



**STUDI PUSTAKA SISTEMATIS:
PENGARUH POLIFENOL DELIMA (*Punica granatum L.*)
TERHADAP KADAR PROSTAGLANDIN E2 PADA SEL
MAKROFAG RAW264.7**

SKRIPSI

Untuk Memenuhi Persyaratan

Memperoleh Gelar Sarjana Kedokteran



Oleh

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**PROGRAM STUDI KEDOKTERAN
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RINGKASAN

Aini, F.D.Q., Fakultas Kedokteran, Universitas Islam Malang, Januari 2021.
Studi Pustaka Sistematis: Pengaruh Polifenol Delima (*Punica granatum L.*) terhadap Kadar Prostaglandin E2 pada Sel Makrofag RAW264.7.
Pembimbing I : Doti Wahyuningsih, Pembimbing II : Anita Puspa Widiyana.

Pendahuluan: *Prostaglandin E2* (PGE2) adalah senyawa yang akan meningkat pada jaringan inflamasi dan berkontribusi memodulasi nyeri. Delima (*Punica granatum L.*) dilaporkan memiliki potensi anti-inflamasi dan anti-nyeri neurogenik. Studi pustaka sistematis (SPS) ini mempelajari potensi anti-inflamasi ekstrak dan senyawa polifenol delima terhadap penurunan kadar PGE2 pada sel makrofag RAW264.7.

Metode Penelitian: Studi pustaka sistematis. Data penelitian dikumpulkan dari PubMed Central, PubMed, dan Google Scholar berdasarkan kata kunci *pomegranate* atau *Punica granatum*, *inflammation*, PGE2, dan sel makrofag RAW264.7. Delapan artikel memenuhi kriteria inklusi dan ditetapkan untuk ditelaah.

Hasil dan Pembahasan: Ekstrak kulit dan bunga delima serta senyawa polifenol dalam buah dan kulit delima terbukti mampu menurunkan kadar PGE2 pada sel makrofag RAW264.7. Aktivitas anti-inflamasi ekstrak kulit dan bunga delima serta senyawa polifenol dalam buah dan kulit delima menurunkan kadar PGE2 melalui hambatan ekspresi *Toll-Like Receptor 4* (TLR4), hambatan aktivasi jalur pensinyalan *Mitogen-Activated Protein Kinase* (MAPK), hambatan aktivasi faktor transkripsi *Nuclear Factor-Kappa B* (NF- κ B), serta hambatan ekspresi dan regulasi enzim COX-2. Data menunjukkan bahwa senyawa polifenol delima menghambat sintesis PGE2 secara dependen.

Simpulan : Senyawa polifenol delima mampu menurunkan kadar PGE2 pada sel makrofag RAW264.7.

Kata Kunci : Delima, Inflamasi, PGE2, Sel Makrofag RAW264.7

SUMMARY

Aini, F.D.Q., Faculty of Medicine, Islamic University of Malang, January 2021.
Systematic Literature Review: The Effect Of Pomegranate (*Punica granatum L.*) Polyphenol to Prostaglandin E2 from RAW264.7 Macrophage Cell
Supervisor I : Doti Wahyuningsih, Supervisor II : Anita Puspa Widiyana.

Pendahuluan: Prostaglandin E2 (PGE2) is a compound reported will increase in inflamed tissue and contributed to modulate pain. Pomegranate (*Punica granatum L.*) has been proved to have an anti-inflammatory property and ability to attenuate neurogenic pain. This systematic literature review studies the anti-inflammation potentation of extract and bioactive compound of pomegranate in decreasing PGE2 in RAW264.7 macrophage cell.

Metode Penelitian: Systematic literature review. Data were collected from PubMed Central, PubMed, and Google Scholar using pomegranate, inflammation, PGE2, and RAW264.7 macrophage cell as the keyword. Eight articles according to the inclusion criteria were chosen to be reviewed.

Hasil dan Pembahasan: Pomegranate peel and flower extracts along with pomegranate fruit and peel polyphenols were proven to decrease PGE2 of RAW264.7 macrophages cell. This pomegranate extracts and polyphenols decrease PGE2 by inhibiting; expression of *Toll-Like Receptor 4* (TLR4), *Mitogen-Activated Protein Kinase* (MAPK) pathway, *Nuclear Factor-Kappa B* (NF- κ B) transcript factor activation, and expression and regulation of COX-2 enzyme. Accordingly, the data showed polyphenol of pomegranate inhibit PGE2 synthesis dependently.

Simpulan : Pomegranate polyphenol has potency to reduce PGE2 in RAW264.7 macrophage cell.

