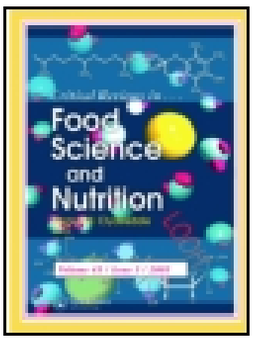

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Management of hyperuricemia through dietary polyphenols as a natural medicament: A comprehensive review

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ABSTRACT

Hyperuricemia, a condition due to high serum uric acid level and is notorious to health. It is considered to be a potent risk factor for gout and dramatically associated in the development of many chronic diseases such as malignant tumor, cardiovascular disorders and renal failure. Modern innovative medicinal and therapeutic interventions are underlying these days to combat hyperuricemia. Previously reported studies revealed the significant impact of dietary polyphenols (e.g. anthocyanins, phenolic acids, flavonoids etc.) against hyperurecemia disorder. Dietary plant polyphenols, unlike anti- hyperuricemic agents, are not reported to have any side effects in curing hyperuricemia. The current comprehensive review figure outs the use of dietary polyphenols as a natural remedy for the management of hyperuricemia. The sources, affiliated pathways, mode of actions and factors affecting their efficiency to prevent hyperuricemia are deeply discussed in this article. Additionally, limitations and suggestions regarding previously reported studies are also highlighted.

KEYWORDS

Hyperuricemia; gout; xanthine oxidase; uric acid; therapeutic interventions; polyphenols; mode of action

Abbreviations: ACE: Angiotensin converting enzyme; ADW: Air dried weight; ALT: Alanine transaminase; AST: Aspartate transaminase; ATP: Adenosine triphosphate; BW: Body weight; Bw: Body weight; BUN: Blood urea nitrogen; CDS: Circular dichroism spectroscopy; DW: Dried weight; FAD: Flavin adenine dinucleotide; hsCRP: High sensitivity C-reactive protein; HUA: Hyperuricemia; HUE: Hourly uric acid excretion; LDH: Liver xanthine dehydrogenase; LUA: Liver uric acid; LXO: Liver xanthine oxidase; Mo: Molybdenum; ND: Not determine; NSU: Monosodium urate; PO: Potassium oxanate induce; SCr: Serum creatinine; SUA: Serum uric acid; SXO: Serum xanthine oxidase; TNF-α: Tumor necrosis factor-α; UA: Uric acid; UO: Urinary nitrogen; UUE: Urine urate excretion; XO: Xanthine oxidase

Introduction

Hyperuricemia (HUA), a metabolic disorder due to high serum uric acid level is generally reported in many regions. Instability of uric acid, over production >357 μmol/L in females and >416 μmol/L in males or under excretion results the elevation of uric acid (UA) level in the body. Virtually, 67% of UA produces endogenously while dietary purine contributes 33%. To maintain normal daily body UA levels, approximately 75% UA is eliminated through kidneys and other 25% by the gastrointestinal pathway (Fam *et al.*, 2002; de Oliveira and Burini, 2012). The over production of UA along with renal disorders results in the supersaturation of monosodium urate crystals (NaU). These NaU crystals deposits in the joints which increase inflammation and causes gout. Gout is a form of arthritis accompanying severe pain (Brook *et al.*, 2010; Roddy and Doherty, 2010). Many life-threatening disorders, hypertension (Wang *et al.*, 2013; Krishnan, 2014), cardiovascular disease (Gustafsson and Unwin, 2013) and metabolic syndrome (You *et al.*, 2014) directly link with the hyperuricemia.

There is no single report which predicts the global prevalence of hyperuricemia. The prevalence of hyperuricemia varied from region, study types, social and economic factors (Kuo *et al.*, 2015). However, it is reported that prevalence rate of hyperuricemia higher in Oceanian countries like Taiwan (Chou and Lai, 1998), China (Nan *et al.*, 2006), Australia (Nabipour *et al.*, 2011), USA (Zhu *et al.*, 2011), Thailand (Lohsoonthorn *et al.*, 2006), France (Zalokar *et al.*, 1972), New Zealand, Scotland (Sturge *et al.*, 1977), England (Gimeno *et al.*, 2009), whereas less in Turkey, Saudi Arabia, Iran, Philippines, Malaysia, African countries and Soviet Union regions (Table 1) (Kuo *et al.*, 2015; Gosling *et al.*, 2014).

Hyperuricemia and gout are life menacing disorders which are perpetually accelerating across the world and consider to be 2nd after type 2 diabetes. These life threatening indispositions start untimely in younger peoples. This may predict the load of metabolic syndrome indispositions link with hyperuricemia will be more in coming days because recently imperil factors finally corroborate as disease and public health burden (Chen *et al.*, 2003; Katrine *et al.*, 2004; Bhole *et al.*, 2010).

To curb the hyperuricemia disorder, lowering body UA is the first-line treatment. This can be achieved by preventing the synthesis and reabsorption of UA, as well as promoting UA excretion. For this reason, a number of uricostatic and

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Table 1. Burden of hyperuricemia in various region. (Kuo *et al.*, 2015; Gosling *et al.*, 2014).

Prevalence category	Region
Highly [a]HUA prevalence	Taiwan, China, New Zealand, USA, Cook Islands, Apia, Samoa, Suva, Fiji, Nauru, Tuvalu, Mariana Islands, Australia, Indonesia, Japan and Seychelles
Moderate HUA prevalence	Thailand, England, Scotland, Finland and France
Lower HUA prevalence	Brazil, Saudi Arabia, Turkey and Tanzania
Very low HUA prevalence	Solomon Islands, Trobiand Island, India, Canada, South Africa, Zaire and Sudan

[a]HUA: hyperuricemia.

uricosuric drugs are used. Recently, the side effects of anti-hyperuricemic drugs are more and more conspicuous and physicians advice patients to take fruits and vegetables more in daily life (Chen and Schumacher, 2008; Shipley, 2011; Zgaga *et al.*, 2012; Robinson and Horsburgh, 2014).

Diet rich in plant based foods chiefly vegetables and fruits directly link with the lowering of incidence of various health disorders such as cardiovascular disease, cancers, type 2 diabetes mellitus, hyperuricemia, gout etc (Bravo, 1998; Ramassamy, 2006; Schaffer *et al.*, 2009; Nobili *et al.*, 2009; Badimon *et al.*, 2010; Mulvihill and Huff, 2010; Vayalil, 2012; Zhang *et al.*, 2015; Seyed *et al.*, 2016). These functionalities associated with the presence of a profusion of biologically active components like polyphenols (Badimon *et al.*, 2010; Mulvihill and Huff, 2010). Polyphenols are the most common plant based functional biological active components that hold numerous health benefits and utilize for the formulation of nutraceutical and functional foods. Polyphenols from numerous food plants are reported to have potential to combat the hyperuricemic disorder by reducing UA synthesis via xanthine oxidase blocking, susspress urate renal reabsorption and ameliorate UA secretion (Soobrattee *et al.*, 2005; Gonzalez-Castejon and Rodriguez-Casado, 2011; Zhang *et al.*, 2015; Wang *et al.*, 2017a b c d e). Therefore, the purposes of this review are to provide an overview of the effect of dietary polyphenols on hyperuricemic disorder, their mode of action, safety and limitation.

Prevalence, clinical features and epidemiology of hyperuricemia

Substantially, HUA is over the burden of UA in the blood, due to overproduction or less secretion of UA. Clinically, HUA is directly associated with the SUA concentration, diet, social and economic factors, medications, genetics, age, sex, multiple other metabolic disorders such as hypertension, abnormal lipid/sugar metabolism, cardiovascular, obesity and multiple others diseases (Figure 1). The prevalence of HUA has dramatically increased over the last few decades (Nakamura *et al.*, 2012; Roozbeh *et al.*, 2015; Kuo *et al.*, 2015; Guan *et al.*, 2016; Yu *et al.*, 2017). It is reported HUA prevalence higher in men as compared to women (Liu *et al.*, 2011; Qiu *et al.*, 2013; Liu *et al.*, 2015; Guan *et al.*, 2016). Qiu *et al.* (2013) reported that prevalence rate of HUA in men (21%) were more then compared to women (7.9%) in Heilongjiang Province, China. More recently study conducted by Guan *et al.* (2016) documented that prevalence rate of menopause women in Beijing, China dramatically increases (9.77 to 23.12%) from (2000 to 2009 year).

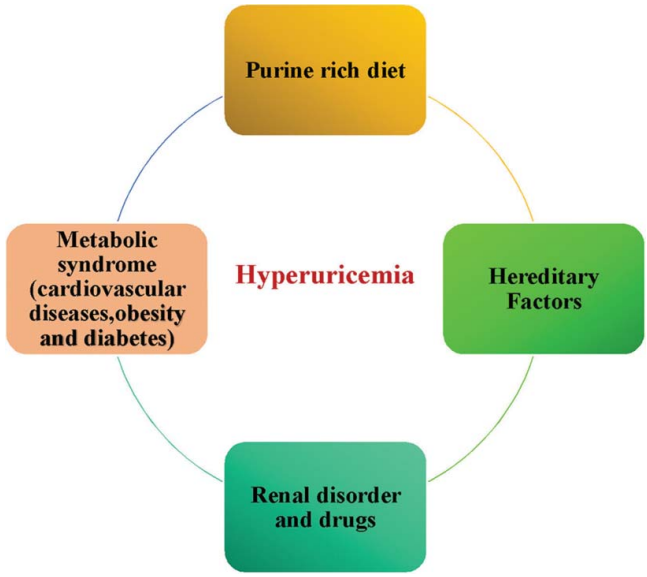

Figure 1. Risk factors for hyperuricemia.

The prevalence of HUA is higher in Oceanian countries and less in Arabic countries as discussed in above (introduction) and also presented in (Table 1) (Kuo *et al.*, 2015). Liu *et al.* (2015) reported that average prevalence of HUA in mainland China 13.3% from 2000 to 2014. The increase in economic condition, change in life style and diet pattern (dairy products, meats, carbohydrates, drinks etc.) of the people of many developed, developing countries resulted in a higher prevalence of HUA (Liu *et al.*, 2015). According to a national wide population-based survey, the prevalence of HUA in Italy also dramatically increase from 8.5% to 11.9% during the years 2005–2009, also in Taiwan (30%), Japan (25.8%), USA (21%), Thailand (10.6%) and other developed countries (Zalokar *et al.*, 1972; Sturge *et al.*, 1977; Mertz and Loewer, 1992; Chou and Lai, 1998; Nagahama *et al.*, 2004; Lohsoonthorn *et al.*, 2006; Nan *et al.*, 2006; Lohsoonthorn *et al.*, 2006; Lawrence *et al.*, 2008; Gimeno *et al.*, 2009; Nabipour *et al.*, 2011; Zhu *et al.*, 201; Uaratanawong *et al.*, 2011; Zhu *et al.*, 2011; Robinson *et al.*, 2012; Trifiro *et al.*, 2013; Yu *et al.*, 2017).

Hyperuricemia is a major etiological factor for the development of gout. Earlier studies reported that SUA can be applied for indication of metabolic syndrome. Liu *et al.* (2006) and Chen *et al.* (2014) reported that serum UA level significantly increased in chronic hepatitis patients due to an overload of fructose. Additionally, SUA concentration was also higher in patients with persistent liver injury (Liu *et al.*, 2006). A recent study conducted in Taiwan reported that hypercholesterolemia and high creatinine levels were significantly associated with HUA in men, whereas type 2 diabetes and high alanine aminotransferase (ALT) levels were significantly associated with HUA in women (Yu *et al.*, 2017). Renal failure results in the increment of UA and decreases in glomerular filtration also participate in HUA which is mostly observed in chronic kidney disease patients. UA also increases the inflammation and progression in kidney damage patients (Nakamura *et al.*, 2012; Roozbeh *et al.*, 2015). Genetic variation, medications and supplements contribute to increasing the risk of HUA and gout. Many medications (e.g loop diuretics, angiotensin converting enzyme (ACE) inhibitors, thiazide, β-blockers, aspirin and non-losartan angiotensin II

receptor blockers etc.) also caused in the increment of UA and results in HUA and gout (Robinson and Horsburgh, 2014).

Management of hyperuricemia: anti-hyperuricemic drugs and associated problems

Nowadays a number of anti-hyperuricemic drugs are available in the market. These drugs are mainly categorized into uricostatic drugs (oxypurinol, febuxostat etc) and uricosuric drugs (probenecid, sulphinpyrazone, BCX4208 and pegloticase etc). All of these drugs given singly or amalgamation for lowering of UA synthesis or ameliorates UA secretion (Gliozzi *et al.*, 2016). The detail of some prominent drugs and their mode of action are described below and also presented in (Figure 2).

Uricostatic drugs

Drugs which inhibit the xanthine oxidase enzyme and prevent from UA synthesis are termed as uricostatic drugs. Allopurinol and febuxostat are the approved drugs which reduce UA generation (Gliozzi *et al.*, 2016).

Allopurinol and oxypurinol

Allopurinol is a purine base drug used for the management of HUA. Allopurinol inhibits UA synthesis by binding with XO enzyme. It is mostly prescribed at the dose of 300–600 mg/day. Albeit, allopurinol is very effective and mostly used drug, but it causes many serious health complications e.g. renal and hepatic failure, skin rashes and gastrointestinal problems (Dalbeth *et al.*, 2006; Crittenden and Pillinger, 2013; Ress *et al.*, 2014; Gliozzi *et al.*, 2016).

Febuxostat

Febuxostat is a non-purine, uricostatic drug and recently gain approved from NICE (National Institute for Health and Care Excellence). Its chemical nature varies from allopurinol. Febuxostat, obstruct $ONOO^-$ and reactive oxygen species (ROS) generation by hindering the XO enzyme (reduce and oxidize form). Additionally, it also block circulating XO and prevent from endothelial injury. It is mostly prescribed at the dose of 80–120 mg/day. Albeit, it is more effective than allopurinol but it also causes some adverse effects such as nausea, diarrhea, headache, skin rashes and even liver abnormalities (Crittenden and Pillinger, 2013; Gliozzi *et al.*, 2016).

