



SYSTEMATIC LITERATURE REVIEW :

**PENGARUH POLIFENOL DELIMA (*Punica granatum L.*)
TERHADAP KADAR *INTERLEUKIN-6* PADA PENYAKIT
YANG MELIBATKAN PATOFISIOLOGI INFLAMASI**

SKRIPSI

Untuk Memenuhi Persyaratan

Memperoleh Gelar Sarjana Keokteran



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PROGRAM STUDI KEDOKTERAN

FAKULTAS KEDOKTERAN

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ABSTRAK

Pendahuluan: Interleukin-6 (IL-6) merupakan salah satu dari sitokin yang dikeluarkan oleh makrofag dan sel patologis yang memiliki peran utama dalam memediasi peradangan. Delima (*Punica granatum l.*) mengandung senyawa polifenol seperti *punicalagin*, *ellagic acid*, *urolithin*, *gallic acid* dan *delphinidin* yang memiliki aktifitas tinggi anti inflamasi. Sejauh ini, yang banyak diteliti dan dikaji adalah kemampuan delima terhadap penurunan kadar IL-6 pada satu jenis penyakit saja. Tinjauan pustaka *systematic literature review* ini melaporkan pengaruh polifenol delima terhadap penurunan kadar IL-6 pada sel makrofag dan sel patologis lain menggunakan metode *in vitro* yang berfokus pada penyakit yang patofisiologinya melibatkan inflamasi yang meliputi *alzheimer's disease*, *inflammatory bowel disease*, kanker, penyakit metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosclerosis.

Metode: *Systematic literature review*. Data (artikel) dicari pada Google Scholar dan PubMed Central. Kata kunci yang digunakan adalah "*punica granatum*, *inflammation*, *interleukin-6*, *in-vitro*" terpilih 19 jurnal sesuai dengan kriteria inklusi yang melaporkan pengaruh delima (*Punicagranatum l.*) terhadap IL-6.

Hasil: Zat aktif *punicalagin*, *ellagic acid*, *gallic acid*, *urolithin A/B*, *granatin A/B* dan *delphinidin* dari bunga, biji, kulit, mesocarp (kulit dalam) dan keseluruhan buah delima terbukti mampu menurunkan kadar IL-6 pada penyakit dengan patofisiologi inflamasi yang meliputi penyakit seperti *inflammatory bowel disease* dan *alzheimer's*, kanker, penyakit metabolik dan degeneratif antara lain rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosclerosis.

Kata Kunci: *Punica granatum*, *Inflammation*, *Interleukin-6*, *in vitro*

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Keyword: *Punica granatum*, *Inflammation*, *Interleukin-6*, *in vitro*

SYSTEMATIC LITERATURE REVIEW:**THE EFFECT OF POMEGRANATE'S (*Punicagranatum L.*) POLYPHENOL TO INTERLEUKIN-6 LEVEL IN DISEASE INVOLVING INFLAMMATION PATOPHYSIOLOGY**

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ABSTRACT

Introduction: Interleukin-6 (IL-6) is one of the cytokines released by macrophage and pathologic cells it has a main role in mediating inflammation. Pomegranate (*Punica granatum l.*) contain polyphenol such as *punicalagin*, *ellagic acid*, *urolithin*, *gallic acid*, and *delphinidin* which has high anti-inflammation activity. Research done this far is the ability of pomegranate to decrease IL-6 level in only one disease. This systematic literature review reports the effect of pomegranate's polyphenol in decreasing IL-6 level on macrophage and other pathologic cells by *in vitro* method focus at inflammatory disease that includes *alzheimer's*, *inflammatory bowel disease*, cancer, metabolic disease and degenerative disease such as rheumatoid arthritis, osteoarthritis, osteoporosis, and atherosclerosis.

Method: Systematic literature review. Data were collected from Google Scholar and PubMed Central. The keywords used are "*punica granatum*, *inflammation*, *interleukin-6*". 19 papers which fulfilled the inclusion criteria reported the effect of pomegranate (*Punicagranatum l.*) to IL-6.

