Botanicals that Normalize Uric Acid Levels and Relieve Symptoms of Gout

Co-authored by Donald R. Yance, RH (AHG), CN and Suzanne E. Sky, L.Ac., MTOM

Discussion

Gout is a metabolic, inflammatory condition that can be debilitating. The characteristic burning pain, redness, and swelling results from deposits of needle-like monosodium urate monohydrate (MSU) crystals. While about 50% of initial gout attacks occur in the big toe joint, gout can occur in any joint. It can also affect the bursae and tendons. Gout attacks are most often acute with limited duration. Chronic arthritic gout involves intermittent acute attacks over time, with periods that are pain- and symptom-free. Chronic arthritic gout can lead to degeneration of bone, cartilage, and tendon tissues.[1-5]

In 2008, the prevalence of gout was estimated at about 4% of the US population. Incidence has more than doubled from the 1960s to the 1990s which is partially attributed to the concurrent rise in obesity, metabolic disease, and hypertension.[6] Twenty percent of those with gout also have urinary tract stones and can develop interstitial urate nephropathy.[5] Arthritic gout is the third most common form of inflammatory arthritis.[4]

GOUT AND ELEVATED SERUM URIC ACID

Elevated serum uric acid is widely accepted as the primary marker of gout. Elevation results from a combination of overproduction of and/or under-excretion of uric acid. Normal levels of uric acid in the blood are 7.0 mg/dL in men and 6.0 mg/dL in women.[1,7] Anything equal to or greater than that concentration defines high serum uric acid. When levels exceed about 6.8 mg/dL, uric acid crystals form as MSU. These needle-sharp crystals deposit primarily in the joints but also in the kidneys or other tissues such as the tendons.[1,7]

High serum levels of uric acid result from either insufficient elimination (about 90%) or excess production (about 10%) of uric acid and, most often, from a combination of both factors.[8] About two-thirds of the body's uric acid is filtered in the glomeruli of the kidneys, while up to about 90% of the filtered urate is reabsorbed in the kidneys' tubules. The remaining one-third is filtered and eliminated through the gastrointestinal tract.[1,7] Renal dysfunction contributes to decreased uric acid elimination.

Diets high in purines from animal foods contribute to excess uric acid in the system. High fructose consumption is a culprit because fructose depletes ATP (adenosine triphosphate) and increases uric acid amounts. Dietary management of gout includes limiting sugar, alcohol, and purine-rich foods. Hydration with water and eating an abundance of vegetables is found to be beneficial.[1;7-9]

URIC ACID BALANCE

Uric acid is a normal product of purine catabolism in the body and is known for its antioxidant actions and ability to inhibit DNA damage.[10] Purines, essential to energy production, modulate cellular energy metabolism and signal transduction. As structural components of conenzymes, they play a key role in human physiology. Cells require purines in a balanced ratio for cellular functions. The purine nucleic acids adenine and guanine are converted to uric acid in the process of producing ATP (adenosine triphosphate), SAMe (the methyl donor S-adeneosylmethionine) and NADH (nicotine adenine dinucleotide – a cofactor in energy production).[1,7] Uric acid production occurs primarily in the liver but also occurs in the intestines, muscles, kidneys, and the vascular endothelium.[7,10]

HIGH URIC ACID IMPLICATED IN OTHER CONDITIONS

Uric acid becomes detrimental to physiological processes when serum levels are elevated. High amounts induce an inflammatory response along with oxidative stress and resultant cellular damage.[7] High serum uric acid levels are associated with many other disease conditions including type 2 diabetes, cardiovascular, cerebrovascular, and renal disease conditions. Studies suggest that hyperuricemia is associated with conditions of hypertension, vascular dementia, preeclampsia, and others.[5,7,11] Increase of serum uric acid is also associated with disease severity.[7]