Kata Kunci : Pomegranate, Inflammation, PGE2, RAW264.7 Macrophage Cell

BAB I PENDAHULUAN

1.1 Latar Belakang

Inflamasi atau peradangan merupakan mekanisme imunitas protektif terhadap kerusakan jaringan akibat infeksi, iritasi, maupun injuri yang ditandai dengan munculnya tanda-tanda kardinal yaitu tumor (bengkak), calor (panas), rubor (merah), dolor (nyeri), dan *functio laesa* (gangguan fungsi) (Medzhitov, 2010; Kawahara *et al.*, 2015). Respon inflamasi akan memicu respon seluler dan molekuler yang berkontribusi pada pemulihan homeostasis jaringan (Zhou *et al.*, 2016). Pada kondisi inflamasi, pelepasan sitokin proinflamasi *Interleukin-1 β* (IL-1 β) dan *Tumor Necrosis Factor α* (TNF- α) oleh makrofag akan merangsang pembentukan mediator inflamasi *Prostaglandin E2* (PGE2) (Sprague dan Khalil, 2010).

Sintesis PGE2 secara signifikan akan meningkat pada jaringan yang mengalami inflamasi dan berkontribusi dalam meningkatkan permeabilitas pembuluh darah, menyebabkan vasodilatasi dan migrasi neutrofil ke lokasi injuri sehingga terjadi edema, serta berperan sebagai mediator utama timbulnya nyeri pada berbagai penyakit dengan patofisiologi inflamasi seperti osteoarthritis dan *Inflammatory Bowel Disease* (IBD) (Morimoto *et al.*, 2014; Lee *et al.*, 2013). Berdasarkan implikasi PGE2 pada berbagai penyakit yang melibatkan peradangan dalam patofisiologinya, penghambatan sintesis PGE2 merupakan salah satu modalitas terapi anti-inflamasi potensial yang juga mampu mengurangi rasa nyeri.

Salah satu terapi farmakologi anti-inflamasi yang mampu menghambat sintesis PGE2 dan mengurangi rasa nyeri adalah *Non Steroid Anti-inflammatory Drugs* (NSAIDs), namun penggunaan NSAIDs dalam jangka panjang dapat

menimbulkan efek samping berupa ulkus peptikum, hiperkalemia, perforasi dan perdarahan saluran gastrointestinal, hipertensi, sindrom nefrotik, hingga gagal ginjal kronis (Wongrakpanich *et al.*, 2018). Terapi alternatif yang dapat digunakan sebagai anti-inflamasi dalam jangka panjang dengan efek samping minimal adalah dengan memanfaatkan tanaman herbal. Salah satu tanaman herbal yang dilaporkan memiliki sifat anti-inflamasi dan terbukti mampu menurunkan kadar PGE2 adalah delima (*Punica granatum L.*) (Velagapudi *et al.*, 2015).

Delima (*Punica granatum L.*) merupakan salah satu buah yang disebutkan dalam Al-Qur'an pada surah al-An'am ayat 99 dan 141 serta pada surah ar-Rahman ayat 68. Buah ini banyak dikonsumsi di seluruh dunia dan banyak dimanfaatkan sebagai obat tradisional. Delima kaya akan kandungan polifenol, senyawa yang memiliki manfaat sebagai anti-inflamasi serta memiliki khasiat sebagai antioksidan (Akhtar *et al.*, 2017; Lee *et al.*, 2010). Buah ini juga dilaporkan dapat mengurangi nyeri neurogenik (Jain *et al.*, 2013). Senyawa polifenol dalam kulit, buah, biji, dan bunga delima memiliki sifat anti-inflamasi yang mampu menghambat sintesis sitokin proinflamasi (Colombo *et al.*, 2013). Senyawa polifenol delima seperti *Ellagic Acid*, *Gallic Acid* dan *Punicalagin A&B* telah diteliti mampu menekan ekspresi *Cyclooxygenase-2* (COX-2) dan *Inducible Nitric Oxide Synthase* (iNOS), serta menekan pelepasan PGE2 pada sel makrofag yang diinduksi dengan *Lipopolysaccharide* (LPS) (BenSaad *et al.*, 2017; Xu *et al.*, 2014; Du *et al.*, 2018). Enzim *Cyclooxygenases* (COXs) dan *Microsomal Prostaglandin E Synthase 1* (mPGES-1) mengkatalis pembentukan PGE2 melalui reaksi pemecahan asam arakidonat yang dikeluarkan oleh membran fosfolipid ke sitosol sebagai respon terhadap kerusakan jaringan (Kapoor *et al.*, 2010).

Salah satu metode untuk mengevaluasi potensi anti-inflamasi senyawa polifenol delima adalah dengan menggunakan sel makrofag. Makrofag berperan penting dalam kekebalan tubuh manusia dan merupakan mediator seluler pertama respon imun bawaan atau *innate immune response* pada kondisi peradangan (Carralot *et al.*, 2009; Shi *et al.*, 2009). Selama proses ini, makrofag menghasilkan berbagai jenis mediator inflamasi seperti IL-1 β , TNF- α , *Nitric Oxide* (NO $^{\bullet}$), dan *Prostaglandin* (PG) (Shi *et al.*, 2009). Berdasarkan fakta di atas, peneliti ingin melakukan *Systematic Literature Review* (SLR) atau Studi Pustaka Sistematis untuk memberikan gambaran yang jelas dan komperhensif serta mengkaji lebih dalam potensi polifenol delima sebagai anti-inflamasi dengan menghambat sintesis PGE2 pada sel makrofag RAW264.7 dari berbagai artikel hasil penelitian yang relevan.

