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**Lampiran 1. Tabel uji praklini secara in vivo**

No	Bagian yang digunakan	Tipe ekstrak dan metode ekstraksi	Pelarut	Dosis efektif	Kandungan kimia	Mekanisme kerja	Hasil	Referensi
1.	Akar	Ekstrak etanol dengan metode maserasi	Etanol 70%	Tidak ada	Flavonoid, alkaloid, asparagin, dan glutamin	Flavonoid menghalangi aksi xantin oksidase yang terjadi melalui mekanisme inhibisi kompetitif serta interaksi enzim dalam gugus samping	Suspensi ekstrak akar seledri dengan dosis 50 mg/kgBB, 100 mg/kgBB, 200 mg/kgBB tidak memiliki efektivitas sebagai antihiperurisemia pada tikus putih jantan	(Subagja <i>et al.</i> , 2021)
2.	Daun	Ekstrak etanol dengan metode maserasi	Etanol 96%	50 mg/kgBB	Alkaloid, flavonoid, saponin, tanin	Alkaloid memiliki efek penghambatan sintesis serta melepas leukotriene, flavonoid sebagai penghambat aktivitas xantin oksidase, saponin menurunkan aksi enzim xantin oksidase dan tanin menghambat radikal bebas saat proses purin	Dosis efektif ekstrak etanol daun seledri yang mampu menurunkan kadar asam urat yaitu 50 mg/kgBB	(Rakanita <i>et al.</i> , 2017)

						berubah menjadi asam urat		
3.	Herba	Ekstrak air dengan metode seduhan	Air	1,8 g/ 1,5 kgBB	Flavoniod, apigenin, apiin, saponin, dan tanin	Flavonoid, apigenin, apiin, saponin, dan tanin bekerja dengan menghalangi aktivitas xantin oksidase	Dosis efektif seduhan serbuk herba seledri yang memiliki aksi menjadi agen antihiperurisemia yaitu 1,8 g/ 1,5 kgBB pada kelompok 3 sebab mempunyai efek yang sebanding dengan allopurinol (kontrol positif)	(Kristyani, 2019)
4.	Daun	Tidak ada	Tidak ada	10mg/200grBB	Tidak ada	Tidak ada	Dosis efektif ekstrak daun seledri yang mampu mengurangi kadar asam urat rata-rata sebesar 5.047 mg/dl (p=0.000) yaitu 10 mg/200 grBB.	Fitriani <i>et al.</i> , 2018)
5.	Herba	Ekstrak etanol dengan metode maserasi	Etanol 70%	25 mg/ kgBB	Flavonoid dan apigenin	Menghalangi kerja enzim xantin oksidase	Fraksi air herba seledri dengan dosis 12,5 mg/kgBB, 25 mg/kgBB dan 50 mg/kgBB mampu mengurangi kadar asam urat pada darah mencit	(Juwita <i>et al.</i> , 2014)
6.	Daun	Ekstrak air dengan metode seduhan	Air	50 mg/ kgBB	flavonoid dan 3-n	flavonoid dan 3-n butilphtalide (3nB)	Seduhan seledri pada dosis 50 mg/ kgBB, 100	(Deviandra <i>et al.</i> , 2013

					butilphtalide (3nB)	menghalangi kerja dari enzim xantin oksidase sehingga mengurangi kadar asam urat dalam serum	mg/kgBB dan 150 mg/ kgBB mampu menurunkan kadar asam urat sedangkan penurunan kadar asam urat terendah yaitu pada dosis 150 mg/kgBB	
7.	Biji	Ekstrak air biji seledri dengan metode maserasi dan ekstrak minyak dengan sistem ekstraksi karbon dioksida superkritis	Air suling	Air pada dosis 50 mg/kgBB sedangkan pada minyak 0,039 ml/kgBB	flavonoid	Menghambat aktivitas xantin oksidase	Ekstrak air biji seledri pada dosis rendah dan tinggi (50 mg dan 200 mg/kgBB) serta ekstrak minyak biji seledri pada dosis rendah dan tinggi (0,039 ml dan 0,155 ml/kgBB) mampu dalam menurunkan kadar asam urat pada mencit dan mengurangi pembengkakan pada sendi gout	(Shaopengli <i>et al.</i> , 2019)
8.	Daun	Ekstrak air dan ekstrak etanol	Air suling dan etanol absolut	5 g/ kg	Flavonoid	Menghalangi aktivitas xantin oksidase	Pada dosis 5g/kg ekstrak daun seledri baik ekstrak air maupun ekstrak etanol mampu menurunkan kadar asam urat pada tikus	(Rahman dan elhak, 2015)

9.	Seluruh bagian tanaman	Ekstrak hidroalkohol dengan metode maserasi	Etanol 70%	500 mg/kgBB	Flavonoid, apiin, dan apigenin	Flavonoid, apiin, dan apigenin menghalangi aksi dari xantin oksidase secara reversibel dengan menempati pusat katalik enzim	Ekstrak seledri secara signifikan mampu menurunkan kadar asam urat pada tikus hiperurisemia tergantung dosis yang digunakan. Pada dosis 500 mg/kgBB ekstrak seledri memiliki efek yang sebanding dengan allopurinol (kontrol positif)	(Dolati <i>et al.</i> , 2018)
10.	Seluruh bagian tanaman	Ekstrak air seledri metode sentrifugasi	Etanol 70%	500 mg/kgBB	Flavonoid	Menghalangi aktivitas xantin oksidase	Ekstrak seledri pada dosis 500 mg/kgBB mampu menurunkan kadar asam urat pada serum	(Soliman <i>et al.</i> , 2020)

**Lampiran 2. Tabel uji praklinis secara in vitro**

No	Bagian yang digunakan	Tipe ekstrak dan metode ekstraksi	Pelarut	Dosis efektif	Kandungan kimia	Mekanisme kerja	Hasil	Referensi
1.	Batang dan daun	Ekstrak air dengan metode infudasi	Air bebas mineral	Tidak ada	Flavonoid dan alkaloid	Flavonoid menghambat aktivitas dari enzim xantin oksidase sedangkan alkaloid menghambat sintesis dan pelepasan leukotrien sehingga menghilangkan rasa nyeri	Ekstrak infusa air batang seledri memiliki aktivitas penghambatan yang lebih baik terhadap enzim xantin oksidase dibandingkan dengan ekstrak infusa daun seledri. Persentase hambat terbaik dari ekstrak infusa air batang seledri adalah $90,25\% \pm 1,27$ pada konsentrasi ekstrak 20% dan persentase penghambatan terbaik dari ekstrak infus daun seledri adalah $69,07\% \pm 1,39$ pada konsentrasi 20%	(Zumamah <i>et al.</i> , 2018)
2.	Batang	Ekstrak air dengan metode infudasi	Air	Tidak ada	Flavonoid	Menghambat aktivitas dari enzim xantin oksidase	Penambahan infusa batang seledri berpengaruh terhadap parameter kinetik enzim xantin oksidase yang ditandai dengan perubahan nilai pada grafik langmuir dari 90,00 ppm dan 3,51 U/mL menjadi 125,42 ppm dan 2,97 U/mL setelah penambahan infusa batang seledri	(Martha <i>et al.</i> , 2018)

3.	Daun dan batang	Ekstrak hidroetanol dengan metode sokletasi	Hidroetanol	Tidak ada	Flavoniod	Mempengaruhi kinetika dari enzim xantin oksidase sehingga menghambat aktivitas dari enzim xantin oksidase	Ekstrak hidroetanol daun seledri menunjukkan inhibisi terbaik sebesar 86.86% (konsentrasi 30%) dan ekstrak hidroetanol batang seledri menunjukkan inhibisi terbaik sebesar 87.71% (konsentrasi 40%)	(Zumamah <i>et al.</i> , 2018)
4.	Akar dan Herba	Ekstrak air dan ekstrak etanol dengan metode maserasi	Air dan etanol	Tidak ada	Flavonoid seperti apigenin dan alkaloid	Flavonoid seperti apigenin bekerja dengan menghambat aktivitas dari enzim xantin oksidase sedangkan alkaloid menghambat sintesis dan pelepasan leukotrien sehingga menghilangkan rasa nyeri	Uji enzimatis menunjukkan bahwa fraksi 4 merupakan fraksi dengan daya hambat tertinggi dengan persen penghambatan sebesar 88,62%, diikuti oleh fraksi 5 dengan persen penghambatan sebesar 85,44%	(Iswantini <i>et al.</i> , 2012)
5.	Batang dan daun	Ekstrak etanol metode maserasi	Etanol 70%	Tidak ada	Flavonoid	Menghalangi aksi dari enzim xantin oksidase	Kinetika penghambatan fraksi menyebabkan kenaikan $K_m$ dan tidak berubahnya $V_m$ dengan jenis penghambatan kompetitif.	(Iswantini <i>et al.</i> , 2012)