Uricosuric drugs

Uricosuric drugs generally increase renal UA secretion and prevent from its reabsorption. Probenecid, sulphinpyrazone, pegloticase, benzbromarone, levotofisopam and arhalofenate are some well-known uricosuric drugs available in the local market (Gliozzi *et al.*, 2016).

Probenecid

Probenecid also known as probalan is an uricosuric drug which increases the excretion of UA by up or down regulating the urate transporters in the kidney. Regrettably, it also causes some adverse effects such as skin allergy and gastrointestinal problems. Moreover, it also contributes in hemolytic anemia with the involvement of glucose-6-posphate dehydrogenase deficiency (Harris *et al.*, 2000).

Sulphinpyrazone

Sulphinpyrazone is also an uricosuric drug and its mode of action is identical to probenecid. Chemical nature of sulphinpyrazone resemble to phenylbutazone. However, some adverse effects like peptic ulcer and gastrointestinal problems are reported after its consumptions. Withal, it is not recommended

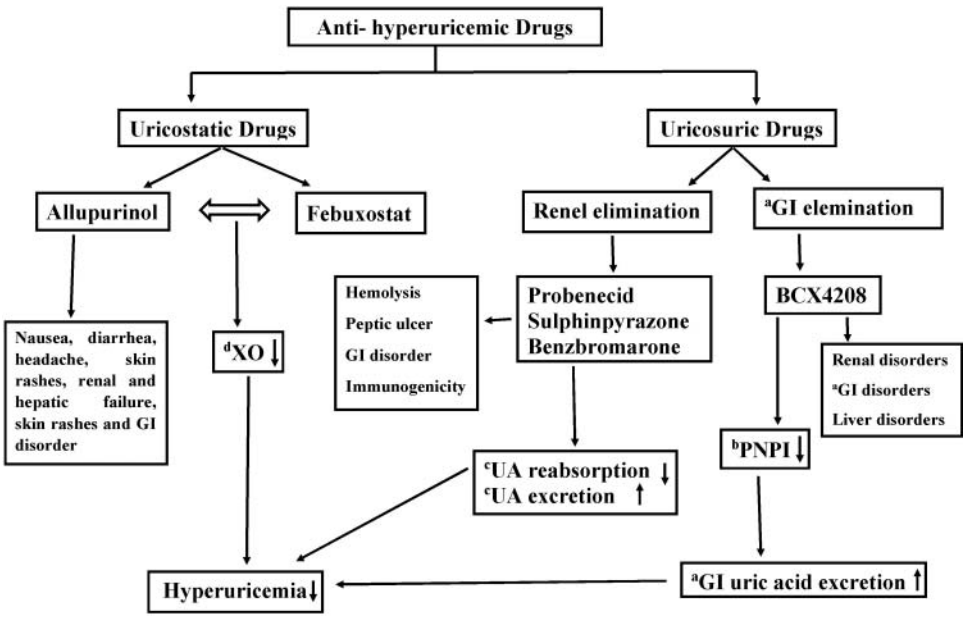

Figure 2. Anti-hyperuricemic drugs, their mode of action and side effects. [a]GI: Gastrointestinal, [b]PNPI (purine nucleotide phosphorylase), [c]UA (Uric acid), [d]XO (Xanthine oxidase).

for the patients suffering from kidney stone and renal abnormalities (Gliozzi *et al.*, 2016).

Pegloticase

Drug recommended for the treatment of severe HUA and chronic disorder is available in the market with trading names puricase and krystexxa. Pegloticase convert UA to allantoin and reduces serum UA level. The permissible dose is about 8 mg every two weeks. It is very effective medicine for the management of severe HUA and chronic gout. However, hemolysis, immunogenicity, methemoglobinemia and some intense side effects are associated with its usage (Sundy *et al.*, 2011; Domb and Kumar, 2011).

Woefully, all anti-hyperuricemic drugs persist with some adverse effects and even cause life threating problems (Figure 2). Hence, curing HUA through drugs without any adverse effects is still a challenge for pharmaceutical industry. Thus, alternative strategies are still needed to handle this disorder without any adverse effects.

Dietary polyphenols: potential anti- hyperuricemic agents

Dietary polyphenols are non-nutritive compounds with prophylactic activities, mainly present in vegetables, fruits, cereals, nuts, legumes, seeds, spices and herbs. Dietary polyphenols are being extensively studied for their potential therapeutic effects against many health abnormalities. Dietary polyphenols are still under research and mainly classified into i) phenolic acids (e.g. chlorogenic acid, ellagic acid, vanillic acid, caffeic acid, p-coumaric acid, gallic acid, hydroxybenzoic acid and ferulic acid), ii) stilbenes (resveratrol), iii) lignans (secoisolariciresinol and matairesinol), iv) curcuminoids (curcumin), v) flavonoids (flavones: apigenin and luteolin), (flavonols: quercetin), (flavanones: naringenin), (flavanols: oligomeric, catechin and epicatechin), anthocyanins (cyaniding), (flavanonols: taxifolin), (isoflavones: genistein), vi) chalcones (phlorizin, chalcone and naringenin) (Figure 3) (Harborne and Baxter, 1999; Bravo, 1998; Williams *et al.*, 2004; Gonzalez-Castejon and Rodriguez-Casado, 2011). Dietary polyphenols possesses strong antioxidant activity, potential to scavenge nitrogen and reactive oxygen species. From last few decades, it is noted that rapidly growing interest of alternative therapeutic and phytoremedies in hyperuricemic patients. Reliable reported traditional knowledge, along with newly discovered modern scientific approaches, it is mandatory to cross-check the medicinal potential of polyphenols. In this respect polyphenols have in last few years been widely screened by numerous researches for their potential anti-hyperuricemic activity using both *in-vitro* and *in-vivo* experiments (Bravo, 1998; Ramassamy, 2006; Schaffer *et al.*, 2009; Nobili *et al.*, 2009; Badimon *et al.*, 2010; Mulvihill and Huff, 2010; Vayalil, 2012; Lin *et al.*, 2015; Zhang *et al.*, 2015; Seyed *et al.*, 2016).

Dietary polyphenols rich diet, vegetables (Wang *et al.*, 2017e), fruits (Wang *et al.*, 2004), cereals (Lin *et al.*, 2015), nuts (Wang *et al.*, 2015b; Wang *et al.*, 2016), spices (Irondi *et al.*, 2016 b), coffee and tea (Gawlik-Dziki *et al.*, 2017) decrease the risk of hyperuricemia by lowering UA. Polyphenols prevent from UA disorder through following ways i) inhibiting the enzyme responsible for the production of UA, ii) increase the excretion of UA and prevent from its reabsorption in kidney iii) ameliorate UA excretion via intestine. This section of present review highlight the mode of action of polyphenols towards HUA, dietary plant sources and their effect on HUA, limitation and suggestion for future research to handle HUA (Figure 4, 5, 6 and Table 2).

I) Suppressing uric acid synthesis by the inhibition of xanthine oxidase

XO is a Molybdenum (Mo) containing enzyme which convert the hypoxanthine to xanthine and then xanthine to UA. Due to the absence of uricase enzyme in human body, UA is the final product in this pathway and not catalyze further. This UA is eliminated via kidney/intestine and overproduction or less excretion of UA results rise of UA which cause HUA and gout. During re-oxidation hydrogen peroxide (H_2O_2) and superoxide radical ($O_2^{\bullet-}$) are produce. O_2 catalyzed by superoxide dismutase whereas $O_2^{\bullet-}$ change into hydrogen peroxide H_2O_2. Thus, over activity of XO results in storage of UA in the tissue which modulate the inflammatory pathway with the association of reactive oxygen spices. Therefore, inhibiting UA synthesis by XO inhibition is the first line treatment for reducing body UA level (Figure 4, 6) (Mittal *et al.*, 2008; Kelley *et al.*, 2010).

In this regard, the dietary polyphenols have been shown to be effective in inhibiting XO and reducing UA synthesis. The structure of the polyphenols make them able to inhibit XO (Figure 3, 4). In specifically, hydroxyl groups (C-5 and C-7) may replace with the C-2 and C-6 ones of xanthine in the active site of XO (Cos *et al.*, 1998; Lin *et al.*, 2015b; Dong *et al.*, 2016). *In-vitro* and animal studies reported that polyphenolic extract inhibit the XO in serum, liver and kidney. Dietary polyphenols such as quercetin, galangin, chrysin, apigeni, galangin and pinobanksin formed complexes with the amino acids by hydrophobic binding in the pocket of XO and thus inhibit XO activity (Lin *et al.*, 2015 ab; Dong *et al.*, 2016). The high pKa value (>8) and strong longitudinal dipole moment of polyphenols make them best inhibitors of XO. Albeit, some other polyphenols like galangin and ellagic acid which have weak or no longitudinal dipole moment can also inhibit XO if they have a sufficiently important quadrupole moment. Consequently, weakly dissociated physiological pH and polarity of molecule along with longitudinal dipole moment significantly impact on XO inhibition (Lespade and Bercion, 2010).

Luteolin abundantly present in green pepper, celery, broccoli and possess anti- hyperuricemic effect by reducing UA generation. It is reported that luteolin inhibits XO (IC_{50}: $4.79 \pm 0.02 \times 10^{-6}$ mol l^{-1}) with a competitive manner and its rate of inhibition close to allopurinol. Furthermore, hydrophobic interactions, enthalpy and entropy amendments confirmed that these factors play a significant role in the inhibition of XO by luteolin. The reported postulated mechanism of luteolin to make conformational changes in the XO by binding with the amino acid present in the active site of XO and inhibiting UA synthesis (Yan *et al.*, 2013). Later, a theoretical study conducted by (Lespade and Bercion, 2010) also confirmed that luteolin inhibits the XO due to larger longitudinal dipole moment and weakly dissociated pH. In another study,

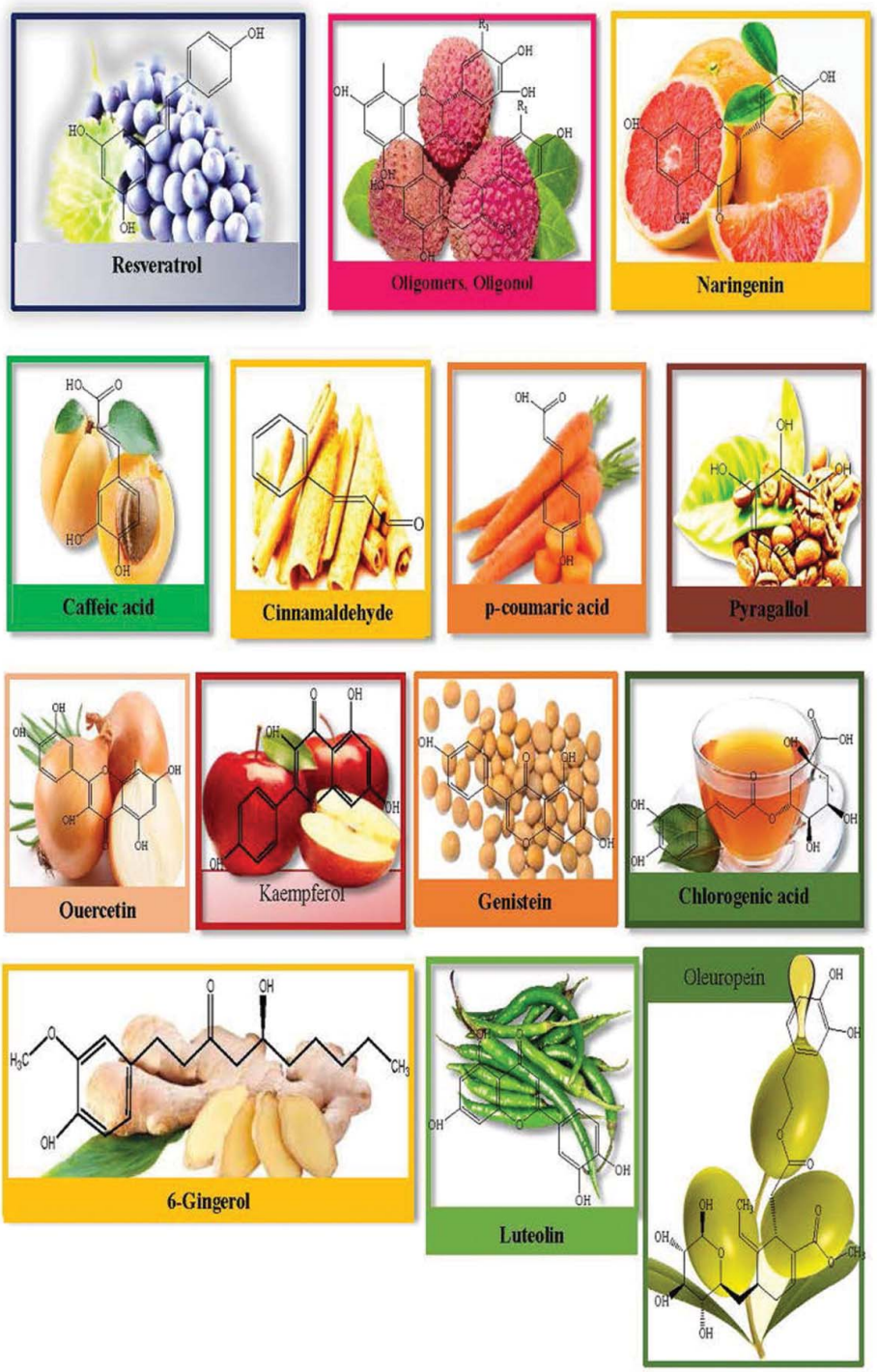

Figure 3. Dietary polyphenols, their sources and structure.

kaempferol a major flavonoid (flavonols) compound present in the fruits and vegetables are reported as a potent XO inhibitor. A mechanistic insight study was conducted by using molecular simulations and multi-spectroscopic protocols to show its inhibitory behavior on XO. The results reported that kaempferol inhibited XO same like luteolin. The kaempferol form XO- kaempferol static complex, hydrophobic forces, conformational alternation to XO and bind with some amino acid residue in XO pocket and inhibit XO (Wang *et al.*, 2015d). More recently study conducted by Zhang *et al.* (2016) reported the XO inhibitory mechanism of galangin. They predicted that galangin enter the Mo centre of XO and thwart electron transfer, alter the structure of XO which facilitate in blocking the oxygen binding to flavin adenine dinucleotide (FAD), inhibiting superoxide anion formation and results in impeding UA generation.

