetin (Lee *et al*., 2008) and resveratrol (Yu *et al*., 2018) inhibit enzymes that trigger increased inflammation, such as COX-2 and iNOS, on RAW 264.7 cells which are

also able to reduce the amount of NO by regulating the NF-κβ pathway. Phytochemical compounds, such as resveratrol, and a class of flavonoids, such as luteolin and quercetin, are known to have the activity of stimulating the expression of the anti-inflammatory cytokine IL-10 (Comalada *et al*., 2006; Imler *et al*., 2009). Flavocoxid shows a significant anti-inflammatory activity inhibition of the MDA, TNFα, nitrite levels, COX-1, and COX-2 (Altavilla *et al*., 2009; Bitto *et al*., 2014). The combined effect of vitamin D and curcumin fights inflammation by reducing T-cell activation and proliferation, thereby preventing altered lymphocyte activity in rheumatic rats (da Silva *et al*., 2019). The combination of curcumin with these components has cell-specific interactions, signaling pathways, and inflammatory markers. Two or more components can focus on the same immune cell or different cells, regulating the production of inflammatory markers along the same or different pathways to cause a synergistic anti-inflammatory effect.

Chronic inflammation that leads to carcinogenesis involves the occurrence of molecular events, including upregulation of enzymes that promote inflammation, such as cytokines, and activation of immune cells. mammalian target of rapamycin complex 1 (mTORC1) dysregulation initiates the pathology of human diseases, one of which is cancer. The combination of curcumin and piperine is able to regulate mTORC1 activity that is stronger than the use of curcumin alone. In this combination, piperine acts via mTORC1 to suppress the TNF-α signaling pathway and COX-2 expression (Kaur *et al*., 2018). The ability of curcumin and piperine to suppress the NF-κβ signaling pathway can trigger inflammation; this inhibition blocks the production of TNF-α and reduces the expression of intercellular protein, adhesion molecule-1, and vascular cell adhesion molecule-1 (VCAM-1) (Karimian *et al*., 2017; Kumar *et al*., 2007).

The main inflammatory mediators, such as TNF-α, without proper control and chronic secretion of TNF-α cause intermediates for various chronic inflammatory diseases, autoimmune or more severe cancer (Aggarwal *et al*., 2006). The addition of luteolin synergistically inhibits TNF-α-induced monocyte adhesion and MCP-1 and VCAM-1 expression by suppressing translocation of NF-κβ into the nucleus (Zhang, *et al*., 2019). The combined synergistic effect of curcumin and resveratrol gives a CI value of CI < 1.0 on inhibition of colon cancer growth, which is associated with inhibition of proliferation and stimulation of apoptosis, accompanied by weakened NF-κβ activity (Majumdar *et al*., 2009). Curcumin and capsaicin have been shown to attenuate the activation of NF-κβ; the inhibitory effect of inflammation of both components occurs in the enzyme 5-lipoxygenase in animals injected with carrageenan (Manjunatha *et al*., 2006). Mixed curcuminoid extract, hydrolyzed collagen, and green tea extract can reduce inflammation and reduce the inflammatory synthesis and catabolic mediators by chondrocytes, by way of inhibiting the activation of NF-κβ (Comblain *et al*., 2015). Both resveratrol and curcumin have activity in suppressing the NF-κβ signal transduction pathway with the ability of resveratrol to retain phosphorylated IκBα and inhibit translocation of activated NF-κβ to the nucleus. The activity of lowering the translocation of activated NF-κβ to the nucleus is also exerted by curcumin (Csaki *et al*., 2009).

The inflammatory process involves cytokines which are the main signaling proteins in response to inflammation. Their immune system is divided into proinflammatory cytokines IL-1, IL-6, IL-15, IL-17, IL-23, and TNF-α and anti-inflammatory cytokines IL-4, IL-10, and IL-13, thereby altering growth factor β and interferon γ (Berczi *et al*., 2003). Interleukins are a major class of cytokines that play an important role in immune modulation. This modulation includes IL-1 which regulates the transformation of phagocytes that infiltrate during inflammation or cancer which triggers the production of free radicals, such as ROS and reactive nitrogen species, and the formation of inflammatory molecules, such as chemokines, integrins, and MMP (Apte *et al*., 2006). Curcumin of 1 gr/kg and piperine of 50 mg/kg can reduce the weight of mice induced by high fat and significantly reduce IL-1β (Miyazawa *et al*., 2018). In acute inflammation, the presence of IL-6 plays an important role, if uncontrolled production causes various types of inflammatory diseases (Balkwill *et al*., 2010). The combination of curcumin and ursolic acid has a significant effect on inhibiting the phosphorylation of IκBα and NF-κβ. Inhibition of the NF-κβ signaling pathway is due to decreased COX-2 protein levels and reduced expression of inflammatory marker genes, such as IL-1β, IL-6, and CXCL2 (Tremmel *et al*., 2019). Puerarin with curcumin suppresses the proinflammatory cytokines IL-1β and MMP-9 and increases anti-inflammatory cytokines, such as IL-10 in LPS-induced Sprague Dawley rats so that it is more effective and nontoxic (Singh *et al*., 2013). Administration of LPS causes a change in behavior and an increase in cytokine levels in mice, while administration of 5 mg/kg salidroside and 20 mg/kg of curcumin shows antidepressant-like effects comparable to fluoxetine and potential synergistic reduction of IL-6 and TNF-α and anti-stress effects (Vasileva *et al*., 2018).

The action of anti-inflammatory combination regulates multiple pathways, blocks the MAPK pathway, and activates NF-κβ induced by cytokines and proinflammatory gene expression by inhibiting the activity of the inhibiting I-kB kinase. It also inhibits prostaglandin production by blocking arachidonic acid pathways and iNOS expression and blocking the proinflammatory cytokine synthesis pathway, which in turn suppresses the proliferation and reduces the production of proinflammatory markers and migration of immune cells and ultimately inhibits inflammation

CONCLUSION

The anti-inflammatory effect of the curcumin combination results from increased antioxidant, increased bioavailability of curcumin, regulation of multiple pathways, and inflammatory markers. The combination with some components can directly scavenge intensified ROS and increase antioxidants to reduce the effects of oxidative stress. The reduced ROS directly regulates further attenuation of the NF-κβ signaling pathway. Attenuated NF-κβ deregulates transcription and translation processes in proinflammatory markers, and increases anti-inflammatory molecules. The bioavailability of curcumin can be increased by combining it with piperine. This review provides clues to encourage more researches on combined compounds as a way to reduce inflammation. The current review has provided an overview of how the molecular mechanisms of inflammation occur and their pharmacological treatments and also the way

curcumin compounds may interact in their pharmacological effects while avoiding adverse side effects. The development of drug combination strategies is essential for better treatment of a variety of acute and chronic inflammatory conditions. In this review, we collected and analyzed research data on the curcumin combination and concluded that there are several components to be combined with curcumin as a way to incur anti-inflammatory activity, and such experiments have been in clinical trials.

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AUTHOR CONTRIBUTION

Putu Yudhistira Budhi Setiawan contributed to the conception and design in this study, as well as collecting and analyzing data. Subagus Wahyuono, Nyoman Kertia, and Arief Nurrochmand contributed to critical revisions and supervision.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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