1.2 Rumusan Masalah

Apakah kandungan polifenol delima (*Punica granatum L.*) dapat menurunkan kadar PGE2 pada sel makrofag RAW264.7 yang ditinjau dengan metode penelitian *Systematic Literature Review* (SLR)?

1.3 Tujuan Penelitian

Mengetahui potensi kandungan polifenol delima (*Punica granatum L.*) terhadap penurunan kadar PGE2 pada sel makrofag RAW264.7 dari berbagai artikel hasil penelitian yang relevan dengan metode penelitian *Systematic Literature Review* (SLR).

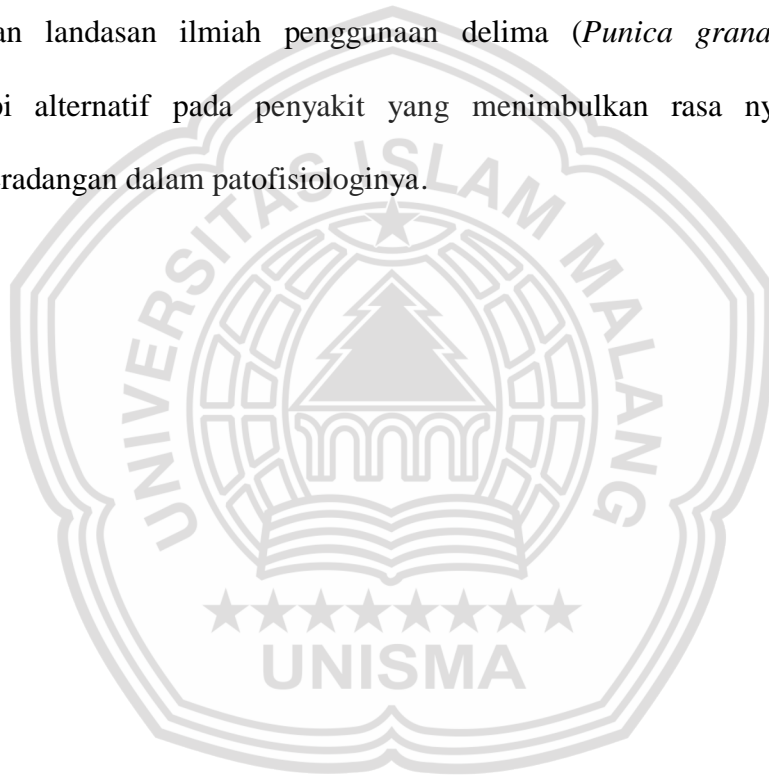
1.4 Manfaat Penelitian

1.4.1 Manfaat Teoritis

Penelitian ini diharapkan dapat menjadi landasan ilmiah penggunaan delima (*Punica granatum L.*) sebagai anti-inflamasi dengan menurunkan kadar PGE2 yang dihimpun dari berbagai literatur dengan metode *Systematic Literature Review* (SLR).

1.4.2 Manfaat Praktis

Memberikan landasan ilmiah penggunaan delima (*Punica granatum L.*) sebagai terapi alternatif pada penyakit yang menimbulkan rasa nyeri dan melibatkan peradangan dalam patofisiologinya.



BAB VII PENUTUP

7.1 Kesimpulan

1. Ekstrak buah, kulit, dan bunga delima (*Punica granatum L.*) serta kandungan polifenol yang ada di dalamnya, antara lain *Punicalagin*, *Punicalagin A&B*, *Ellagic Acid*, *Gallic Acid*, dan *Granatin B*, terbukti mampu menurunkan kadar *Prostaglandin E2* (PGE2) pada sel makrofag RAW264.7 pada kondisi inflamasi.
2. Mekanisme penghambatan PGE2 oleh aktivitas anti-inflamasi ekstrak kulit delima dan senyawa *Punicalagin* ekstrak buah delima diperantarai oleh hambatan COX-2, IL-1 β , NF- κ B dan MAPK serta hambatan jalur TLR-4.
3. Mekanisme penghambatan PGE2 oleh aktivitas anti-inflamasi ekstrak bunga delima diperantarai oleh hambatan COX-2, IL-1 β , NF- κ B dan MAPK.
4. Mekanisme penghambatan PGE2 oleh aktivitas anti-inflamasi senyawa *Granatin B* diperantarai oleh hambatan COX-2.
5. Penghambatan sintesis PGE2 secara dependen dilaporkan oleh aktivitas anti-inflamasi senyawa *Ellagic Acid*, *Gallic Acid*, *Punicalagin A&B*.

7.2 Saran

1. Melakukan penelitian *Systematic Literature Review* (SLR) lanjutan untuk mengetahui potensi anti-inflamasi delima (*Punica granatum L.*) terhadap kadar PGE2 pada penelitian dengan metode *in vivo* serta untuk mengetahui kemampuan delima dalam menghambat nyeri.

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