## Lampiran 3. Jurnal 1

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12

**EFEKTIVITAS ANTIHIPERURISEMIA SUSPENSII EKSTRAK AKAR SELEDRI  
 (*Apium graveolens L.*) TERHADAP TIKUS PUTIH JANTAN (*Rattus norvegicus*)  
 YANG DIINDUKSI KALIUM BROMAT**

**THE EFFECTIVENESS OF ANTIHIPERURISEMIA SUSPENSION OF  
 CELERY ROOT EXTRACT (*Apium graveolens L.*) ON MALE WHITE  
 MICE (*Rattus norvegicus*) INDUCED BY POTASSIUM BROMAT**

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### ABSTRAK

Telah dilakukan penelitian yang berjudul "Efektivitas Antihiperurisemia Suspensi Ekstrak Akar Seledri (*Apium graveolens L.*) Terhadap Tikus Putih Jantan (*Rattus norvegicus*) Yang Diinduksi Kalium Bromat". Penelitian ini bertujuan untuk mengetahui efektivitas antihiperurisemia suspensi ekstrak akar seledri (*Apium graveolens L.*) terhadap tikus putih jantan dan pada dosis tertentu suspensi ekstrak akar seledri (*Apium graveolens L.*) memberikan efektivitas antihiperurisemia dibandingkan dengan kontrol positif.

Sebanyak 15 ekor tikus dibagi menjadi 5 kelompok selama 21 hari. Kelompok 1 diberikan kontrol positif Allopurinol dan kelompok 2 diberikan kontrol negatif basis suspensi. Kelompok 3, 4, dan 5 masing-masing diberikan suspensi ekstrak akar seledri dengan dosis yang berbeda-beda 50mg/kgBB, 100mg/kgBB, dan 200mg/kgBB secara peroral. Semua kelompok diinduksi dengan Kalium Bromat dosis 22,2mg/200gram BB. Pengukuran kadar asam urat dilakukan pada minggu ke 1, ke 2, dan ke 3. Jenis penelitian yang digunakan adalah eksperimen dan analisa data menggunakan ANAVA satu arah dan dilanjutkan uji T.

Hasil penelitian menunjukkan bahwa sediaan suspensi ekstrak akar Seledri (*Apium graveolens L.*) dengan dosis : 50 mg/kgBB, 100 mg/kgBB, dan 200 mg/kgBB tidak memiliki efektivitas sebagai antihiperurisemia terhadap tikus putih jantan.

**Kata Kunci** : akar seledri, antihiperurisemia, suspensi, tikus



## Lampiran 4. Jurnal 2

**EFEKTIVITAS ANTIHIPERURISEMIA EKSTRAK ETANOL DAUN SELEDRI (EEDS) PADA TIKUS INDUKSI KALIUM OKSONAT**

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**ABSTRACT**

*Celery (Apium graveolens Linn) is a plant that contains phytochemicals like alkaloids, flavonoids, saponins, and tannins. This study aims to prove the effectiveness of the ethanol extract of celery leaf in lowering uric acid levels in white male rats and determine the dose of celery leaf extract which is effective in lowering uric acid levels in male rats. Celery leaf extract prepared by maceration with 96% of ethanol. The design of the study is a randomized block design. Data were analyzed by using statistical test Analysis of Variance (ANOVA) at a significant level 95% and were using 30 male rats divided into 6 treatment groups, each treatment consisted of five rats. Animals model hyperuricemia were induced by potassium oxonate 250 mg/kg except the normal group. Group I (normal) researcher provides a standard, group II (negative) suspension given Na CMC 0.5%, group III (positive) by the suspension of allopurinol 5,4 mg/kg, groups IV, V, and VI were given ethanol extract of celery leaf each with a dose of 50 mg / kg, 100 mg / kg, and 200 mg / kg. Based on the test result that further BNJ dose of ethanol extract of celery leaf is effective with 50 mg/kg.*

**Keywords:** *Hyperuricemia, Celery Leaf Extract, Potassium Oxonate*

**ABSTRAK**

Seledri adalah tanaman yang memiliki kandungan kimia seperti alkaloid, flavonoid, saponin, dan tanin. Penelitian ini bertujuan untuk membuktikan efektivitas ekstrak etanol daun seledri dalam menurunkan kadar asam urat pada tikus putih jantan dan menentukan dosis ekstrak daun seledri yang efektif dalam menurunkan kadar asam urat pada tikus putih jantan. Ekstrak daun seledri dibuat secara maserasi dengan pelarut etanol 96%. Rancangan penelitian yang digunakan adalah Rancangan Acak Kelompok. Data yang diperoleh dianalisis dengan menggunakan uji statistik Analisis Sidik Ragam pada taraf kepercayaan 95% yang menggunakan 30 ekor tikus putih jantan dibagi 6 kelompok perlakuan, tiap perlakuan terdiri dari 5 ekor. Model hewan dibuat hiperurisemia menggunakan penginduksi kalium oksonat dengan dosis 250 mg/kg BB. Kelompok I (normal) diberikan pakan standar, kelompok II (negatif) diberi suspensi Na CMC 0,5%, kelompok III (positif) diberi suspensi allopurinol 5,4 mg/kg BB, kelompok IV, V, dan VI diberi ekstrak etanol daun seledri masing-masing dengan dosis 50 mg/kg BB, 100 mg/kg BB, dan 200 mg/kg BB. Berdasarkan uji lanjut BNJ diperoleh hasil bahwa dosis ekstrak etanol daun seledri yang efektif adalah 50 mg/kg BB.

**Kata kunci:** Hiperurisemia, Ekstrak Daun Seledri, Kalium Oksonat

## Lampiran 5. Jurnal 3

*Media Farmasi Indonesia Vol 16 No 1*

**EFEK PEMBERIAN SEDUHAN SERBUK HERBA SELEDRI (*Apium graveolens* L.) TERHADAP KADAR ASAM URAT SERUM DARAH AYAM LEGHORN JANTAN HIPERURIKEMIA**

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**Abstract**

*Apium graveolens* L. is a medicinal plant that is useful for treating gout. Flavonoids are components of chemical compounds found in celery because they can work as antioxidants and inhibit the action of the xanthine oxidase enzyme to form uric acid. This study aims to determine the effect of giving celery herb powder on the blood serum uric acid levels of hyperuricemia male leghorn chickens. This study used twenty-five male leghorn chickens which were randomly divided into 5 groups. All groups were made hyperuricemia by being given 100% chicken liver juice 5 mL/1 kg BW once a day orally during treatment. Group 1 was given 0.5% CMC suspension solution as a negative control group. Group 2 was treated with allopurinol 14 mg/1.5 kg BW in CMC 0.5% as a positive control. Groups 3, 4, 5 received infusion of celery herb powder in the order of doses (0.6 g/1.5 kg BW), (1.2 g/1.5 kg BW), (1.8 g/1.5 kg BW). Examination of uric acid levels was carried out on days 0, 4, 8, 12. The results showed that steeping celery could reduce uric acid levels in proportion to the dose. The greater the dose given, the greater the decrease in uric acid levels. The dose of celery herb group 3 (1.8 g/1.5 kg BW) was the most effective doses because it had the same value as the positive control.

**Keywords:** celery, uric acid, hyperuricemia

**1. PENDAHULUAN**

Asam urat disebabkan karena makanan atau minuman yang mengandung purin. Makanan dan minuman yang mengandung purin antara lain bir, biji-bijian, daging merah serta organ dalam seperti hati, ginjal, daging kelenjar, timus, pancreas, seafood (udang, lobster, teri, sarden) dan produk kaya fruktosa misalnya soda, makanan cepat saji (David, 2019). Pola makan yang tidak baik dapat meningkatkan morbiditas dan mortalitas yang berkaitan dengan penyakit kronis. Konsentrasi serum asam urat pada setiap individu mewakili interaksi yang kompleks antara faktor-faktor yang tidak dapat

dimodifikasi misalnya genetik dan faktor-faktor yang dapat dimodifikasi seperti berat badan dan gaya hidup. Diet dan kandungan purin berperan dalam perubahan fungsi fisiologis tersebut (Jakše dkk, 2019).

Kadar asam urat serum yang tinggi berisiko lebih tinggi untuk semua penyebab kematian akibat kardiovaskular. Asam urat juga meningkatkan risiko kematian baik pada pria maupun wanita terutama pada penyakit ginjal, penyakit endokrin dan metabolisme, serta penyakit kardiovaskular (Lin dkk, 2013).

