



**SYSTEMATIC LITERATURE REVIEW : PENGARUH
DELIMA (*Punica granatum L.*) TERHADAP KADAR
MATRIX METALLOPROTEINASE-9 PADA KONDISI
INFLAMASI**

SKRIPSI

Untuk Memenuhi Persyaratan

Memperoleh Gelar Sarjana Kedokteran



Oleh

FIDURROTY BAIDHO

21601101006

**PROGRAM STUDI KEDOKTERAN
FAKULTAS KEDOKTERAN
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RINGKASAN

Baidho, Fidurroty. Fakultas Kedokteran, Universitas Islam Malang, Januari 2021. *Systematic literature review* : pengaruh delima (*Punica granatum L.*) terhadap kadar matrix metalloproteinase-9 pada kondisi inflamasi. Pembimbing 1: Doti Wahyuningsih. Pembimbing 2: Yoyon Arif Martino.

Pendahuluan: Matrix Metalloproteinase-9 (MMP-9) merupakan suatu enzim yang dilaporkan meningkat pada keadaan radang akut maupun kronis. Beberapa penelitian melaporkan, peningkatan kadar MMP-9 dalam tubuh akan menyebabkan komplikasi pada organ vital. Delima (*Punica granatum L.*) dilaporkan memiliki sifat anti inflamasi sehingga mampu menurunkan kadar MMP-9. Zat aktif *ellagitannin, punicalagin, punicalin, ellagic acid, puniced acid* dan *luteolin* dilaporkan mampu menurunkan kadar MMP-9 pada kondisi inflamasi. Tinjauan ini melaporkan pengaruh delima terhadap kadar MMP-9 pada kondisi inflamasi akibat infeksi dan non infeksi dalam penelitian *in vivo* dan *in vitro*.

Metode: *Systematic literature review* mengenai pengaruh delima terhadap kadar MMP-9 pada kondisi inflamasi dilakukan dengan melakukan pencarian data pada Google Scholar, PubMed Central, dan PubMed. Kata kunci yang digunakan adalah “*punica granatum AND inflammation AND MMP-9*”. Dari 953 jurnal, sebanyak 931 jurnal dikecualikan dan terpilih 22 jurnal sesuai dengan kriteria inklusi yang telah ditetapkan antara lain tahun terbit antara 2007-2020, *original article*, terindeks SCOPUS dan dapat diakses secara *full text*.

Hasil: Zat aktif delima *ellagitannins, punicalagin, punicalin, ellagic acid, puniced acid*, dan *luteolin* dilaporkan mampu menurunkan kadar MMP-9 pada kondisi inflamasi. Mekanisme hambatannya yaitu hambatan pada jalur NF-kB, jalur TIMPs, jalur MAPK dan jalur PI3K, serta mampu menurunkan sekresi mediator inflamasi TNF- α dan memicu terjadinya autofagi dan apoptosis.

Kata Kunci : *Pomegranate, Inflammation, MMP-9*

SUMMARY

Baidho, Fidurroty. Faculty of Medicine, Islamic University of Malang, December 2020. Systematic literature review : Effect of *Punica granatum L.* on matrix metalloproteinase-9 serum in inflammation. Supervisor 1: Doti Wahyuningsih. Supervisor 2: Yoyon Arif Martino.

Introduction: Matrix Metalloproteinase-9 (MMP-9) is an enzyme that reported to increase by the acute or chronic inflammation. Some studies reported the increasing of MMP-9 value in the body will affect the vital organ condition. Pomegranate (*Punica granatum L.*) reported to have anti-inflammatory effect so it can decrease the MMP-9. Substance of pomegranate, named *ellagitannin, punicalagin, punicalin, ellagic acid, punicid acid, and luteolin* can decrease the MMP-9 at the inflammation phase. This study aims to report the pomegranate effect on MMP-9 value at the inflammation and non-inflammation phase by in vitro and in vitro study.

Method: *Systematic literature review* about the pomegranate effect on MMP-9 value at the inflammation phase will be conducted by looking for the data in Google Scholar, Pubmed Central, and PubMed. The keyword used is "*punicagranatum AND inflammation AND MMP-9*". In the screening step, 931 journals were excluded and 22 journals were selected according to the inclusion criteria, the year published between 2007-2020, original article, detected SCOPUS and can be accessed in full text.