INFLAMMATION AND GOUT

MSU crystals are highly inflammatory. It is found that proteins coat the MSU crystals and they change with the inflammatory response. The innate immune systems response to MSU crystals are studied particularly in regard to neutrophils, which are involved with tissue breakdown and repair. The presence of neutrophils in the synovial and joint fluid is a key indicator of gout since there are no neutrophils in healthy joints.[12,13]

Neutrophils migrate in large amounts to the sub-endothelial tissues in response to MSU-induced inflammation. Therapies that decrease neutrophils are found to relieve acute gout symptoms.[11-14] The interaction of MSU crystals with neutrophils stimulates production of pro-inflammatory compounds including lysosomal enzymes, transcription factor-dependent genes, and free radical oxygen species.[12-14]

Cytokines and chemokines play a role in the inflammatory processes associated with gout. MSU crystals also induce production of a wide variety of inflammatory mediators including eicosanoids, COX-2, TNF, IL-6, IL-8, and cytokines such as IL-1β. MSU crystals activate NFKβ and other pathways.[12-14] IL-1β is thought to play a primary role in driving inflammation in gout.[12,13]

XANTHINE OXIDOREDUCTASE AND OXIDATIVE INJURY

The enzyme xanthine oxidoreductase (XO) plays a key role in urate formation. It catalyzes oxidation of hypoxanthine to xanthine and then to uric acid. XO is also a major source of oxygen-derived free radicals including the superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals. XO is thought to be the main mechanism of oxidative injury in gout, ischemia, kidney damage, diabetes, and hypertension. One therapeutic approach to gout is inhibition of XO.[1,10]

THERAPEUTIC APPROACH TO GOUT

The primary goals in treating gout are to lower uric acid levels and calm inflammation. Extensive research on botanicals finds that many show promise as antigout agents. Numerous botanicals are well-known for their anti-inflammatory and antioxidant activity, which is primarily attributed to their flavonoid constituents. Plants with flavonoids, alkaloids, essential oils, phenolic compounds, iridoid glucosides, and coumarins show activity in treating gout both through inhibiting XO and/or through anti-inflammatory influence.[8] Flavonoids are also noted for their ability to inhibit the XO pathway.[10]

KIDNEY PROTECTIVE HERBS

Hyperuricemia is associated with increased risk of many diseases including renal disease.[1,7] At the same time, renal disease and/or decreased kidney function contribute to the development of high serum uric acid. The kidneys eliminate about two-thirds of the uric acid created daily, via filtration in the glomeruli. Renal function also influences the amount of uric acid reabsorbed into the blood.[7] Hence, efficient urate clearance is dependent upon renal health.

Several herbs support kidney function through multiple mechanisms. Phellodendron, Celery Seed, Juniper, and White Mulberry Fruit are all known for their nephroprotective qualities. These botanicals directly support kidney function through their protective influence combined with their action as anti-inflammatory and antioxidant agents. Mulberry Fruit and Celery Seed are both known for their ability to support healthy kidney function. When all of these botanicals are combined in a synergistic formula, kidney health and function is protected by their ability to inhibit the XO pathway, normalize serum uric acid levels, and calm inflammatory pathways.

Botanicals that Normalize Uric Acid Levels and Relieve Symptoms of Gout

Phellodendron Bark (*Phellodendron amurense*)

Phellodendron bark is valued in Chinese medicine as an herb that strongly clears heat from the lower part of the body. It is considered to be bitter, cold, and draining.[15,16] The main active constituents of Phellodendron include isoquinoline alkaloids such as berberine, phellodendrine, and magnoflorine. Berberine is known to inhibit COX-2 expression. It has recently been shown to suppress IL-1β, a key inflammatory mediator in gout. Phellodendron also demonstrates anti-proliferative influence.[11,17,18]

Animal studies find Phellodendron is anti-inflammatory and reduces serum uric acid levels. It is found to inhibit XO and to exert antigout activity.[17] The phenylpropanoid glycoside syringin, from Phellodendron bark, is found to suppress expression of MSU-induced inflammation. Syringin inhibits the expression of inflammatory cytokines, including IL-1β, IL-6, and COX-2. It also weakens adhesion between neutrophils and endothelial cells and is found to prevent acute gout.[19]

