Effect of Mangosteen Pericarp Extract on the Lipopolysaccharide-Induced Prostaglandin E_2 Production in Monocytes/Macrophages

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Abstract

Prostaglandin E_2 (PGE_2), secreted by monocytes/macrophages in the presence of bacterial lipopolysaccharide (LPS), has been implicated in the pathogenesis of periodontal disease. The extract from mangosteen pericarp has been shown to have anti-inflammatory activity by inhibiting PGE_2 production in rat glioma cells. This study examined the inhibitory effect of the extract on the PGE_2 production in LPS-activated RAW 264.7 mouse macrophage-like cells and human peripheral blood monocytes. Monocytes/macrophages were stimulated with LPS from *Porphyromonas gingivalis*, and concomitantly treated with varying concentrations of the extract. After 24 hours, the PGE_2 level was measured by enzyme-linked immunosorbent assay. The results showed that LPS-stimulated cells produced a high level of PGE_2. The mangosteen pericarp extract significantly inhibited LPS-induced PGE_2 production in a concentration-dependent manner. The 50% inhibitory concentration (IC_{50}) values were approximately 0.5 and 3.3 µg/ml for RAW 264.7 cells and peripheral blood monocytes, respectively. Cytotoxicity test revealed that the concentrations of the extract that inhibited PGE_2 synthesis had no significant effect on cell viability. These findings indicate that the extract from mangosteen pericarp has potent anti-inflammatory property that may be beneficial for periodontal treatment.

Key words: anti-inflammatory; *Garcinia mangostana*; lipopolysaccharide; periodontal disease; prostaglandin E_2

Introduction

Periodontal disease is a chronic inflammatory disease caused by a group of Gram-negative anaerobic bacteria in dental plaque. Bacteria that have been implicated in the etiology of periodontal disease include *Porphyromonas gingivalis*, *Tannerella forsythia* (formerly *Bacteroides forsythus*) and *Actinobacillus actinomycetemcomitans*.[1] One of the virulence factors common to these periodontopathic bacteria is lipopolysaccharide (LPS).

It has been known to interact with host immune cells and non-immune cells, leading to the release of inflammatory mediators such as prostaglandin E_2 (PGE_2), interleukin-1β, interleukin-6 and tumor necrosis factor-α (TNF-α).[2] These released molecules are responsible, at least in part, for periodontal destruction.

There is considerable evidence suggesting that PGE_2 is involved in the pathogenesis of periodontal disease. According to immunohistochemical studies, monocytes/macrophages are considered to be the major source of PGE_2 in infected periodontal tissues.[3] PGE_2 acts as an inflammatory mediator and a potent stimulator of bone resorption. Its level in gingival crevicular fluid is increased in association with gingival inflammation and periodontal destruction.[4] In addition, non-steroidal anti-inflammatory drugs (NSAIDs), which block PGE_2 synthesis, have been shown to be effective for inhibiting periodontal destruction.[5] Extracts from several medicinal plants have been shown to possess anti-inflammatory activity through inhibition of inflammatory mediators including PGE_2.[6-8] Therefore, they may provide an effective approach for periodontal therapy.

Garcinia mangostana Linn., commonly known as mangosteen, is a fruit tree found in Southeast Asia and South India. It has been used in Thai traditional medicine for treatment of diarrhea, skin infection and chronic wound.[9] Previous studies have shown that extract from mangosteen pericarp has low toxicity[10-14] and possesses both antibacterial,[15-18] and anti-inflammatory activities.[6,19-21] Its anti-inflammatory activity is exerted through inhibition of PGE_2 production. A short-term treatment (10 minutes) with mangosteen pericarp extract inhibited Ca^{2+} ionophore-induced PGE_2 release in C6 rat glioma cells.[6,19,21] A long-term treatment (18 hours) also decreased spontaneous PGE_2 synthesis in these cells.[20]

To study the potential application of mangosteen pericarp extract for periodontal treatment, its anti-inflammatory activity should be assessed on LPS-stimulated monocytes/macrophages, which are the major source of PGE_2 in infected periodontal tissues. Therefore, the objective of this study was to examine the effects of the extract on PGE_2 production from LPS-activated RAW 264.7 macrophage-like cells and human peripheral blood monocytes. For the viewpoint of safety, its effects on cell viability were also examined.

