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,
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](image_url)

**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).
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; Kunnunakkara 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-κB, activator protein 1, inducible nitric oxide synthase (iNOS), TNF-α, and IL-6 (Galubak et al., 2013). The ability of curcumin to inhibit the mitogen-activated protein kinase (MAPK) and NF-κB 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>
<thead>
<tr>
<th>No.</th>
<th>Component</th>
<th>Pharmacology model</th>
<th>Induction/treatment</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piperine</td>
<td>Male Swiss albino mice</td>
<td>LPS</td>
<td>Suppresses proinflammatory cytokines (IL-1β and TNF-α)</td>
<td>(Jangra et al., 2016)</td>
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<td></td>
<td></td>
<td>Male Wistar mouse</td>
<td>Olfactory bulbectomy model</td>
<td>Lower brain TNF-α and caspase 3 levels</td>
<td>(Rimawi et al., 2013)</td>
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<tr>
<td></td>
<td></td>
<td>Male C57BL/6J mice</td>
<td>High fat</td>
<td>Downregulates proinflammatory cytokines (IL-6 and TNFα)</td>
<td>(Neyrinck et al., 2013)</td>
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<td></td>
<td></td>
<td>Epithelial cells HT-29</td>
<td>TNF-α</td>
<td>Inhibits TNF-α and COX-2</td>
<td>(Kaur et al., 2018)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Albino Wistar Rat</td>
<td>-</td>
<td>Increases bioavailability</td>
<td>(Shoba et al., 1998)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male C57BL/6 mice</td>
<td>High fat</td>
<td>Suppresses proinflammatory cytokines IL-1β</td>
<td>(Miyazawa et al., 2018)</td>
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<td></td>
<td></td>
<td>Male Wistar rats</td>
<td>Haloperidol</td>
<td>Inhibits NO, TNF-α, and NF-κβ</td>
<td>(Bishnoi et al., 2011)</td>
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<td></td>
<td></td>
<td>RAW 264:7</td>
<td>RANKL</td>
<td>Inhibits osteoclastogenesis</td>
<td>(Martins et al., 2015)</td>
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<td>2</td>
<td>Resveratrol</td>
<td>Male Wistar rats</td>
<td>Fipronil</td>
<td>Increases glutathione (GSH), GPx, SOD, and CAT; malondialdehyde (MDA) and NO decrease</td>
<td>(Al Basheer et al., 2020)</td>
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<td></td>
<td></td>
<td>Chondrocyte</td>
<td>IL-1β</td>
<td>Inhibits expression IL-1β, COX-2, MMP-3, MMP-9, and VEGF</td>
<td>(Csaki et al., 2009)</td>
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<td></td>
<td></td>
<td>Colon cancer HCT-116</td>
<td>-</td>
<td>Reduces proliferation and stimulation of apoptosis accompanied by attenuation of NF-κβ activity</td>
<td>(Majumdar et al., 2009)</td>
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<tr>
<td></td>
<td></td>
<td>HO radical</td>
<td>-</td>
<td>Resveratrol is able to protect curcumin from degradation</td>
<td>(Coradini et al., 2014)</td>
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<tr>
<td></td>
<td></td>
<td>Male rat Wistar</td>
<td>complete Freund's adjuvant (CFA)</td>
<td>Reduces paw thickness and arthritis score</td>
<td>(Coradini et al., 2015)</td>
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<tr>
<td></td>
<td></td>
<td>Male Laka mice</td>
<td>Benzylalcohol</td>
<td>Brings down the enzyme activity of COX-2, significantly improved protein expressions of p21</td>
<td>(Malhotra et al., 2011)</td>
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<tr>
<td></td>
<td></td>
<td>Weaned piglets</td>
<td>-</td>
<td>Inhibits IL-1β and TNF-α</td>
<td>(Gan et al., 2019)</td>
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<td></td>
<td></td>
<td>Male Wistar rats</td>
<td>Cotton ligature</td>
<td>Inhibits IL-1β and IL-4</td>
<td>(Corrêa et al., 2017)</td>
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<tr>
<td></td>
<td></td>
<td>Male adult Wistar</td>
<td>Aluminum chloride</td>
<td>Inhibits COX-2 and increase SOD, GSH, CAT, and glutathione S-transferase</td>
<td>(Zaky et al., 1997)</td>
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<td>3</td>
<td>Quercetin</td>
<td>Male albino rats</td>
<td>Carrageenan</td>
<td>Increases GSH levels and HO-1 mRNA expression, reducing paw thickness, induced elevation in MDA, NO, and TNF-α</td>
<td>(Heeba et al., 2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Albino rat</td>
<td>Diazinon</td>
<td>Increases antioxidant parameters (GSH and GPx SOD, and CAT)</td>
<td>(Abdel-Daim et al., 2019)</td>