Chrysin a flavone was reported to inhibit UA synthesis in a same manner. The proposed mechanism of chrysin is just like other polyphenols. Chrysin acts on the active site of XO and form XO-chrysin complex. Van der Waals forces and hydrogen bonds facilitate this binding and conformational change to XO which prevent substrate (xanthine/hypoxanthine) binding (Lin *et al.*, 2015a). The above literature stated that unique

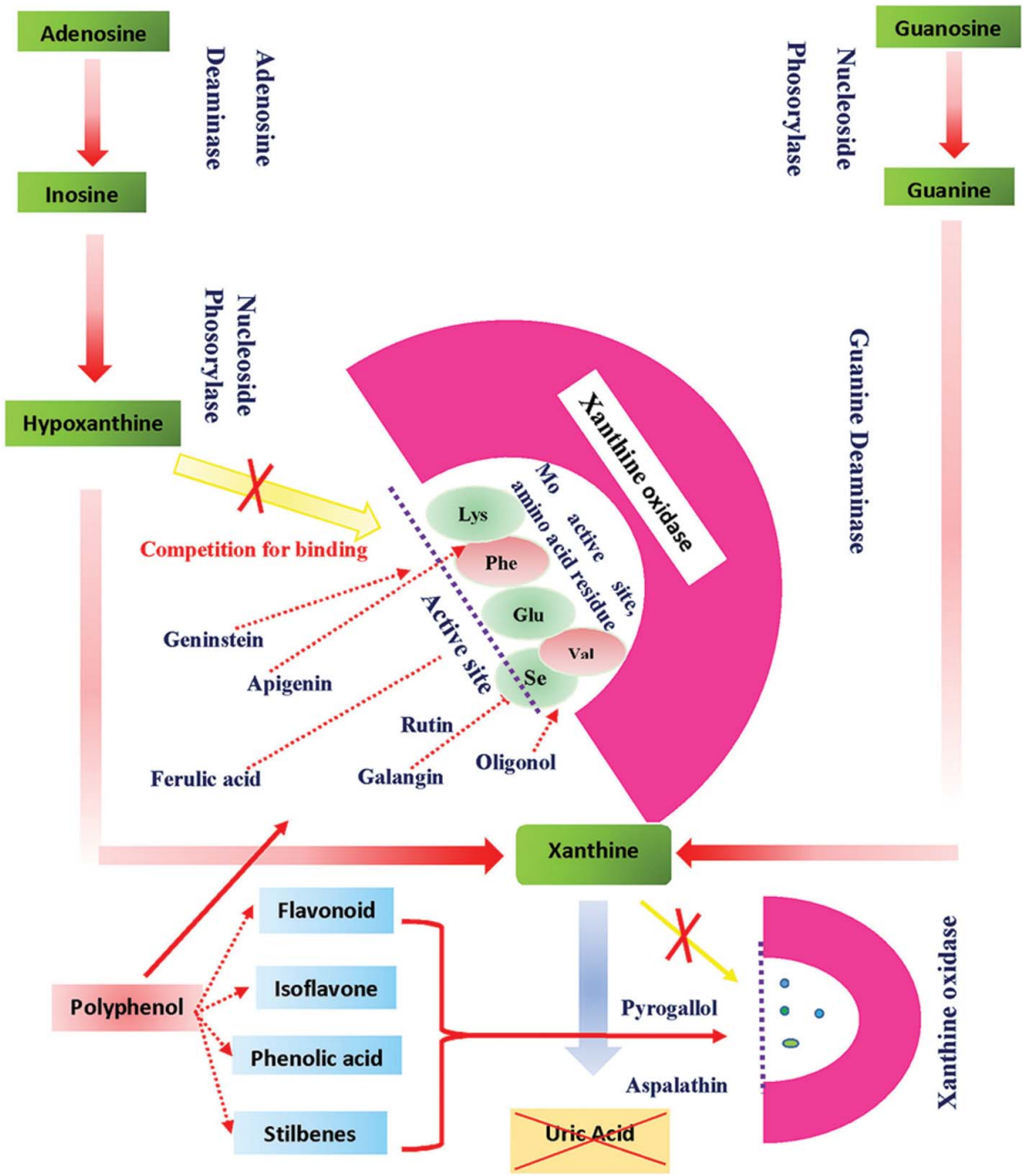

Figure 4. Xanthine oxidase inhibitory mechanism of dietary polyphenols. (Zhang et al., 2015).

characteristic of polyphenols such as planar structure, hydrophobicity, binding mode, hydroxyl group, suitable pKa and longitudinal dipole moments make them able to reduce UA synthesis in the serum, liver and kidneys by binding XO.

II) Ameliorates renal uric acid secretion and suppressing uric acid reabsorption

Polyphenols not only inhibit XO and reduce serum or liver UA synthesis but also take part in renal UA discharge (Figure 5, 6). Around 70% UA secrete through kidney whereas 30% by intestine pathway (Perez-Ruiz *et al.*, 2015). Urate transporter present in the kidney play a vital role for the removal of UA. It is reported that many urate transporters organic anion transporter (OAT1 and OAT3) facilitate the elimination of urate in kidney. SLC22A6 (OAT1) and SLC22A8 (OAT3) are the organic anion and urate transporters present in the basolateral membrane of proximal convoluted tubule cells (PCTC). OAT1 and OAT3 urate transporters engage in peritubular cellular urate uptake and in this way UA eliminate (Ichida *et al.*, 2003). Gene knock out study reported that without the presence of OAT1 and OAT3 transporters level of UA increased (Eraly *et al.*, 2008).

Contrary to this, some transporters reabsorb the UA and results in rise of UA. It is reported that 90% of UA reabsorbed in the kidney. Reabsorption of UA categorized into two steps, i) renal tubula cavity to renal tubular epithelial cells (URAT1), ii) absorb into blood over tubular epithelial basement membrane (GLUT9). In these two steps, URAT1 and GLUT9 facilitate the UA reabsorption. URAT1 is a renal urate transporter present in the proximal tubule. URAT1 contribute luminal urate uptake from primary membrane to

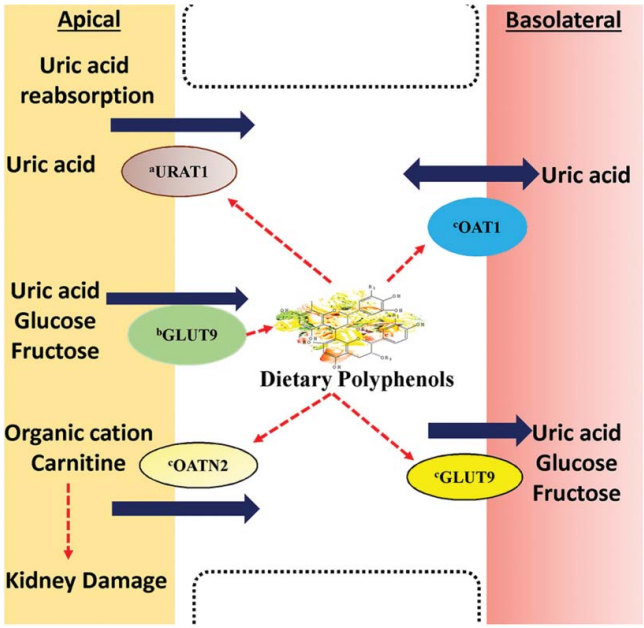

Figure 5. Effect of dietary polyphenols on renal transporters. (Zhang et al., 2015) [a]URAT1 (Urate transporter), [b]GLUA9 (Glucose transporter 9), [c]OAT1 and OAT2 (Organic anion transporter).

proximal tubule cells. GLUT9 is localized in the basal side and facilitate UA from epithelial cell into blood. It is reported that GLUT9 contribute more than URAT1 for UA reabsorption (Dinour *et al.*, 2010; Liu *et al.*, 2016b).

Numerous studies proclaimed that dietary polyphenols increased urate elimination by up-regulating (OAT1 and OAT3) and down-regulating (URAT1 and GLUT9) urate transporters in kidney (Zhang *et al.*, 2015; Chen *et al.*, 2015; Lee *et al.*, 2017). Quercetin present abundantly in fruits, vegetables and cereals act as uricostatic and uricosuric by reducing serum UA, down-regulating URT1 and GLUT9, up-regulating mOCT1 and mOCT2 in kidney and up-regulating uromodulin (UMOD) expression in distal convoluted tubule (Hu *et al.*, 2012). In another study, resveratrol was found to improve HUA and renal dysfunction through up regulating OAT1 (Lee *et al.*, 2017). Chen *et al.* (2015) reported that green tea significantly facilitated the UA secretion by suppressing URAT1 and GLUT9 and ameliorating OAT1 and OAT3 transporters in animal model. So, many dietary polyphenols enrich foods (fruits, vegetables, cereals, nuts and spices) could facilitate UA secretion by suppressing or ameliorating the urate transporters.

III) Ameliorates intestinal UA secretion

Similar as kidneys, intestine also play an important role in the elimination of UA. It is documented that intestine contributed around 30% UA elimination whereas other 70% via the kidney. Albeit, kidneys are the main contributor for handling of UA, tubular reabsorption secretion and glomerular filtration. It is reported that around 90% HUA occurred due to inadequate secretion of UA via the kidneys. Most of the studies' eminence only UA elimination via kidneys or prevention of UA synthesis (Perez-Ruiz *et al.*, 2015). Gastrointestinal elimination of UA is another open gateway for research and mechanism of elimination via this way still not well-known. However, some researchers suggested that breast cancer resistance protein (BCRP) also known (ABCG2), ATP binding cassette transporter take an important role for the removal of intestinal UA (Figure 6) (Kamatani *et al.* 2010; Matsuo *et al.*, 2015).

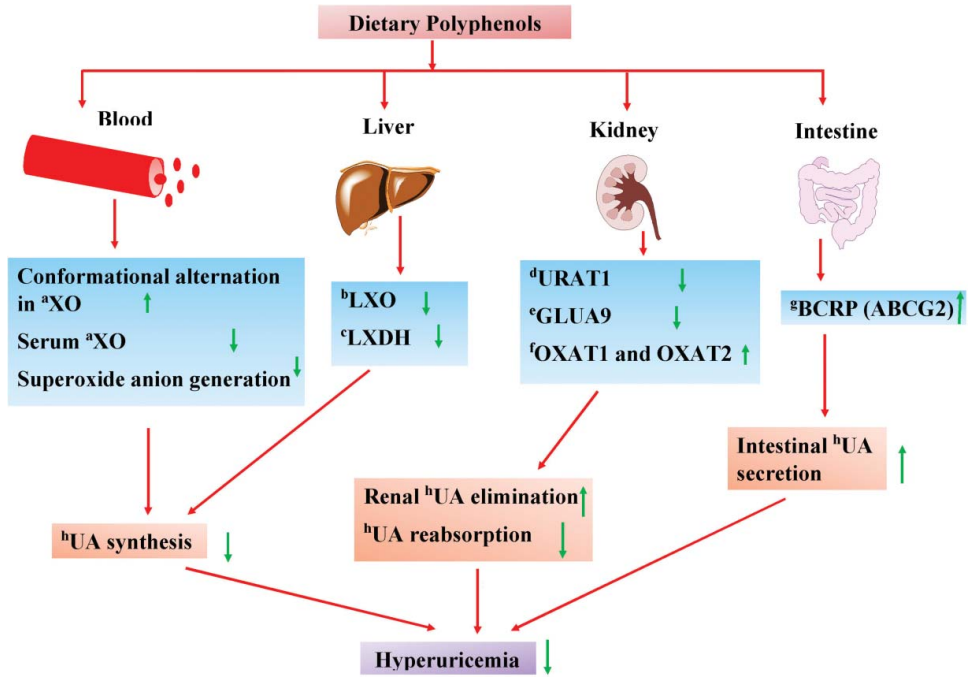

Figure 6. Mode of action of dietary polyphenols for combating hyperuricemia. [a]XO (Xanthine oxidase), [b]LXOD (Liver xanthine oxidase), [c]LXDH (Liver xanthine dehydrogenase), [d]URAT1(Urate tranporter), [e]GLUA9 (Glucose transporter 9), [f]OAT1 and OAT2 (Organic anion transporter), [g]ABCG2 (Breast cancer resistance protein), [h]UA (Uric acid).

Table 2. Dietary polyphenols, sources, anti-hyperuricemic activities and mode of actions.