Materials and methods

Preparation of mangosteen pericarp extract

Pericarps of mangosteen were collected from Thewate market in Bangkok in July 2003. Crude extract was prepared as previously described.[22] Briefly, dried and ground pericarps were macerated in hexane for 24 hours to remove non-polar substances. The resulting marc was subsequently macerated in ethyl acetate for 24 hours. The ethyl acetate extract was then recrystallized, and ground into powder. The yield of mangosteen extract from the dried pericarp was approximately 3% (w/w).

RAW 264.7 cell culture

RAW 264.7 cells, a mouse macrophage-like cell line transformed with the Abelson leukemia virus, were a gift from Professor Stitaya Sirisinha (Faculty of Science, Mahidol University, Bangkok, Thailand). The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 2 mM glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin (Gibco-Invitrogen, Carlsbad, CA, USA). They were maintained at 37°C with 5% CO_2. The cells were detached from plates by vigorous pipetting, and subcultured every 48 hours at a dilution of 1:3.

Isolation of human peripheral blood monocytes

Human peripheral blood monocytes were isolated using OptiPrep density-gradient medium (Axis-Shield PoC AS, Oslo, Norway) according to the method modified from Graziani-Bowering and colleagues.[23] Informed consent was obtained from all subjects. The protocol was reviewed and approved by the Ethical Review Committee of the Faculty of Medicine at Chulalongkorn University.

Peripheral blood from healthy subjects aged 18 to 30 was collected in a tube containing ethylenediaminetetraacetic acid (EDTA). OptiPrep (density 1.32 g/ml) was diluted with 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)-buffered saline (HBS) containing 1 mM EDTA and 0.5% bovine serum albumin to obtain 1.078 and 1.068 g/ml solution. The collected blood was mixed with OptiPrep at a ratio of 2.5:1. The mixture was then overlaid with 1.078 g/ml solution, followed by 1.068 g/ml solution and HBS. The tube was centrifuged at 700 xg for 30 minutes at 4°C with a swinging bucket rotor. The monocytes that floated to the top of the 1.068 g/ml layer were collected. The cells were then resuspended in RPMI 1640 medium (Cambrex, Rockland, Maine, USA) supplemented with 10% heat-inactivated FBS, 2 mM glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin.

Experimental conditions

Highly purified LPS from *P. gingivalis* strain 381 was a generous gift from Dr. Robert E. Schifferle (Department of Periodontics and Endodontics, State University of New York at Buffalo, NY, USA).[24] Mangosteen pericarp extract was dissolved in dimethyl sulfoxide (DMSO) (Sigma-Aldrich, St. Louis, MO, USA) and further diluted in

the cell culture medium to obtain the final concentrations. Cells were cultured in 96-well plates at the density of 2 x 10^5 cells/well for RAW 264.7 cells, and 4 x 10^5 cells/well for freshly prepared peripheral blood monocytes. The cells were allowed to attach for 2 hours in an incubator at 37°C with 5% CO_2. The cells were then stimulated with 1 µg/ml LPS in the presence or absence of the extract. Cells received neither LPS nor extract served as a control. DMSO, a solvent for mangosteen extract, was kept at a final concentration of less than 0.5% (w/v),[25] which had no significant effect on cell growth or PGE_2 production (data not shown). After incubation for 24 hours, cell culture medium was collected for measurements of PGE_2 levels. The samples were stored at –20°C until used. The experiments were repeated four times using RAW 264.7 cells from different passages and human monocytes from different subjects.

