Review Article

Promising actions of certain medicinal and dietary plants for the management of hyperuricemia as a natural remedy: A review

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Abstract

Hyperuricemia ensues due to the reabsorption and diminished evacuation of uric acid which is accountable for the advancement of gout and radically concomitant with the progress of numerous long-lasting ailments for instance malignant tumor, cardiovascular ailments, and kidney failure. Underlying factors such as excessive intake of purine containing supplements, obesity, age, sex, sugar, and alcohol intake may condense the formation of uric acid and exaggerate the injurious effects of uric acid. Novel inventive pharmaceutical and curative mediations are being used for the tackling of hyperuricemia but the problem arises when patients complain about adverse reactions with serious complications that may increase the rate of developing new diseases. Medicinal and dietary plants with bioactive phytochemicals like polyphenols, flavonoids are more feasible due to less toxicity, more economical for developing countries, formulation advantages for primary healthcare, better appropriateness with human physiological conditions. To facilitate the design of plant-based alternative therapy it is a prerequisite to connecting herbal medicine with novel prescription and additional precise explorations have to be ensured for the authentication of the effectiveness and safety of herbal formulations. The existing assessment outlines production, metabolism, and excretion of uric acid, hazard influences (overabundance and low excretion of uric acid), conventional pharmacotherapy for hyperuricemia and its related complications, the use of plants, its origin; parts to be used, mechanism of actions to preclude hyperuricemia are highlighted based on of previously issued literature.

Keywords: Uric acid, hyperuricemia, dietary plants, bioactive phytochemicals, xanthine oxidase inhibitory activity

Introduction

Uric acid (UA) {$C_5H_4N_4O_3$ [IUPAC: 7, 9- dihydro-1H purine-2, 6, 8(3H) trione]} plays an important role in the balance of potassium, sodium, bicarbonate, or alkaline and other electrolytes which specially produced from the dead cells and purine that presents in dietary elements. It is the heterogeneous compound having C, H, N, and O in its constitutional configuration presents 3-7 mg/dL (standard level) in the blood (El Ridi and Tallima, 2017; Hafez et al., 2017).

Xanthine oxidase enzyme catalyzes the construction of uric acid (290 kDa) by the oxidation of hypoxanthine to xanthine in the manifestation of molecular oxygen specifically superoxide anions and hydrogen peroxide and consequently to uric acid (Lin and Shih, 1994; Candan, 2003).

Excessive production (≥ 7 mg/dL in males and ≥ 6 mg/dL in females) or less excretion of uric acid is responsible for hyperuricemia (HUA) which is a metabolic ailment. The prevalence of serum uric acid is short in children, higher in men than women (Desideri et al., 2014; Johnson et al., 2003).

Innumerable threats influence the production of uric acids (UA) such as age, gender; race, genetic makeup, environmental, socioeconomic factors, geographic location as well as endogenous sources like meat, seafood, and alcohol intake are associated with development of high UA formation in the blood. Additionally, hyperuricemia (HUA) correspondingly surges production of reactive oxygen

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species (ROS), endothelin-1 production and nitric oxide (NO) system reticence, enriched synthesis of renin-angiotensin-aldosterone system stimulation (De Oliveria and Burini, 2012; Choi and Churhan, 2007). UA starts inducing crystals in renal tubules recognized as monosodium urate crystals (NaU) ensues gout owing to the installation of urate crystals in joints that are connected with inflammation (Brook et al., 2010; Roddy and Doherty, 2010). HUA possibly will trigger numerous prolonged and acute ailments, e.g. gout, renal failure, tumor lysis syndrome (TLS), coronary heart disease, hemospermia, arterial hypertension, and metabolic syndrome (Krishnan, 2014; Gustafsson and Unwin, 2013).

In recent times newly exploited therapeutic tactics are available for HUA to persevere with certain adverse properties. In the future, alternative prescriptions or bioactive components in dietary foods like fruits and vegetables with lesser side effects as well as its antioxidant potentiality are necessary to confront HUA complaints (Yang et al., 2015; Wang et al., 2017). Consequently, the rationales of this present review are to deliver an outline of the influence of various plant parts, vegetables, fruits, and herbal products on the hyperuricemic conditions, their mode of action, and active constituents.

Production, metabolism, and elimination of uric acid

Uric acid is the natural waste product of purine degradation. It can be generated not only within the body or endogenously during cell turnover but also in association with various exogenous sources. Purine nucleotides namely two such as adenine (6-aminopurine), guanine (2-amino-6-oxypurine) which is a constitutional component present in DNA (Deoxyribonucleic acid), RNA (Ribonucleic acid), ATP (Adenosine triphosphate), AMP (Adenosine monophosphate), cyclic AMP (Cyclic Adenosine monophosphate), CGMP (Cyclic Guanosine monophosphate), GTP (Guanosine triphosphate), NADH (Nicotinamide Adenine Dinucleotide), NADPH (Nicotinamide Adenine Dinucleotide Phosphate), and coenzyme Q. Purine is mainly synthesized in the liver by de novo and salvage pathway (Itakura et al.,1981).