Dietary sources	Bioactive compound	Study Type	IC_{50}/ EC_{50}/%	Mode of action	References
Grapefruit, oranges	Naringenin	*In-vitro*	77.4 ± 20.9μM	Inhibit [a]XO	Dew *et al.* (2005)
Orange	Hesperetin	*In-vivo* (5 mg/kg) orally given to hyperuricemic rats for 14 dayss	—	Orange juice and hesperetin decrease [b]SUA, inhibit [c]LXO and [d]LXDH	Haidari *et al.* (2009a)
Citrus aurantium, Citrus limon and Citrus limetta	[e]ND	*In-vitro*	[**]0.16 ± 0.88μg/ml	[**]*C. limetta* peel more potent [a]XO inhibitor as compare to other	Muthiah, (2012)
Citrus aurantium L	Naringin, hesperidin, neohesperidin, naringenin, hesperetin, nobiletin and tangeretin	*In-vitro*	[**]16.48 μM	[**]Hesperetin showed potent [a]XO inhibitor as compare to other isolated compounds	Liu *et al.* (2016a)
Lemon fruit juice	[e]ND	*In-vivo*: lemon juice (10 mg/kg [v]bw) to hyperuricemic mice for 11 days and human (30 ml/day, 6 week)	—	Decrease [b]SUA level in mice and volunteers	Wang *et al.* (2017a)
Pomegranate	[e]ND	*In-vitro*	0.058 ± 0.011 mg/mL	Methanolic extract of pomegranate flower inhibit [a]XO	Rummun *et al.* (2013)
Pomegranate	[e]ND	*In-vitro*	15.53 ± 0.0010%	Methanolic extract of pomegranate seed inhibit [a]XO	Wong *et al.* (2014)
Lychee	Oligonol	*In-vitro* and human, Oligonol (600 mg/ 300 ml water) given to 6 men for every hour (1 to 4 h)	—	Inhibit [a]XO, lower [b]SUA, [f]HUE and not-significantly effect on creatinine clearance	Moriwaki *et al.* (2011)
Blue berries	[e]ND	Human, daily two time 35 g powder to older (40–80 year) men and women were given for 180 days	—	Decease [b]SUA	Cheatham *et al*. (2016)
Montmorency tart cherry	[e]ND	Human, 12 volunteer (11male and 1female), age (26 ± 3 year) were given concentrate (30 and 60 ml) for 2 days montmorency tart cherry	—	Lower [b]SUA, [g]hsCRP whereas increase urinary urate excretion	Bell *et al.* (2014)
Tart cherry	[e]ND	*In-vivo*, tart cherry juice was orally given (5 ml/kg bw) to the hyperuricemic mice for 14 days	—	Lower [b]SUA, inhibit [c]LXO and [d]LXDH	Haidari *et al.* (2009b)
Bing sweet cherries	[e]ND	Human, 280 g of cherries were given to women (22–44 year) for overnight	—	Decrease [b]SUA, [h]NO and [g]hsCRP but no impact on [y]TNF-α and serum albumin	Jacob *et al*. (2003)
Cranberry	[e]ND	*In-vitro*	2.4 ± 0.1%	Inhibit [a]XO	Dew *et al.* (2005)
Grape Seed	Procyanidins	*In-vivo*, procyanidins were given orally (200–400 mg/kg bw) to hyperuricemic mice for three days	—	Decrease [b]SUA and inhibit [c]LXO and [c]LXDH	Wang *et al.* (2004)
Purple grapes juice	[e]ND	*In-vitro*	3.5 ± 0%	Inhibit [a]XO	Dew *et al.* (2005)
Sea buckthore berries	gallocatechin-(4α-2)- phloroglucino, cpigallocatechin-(4β-2)-phloroglucino, catechin-(4α-2)-phloroglucino, epicatechin-(4α-2)- phloroglucino, gallocatechin, epigallocatechin, catechin and epicatechin	*In-vitro*	[**]6.2 ± 0.3 μg/ml	The compound [**]epigallocatechin-(4β-2)-phloroglucinol shows strong [a]XO inhibition *in-vitro*	Arimboor and Arumughan, (2012)
Guava	Quercetin, kaempferol, catechin, quercitrin rutin luteolin, epicatechin, caffeic acid, chlorogenic acid and gallic acid	*In-vitro*	38.24 ± 2.32 μg/mL	Inhibit [a]XO	Irondi *et al.* (2016a)
Pear	[e]ND	*In-vitro*	20.75 ± 0.11 mg/ml	Inhibit [a]XO	Baltas, (2017)

Noni fruit	[e]ND	*In-vitro*	3.8 mg/ml	Inhibit [a]XO	Palu *et al.* (2009)
Mulberry	Mulberroside A	Mulberroside A was orally given (10, 20 and 40 mg/kg bw) to the [t]PO induced mice for 7 days	—	Decrease [b]SUA, [f]Ucr and increase urinary urate excretion. Moreover, down-regulate ([i]mURAT1 and [j]mGLUT9) and up-regulate [k](mOCTN1, mOCTN2, mOCT1, mOCT2)	Wang *et al.* (2011)
Mango	[e]ND	Mango leaf extract (50, 100 and 200 mg/kg) was given to [Z]NSU induce gouty mice for 9 days	—	Decrease [b]SUA, ankle swelling, [y]TNF-α, and [l]IL-1β	Jiang *et al.* (2012)
Longan	Gallic acid, corilagin and ellagic acid	Longan seed extract (80 mg/kg bw) were given intraperitoneally to hyperuricemic male Sprague-Dawley rats for (1–3 h)	277.78 μg/ml	Inhibit [a]XO and increase urate excretion by down regulate [j]mGLUT9	Hou *et al.* (2012)
Onion and onion waste	Quercetin-4′-O-monoglucoside, Quercetin-3, 4′-O-diglucoside, Isorhamnetin-3-glucoside	*In-vitro*	14.2 $\pm$ 0.2 μg/ml	[m]MeOH extract of onion and onion waste shows strong [a]XO inhibition activity	Nile and Park, (2013) and Nile *et al.* 2017)
Perilla frutescens	Caffeic acid, vinyl caffeate, rosmarinic acid, methyl rosmarinate and apigenin	The plant extract (500, 1000, and 2000 mg/kg) was orally given to [t]PO induced mice for 7 days	121.22 μM	Inhibit [a]XO and reduce [b]SUA	Huo *et al.* (2015)
Perilla frutescens	Protocatechuic acid, chlorogenic acid, caffeic acid, 4-methoxycinnamic acid, oleanolic acid, kaempferol-3-O-rutinoside, rosmarinic acid, luteolin, methyl-rosmarinic acid, apigenin and 4,5,7-trimethoxyflavone	*In-vitro*	[**]6.33 $\pm$ 0.18 μM	[**]Apigenin exhibit stronger [a]XO inhibitory activity as compare to other compounds. Due to highly hydrophobic property make it fit for bind with [a]XO surrounding amino acid residue and make structural changes in [a]XO which prevent substrate binding	Wang *et al.* (2017e)
Sweet purple potato	Anthocyanins	*In-vitro* and *in-vivo*, purple sweet potato extract (75, 150 and 300 mg/kg bw) orally given to hyperuricemic mice for 7 days	2.21 $\pm$ 0.31 (10 mg/ml)	Inhibit [a]XO, decrease [b]SUA, [c]LXO, [n]BUN, [o]Scr, inflammation cell infiltration in renal and improve interstitial fibrosis. Furthermore also down-regulate ([i]mURAT1 and [j]mGLUT9) and up-regulate [p](mOCTN2, mOCT1)	Zhang *et al.* (2015)
Sweet purple potato	Cyanidin 3-sophoroside-5-glucoside and Cyanidin 3-(6 caffeoyl-600-feruloyl sophoroside)-5-glucoside)	*In-vitro*	7.194 $\pm$ 0.858 $\times$ 10^{-5} molC3G equivalents L^{-1}	Anthocyanin bind with amino acid residue surrounding by the active side of xanthine oxidase enzyme and inhibit [a]XO	Zhang *et al.* (2017)
Angelica keiskei	Xanthoangelol as compare to others 4-Hydroxyderricin, Isobavachalcone, Xanthoangelol F and Xanthoangelol B	*In-vitro*	[**]8.1 $\pm$ 1.1 μM	[**]Xanthoangelo was the more potent anti-hyperurecemic compound by inhibiting [a]XO	Kim *el al.* (2014)
Persicaria hydropiper	[e]ND	*In-vitro*	28.72 $\pm$ 7.61 μg/ml	The butanol fraction of *Persicaria hydropiper* exhibit strong [a]XO inhibitory	Hashim *et al.* (2013)
Bottle gourd	Terpenoids, phenolic	*In-vitro*	>45% (0.07 mg/ml)	n-butanolic extract inhibit more [a]XO as compare to others	Ahmed *et al.* (2017)
Parsley, molokhia, leek and celery	[e]ND	*In-vitro* and *In-vivo* (4, 4.8, 5 and 6 g/kg bw) orally given to [t]PO induced hyperuricemic mice	ND	Lower SUA and inhibit [a]XO	El-Rahman, (2015)
Broccoli sprouts	[e]ND	*In-vitro*	1.87 $\pm$ 0.12 mg/ml	Inhibit [a]XO	Gawlik-Dziki *et al.* (2012a)
Ginger	6-gingerol, 6-shogaol, 6-paradol	*In-vitro*	[**]10.5 $\pm$ 0.5 uM	[**]6-gingerol showed greater [a]XO inhibitory activity as compare to other compounds	Nile and Park, (2015)

(*Continued on next page*)

Wheat flour	trans- and cis-ferulic acids	*In-vitro*	42.68 ± 2.25 μg/ml	Inhibit [a]XO	Gawlik-Dziki *et al.* (2017)
Maize	Phenolic compounds	*In-vitro*	5.5 ± 0.4 μM	Hirsutrin showed greater [a]XO inhibitory activity as compare to other compounds	Nile and Park, (2014)
Adlay	Protocatechuic acid, chlorogenic acid, vanillic acid, caffeic acid, p-coumaric acid and ferulic acid	*In-vitro* and *in-vivo*, [t]PO induced hyperurecemia mice were orally given (166 mg/kg bw) for seven days	[**]176 ± 7μ/100 g	[**]Chlorogenic acid inhibit [a]XO, reduce [b]SUA, [o]SCr and [f]Ucr	Zhao *et al.* (2014)
Soya bean, coffee	Genistein	*In-vitro*	1.73 μM	Inhibit [a]XO	Hoorn *et al.* (2002) and Lin *et al.* (2015)
Green Tea	Chlorogenic and ferulic acids	*In-vitro*	14.65 ± 1.24 EC_{50} (mg [u]DW/ml)	Inhibit [a]XO	Gawlik-Dziki *et al.* (2017)
Pu-erh tea	Gallocatechin, epigallocatechin, epicatechin gallate, gallic acid, 3, 4-dihydroxy-benzoic acid and myricetin	Pu-erh tea extracts (2000, 1000 and 500 mg/kg bw) were given to the hyperuricemic mice for seven days	—	Reduce [b]SUA, inhibit [c]LXO, down-regulate [i]URAT1 and [j]mGLUT9	Zhao *et al.* (2017)
Rooibos herbal tea	Aspalathin	*In-vitro* and *in-vivo* (aspalathin was orally (18, 37, 110 mg/kg bw) given to male mice for four weeks	70% (7.3 μg/ml)	Inhibit [a]XO and also reduce [b]SUA	Kondo *et al.* (2013)
Coffee	4-caffeoylated 5-lactone and 3-caffeoylated chlorogenic 5-lactone	*In-vitro*	210 μmol L^{-1}	Inhibit [a]XO	Honda and Masuda, (2014)
Coffee	Pyrogallol	*In-vitro*	0.73 μmol L^{-1}	Inhibit [a]XO	Honda and Masuda, (2016)
Pogostemon Cablin (Blanco) Benth	Rosmarinic acid	*In-vitro*	8.53 ± 0.91 mg/ml	Rosmarinic acid potent [a]XO inhibitor in *Pogostemon Cablin* (Blanco) Benth extract	Liu *et al.* (2017)
Green tea powder	[e]ND	Green tea powder (150, 300 and 600 mg/kg) was orally administrated to the [t]PO induced hyperuricemic mice for seven days	—	Green tea powder decease [b]SUA, [c]LXO and down-regulate [i](mURAT1) and up-regulate [p](mOAT1 and mOAT3).	Chen *et al.* (2015)
Walnut	Coumaric aldehyde, coumalic acid, cinnamic aldehyde, 4-hydroxybenzaldehyde	Walnut extract (166 mg/kg bw) given orally to [t]PO induced hyperuricemic mice for 30 days	[**]20.17 μg/ml	[**]p-coumaric aldehyde a potent [a]XO inhibitor and in animal model reduce [b]SUA	Wang *et al.* 2015b and Wang *et al.* 2016)
Olive	Caffeic acid, luteolin, apigenin, tyrosol, hydroxytyrosol, verbascoside	*In-vitro*	[e]ND	Oleuropein (K_i 53 uM) potent [a]XO inhibitor as compare to other polyphenolic compounds	Flemmig *et al.* (2011)
Rhus coriaria L.	[e]ND	*In-vitro*	172.5 mg/ml	Inhibit [a]XO	Candan, (2003)
Whole dried ginger, thymes, rosemary, cardamom, clove and cinnamon	[e]ND	*In-vitro*	[**]29 ± 4%	[**]Clove extract shows more [a]XO inhibitory activity	Dew *et al.* (2005)
Tarragon, cinnamon, rosemary, basil, oregano, thyme, white pepper and black pepper	[e]ND	*In-vitro*	[**]60%	[**]Tarragon extract shows more potent [a]XO inhibition as compare to others	Gawlik-Dziki, (2012b)
Cassia oil	[e]ND	Cassia oil was orally administrated (300, 450 and 600 mg/kg bw) to the [t]PO induced hyperureemic mice for 7 days	—	Reduce [b]SUA, [d]LXDH and [c]LXO	Zhao *et al.* (2006)
Cinnamomum cassia twigs	Cinnamaldehyde, cinnamic acid, coniferaldehyde, cinnacasolide B, O-coumaric acid, dihydromelilotoside, cinnamic alcohol, cinnacasolide A, and cinnacasolide C	*In-vitro*	[**]96.7 ± 2.3%	[**]Cinnamaldehyde potent [a]XO inhibitor as compare to other identified compounds	Ngoc *et al.* (2012)
Myristica fragrans	[e]ND	*In-vitro*	60% 250 (μg/ml)	Inhibit [a]XO	Ullah *et al.* (2016)