Celery Seed (*Apium graveolens*)

All parts of the Celery plant are valued as food and medicine. While native to Southern Europe and the Mediterranean, Celery is also found in other areas of the world. *Apium graveolens L.* grows wild in areas of the Himalayas, Punjab, and western India. Celery seed is used in traditional Iranian medicine to treat rheumatoid arthritis, gout, and kidney conditions. Celery also has a long history of use in Ayurveda and Unani medical systems in formulations to treat rheumatism and gout. It was also used for asthma, bronchitis, and inflammatory conditions. Celery seed is traditionally used in many areas to regulate blood pressure, benefit joint health, and decrease uric acid levels. It is used for bone spurs and other types of calcifications. Known as a diuretic, it is also valued to improve kidney function.[20,21]

Celery seeds contains about 3% volatile oils including about 80% limonene. The seeds are rich in vitamin B, and contain flavonoids, coumarins, and linoleic acid.[10,20,22]

Celery seeds are found to exert anti-inflammatory, antioxidant, and antiseptic activity.[10,22] Studies find that Celery seed is beneficial in treating gout as it helps eliminate uric acid. It is also found helpful for conditions of elevated lipids, obesity, and hypertension. Celery seeds are high in phthalides, which give celery its distinct flavor.[23] Luteolin, a major constituent of celery seed, is noted for its inhibitory activity on XO.[24]

Tart Cherry Fruit (*Prunus cerasus*)

While the cherry family is quite large, the primary differentiation is between sweet and sour or tart cherries. Both fruits are high in anthocyanins, which are known for their powerful anti-inflammatory and antioxidant activity. The primary anthocyanins in sour cherries are derivatives of cyanidin. They are noted for strong antioxidant activity, especially in metabolic reactions.[25,26]

P. cerasus L. is the sour or tart cherry, of which there are three main types. The sour flavor in cherries is due to the presence of malic acid and a lower content of simple sugars in relation to sweet cherries. Cherries contain vitamins A, E, K, C, and B. They contain carotenoids and a small amount of lutein and zeaxanthin. They also contain minerals and are high in potassium. Sour cherries are found to contain a higher phenolic content than sweet cherries due to higher concentrations of anthocyanins and hydroxycinnamic acids. Sour cherries are high in flavonols including epicatechin, quercetin, and kaempferol.[27]

Sour cherries are anti-inflammatory and antioxidant. They are found to increase antioxidant enzymes and decrease lipid peroxidation. Sour cherries inhibit inflammatory pathways including COX-2, NO (nitrous oxide), and TNF, which are all implicated in rheumatic conditions and are thought to contribute to the ability of cherries to alleviate arthritic pain and gout.[27-29]

Cherry consumption is found to lower serum uric acid levels and to inhibit XO.[28-31] In a large human study of about 633 participants, researchers reported sour cherry intake to be correlated with lower risk of gout attacks.[32]

Tart cherries have the potential to reduce the pain associated with gout and some patients use cherries as a strategy to avoid and/or treat gout attacks.[33] Sour cherry concentrate is found to decrease serum urate and to increase excretion of urinary urate.[28,34]

White Mulberry Fruit (*Morus alba L.*)

Mulberry trees, native to northern China, grow throughout Asia and the fruit is widely used as food and medicine.[35] White mulberry tree fruit is highly nutritious and can be white, lavender, or dark purple in color. The fruit is juicy, sweet, bland, and sometimes slightly sour.[36]

In Chinese medicine, the fruit is valued as a blood tonic. Mulberry fruit is used to benefit the kidneys, treat weakness, fatigue, anemia, and as a tonic for the elderly.[36] The traditional

medicinal use of Mulberry fruit is to protect against liver and kidney damage, strengthen joints, improve eyesight, and for their anti-aging influence.[37]