Result: *Ellagitannins, punicalagin, and punicalin, ellagic acid, punicid acid, and luteolin*, substance of pomegranate, reported to decrease MMP-9 value at inflammation phase. The inhibiting mechanism of NF-kB, TIMPs, MAPK, PI3K, decreases the secretion of the inflammatory mediator TNF- α and causes autophagy and apoptosis.

Keyword : *Pomegranate, Inflammation, MMP-9*

BAB I

PENDAHULUAN

1.1 LATAR BELAKANG

Penyakit infeksi dan non infeksi dilaporkan didasari atau diawali oleh mekanisme radang ((Parks *et.al*, 2014). Mekanisme radang pada penyakit infeksi dipicu oleh beberapa patogen antara lain bakteri, jamur, parasit atau virus, sedangkan pada penyakit non infeksi dipicu oleh beberapa penyakit seperti halnya penyakit degeneratif, kanker, dan penyakit lain yang dapat menimbulkan kondisi radang (Baud *et.al.*, 2009). Dalam proses ini terjadi peningkatan sitokin proinflamasi yang dapat meningkatkan MMP-9 (Korochina *et al.*, 2016).

Matrix Metalloproteinase (MMPs) merupakan peran utama dalam proses inflamasi (Sternlicht & Werb, 2011). Terlepasnya MMPs dapat dijadikan sebagai parameter telah terjadi produksi sitokin proinflamasi yang akan mengakibatkan kondisi peradangan dalam tubuh. Terdapat banyak jenis MMPs yang memiliki kesamaan dalam strukturnya dan berbeda pada kekhususan substratnya. Salah satu jenis dari MMPs adalah MMP-9 (Manicone *et.al*, 2008). Beberapa penelitian menyebutkan kadar MMP-9 meningkat pada penyakit radang baik akut maupun kronis, penyakit tersebut antara lain hipertensi, aterosklerosis, gastritis, rheumatoid arthritis, hingga malaria (Ahmed *et al*, 2017; Wahyuningsih *et al.*, 2020; Gomez *et al.*, 2020).

Peningkatan MMP-9 diperantarai oleh terlepasnya kandungan protease pada neutrofil ataupun melalui mekanisme makrofag yang mensekresikan sitokin TNF- α .

Sebuah penelitian melaporkan saat kadar MMP-9 meningkat dalam tubuh yang ditemukan pada penyakit radang sendi, hal tersebut akan mempengaruhi kondisi jantung. Gangguan sirkulasi mikro yaitu insufisiensi vascular perifer berat yang terjadi pada radang sendi, selanjutnya berpengaruh pada hemodinamik sentral yang akan mengakibatkan komorbiditas gagal jantung kronik (Korochina *et al.*, 2016). Penelitian lain juga melaporkan bahwa kadar MMP-9 tinggi pada penyakit akut pankreatitis, selanjutnya akan disertai dengan penurunan kapasitas pernapasan yang menandakan adanya komplikasi pada paru (Keck *et al.*, 2006).

Allah SWT menurunkan air hujan dan kemudian air tersebut yang menumbuhkan berbagai tanaman di muka bumi, salah satu tanaman tersebut adalah buah delima. Dan sesungguhnya demikian tersebut mengandung tanda-tanda kekuasaan Allah (QS. Al-Anam ayat 99 dan 141). Sehubungan dengan hal tersebut, banyak penelitian melaporkan bagian dari buah delima memiliki kandungan yang bermanfaat untuk pengobatan (Rajan *et al.*, 2011). *Ellagitannins*, *punicallagin*, *punicalin* merupakan senyawa fenolik utama yang terdapat pada kulit, biji ataupun sari dari buah delima berperan sebagai antioksidan dan anti *inflamasi* dengan menghambat pembentukan *Reactive Oxygen Species* (ROS) dan sitokin pro inflamasi (Rahmani *et al.*, 2017; Newman *et al.*, 2014). Senyawa tersebut bekerja dengan menghambat mitogen-38 dan mengaktifkan protein kinase jalur (p38-MAPK dan NF-KB). Molekul p38-MAPK dan NF-KB membantu mengaktifkan sel B dan berhubungan dengan peningkatan ekspresi gen MCP1, COX-2, IL-1 β , TNF- α , dan iNOS (Camp *et al.*, 2013). Satu penelitian melaporkan bahwa delima merah yang

digunakan dalam penelitian tidak ditemukan efek sitotoksitasnya atau masih dalam kategori tidak beracun (BenSaad, 2017).