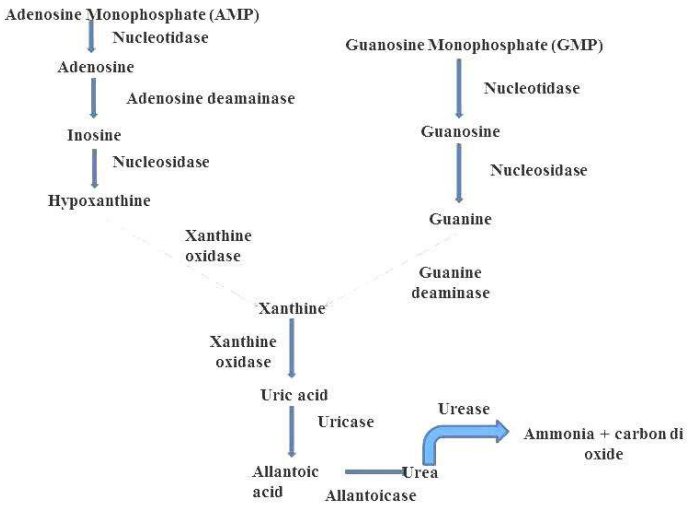

Figure 1. Production and metabolism of uric acid (Maiuolo et al., 2016; Kushiyama et al., 2016)

Xanthine oxidoreductase (XOR) is the enzyme responsible for the expression of reactive oxygen species and uric acid and predominantly existing into two versions xanthine oxidase (XO) and xanthine dehydrogenase (XDH). XOR converts to XDH and then XO. Hypoxanthine is formed from adenine by the action of adenase enzyme, which is converted into xanthine by xanthine oxidase to end with uric acid. By guanase enzyme catalysis guanine converts into xanthine.

XO is the main enzyme for the breakdown of hypoxanthine and xanthine that leads to the subsequent formation of uric acid. Purine from exogenous or dietary sources is being mainly catabolized by xanthine dehydrogenase. The cells and tissues like liver, skeletal muscle, intestine, kidney, vascular endothelial are highly capable of expressing XDH which plays a significant role in the formation of uric acid (Waring et al., 2000; Waring 2005; Maiuolo et al., 2016).

Uric acid is further processed to allantoin by the presence of urate oxidase (uricase) enzyme that is 5-10 times an extra soluble form of uric acid in mammals excluding primates (human and higher apes) (Yeldandi et al., 1992; Vigetti et al., 2000). Oxidative stress is measured via allantoin as a biomarker as it is formed when uric acid responds with reactive oxygen species and readily excreted through the urine (Kandar et al., 2006; Barsoum and Khatib, 2017). The kidney is responsible for the evacuation of 75% UA and the other 25% is eliminated by the gastrointestinal tract that supports to conserve the regular body uric acid levels (De Oliveria and Burini, 2012). Urate-anion transporter (URAT) l, organic anion transporter (OAT) 1, and 3 in kidneys are the key transporters for uric acid excretion (Chen et al., 2015).

Aspects amalgamate with excessive production of uric acid

Overproduction appears in fewer percentages of patients who have hyperuricemia. Circumstances that provoke excess production of uric acid

Exterior issues in the form of diet (Bobulescu and Moe, 2012; Dehgan et al., 2008)

Foods associated with excessive purine meat from animal or marine origin, organ foods or legumes, beverages, alcohol intake (beer), fructose foods, and juices.

Inner issues (Reginato and Olsen, 2007; Torres and Puig, 2007)

- Enhanced purine cessation.
- Lack of enzymes participating in purine digestion (hypoxanthine–guanine phosphoribosyltransferase, uricase).
- Overabundance of phosphoribosyl pyrophosphate synthetase.
- Dearth of Glucose-6-phosphatase.

Metabolic syndromes (Kang et al., 2002; Choi et al., 2005; Bos et al., 2006)

Lesch-Nyhan syndrome, tumor lysis syndrome (a tricky situation of cancer chemotherapy), cardiovascular disorder, Type 2 diabetes, gout, hypertension, myocardial infarction, stroke, and renal disease, Kelley- seegmiller syndrome.

Particular categories of medications (Taniguchi et al 2005; Han et al., 2013)

Loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, thiazide, b-blockers, minute amount aspirin (<1 g per day), and non-losartan angiotensin II receptor blocker, cyclosporine, levodopa, ethambutol, pyrazinamide, lead, nicotinic acid, vitamin B_{12}, radiographic contrast agents, etc.

Other conditions (Bos et al., 2006; Bedir et al., 2003; Towiwat and Li, 2015; Robinson and Horsburgh, 2014).

- When cell casualty occurs in cancer, heamatological and inflammatory complications are liable for uric acid acceleration.
- Sunstroke, overweightness indicate the improved formation of uric acid exaggerating the risk of hyperuricemia.
- Leptin was noticed to raise serum altitudes of urate.

Underexcretion of uric acid

Underexcretion is the main reason for hyperuricemia. Kidneys separate out urate which is a salt of uric acid and exits the body across urine. Renal inadequacy happens if any inaccuracy ensues in this consistent procedure which leads to a reduced uric acid excretion (Cho et al., 2015).

Frequent polymorphisms in numerous genes (Iseki et al., 2001; Kang et al., 2002)

- Genes participating in renal UA transportation, comprising SLC2A9, ABCG2, SLC17A3, and SLC22A12.

Several autosomal dominant conditions (Gnanenthiran et al., 2011)

- In the thick ascending limb of the loop of Henle a gene called uromodulin controls water penetrability. If any transformations happen in the uromodulin gene the normal process will be prohibited, which sequentially enhances SUA.

Medications (Terkeltataub, 2006)

Pyrazinamide, nicotinate, and lactate rise urate reabsorption via performing on URAT1

Additional conditions (Choi et al., 2005)

Renal insufficiency, acidosis (alcoholic ketoacidosis, lactic acidosis, starvation acidosis and diabetic ketoacidosis), metabolic disorder, hypertension, pre-eclampsia, and eclampsia, hypothyroidism, hyperparathyroidism, sarcoidosis, trisomy 21, obesity, insulin resistance lessen flux of uric acid through urine and subsequently elevate serum UA.