The fruit is high in anthyocyanins, phenolic acids, and flavonoids, including apigeninum, luteolin, and quercetin, which are noted for their antioxidant activity.[36,38,39] Mulberry fruit is antioxidant, anti-diabetic, and hepatoprotective.[39] The fruit is found to exert a protective, tonic influence on the kidneys.[40]

The flavone morin, abundant in Mulberry fruit, is found to lower uric acid levels through various pathways in animal studies. It powerfully inhibits urate uptake in rat kidneys and moderately inhibits XO.[41] In animal studies, morin is found to decrease symptoms of arthritic gout including swollen ankles and synovial hyperplasia. It down-regulates many inflammatory responses including COX-2, NF-kβ, and TNF. Morin demonstrates antioxidant activity and increases catalase and SOD (superoxide dismutase) in the joints.[42]

Paederia (*Paederia scandens/foetida*)

Paederia is an important Ayurvedic herb traditionally used for gout and other inflammatory conditions. It grows as a perennial twining vine in East and South Asia.[43] The plant is also found in the Himalayas and areas of India where it is traditionally used as a food and medicine.[43-45] The leaves are cooked with rice to treat joint diseases including rheumatism and gout.[44] Paederia was valued in polyherbal formulas for arthritis.[43] It is also used for the gastrointestinal system.[44,45]

Chemical constituents in Paederia include iridoid glycosides, sitosterols, alkaloids, polysaccharides, flavonoids, and ascorbic acid. It contains a high percentage of minerals including phosphorus, nitrogen, potassium, and magnesium.[44,45]

Paederia is found to be antiviral, antipyretic, antioxidant, and anti-inflammatory. It is also hepatoprotective and antiproliferative.[43,44] Paederia extract is found to modulate the production of pro-inflammatory mediators in synovial tissue.[46]

Paederia inactivates NF-κβ pathway transmembrane signal transduction, which plays a crucial role in the pathogenesis of gout.[46] Paederia extract is also found to be hypouricemic and to inhibit XO.[47]

Mango Leaf (*Mangifera indica*)

Mango trees grow wild in India and are cultivated worldwide in tropical areas.[48] Mango leaf is a traditional medicine used to treat inflammatory conditions.[49] It contains saponins, tannins, steroids, flavonoids, and cardiac glycosides.[49]

Mango leaf exerts an anti-inflammatory influence and Mango leaf extract (MLE) is found to decrease TNF and IL-1β in tissues. It is thought that Mango leaf gives relief from arthritic gout because it inhibits these inflammatory pathways.[48,49] Mango leaf exerts antioxidant activity and is found to inhibit lipid peroxidation.[48]

The polyphenol mangiferin is found to significantly reduce uric acid, creatinine, and urea nitrogen levels. It modulates urate transporters, enhances uric acid excretion, and decreases uric acid reabsorption.[50] In animal studies, mangiferin is found to decrease serum uric acid through inhibiting XO.[51]

Juniper Berry (*Juniperus communis*)

Juniper is a small evergreen best known for its volatile oils. Traditionally known as a diuretic, it was valued as a urinary and kidney remedy in Europe and the Mediterranean.[52] The American Eclectic physicians used Juniper berry to treat arthritic gout and relieve renal hyperemia. They used it as a protective against nephritis and as a restorative for the epithelium of the renal tubules.[53]

The berries are high in flavonoids including apigenin, rutin, luteolin, and quercetin. Juniper berry oil predominantly contains monoterpene hydrocarbons.[52] Juniper berry is noted to exert powerful antioxidant activity.[54] It is also found to be anti-inflammatory, antimicrobial, analgesic, and hepatoprotective.[52]

Phyllanthus Herb (*Phyllanthus niruri*)

Phyllanthus is traditionally used in South America to treat excess uric acid.[55,56] The leaf extract shows antihyperuricemic activity in animal studies. This is attributed to several lignans that demonstrate specific activity to lower serum uric acid levels. The three lignans – phyllanthin, hypophyllanthin, and pyltetralin – are found to increase urinary uric acid excretion.[55,56] A study shows that Phyllanthus extract decreases serum uric acid through inhibition of XO.[56]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please contact Natura at 888.628.8720.

