Renoprotective Effects of Anthocyanins Against Uric Acid-Instigated Injury: Mini Review with a Special Emphasis on Purple Sweet Potato (*Ipomoea batatas* L.) Anthocyanins

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Anthocyanins are ubiquitous phytoconstituents found in a wide array of natural products. Purple sweet potato (Ipomoea batatas L.) is an important source of anthocyanins, a group of flavonoids with various medicinal benefits. One of the medicinal benefits of anthocyanins is their protection against the detrimental effects of stressors such as uric acid. On the other hand, hyperuricemia and its associated effects are considered significant challenges in human health. Since kidneys are essential organs in uric acid handling and uric acid is associated with kidney disease, this review focuses on re-appraising the role of purple sweet potato anthocyanins as renoprotectors against uric acid-related pathobiology. Future studies regarding the potential of these anthocyanins as renoprotectors are also discussed.

Keywords: Anthocyanins; Ipomoea batatas L.; kidney; NLRP3 inflammasome; Nox4; Nrf2; Uric acid; Xanthine oxidase.

Anthocyanins are recognized as widely available-bioactive agents in various natural products. Purple sweet potato (abbreviated as PSP in this manuscript), taxonomically known as *Ipomoea batatas* L., is an important source of anthocyanins. The tuber of this crop has special niche in human civilizations, by serving as both energy source and also regarded as highly nutritious, thus becoming natural product with important pharmaco-nutritional values. PSP tuber contains significant amount of anthocyanins, a group of flavonoid compounds with an array of medicinal benefits[1–4]. One of such potential benefits is their effects in mitigating negative effects of uric acid (UA) on health, especially on kidneys[5].

Nowadays, acute kidney injury (AKI) and chronic kidney disease (CKD) pose as significant challenges in the field of medicine, which are

associated with metabolic dysfunction such as elevated serum level of UA (hyperuricemia). This elevated SUA level promotes the precipitation of UA[6], which can be regarded as a culprit in kidney diseases. This is supported by the fact that AKI risk could be enhanced by the occurrence of hyperuricemia[7], and chronic hyperuricemia might both trigger alterations resulting in CKD and also act as CKD progression-promoting factor[8].

Since kidney is important organ in UA metabolism and handling, and hyperuricemia is associated with renal disease involving various mechanisms[9], this review will be focused on re-appraising the role of anthocyanins in general, and especially those found in PSP as renoprotectors against UA adverse effects. Specifically, we propose gut dysbiosis, Nox4, Nrf2, endoplasmic reticulum stress, and the NLRP3 inflammasome as potential targets of PSP anthocyanins renoprotection against UA-induced injury. Future directions regarding the development of anthocyanins as protective agents against UA-instigated kidney injuries are also discussed.

The Use of Purple Sweet Potato as Folk Remedies

The highly nutritious PSP belongs to family of Convolvulaceae[1], also known as morning glory family. Besides its use as energy source, food colorant and edible food packaging[10], PSP is regarded as a promising source of biotherapeutics and as a natural product with diverse array of medicinal values, as reviewed elsewhere[11]. PSP is known to be traditionally used as antiasthmatic agent, antipyretic agent, maintaining oral health, treatment of dermatological issues (bugbites, burns) and gastrointestinal issues (nausea, constipation), as well as aphrodisiac, to name a few[1]. This natural product had been also classified as folk remedy for gynaecological health in Gilgit area, Pakistan[12]. Closely related with the focus of this review, is the ethnomedicinal use of *Ipomoea batatas* L. leafy stems macerate as oral preparation to treat urinary signs and symptoms such as hematuria, and difficult and painful micturition in Cameroon[13]. Up to date, we are lacking data on the effect of PSP parts handling during their preparation as these aforementioned folk remedies on anthocyanins composition and clinical outcomes (regarding safety and efficacy). Data on clinical outcomes of pharmacokinetic and pharmacodynamic interaction

between phytochemicals contained in PSP and other natural ingredients are also not available currently. Since PSP has been used traditionally as folk remedies, the fulfilment of this research gaps will broadens our understanding on the potentials and development of PSP as source of drugs.

Extraction of Purple Sweet Potato Anthocyanins

To facilitate the establishment of its therapeutic effects in more predictive and measureable manners, extraction of *Ipomoea batatas* L. tuber is essential. Wide techniques are available in extracting the tubers, one of such is solvent extraction. This extraction method is still regarded as the most convenient way (if not easy) in the production of crude extract of natural products. One of the important potentially-renoprotective compounds group isolated after the extraction process is anthocyanins. In a study using two local Javanese PSP varieties, solvent extraction using repeated maceration technique for as long as 24 hours was reported to yield anthocyanins for as much as 5 mg/100 g and 10 mg/100g from the investigated cultivars[4]. Although regarded as a simple extraction method, solvent extraction is time-consuming and lead to the accumulation of solvent waste over time[14].