Mesona procumbens Hemsl	[e]ND	*Mesona procumbens* extracts (0.25, 0.5 and 1g/kg bw) were orally given to hyperuricemic mice and streptozocin (STZ)-induced SD rats	—	Reduce [b]SUA, [c]LXO, upregulate [p]OAT1, down-regulate [j]GLUT9 and non-significantly effect on blood glucose, insulin sensitivity and renal nephropathy	Jhang *et al.* (2016)
Hibiscus sabdariffa L	Epigallocatechin galla caffeicacid, epigallocatechin,catechin and protocatechuic acid	*Hibiscus sabdariffa* L extract (1, 2 and 5%) was orally given to hyperuricemic male Sprague-Dawley rats for five weeks	—	*Hibiscus sabdariffa* extract reduce [b]SUA and non-significantly impact on [q]ALT, [r]AST, [o]Scr, [s]SXO, [c]LXO, increase serum and liver urease.	Kuo *et al.* (2012)
Indian gooseberry	[e]ND	Orally (200–400 mg/kg bw) berry extract administrated to hyperuricemic sprague-dawely rats for 28 days	—	Reduce [b]SUA	Sarvaiya *et al.* (2015)
Rosemary, turmeric, celery (leaves and seeds), fig and cinnamon	[e]ND	Plant extracts (500 mg/kg bw) were given orally once	—	Petroleum ether extract of celery seeds shows more anti-hyperurecemic activity as compare to other	Mohamed and Al-Okbi, (2008)
Soursop	[e]ND	*In-vitro*	70.15 ± 0.70%	Inhibit [a]XO	Ewadh *et al.* (2015)
Carica papaya	[e]ND	*In-vitro* and *in-vivo* aqueous extract was given (1, 2, 3 g/kg bw) for 14 days	79.28 ± 0.2%	Inhibit [a]XO and reduce [b]SUA	Azmi *et al.* (2012) and Calderon *et al.* (2015)

[a]XO: Xanthine oxidase, [b]SUA: Serum uric acid, [c]LXO: Liver xanthine oxidase, [d]LXDH: liver xanthine dehydrogenase, [e]ND: Not determine/ reported, [f]HUA: hyperuricemia, [g]hsCRP: High-sensitive-C- Reactive protein, [h]NO: Nitric oxide, [i]UO: urinary nitrogen, [l]URAT1: urate transporter, [j]GLUT9: glucose transporter 9, [K]Organic anion transporters: OAT1, OAT2, OAT3, [l]IL-1β: Interleukin 1-beta, [m]MeOH: Methanol, [n]BUN: Blood urea nitrogen, [o]Scr: Serum creatinine, [q]ALT: Alanine transaminase, [r]AST: Aspartate transaminase, [s]SXO: Serum xanthine oxidase, [t]PO: Potassium oxanate, [u]DW: dry weight, [v]bw: body weight, [x]K_i: Reaction kinetic, [y]TNF-α: Tumor necrosis factor alpha, [z]NSU: monosodium urate, [**]activity of specific compound

BCRP is present in the apical membrane of various tissues, such as liver and intestine, and incapacitated function of BCRP directly linked with the elevation of SUA level (Bakhiya *et al.*, 2003). Studies conducted by Yano *et al.* (2014), Kolz *et al.* (2009) and Hosomi *et al.* (2012) reported that ABCG2 play a significant role in an elimination of intestinal UA. Moreover, Wang *et al.* (2017c) also confirmed that chicory extract ameliorates the intestinal elimination by modulating the ABCG2 transporter (Figure 6). However, there is lack of data about the effect of dietary food plant on the ABCG2 transporter or the other proposed mechanism of UA elimination via intestine.

Management of hyperuricemia through dietary polyphenols

Fruits polyphenols

In-vivo and *in-vitro* studies confirmed that fruits polyphenols possessed tangible effect on UA disorder by blocking XO, increase renal UA secretion, prevent from reabsorption of UA and not reported yet about intestinal elimination of UA (Arimboor and Arumughan, 2012; Bell *et al.*, 2014; Irondi *et al.*, 2016a; Wang *et al.*, 2017a e).

Many fruits i.e., citrus fruits, (Muthiah *et al.*, 2012; Umamaheswari, 2013; Wang *et al.*, 2017), pomegranate (Les *et al.*, (2015), lychee (Moriwaki *et al.*, 2011), cherries (Bell *et al.*, 2014; Cheatham *et al.*, 2016), sea buckthore (Arimboor and Arumughan, 2012), longan (Hou *et al.*, 2012), pear (Baltas, 2017), mango (Jiang *et al.*, 2012), guava (Irondi *et al.*, 2016a) have been reported for their anti- hyperuricemic effect. The detail of each reported fruit bioactive compounds and their anti- hyperuricemic activity describe below and also presented in the (Table 2).

From the last few years, citrus fruits gained much attraction due to promising health benefits and minimum toxicity to animal (Haidari *et al.*, 2009a; Muthiah, 2012; Wang *et al.*, 2017a). The citrus fruits contain hesperidin, naringin, nobiletin, neohesperidin and many other compounds together inhibit the XO and lower the UA level (Umamaheswari, 2013), calcium oxalate calculus (Kulaksizoglu *et al.*, 2008), hyperuricemia urinary calculus (Aras *et al.*, 2008) and kidney calculus (Touhami *et al.*, 2007). Naringenin and naringin prominent flavonoids abundantly present in citrus fruits hold anti- hyperuricemic activities by inhibiting UA generation via blocking the enzyme XO (IC_{50}: 77.4 ± 20.9 and 94 ± 9.9 μM). (Umamaheswari, 2013; Dew *et al.*, 2005). In another study Dew *et al.* (2005) reported that orange juice possessed anti-hyperurecemic properties and promoted XO inhibition (IC_{50}:7 ± 1 μM).

The results of Haidari *et al.* (2009a) also positively supported the previous researcher finding. In their study, orange (5 ml/kg) and hesperetin (5 mg/ml) were orally administrated to potassium oxonate (PO) induced hyperurecemic rats for 14 days. The results revealed that orange, hesperetin and positive control (allopurinol) shows hepatic XO inhibition (24.49, 23.69 and 57.83%) and reduce SUA level (169.98, 185.81 and 72.38 μmol/l) in PO induced hyperuricemic rats. Albeit, the effect was weak but if the concentration of orange juice increase it will more effect on UA level and XO. More recently study conducted by Wang *et al.* (2017a) reported that lemon fruit juice orally given to volunteer (30 ml/day, 6 weeks) and mice (10 mg/kg, 11 days) lowered SUA level in volunteer (588.88 to 552.22 μmol/l) and mice (150 to 90 μmol/l) without damaging kidney and liver function. Previously reported, that lemon fruit juice enhanced glomerular filtration and increased UA elimination in kidney (Touhami *et al.*, 2007; Aras *et al.*, 2008). In another study, different parts (leaf, peel and fruit) of *Citrus limetta, Citrus aurantium*, and *Citrus limon* also showed anti-hyperuricemic effect *in-vitro*. The results reported that peels of all citrus varieties showed more potent XO inhibitory activity as compare to the leaves and fruit (peel, leaves and fruit), *Citrus limetta* (IC_{50}: 40.16 ± 0.88 peel, 74.83 ± 2.42 leaves and 95.16 ± 0.60 fruit μg/ml) > *Citrus aurantium* (IC_{50}: 51.50 ± 2.05 peel, 73.50 ± 1.26 leaves, μg/ml) > *Citrus limon* (IC_{50}: 64.90 ± 1.24 peel, 76.83 ± 2.02 leaves μg/ml) (Muthiah *et al.*, 2012). In another study Liu *et al.* (2016a) isolated seven bioactive compounds (naringin, hesperidin, neohesperidin, naringenin, hesperetin, nobiletin and tangeretin) from dried immature fruit of *Citrus aurantium* and screened for anti-hyperuricemic effect. Two isolated compounds (hesperetin and nobiletin) shows more potent XO inhibitory activity (IC_{50}: 16.48 and 107.53 μM) as compare to other isolated compounds.

Pomegranate (*Punica granatum*) is considered as a functional fruit and used as folk medicine in the treatment of cancer, cardiovascular disease, inflammatory, diabetes, diarrhea and arthritis (Wong *et al.*, 2014). Different parts of pomegranate have been utilized *in-vitro* for anti-hyperuricemic properties via enzyme (XO) inhibition assay. Rummun *et al.* (2013) reported that only flower of pomegranate plant shows XO inhibition activity with IC_{50} (mg ADW/ml) of 0.058 ± 0.011. In another study, methanolic extract of pomegranate seed also exhibit 15.53% of XO inhibitory activity. However, the results of Les *et al.* (2015) didn't support the previous finding of Wong *et al.* (2014) and Rummun *et al.* (2013). Les *et al.* (2015) demonstrated that commercialized pomegranate juice does not inhibit XO which may be associated with the loss of polyphenolic compounds during processing.

Cranberries, blue berries and various kinds of cherry fruits have been reported for their anti-hyperuricemic and anti-gout activities. Anecdotal evidence of cherries on anti-gout and anti-inflammatory early reported by Blau, (1950). These activities associated due to high antioxidant properties owing to their high polyphenolic contents and the ability to increase UA excretion (i.e., uricosuric effect) or inhibit UA synthesis (Jacob *et al.*, 2003). In addition, Dew *et al.* (2005) reported that cranberry contained polyphenols and showed strong XO inhibitory activity (IC_{50}: 2.4 ± 0.1%). In another study, Jacob *et al.* (2003) reported that Bing sweet cherries increased UA elimination (214 to 188 μmol/L) in healthy women (22–44 year) and this effect directly associated with the presence of phenolic compounds, including procyanidins, hydroxycinnamates, anthocyanins and flavanols. They suggest that Bing berries also reduced tubular reabsorption/or renal glomerular filtration of UA. Furthermore, He *et al.* (2006) documented that cherries fruit possessed anti-inflammatory activity by suppressing the prostaglandin E2 (PGE2) and tumor necrosis factor alpha (TNF-α). Moreover, response of inflammatory biomarkers, such as decreasing nitric oxide and C-reactive protein, indicating the anti-inflammatory property of cherries may be used in gouty pain (Kelley *et al.*, 2006).

In an animal model study conducted by Haidari *et al.* (2009b) revealed that decreased plasma UA concentration in the cherry-fed group was associated with the inhibition of hepatic activities of XO and xanthine dehydrogenase; this suggests cherries may possess the capacity to reduce UA production, which is a plausible mechanism for its hyperuricemic effect. Cherry juice consumption reduce risk of gout (35%) when given to 633male (21–88 year) for 2 days (Zhang *et al.*, 2012). Bell *et al.* (2014) reported that Montmorency tart cherry concentrate in volunteers (age 26 ± 3 years) for 48 h significantly reduced serum urate and high-sensitive-C- reactive protein (hsCRP), whereas increased urinary urate excretion. More recent study results also support the above discussion, daily consumption of blue berries (35 g powder) for 6 months significantly lower the SUA level in older (40–80 year) men and women (Cheatham *et al.*, 2016).

In-vivo anti-hyperuricemic activity of grape seed procyanidins were reported by Wang *et al.* (2004). The results revealed that grape seed procyanidins (400 mg/kg 3 days) suppressed the hepatic xanthine dehydrogenase (44.6%), XO (21.0%) and serum UA (5.21 ± 0.42 to 3.53 ± 0.29 mg/dl) in PO induced hyperuricemic mice. Earlier, *in-vitro* study also reported inverse relation between purple grapes juice consumption and UA synthesis (Dew *et al.*, 2005). Sea buckthore berries and its products are well-known as functional food due to high antioxidant activity and phytochemicals. Arimboor and Arumughan, (2012) isolate eight compounds (gallocatechin-(4α-2)-phloroglucino, epigallocatechin-(4β-2)-phloroglucino,catechin-(4α-2)-phloroglucino, epicatechin-(4α-2)- phloroglucino, gallocatechin, epigallocatechin, catechin and epicatechin) from the proanthocyanidins extract of sea buckthore seed and evaluate XO inhibition activity by *in-vitro* assay. Polyphenols enrich extract of Sea buckthore shows strong anti- hyperuricemic activity via inhibiting UA synthesis and they suggested that it may be used for the management of UA disorder.

Oligonol, a bioactive compound present in the lychee fruit was evaluated for its anti- hyperuricemic effect on healthy male volunteer. Oligonol (600 mg) was orally given with water (300 ml) to healthy (6 men) volunteer for four hours. The results predicted that oligonol decrease SUA level (316.7 ± 54.2 to 305.4 ± 56.0 μmol/L), hourly uric excretion (0.406 ± 0.060 to 0.296 ± 0.072 (Uua (μmol)/Ucr (mol)), inhibit XO (70% at 40μg/ml) and not significantly effect on creatinine clearance (158.8 ± 29.7 to 153.3 ± 29.9 mL/min) as compared to control in healthy male volunteers (Moriwakia *et al.*, 2011). Irondi *et al.* (2016a) claimed that flavonoids enrich guava leaf extract showed strong antioxidant and XO inhibitory (IC_{50}:38.24 ± 2.32 μg/mL) effect as compare to allopurinol (5.78 ± 0.25 μg/mL). They sum up that this prophylactic activity of guava leaf extracts due to the presence of flavonoids (epicatechin, quercetin, luteolin, kaempferol, rutin and catechin) and phenolic compounds (caffeic acid, chlorogenic acid and gallic acid).

Pear fruit belong to the rosaceae family and grown in many countries. Numerous health attribute of this plant have been confirmed. A study conducted in Turkey, by Baltas, (2017) confirmed that polyphenols enrich extract of wild pear fruit (*Pyrus elaeagnifolia* subsp. *elaeagnifolia Pallas*) exhibit anti- hyperuricemic effect (IC_{50}: 20.75 ± 0.11 mg/ml) via inhibiting the XO *in-vitro*. Earlier, study results of Nile and Khobragade, (2011) also elucidated the anti- hyperuricemic effect of pear fruit. Mulberroside A, a stilbene glycoside compound present in *Morus alba L.* possess anti-gout/hyperurecemic activity *in-vivo*. Mulberroside A was orally administrated (10, 20 and 40 mg/kg bw) to the potassium oxonate (250 mg/kg BW) induced hyperuricemic male Kun-Ming mice for up to seven days. The results revealed that Mulberroside A decrease SUA level, serum creatinine, urea nitrogen, urinary N-acetyl-β-D-glucosaminidase activity and increase urinary urate excretion. Moreover, it also up-regulate the mRNA and protein level of organic carnitine and cation transporters (mOCTN1, mOCTN2, mOCT1, mOCT2), down regulate protein and mRNA levels of renal urate transporter (mURAT1) and glucose transporter 9 (mGLUT9) (Wang *et al.*, 2011).

