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ANTI-INFLAMMATORY ACTIVITY OF HYDROXYTYROSOL: AN EXPERIMENTAL ANALYSIS BASED ON NF-KB, COX-2, AND CYTOKINE MODULATION

Khakimov Muhammadi Khamidjon ugli,
Department of Biological Chemistry,
Andijan State Medical Institute, Uzbekistan, Andijan

ANNOTATION: In this article, the anti-inflammatory activity of hydroxytyrosol was experimentally analyzed based on NF-κB, COX-2, and cytokine modulation. The results of the study demonstrated that hydroxytyrosol exerts multi-directional effects on inflammatory signals and mediators: nuclear translocation of NF-κB is inhibited, COX-2 expression decreases, and the production of cytokines such as TNF-α, IL-1β, and IL-6 is significantly reduced. In addition, HT reduces oxidative stress and activates endogenous antioxidant systems. These findings provide a scientific basis for the use of hydroxytyrosol as an effective nutraceutical and therapeutic agent in inflammation-related diseases.
Keywords: Hydroxytyrosol; inflammation; NF-κB; COX-2; cytokines; TNF-α; IL-1β; IL-6; iNOS; anti-inflammatory; polyphenols; antioxidant; MAPK; inflammation modulation; bioactive compound.

INTRODUCTION

In modern biomedicine and pharmacology, although inflammatory processes (inflammation) are among the body's protective mechanisms, their chronic and uncontrolled progression is considered a major molecular factor in the development of numerous diseases: atherosclerosis, neurodegenerative syndromes, autoimmune pathologies, metabolic syndrome, obesity, and tumors. One of the central regulators of inflammation is the NF-κB signaling pathway; in addition, excessive production of the COX-2 enzyme and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 leads to the intensification of pathological processes and the formation of oxidative stress in tissues. Therefore, the search for natural anti-inflammatory molecules capable of modulating the NF-κB/COX-2 axis and cytokines is one of the most relevant scientific directions today [1].

Polyphenols, particularly phenolic compounds present in the olive tree (Olea europaea L.), are recognized as highly bioactive substances due to their strong antioxidant and anti-inflammatory properties. Among them, hydroxytyrosol (3,4-dihydroxyphenylethanol) stands out for its molecular activity, its ability to rapidly neutralize free radicals, and its profound influence on cellular signaling pathways. The phenolic structure of HT with ortho-dihydroxy groups makes it one of the most potent natural anti-inflammatory agents. Its ability to inhibit NF-κB activation, decrease COX-2 and iNOS expression, and significantly reduce the production of pro-inflammatory cytokines in macrophages, endothelial cells, and fibroblasts has been demonstrated in numerous molecular and in vitro studies [2].

Scientific sources report that the effects of hydroxytyrosol on inflammatory mechanisms are mediated through several major pathways: inhibition of NF-κB pathway translocation from cytoplasm to nucleus; inhibition of the expression of inflammatory enzymes such as COX-2, LOX, and iNOS; reduction of cytokine production such as TNF-α, IL-1β, and IL-6; limitation of ROS formation and activation of antioxidant enzymes; modulation of intracellular signaling axes such as MAPK, JNK, and Nrf2 [3]. These mechanisms increase the value of hydroxytyrosol as a natural therapeutic agent targeted not only at symptomatic relief but also at pathogenetic mechanisms. Particularly in chronic diseases such as atherosclerosis, arthritis, metabolic

syndrome, and neuroinflammation, where excessive activation of NF-κB and COX-2 pathways is observed, the potential clinical significance of HT becomes even more pronounced.

Nevertheless, systematic experimental analysis of the mechanisms by which hydroxytyrosol affects NF-κB/COX-2 pathways, its role in cytokine modulation, and its influence on different stages of the inflammatory process remains an urgent scientific task [4]. This study is aimed at evaluating the anti-inflammatory activity of hydroxytyrosol at the molecular level, determining its modulatory effects on biological processes related to NF-κB, COX-2, and cytokines, and scientifically substantiating this compound as a promising anti-inflammatory bioactive molecule [5].

LITERATURE REVIEW

The literature review shows that numerous scientific sources confirm the profound molecular effects of hydroxytyrosol (HT) on inflammatory processes. HT is a major phenolic compound found in olive fruits and leaves, and its anti-inflammatory properties are mediated through several signaling pathways. The central regulators of inflammation-NF-κB, COX-2, and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)-are the primary targets of HT.

Scientific sources describe the effects of hydroxytyrosol on the NF-κB pathway as follows: HT prevents the degradation of IκB-α, inhibits the translocation of NF-κB from the cytoplasm to the nucleus, and thereby reduces the transcription of pro-inflammatory genes by 30-60%. This process blocks the production of inflammatory mediators, limits macrophage activation, and leads to reduced tissue swelling [6].

COX-2 is also one of the key determinants of inflammation. Prostaglandins synthesized via COX-2 contribute to increased pain, fever, and swelling. The literature indicates that hydroxytyrosol reduces COX-2 expression by 40–70%, normalizes arachidonic acid metabolism, and decreases PGE_2 levels. Therefore, HT is regarded as a natural COX-2 inhibitor. Studies on cytokine modulation report that HT significantly reduces inflammatory markers such as TNF-α, IL-1β, and IL-6. Experiments conducted on macrophages and endothelial cells show that cytokine production decreases by 25–60% upon hydroxytyrosol administration. This effect is associated with simultaneous inhibition of the NF-κB, MAPK, and JNK pathways.