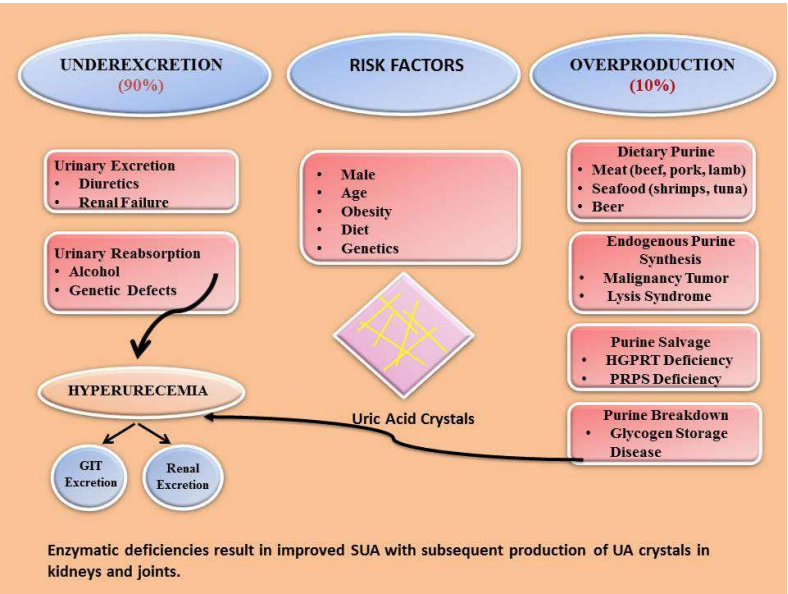

Figure 2. Overproduction and underexcretion of uric acid with underlying risk factors (Ragab et al., 2017)

Pharmacotherapy for controlling hyperuricemia

Numerous management approaches are present to efficiently decline as well as conserve SUA intensities beneath the saturation point and for this purpose; several anti-hyperuricemic preparations are available in the market. These preparations generally characterized into **uricostatic medicines** that show inhibitory action towards urate production (allopurinol, oxypurinol, febuxostat, etc) as well as **uricosuric medicines** that raises the frequency of uric acid excretion (probenecid, sulphinpyrazone, benzbromarone, etc). Other medications like uricase therapy (pegloticase, rasburicase) or can be said enzymatic preparations are also prescribed frequently by physicians. They are either prescribed separately or as a mixture aimed at depressing UA production otherwise enriches UA discharge. Additionally, the medications embrace anti – hyperuricemic actions but extremely accompanying with sundry complications (Dalbeth et al., 2006; Crittenden and Pillinger, 2013). Moreover, the invention of novel medications has been expanded day by day and some of them are in the developmental state (Gliozzi et al., 2016). Feature of some conspicuous medications, their dose and dosage form, mechanism of actions and reported complications are expounded and delineated in (Table 1 and figure 3).

Natural compounds that reduce SUA production

Established medications such to xanthine oxidase blocker in addition as urate lowering agents that are consumed to diminish SUA intensity inside the body by blocking XO produces frequent unfavorable outcomes that provide rise to other obstacles (Bustanji et al., 2011; Fagugli et al., 2008). Thus, XO blocker from plants or their metabolites requires more and more investigation because they hold greater beneficial potential with less adverse outcomes as well as discourage hyperuricemia, gout, gouty arthritis, calculus and other ailments.