MTT assay

The effect of mangosteen pericarp extract on cell viability was determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay. The method was previously described.[14] The cell viability was represented as the OD values corrected for the background absorbance from the assay control.

PGE_2 production assay

PGE_2 production was measured by a competitive enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (R&D Systems, Inc, Minneapolis, MN, USA). The assay was performed according to the manufacturer's protocol. The OD was measured at an absorbance of 405 nm using a micro-plate reader (Zenyth 200rt, Anthos Labtec Instruments GmbH, Salzburg, Austria). A standard curve was constructed using a four-parameter logistic curve-fit between OD values and varying concentrations of PGE_2 standard. The PGE_2 concentrations in the samples were then calculated corresponding to the OD values. The assay was performed in duplicate. The detection limit of the assay was <13.4 pg/ml.

Statistical analysis

Statistical analyses were performed by SPSS software (version 10.0; SPSS Inc., Chicago, IL) and SigmaPlot software (version 6.0; SPSS Inc.). Data were presented as means and standard errors. Differences between group means were analyzed by one-way analysis of variance (ANOVA), followed by Dunnett's pairwise comparisons. P values of 0.05 or less was considered significant. The 50% inhibitory concentration (IC_{50}) value of the extract was estimated using four-parameter logistic regression model.

Results

Anti-inflammatory effects on RAW 264.7 cells

Cytotoxic effects of mangosteen pericarp extract on RAW 264.7 cells were determined using MTT assay (Fig. 1A). The group treated with LPS from *P. gingivalis* showed a 1.6-fold increase in the cell viability as compared to the untreated control. In the presence of LPS, there was no significant difference between the groups treated with and without the extract.

The effects of mangosteen pericarp extract on LPS-stimulated production of PGE_2 in RAW 264.7 cells were demonstrated in Fig. 1(B). At baseline, PGE_2 level was almost undetectable. When cells were treated with LPS, the mean PGE_2 level was drastically increased. The extract inhibited PGE_2 production in the LPS-activated RAW 264.7 cells in a concentration-dependent manner. The IC_{50} value of the extract was approximately 0.5 µg/ml.

Anti-inflammatory effects on human peripheral blood monocytes

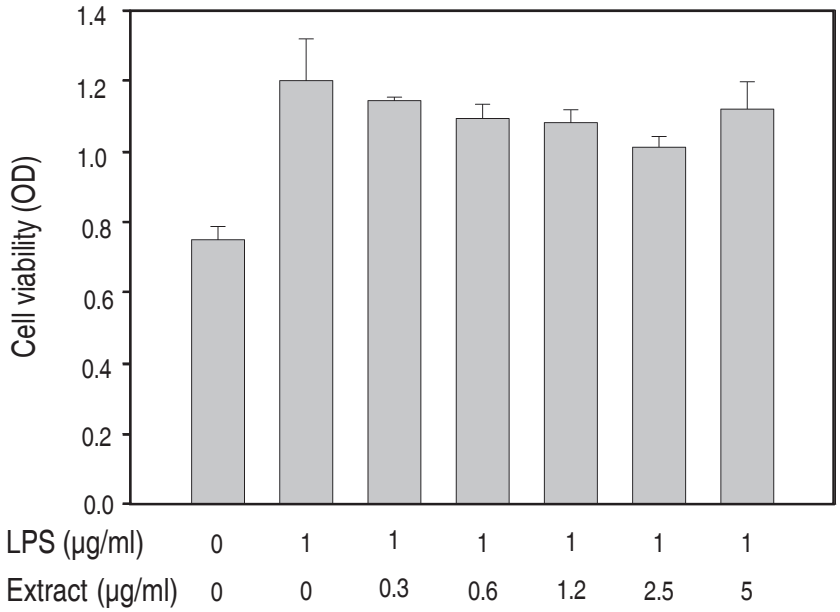
Similar to RAW 264.7 cells, the mangosteen pericarp extract had no significant cytotoxic effects on human peripheral blood monocytes (Fig. 2A). In LPS-activated cells, the extract inhibited PGE_2 synthesis in a concentration-dependent manner (Fig. 2B). However, the concentrations required for significant inhibition of PGE_2 in these cells were slightly higher than those in RAW 264.7 cells. The IC_{50} value for human monocytes was approximately 3.3 µg/ml.