Indonesia memiliki berjuta ragam tanaman obat yang berpotensi

## Perbandingan Efektivitas Ekstrak Daun Seledri (*Apium graveolens L.*) dengan Allopurinol Terhadap Penurunan Kadar Asam Urat pada Tikus Putih Jantan (*Rattus norvegicus*) dibuat Hiperuresemia

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### ABSTRAK

**Latar Belakang :** Hiperuricemia yang berkepanjangan dapat menyebabkan gout atau punai. Allopurinol merupakan obat pilihan utama untuk menurunkan kadar asam urat, namun jika dikonsumsi terus menerus dapat mengakibatkan efek samping. Oleh sebab itu, diperlukan alternatif terkandung dalam daun seledri yang mampu menghambat pembentukan asam urat. **Tujuan :** Untuk mengetahui perbandingan efektivitas ekstrak daun seledri (*Apium graveolens L.*) dengan allopurinol terhadap penurunan kadar asam urat tikus putih jantan (*Rattus norvegicus*) dibuat hiperuresemia. **Metode :** Penelitian eksperimental dengan rancangan pretest dan posttest control group design. Penelitian ini menggunakan empat kelompok yaitu dua kelompok kontrol K(N) diberi makan standar dan K(-) diberi makan tinggi purin serta dua kelompok perlakuan (P1 diberi ekstrak daun seledri 10mg/200grBB dan P2 diberi allopurinol 3,6mg/kgBB). **Hasil :** Pada kelompok K(N) mengalami perubahan bermakna yaitu nilai  $p=0,010$  ( $p<0,05$ ). Kelompok K(-) mengalami perubahan bermakna yaitu nilai  $p=0,004$  ( $p<0,05$ ). Kelompok (P1) mengalami perubahan dengan nilai  $p=0,000$  ( $p<0,05$ ). Kelompok (P2) mengalami perubahan dengan nilai  $p=0,000$  ( $p<0,05$ ). **Simpulan :** Pemberian allopurinol lebih efektif dalam menurunkan kadar asam urat darah dibandingkan pemberian ekstrak daun seledri.

**Kata Kunci :** Allopurinol, Asam Urat, Daun Seledri.

### ABSTRACT

**Background :** Long term hyperuricemia can lead to gout. Allopurinol is the first choice treatment to reduce uric acid concentration, but if consumed continuously it can lead to various side effects. Therefore, there is a need for an alternative that can inhibit the formation of uric acid, which is found in celery leaves. **Goal :** To effectivity comparison between celery (*apium graveolens L.*) leaves extract and allopurinol towards uric acid reduction in hyperuricemia created male white rat (*Rattus norvegicus*). **Method :** Experimental research with pretest and posttest control group design. This research used four groups which were two control groups K(N) who were given a standard diet and K (-) who were given a high purine diet, as well as two treatment groups (P1 group were given 10mg/200grBW celery leaves and P2 were given 3.6mg/kgBW allopurinol). **Results :** K(N) group had a significant difference with  $p=0,010$  ( $p<0,05$ ). K(-) group had a significant difference with  $p=0,004$  ( $p<0,05$ ). (P1) group showed difference with  $p=0,000$  ( $p<0,05$ ). (P2) group showed difference with  $p=0,000$  ( $p<0,05$ ). **Conclusion :** Allopurinol treatment is more effective in reducing uric acid concentration than celery leaves treatment. **Keywords :** Allopurinol, Uric Acid, Celery Leaves.

### PENDAHULUAN

Asam urat merupakan asam yang berbentuk kristal-kristal dari hasil akhir metabolisme purin. Patokan yang menentukan hiperuricemia yaitu kadar asam urat lebih dari 7,0 mg/dl pada laki-laki dan lebih dari 6,0 mg/dl pada perempuan. Dalam keadaan normal terjadi keseimbangan antara pembentukan dan degradasi nukleotida purin serta kemampuan ginjal dalam mengekskresikan asam urat. Apabila terjadi kelebihan pembentukan atau penurunan ekskresi atau keduanya maka akan terjadi peningkatan konsentrasi asam urat darah yang disebut dengan hiperuricemia.<sup>(1)</sup>

Hiperuricemia yang berkepanjangan dapat menyebabkan gout atau punai, namun tidak semua hiperuricemia akan menimbulkan kelainan patologi berupa gout. Gout atau punai adalah penyakit akibat penumpukan kristal monosodium urat pada jaringan akibat peningkatan kadar asam urat. Penyakit gout terdiri dari kelainan *arthritis gout*, kelainan ginjal berupa *uric acid nephropathy* dan pembentukan batu urat pada saluran kemih.<sup>(2)</sup>

Center for Disease Control and Prevention (CDC) mencatat sekitar 8,3 juta orang di Amerika Serikat tahun menderita *arthritis gout* pada tahun 2007-



## Lampiran 7. Jurnal 5

*Prosiding Seminar Nasional dan Workshop "Perkembangan Terkini Sains Farmasi dan Klinik II" tahun 2014*

### PENGARUH FRAKSI AIR HERBA SELEDRI (*Apium graveolens* L.) TERHADAP KADAR ASAM URAT MENCIT PUTIH JANTAN HIPERURISEMIA

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#### ABSTRACT

The effect of the water fraction herbaceous celery (*Apium graveolens* L.) on blood uric acid level has been observed on white male mice hyperuricemia. As much as 30 white mice males aged 2-3 months and weighing 20-30 grams were used. Induction hyperuricemia was done by giving chicken fresh homogenate's liver 0.5 mL/20g BW during even days. Mice were divided into 6 groups, negative control, positive control, group dose 12.5 mg/kg, group dose 25 mg / kg BW, group dose 50 mg/kg BW, comparison group allopurinol at dose of 10 mg/kg BW. Blood uric acid level were measure with digital tool Nesco<sup>®</sup>Multicheck. The data were analyzed two-way ANOVA and followed by Duncan's multiple range test. The results showed that administration of water fraction herbaceous celery (*Apium graveolens* L.) at a dose of 12.5, 25, and 50 mg/kgBW can lower blood uric acid levels in white male mice are highly significant ( $p < 0.01$ ). Effect is shown by the highest dose of 50 mg/kgBW, while the difference in duration of effect was significantly ( $p < 0.05$ ).

**Keywords:** celery, mice, uric acid

#### PENDAHULUAN

Indonesia adalah negara yang dikenal dengan megabiodiversiti, memiliki keanekaragaman hayati flora dan fauna yang sangat melimpah. Sumber daya alam bahan obat dan obat tradisional merupakan aset nasional yang perlu digali, diteliti, dikembangkan, dan dioptimalkan pemanfaatannya (Depkes, 2008). Tanaman obat adalah kelompok tanaman yang umumnya digunakan sebagai obat dan sebagai sumber bahan baku obat. Tanaman obat yang digunakan biasanya dalam bentuk simplisia yang berupa akar, daun, buah, dan biji. Penggunaan tumbuhan-tumbuhan sebagai obat tradisional ternyata telah lama dikenal masyarakat Indonesia jauh sebelum pelayanan kesehatan menggunakan obat-obatan sintetik. Obat tradisional selain murah dan mudah di dapat, obat tradisional juga memiliki efek samping yang jauh lebih rendah dibandingkan obat-obatan kimia (Setiawan, 2010). Penelitian dan pengembangan tanaman obat telah banyak dilakukan, terutama pada segi farmakologi maupun fitokimianya.

Penelitian ini digunakan untuk mencari tanaman yang berpotensi sebagai tanaman obat (Armi, 2010).

Seledri (*Apium graveolens* L.) merupakan tanaman suku umbeliferase yang mempunyai khasiat sebagai obat. Komponen metabolit sekunder yang berhasil diisolasi dari seledri di antaranya apiin, apigenin. Herba seledri sering digunakan sebagai obat peluruh keringat, penurun demam, rematik, sukar tidur, dan darah tinggi asam urat, dan memperbaiki fungsi darah yang terganggu, selain itu juga dapat berfungsi sebagai antiinflamasi (Fazal, 2012). Apigenin merupakan salah satu senyawa yang terdapat dalam seledri dan dapat digunakan sebagai obat asam urat (Duke, 2001).

Asam urat sering dialami masyarakat saat ini, dan banyak diderita oleh kelompok usia produktif yaitu usia 30-50 tahun, hal ini dapat menurunkan produktivitas kerja. Pada kondisi patofisiologis terjadi peningkatan kadar asam urat dalam darah melewati batas normal yang disebut hiperurisemia.