Several isolated aromatic herbs from plants, medicinal plants,

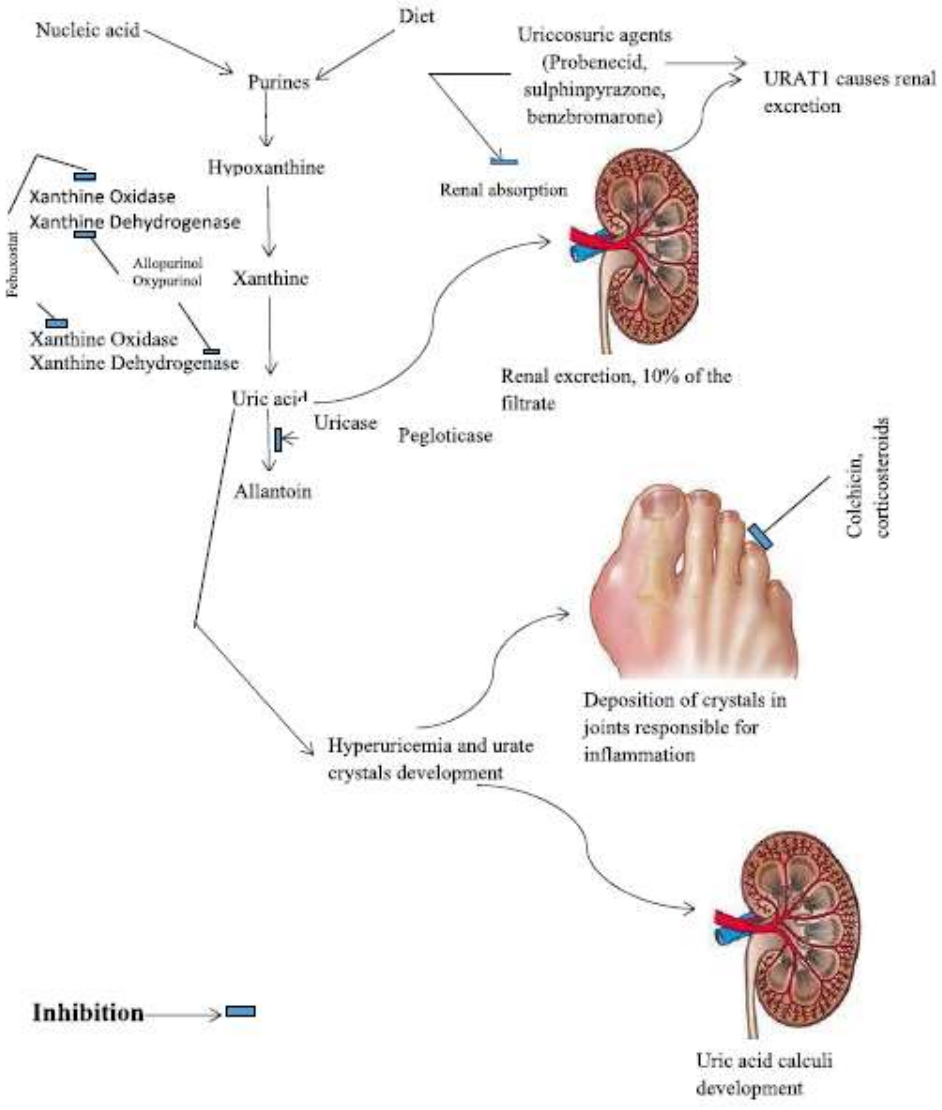

Figure 3. Pharmacotherapy for controlling hyperuricemia and how they react within normal physiological condition within the human body (Azevedo et al., 2017)

Table 1. Anti-hyperuricemic medications and related complications

Classification	Drugs	Dose and dosage form	Mechanism of action	Complications	References
Uricostatic preparations (Shows inhibitory action towards urate production)	Allopurinol (Leading therapeutic choice due to low price and prolonged safety issues)	300–600 mg/day (oral as well as an intravenous application)	1. Impedes xanthine oxidase. 2.Diminishes urate construction	Hypersensitivity, renal and hepatic failure, skin rashes, and gastrointestinal complications are considered detrimental for the human body.	(Terlkeltaub,2003; Dalbeth et al., 2006; Schumacher et al., 2008; Vargas and Neogi, 2017)
	Febuxostat	40 and 80-mg (orally as tablets)	1. An innovative non-purine selective inhibitor of xanthine oxidase. 2. Hamper ONOO and reactive oxygen species (ROS) creation non-competitively. 3. Counteracts endothelial damage.	Headache, nausea, liver abnormalities diarrhea, and even skin rashes.	(Perez et al., 2008; Schumacher et al., 2008; Becker et al., 2005a, 2005b)
Uricosuric drugs (Rises the frequency of uric acid excretion)	Probenecid	Initial quantity is 250 mg/day (two times) and so subsequently rising to 500-1000 mg/day (two times) for 7-14 days orally.	1. Block the resumption of uric acid through URAT-1	Hemolytic anemia with the engrossment of glucose-6 phosphate dehydrogenase insufficiency	(Reinders et al., 2009)
	Sulphinpyrazone	200-800 mg/day	1. Abolition of uric acid through kidney	Peptic ulcer likewise gastrointestinal complications.	(Gliozzi et al., 2016)
	Benzbromarone	100-200 mg/day (one time)	1. Exerts strong uricosuric effect	Hemolysis, peptic ulcer	(Reinders et al., 2009; Perez et al., 1998)
Uricase therapy	Pegloticase (pegylated uricase)	The tolerated amount is approximately 8 mg/14 days dispensed intravenously	1. Uric acid convert into soluble allantoin in presence of pigloticase and then in reduce serum uric acid.	Methemoglobinemia, hemolysis, and immunogenicity are recorded with its consumption	(Sundy et al., 2011).
	Rasburicase (Chemotherapy- induced hyperuricemia)	0.15 mg/kg/day or 0.2 mg/kg/day (5 days) Intravenously	1. Facilitates oxygen addition to uric acid by allantoin which is not active	Hypersensitivity reaction.	(Bosly et al., 2003; Richette et al., 2007).
Medications in experimental exploration	Anakinra(IL-1 receptor competitor) Nilonacept (IL-1 receptor) Canakinumab (Monoclonal anti-IL-1beta antibody) Lesinurad (URAT1 blocker) Arhalofenate (URAT1 blocker) Levotofisopam (URAT1 blocker), RDEA3170 (URAT1 blocker),				(Lu et al., 2013; Crittenden and Pillinger, 2013; Gliozzi et al., 2016)

vegetables, fruits, cereals, nuts, legumes, seeds, spices, green and black tea hold oxygen scavenging capacity to obliterate the oxidation and inflammation reaction formed through enzyme xanthine oxidase. To dam, the formation of uric acid XO is clogged by active constituents of plant metabolites and via hydrophobic bonds produced XO-active metabolites composite besides blocked the free active site that dosen't allow additional binding. Conspicuously, a surplus of active constituents present in plants impedes XO around alternatively over recommended medications (Sweeny et al., 2001; Alloway, 1999).