Discussion

PGE_2 produced by monocytes/macrophages upon stimulation with bacterial LPS is involved in the pathogenesis of periodontal disease.[2] Therefore, suppression of PGE_2 would be beneficial in periodontal therapy.[5] Previous studies have shown that the mangosteen pericarp extract had a potent inhibitory effect on Ca^{2+} ionophore-induced and spontaneous PGE_2 synthesis in rat glioma cells.[6,19-21] This study demonstrated that the extract strongly inhibited LPS-induced PGE_2 production in both RAW 264.7 mouse macrophage-like cells and human peripheral blood monocytes as well. The concentrations of the extract that inhibited PGE_2 synthesis had no significant effect on cell viability. Therefore, the inhibitory effect of the mangosteen pericarp extract resulted from its anti-inflammatory activity, not from a reduction in the cell viability.

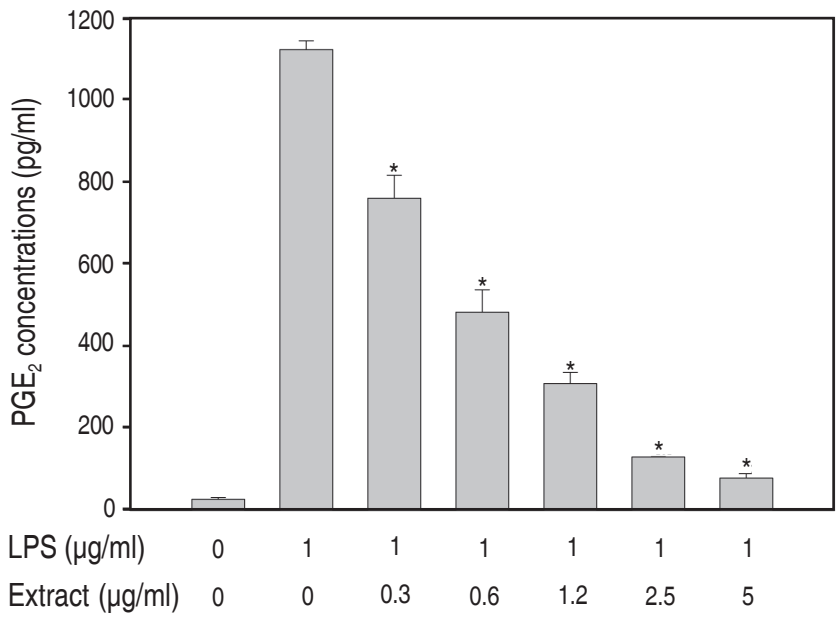
The inhibitory effect of the mangosteen extract on LPS-induced PGE_2 production was concentration-dependent, with the IC_{50} values of 0.5 µg/ml for RAW 264.7 cells and 3.3 µg/ml for peripheral blood monocytes. In a previous study, treatment with the 40% ethanol

Fig. 1(A)



*Indicates the significant difference from the group treated with LPS only at $p < .01$