Result: Active substance like *punicalagin*, *ellagic acid*, *gallic acid*, *urolithin A/B*, *granatin A/B* and *delphinidin* from the flower, seed, skin, mesocarp (inner skin) and all parts of pomegranate are reported to decrease the interleukin-6 (IL-6) level in diseases involving inflammation pathophysiology, which include inflammatory disease such as inflammatory bowel disease and *alzheimer's*, cancer, metabolic disease and degenerative disease include rheumatoid arthritis, osteoarthritis, osteoporosis, and atherosclerosis.

Keyword: *Punica granatum*, *Inflammation*, *Interleukin-6*, *In Vitro*

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BAB I

PENDAHULUAN

1.1 LATAR BELAKANG

Punica granatum l. di Indonesia sering dikenal dengan buah delima dan telah banyak di gunakan oleh masyarakat untuk obat tradisional (Shaygannia *et al.*, 2015). *Punica granatum l.* terbukti memiliki komponen senyawa tinggi polifenol seperti *punicalagin*, *ellagic acid*, *urolithin*, *galic acid* dan *delphinidin* (Cao *et al.*, 2019). Dalam studi epidemiologis melaporkan bahwa asupan buah yang memiliki kandungan kaya polifenol mampu melindungi terhadap penyakit arthritis, diabetes miletus, penyakit neurodegeneratif dan kanker (Cao *et al.*, 2019). Sehubungan hal itu *Punica granatum l.* memiliki banyak khasiat untuk obat anti inflamasi (Shaygannia *et al.*, 2015).

Penelitian melaporkan bahwa kandungan polifenol pada *Punica granatum L.* dapat menurunkan ekspresi gen inflamasi dan produksi *IL-6* dan *IL-8* (Miguel, *et al.*, 2010). *Ellagic acid* yang merupakan senyawa polifenol dilaporkan mampu menurunkan ekspresi dari *NF-kB*, *COX-2*, *iNOS*, dan *IL-6* pada kanker kolon tikus yang di induksi oleh 1,2 – *Dimethylhydrazine* (Umesalma dan Sudhandiran, 2010). Studi lain yang di lakukan oleh Pratiwi dan Cahya, 2013 membuktikan bahwa pemberian dosis 18mg/hari senyawa polifenol mampu menghambat dari kenaikan kadar serum *IL-6* pada tikus wistar jantan.

Interleukin-6 merupakan salah satu jenis sitokin yang dikeluarkan oleh makrofag memiliki peran utama dalam memediasi sistim peradangan dan *IL-6*

dapat dijadikan sebagai *marker* tanda terjadinya suatu inflamasi (Jayanta, *et al*, 2012). *Interleukin 6* pada saat terjadi inflamasi akan mengaktifkan jalur *JAK-STAT3* untuk menginduksi terjadinya suatu peradangan, proliferasi sel, metastatis dan angiogenesis (Taniguchi K dan Karin M, 2014), ketika *Interleukin-6* menuju ke sel hepatosit akan mampu menaikkan kadar *CRP*, pada jaringan *synovial IL-6* akan menginduksi kenaikan *RANKL* untuk menaikkan fungsi osteoklas dan menginduksi kenaikan *angiogenesis* (Toshio *et al.*, 2014). Sehubungan dengan laporan hasil tersebut maka *IL-6* menjadi fokus utama untuk target terapi antiinflamasi dalam penyakit yang berpatofisiologi radang (Tanaka *et al.*, 2016).