Several investigations establish that polyphenols are the foremost group amongst active constituents and others including lignans (secoisolariciresinol and matairesinol), flavonoids (flavones, apigenin, and luteolin, quercetin, naringenin), flavanols, oligomeric, catechin and epicatechin, anthocyanins (cyaniding, isoflavones, genistein), phenolic acids (chlorogenic acid, ellagic acid, vanillic acid, caffeic acid, p-coumaric acid, gallic acid, hydroxybenzoic acid and ferulic acid), curcuminoids (curcumin), stilbenes (resveratrol), chalcones (phlorizin, chalcone) and several alkaloids like costinones A, costinones B, isatinones A, isatinones B, indirubin, and trisindoline. More and more clinical investigations and research work should be performed to determine the opportunities of polyphenol for treating hyperuricemia (Vauzour et al., 2008; Gonzalez and Rodriguez, 2011; Bravo, 1998; Ahmad et al., 2010).

Table 2. Medicinal and dietary plants sources, common name, functional metabolites and mechanism of action

Scientific Name	Family	Local Name	Parts used	Active constituents	Mechanism	References
Allium cepa	Liliaceae	Onion	Bulbs and leaves	Phytonutrients including phenolics and flavonoids (e.g., Sugars, fibers, vitamins, anthocyanins, quercetin, and glucosides)	Xanthine Oxidase and xanthine dehydrogenase inhibitor	(Ouyang et al., 2018)
Allium sativum	Liliaceae	Garlic	Bulbs	Allicin and its derivatives S-allyl cysteine, diallyldisulfide, diallyltrisulfide	Xanthine Oxidase inhibitor	(Ghalehkandi et al., 2012)
Mangifera indica	Anacardiaceae	Mango	Extract of leaf	Not reported	Diminish serum uric acid level	(Jiang et al., 2012)
Ocimum sanctum L.	Lamiaceae	Ban Tulsi	All parts including seeds	Triterpene, ursolic acid	Decrease level of uric acid	(Singh et al., 2010; Kelm et al., 2000)
Apium gravelens	Umbelliferae	Celery	Dried powdered leaves	Polyphenols and flavonoids	Anti-hyperurecemic activity	(Mohamed and Al- Okbi, 2008)
Hibiscus sabdariffa	Malvaceae	Roselle	Whole plant	Epigallocatechin galla caffeicacid, epigallocatechin, catechin, and protocatechuic acid	Rising uricase activity, decline uric acid levels, impact on serum and liver xanthine oxidase	(Kuo et al., 2012)
Carica papaya	Caricaceae	Papaya	Unripe fruit and it's peels and leaf extracts	Not reported	Inhibit xanthine oxidase and serum uric acid	(Azmi et al., 2012; Calderon et al.,2015)
Phyllanthus emblica	Phyllanthaceae	Indian gooseberry/ amla	Fruits exract	Ascorbic acid, several active tannoid principles (emblicanin A, emblicanin B, punigluconin, and pedunculagin) and other polyphenols, Flavonoids, kaempferol, ellagic acid, and gallic acid.	Decrease serum uric acid	(Sarvaiva et al., 2015)
Prunus mume	Rosaceae	Japanese apricot and Chinese plum	Fruit	Triterpenoids such as oleanolic acid, ursolic acid, lupeol, and α-amyrin	Decrease serum and liver uric acid and xanthine oxidase	(YiLT et al., 2012)
Cassia fistula L.	Caesalpiniaceae	Badorlathi	Leaves, Pulps, Barks	Flavonoids	Xanthine oxidase inhibitors	(Argulla and Chichioco, 2014; Rahman and Debnath, 2015)
Cinnamomum cassia	Lauraceae	Cinnamon	Whole plants, bark, twigs	Cinnamic acid, cinnamaldehyde, coniferaldehyde, cinnacasolide B, Ocoumaric acid, cinnamic alcohol, dihydromelilotoside, cinnacasolide A, and cinnacasolide	Inhibits xanthine oxidase	(Ngoc et al., 2012)
Zingiber officinale	Zingiberaceae	Zinger	Rhizomes	6-gingerol, 6-shogaol, 6-paradol, quercetin, glutathione	Inhibits xanthine oxidase	(Nile et al., 2017)
Coix lachryma-jobi L. var	Gramineae / Poaceae	Adlay seed or Job's tears	Fruits and seeds	Phenolic antioxidants, including phenolic acids such as protocatechuic acid, chlorogenic acid, vanillic acid, caffeic acid, p-coumaric acid, and ferulic acid	Inactivation of xanthine oxidase	(Zhao et al., 2014)