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<td></td>
<td></td>
<td>K562 cells</td>
<td>-</td>
<td>Inhibits total NO, NF-κβ, and COX-2</td>
<td>(Güran et al., 2016)</td>
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<td>4</td>
<td>Puerarin</td>
<td>Male Sprague Dawley rat</td>
<td>LPS</td>
<td>Reduces IL-1 and MMP-9; increases IL-10</td>
<td>(Singh et al., 2013)</td>
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<tr>
<td>5</td>
<td>Turmeron</td>
<td>Male rats</td>
<td>dimethylhydrazine</td>
<td>Reduces expression of iNOS and COX-2, decreasing NF-κβ transcription activity</td>
<td>(Murakami et al., 2013)</td>
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<td>6</td>
<td>Fish oil</td>
<td>Mice</td>
<td>dextran sulfate sodium (DSS)</td>
<td>NF-κβ activity and inflammatory score in the colonic mucosa</td>
<td>(Ja et al., 2011)</td>
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<td>7</td>
<td>Rhizoma Paridis saponins</td>
<td>Male Sprague Dawley rat</td>
<td>-</td>
<td>Reduces COX-2, IL-1β, NF-κβ, enhancement of HO-1, GSH, SOD, and NFκB activities</td>
<td>(Man et al., 2016)</td>
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<tr>
<td>8</td>
<td>Hydrolyzed collagen and green tea extract</td>
<td>Osteoarthritic human chondrocytes</td>
<td>IL-1β</td>
<td>Reduces NO, MMP-3, and IL-6</td>
<td>(Comblain et al., 2015)</td>
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<td>9</td>
<td>Emu oil</td>
<td>Male Sprague Dawley rat</td>
<td>Carrageenan and CFA</td>
<td>Inhibits paw volume, reduces TNF-α, IL-6, and IL-1β</td>
<td>(Jeengar et al., 2014)</td>
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<tr>
<td>10</td>
<td>Vitamin E</td>
<td>Mice</td>
<td>High calorie</td>
<td>Increases activity (GPx) and Nf-κB and reduces lobular inflammatory score and numeric analog scale score</td>
<td>(Heritage et al., 2017)</td>
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<td>11</td>
<td>Vitamin B2, carmine, and N-acetyl-cysteine</td>
<td>16HBE cell</td>
<td>Cigarette smoke extract</td>
<td>Decreases the inflammatory cytokine gene IL-1β, IL-6, TNFα, and NOS</td>
<td>(Vanella et al., 2017)</td>
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<tr>
<td>12</td>
<td>Berberine</td>
<td>Male Sprague Dawley rats</td>
<td>High calorie</td>
<td>Decreases expression of Sterol regulatory element-binding transcription factor 1, protein extracellular signal-regulated kinase, TNF-α, and protein c-Jun N-terminal kinase</td>
<td>(Feng et al., 2018)</td>
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<td>13</td>
<td>Vitamin D3</td>
<td>Adult female Wistar rats</td>
<td>High calorie</td>
<td>Reduces arthritis score and myeloperoxidase activity</td>
<td>(da Silva et al., 2019)</td>
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<tr>
<td>14</td>
<td>Ursodeoxycholic acid</td>
<td>Rat</td>
<td>NAFLD</td>
<td>Increases total antioxidant capacity, GSH, GPx, and SOD; decreases MDA levels and iNOS expression</td>
<td>(Gheibi et al., 2019)</td>
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<td>15</td>
<td>Ursolic acid</td>
<td>Female ICR mice</td>
<td>tissue plasminogen activator (TPA)</td>
<td>Inhibits the expression of IL-1β, IL-6, IL-19, IL-22, cemokine ligand 2 (CXCL2), COX-2, and VEGF</td>
<td>(Tremmel et al., 2019)</td>
</tr>
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<td>16</td>
<td>Boswellic acids</td>
<td>Rat</td>
<td>CFA</td>
<td>Reduces paw volume, but does not significantly reduce TNF-α and IL-6</td>
<td>(Khayyal et al., 2018)</td>
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<td>17</td>
<td>Salidroside</td>
<td>Rat</td>
<td>LPS</td>
<td>Reduce in the IL-6 and TNF-α</td>
<td>(Vasilieva et al., 2018)</td>
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<td>18</td>
<td>Silymarin</td>
<td>Male Wistar albino rat</td>
<td>Gamma radiation</td>
<td>Decreases the level of IL-18, TNF-α, C-reactive protein, Bax, factor-related apoptosis, and the activity of Casp-3</td>
<td>(Abdel-Magied et al., 2019)</td>
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<td>19</td>
<td>Prednisolone</td>
<td>Rat</td>
<td>Adjuvant-induced arthritis</td>
<td>Reduces TNF-α, IL-1β, and IL-6 and increases IL-10</td>
<td>(Yan et al., 2019)</td>
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<tr>
<td>20</td>
<td>Thymoquinone</td>
<td>Sprague Dawley rats</td>
<td>Cisplatin</td>
<td>Reduces TNF-α, IL-6, and MCP-1</td>
<td>(Al Faiy et al., 2020)</td>
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<tr>
<td>21</td>
<td>Flavocoxid</td>
<td>Chondrocytes</td>
<td>LPS</td>
<td>Reduces IL-1β of NF-κB and signal transducer and activator of transcription 3 mRNA expression</td>
