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# The effect of α-mangostin on TLR-4 and PGE2 in the dentin-pulp complex exposed to HEMA

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## Abstract

Mangosteen is abundant in Indonesia. Most mangosteen pericarp contains Alpha (α) mangostin, which has numerous biological benefits, especially antioxidant, antibacterial and anti-inflammatory properties. The purpose of this study is to analyse the effect of α-mangostin on toll-like receptor 4 (TLR-4) and prostaglandin E2 (PGE2) in vivo. An in vivo study was conducted using 42 male Wistar rats (*Rattus norvegicus*) in randomised post-test control groups. The rats were divided into a control group applied 2-hydroxyethyl methacrylate (HEMA) and a treatment group applied HEMA and 12,5µg/ml of α-mangostin. The inflammatory factors on the dentin-pulp complex of the rat's model were examined. TLR-4 was detected via immunohistochemistry and PGE2 was assayed via ELISA after 24, 48 and 72 hours. In vivo results showed a decrease in TLR-4 and PGE2 after α-mangostin treatment. Recent studies have shown that α-mangostin can significantly decrease TLR-4 and PGE2 on a dentin-pulp complex after exposure to HEMA.

**Keywords:** TLR-4, PGE2, α-mangostin**,** HEMA, dentin-pulp complex, human&health

## Introduction

### Background

Tooth and oral diseases are significant problems in Indonesia. Based on the results of a Riset Kesehatan Dasar survey of Indonesia in 2018, the prevalence of dental caries was high, occurring in 56.4% of the Indonesian population. As one of the most common dental filling materials, composite resin has frequently been used in restorative dentistry. Treating dentin with 2-hydroxyethyl methacrylate (HEMA) prior to the application of composite resin can increase the bond of composite resin to dentin.[1] However, several studies have shown that

HEMA can release residual monomers during deep polymerisation (24 to 96 hours) after tooth filling.[2] Clinical studies have also reported that in up to 30% of the population studied, tooth sensitivity increases after restoration with a posterior composite resin.[3] The application of HEMA to pulp with a thin or exposed dentine layer can cause cytotoxicity and a chronic inflammatory pulpal response. Incomplete polymerisation can lead to an imbalance of reactive oxygen species (ROS), resulting in oxidative stress and inflammation of the pulp.

HEMA, which is toxic to the pulp, has been shown to increase the expression of cyclo-oxygenase 2 (COX2) and prostaglandin E2 (PGE2) through ROS, which can cause damage to cells.[4] PGE2 is one of the inflammatory mediators that is elevated during pulpal inflammation.[5] HEMA can cause inflammation via the toll-like receptor 4_(TLR-4) pathway by activating mitogen-activated protein kinases_and nuclear factor kappa B (NFkB) signals that produce inflammatory mediators.[6]

Recently, various types of medicinal plants have been studied and a great deal of evidence has been gathered to demonstrate their vast potential. Alpha (α) mangostin, a derivative of xanthone in mangosteen pericarp extract,[7] has been reported to show inhibitory responses to many microorganisms, especially gram-positive bacteria.[8] It also displays anti-inflammatory behaviour.[9] α-mangostin is rich in antioxidants and is expected to reduce the toxic effect of HEMA through its role in breaking the chain of ROS.

α-mangostin is commonly used as a treatment for inflammation but few studies have evaluated its direct effect on the dentin-pulp complex. This study aims to evaluate the efficiency of α-mangostin in decreasing TLR-4 and PGE2 on a dentin-pulp complex after exposure to HEMA.

## Materials and methods

### Preparation of α-mangostin

α-mangostin (purity >98%) was obtained from the Tokyo Chemical Industry Co., Ltd. *(product number M2793)*. α-mangostin was combined with polyethylene glycol (PEG) to achieve a concentration of 12.5 $\mu$g/ml. This process was conducted at the Faculty of Pharmacy at Universitas Airlangga, Surabaya.

### Animals

42 male Wistar rats (*Rattus norvegicus*) were placed in a randomised post-test only control group design. Each rat was anesthetised intramuscularly, and cavity preparation was performed on the occlusal first molar of the rat's upper left jaw. Then, a pure HEMA solution (Sigma) 95% was applied to the cavity.[10] α-mangostin with a concentration of 12.5 $\mu$g/ml was

applied to the treatment group. Before each rat was terminated, blood was drawn from its heart (intracardiac) with a syringe to analyse the serum PGE2 level. The animals were anesthetised with ether and decapitated. The teeth and the surrounding bone were resected, fixed in Bouin's fixative for periods of 24, 48 and 72 hours, then decalcified with 10% formalin buffer (pH 7.4).

