

# The Involvement of Honokiol in Inflammation

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## 1. Abstract

Honokiol (HNK) is a biphenolic compound derived from the bark of *magnolia officinalis*. Over the past decades, HNK is frequently prescribed as a pharmaceutical ingredient for inflammatory disease, which is a complex pathological process closely related to oxidative stress and immune response. The existing literature on HNK is extensive and focuses particularly on its role of anti-inflammation, anti-oxidative effect and immune response regulation. Based on recent research, this paper addresses the anti-inflammatory effect of HNK, and highlight its important role in improving herbal remedy for inflammatory diseases.

**2. Keywords:** Honokiol; Anti-inflammation; Anti-oxidative; Immune response

## 3. Introduction

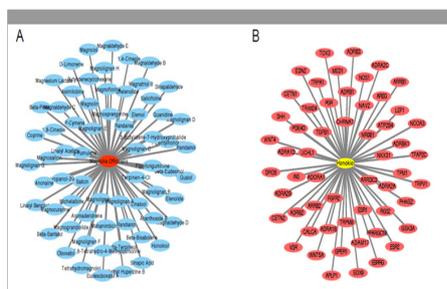
Honokiol (HNK), a natural biphenolic compound extracted from the bark of the *Magnolia* tree, have emerged as the drug with anti-oxidative, anti-inflammatory, and anti-tumor properties[1,2]. HNK has subscribed to the belief with its potent antioxidative and anti-inflammatory effects. There is evidence that HNK has an extensive research in application for a wide variety of inflammatory diseases [3]. Over the past decades, a considerable literature has grown up around the theme of anti-inflammation of HNK. HNK was reported to attenuate the inflammation in asthmatic mouse model[4]. Previous research has indicated that HNK was involved in modulating inflammation-mediated damage to rat muscle cells[5]. Robust evidence from trials shows that HNK plays a protective role in septic shock. It was also determined that HNK suppressed the lethal response and acute lung injury induced with sepsis[6], and our research group recently found the protective role of HNK on sepsis-induced AKI against oxidative stress and inflammatory signals[7]. A considerable amount of literature has been published on the anti-inflammatory effect of HNK. This study aims to provide a short review on this biological function of HNK for the cellular response to the stress.

## 4. Fundamental Characteristic of Honokiol

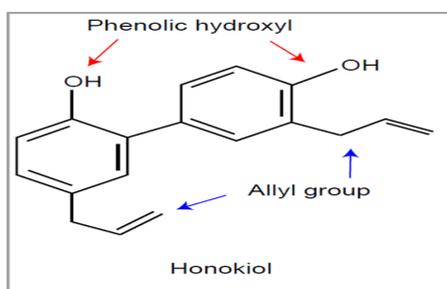
Honokiol, with the other ingredient Magnolol, is separated from *Magnolia Officinalis* to be applied for the anti-bacterial, anti-oxidant, anti-inflammatory, anti-free radical, cholesterol-lowering effect and inhibitory effect of central nervous system (CNS)[8,9]. There are two major species of *Magnolia Officinalis*, including *Magnolia officinalis* Rehd.et al. [10]Wils and *Magnolia officinalis* Rehd.et Wils.var.biloba Rehd.et Wils. The cortex and root bark of *Magnolia Officinalis* are usually used as herbal medicine, which was earlier recorded in ancient medical books, such as *Shen Nong Ben Cao Jing*. The bark of *Magnolia officinalis* needs to be stripped off during April to May, and dried in the shade directly, then taken to a boil for medical application or reserve.

According to bioinformatic methods, it was analyzed by our group that *Magnolia Officinalis* contains 95 compounds, among which 28 compounds had no putative molecular targets due to absent structural information (**Figure 1A**). As one of the main components, HNK is now well known as a pharmaceutical ingredient for bacterial infection, inflammatory diseases and carcinoma[10,11]. The Molecular formula of HNK is  $C_{18}H_{18}O_2$  with low molecular weight of 266.32. HNK is difficult to dissolve in water but easy to dissolve in organic solvents, such as benzene, acetone, and chloroform. HNK has remarkable anti-microbial

activity of gram-positive bacteria and filamentous fungi. It is therefore used in anti-fungal, anti-ulcer and anti-inflammation. The function of HNK depends on the biological process and cellular components of its molecular targets. It was examined in our current study that there were 57 molecular targets of honokiol (**Figure 1B**). However, these results still need to be verified upon solid data from experiments and researches.