References

1. Gliozzi M, Malara N, et al. *The treatment of hyperuricemia: Review*. Int J Cardiology. 2016 June 15. 213:23-27.
2. Chilappa CS, Aronow WS, et al. *Gout and hyperuricemia*. Compr Ther. 2010. 36:3-13.
3. Liu-Bryan R. *Intracellular innate immunity in gouty arthritis: role of NALP3, Inflammasome*. Immunol Cell Biol. 2010 January. 88(1): 20–23. doi:10.1038/icb.2009.93.
4. Kumar KA, Kumar MS. *Herbal approach toward Vatarakta (Gout), a metabolic syndrome: a review*. Int J Ayu Pharm Chem. 2014. 1(2):22-43.
5. Grassi W, De Angelis R. *Clinical features of gout*. Reumatismo. 2012 January 19. 63(4):238-245.
6. Zhu Y, Pandya BJ, Choi HK. *Prevalence of gout and hypertension in the US general population*. The National Health and Nutrition Examination Survey 2007-2008. Arthritis & Rheumatism. 2011 October. 63(10):3136-3141.
7. 7. Maiuolo J, Oppedisano F, et al. *Regulation of uric acid metabolism and excretion*. Int J Cardiology. 2016. 213:8-14.
8. Ling X, Bochu W. *A review of phytotherapy of gout: perspective of new pharmacological treatments*. Pharmazie. 2014. 69:243-256.
9. Schumacher HR, Chen LX. *Newer Therapeutic Approaches: Gout*. Rheum Dis Clin N Am. 2006. 32:235–244.
10. El-Rahman HSMA, Abd-El Hak, NAM. *Xanthine oxidase inhibitory activity and antigout of celery, leek, parsley, and molokhia*. Advances in Biochemistry. 2015. 3(4):40-50.
11. Pillinger MH, Bangalore S, et al. *Cardiovascular Disease and Gout: Real-World Experience Evaluating Patient Characteristics, Treatment Patterns, and Health Care Utilization*. J Manag Care Spec Pharm. 2017 June. 23(6):677-683. doi: 10.18553/jmcp.2017.23.6.677.
12. Kawai T, Akira S. *The roles of TLRs, RLRs and NLRs in pathogen recognition*. Int Immunol. 2009; 21:317–337.
13. Landis RC, Haskard DO. *Pathogenesis of crystal-induced inflammation*. Curr Rheumatol Rep. 2001; 3:36–41.
14. Popa-Nita O, Naccache PH. *Crystal-induced neutrophil activation*. Immunology and Cell Biology. 2010. 88:32-40.

Phellodendron

15. Dharmananda S. Ermiao San: Two Marvels Powder. 2002 March.
16. Chen JK, Chen TT. *Chinese Medical Herbology and Pharmacology*. Art of Medicine Press. 2004. City of Industry, CA.
17. Yang C, Zhu JX, et al. *Effects of processing Phellodendron amurense with salt on anti-gout*. Zhongguo Zhong Yao Za Zhi. 2005 Jan. 30(2):145-148. (Article in Chinese).
18. Jin H, Jin X, et al. *Berberine affects osteosarcoma via downregulating caspase-1/IL-1 β signaling axis*. Oncology Reports. 2017. 37:729-736.
19. Yin L, Yang YH, et al. *Effects of syringing from Phellodendron chinensis on monosodium urate crystal-induced inflammation and intercellular adhesion molecule-1 (ICAM-1) expression*. African J Pharmacy and Pharmacology. 2012 June 8. (62)1:1515-1519.