Prunus cerasus L.	Rosaceae	Tart cherry	Cherry juice	Anthocyanins	Diminish synthesis of serum uric acid	(Bell et al., 2014)
Myristica fragrans	Myristicaceae	Nutmeg	Mace or aril or nut	Phytochemicals, such as phenolics, flavonoids, alkaloids, tannins and saponins.	Obstruct uric acid metabolism by impeding xanthine oxidase	(Ullah, 2017)
Olea europea	Oleaceae	Olive	Leaves	Luteolin-7-O-β-D-glucoside, luteolin , caffeic acid, oleuropien, and apigenin	Inactivate xanthine oxidase	(Flemmig et al., 2011)
Perilla frutescens	Lamiaceae	Perilla or Korean perilla	Leaves	Protocatechuic acid, chlorogenic acid, caffeic acid, 4-methoxy cinnamic acid, oleanolic acid, kaempferol-3 orutinoside, rosmarinic acid, luteolin, methyl-rosmarinic acid, apigenin, and 4,5,7-trimethoxyflavone	Inactivate xanthine oxidase and reduce serum uric acid	(Wang et al., 2017)
Caryophyllus aromaticus	Myrtaceae	Clove	Flower buds	Polyphenols and flavonoids	Inactivate xanthine oxidase	(Havlik et al., 2010)
Punica granatum	Punicaceae	Pomegranate	Fruits, (peel, aril, seeds, and juice, leaves, roots, and stem)	Phenolic acids, flavanols, flavones, flavanones, anthocyanidins, and anthocyanin (pelargonidin 3,5-diglucoside, pelargonidin 3-glucoside)	Inactivate xanthine oxidase	(Wong et al., 2014; Rummun et al., 2013)
Psidium guajava Linn	Myrtaceae	Guava	Root, stem bark especially leaf	Quercetin, kaempferol, catechin, quercitrin rutin luteolin, epicatechin, caffeic acid, chlorogenic acid and gallic acid	Incapacitate xanthine oxidase	(Irondi et al., 2016)
Pyrus elaeagnifolia	Rosaceae	Wild pear	Fruits	Not reported	Incapacitate xanthine oxidase	(Baltas , 2017)
Litchi chinensis	Sapindaceae	Litchi	End product of litchi fruit, flowers, pericarp, and seed	Proanthocyanidins, Oligonol	Incapacitate xanthine oxidase and reduce serum uric acid	(Li et al., 2013)
Vitis vinifera	Vitaceae	Grape berries	Aqueous acetone of seeds	Sugars, flavonoids, anthocyanins and proanthocyanins, organic acids, tannin, mineral salts, and vitamins.	Deactivate xanthine dehydrogenase	(Wang et al., 2004)
Angelica keiskei	Apiaceae	Not reported	Whole plant	Coumarins and chalcones	Deactivate xanthine oxidase	(Kim et al., 2014)
Persicaria hydropiper	Polygonaceae	Kesum/water pepper/ *Biskathali*	Flower	Flavonoids, sesquiterpenes, sesquiterpenoids, and phenylpropanoids	Deactivate xanthine oxidase	(Rahman and Kumar, 2015; Huq et al., 2014)
Lagenaria siceraria	Cucurbitaceae	Ghia or ghia kaddu or bottle gourd	Fruits	Ascorbic acid, fructose, glucose, raffinose, caffeoylquinic acid, cucurbitacins, pectin, β-carotene, iso-fucosterol, campesterol, spinasterol, leucine, tyrosine, amaino alkanoic acid, quercetin, iso-quercetin, kaempferol, palmtic acid, oleanolic acid, and linoleic acid	Deactivate xanthine oxidase	(Ahmed et al.,2017)
Camellia sinensis	Theaceae	Green tea	Dried leaves of plant	Polyphenolic components recognized as catechins like (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC), (-)-gallocatechingallate (GCG) and (+)-Catechin (C)	Deactivate xanthine oxidase	(Chen et al., 2015)
Beetroot pomace	Amaranthaceae	Beetroot	Peel (main), crown, flesh	Phenolic (ferulic acid, vanillic acid, p-hydroxybenzoic acid, caffeic acid, protocatechuic acid, catechin, epicatechin, and rutin) and betalain combinations (betanin, isobetanin and vulgaxanthin I)	Deactivate xanthine oxidase	(Vulic et al., 2014)
Aspalathus linearis	Fabaceae	Rooibos herbal tea	Leaves and stems	Orientin, rutin, and aspalathin	Deactivate xanthine oxidase and reduce serum uric acid	(Kondo et al., 2013)
Juglans regia L.	Juglandaceae	Walnut	Fruit, stem, leaf, green husk and shell	Coumaric aldehyde, coumalic acid, cinnamic aldehyde, 4hydroxybenzaldehyde	Deactivate xanthine oxidase and anti-hyperuricemic	(Wang et al., 2015; Wang et al., 2016)