<td>(D’Ascola et al., 2019)</td>
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<td>22</td>
<td>Tolfenamic acid</td>
<td>Female BALB/c mice</td>
<td>TPA</td>
<td>Reduces levels of COX-2 and inhibition of IKK and NF-κB</td>
<td>(Zhou et al., 2020)</td>
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<td>23</td>
<td>Luteolin</td>
<td>Male C57BL/6 mice</td>
<td>TNF-α</td>
<td>Reduces TNF-α vascular inflammation</td>
<td>(Lijaan et al., 2019)</td>
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<td>24</td>
<td>Polyunsaturated fatty acid</td>
<td>RAW 264.7 cells</td>
<td>LPS</td>
<td>Suppresses iNOS, COX-2, 5-lipoxygenase, and cytosolic phospholipase A2</td>
<td>(Saw et al., 2010)</td>
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<tr>
<td>25</td>
<td>Sulforaphane</td>
<td>RAW 264.7 cells</td>
<td>LPS</td>
<td>Reduces TNF-α, IL-1, NO, and PGE2</td>
<td>(Cheung et al., 2009)</td>
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<td>26</td>
<td>Augmentin</td>
<td>Mice</td>
<td>K. Pneumoniae</td>
<td>Decreases TNF-α, NO, MPO, and MDA</td>
<td>(Bansal et al., 2010)</td>
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<td>27</td>
<td>Saikosaponin A</td>
<td>Male Sprague Dawley rats</td>
<td>CCl4</td>
<td>Decreases interferon-γ, TNF-α, IL-1β, and IL-6, by the inhibition of NF-κB activation</td>
<td>(Wu et al., 2010)</td>
</tr>
<tr>
<td>28</td>
<td>Essential turmeric oils</td>
<td>Male mice</td>
<td>DSS cholangitis</td>
<td>Increases anti-inflammatory cytokines IL-10 and IL-11</td>
<td>(Toden et al., 2017)</td>
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<td>29</td>
<td>Erythromycin</td>
<td>Rat</td>
<td>Osteomyelitis model</td>
<td>Reduces levels TNF-α and IL-6, suppress bone lesions, and decreases the histopathological score</td>
<td>(Zhou et al., 2017)</td>
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<tr>
<td>30</td>
<td>Metformin</td>
<td>Male Wistar rat</td>
<td>Gentamicin</td>
<td>Reduces MDA and NO and an increase in the levels of SOD, CAT, GSH, and GPx</td>
<td>(Cao et al., 2019)</td>
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<td>31</td>
<td>Salisalate</td>
<td>Mice</td>
<td>High fat</td>
<td>Reduce IL-1β and IL-6</td>
<td>(Wu et al., 2017)</td>
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<td>32</td>
<td>Capsaicin</td>
<td>Male Wistar rats</td>
<td>Carrageenan</td>
<td>Reduces paw inflammation and 5-lipoxygenase</td>
<td>(Manjunatha et al., 2006)</td>
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<td>33</td>
<td>Selenium</td>
<td>Male albino Wistar</td>
<td>LPS</td>
<td>Reduces IL-6</td>
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<td>Ibeseartan</td>
<td>Male albino rats</td>
<td>Streptozotocin</td>
<td>Reduces serum levels of IL-6 and TNF-α</td>
<td>(Khaleed et al., 2010)</td>
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<td>35</td>
<td>Acetylsalicylic acid</td>
<td>Wistar albino rats</td>
<td>Carrageenan</td>
<td>Decreases in paw edema and MDA and increases GSH and SOD</td>
<td>(Mohapatra et al., 2019)</td>
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<tr>
<td>36</td>
<td>Hyaluronic acid</td>
<td>Male Wistar rat</td>
<td>CFA</td>
<td>Reduce paw edema levels of the TNF-α, IL-1, and VEGF</td>
<td>(Fan et al., 2018)</td>
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The presence of oxidative stress causes chronic inflammation, which exerts a strong influence leading to modulation of the expression of the nucleus-κB (NF-κB) factor pathways and TNF-α pathways that amplify the inflammatory response (Reuter et al., 2010; Sethi et al., 2008). Curcumin inhibits constitutive NF-κB and 1κB 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-κB (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-κB. Piperine has the activity of inhibiting gluconoridation 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 microbes 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-1β, 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-κB, which eventually directs proinflammatory degradation and phosphorylation of IkBα. This process will result in translocation that continues on the binding of NF-κB 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 Bashet et al., 2020; Coradin, 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-Daim 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 ability 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 IκB 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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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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