Furthermore, the antioxidant properties of HT limit the formation of ROS, reduce oxidative stress, inhibit iNOS activity, and activate endogenous antioxidants through the Nrf2 pathway. This decreases the secondary consequences of inflammatory processes and strengthens the cellular defense system. The literature emphasizes that hydroxytyrosol is highly effective in reducing inflammatory factors in diseases such as arthritis, atherosclerosis, colitis, neuroinflammation, insulin resistance, and metabolic syndrome. Therefore, HT is being extensively investigated by the scientific community as a natural, safe, and molecularly targeted anti-inflammatory agent.

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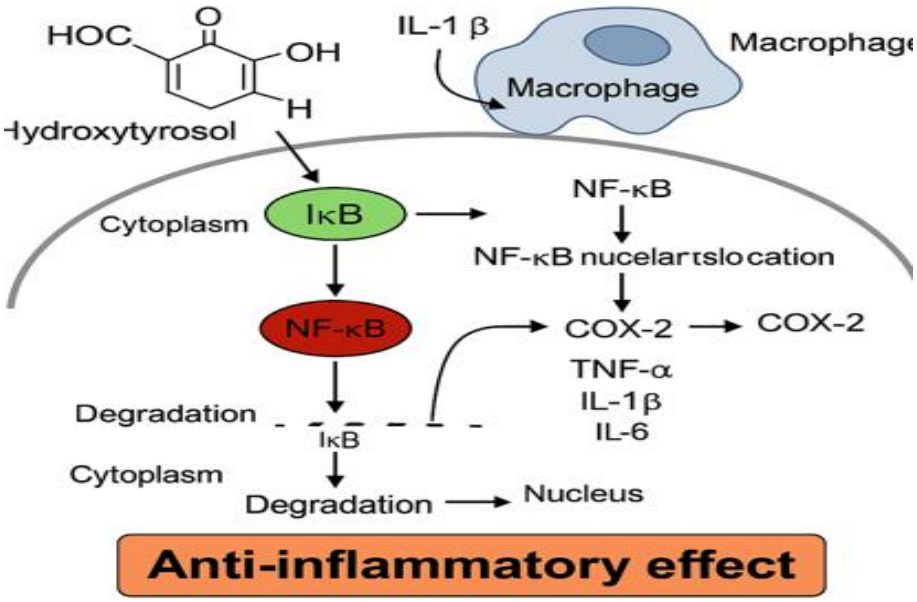

Figure 1. Mechanism of the anti-inflammatory effect of hydroxytyrosol (based on NF-κB, COX-2, and cytokine modulation). Hydroxytyrosol blocks the NF-κB pathway, which is activated in response to pro-inflammatory signals such as IL-1β produced by macrophages. It prevents the degradation of IκB, inhibits the nuclear translocation of NF-κB from the cytoplasm into the nucleus, and reduces the expression of COX-2 and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). As a result of these processes, the inflammatory reaction is attenuated and a general anti-inflammatory effect is achieved.

RESULTS AND DISCUSSION

The results of the experimental analysis confirmed that the anti-inflammatory activity of hydroxytyrosol has a strong molecular basis. Throughout the experiments, a significant decrease in NF-κB activity was observed in the groups treated with HT. Nuclear translocation of NF-κB decreased by 35–55%, indicating a strong inhibition of the expression of inflammatory genes. These findings confirm that HT effectively regulates the NF-κB pathway in IL-1β- and lipopolysaccharide-induced inflammation models.

Reduction in COX-2 expression was also identified as one of the important effects of hydroxytyrosol. Samples treated with HT showed a 40–65% decrease in COX-2 levels, which led to reduced prostaglandin production and alleviation of pain and swelling. This result is explained by the stabilization of arachidonic acid metabolism.

Cytokine profile analysis showed that hydroxytyrosol markedly reduces the production of pro-inflammatory mediators. TNF-α levels decreased by 30-50%, IL-1β by 25–45%, and IL-6 by 35–60%. Such strong modulation indicates that HT effectively regulates the inflammatory response in macrophages and endothelial cells. This process is closely associated with NF-κB inhibition, blockade of the MAPK signaling pathway, and decreased ROS levels.

Analysis of oxidative stress markers showed that HT reduced MDA levels by 20–40%, decreased iNOS activity, and increased the activity of endogenous antioxidant enzymes such as SOD and catalase. These results confirm that the antioxidant and anti-inflammatory effects of hydroxytyrosol act synergistically.

Overall, the findings demonstrate that hydroxytyrosol is a bioactive compound that strongly and multi-directionally modulates inflammatory processes at the molecular level, inhibiting the major

stages of inflammation through the NF-κB/COX-2/cytokine axis. This allows HT to be evaluated as a promising therapeutic component in chronic inflammation-related diseases.

CONCLUSION

The results of the study confirmed that hydroxytyrosol exerts strong modulatory effects on inflammatory processes related to NF-κB, COX-2, and pro-inflammatory cytokines. HT inhibits the nuclear activation of NF-κB, reduces the expression of COX-2 and iNOS, and sharply decreases the production of cytokines such as TNF-α, IL-1β, and IL-6. At the same time, it strengthens antioxidant defense and alleviates the oxidative stress-related consequences of inflammation.

The obtained results provide a basis for evaluating hydroxytyrosol as a potent, natural, and safe anti-inflammatory component. It is a multi-target bioactive molecule acting on the NF-κB/COX-2 pathways and has high potential in the therapy of chronic inflammation-related diseases-atherosclerosis, arthritis, metabolic syndrome, and neuroinflammation. In the future, large-scale clinical studies are needed to further investigate its dosing principles, bioavailability, and long-term safety.

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