Celery Seed

20. Ramezani M, Nasri S, Yassa N. *Antinociceptive and anti-inflammatory effects of isolated fractions from Apium graveolens seeds in mice*. Pharmaceutical Biology. 2009. 47(8):740-743.
21. Fazal SS, Ansari MM, et al. *Isolation of 3-n-butyl phthalaide and sedanenolide from Apium graveolens Linn*. Indo Global J Pharmaceutical Sciences. 2012. 2(3):258-261.
22. Fazal SS, Singla RK. *Review on the pharmacognostical and pharmacological characterization of Apium graveolens Linn*. Indo Globabl J Pharmaceutical Sciences. 2012. 2(1):36-42.
23. Tsi D, Das NP, Tan BK. *Effects of aqueous celery (Apium graveolens) extract on lipid parameters of rats fed a high fat diet*. *Planta Med*. 1995. 61:18-21.
24. Yan J, Zhang G, et al. *Effect of luteolin on xanthine oxidase: inhibition kinetics and interaction mechanism merging with docking simulation*l Food Chem. 2013 Dec 15. 141(4):3766-3773. doi: 10.1016/j. foodchem.2013.06.092. Epub 2013 Jun 28.

Tart Cherry Fruit

25. Kirakosyan A, Seymour EM, et al. *Chemical profile and antioxidant capacities of tart cherry products*. Food Chem. 2009. 115:20-25.
26. Wang H, Nair MG, et al. *Novel antioxidant compounds from tart cherries (Prunus cerasus).* J Nat Prod. 1999. 62:86-88.
27. Ferretti G, Bacchetti T, et al. *Cherry antioxidants: from farm to table*. Review. Molecules. 2010. 15:6993-7005. doi: 10.3390/ molecules15106993
28. Tiernan C, Imrhan V, et al. *Tart cherry in amelioration of pain in the elderly*. Nutrition and Aging. 2015. 3:203-217.
29. Seeram NP, Momin RA, et al. *Cyclooxygenase inhibitory and antioxidant cyanidin glycosides in cherries and berries*. Phytomedicine. 2001; 8:362-369.
30. Jacob RA, Spinozzi GM, et al. *Consumption of cherries lowers plasma urate in healthy women*. J Nutr. 2003. 133:1826-1829.
31. Haidari F, Mohammad SM, et al. *Inhibitory Effects of Tart Cherry (Prunus cerasus) Juice on Xanthine Oxidoreductase Activity and its Hypouricemic and Antioxidant Effects on Rats*. Mal J Nutr. 2009. 15:53-64.
32. Zhang Y, Neogi T, et al. *Cherry consumption and decreased risk of recurrent gout attacks*. Arthritis Rheum. 2012. 64(12):4004-4011. doi:10.1002/art.34677.
33. Harrold LR, Mazor KM, et al. *Patients and providers view gout differently: a qualitative study*. Chronic Illn. 2010. 6:263-271.
34. Bell PG, Gaze DC, et al. *Montmorency tart cherry (Prunus cerasus L.) concentrate lowers uric acid, independent of plasma cyaniding-3-O-glucosiderutinoside*. J Functional Foods. 2014 November. 11:82-90.

White Mulberry Fruit

35. Anis S, Bhargava T, Upadhyay H. *A Review on phytotherapy by Morus alba*. Int J Pharm Chem Sci. 2012 Oct-Dec. 1(4):1563-1566
36. Dharmananda S. *Fruit as Medicine: Morus Fruit (Mulberry).* 2003 Sept. Online. Institute for Traditional Medicine. Portland, Oregon.
37. Wattanathorn J, Thukummee W, et al. *Acute and subchronic toxicity of mulberry fruits*. Am j Agricultural and Biological Sciences. 2012. 7(3):378-383.
38. Arfan M, Khan R, et al. *Antioxidant activity of Mulberry fruit extracts*. Int J Mol Sci. 2012. 13:2472-2480. doi: 10.3390/ijms13022472
39. Chan EW, Lye PY, Wong SK. *Phytochemistry, pharmacology, and clinical trials of Morus alba*. Chin J Nat Med. 2016 Jan. 14(1):17-30.