Table 2. Continue.....

Dinocarpus longan Lour	Sapindaceae	Longan	Water extract of seed	Gallic acid, corilagin, ellagic acid	Decline uric acid production and uricosuric actions	(Hou et al., 2012)
Lychnophora trichocarpha	Asteraceae	Malva nut	Ethanol extract of aerial parts	Apigenin (XO inhibition), luteolin, apigenin, lupeol, lychnopholide and eremantholide	Anti-inflammatory and urate-depressing actions	(DE Souza et al., 2012)
Piper nigrum L.	Piperaceae	Black pepper	Not reported	Piperine	Deactivate xanthine oxidase	(Sabina et al., 2011)
Chrysanthemum indicum	Asteraceae	Indian Chrysanthemum	Methanol extract of flowers	Luteolin and apigenin	Decline uric acid production	(Kong et al., 2000)
Morinda citrifolia L.	Rubiaceae	Noni	Fruit juice	Not determined	Inactivate xanthine oxidase	(Palu et al., 2009)
Lagerstroemia speciosa (L.) Pers.	Lythraceae	Queen's *crepe-myrtle or pride of India*	Leaves	Valoneic acid dilactone (VAD), Ellagic acid (EA)	Inactivate xanthine oxidase and anti-hyperuricemic	(Unno et al., 2004)
Erythrina strica roxb	Papilionaceae	Coral tree	Hydromethanolic extract of leaves	Flavonoids, saponins, tannins, phenolics, and triterpenoids	Obstruct xanthine oxidase (XO) and xanthine dehydrogenase (XDH)	(Raju et al., 2012)
Rhus coriaria	Anacardiaceae	Sicilian sumac	Hydroalcoholic fruits extract	Protocatechuic acid, methyl gallate, and phenolic (as gallic acid)	Inactivate xanthine oxidase	(Mahdabadi et al., 2013)
Juniperus phoenicea	Cupressaceae	Juniper	Decoction of fresh leaves in water	Phenols	Reduce uric acid level and antioxidant	(Gdoura et al., 2013)
Momordica charantia	Cucurbitaceae	Bitter gourd	Methanol-water extract of pulp	Phenols and Flavonoids	Reduce xanthine oxidase	(Alsultanee et al., 2014)
Origanum majorana Linn.	Labiatae	Sweet majorana	Root and stem extracts in ethanol and water	Saponins, phenols, flavonoids, tannins, valoneic acid dilactone triterpenoids, saponins, coumarins, polyphenols, ellagic acid	Hinder xanthine oxidase	(Vasudeva et al., 2014)
Phyllanthus niruri Linn.	Euphorbiaceae	Stonebreaker	Methanolic extract of plant	Lignans	Uricosoric activities and inactivate Xanthine oxidase	(Murugaiyah and Chan, 2009)
Glycine max	Leguminosae	Soya bean	Plant extract	Allantionase	Hinder xanthine oxidase	(Al-Masri , 2016)
Biota orientalis	Cupressaceae	Westmot	Leaves	Quercetin rutin	Hinder xanthine oxidase	(Zhu et al., 2004)
Caesalpinia sappan	Caesalpiniaceae	Pathimughom	Heartwood	Neosappanone A	Hinder xanthine oxidase	(Nguyen et al., 2004)
Conyza bonariensis	Asteraceae	Flax-leaf fleabane	Whole plant	Syringic acid, takakin 8 – O glucuronide	Hinder xanthine oxidase	(Kong et al., 2001)
Petroselinum crispum	Apiaceous	Parsley	Seeds and leaves	Flavonols (kaempferol and quercetin) and flavones (apigenin and luteolin)	Hinder liver xanthine oxidase and xanthine dehydrogenase	(Haidari et al., 2011)
Coccinia grandis	Cucurbitaceae	Ivy Gourd	Leaves	Saponins, cardenolides, flavonoids and polyphenols	Hinder xanthine oxidase and anti-inflamatory	(Umamaheswari et al., 2007)
Vitex negundu	Verbenaceae	Horseshoe vitex or Pochatia	Leaves	Flavonoids (vitexicarpin), triterpenoids (betulinic acid and ursolic acid), lignans (negundins, vitedonin), alkaloid (vitedoamine) and diterpene (vitedoin)	Hinder xanthine oxidase and anti-inflamatory	(Umamaheswari et al., 2007)
Coriandrum sativum	Apiaceae	Coriander	Fruit	Polyphenols	Hinder xanthine oxidase and anti-inflammatory	(Havlik et al., 2010)
Chamomilla recutita	Asteraceae	Pineapple weed	Flowers	Polyphenols	Hinder xanthine oxidase and anti-inflammatory	(Havlik et al., 2010)
Gossypium herbaceum	Malvaceae	Cotton or kapas	Leaves	Carbohydrates, tannin, phenolic compounds, flavonoids, saponins, glycosides, steroids	Hinder xanthine oxidase and anti-oxidant	(Kumar et al., 2011)
Vinca sp.	Apocynaceae	Unknown	Plant extract	Vinblastine alkaloid	High potential anti-gout	(Costantini, 1992)
Colchicum sp.	Colchicaceae	Unknown	Plant extract	Colchicine alkaloid	High potential anti-gout	(Dalbeth et al., 2014)
Azadirachta indica	Meliaceae	Neem	Leaves	Flavonoids, tannins, alkaloids and tetranortriterpenes, including nimbin, nimbinin, nimbidinin, nimbolide, and nimbidic acid	Anti-inflammatory	(Rahman and Kumar,2015; Mahabub et al., 2009)
Adenanthera pavonina	Fabaceae	Rakta kombol	Barks	Flavonoids, steroids, saponins, and triterpenoids	Anti-inflammatory	(Ara et al., 2010)
Curcuma longa	Zingiberaceae	Turmeric	Whole plant	Curcumin	Decrease uric acid level	(Mohamed and Okabi, 2008; Panahi et al., 2016)
Swietenia mahagoni	Meliaceae	Mahagoni	Seed	Gallic acid, flavonoids	Inactivate xanthine oxidase	(Sahgal et al., 2009)
Cymbopogan citrates	Poaceae	Lemon grass	Leaves and stalks	phenols	Inactivate xanthine oxidase	(Mirghani et al., 2012)
Physalis alkekengi	Solanaceae	Strawberry tomato	Leaves and tomato	Flavonoid, phenol, and carotenoid compounds	Inactivate xanthine oxidase	(Hoshani et al., 2011)
Solanum nigrum	Solanaceae	Black Nightshade	Leaves	Polyphenols	Inactivate xanthine oxidase	(Mukherjee et al., 2015)
Daucus carota	Apiaceae	Carrot	Roots	Polyphenols. alkaloids, carbohydrates, flavonoids, and protein	Inactivate xanthine oxidase	(Patil et al., 2012)
Withania somnifera	Solanaceae	Ashwagandha	Roots and stem	Sitoindosides VII–X, withaferin A, 5-dehydroxywithanolide-R, withasomniferin-A, 2,3-dihydrowithaferinA, 24,25-dihydro27-desoxywithaferinA, 1-oxo-5,6-epoxy-witha-2-ene-27- ethoxy-olide, 27-O--d-glucopyranosylphysagulin D, physagulin D, withanoside I–VII, 27-O-- d-glucopyranosylviscosalactone B, 4,16-dihydroxy5,6-epoxyphysagulin D, alkaloids, diacetylwithaferin A and viscosalactone B, withanolides, particular reducing sugars and flavonoids	Preclude monosodium urate crystal-induced swelling	(Rasool and Varalakshmi, 2006)
Citrus aurantium L.	Rutaceae	Bitter orange	Immature fruits peels are more useful	Hesperidin, neohesperidin, naringin, naringenin, hesperetin, nobiletin, and tangeretin	Incapacitate xanthine oxidase and relegate serum uric acid	(Liu et al., 2016)