EFEK PEMBERIAN SEDUHAN SELEDRI (*APIUM GRAVEOLENS L.*) TERHADAP  
KADAR ASAM URAT PADA TIKUS PUTIH JANTAN STRAIN WISTAR  
(*RATTUS NORVEGICUS*) HIPERURISEMIA

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ABSTRAK

Efek Pemberian Seduhan Seledri (*Apium graveolens L.*) Terhadap Kadar Asam Urat Pada Tikus Putih Jantan Strain Wistar (*Rattus norvegicus*) Hiperurisemia. Latar Belakang: Seledri atau jenis tanaman yang diduga dapat menurunkan kadar asam urat adalah seledri. Seledri mengandung flavonoid dan 5-n-buryptalide (5n) dapat menurunkan kadar asam urat dengan mengubah kerja enzim xantin oksidase. Tujuan: Penelitian ini bertujuan untuk mengetahui pengaruh seduhan seledri (*Apium graveolens L.*) terhadap penurunan kadar asam urat pada tikus putih jantan hiperurisemia. Metode Penelitian: Menggunakan eksperimen acak, dengan menggunakan *Randomized Post Test Control Group Design*. Sampel penelitian dibagi menjadi 5 kelompok. Kelompok I: Kontrol positif (Sapiati hari ayam normal 3 ml/150grBB) selama 21 hari + pakan normal selama 7 hari, II, III dan IV: diberikan Sapiati hari ayam normal 3 ml/150grBB selama 21 hari + seduhan seledri dengan dosis 50, 100, 150mg/ekst/hari selama 7 hari, V: Kontrol negatif (Pakan normal selama 28 hari). Pengukuran kadar asam urat dengan menggunakan metode kolorimetri urazirak. Hasil: Hasil pengukuran asam urat kelompok dengan pemberian seduhan seledri dosis 150 mg/ekst/hari menunjukkan kadar asam urat paling rendah (4,679±0,687) dibandingkan dengan kelompok kontrol positif menunjukkan kadar asam urat paling tinggi (11,563±1,541). Kesimpulan: Ada hubungan antara dosis seduhan seledri (*Apium graveolens L.*) terhadap kadar asam urat pada tikus putih jantan (*Rattus Norvegicus*) hiperurisemia.

**Kata Kunci:** Seledri, Hiperurisemia, Kadar Asam Urat, Sapiati Hari Ayam,

ABSTRACT

The Effect of Water Steeping Celery (*Apium graveolens Linn.*) on Level of Uric Acid White Male Rat (*Rattus norvegicus*) Hyperuricemia. Introduction: One type of plant that could be expected to reduce level of uric acid is celery (*Apium graveolens L.*). Celery contains flavonoid and 5-n-buryptalide (5n) expected to reduce level of uric acid by inhibiting the action of the xanthine oxidase. Objective: This study was aimed to determine the effect of steeping celery (*Apium graveolens L.*) in the level of uric acid on white male rat hyperuricemia. Method: This study was true experimental, by using *randomized post test control group design*. The sample of this study was divided into 5 groups. Group I: positive control (an amount of raw chicken liver 3ml/150mg body weight for 21 days + normal food for 7 days) Group II, III and IV: was given an amount of raw chicken liver 3ml/150mg body weight for 21 days + celery steeping with a dose: 50, 100, 150 mg/leaf/day for 7 days. Group V: negative control (normal food for 28 days). The level measurement of uric acid by using enzymatic substrate method. Result: The results measurement of uric acid group with steeping celery dose 150 mg/leaf/day showed the least amount of uric acid (4,679 ±0,687) compared with positive control group showed the highest uric acid levels (11,563 ± 1,541). Conclusion: Steeping celery (*Apium graveolens L.*) is known to decrease the level of uric acid on white male rat (*Rattus norvegicus*) hyperuricemia.

**Key words:** Celery, Hyperuricemia, Uric Acid Levels, Nectas Chicken Liver

PENDAHULUAN

Asam urat merupakan asam yang berbentuk kristal-kristal yang merupakan hasil akhir dan metabolisme purin (bentuk nukleosoprotein). Patokan untuk menentukan hiperurisemia yaitu kadar asam urat lebih dari 7,0 mg/dl pada laki-laki dan lebih dari 6,0 mg/dl pada perempuan. Dalam keadaan normal terjadi keseimbangan antara pembentukan dan degradasi nukleotida purin serta kemampuan ginjal dalam mengeliminasi asam urat.

Apabila terjadi kelebihan pembentukan (*overproduced*) atau penurunan eliminasi (*undereliminated*) atau keduanya maka akan terjadi peningkatan konsentrasi asam urat darah yang disebut dengan hiperurisemia (Hansen, 2007; Wicusa dan Susanto, 2009; Wierman, 2009; Putra, 2007). Bahan ada data purin, kejadian hiperurisemia pada masyarakat Indonesia.

## Anti-gouty arthritis and anti-hyperuricemia properties of celery seed extracts in rodent models

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**Abstract.** Gout is a type of serous arthritis that is caused by hyperuricemia. Celery is an umbelliferous plant that was shown to exhibit anti-inflammatory activity in rodent. The present study aimed to investigate the effects and potential preliminary mechanisms of celery seed aqueous extract (CSAE) and celery seed oil extract (CSOL) for gout treatment. The components of CSAE and CSOL were systematically analyzed. In mice with hyperuricemia induced by potassium oxonate and yeast extract, CSAE and CSOL treatment reduced the serum levels of uric acid and xanthine oxidase. In addition, CSAE and CSOL reduced the levels of reactive oxygen species and increased the serum levels of superoxide dismutase and glutathione peroxidase in mouse serum. In rats with acute gouty arthritis induced by intra-articular injection of monosodium urate crystals, CSAE and CSOL treatment alleviated the swelling of the ankle joints and reduced inflammatory cell infiltration around the ankle joint. In addition, CSAE and CSOL reduced the levels of interleukin (IL)-1 $\beta$  and tumor necrosis factor  $\alpha$  and increased the levels of IL-10. The results of the present study suggested that celery seed extracts may have anti-gout properties, partially through anti-inflammatory and antioxidative effects.

### Introduction

Gout is a common form of arthritis associated with pain, fatigue and high fever (1). According to epidemiological studies, the

incidence of gout increased from 1.42% in 1997 to 2.49% in 2012 in Britain (2), which is partly influenced by dietary changes and age (3). Hyperuricemia, defined as a level of serum uric acid (UA) >6.8 mg/dl, is caused by the overactivation of xanthine oxidase (XO) following excessive purine intake (4,5). High levels of UA contribute to the deposition of monosodium urate (MSU) in joints and other tissues (6). The deposition of MSU in the joint cavity activates inflammatory cytokines, inducing the accumulation of macrophages and neutrophils, which leads to gouty arthritis (7,8). Oxidative stress serves an important role in the pathogenesis of gout (9) and is responsible for a series of inflammatory events (10), such as the production of interleukin (IL)-1 $\beta$  (11).

Based on the pathogenesis of gout, inhibiting inflammation and lowering the serum UA level are considered to be effective treatment strategies. Colchicine (COL), corticosteroids and non-steroidal anti-inflammatory drugs are commonly used in the treatment of gouty arthritis (12,13). Allopurinol and febuxostat (FBX) are the main clinical agents for treating hyperuricemia (14,15). However, a number of adverse effects have been reported, including liver damage, nephrotoxicity, bone marrow suppression and hypersensitivity bodily reactions (14–16). It is therefore particularly important to find alternative treatment agents for hyperuricemia and gouty arthritis.

Natural products have received increasing attention in clinical applications owing to their diverse efficacies and low adverse effects (17). Celery is an annual or perennial umbelliferous plant widely distributed in subtropical and tropical regions of Europe, Africa and Asia (18). Celery has exhibited antifungal, anti-inflammatory and anti-gastric ulcer effects in rodents, and may lower blood pressure in patients with hypertension (19–23). n-Butanol extracts from celery seeds have been reported to improve lipid peroxidation through antioxidant in diabetic rats (24). Methanol and petroleum extracts from celery seeds reduced blood UA levels in rats (25). However, the antioxidant and anti-inflammatory activities of celery seeds, especially their aqueous extracts and volatile oil, have not been fully reported in gout.