Jiang *et al.* (2012) demonstrated that *Mangifera indica* leaf commonly known as (mango) is very effective against the treatment of hyperuricemia and gout. The results divulge that orally admiration of mango leaf extract (50, 100 and 200 mg/kg) to the monosodium urate induced hyperuricemic Sprague-Dawley rats for nine days reduce the ankle swelling and decrease the TNF-α, and IL-1β mRNA level. A subtropical fruit (longan) seed also possess anti hyperuricemic properties by inhibiting XO and increasing the urate excretion *in vivo* and *in vitro* (Hou *et al.*, 2012). Noni fruit also known as Indian mulberry use as (i.e., raw, juice, cooked and processed etc.), polyphenolic enrich juice of this fruit shows potent *in-vitro* XO inhibitory activity with dose depended manner (11, 113 and 148%). However, mechanism and responsible key active compounds were not reported (Palu *et al.*, 2009).

Vegetables polyphenols

Vegetables play an important role in human life. Vegetables are a rich source of various kind of bioactive compounds such as polyphenols, flavonoids, carotenoids, ascorbic acid and many other micro and macro nutrients in different proportion. A diet rich in vegetables are associated with a lower incidence of illnesses such as enzyme inhibitory activities, antioxidant, anticancer, antimicrobial, coronary heart, neurodegenerative ailments, hyperuricemia, gout and anti-inflammatory (Sharma *et al.*, 2016; Nile *et al.*, 2017; Zhang *et al.*, 2017).

Various *in-vitro* and animal model studies reported that the regular consumption of vegetables i.e. onion (Nile *et al.*, 2017), sweet purple potatoes (Zhang *et al.*, 2017), eggplant (Chiang and Chen, 1993), broccoli sprouts (Gawlik-Dziki *et al.*, 2012 a), *Perilla frutescens* (Wang *et al.*, 2017e), beet root (Vulić *et al.*, 2013) and *Angelica keiskei* (Kim *et al.*, 2014) lower the risk of hyperuricemia and gout disorder (Table 2).

Onion (*Allium cepa*) is a vegetable crop belongs to the family Alliaceae and has considerable economic importance as it is one of the most valuable vegetable crop grown and utilized globally for domestic food preparations with important medicinal, nutritional, and functional properties. Onion bulbs and onion waste consist of numerous dietary compounds and bioactive phytonutrients, including phenolics and flavonoids (e.g., sugars, fibers, vitamins, anthocyanins, and quercetin glucosides). These polyphenolic compounds link inversely with the generation of UA because these compounds inhibit xanthine oxidase enzyme (XO) responsible for UA generation or help in renal elimination of kidney (Haider *et al.*, 2008; Nile and Park,

2013; Nile *et al.,* 2017). More recently, *in-vitro* study conducted by Nile *et al.* (2017) reported the anti- hyperuricemic activity of onion waste. They identified quercetin and quercetin glycosides from the methanolic extract of onion waste and evaluate anti- hyperuricemic activity by enzyme inhibition assay. Total flavonol glucoside (501.55 mg/100 DW) among which, quercetin-4′-O-monoglucoside, (254.85 ± 10.5 mg/100 DW), quercetin-3, 4′-O-diglucoside (162.34 ± 8.6 mg/100 DW), quercetin aglycone (60.44 ± 2.3 mg/100 DW) and isorhamnetin-3-glucoside (23.92 ± 1.1 mg/100 DW) were the major isolated quercetin glycosides from onion waste. Quercetin and quercetin glycoside (quercetin-3, 4′-O-diglucoside) were the key active component responsible for enzyme inhibition activity as compared to other. The increasing order of XO inhibition of isolated compounds were with IC_{50} (μg/mL) value quercetin (10.5 ± 0.06)>quercetin-3, 4′-O-diglucoside (15.3 ± 0.02)> quercetin-4′-O-monoglucoside (17. ± 0.04)>isorhamnetin-3-glucoside (20.8 ± 0.05) as compared to allopurinol (6.5 ± 0.05). Moreover, kinetic study disclose that quercetin showed the competitive type of inhibition. In another study Nile and Park (2013) elucidated the *in-vitro* anti- hyperuricemic and antioxidant activity of three different onion varieties (white, red and yellow). The results divulge that all onion varieties exhibit strong antioxidant and enzyme (XO) inhibitory activity. However, red (IC_{50} μg/ml: 14.2 ± 0.2) onion variety shows stronger inhibition as compare to yellow (IC_{50} μg/ml: 15.5 ± 0.3) and white (IC_{50} μg/ml: 17.0 ± 0.1) and this is due to the presence of bioactive compounds presents in the onion varieties. Earlier, animal model study conducted by Haider *et al.* (2008) also reported the anti- hyperuricemic effect of onion. Onion extract (5 g/kg BW) was orally given to male Wister rats for fourteen days. The results divulge that onion extract reduce serum uric acid (SUA), liver xanthine oxidase and liver xanthine deoxygenase activities in rats. They concluded that this effect due to the presence of polyphenolic compounds in onion.

Perilla frutescens Britt, widely grown in China, Korea and Japan. The leaves and stems of this plant used as a vegetable in daily life. *Perilla frutescens* have been used for the treatment of different disorder such as depression, anxiety, tumors, chronic coughs, bacterial and fungal infections, allergies, intoxication and some intestinal disorders (Engermanand *et al.*, 1993; Brownlee, 2001). The anti- hyperuricemic effect of *Perilla frutescens* was reported early in 1990 by Nakanishi and coworker (Nakanishi *et al.*, 1990). They isolated two new compounds from the leaves of *Perilla frutescens* (Z, E)-2-(3, 4-dihydroxyphenyl) ethenyl ester (1) and (Z, E)-2-(3, 5-dihydroxyphenyl) ethenyl ester (2) of 3-(3, 4-dihydroxyphenyl)-2-propenoic acid. These both compounds shows strong XO inhibition *in-vitro* and their mode of inhibition was non-competitive (Nakanishi *et al.*, 1990). Huo *et al.* (2015) also demonstrated the anti-hyperuricemic effect of *Perilla frutescens* leaves extract *in-vitro* and *in-vivo* study. They reported that various phytochemicals are responsible for the inhibition of XO such as caffeic acid, vinyl caffeate, rosmarinic acid, methyl rosmarinate and apigenin with IC_{50} value of (121.22, 31.26, 91.72, 26.59 and 0.44 μM). Lineweaver-Burk plots analysis showed that mode of inhibition of all these compounds were competitive type except apigenin which exhibit mixed type inhibition. Furthermore, aqueous extract of *Perilla frutescens* leaves were orally administrated to the hyperuricemic mice at the concentration of (500, 1000, and 2000 mg/kg) for seven days. After seven days *Perilla frutescens* aqueous significantly reduce the SUA level from (193.7 ± 9.9 to 131.0 ± 10.4 μmol/L).

Recently study conducted by Wang *et al.* (2017e) also documented that *Perilla frutescens* leaves are effective against the treatment of hyperuricemia. They isolate eleven bioactive compounds (Protocatechuic acid, chlorogenic acid, caffeic acid, 4-methoxycinnamic acid, oleanolic acid, kaempferol-3-O-rutinoside, rosmarinic acid, luteolin, methyl-rosmarinic acid, apigenin and 4′,5,7-trimethoxyflavone) from the dried leaves of *Perilla frutescens*. Among all only three compounds (apigenin> luteolin> 4′,5,7-Trimethoxyflavone) manifest strong XO inhibition. Thus, *in-vitro* and *in-vivo* studies confirmed that the polyphenolic compounds present in the *Perilla frutescens* leaves are helpful for the management of hyperuricemia and gout disease (Wang *et al.* 2017e).

In-vitro and animal model studies also disclose that sweet purple potato shows anti- hyperuricemic effect due to the presence of polyphenolic compounds i.e. anthocyanindes (Hwa *et al.*, 2011; Hwa *et al.*, 2011; Zhang *et al.*, 2015). In animal model study conducted in Korea, reported that anthocyanin rich extract of sweet purple potato shows strong anti- hyperuricemic effect. Sweet purple potato extract was given to the PO induced hyperuricemic mice once only. The results reveal that sweet purple potato extract (4.10 ± 0.04 mg/dL) reduce SUA level in PO induced hyperuricemic mice (10.25 ± 0.63 mg/dL) (Hwa *et al.*, 2011). In another study Zhang *et al.* (2015) also reported that sweet purple potato extract decrease the serum uric acid level (134.67 μmol L^{-1} (PO group) to 95.50 μmol L^{-1}) 300 mg/kg bw and also significantly inhibit the xanthine oxidase activity in mice liver (1.23, 1.15, 0.99 and 0.87μ/g) at the concentration of (75, 150, 300 mg/kg BW) and allopurinol at (5 mg/kg BW). Furthermore, they also reported that sweet purple potato extract improve the kidney function via regulate the blood urea nitrogen (BUN), creatinine (Cr) level, decreased amount of inflammatory cells infiltrated in renal interstitium and contribute in the improvement of tubular ectasia and interstitial fibrosis. Additionally, sweet purple potato also up-regulate the mRNA level of renal mOCTN2 in hyperuricemia mice, which is related to the improvement of kidney function. There are many bioactive compounds present in the sweet purple potato which may play role together for the reducing SUA, inhibit liver xanthine oxidase, liver xanthine dehydrogenase and improvement in the kidney. To confirm this Zhang *et al.* (2017) conducted a study to elucidate key bioactive compounds in sweet potato which play a vital role for management of hyperuricemia. They separated various bioactive compounds by HPLC using Diamonsil Plus C18-A column and evaluate XOD inhibitory activity *in-vitro*. Among all two anthocyanide compounds, (Cyanidin 3-sophoroside-5-glucoside and Cyanidin 3-(6 caffeoyl-600-feruloyl sophoroside)-5-glucoside) shows strong XOD inhibitory activity and mechanism of these compounds were further elucidated by molecular docking, fluorescence measurements and circular dichroic (CD) spectroscopy methods. The principal inhibitory mechanism of dietary anthocyanins on XO activity could be the insertion of acylated group of anthocyanins into the hydrophobic pocket of XO and the occupation of anthocyanins on the catalytic centre of the

enzyme by competing with the substrate. The acylated groups on the sophoroside may play an important role in the binding process of anthocyanin with XO, and the category of anthocyanins (cyanidin or peonidin) does not affect the inhibition. Both the fluorescence and CD spectroscopy results predicted that the formation of anthocyanin-XO complex may be the possible inhibition mechanism. After the complex is formed, it is harder for xanthine to bind with XO active site, which finally leads to a reduction in enzymatic activity.

Angelica keiskei is a functional food stuff and have been used as vegetables, tea, ice cream and pasta etc. *Angelica keiskei* have potential to combat many health ailments due to abundantly presence of phytochemicals. Kim *et al.* (2014) reported that *Angelica keiskei* root have potential for the treatment of hyperurecemia. They separated many bioactive compounds from the root of *Angelica keiskei* by using HPLC–ESI MS/MS and evaluate XO inhibition *in-vitro*. The key bioactive compound for XO inhibition was Xanthoangelol as compare to XO others, 4-hydroxyderricin, isobavachalcone, xanthoangelol F and xanthoangelol B. The order for the XOD inhibition with IC_{50} (μM) xanthoangelol (8.1 $\pm$ 1.1)> xanthoangelol B (20.3 $\pm$ 1.2)> isobavachalcone (27.1 $\pm$ 1.4)> xanthoangelol F (34.6 $\pm$ 1.6)> 4-hydroxyderricin (54.3 $\pm$ 2.3) as compared to the control allopurinol (1.3 $\pm$ 0.5 μM) respectively.

Beet root pomace extract also shows XO inhibition in rat liver homogenate. This activity link with the presence of high amount of phenolic (ferulic acid, vanillic acid, p-hydroxybenzoic acid, caffeic acid, protocatechuic acid, catechin, epicatechin and rutin) and betalain compounds (betanin, isobetanin and vulgaxanthin I) (Vulić *et al.*, 2013). A total of 27 extracts from non-cultivated and weedy vegetables traditionally consumed by ethnic Albanians (Arbëreshë) in the Vulture area (southern Italy) were used for screening of anti-hyperuriccemic effect. Extracts from non-cultivated *Cichorium intybus, Chondrilla juncea* and *Stellaria media* showed strong *in-vitro* inhibition of XO as compare to other vegetables (Pieroni *et al.*, 2012). Three phytosterols (stigmasterol, stigmasterol-β-D-glycosid and β-sitosterol-β-D glycosid) and three steroidal glycosides (dioscin, protodioscin and methylprotodioscin) from the root of eggplant (*Solanurn rnelongena* L.) also shows XO inhibition activity *in-vitro*. However, the xanthine oxidase inhibition rate was more in phytosterols (IC_{50}: 98.7 $\pm$ 4.54, 87.8 $\pm$ 3.44 and 110 $\pm$ 5.02 μM) as compare to the steroidal glycosides (IC_{50}: 115 $\pm$ 5.18, 106 $\pm$ 4.27 and 156 $\pm$ 5.15 μM). Albeit, the XO inhibitory activity was not very strong but due to the presence of various phytochemicals in this vegetable together help to combat the hyperuricemia and gout disorder (Chiang and Chen, 1993).

Persicaria hydropiper also known as (Water-pepper) used as vegetable and spice in Japan, Europe, America and many other regions. The butanol fraction of this plant also exhibits strong XO inhibitory activity (IC_{50}: 28.72 $\pm$ 7.61 μg/ml) *in-vitro* (Hashim *et al.*, 2013). Ahmed *et al.* (2017) demonstrated that butanolic and methanolic extract of bottle gourd (*Lagenaria siceraria*) showed anti- hyperuricemic activity by inhibiting uric acid synthesis *in-vitro*. They reported that this activity due to the presence of phenolic compounds. Methanolic extract of parsley, molokhia, leek and celery shows anti- hyperuricemic effect via lowering the SUA level (*in-vivo*) and inhibiting XO enzyme (*in-vitro*). However, parsley (82.56%) extract shows the more potent anti-hyperuremei effect as compare to the celery (73.88%), leek (43.71%) and molokhia (36.71%) (El-Rahman *et al.*, 2015). Gawlik-Dziki *et al.* (2012 a) reported that regular consumption of broccoli sprouts may alter the UA level via inhibiting UA synthesis.