40. Ullah N, Khan MA, et al. *Nephro-protective potential of Morus alba, a prospective experimental study on animal models*. Pharm Biol. 2015. 54(3):530-535.
41. Yu Z, Fong WP, Cheng CHK. *Morin (3,5,7,2',4'-pentahydroxyflavone) exhibits potent inhibitory actions on urate transport by the human urate anion transporter (hURAT1) expressed in human embryonic kidney cells.* Drug Metabolism and Disposition. 2017. 35(6):981-986.
42. Dhanasekar C, Rasool M. *Morin, a dietary bioflavonol suppresses monosodium urate crystalinduced inflammation in an animal model of acute gouty arthritis with reference to NLRP3 inflammasome, hypo-xanthine phospho-ribosyl transferase, and inflammatory mediators*. European Journal of Pharmacology. 2016 786:116-127.

Paederia

43. Wadud MA, Akhter R, et al. *In vivo pharmacological investigations of leaf extracts of Paederia foetida (L.)*. Int J Pharm Sci Rev Res. 2015 March-April. 31(2):166-172.
44. Chanda S, Sarethy IP, et al. *Paederia foetida – a promising ethnomedicinal tribal plant of northeastern India*. J Forestry Res. 2013. 24(4):801-808. doi: 10.1007/s11676-013-0369-2
45. Kumar V, Anwar F, et al. *Paederia foetida Linn. leaf extract: an antihyperlipidemic, antihyperglcaemic and antioxidant activity*. Complementary and Alternative Medicine. 2014. 14: 16 pages.
46. Ma Y, Zhou LL, et al. *Effects of extracts from Paederia scandens (LOUR.) MERRILL (Rubiaceae) on MSU crystal-induced rats gouty arthritis.* Am J Chin Med. 2009. 37:669
47. Yan H, Ma Y, et al. *The dual actions of Paederia scandens extract as a hypouricemic agent:xanthine oxidase inhibitory activity and uricosuric effect*. Planta Med. 2008 Sep. 74(11):1345-1350. doi: 10.1055/s-2008-1081344. Epub 2008 Aug 26.

Mango Leaf

48. Jiang Y, You XY, et al. *Effects of extract from Mangifera indica leaf on monosodium urate crystal-induced gouty arthritis in rats*. Hindawi Publishing Corporation. Evidence-Based Complementary and Alternative Medicine. 2012. Article ID 967573. 6 pages.
49. Oluwole OG. *Bioactive compounds in Magnifera indica demonstrates dose-dependent anti-inflammatory effects*. Inflamm Cell Signal. 2015. 2:7 pages.
50. Hu QH, Zhang X, et al. *Mangiferin promotes uric acid excretion and kidney function improvement and modulates related renal transporters in hyperuricemic mice*. Yao Xue Xue Bao. 2010 Oct. 45(10):1239-1246.
51. Niu Y, Lu W, et al. *Reducing effect of mangiferin on serum uric acid levels in mice*. Pharm Biol. 2012 Sep. 50(9):1177-1182. doi: 10.3109/13880209.2012.663763.

Juniper Berry

52. Bais S, Gill NS, et al. *A phytopharmacological review on a medicinal plant: Juniperus communis*. Review Article. Hindawi Publishing Corporation. International Scholarly Research Notices. 2014. Article ID 634723. 6 pages.
53. Ellingwood's American Materia Medica. Therapeutics and Pharmacognosy - Page 270
54. Elmastas M, Gulcin I, et al. *A study on the in vitro antioxidant activity of Juniper (Juniperus communis L.) fruit extracts*. J Analytical Letters. 2006. 39(1)

Phyllanthus

55. Murugaiyah V, Chan KL. *Antihyperuricemic lignans from the leaves of Phyllanthus niruri*. Planta Med. 2006. 72(14):1262-1267.
56. Murugaiyah V, Chan KL. *Mechanisms of antihyperuricemic effect of Phyllanathus niruri and its lignan constituents*. J Ethnopharmacol. 2009 July 15. 124(2):233-239. doi: 10.1016/j.jep.2009.04.026