Rats with acute gouty arthritis, which was induced by MSU to simulate acute gout in humans, have been used to investigate the effects of various agents on joint swelling and inflammation (26). Mice with hyperuricemia, which was

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**Key words:** celery seed, hyperuricemia, acute gouty arthritis, oxidative stress, inflammation



## Xanthine Oxidase Inhibitory Activity and Antigout of Celery Leek Parsley and Molokhia

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**Abstract:** The present study was aimed at investigating *in vitro* xanthine oxidase inhibitory (XOI) and *in vivo* antigout activity extracts of celery, leek, parsley, and molokhia. The degree of XO inhibitory activity was determined by measuring the absorbance spectrophotometrically at 295 nm, which is associated with uric acid formation which is linked to gout. Our preliminary screening study had employed the use of distilled water, and absolute ethanol to determine NOI from celery, leek, parsley, and molokhia. In general, our study showed that the ethanolic extracts were found to be more active than the aqueous extracts. Further *in-vivo* antigout was studied gout induced in rats by potassium oxonate. A total of 36 male albino rats were randomly divided into 6 equal groups. Group 1 negative control given only standard diet, and group 2-6 given Potassium oxonic acid (250 mg/kg, i.p.), Potassium oxonate an uricase inhibitor was used to induce gout. Oral administration (G3, G4, and G5) of celery, leek, parsley (5 g/Kg), and (G6) molokhia (4.8 g/Kg) showed a significant decrease in uric acid, and Creatinine levels in the gouty rats. All extracts (celery, leek, parsley, and molokhia) have shown significant decrease in level of Malonaldehyde (MDA) and increase in activity of antioxidant enzyme level, comparable to positive rat (G2). No significant changes between all extracts used and negative control in gain weights and organic phosphorus was noticed. The results showed that increasing serum total calcium level with extracts of celery, leek, parsley, and molokhia in comparison to positive control. The celery, leek, parsley, and molokhia extracts have some protective effects on the gout.

**Keywords:** Celery, Leek, Parsley, Molokhia, Gout, Xanthine Oxidase Inhibitory

## 1. Introduction

Gout is a multi-factorial disease affecting the flexibility of joints. It is usually characterized by re-curent attacks of acute inflammatory arthritis-a red, tender, hot, swollen joints leading to bursts (1). It is a serious disease that has been growing in prevalence during the past several years in Western civilizations (2). Gout is characterized by abnormally high levels of uric acid in the body, resulting in the formation and deposition of urate (as monosodium urate-monohydrate) crystals, generally known as tophi crystals in joints, tendons and surrounding tissues, characterized by hyper-uricemia and in chronic stage, may lead to renal failure(3). These crystals cause an acute inflammatory response and can induce a permanent tissue damage which is characterized by the appearance of ulceration of the joint cartilage, marginal osteophytosis, geodic and erosive lesions and chronic inflammation of synovial membrane (4 and

5). This is partly a reflection of changes in diet, increases in longevity, hypertension, metabolic syndrome, and advanced renal disease, and the broad use of diuretics in clinical practice. Management of gout in the elderly, in organ transplant recipients, and in patients with renal insufficiency and allopurinol intolerance can be particularly challenging (6). Uric acid is the end product of purine metabolism in humans, and its overproduction by xanthine oxidase (XOI) from purine compounds or under excretion can lead to hyperuricemia as gout. Enzymatic degradation of hypoxanthine and xanthine leads to the production of uric acid (7 and 8). The major site of purine synthesis is in the liver. The synthesis of uric acid occurs along two pathways, referred to as the *de novo* and the *salvage* pathways. Synthesis of the purine nucleotides begins with the formation of phosphoribosyl pyrophosphate (PRPP) by PRPP synthetase and leads to the first fully formed nucleotide, inosine 5'-monophosphate (IMP). IMP is converted into either adenosine 5'-monophosphate (AMP) or guanosine 5'-

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## Inhibitory Effects of *Apium graveolens* on Xanthine Oxidase Activity and Serum Uric Acid Levels in Hyperuricemic Mice

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**ABSTRACT:** Celery (*Apium graveolens*) is traditionally used to treat rheumatism and cardiovascular disorders. Hyperuricemia is considered as a predisposing factor for gout and is also suggested to be associated with coronary artery disease. In the present study, the effect of hydromethanolic extracts from *A. graveolens* (AGE) against potassium oxonate (PO)-induced hyperuricemia was investigated in mice. AGE (250, 500, and 1,000 mg/kg) or allopurinol (5 mg/kg, as positive control) were orally administered 1 h after PO injection (250 mg/kg, ip) for two weeks. After that, the serum uric acid level and hepatic xanthine dehydrogenase (XDH) and xanthine oxidase (XO) activities were measured. In addition, the antioxidant activity of AGE was determined by assessment of hepatic lipid peroxidation, *in vivo* and the ferric reducing/antioxidant power assay, *in vitro*. The extract exhibited good capacity to reduce ferric ion to ferrous ion with mean value of 63.8±8.5 µmol/g. The data also showed that oxonate treatment produced a significant increase in serum uric acid level (4.6 vs. 2.3 mg/dL,  $P<0.001$ ), liver XO/XDH activities ( $P<0.01$  and  $P<0.001$ , respectively), and hepatic lipid peroxide levels (about two fold,  $P<0.01$ ), compared to the healthy mice. AGE significantly decreased the serum uric acid level, hepatic XO/XDH activities, and lipid peroxidation, in a dose-dependent manner. Oral administration of 1,000 mg/kg AGE for two weeks reversed the elevated serum uric acid level (2.7 vs. 4.6 mg/dL,  $P<0.001$ ) and significantly inhibited liver XO/XDH activities ( $P<0.001$ ) and diminished hepatic lipid peroxidation (0.45 vs. 0.82 nmol/mg protein,  $P<0.05$ ), compared with hyperuricemic mice. AGE (1,000 mg/kg) *per se* did not significantly modify these parameters. Our results demonstrated that AGE could reduce the serum uric acid level via inhibition of hepatic XDH/XO and indicated its potential utility as an effective hyperuricemic bioactive agent or functional food.

**Keywords:** *Apium graveolens*, hyperuricemia, xanthine dehydrogenase (XDH), xanthine oxidase (XO), hypouricemic agent

### INTRODUCTION

Excessive production of uric acid leads to deposition of monosodium uric acid crystals in soft tissues and joints which are associated with gout (1-3). These crystals cause the pathology of gout by activating the inflammatory responses, resulting in bone and cartilage erosions (4). Oxidative damage is also closely related to the pathogenesis of gout disease (2). Therefore, inhibition of uric acid overproduction, inflammation, and oxidative stress have importance in gout management (2). The most therapeutic strategies to treat hyperuricemia is the development of xanthine oxidase (XO) inhibitors which could effectively reduce the uric acid contents of plasma and urine and decrease topaceous uric acid deposition (1). Allopurinol, a

XO inhibitor, is widely used as a uric acid-lowering agent (5). However, the clinical use of allopurinol is limited because of severe adverse effects such as hepatotoxicity, nephrotoxicity or hypersensitivity reactions. Therefore, searching the new XO inhibitors, in particular from natural sources, is a promising approach (5-8).

*Apium graveolens* Linn. (Apiaceae), commonly known as celery, has a long history of usage in Ayurveda and Unani medicine. *A. graveolens* is widely cultivated in Central Europe, North Africa, North-Western Himalaya, and Western India. The whole plant or its seeds have been used as food or medicine (9,10). Celery has been effective in the prevention of cardiovascular disease (11) and lowering blood pressure (12). It also has antifungal (13), anti-inflammatory (14,15), antioxidant (16), anti-gastric ulcer

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OPEN

# Molecular and Histopathological Study on the Ameliorative Impacts of *Petroselinum Crispum* and *Apium Graveolens* against Experimental Hyperuricemia

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Hyperuricemia is an abnormal metabolic condition characterized by an increase in uric acid levels in the blood. It is the cause of gout, manifested by inflammatory arthritis, pain and disability. This study examined the possible ameliorative impacts of parsley (PAR) and celery (CEL) as hypouricemic agents at biochemical, molecular and cellular levels. PAR and CEL alone or in combination were orally administered to hyperuricemic (HU) mice and control mice for 10 consecutive days. Serum levels of uric acid and blood urea nitrogen (BUN), xanthine oxidase activity, antioxidants, inflammatory (IL-1 $\beta$ ) and TNF- $\alpha$ ) and anti-inflammatory cytokines (IL-10) were measured. mRNA expression of urate transporters and uric acid excretion genes in renal tissues were examined using qRT-PCR (quantitative real time PCR). Normal histology and immunoreactivity of transforming growth factor-beta 1 (TGF- $\beta$ 1) in kidneys was examined. Administration of PAR and CEL significantly reduced serum BUN and uric acids in HU mice, ameliorated changes in malondialdehyde, catalase, and reduced glutathione, glutathione peroxidase (GPX), IL-1 $\beta$ , TNF- $\alpha$  and IL-10 in hyperuricemic mice. Both effectively normalized the alterations in mURAT-1, mGLUT-9, mOAT-1 and mOAT-3 expression, as well as changes in TGF- $\beta$ 1 immunoreactivity. Interestingly, combined administration of PAR and CEL mitigated all examined measurements synergistically, and improved renal dysfunction in the hyperuricemic mice. The study concluded that PAR and CEL can potentially reduce damaging cellular, molecular and biochemical effects of hyperuricemia both individually and in combination.