A natural flavonol (galangin) present in many plants (i.e. vegetables) is the promising anti- hyperuricemic compounds through inhibiting UA generation (Dong *et al.*, 2016; Zhanng *et al.*, 2016). Galangin is a ketone-containing structure with C-5 and C-7 hydroxyl groups and an additional double bond between C-2 and C-3. The C-3 linked hydroxyl group on the C ring make galangin potent XO inhibitor (Dong *et al.*, 2016). Moreover, molecular docking study discloses that galangin may enter onto the enzyme at catalytic center and form hydrogen bond with amino acid residues (Ser, Thr, Glu and Asn) around the active site and link through (π- π linkage) (Dong *et al.*, 2016). Zhanng *et al.* (2016) results support previous results, they also reported that galangin bind with XO through hydrophobic interaction and hydrogen bonding ($\Delta S°$: 21.81 $Jmol^{-1}$ K^{-1} and -19.60 $kJmol^{-1}$). Additionally, galangin linkage decrease (β-turn and β-sheet) while increase random coil and α-helix contents of XO. Galangin bind at the centre of molybdenum (Mo) may suppress electron transfer and aid in the structural alternation of XO which may suppress oxygen linkage to flavin adenine dinucleotide (FAD) results inhibition of superoxide anion formation as discussed in the above section (suppressing UA synthesis by the inhibition of XO).

Cereal polyphenols

Gawlik-Dziki *et al.* (2017) reported that wheat flour (42.68 $\pm$ 2.25 EC_{50} μg/ml) suppress the UA (uric acid) generation *in-vitro*. The bread prepared with the addition of green coffee flour (3–5%) into wheat flour significantly inhibit UA synthesis in XO assay. They demonstrated that this attribute due to the presence of phenolic compounds in green coffee (5-caffeoylquinic acid, 39.92 mg/g dw) and wheat flour trans- and cis-ferulic acids (165.57 mg/100 g dw). These phenolic compounds work synergistically and decrease the formation of UA.

Ten phenolic compounds (protocatechuic acid, vanillic acid, 2,4,6-trihydroxybenzoic acid, *p*-hydroxycinnamic acid, ferulic acid, hirsutrin, 3′- methoxyhirsutrin, cyanidin-3-glucoside, pelargonidin-3-glucoside and peonidin-3-glucoside) were isolated from maize by Nile and Park (2014). Furthermore, *in-vitro* hyperurecemic activity of all these compounds were also determined. All compounds exhibit strong XO inhibitory activity i.e., hirsutrin (IC_{50}: 5.5 $\pm$ 0.4 μM) > protocatechuic acid (5.8 $\pm$ 0.4 μM)> 2,4,6-trihydroxybenzoic acid (6.5 $\pm$ 0.5 μM)> *p*-hydroxycinnamic acid (6.8 $\pm$ 0.2 μM) > pelargonidin-3-glucoside (7.0 $\pm$ 0.4 μM)> cyanidin-3-glucoside (7.2 $\pm$ 0.1 μM)> ferulic acid (8.2 $\pm$ 0.3 μM)> vanillic acid (8.5 $\pm$ 0.3 μM)> 3′- methoxyhirsutrin (8.6 $\pm$ 0.2 μM) > peonidin-3-glucoside (8.7 $\pm$ 0.1 μM). Lineweaver-Burk plot analysis divulge that the inhibition was a mixed type.

Coix (*Coix lachryma-jobi* L) also known as Chinese pearl barley, Job's tears and adlay is a cereal crop from gramineae family and used as food in many countries. Due to the presence of various phytochemicals present in adlay, make it functional

crop and used for curing of many health disorders. *In-vivo* and *in-vitro* study reported that adlay is very effective for the treatment of a UA disorder. Protocatechuic acid, chlorogenic acid, vanillic acid, caffeic acid, p-coumaric acid and ferulic acid are the major polyphenol compounds detected in polished adlay, brown adlay, adlay hull and bran. The descending order of XO activity of adlay with IC_{50} (μg of Allopurinol equiv/100 g of dry wt) adlay bran (908 ± 46) < adlay hull (741 ± 31) <brown adlay (348 ± 16) <polished adlay (167 ± 8). From the isolated compounds, chlorogenic acid (176 ± 7 μg of Allopurinol equiv/100 g of dry wt) shows more activity as compare to the p-coumaric acid (17976 ± 10 μg of Allopurinol equiv/100 g of dry wt) and ferulic acid (18637 ± 11 μg of Allopurinol equiv/100 g of dry wt). Moreover, an animal study also confirms that adlay significantly effect on SUA, serum creatinine and urea nitrogen in PO hyperuricemic Sprague-Dawley rats (Zhao *et al.*, 2014). Genistein is an isoflavone compound abundantly present in many food plants especially soya bean and possess various biological values. Many researchers reported its anti-hyperuricemic (Hoorn *et al.*, 2002) effects by using various experimental approach spectrophotometric and molecular docking etc. (Lin *et al.*, 2015c). The IC_{50} value of genistein (1.73 μM) reported more than compare to allopurinol (3.53 μM) and inhibition kinetic reveals that its inhibition competitive manner (Ki, 1.39 μM). The surrounding amino acid residue of XO helps genistein for binding and prevent the binding of substrate (Lin *et al.*, 2015c).

Spices polyphenols

Numerous *in-vitro* and *in-vivo* studies reported that spices are very effective for the management of hyperuricemia and gout disorder. Earlier studies conducted by (Candan, 2003; Dew *et al.*, 2005; Zhao *et al.*, 2006) demonstrated that polyphenolic enrich extract of spices inhibit UA synthesis. *Rhus coriaria* is a well-known spice, grown in middle-East and Anatolia region. *In-vitro* study reported that it possess anti- hyperuricemic and superoxide radical scavenging activity by inhibiting XO enzyme (Candan, 2003).

In another study conducted by Dew *et al.* (2005) documented the anti- hyperuricemic effect of different spices (whole dried ginger, thymes, rosemary, cardamom, clove and cinnamon). The decreasing order for XO enzyme inhibition of spices was following cardamom <whole dried ginger < rosemary < thyme < cinnamon < sage < clove with IC_{50} (29 ± 4, 20 ± 8, 20 ± 1, 18 ± 0, 17 ± 1, 13 ± 0 and 6.1 ± 0.38%) respectively. Among all spices clove extract possess strong anti- hyperuricemic via inhibiting *in-vitro* XO enzyme. Gawlik-Dziki, (2012 b) results also support that spices (tarragon, cinnamon, rosemary, basil, oregano, thyme, white pepper and black pepper) reduce UA generation *in-vitro* and are potent anti- hyperuricemic agents.

Moreover, an animal model study conducted by Zhao *et al.* (2006) also support the previous findings. Cassia oil was orally given (300, 450 and 600 mg/kg BW) to the PO induced hyperuricemic mice for seven days and investigated SUA, liver xanthine oxidase (LXO), liver xanthine dehydrogenase (LXDH) and serum and liver uric acid ratio. The results reveal that at high concentration (600 mg/kg BW) cassia oil suppress SUA, SUA/LUA ratio × 10^{-2} (8.80 ± 0.23 to 6.60 ± 0.19), inhibit LXDH (47.58%) and LXO (40.77%).

In another study, *Cinnamomum cassia* twigs were screened for bioactive compounds and their anti- hyperuricemic effect *in-vitro*. The results disclose that methanolic extract of twigs and isolated compounds show anti- hyperuricemic effect *in-vitro*. Thirteen phenol glycosides (cinnamaldehyde, 2-hydroxycinnamaldehyde, 2-methoxycinnamaldehyde, cinnamic acid, coniferaldehyde, cinnacasolide B, p-coumaric acid, dihydromelilotoside, cinnamic alcohol, methyl dihydromelilotoside, rosavin, cinnacasolide A and cinnacasolide C) were isolated from the twigs of *Cinnamomum cassia*. The results reported that cinnamaldehyde, 2-methoxycinnamaldehyde, 2-hydroxycinnamaldehye, cinnamic acid, p-coumaric acid and coniferaldehyde shows strong XO inhibitory activity (96.7 ± 2.3, 95.8 ± 1.6, 94.2 ± 2.1, 93.4 ± 2.3, 73.2 ± 1.6 and 72.5 ± 2.5%) as compared to other isolated compounds (Ngoc *et al.*, 2012).

Recently two studies reported that spices reduce the risk of hyperuricemia via inhibiting UA synthesis (Irondi *et al.*, 2016 b; Ullah, 2017). *Tetrapleura tetraptera* use as a spice in West Africa possess anti- hyperuricemic property. Irondi *et al.* (2016b) demonstrated that *Tetrapleura tetraptera* is very effective for the management of hyperuricemia. For this purpose they isolated ten phenolic compounds (gallic acid 2.95 ± 0.01, catechin 0.43 ± 0.03, chlorogenic acid 0.21 ± 0.01, caffeic acid 3.72 ± 0.02, ellagic acid 3.69 ± 0.04, epicatechin 1.38 ± 0.01, rutin 1.74 ± 0.01, quercetin 3.65 ± 0.03, luteolin 0.45 ± 0.02 and apigenin 3.73 ± 0.01 mg/g) in the fruit of *Tetrapleura tetraptera*. Moreover, *Tetrapleura tetraptera* extract inhibit XO in rat kidney (IC_{50}; 39.53 ± 1.02 μg/ml) and liver (IC_{50}; 45.71 ± 1.44 μg/ml).

Ginger is a well-known spice and notable for the treatment of many health ailments such as rheumatism, anti-cancer, anti-microbial and anti-inflammatory etc (Zhang *et al.*, 2017). A study conducted by Nile and Park, (2015) reported that ginger also possesses anti- hyperuricemic property. They isolated five bioactive compounds (6-gingerol, 6-shogaol, 6-paradol, quercetin, glutathione) from ginger by using HPLC 1100 C18 column (4.6 mm × 50 mm, 1.8 μm) and evaluated XO inhibitory activity *in-vitro*. The results reveal that 6-gingerol the main bioactive component in ginger prevents UA generation by inhibition the enzyme (XO) as compared to other isolated bioactive components (6-shogaol, 6-paradol, quercetin and glutathione). Moreover, IC_{50} value of 6-gingerol (10.5 ± 0.5 μM) and positive control (Allupurionol) (8.4 ± 0.4 μM) almost similarly. They recommend that there is still need of animal model study to further elucidate the ginger extracts effect on SUA and other biomarkers of hyperuricemia. More recently, a study conducted by Ulla *et al.* (2017) reported that *Myristica fragrans* (nutmeg) extract also possess anti- hyperuricemic activity by inhibiting UA synthesis.

Nuts and plants oil polyphenols

Plant oils and nuts are the good source of phytochemicals, antioxidant and are used for the management of various diseases. Some studies reported that by using nuts and oils plant parts (leaves, stem, shell and bark) helpful for the management of UA problem due to the presence of phytochemicals. There is still needed of elucidating new bioactive componets from the different parts of nuts and oil plants which may be helpful for the decreasing of UA by inhibiting XO enzyme or increase UA elimination from the body (Leporatti *et al.*, 1985; Cecchini,

1992; Aggarwal *et al.*, 2004; Flemmig *et al.*, 2011; Wang *et al.*, 2015b; Wang *et al.*, 2016).

Different parts of walnut (fruit, stem, leaf, green husk and shell) show strong anti- hyperuricemic effect *in-vitro* and *in-vivo* via blocking the XO enzyme (Wang *et al.*, 2015b; Wang *et al.*, 2016). Four aldehyde compounds (coumaric aldehyde, coumalic acid, cinnamic aldehyde, 4-hydroxybenzaldehyde) were separated from the walnut shell and evaluate their activity against the XO enzyme. *In-vitro* XO inhibition activity order p-coumaric aldehyde (IC_{50}: 20.17 μg/ml)> coumalic acid (107.45 μg/ml)> cinnamic aldehyde (1370.50 μg/ml)> 4-hydroxybenzaldehyde (1158.93 ug/ml), respectively. The molecular docking study of p-coumaric aldehyde confirms that due to the presence of stabilized four hydrogen bonds and arene–arene interactions make this compound (p-coumaric aldehyde) suitable to inhibit the XO enzyme. Additionally, reported that walnut shell extract (166 mg/kg BW) at 30 days significantly lower the UA level (76.41%) as compared to the model group in Sprague Dawley normal rats without damaging the kidney (Wang *et al.*, 2016).

Peanuts and others nuts contain compound resveratrol (Shishodia and Aggarwal, 2006; Wang *et al.*, 2016) which play very important role in gouty arthritis due to down-regulate inflammatory gene products (IL-6 and IL-1b (Aggarwal *et al.*, 2004).Olive plant is well-known all over the world due to its health benefits and use as food. This small plant is grown in Mediterranean, Southern and East Asia, Europe, America etc. The abundant presence of phytochemicals makes this plant nutritious. The health benefits of this plant have been studied very extensively for many years but there is still needed to elucidate more its effect (Leporatti *et al.* 1985; Cecchini, 1992).

Flemmig *et al.* (2011) isolated nine phenolic compounds (oleuropein, apigenin, caffeic acid, luteolin, luteolin-7-O-d-glucoside, verbascoside, apigenin-7-O-d-glucoside, hydroxytyrosol, and tyrosol) from leafs of *Olea europaea* leaf (Ph.Eur.) by using RP-HPLC-UV/DAD. Anti- hyperuricemic properties of each compound was also determined by XO inhibition, reaction kinetic analysis (Lineweaver–Burk plot and Dixon plot). Four compound shows (luteolin-7-O–d-glucoside, caffeic acid, luteolin, apigenin) mixed type of inhibition while only one compound exhibit competitive type inhibition (oleuropein) and other four (apigenin-7-O-d-glucoside, hydroxytyrosol, tyrosol and verbascoside) compound didn't exhibit anti- hyperuricemia effect. However, oleuropein (K_i 53 μM), luteolin (K_i 2.9 μM) and apigenin (K_i 0.52 μM) exhibit very strong xanthine oxidase inhibition. Although, the concentration of luteolin (0.086 μM/100 mg) and apigenin (0.033μM/100 mg) in the olive leaf extract very little but their effect was very strong (Flemmig *et al.*, 2011).