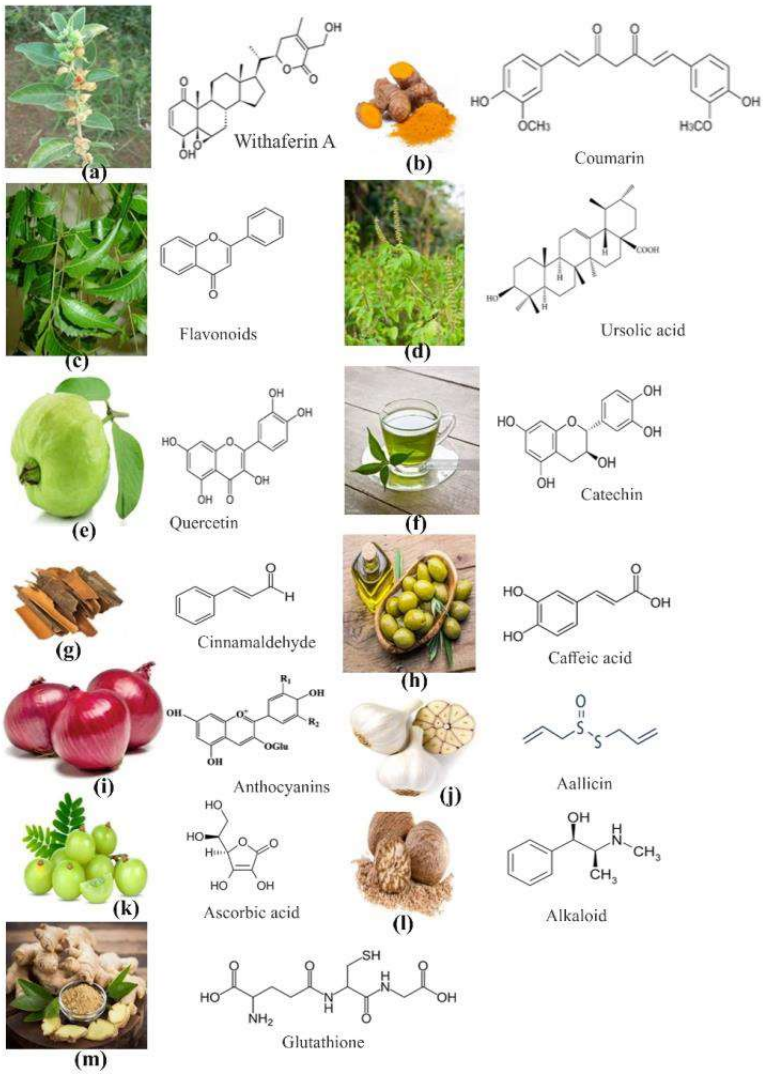

Figure 4. Selected herbs with their functional metabolites configuration (Congregated from various online images): a) *Withania somnifera*, b) *Curcuma longa*, c) *Azadirachta indica*, d) *Ocimum sanctum*,e) *Psidium guajava*, f) *Camellia sinensis*, g) *Cinnamomum cassia*, h) *Olea europea*, i) *Allium cepa*, j) *Allium sativum*, k) *Phyllanthus emblica,* l) *Myristica fragrans,* m) *Zingiber officinale*

Conclusions

Hyperuricemia (HUA) could be a serious phenomenon which isn't only confined in the local region but also spread globally. To beat the injurious consequences of this life-endangering disease consequential development within the medication should be brought as soon as possible in alliance with scientists and other health care professionals in various segments. Though approved anti-hyperuricemic medications are randomly prescribed by physicians, sometimes these medications don't seem to be preferred by the patients for its side effects and even modern medications are out of reach for people in most of the developing countries because of economic problem. For this reason, physicians suggest dietary plant foods to diminish the injurious effects of elevated uric acid in addition on inhibit the supreme threatening enzyme xanthine oxidase with more brilliant effects likewise as similar pharmacologic effects of conventional medications like allopurinol. Researchers are susceptible to conduct more in vivo, in vitro studies to guage the effect of varied bioactive metabolites of plants, fruits, and vegetables that reduce the reabsorption of uric acid in intestine and enhance its excretion through urine. The mentioned plants during this review article reveal anti-hyperuricemic activity by distinctive cellular pathways, for instance, xanthine oxidase obstruction, anti-inflammatory, antioxidant, and uricosuric because of the presence of most promising functional constituents phenolic glycosides and flavonoids (quercetin, rutin, genistein, and luteolin).

Future perspective

This review outlines the crucial outcome of using conventional medications as well as the possibility to develop novel therapy in this sector by using technology. Additionally, the review also provides an overall image about the chance of traditional plants and their constituents to become a source of the management of hyperuricemia.

So, more and more plant extracts screening should be conducted to judge the protection, efficacy, potency, how the metabolites react with the active site of enzyme xanthine oxidase, their synergistic effects, internal toxicity, purity, drug- constituents interactions., quality control and all the procedures should be validated consistent with guidelines. By ongoing preclinical and clinical trials, suitable formulations are often developed to motif the medications for future purposes.

Conflicts of interest declaration

The authors assert that they need no conflict of interest.

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