Hyperuricemia (HU) is defined as an increase in the levels of uric acid over normal ranges (6 mg/dL in females and 7 mg/dL in males)<sup>1,2</sup>. HU is associated with meat and seafood ingestion, hypertension and obesity<sup>1-3</sup>. Advanced HU is associated with gout<sup>4</sup>. Gout results in deposition of urate in soft tissues and joints, and arthritis in men over 40 years old<sup>5</sup>. Uric acid (UA) is the end product of the catabolism of purine compounds in the liver. UA is excreted mainly by the kidneys and to a lesser extent by the gastrointestinal tract<sup>6,7</sup>. It is degraded by gut microbiota (one third) in a process known as intestinal uricolysis<sup>8</sup>. The remaining two thirds depends on interchanges between UA secretion and reabsorption in the kidney tubules<sup>9-10</sup>. Treatment of gout mainly depends on allopurinol (ALP). ALP is an inhibitor of xanthine oxidase and stimulates renal excretion of UA<sup>11,12</sup>. Other anti-inflammatory drugs (indomethacin) can be used, but these may cause side effects<sup>13</sup>. Therefore, identifying safe herbal medications is the goal for both patients and physicians.

The use of organic drugs and therapies is cost-effective<sup>14</sup>. The positive and promising effects of medicinal herbs on renal diseases, infertility, liver disorders and diabetes are clearly established and are accepted by patients and clinicians as a safe medication for these disorders<sup>15-17</sup>. Plants of medical importance contain flavonoids and

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## Antihyperuricemic Activity of Aqueous Celery Infusion by Xanthine Oxidase Enzyme Inhibition

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### ABSTRACT

Hyperuricemia is a metabolic disorder because of excessive uric acid production. The high prevalence of hyperuricemia in the world, especially in Indonesia makes the research of antihyperuricemic drugs very needed today. The purpose of this study was to determine the activity of water infusion extract from celery stems and leaves to inhibited xanthine oxidase enzyme. Xanthine oxidase enzyme plays a role in change of hypoxanthine to xanthine and then becomes uric acid. The activity of xanthine oxidase enzyme was determined by UV spectrophotometry method and using xanthine substrate. Absorption at 290 nm indicates the presence of a uric acid product from xanthine oxidation by the xanthine oxidase enzyme. Infused extract which has the smallest absorption at 290 nm showed a better inhibitory ability of the xanthine oxidase enzyme because the change of xanthine substrate to uric acid is inhibited. The result showed the celery stems water infusion extract had better inhibition activity than celery leaves water infusion extract. The best inhibition percentage of celery stems water infusion was 90.25%, while the celery leaves water infusion was 69.07% both of at 20% concentration. The type inhibition of celery stems water infusion extract to xanthine oxidase enzyme showed an uncompetitive inhibition type because showed change in  $K_m$  and  $V_{max}$  values.  $K_m$  and  $V_{max}$  values before the addition of water infusion of celery stems were 104.33 ppm and 3.83 U/mL, respectively changed to 74.49 ppm and 2.69 U/mL after the addition of extract.

**Key words:** Celery; water infuse; Xanthine oxidase; uric acid; antihyperuricemic

### INTRODUCTION

Hyperuricemia is a metabolic disorder due to impaired uric acid excretion (Wyrngarden, 1976). According to Wolf et al., (1999), hyperuricemia could directly induce kidney damage. Hyperuricemia prevalence in Indonesia alone is estimated to have reached 2.3-17.6% per thousand population (Sudoyo et al., 2006). For patients with hyperuricemia, there will be an increase in serum uric acid levels above normal. It is diagnosed as hyperuricemia if uric acid levels are above 7.0 mg/dl in adult male and above 6.0 mg/dl in adult female (Munadiary, 2008).

Uric acid is the end product of purine metabolism in humans resulted from the digestion of several foods such as liver, nuts, and others. Normally, uric acid will flow in the blood and carried to the kidneys, which is then excreted in the urine. Due to its low solubility, excessive levels of uric acid can accumulate in various places in the body such as joints and kidneys (Murray, 2003).

One of synthetic drugs used to treat hyperuricemia is allopurinol. The drug can be used to reduce uric acid levels by inhibiting the activity of xanthine oxidase enzyme, an enzyme that plays a role in the formation of uric acid. However, the

use of this synthetic drug can cause several side effects such as skin rash, fever, and leucopenia (Dipiro et al., 2008). Thus, it is necessary to encourage research in finding safe therapeutic drugs for hyperuricemia.

Safe alternative treatments for hyperuricemia are possible through the utilization of natural ingredients such as plant extracts. The plants, whose extract is applicable for hyperuricemia treatment, are celery. Celery plants are known to contain useful chemical compounds, such as flavonoids, alkaloids, glycosides, and steroids in methanol extract of its seeds. It also contains phenols and ferrocumarins compounds. The seeds, leaves, and stems of celery are also known to contain essential oils, sesquiterpene alcohols, and fatty acids (A-Snafi, 2014). Some researchers state that celery has many bioactivity properties, including anti-inflammatory and pain relievers, antioxidants, antibacterial, antitumor, antimalarial and larvicidal properties. Anticancer, anti-calcium, antifungal, antihypertensives, fertility enhancer, antithyroid, and antidiabetic (Syahidiah, 2018). Plant extracts known to possess activity as hyperuricemia therapy are those containing compounds with the potential to inhibit xanthine oxidase enzymes, namely tannin, flavonoids, polyphenolic, and ellagic acid (Azmi et al., 2012). Zhou et al., (2009)

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**PENGUJIAN FITOKIMIA DAN PENENTUAN PARAMETER KINETIK ENZIM DENGAN PENAMBAHAN EKSTRAK INFUSA AIR SELEDRI**

**PHYTOCHEMICAL TESTING AND DETERMINATION OF KINETIC PARAMETERS ENZYME WITH WATER INFUSION OF CELERY EXTRACTS**

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Celery, Phytochemicals, Xanthine oxidase, Water Infuse

**Abstrak**

**Latar belakang:** Hiperurisemia merupakan kelainan metabolisme karena produksi asam urat yang berlebih. Prevalensi hiperurisemia di Indonesia diperkirakan antara 2,3-17,6%, sehingga penelitian mengenai obat antihiperurisemia sangat dibutuhkan saat ini. **Tujuan:** untuk mengetahui aktivitas infusa batang seledri terhadap parameter kinetik enzim xantin oksidase.

**Metode:** spektrofotometri UV untuk mengukur kadar asam urat. **Hasil:** pengujian kandungan senyawa bahan aktif menunjukkan hasil positif pada pengujian flavonoid. Parameter kinetik enzim  $K_m$  dan  $V_{max}$  menunjukkan perubahan nilai dengan adanya penambahan infusa batang seledri. Nilai  $K_m$  enzim adalah sebesar 90,00 ppm, dan nilai  $V_{max}$  enzim sebesar 3,51 U/ml, sebelum adanya penambahan ekstrak air batang seledri dan nilai  $K_m$  dan  $V_{max}$  berubah menjadi 125,42 ppm dan 2,97 U/ml, dengan adanya penambahan ekstrak infusa air batang seledri. **Simpulan dan saran:** pengujian kandungan senyawa bahan aktif menunjukkan hasil positif pada pengujian flavonoid, selangkan uji parameter kinetik enzim menunjukkan kenaikan  $K_m$  dan  $V_{max}$  menunjukkan penurunan dengan adanya penambahan ekstrak infusa air batang seledri.

**Abstract**

**Background:** Hyperuricemia is a metabolic disorder because of excessive production of uric acid. The prevalence of hyperuricemia in Indonesia is estimated to be between 2.3-17.6%, so makes the research of antihyperuricemia drugs very needed today. **Objective:** determine the infusion activity of celery stem on kinetic parameters of xanthine oxidase enzyme. **Method:** UV spectrophotometry to measure uric acid levels. **Results:** testing the content of the active ingredients showed positive results on flavonoid testing. Kinetic parameters of  $K_m$  and  $V_{max}$  enzymes showed changes in values by the addition of infusion of celery stem. The enzyme  $K_m$  value was 90.00 ppm, and the enzyme  $V_{max}$  value was 3.51 U / ml, before the addition of celery stem water extract and  $K_m$  and  $V_{max}$  values changed to 125.42 ppm and 2.97 U / ml, with the addition of extract infusion of celery stem water. **Conclusions and suggestions:** testing the content of active ingredients showed positive results on flavonoid testing, while the kinetic parameter test showed that the increase of  $K_m$  and  $V_{max}$  showed a decrease with the addition of infusion extract of celery stem water.