**Figure 1.A:** 67 compounds of Magnolia Officinalis. B: Molecular targets of honokiol (score >20).



**Figure 1.B:** The structure of honokiol.

## 5. The Anti-inflammatory Effect of Honokiol

Several studies on the anti-inflammation of honokiol have been proposed. Research such as that conducted by N. Li has shown that honokiol plays its protective role in sepsis-associated AKI against inflammatory signals[7,12]. This mechanism underlying the anti-inflammation of HNK was investigated in animal model assay, which showed obviously that HNK-mediated morphological amelioration of kidney injury was regulated with TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. TNF- $\alpha$  has promotive effects on inflammatory cytokines released by T cell[13]. IL-1 $\beta$  and IL-6 play an important role in the procession of inflammatory reaction and immune response[14,15]. In recent years, the anti-inflammatory function of HNK is focused on the research of sepsis-associated AKI. It was also found that inflammatory cytokines in sepsis-associated AKI were decreased by honokiol in animal experiment[13]. Another sepsis-induced organ injury was investigated to show that HNK reversed the elevated level of TNF- $\alpha$  and nitric oxide in sepsis-associated lung injury mice[6]. Several attempts have been made to examining the function of honokiol in sepsis model. Sepsis is one of the most tough clinical case in the intensive care unit, which has still no therapy effectively and need integrative

medicine. Therefore, the research of HNK would provide a new sight for the therapeutic approach to sepsis.

Based on the research of macrophages, it was reported that honokiol inhibited inflammation via the cyclooxygenase-2 (COX-2)[16]. COX-2 has a low activity in normal condition but extremely high level under the inflammatory stimulation with the capability of catalytic functions between cyclooxygenase and catalase[17,18]. It is thus indicated that the COX-2 regulation by HNK would have a marked impact on the development of inflammation. Like COX-2, many factors involved in inflammation were identified to be suppressed by HNK, including TRPV1, P2Y, CXCL8, CXCL1, CCL2, and VEGF[3,19-21]. Data from several studies extend our understanding of the anti-inflammatory properties of HNK.

## 6. Honokiol Possessed Anti-oxidant Effect

It is now well confirmed from a variety of studies that oxidative stress and inflammation are closely related. Oxidative stress results directly in the oxidative damage to body tissues, further activating damage associated molecular patterns and releasing the cytokines. Additionally, more cytokines and chemokines are generated, further aggravating the inflammatory reaction[22,23]. It is thus that the antioxidation is conducive to control the inflammation. There is a consensus that the structure of honokiol contributes to its antioxidant capacity (Figure 1 and 2). The phenolic hydroxyl of HNK can be easily oxidized under oxidative-enriched environment. 2) The Phenolic compounds with allyl group play an important role in the elimination of hydroxyl radicals, which is the fundamental function of pharmacological application.

It has been observed from in vivo experiments that UDP-glucuronosyl transferase (UGT) and superoxide dismutase (SOD) was increased after HNK treatment[24]. UGT, as an important enzyme, is widely expressed in the liver, kidney and glandular organs[25]. SOD is well-known enzyme to switch the superoxide radical to hydrogen peroxide, which is further decomposed into water by catalase (CAT) and peroxidase (POD) [26]. SOD is found to be modulated by HNK, suggesting that HNK is involved in the promotion progress of maintaining the anti-oxidation ability. There is evidence that the level of lipid peroxidation was decreased due to the intervention effect of HNK[27]. Existing research recognizes that both honokiol and magnolol have the capability of free radical elimination[28,29].

## 7. Honokiol Involved in Cellular Immune Response

The immune system is a host defense system comprising multiple cells and immune factors to prevent our body from exogenous

attack. Abnormal immune response would cause tissue and cell damage, which finally lead to inflammatory response[30]. It is necessary for scientists to address the issue of how to explore the mechanism underlying the inflammatory influence under abnormal immune response. Much of the current literature on traditional herbal pays particular attention to immunoregulatory effect, including the ingredients of codonopsis pilosula, ganoderma lucidum, angelica and so on[31-33]. The effects of honokiol on the host immune response was not investigated as much as the inflammatory process. Also, HNK was found to increase the frequency of CD4 T cells and increased activation of CD4 T cells as measured by the activation marker CD69 in the sepsis research. However, HNK failed to alter survival[34]. It is hence suggested that time and concentration of HNK treatment are supposed to be modulated according to the previous data.

T cell is not the only species immune cell regulated by HNK. The honokiol treatment was determined to enhance splenic dendritic cells[34]. Dendritic cells are antigen-presenting cells processing antigen material and present it to the T cells[35]. Simultaneously in this study, HNK cannot decrease frequency and number of CD8 T cells, suggesting that HNK has its function to distinct immune cells. The Study on immunity of HNK should be carried out, in order to find more effective therapeutic methods.

## 8. Conclusions

A great deal of previous research into therapeutic function of tradition herbal has focused on regulation on the occurrence and development of inflammation. Previous studies have explored the relationships between honokiol and some diseases. As this review discussed above, it is demonstrated that HNK has been involved in the process of oxidative stress and immune response, or directly applied to attenuate some symptoms. HNK has actually multiple functions including block to platelet aggregation, regulation of immune resistance and modulation of oncogene expression[36,37]. Notwithstanding these researches, the precise mechanism of honokiol underlying inflammatory reaction remains to be elucidated. It was concluded that honokiol is clinically available for inflammatory regulation and may serve as a potential therapeutic drug to increase the chance of the patient's recovery.

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