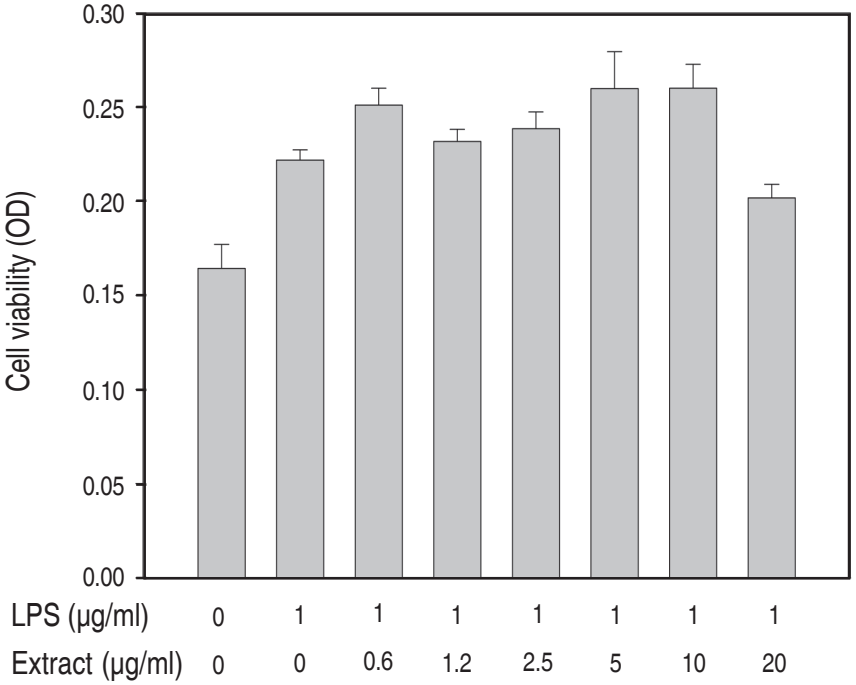
Fig. 1(B)



*Indicates the significant difference from the group treated with LPS only at $p < .01$

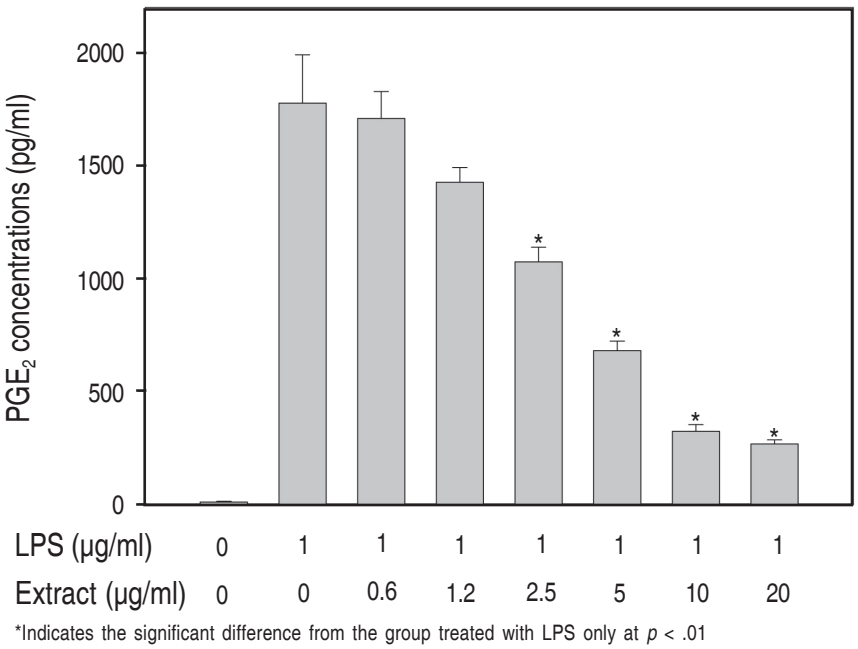
Fig. 1 *Effect of mangosteen pericarp extract on (A) cell viability and (B) LPS-induced PGE_2 production of RAW 264.7 cells. The cells were treated with 1* mg/ml *of LPS only or in combination with the varying concentrations of the extract. Data are expressed as means±standard errors of four independent experiments.*

Fig. 2(A)



*Indicates the significant difference from the group treated with LPS only at $p < .01$

Fig. 2(B)