**TLR-4 expressions**

The dental tissue removed from the rats' teeth was kept in a sample pot with 10% formalin buffer (pH 7.4) for 24 hours. Then, the tissue was decalcified using EDTA 10% at 37°C, which was replaced every day until the soft tissue broke down (taking approximately two months). After the teeth were soft enough to be pricked with a needle, they were embedded in a paraffin block and underwent the processes of dehydration, clearing, impregnation and embedding. Dehydration was achieved by immersing the samples in various percentages of ethanol (70%, 80%, 95% and 96%) for two hours. Following dehydration, the samples were placed in n-xylol for four hours to clear any remaining ethanol. The next step was impregnation, in which the samples were placed in solid paraffin for four hours and subsequently embedded into a mould base on a cold plate. The paraffin block was then ready to be cut into ultrathin slices (0.5 cm) using a microtome. An antibody *(Novusbio; NB100-56566)* was applied to the tissue sections and used to check expressions of TLR-4. The expressions were observed under a light binocular microscope (Olympus) at 400 × magnification.

**PGE2 levels**

The blood from the rats' hearts (intracardiac) was stored in a tube and put in a centrifuge (3000 rpm) for 10 minutes to obtain a blood serum for analysing the PGE2 levels (Rat Prostaglandin E2 ELISA Kit, Cat. No. E0504Ra, Bioassay Technology Laboratory, China). The analysis of PGE2 levels in the serum was read using a microplate reader at a wavelength of 450 nm.

**Statistical methods**

Normality testing was performed using a Kolmogorov-Smirnov test, and a homogeneity test was performed using a Levene's test. One-way ANOVA was used to assess the differences between groups, followed by post-hoc least significant difference tests to check the homogeneous data and a Kruskal-Wallis test to check the non-homogeneous data. A P value of $>0.05$ was considered to be significant.[11]

## Result and Discussion

### TLR-4 expression in dentin-pulp complex

To visualise the expression of TLR-4 in dentin-pulp complexes exposed to HEMA, an immunohistochemical staining was performed and observed at 400 × magnification. The TLR-4 positive cells were observed in the dentin-pulp complexes of the control group at 24, 48 and 72 hours (Figure 1). The TLR-4 expressed cells in the control group showed a gradual increase at 24, 48 and 72 hours, while the group treated with α-mangostin showed a significant decrease in the number of TLR-4 expressed cells (Table 1).