Anthocyanins Structure and General Functions: Unity of Role in a Chemical Diversity

As flavonoids, anthocyanins retain C6-C3-C6 carbon skeleton pattern. These bioactives occurs more frequently in plants as anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin), while also present as glycone forms (sugar conjugates of anthocyanidins)[15]. Anthocyanins are structurally-diverse flavonoids, but in whatever chemical structure does the individual anthocyanin exist, as secondary metabolites they perform ultimate role, i.e, stress protectants. Anthocyanins confers photoprotection to plant against excessive light exposure as a form of protective capacity against abiotic stressor[16]. Abiotic stressors trigger ROS biogenesis in plant which in turns upregulates anthocyanins synthesis to confers tolerance against the aforementioned stressors[17]. In PSP, the tuber roots are the dominant organs in anthocyanins synthesis, which is regulated under specific transcriptional regulatory mechanism[18]. This spatial distribution of anthocyanins presumably protect the tubers as food storage and reproductive

components against wide array of abiotic stressors, thus promoting evolutionary fitness.

Anthocyanins Identified in Purple Sweet Potato

As mentioned before, two Javanese cultivars of PSP, namely Lawang and Kawi Mountain, had been revealed to contain 10 mg of C3G/100 g and 5 mg of C3G/100 g, respectively. Interestingly, the antioxidant activity of these cultivars was similar, which was presumably contributed by the presence of other antioxidants (4). PSP of 5 varieties from Korea (Sinjami, Jami, Danjami, Yeonjami, and Borami) was shown to be predominantly rich in peonidin. Other anthocyanins such as cyanidin and pelargonidin were also identified in these varieties[19]. In a study conducted in China, hot air-dried PSP was revealed to contain cyanidin 3-sophoroside-5-glucoside, peonidin 3-sophoroside-5-glucoside, cyanidin 3-p-hydroxybenzoylsophoroside-5-glucoside and peonidin 3-p-hydroxybenzoylsophoroside-5-glucoside, with total anthocyanin contents ranging from 82,75 to 609,08 mg/100 g dry weight[20]. These findings provide clues that biogeographical factors determine the composition of anthocyanins in PSP tubers.

Pharmacokinetic Overview of Anthocyanins

In order to integrate anthocyanins into daily diets using oral formulation to prevent disease establishment and progression via appropriate dosing, elucidation of anthocyanins pharmacokinetics after oral administration is mandatory. Stomach and intestines were reported as the major sites of anthocyanins absorption. Uptake of anthocyanins from stomach and kidney was known to be facilitated by special transporter. Anthocyanins were found both as parent compounds and metabolites, with the later existed in much higher level in the systemic circulation. Gut microbiota were also observed to facilitate in decomposing a relatively large portion of anthocyanins reaching the colon[21]. In a recently conducted study using a human small intestinal epithelial line INT-407, PSP acylated anthocyanins were not found intracellularly, meaning that acylation impede the cellular uptake of anthocyanins[22], In line with the result, acylated cyanidin-based anthocyanins from purple carrots exhibited lower absorption efficiencies, shorter half-life and higher elimination rate compared to their non-acylated counterparts[23]. Using Caco-

2 cells as other *in vitro* model for intestinal absorption, anthocyanin absorption efficiency were demonstrated to be determined by several factors (as presented in **Table 1**). "Structure determines fate" thus can be consolidated as a universal regulatory principle in anthocyanin pharmacokinetics.

The Roles of Anthocyanins as Antihyperuricemic Agents

Hyperuricemia can be potentially controlled via several targets, i.e., classical target such as xanthine oxidase (XO) inhibition and urate transporters, and novel target such as management of gut dysbiosis. PSP highly acylated anthocyanins has been revealed to act synergistically with xanthine oxidase inhibitor (XOI) allopurinol in reducing serum UA level (2). As a modulator of urate transporters, anthocyanins administration facilitate the establishment of UA homeostasis in animal model of hyperuricemia (32), as summarized in **Table 2**. Intestines are also gaining increasing attention, as important organs in both UA handling and also xenobiotics metabolism. Intriguingly, patients with gout in a study were revealed to exhibit gut microbiota composition with attenuated potential of purine metabolism, which can be reversed using febuxostat, an UA-lowering medication[33]. On the other hand, PSP anthocyanins and its peonidin-based individual monomers were reported to enhance the population of probiotic gut microbiota while also suppressed the population of pathogenic microbiota. The gut microbiota modulating effects of PSP anthocyanins points out that these natural pigments also act as prebiotics[34]. The role of gut microbiota in UA handling (i.e., maintaining UA homeostasis) and its interactions with pro- and prebiotics had been discussed elegantly elsewhere[35]. Based on the aforementioned results regarding gut microbiota modulating actions, it can be predicted that the ultimate result of anthocyanins-gut microbiota interactions is the establishment of antihyperuricemic and anti-inflammatory milieus.