*Indicates the significant difference from the group treated with LPS only at $p < .01$

Fig. 2 *Effect of mangosteen pericarp extract on (A) cell viability and (B) LPS-induced PGE_2 production of human peripheral blood monocytes. The cells were treated with 1* mg/ml *of LPS only or in combination with the varying concentrations of the extract. Data are expressed as means±standard errors of four independent experiments.*

extract of mangosteen pericarp for 10 minutes was shown to inhibit Ca^{2+} ionophore-induced PGE_2 synthesis in rat glioma cells. Its activity was increased with increasing concentrations, with the IC_{50} value graphically estimated to be 8 μg/ml.[6] Another study used γ-mangostin, a purified compound from mangosteen pericarp extract, and also observed the concentration-dependent inhibitory effect on spontaneous PGE_2 production in rat glioma cells after treatment for 18 hours. The IC_{50} value in this latter study was approximately 0.8 μg/ml.[20] Although a direct comparison cannot be made due to differences in cell types, methods of extract preparation and treatment time, it is evident from these studies that the mangosteen pericarp extract strongly inhibits PGE_2 synthesis in a dose-dependent manner.

The IC_{50} value of the extract for human monocytes was slightly higher than the value for RAW 264.7 cells. The higher concentration required for inhibition of PGE_2 or other inflammatory mediators in human monocytes is not unprecedented. Isoflavones from red clover suppressed PGE_2 synthesis at a concentration range of 1-40 μM for RAW 264.7 cells and 10-100 μM for human monocytes.[8] Extract from *Mallotus japonicus* at the concentration of 10 μg/ml reduced LPS-activated TNF-α production by 40% in RAW 264.7 cells, but only 15% in human monocytes.[7] RAW 264.7 cell line is the most frequently used model to evaluate anti-inflammatory activity because it is easy to handle and has minimal variation between cultures. However, the results from these studies suggest that the human monocytes are also required to confirm the results from RAW 264.7 cells.

Phytochemical studies have shown that the active components of mangosteen pericarp extract belong to a group of xanthone derivatives such as α-, β- and γ-mangostin, gartinin, 1- and 3-isomangostin, etc.[26] Among these, α- and γ-mangostin have been reported to inhibit PGE_2 synthesis.[6,19,20] The chemical components of the extract often vary according to the extraction protocol. When using 40% ethanol as a solvent, the extract contained 10% α-mangostin and 12% γ-mangostin. When ethanol concentration was increased to 100%, the yield of γ-mangostin was increased to 55%.[6] The extract used in this study was prepared using ethyl acetate as a solvent, which was reported to obtain 78-80% α-mangostin and 16% γ-mangostin.[22,27] The high yield of α- and γ-mangostin in the extract may explain its strong anti-inflammatory activity observed in this study.

The mechanisms underlying PGE_2 inhibition by the mangosteen extract have been investigated. The *in vitro* enzyme assay experiments demonstrated that α- and γ-mangostin suppressed PGE_2 synthesis by directly inhibiting the enzymatic activities of both cyclooxygenase-1 (COX-1) and -2 (COX-2).[6,19] In addition, γ-mangostin inhibited inhibitor of κB kinase (IKK) activity, which subsequently prevented nuclear factor-κB (NF-κB)-mediated transcription of COX-2 gene.[20] Therefore, mangosteen pericarp extract appears to inhibit PGE_2 synthesis by blocking COX enzymes at both transcription level and protein level.

Periodontal disease is an inflammatory response to infection by specific bacteria in dental plaque. Most treatment modalities for periodontal disease target either at elimination of dental plaque bacteria or at suppression of inflammatory mediators such as PGE_2. A previous study showed that mangosteen pericarp extract possessed strong antibacterial activity against periodontal pathogens including *Porphyromonas gingivalis* and *Tannerella forsythia*.[18] The minimum inhibitory concentrations (MIC) for these pathogens were 20 and 10 μg/ml, respectively. The results from this study showed that the extract possessed strong anti-inflammatory activity as well. It inhibited LPS-induced PGE_2 synthesis in monocytes/macrophages with the IC_{50} values of 0.5-3.3 μg/ml. Therefore, mangosteen pericarp extract may provide a novel approach for periodontal treatment by concomitantly suppressing both dental plaque bacteria and PGE_2 production.