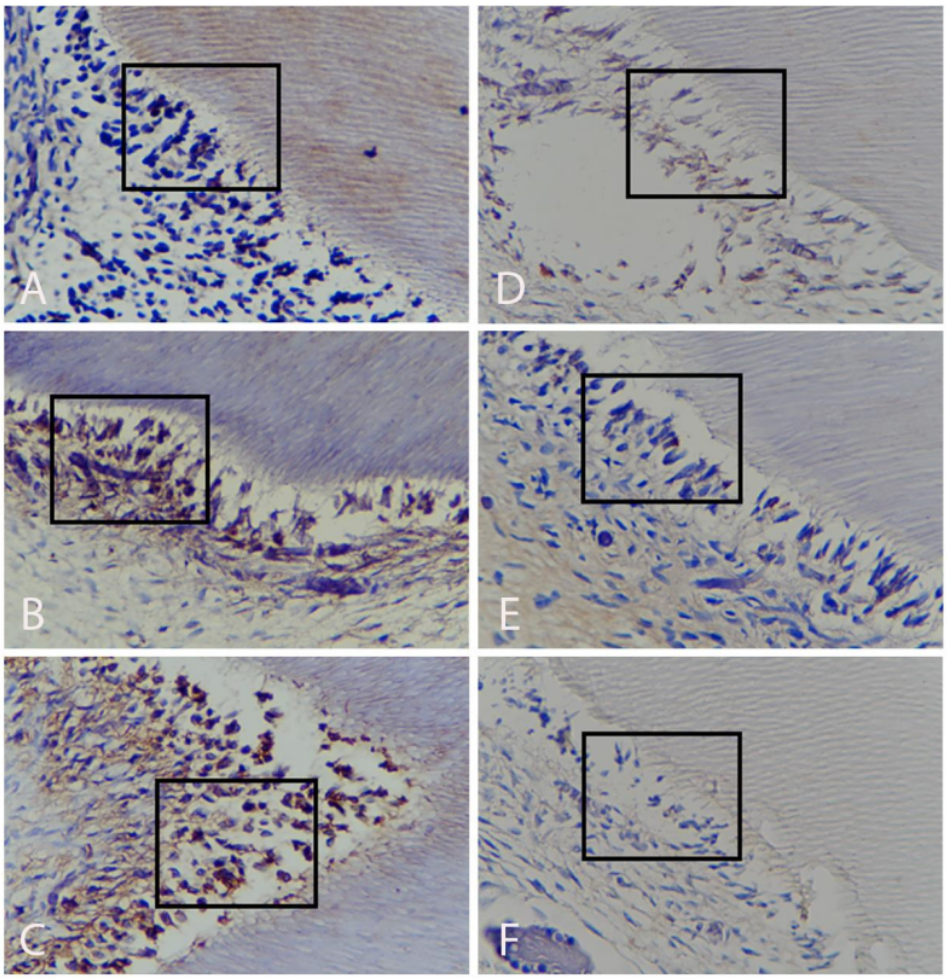


**Figure 1.** The expression of TLR-4 in a dentin-pulp complex exposed to HEMA for 24, 48 and 72 hours with an immunohistochemical examination at 400 × magnification. The squares indicate TLR-4 positive cells; the cytoplasm is brown, and the nucleus is blue. A. Control at

24 hours, B. Control at 48 hours, C. Control at 72 hours, D. Treatment at 24 hours, E. Treatment at 48 hours, F. Treatment at 72 hours.

Toll-like receptors (TLRs) are type I transmembrane proteins that are activated by a variety of pathogen-associated molecular patterns, thus initiating an innate immune response and inflammation in higher animals.[12] Like other TLRs, TLR-4 has a modular structure composed by a domain which is constituted by leucine-rich repeats.[13] TLR-4 is one of the receptors related to innate immunity and several inflammatory reactions.[14]

| Group | TLR4 expression (cell/large field of view) | | |
|---|---|---|---|
| | 24hr | 48hr | 72hr |
| Control | 11,57±1,40 | 13,57 ±3,10 | 16,29 ±2,06 |
| α-mangostin | 6,86 ±1,95 | 8,57 ±1,72 | 6,86 ±2,55 |
| P value | 0.000* | 0,002* | 0.000* |

**Table 1.** The difference in TLR-4 expressions at various time periods for each group

The possible mechanisms by which HEMA monomer and ROS as a result of incomplete polymerisation of HEMA stimulated inflammation via TLR-4 were investigated. TLR-4 recognises exogenous and endogenous ligands and its signalling pathway is activated upon the invasion of cells by these ligands.[15] This triggers a cascade of reactions to promote the production and release of inflammatory cytokines.[16] An in-silico study conducted by Goenharto et al. (2020) mentioned that methyl methacrylate (MMA) ligands activate TLR-4 receptors through His 228.[17]

Oxidative stress has also been thought to play a general role in the activation of the TLR-4 signalling pathway.[18] Exposure to MMA acting as a free radical or ROS produces a free radical product, causing changes in cell membrane potential that, in turn, cause membrane rupture and cell death.[19] Oxidative stress in cell membranes increases malondialdehyde, a lipid membrane peroxidation product that can cause cell damage-associated molecular patterns (DAMPs). DAMPs are recognised and bound to macrophages through the surface receptor system.

The possible mechanism by which HEMA monomer stimulates inflammation begins with the interaction of HEMA monomer and TLR-4. Consequently, in the cytosol, the signalling process begins with the activation of myeloid differentiation factor 88. Next, inhibitory-κB kinase (IKK) activates a phosphorylase. IKK inhibits IkB, which subsequently

releases and activates NFkB to form active NF-kB.[20] NF-kB is then translocated to the nucleus to induce DNA recombination.[21,22] As a result of gene transcription, translation and engagement of the COX2 promoter in the nucleus occurs. Once COX2 is transcribed and translated, it uses arachidonic acid to generate PGE2.[23] Other pro-inflammatory cytokines, such as IL1, IL1β, IL-6, IL-8 and TNF-α, are also produced.[24]

In addition, TLR-4 can trigger the transcription of the inducible nitric oxide synthase (iNOS) gene, which promotes nitric oxide (NO) production. Furthermore, iNOS produces peroxide and oxygen radicals. The significant increase in the expression of iNOS and NO accelerates the inflammatory response.[16]

The expressions of TLR-4 in the dentin-pulp complexes exposed to HEMA treated with α-mangostin at 24 hours, 48 and 72 hours were significantly downregulated. This study proposes that antioxidants from α-mangostin may provide a possible mechanism by which the exposure of cells to ROS and cytokine-induced activation of NFkB can be prevented.[25] However, the assumption that oxidants play a general role in the activation of NFkB has not yet been elucidated.