Penelitian *in vitro* melaporkan model penyakit yang berpatofisiologi radang telah ditemukan adanya peningkatan pada kadar *interleukin-6* (Sergent *et al.*, 2010). Penelitian oleh Mastrogiovanni F, *et al.*, 2019 melaporkan bahwa pada sel *Caco-2* model peradangan colon telah terjadi kenaikan kadar *IL-6* setelah distimulasi dengan *lipopolysakarida* (LPS). Penelitian lain mengenai inflamasi disease menggunakan sel *makrofag RAW 264,7* dikarenakan sel makrofag *RAW264,7* akan menginisiasi munculnya respon inflamasi mengaktifkan sitokin *IL-6* melalui jalur *NF-kB* (Liu *et al.*, 2017). *Punica granatum l.* memiliki kandungan senyawa kaya akan polifenol seperti *punicalagin*, *ellagic acid*, *urolithin*, *galic acid* dan *delphinidin* yang memiliki aktifitas tinggi anti inflamasi (Shaygannia *et al.*, 2015). Sehubungan dengan uraian diatas sejauh ini, yang banyak diteliti dan dikaji adalah kemampuan delima terhadap penurunan kadar *IL-6* pada satu jenis penyakit saja.

Tinjauan pustaka *systematic literature review* ini melaporkan pengaruh polifenol delima terhadap penurunan kadar *IL-6* pada sel *Caco-2*, makrofag *RAW*, *BV-2*, *MCF-7*, *HepG2*, *3T3-L1*, *3T3-E1*, sel kondrosit, *MH-7A*, *HUVEC*

menggunakan metode *in vitro* yang berfokus pada penyakit yang patofisiologinya inflamasi. Penyakit dengan patofisiologi inflamasi yang akan dibahas yakni penyakit alzheimer's disease, inflammatory bowel disease, kanker, penyakit metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosclerosis, yang angka kejadian penyakitnya masih terbilang tinggi.

1.2 Rumusan Masalah

Apakah *Systematic literature review* yang akan dilakukan membuktikan bahwa kemampuan polifenol *Punica granatum l.* mampu menurunkan kadar *Interleukin-6 (IL-6)* pada penyakit dengan patofisiologi melibatkan inflamasi yang berfokus pada penyakit golongan inflamasi disease meliputi alzheimer's disease, inflammatory bowel disease, kanker, penyakit metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosclerosis?

1.3 Tujuan Penelitian

Membuktikan kemampuan polifenol *Punica granatum l.* mampu menurunkan kadar *Interleukin-6 (IL-6)* pada penyakit dengan patofisiologi melibatkan inflamasi berfokus pada penyakit golongan inflamasi disease meliputi alzheimer's disease, inflammatory bowel disease, kanker, penyakit metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosclerosis yang di kaji melalui berbagai *literature review* jurnal.

1.4 Manfaat Penelitian

1.4.1 Manfaat Teoritik

Systematic literature review diharapkan dapat memberikan dasar teoritis pemanfaatan polifenol *Punica granatum* terhadap penurunan kadar *Interleukin-6* pada penyakit dengan patofisiologi melibatkan inflamasi yang berfokus pada penyakit golongan inflamasi disease meliputi alzheimer's disease, inflammatory bowel disease, kanker, penyakit metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosklerosis.

1.4.2 Manfaat Praktis

Systematic literature review ini diharapkan dapat menjadi dasar ilmiah penggunaan *Punica granatum* sebagai obat bagi penyakit golongan inflamasi disease meliputi alzheimer's disease, inflammatory bowel disease, kanker, penyakit metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosklerosis yang patofisiologinya melibatkan proses inflamasi dan mengakibatkan peningkatan *Interleukin-6*.