In conclusion, the extract from mangosteen pericarp strongly inhibited LPS-induced PGE_2 synthesis in monocytes/macrophages in a concentration-dependent manner. The concentrations of the extract that inhibited PGE_2 synthesis had no significant effect on cell viability. The strong anti-inflammatory activity of the extract suggests that it may be useful for the treatment of periodontal disease.

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บทวิทยาการ

ผลของสารสกัดจากเปลือกมังคุดต่อการหลั่งสารพรอสตาแกลนดินอีสองในเซลล์โมโนไซต์/มาโครฟาจ เมื่อถูกกระตุ้นด้วยไลโพพอลิแซคคาไรด์

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บทคัดย่อ

พรอสตาแกลนดินอีสองที่ผลิตจากเซลล์โมโนไซต์/มาโครฟาจ เมื่อได้รับการกระตุ้นด้วยไลโพพอลิแซคคาไรด์ มีส่วนสำคัญในการเกิดโรคปริทันต์ มีรายงานว่าสารสกัดจากเปลือกมังคุดมีคุณสมบัติต้านการอักเสบ โดยสามารถยับยั้งการหลั่งสารพรอสตาแกลนดินอีสองจากเซลล์กลิโอมาของหนูได้ วัตถุประสงค์ของงานวิจัยนี้เพื่อศึกษาผลของสารสกัดต่อการหลั่งสารพรอสตาแกลนดินอีสองในเซลล์มาโครฟาจจากหนู และเซลล์โมโนไซต์จากคน เซลล์เหล่านี้ได้รับการกระตุ้นด้วยไลโพพอลิแซคคาไรด์จากเชื้อพอร์ไฟโรโมแนส จินจิวาลิส ร่วมกับการได้รับสารสกัดจากเปลือกมังคุดที่ความเข้มข้นต่าง ๆ หลังจากนั้น 24 ชั่วโมง จึงทำการวัดระดับพรอสตาแกลนดินอีสอง ด้วยวิธีเอนไซม์ลิงค์ อิมมูโนซอร์เบนท์ แอสเส ผลการศึกษาพบว่าเซลล์ที่ได้รับการกระตุ้นด้วยไลโพพอลิแซคคาไรด์ สามารถผลิตพรอสตาแกลนดินอีสองได้ในปริมาณมาก สารสกัดสามารถยับยั้งการหลั่งพลอสตาแกลนดินอีสองในเซลล์ที่ถูกกระตุ้นได้ โดยมีฤทธิ์มากขึ้นตามความเข้มข้นที่เพิ่มขึ้น ความเข้มข้นของสารสกัดที่มีฤทธิ์ยับยั้งการผลิตพรอสตาแกลนดินอีสองได้ครึ่งหนึ่ง มีค่าประมาณ 0.5 µg/ml สำหรับเซลล์มาโครฟาจจากหนู และมีค่าประมาณ 3.3 µg/ml สำหรับเซลล์โมโนไซต์จากคน จากการศึกษาความเป็นพิษต่อเซลล์พบว่าความเข้มข้นของสารสกัดที่ใช้ไม่มีผลต่อความมีชีวิตของเซลล์อย่างมีนัยสำคัญทางสถิติ การศึกษานี้แสดงให้เห็นว่าสารสกัดจากเปลือกมังคุดมีคุณสมบัติต้านการอักเสบได้ดี ซึ่งอาจนำมาพัฒนาเพื่อใช้ในการรักษาโรคปริทันต์อักเสบได้