**PGE2 levels**

ELISA was performed to evaluate the effect of α-mangostin on the treatment group at 24, 48 and 72 hours, and the results showed decreased PGE2 levels when compared to the control group (Table 2). In the control group, there was a significant increase in PGE2 levels at 24, 48 and 72 hours ($p<0.05$). According to Di Nisio et al. (2013), ROS production and COX2 significantly increase in human gingival fibroblasts (HGFs) treated with a relatively low HEMA with a time of 24 to 96. As explained, monomers are toxic substances that can cause cell damage, an undesirable side effect of restorative procedures. Although HEMA is not the most toxic monomer,[26] it is used because of its low molecular weight, which allows the compound to diffuse through the dentine tubules, reaching the pulp tissue.[27]

| Group | Concentration PGE2 ($\mu$g/ml) after exposure | | |
|---|---|---|---|
| | 24hr | 48hr | 72hr |
| Control | 3.636±0.038 | 3.990±0.006 | 3.864±0.010 |
| α-mangostin | 3.212±0.007 | 2.784±0.012 | 2.717±0.047 |
| P value | 0.000* | 0.000* | 0.000* |

**Table 2.** The serum PGE2 level after 24, 48 and 72 hours. *significant different with independent t-test ($p<0.05$)

The increase of PGE2 levels could have been caused by HEMA induction. Incomplete polymerisation can lead to an imbalance of ROS, resulting in oxidative stress and pulpitis. ROS serve as intracellular and extracellular signalling messengers and regulate numerous downstream signal transductions and gene expressions.[28] PGE2 can be synthesised due to the breakdown of the phospholipid bilayer of macrophages caused by oxidative stress. Production of PGE2 will subsequently increase the production of proteolytic enzymes, thus damaging cartilage.[29] PGE2 also plays a role in stimulating pain through its receptors on peripheral nerves and the spinal cord.[30] In the superficial dentin layer, the sensory potential of the pulp remains in the presence of a pain response.[31] In pathological conditions, PGE2 is primarily regulated by COX2 as a pro-inflammatory mediator, and PGE2 overexpression can cause the development of many inflammatory diseases, such as rheumatoid arthritis and osteoarthritis.[5]

The effect of α-mangostin on PGE2 levels was evaluated after 24, 48 and 72 hours. PGE2 levels were significantly downregulated after α-mangostin administration when compared to the control group ($p<0.05$). α-mangostin, a xanthone derivative of mangosteen, is a compound known for its analgesic and anti-inflammation properties.[9] These results demonstrate that an α-mangostin concentration of 12.5$\mu$g/ml could decrease PGE2 levels during pulp inflammation in the dentin-pulp complex after exposure to HEMA at 24, 48 and 72 hours. Several studies have reported that α-mangostin suppresses the secretion of iNOS and COX2, while it also inhibits TNF-α and IL4,[32] through TLR-4 mediated NFkB signalling pathways [17]. Other studies have provided information about the use of α-mangostin as an anti-inflammatory using in silico, in vitro and in vivo models.[9,33] The anti-inflammatory effect of α-mangostin in LPS-stimulated BV-2 cells involves the inhibition of the NFkB (but not the MAPK) signalling pathway.[34] Xanthones produce an anti-inflammatory effect by inhibiting COX2 and prostaglandin synthesis of glioma cells in rats without affecting the constitutive CO.[35,36] Secretion of IL-1β, COX2, and IL-6 in LPS-induced RAW 264.7 macrophages can be inhibited by α-mangostin.[37]

**Conclusion**

In summary, the results shed light on the mechanism of ROS and its involvement in the activation of TLR-4 and PGE2, which is responsible for inflammation in the dentin-pulp complex. A treatment of α-mangostin can significantly downregulate TLR-4 and PGE2 in the dentin-pulp complex after exposure to HEMA.

**Acknowledgments**

None

**Conflict of Interest**

All author declares no conflict of interest

**Ethical policy and instutional review board statement**

Ethical clearance had been obtained from the Ethics Commision of the Faculty of Dental Medicine, Universitas Airlangga, Surabaya (No. 607/HRECC.FODM /IX/2019).

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