Tea and coffee polyphenols

After water, tea and coffee are the most commonly consume beverage around the world. A large proportion of the population consume coffee and tea in every region and trend of its consumption increase due to well-known health benefits. Coffee made from the roasted beans of coffee plant whereas tea made from the dried leafs of many plant (i.e., *Camellia sinesis* etc.) depending upon the type of tea (green, oolong, black etc) (Bhatti *et al.*, 2013).

Various phytochemicals abundantly present in tea, coffee and these compounds link with the prevention of many diseases such as hyperuricemia (Honda and Masuda, 2016; Zhao *et al.*, 2017; Gawlik-Dziki *et al.*, 2017). *In-vitro, in-vivo* and epidemiological studies confirm that regular consumption of coffee and tea decreases the risk of hyperuricemia (Choi *et al.*, 2007; Chen *et al.*, 2015; Honda and Masuda, 2016; Zhao *et al.*, 2017).

A cross-sectional study conducted in Beijing, China reported that tea consumption and hyperuricemia inversely link to each other (Li *et al.*, 2015). Recently study conducted by Gawlik-Dziki *et al.* (2017) reported that green tea more effective than wheat flour for reduction of UA due to presence of (chlorogenic and ferulic acids). Earlier, two cross-sectional studies in (1) Japan (Choi *et al.*, 2007) and (2) America (Kiyohara *et al.*, 1999) also reported that consumption of coffee decrease the risk of hyperuricemia. Contrary to above results, recently meta-analysis study reported that there is no link between consumption of tea and UA, hyperuricemia and gout (Zhang *et al.*, 2017).

However, more recently, animal model study conducted by Zhao *et al.* (2017) in China demonstrated that Pu-erh tea is very effective for the treatment of hyperuricemia. Pu-erh tea is native to Yunnan province China and made by the fermentation or non-fermentation dry leaves of *Camellia sinensis* var. *assamica*. They identified six polphenolic compounds gallocatechin (6.29 $\pm$ 0.27 mg/g), epigallocatechin (14.43 $\pm$ 0.03 mg/g), epicatechin gallate (3.74 $\pm$ 0.03 mg/g), gallic acid (12.71 $\pm$ 0.11 mg/g), 3, 4-dihydroxy-benzoic acid (7.11 $\pm$ 1.25 mg/g) and myricetin (2.2 $\pm$ 0.2 mg/g). Pu-erh tea extracts (2000, 1000 and 500 mg/kg BW) were orally given to the potassium oxonate induced hyperuricemic mice for seven consecutive days. The results reveal that Pu-erh tea reduces serum uric acid (23, 15 and 0%), inhibit liver xanthine oxidase (13, 12.5 and 0%) and liver adenosine deaminase activity (LADA) (29, 15 and 0%). Furthermore, Pu-erh tea also down-regulate the mURAT1 and mGLUT9 protein level and mRNA in the kidney.

Kondo *et al.* (2013) reported that rooibos herbal tea extract and isolated flavonoid (Aspalathin) reduce the risk of hyperuricemia both *in-vitro* and *in-vivo*. The results disclose that Rooibos herbal tea extract and Aspalathin shows similar xanthine oxidase enzyme inhibition activity and there is need of further investigation to elucidate more potent compounds from rooibos herbal tea. Honda *et al.* (2014) and Honda and Masuda (2016) reported the anti- hyperuricemic effect of coffee (roasted, dried and green) *in-vitro*. They reported that roasted beans indicate XO inhibition however, dried and green beans of coffee didn't exhibit XO inhibition activity. Moreover, they stated that this effect was due to the presence of two active compounds, 4-caffeoylated 5-lactone and 3-caffeoylated chlorogenic 5-lactone with IC_{50} (μmol L^{-1}) value 210 and 360 (Honda *et al* 2014 161). In another study, Honda and Masuda (2016) isolate pyrogallol (1,2,3-trihydroxybenzene) in the ethyl acetate-soluble part of coffee which significantly contribute to reduction of UA formation with IC_{50} of 0.73 (μmol L^{-1}) *in-vitro* xanthine oxidase assay.

Green tea powder was investigated for its anti- hyperuricemic effect on PO induced induce hyperuricemic mice. Green tea powder (150, 300 and 600 mg/kg) was orally administrated to the PO induced hyperuricemic mice for seven days. The results divulge that green tea powder lower SUA level (15 and

22%), lower serum XO (13 and 17%), inhibit heptic XO (12 and 19%) and inhibit hepatic XO expression (23, 28% $P<0.05$, $P<0.01$) in potassium oxonate induced hyperuricemic mice at (300 and 600 mg/kg extract). Additionally, green tea powder increase urate secretion and inhibit urate reabsorption by down-regulate (URAT1) expression and up-regulate urate transporters (OAT1 and OAT3) expressions in the kidney of PO induced hyperuricemic mice. These results predicted that green tea powder is very effective for management of hyperuricemia and gout disorder (Chen *et al.*, 2015).

Miscellaneous food polyphenols

Fifteen polyphenolic compounds (naringin dihydrochalcone, kaempferol, formonoetin, luteolin, quercetin, daidzin, apigenin, naringenin, morin, baicalin, genistein, myricetin, puerarin, icariin and silibinin) were evaluated for anti- hyperuricemic effect in animal model study. All polyphenolic compounds (50 and 100 mg/kg BW) reduced SUA level in PO induced hyperuricemic mice however, the results of quercetin, morin, myricetin, kaempferol, apigenin and puerarin were more potent as compared to others. These compounds were further investigated for liver xanthine oxidase activity. These polyphenolic compounds were given (50, 100 and 150 mg) to PO induced hyperuricemic mice and determined liver xanthine oxidase (LXOD) activity. The results confirmed that kaempferol (36.84%) exhibit potent LXOD inhibition as compare to other polyphenolic compounds (morin 30.70%, myricetin 30.70%, puerarin 23.68%, quercetin 20.17%) whereas apigenin didn't show LXOD reducing activity (Mo *et al.*, 2007).

In-vitro and two animal model study also confirm anti-hyperuricemic effect of *Mesona procumbens Hemsl* plant, which is used in food desserts, tea and herbal medicine. *Mesona procumbens Hemsl* plant extracts (0.25, 0.5 and 1 g/kg BW) were orally given to PO induced hyperurecemia ICR mice and streptozocin (STZ)-induced SD rats. The plant extract decrease SUA in PO induced hyperurecemia ICR mice and streptozocin (STZ)-induced SD rats. Moreover, *Mesona procumbens Hemsl* plant non-significantly impact on insulin sensitivity, blood glucose, renal nephropathy, reduce liver XO, down-regulate GLUT9, up-regulate OAT1 and decrease interleukin-B (12-B) and TNF- α in streptozocin (STZ)-induced SD rats (Jhang *et al.*, 2016).

In another *in-vitro* study reported that polyphenols enrich ethanolic extract of glossy privet fruit also exhibit (32.4 $\pm$ 1.6%) anti- hyperuricemic effect. Furthermore, they reported that this activity is due to presence of phenolic acid (gallic acid, caffeic acid, ferulic acid and ellagic acid) and flavonoids (quercetin, rutin, epicatechin, oleanolic acid, and ursolic acid) compounds (Wang *et al.*, 2009).

Li *et al.* (2016) optimize the extraction condition for polyphenolic compounds in *Prunus salicina Lindl* (plum) by using response surface methodology and evaluate anti- hyperuricemic effect of optimize extract *in-vitro*. The results reveal that plum polyphenols enrich extract significantly reduce UA generation (IC_{50}: 179 g/mL) by inhibition enzyme (XO) *in-vitro* as compare to control (allopurinol). However, they didn't find active compounds responsible for this activity.

Pogostemon cablin is herb grown in many countries and is used as herbal tea, vegetable and for seasoning. A study conducted in China reported that this plant contain bioactive compounds (rosmarinic acid, (7E,9S)-9- hydroxy-2,5,7-megastigmadien-4-one 9-O- β -D-glucopyranoside, 5,7-dihydroxy-4-((2R)-2-methylbutan-1-onyl)-phenylacetic acid 7-O- β -D-apiofuranosyl (1–3)- β – D- glucopyranoside mg/mL) which prevent UA generation and it may be applied for the management of hyperuricemia (Li *et al.*, 2016).

Hibiscus sabdariffa L.(Rossella) a notable herb cultivated in many region and used as in cold beverages, jams, tea, vegetables and herbal medicine. Polyphenolic acid, anthocyanin and other phytochemicals are present abundantly in rosella. It has been used for the treatment of various diseases such as hypertension, liver disorder, cancer etc. Kong *et al.* (2012) isolated some polyphenolic compounds from rossa and determine anti- hyperuricemic effect *in-vitro* and animal model. They isolated, epigallocatechin gallate (20.34 $\pm$ 1.64%) > caffeic acid (18.24 $\pm$ 0.39%)> epigallocatechin (10.11 $\pm$ 1.48%)> catechin (9.86 $\pm$ 1.02%)> protocatechuic acid (8.62 $\pm$ 0.91%) in rossella. In animal model rossa extracts (1, 2 and 5%) were given to in hyperuricemia mice for 35 days. Rossella extract reduces SUA, and non-significantly impact on alanine transaminase (ALT), aspartate transaminase (AST), creatinine (Cr), serum xanthine oxidase (SXO), liver xanthine oxidase (LXO), increase serum and liver urease. They concluded that rossa extract can apply for the treatment of a uric acid disorder.

In another animal study conducted in India, reveals the anti-hyperuricemic effect of *Phyllanthus emblica* (Indian gooseberry) when orally (200–400 mg/kg BW) administrated to Sprague-Dawely rats for 28 days. Indian gooseberry extract, reduce SUA without damaging kidney and liver (Sarvaiya *et al.*, 2015).

Mohamed and Al-Okbi, (2008) elucidated the anti- hyperuricemic effect of petroleum ether and methanolic extract rich in polyphenols (flavonoids) of rosemary, turmeric, celery (leaves and seeds), fig and cinnamon. They selected seventy-eight mice and divided into anti- hyperuricemic control group, PO induced control, and others eleven given to plant extracts. The anti-hyperurecima control group were given PO (250 mg/kg BW) intraperitoneally while others groups plant extracts (500 mg/kg BW) were given orally. The results reveal that all the plant extracts show meaningful anti- hyperuricemic activity by reducing SUA. However, petroleum ether extract of celery seeds shows more potent anti- hyperuricemic effect as compared to other. *In-vitro* study reported that polyphenolic rich methanolic extract of soursop fruit extract exhibit the more (70.15 $\pm$ 0.70%) anti- hyperuricemic effect as compared to positive control allopurinol (67.11 $\pm$ 5.01%) (Ewadh *et al.*, 2015).

Prunus mum also called as Japanese apricot and Chinese plum widely distributed in China, Korea, Japan and Vietnam. It is mainly used in beverages, condiments, flour pan cake, liquor and also in numerous traditional dishes. Additionally, it is also used in the treatment of many health disorders (Kim *et al.*, 2008; Kono *et al.*, 2011). A study conducted by Yi *et al.* (2012) reported that *Prunus mum* also showed anti-hyperuricemic effect. In their study, *Prunus mum* extract was orally administrated to the PO induced hyperuricemic mice for 7 days. The results reveal that *Prunus mum* extract reduces serum and liver UA in PO induced hyperuricemic mice.

Carica papaya is a famous fruit plant grown in the various region of the world and possess many medicinal properties. *In-vitro* and *in-vivo* studies reported that various parts of papaya plant show anti- hyperuricemic effect. An *in-vitro* study conducted by Azmi *et al.* (2012) reported that papaya, unripe fruit peels (79.28 ± 0.2%) possess more XO inhibitory activity as compared to the other (leaves 75.68 ± 0.1%) and unripe fruits (60.36 ± 0.2%). Recently, animal model study supports the previous study of Azmi *et al.* (2012) papaya leaf water extract very effective reducing serum UA in potassium bromate induced hyperuricemic mice and can be used for hyperuricemia disorder (Calderon *et al.*, 2015).

Limitations and suggestions

From the above studies, it is confirmed that dietary polyphenols are very helpful for the management of the UA disorder. Some studies reported that outstrip benefits of polyphenols and some studies based on very limited methodology. No doubt, dietary polyphenols possessed tangible anti-hyperuricemic effects. But in previous studies, many limitations exit such as

1) In most of the studies, only crude food plants extracts employed for their anti-hyperuricemic effect without determining bioactive compounds.
2) Mostly researchers conducted *in-vitro* studies and there is lack of comprehensive animal model base studies
3) There is lack of data which explores the effect of fruits, vegetables, cereals, nuts, plant oils, tea, coffee and spices extracts on the intestinal elimination of uric acid
4) Pathways and mechanism of anti-hyperuricemic effects of dietary polyphenols are still not clear in cellular level.

Novel approaches in separation, purification and identification of biologically active components from vegetables, fruits, cereals, nuts, oils, coffee and tea must be employed and polyphenols must be separated from vegetables, fruits, cereals, nuts, oils, coffee, tea and evaluate their efficacy in human and animal models to formulate a sustainable and natural way to handle HUA. Moreover, secretion of UA via intestine should be addressed rather than only focusing on renal elimination. Furthermore, comprehensive studies are needed and on that basis design new dietary guidelines which really helpful for the UA disorder patients.

Conclusion

HUA life menacing disorder is perpetually accelerated across the world. To overcome the burden of HUA, dietary plant foods plays significant role. Enthralling confirmation from animal, epidemiological and *in-vitro* studies have coincided that many dietary plant foods owned anti-hyperuricemic activity due to the presence of a plethora of biologically active compounds like polyphenols. These biologically active compounds decrease UA synthesis, increase renal UA secretion, and prevent renal UA reabsorption. From the above studies, it is concluded that many biologically active compounds possess anti-hyperuricemic activity almost similar synthetic drugs (e.g. Allopurinol etc). However, further deep studies are required to elucidate bioactive compounds, pathways and how polyphenols interact with the cellular components.

Conflict of interests

The authors declare no conflicts of interest.

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