PENENTUAN PARAMETER KINETIK ENZIM XANTIN OKSIDASE  
TERINHIBISI EKSTRAK SELEDRI BERDASARKAN METODE GRAFIK  
LINEWEAVER-BURK DAN LANGMUIR

DETERMINATION OF KINETIC PARAMETERS OF XANTHINE OXIDASE  
ENZYME INHIBITED CELERY EXTRACT BASED ON LINEWEAVER-BURK  
AND LANGMUIR GRAPH METHODS

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**Abstrak**

**Latar belakang:** Seledri merupakan tanaman obat yang diketahui mampu menghambat aktivitas enzim xantin oksidase yang berperan dalam pembentukan asam urat. Prevalensi penyakit asam urat (*gout*) yang tinggi di Indonesia, yaitu 1,6-13,6% per seribu penduduk membuat penelitian tentang sifat penghambatan terbentuknya produk asam urat dalam tubuh sangat diperlukan. **Tujuan:** mengetahui nilai parameter kinetik enzim xantin oksidase dengan adanya penambahan ekstrak seledri. **Metode:** Ekstrak seledri dari daun dan batang diperoleh menggunakan metode sediaan dan pelarut hidroetanol. Penentuan parameter kinetik enzim dilakukan dengan metode grafik linear Lineweaver-Burk dan Langmuir. **Hasil:** Ekstrak hidroetanol daun seledri menunjukkan inhibisi terbaik sebesar 86,86% (konsentrasi 30%) dan ekstrak hidroetanol batang seledri menunjukkan inhibisi terbaik sebesar 87,71% (konsentrasi 40%). Penambahan ekstrak daun seledri pada enzim memberikan nilai  $K_m$  sebesar 27,74 ppm dan  $V_{max}$  sebesar 3,55 U/ml, pada metode grafik Lineweaver-Burk, sedangkan pada metode grafik Langmuir nilai  $K_m$  mencapai 327,66 ppm dan  $V_{max}$  sebesar 6,45 U/ml. Penambahan ekstrak batang seledri menghasilkan nilai  $K_m$  sebesar 145,24 ppm dan  $V_{max}$  sebesar 4,55 U/ml, pada metode grafik Lineweaver-Burk, sementara pada metode grafik Langmuir nilai  $K_m$  sebesar 321,09 ppm dan  $V_{max}$  sebesar 5,21 U/ml. **Kesimpulan:** Metode grafik Langmuir lebih sesuai digunakan untuk penentuan parameter kinetik dalam inhibisi enzim xantin oksidase oleh ekstrak seledri.

**Abstract**

**Background:** Celery is a medicinal plant that is known to inhibit xanthine oxidase enzyme activity in uric acid formation. The high prevalence of *gout* in Indonesia, about 1,6-13,6% per thousand population makes the study of the inhibiting properties of the formation of uric acid products in the body is very necessary. **Objective:** determine the kinetic parameters value of xanthine oxidase enzyme in the presence of celery extract. Celery extract from leaves and stem in this research was obtained using the Soxhletation method and hydroethanol solvent. Determination of enzyme kinetic parameters was carried out using Lineweaver-Burk and Langmuir linear graph method. **Results:** hydroethanol extract of celery leaves showed the best inhibition of 86.86% (concentration 30%) and the hydroethanol extract of celery stems showed the best inhibition of 87.71% (concentration 40%). Enzyme with the addition of celery leaves extract resulted in  $K_m$  value of 27.74 ppm and  $V_{max}$  value of 3.55 U/ml, in the Lineweaver-Burk graph method, while according to Langmuir graph method the  $K_m$  value reached 327.66 ppm and  $V_{max}$  value of 6.45 U/ml. Addition of celery stems extract resulted in  $K_m$  value of 145.24 ppm and  $V_{max}$  value of 4.55 U/ml, in the Lineweaver-Burk graph method, while this extract resulted in  $K_m$  value of 321.09 ppm and  $V_{max}$  value of 5.21 U/ml, in the Langmuir graph method. **Conclusion:** Langmuir graphic method was more suitable to determine kinetic parameters in the inhibition reaction of xanthine oxidase enzyme by celery extract.

## IN VITRO INHIBITION OF CELERY (*Apium graveolens* L.) EXTRACT ON THE ACTIVITY OF XANTHINE OXIDASE AND DETERMINATION OF ITS ACTIVE COMPOUND

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### ABSTRACT

The objective of this study was to determine the inhibition effect of celery extracts toward xanthine oxidase by *in vitro* method, and its active compounds. Roots and herb of celery were extracted using water and ethanol solvents. Results indicated that the herbal ethanol extract had the highest inhibition effect (91.40%) at 1400 ppm. The components contained in the herbal ethanol extract were then separated by column chromatography using the best eluent (chloroform : ethyl acetate at 7:3). All of the fractions had inhibition effect greater than 50%. The fraction number 4 was the one with the highest inhibition effect followed by fraction 5 with inhibition percentage of both fractions at 200 ppm were 88.62 and 85.44%, respectively. The analysis of the ultraviolet spectrum of fraction 4 showed the presence of  $n-\pi$  transition which was resulted by the aromatic C=C, -OH, and C=O chromophores, and also showing the  $n-\sigma$  transition which was given by -C=O chromophore. The infrared spectrum analysis indicated the presence of aromatic -C=C, -OH, and C=O functional groups. Based on the phytochemical assay and both instrumental spectrums, it was thought that the active compounds of fraction 4 and 5 were in the flavonoid group.

**Keywords:** Celery (*Apium graveolens* L.); xanthine oxidase; inhibition; *in vitro*; active compound

### ABSTRAK

Tujuan penelitian ini adalah penentuan efek inhibisi ekstrak seledri terhadap aktivitas xantin oksidase dan penentuan senyawa aktifnya. Akar dan herba seledri diekstraksi menggunakan pelarut air dan etanol. Hasil menunjukkan bahwa ekstrak etanol herba seledri pada konsentrasi 1400 ppm mempunyai kemampuan menghambat aktivitas xantin oksidase tertinggi yaitu sebesar 91,40%. Senyawa kimia dalam ekstrak tersebut dipisahkan menggunakan pelarut kloroform : etil asetat dengan perbandingan 7:3 sebagai pelarut terbaik. Seluruh fraksi yang diperoleh mampu menghambat aktivitas xantin oksidase lebih dari 50%. Fraksi 4 adalah fraksi yang mempunyai daya inhibisi tertinggi pada konsentrasi 200 ppm (88,62%) diikuti oleh fraksi 5 (85,44%). Analisis spektrum ultraviolet fraksi 4 menunjukkan adanya transisi dari  $n-\pi$  yang dihasilkan oleh kromofor C=C aromatik, -OH, dan C=O, dan transisi  $n-\sigma$  yang dihasilkan oleh kromofor -C=O. Analisis spektrum inframerah menunjukkan adanya gugus -C=C aromatik, -OH, dan C=O. Berdasarkan hasil penapisan fitokimia dan data spektrum, diduga senyawa aktif pada fraksi 4 dan 5 merupakan golongan flavonoid.

**Kata Kunci:** Seledri (*Apium graveolens* L.); xantin oksidase; inhibisi; *in vitro*; senyawa aktif

### INTRODUCTION

Gout is a disorder caused by deposition of monosodium urate crystals in joints and other tissues as a result of extracellular urate supersaturation. Hyperuricemia, a concentration of urate in serum above the limit of solubility of this substance (V 7.0 mg/dL), is the most important risk factor for the development of gout and occurs as a result of increased uric acid production, impaired renal uric acid excretion, or a combination of these mechanisms. Control of hyperuricemia is most often achieved by reducing uric

acid production with an inhibitor of xanthine oxidase (XO), the enzyme catalyzing the two terminal reactions in uric acid synthesis. To date, the only commercially available XO inhibitor is allopurinol, a purine analogue in clinical use for more than 30 years. Flavonoids [1], and certain other phenols [2], and tannins as well as coumarins [3], plant growth regulators [4] and phenolic compounds [5] have all been reported to be potent XO inhibitors. The putative therapeutic effects of many traditional medicines have been ascribed to flavonoids in particular due to their enzyme inhibitory and antioxidant activity [6]. Therefore, we expect a positive

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## Pengaruh Pemberian Air Rebusan Seledri (*Apium Graveolens L.*) Terhadap Kadar Asam Urat pada Penderita *Gout Arthritis* di Rasau Jaya

*The Influence of Compress Water of Seledri (Apium Graveolens L.) On Uric Acid To Patient With Gout Arthritis In Rasau Jaya*