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BAB VII

KESIMPULAN DAN SARAN

7.1 Kesimpulan

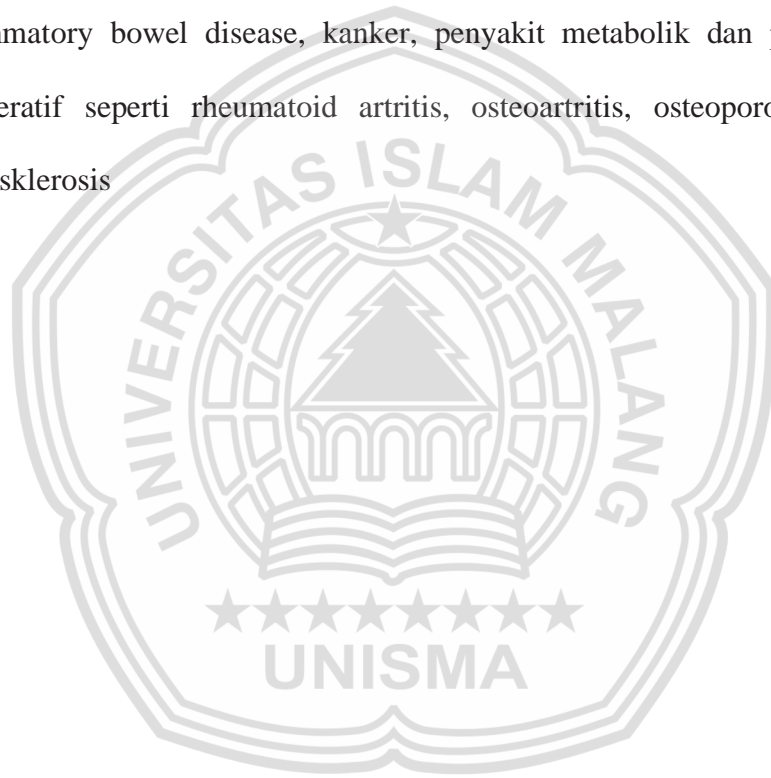
1. Uji *in vitro* menggunakan sel Caco-2, makrofag RAW, BV-2, MCF-7, HepG2, 3T3-L1, 3T3-E1, sel kondrosit, MH-7A, HUVEC terhadap ekstrak buah, kulit, bunga, dan biji delima (*Punica granatum l.*) serta kandungan polifenol yang ada di dalamnya, antara lain *punicalagin*, *ellagic acid*, *gallic acid*, *urolithin A/B*, *granatin A/B* dan *delphinidin* terbukti mampu menurunkan kadar Interleukin-6 (IL-6) pada penyakit dengan patofisiologi inflamasi yang meliputi *alzheimer's disease*, *inflammatory bowel disease*, kanker, penyakit metabolik dan penyakit degeneratif seperti *rheumatoid arthritis*, *osteoarthritis*, *osteoporosis* dan *atherosklerosis*.
2. Penghambatan *IL-6* oleh aktivitas anti-inflamasi oleh produk turunan *Punica granatum l.* diperantarai melalui hambatan pada marker *NF-kB*, *p-65* dan *ikkb* kemudian hambatan pada jalur *JNK*, hambatan pada *NO*, hambatan pada jalur *TLR-4*, hambatan pada jalur *STAT-3*, hambatan dari ekspresi gen *CCL-3*, *CCL-4* dan hambatan pada *monocyte adhesion*.

7.2 SARAN

1. Melakukan penelitian *systematic literature review* (SLR) lanjutan mengenai uji *in-vivo* untuk mengetahui efektifitas dosis yang aman dan uji toksisitas dari polifenol *Punica granatum l.* terhadap penurunan kadar *interleukin-6* (*IL-6*) pada penyakit dengan patofisiologi inflamasi yang meliputi *alzheimer's disease*, *inflammatory bowel disease*, kanker, penyakit

metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosklerosis

2. Melakukan penelitian lanjutan mengenai uji in-vivo menggunakan hewan coba untuk di kembangkan dengan meninjau dari hasil peneletian sebelumnya yang kurang efektif dalam potensi polifenol Punica granatum l. terhadap penurunan kadar interleukin-6 (IL-6) pada penyakit dengan patofisiologi inflamasi dengan pilihan penyakit alzheimer's disease, inflammatory bowel disease, kanker, penyakit metabolik dan penyakit degeneratif seperti rheumatoid arthritis, osteoarthritis, osteoporosis dan atherosklerosis



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