Oleh karena dilaporkan banyak peningkatan kadar MMP-9 pada berbagai kondisi inflamasi dan pengaruh delima sebagai anti inflamasi, sehingga banyak penelitian dilakukan untuk menguji pengaruh delima terhadap penurunan kadar MMP-9 pada kondisi inflamasi. Namun, dalam pelaporan hasilnya masih terdapat perbedaan. Beberapa penelitian menunjukkan adanya pengaruh delima dalam menurunkan kadar MMP-9 pada kondisi inflamasi dan penelitian lain menunjukkan hasil penurunan yang tidak signifikan. Tujuan dari penelitian *systematic literature review* ini adalah untuk mengkaji dan membuktikan hasil riset kemampuan delima terhadap kadar MMP-9 pada kondisi inflamasi sebagai dasar teori pengetahuan dan dasar terapi pengobatan alternatif.

1.2 Rumusan Masalah

Apakah *systematic literature review* yang dilakukan mampu membuktikan pengaruh delima (*Punica granatum L.*) dapat menurunkan kadar Matrix Metalloproteinase-9 pada kondisi inflamasi?

1.3 Tujuan Penelitian

Systematic literature review ini membuktikan pengaruh delima (*Punica granatum L.*) menurunkan kadar Matrix Metalloproteinase-9 pada kondisi inflamasi.

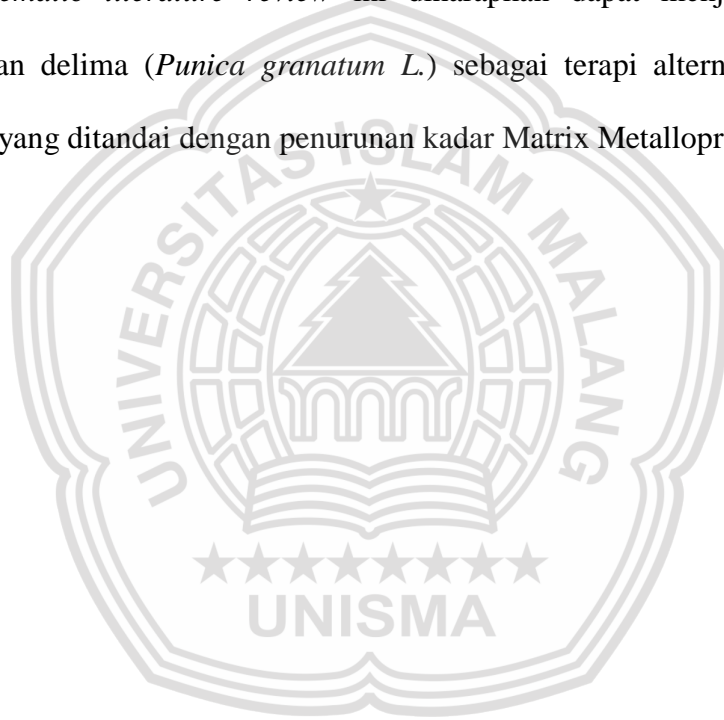
1.4 Manfaat Penelitian

1.4.1 Manfaat Teoritik

Systematic literature review ini diharapkan dapat memberikan dasar teoritis delima (*Punica granatum L.*) terhadap penurunan kadar Matrix Metalloproteinase-9 pada kondisi inflamasi.

1.4.2 Manfaat Praktis

Systematic literature review ini diharapkan dapat menjadi dasar ilmiah penggunaan delima (*Punica granatum L.*) sebagai terapi alternatif pada kondisi inflamasi yang ditandai dengan penurunan kadar Matrix Metalloproteinase-9.



BAB VII

KESIMPULAN DAN SARAN

1.1 KESIMPULAN

Ekstrak daun, ekstrak kulit, ekstrak buah, bubuk, dan jus delima (*Punica granatum L.*) dilaporkan memiliki kandungan zat aktif polifenol *ellagitannin*, *punicallin*, dan *punicallagin*. Selain itu, dilaporkan juga terdapat zat aktif lain dalam delima (*Punica granatum L.*) yaitu *ellagic acid*, *punicid acid*, dan *luteolin*. Zat aktif tersebut diatas yang dilaporkan berperan sebagai anti inflamasi dan mampu menurunkan kadar MMP-9 pada kondisi inflamasi.

1.2 SARAN

1. Melakukan penelitian *systematic literature review* mengenai mekanisme NF-kB terhadap lepasnya MMP-9 pada kondisi inflamasi.

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