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### ABSTRACT

*Gout is frequently suffered by adults because they consume too much food which contains high purine. Water recovery from celery is perceived to lower uric acid degree naturally since it contains aptin and apigenin. It believed that it does not bring any side effect. In addition, celery is easy to obtain and to apply. Hence, it could be used as an alternative treatment to lower uric acid degree. The research aimed to identify the effect of water recovery from celery (*Apium graveolens L.*) to lower uric acid degree on gout patients at Rasau Jaya. The research applied a quasi experiment approach with non-equivalent pre-test and post-test control group design. The data was collected from 64 participants through purposive sampling. The research then used Independent t-test to analyse the data. The characteristics of participants in this research were described as follows. Result of uric acid level in intervention group got p value=0.002, while uric acid level in control group got p value=0.496. the average between control and intervention group has a significant value was p value 0.001. The results showed that there was an effect of giving celery boiled water (*Apium graveolens L.*) to uric acid levels in gout patients in the working area of UPK Puskesmas Rasau Jaya, so that the provision of boiled celery water (*Apium graveolens L.*) could be applied as self-care nursing intervention Handle the problem of gout*

**Keywords:** *Celery, gout, uric acid degree*

### ABSTRAK

*Gout sering dialami oleh orang dewasa disebabkan terlalu banyak mengonsumsi makanan tinggi purin. Air rebusan seledri yang mengandung aptin dan apigenin dipercaya dapat menurunkan kadar asam urat secara alami tanpa menimbulkan efek samping. Selain itu, kemulahan dalam mendapatkan dan mengaplikasikan seledri menjadikan seledri obat alternatif tradisional dalam penurunan kadar asam urat. Penelitian ini bertujuan untuk mengetahui pengaruh pemberian air rebusan seledri (*Apium graveolens L.*) terhadap kadar asam urat pada penderita gout di wilayah kerja Unit Pelayanan Kesehatan (UPK) Puskesmas Rasau Jaya. Penelitian ini menggunakan rancangan quasi experiment dengan rancangan non-equivalent pre-test and post-test control group design. Metode pengambilan sampel dengan purposive sampling berjumlah 64 responden yang dibagi menjadi dua kelompok. Analisa menggunakan uji Independent t-test. Hasil kadar asam urat pada kelompok intervensi didapatkan p value=0.002, sedangkan kadar asam urat pada kelompok kontrol didapatkan p value=0.496. Perbandingan antara kelompok kontrol dan intervensi memiliki nilai signifikansi p value 0.001. Hasil penelitian menunjukkan bahwa terdapat pengaruh pemberian air rebusan seledri (*Apium graveolens L.*) terhadap kadar asam urat pada penderita gout di Rasau Jaya, sehingga pemberian air rebusan seledri (*Apium graveolens L.*) ini dapat diaplikasikan sebagai intervensi mandiri keperawatan dalam menangani masalah asam urat.*

**Kata Kunci:** *Seledri, gout, kadar asam urat*

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**PENGARUH KOMPRES DAUN SELEDRI TERHADAP PENURUNAN  
NYERI PADA LANSIA PENDERITA GOUT ARTHRITIS  
DI DESA KRAPYAK**

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**ABSTRAK**

*Gout* ditandai dengan serangan berulang arthritis (peradangan sendi). Pasien yang mengalami *gout arthritis* mengalami keluhan nyeri hebat di kaki bagian lutut, bengkak dan menjalar ke ujung kaki hingga mengganggu aktivitas klien. Penanganan yang dapat dilakukan pada penderita *Gout* difokuskan pada cara mengontrol rasa nyeri. Penatalaksanaan Non Farmakologi sangat efektif dilakukan untuk mengurangi rasa nyeri yang timbul pada *gout arthritis*. Banyak referensi yang mengatakan bahwa kompres dapat menurunkan nyeri *gout arthritis* dan tidak menimbulkan efek samping yang berbahaya yaitu salah satunya dengan Kompres Daun Seledri terhadap penurunan nyeri. Tujuan penelitian ini untuk mengetahui pengaruh kompres daun seledri terhadap penurunan nyeri pada lansia penderita *gout arthritis* di Desa Krapyak. Sampel ditemukan 72 responden. Metode penelitian *Quasy Eksperimen* dengan *Pre and Post test Without Control* pemilihan sampel dengan Total Sampling. Penelitian ini menggunakan analisis statistik Uji *Wilcoxon Signed Ranks Tes*. Hasil penelitian didapatkan nilai *p-Value* 0,000 < 0,05 maka  $H_0$  ditolak dan dapat disimpulkan bahwa terdapat pengaruh kompres daun seledri terhadap penurunan nyeri pada lansia penderita *gout arthritis* di Desa Krapyak.

Kesimpulan penelitian ini yaitu kompres daun seledri dapat menurunkan nyeri pada penderita *gout arthritis*. Rekomendasi pada penelitian ini yaitu kompres daun seledri dapat diterapkan pada penderita *gout arthritis* secara mandiri di rumah.

Kata Kunci : *Gout Arthritis*, Nyeri, Kompres Daun Seledri.

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### Inhibition Kinetic of *Apium graveolens* L. Ethanol Extract and its Fraction on the Activity of Xanthine Oxidase and its Active Compound

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**Abstract:** *Apium graveolens*, one of the traditional medicinal plants, has a potential as anti-gout. We have reported that flavonoid of *A. graveolens* could inhibit activity of xanthine oxidase enzyme up to 85.44%. The aim of the research was to investigate the type of inhibition kinetic of *A. graveolens* ethanol crude extract and its fraction inhibition kinetic, also to determine the active compound. The result of the research showed that the yield of *A. graveolens* ethanol crude extract was 10.40% (LC<sub>50</sub> 1968.19 mg L<sup>-1</sup>) with the inhibition activity was 6.04% until 74.01% (100-2000 mg L<sup>-1</sup>). Inhibition kinetic of 1500 mg L<sup>-1</sup> crude extract caused increased K<sub>M</sub> of fraction 6 (0.10 mM) and unchanged V<sub>max</sub>. Based on these data, the type of inhibition was competitive. Purification of crude extract resulted 7 fractions and the highest activity was achieved by fraction 6 (inhibition activity was 85.08%). The purification of crude extract caused the increasing of inhibition activity effect. Inhibition kinetic of fraction 6 (150 mg L<sup>-1</sup>) caused increase K<sub>M</sub> (0.30 mM) and unchanged of V<sub>max</sub>. Based on that, the type of inhibition was competitive. Purification of fraction 6 resulted 6 fraction and the highest activity was achieved by fraction 5 (inhibition activity was 88.41%). Based on analysis of LCMS and NMR, the active compound of *A. graveolens* extract (fraction 5) were potential to inhibit the activity of xanthine oxidase, the active compound was 5, 7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one and 2, 3-dihydro-6-hydroxy-5-benzofuran carboxylic acid.

**Key words:** *Apium graveolens* L., ethanol extract, xanthine oxidase, inhibition kinetics, anti-gout

#### INTRODUCTION

Gout is a metabolic disorder disease caused by the deposit of uric salt crystals in joints causing acute inflammatory response or deposit of uric acid crystals in cartilage tissue not causing inflammatory response. In the last decade, gout disease is increasing both in developing and developed countries, especially in 40-50 years old male. In US, gout attacked more than 5 million people (Yu, 2007). Number of patients tended to increase from year to year, in line with the pattern of people that likes to consume more foods with high in protein. Allopurinol is used as anti-gout, the compound can inhibit the activity of Xanthine Oxidase (XO), while the enzyme itself can convert xanthine into uric acid in blood. However, allopurinol can cause side effects such as allergies, fever, chills and gastrointestinal disorders. Therefore, treatment with traditional medicines is important. Methanol extract of *Coryza bonariensis* could *in vitro* inhibited the activity of XO with IC<sub>50</sub> of 50.041 mM (Kocig *et al.*, 2000).

Barzilian medicinal plant of *Lychnoophora* (Filha *et al.*, 2006) and Indian medicinal plants such as: *Coccinia grandis* dan *Vitex negundo* (Umamaheswari *et al.*, 2007) could *in vitro* inhibited the activity of XO up to 50%.

Floral plants having potency as medicinal plants in Indonesia are about 30000 species, one of these plants known its efficacy is celery (*Apium graveolens* L.). Celery is known as vegetable, but this plant is more useful as herbal medicine to treat gout. Celery can be used as an alternative treatment to substitute synthetic drug such as allopurinol. Common known, celery has a curing effect with lower risk and side effect than other synthetic drugs. Iswanti and Darusman (2003) has studied the role of celery active compounds in inhibiting Xanthine Oxidase (XO) activity. But the XO inhibition kinetics of celery crude extract and its fractions study related to gout along to its active compounds determination have not been reported yet. Inhibition kinetics determination of natural active compound used as 'drug-to-be' is important. This is to study the apparent inhibitory mechanism, then

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