The Roles of Anthocyanins as Antioxidants in Kidney

As antioxidant, anthocyanins exert their effects via multiple mechanisms, involving diverse array of targets. Hyperuricemia-hyperglycemia association is a potential therapeutic target of renoprotection conferred by anthocyanins. This

notion is supported by findings from *in vitro*, *in vivo* and clinical endocrinology studies. By causing oxidative stress *in vitro*, diminishing glucose tolerance, and blocking insulin signaling (via inhibition of phosphor-Akt [Ser473] and elevation of phosphor-IRS1 [Ser307]) *in vivo*, hyperuricemia directly promotes insulin resistance (36). In line with these findings, hyperuricemia had been shown to directly affect pancreatic â cells. High UA was shown to promote insulin resistance and curtail insulin secretion via promotion of pro-oxidative state and modulation of IRS2/Akt pathway (phospho-Ser731-IRS2 activation and phospho-S473-Akt inhibition)[37]. In clinical setting, hyperglycemic states (prediabetes and type 2 DM) was observed to show significant linkage to hyperuricemia[38].

Anthocyanins from PSP tuber are recognized as antioxidants that can potentially prevent and ameliorate the progression of hyperglycemia-associated oxidative damage in tissues and organs. Anthocyanins-rich ethanol extract of PSP cultivated in the island of Bali, Indonesia, was observed to attenuate blood glucose and MDA levels, while also enhancing antioxidant capacity under dose-dependent manner in a rat model of hyperglycemia[39]. The extract of PSP harvested from Yogyakarta, Indonesia, has been revealed to attenuate renal MDA, and improve renal function in a rodent model of hyperglycemia[40]. These findings can be partially attributed to the ROS scavenging activity of PSP anthocyanins as direct antioxidants[19,20].

Table 1. Determinants of Transport Efficiency of Anthocyanins across Caco-2 Cells

Determining Factors	Descriptions	References
Aglycone structure	Higher hydroxyl group number à higher lipophobicity ← lesser transport efficiency	(24)
Sugar conjugates	Reported to exert minor effects on transport efficiency due to conflicting results whether simpler sugar conjugates positively associated with higher transport efficiency	(24,25)
Dimerism vs. monomerism	Higher structural complexity contributes to lesser transport efficiency	(26)
Other food components	Ethanol à conflicting results; citric acid enhance transport efficiency across the basolateral plasmalemma; phospholipids and terpenes promotes higher transport efficiency of açaí anthocyanins	(27–31)

Table 2. Anthocyanin effects on urate transporters mRNA of murine kidney (32)

Urate transporters	Effect	Expected Outcomes
ABCG2	Upregulation	Urate reabsorption attenuation
GLUT9	Downregulation	
OAT1	Upregulation	
OAT3	Upregulation	Enhanced urate elimination
OCT1	Upregulation	
OCT2	Upregulation	
OCTN1	Upregulation	
OCTN2	Upregulation	
URAT1	Downregulation	

Other oxidative stress-related potential therapeutic target of renoprotection against hyperuricemia is renal NADPH oxidase 4 (Nox4) and nuclear factor erythroid 2-related factor 2 (Nrf2). This oxidase is a ROS-producing enzyme in ER, an important redox-regulating organelle[41]. As the main renal NADPH isoform, Nox4 mediates ROS (H_2O_2) biogenesis. Under certain conditions such as uremic toxins accumulation, Nox4 predisposes tubular epithelial cell to oxidative stress and apoptosis while also inducing the establishment of pro-fibrotic milieu[42]. Pathogenesis of tubulointerstitial renal damage has been associated with hyperuricemia, even in mild degree. In line with the aforementioned findings, UA was

reported to induce proximal tubular cell apoptosis via Nox4 upregulation[43]. Anthocyanins-containing PSP tuber was shown to exhibit attenuative effect on renal Nox4 protein expression in a murine model of hyperuricemia treated with high-purine diet[5]. Based on these findings, it can be assumed that PSP anthocyanins may also serve as indirect antioxidant to protect renal tubulointerstitial homeostasis from the adverse effects of UA by modulating Nox4 expression. Of note, obstructive stimulus (modelled using unilateral ureteral obstruction) upregulates Nox4 but does not exert structural alteration of kidney[44]. This finding points out that renal damaging effect of Nox4 upregulation is stimulus-specific, and should be keep as an important reminder in studying Nox4 biology. In addition to Nox4 inhibition, activation of Nrf2 could mitigate the harmful effects of oxidative stress on kidney, while also attenuating anemia, a common manifestation of CKD complications. These beneficial effects had been documented *in vivo*, while clinical trials using Nrf2 activators with positive results are ongoing[45].

Endoplasmic Reticulum Stress: Other Potential Target of Anthocyanins Renoprotective Action

We propose endoplasmic reticulum (ER) stress as another potential target of renoprotection against UA-triggered renal injury. Induction of intra-endothelial ROS production was associated with ER stress activation due to UA exposure *in vitro*[46]. In addition with this fact, endothelial dysfunction was shown to play important role in kidney impairment, especially CKD. Of note, low nitric oxide (NO) bioavailability (as an interactive result of multiple factors, including oxidative stress) had been observed as a near-universal cellular event in the most advanced state of CKD. Diminished NO bioavailability was known to impair endothelial functions, and recognized as important player in not only renal diseases, but also cardiovascular diseases[47]. Of note, aged kidney is relatively prone to acute injury due to diminished capacity in adapting to stressors, such as perturbation of proteostasis (i.e., ER stress), which can be partially caused by oxidative stress. As a scientific support of this issue, a murine model of aged kidney had been shown to reveal specific dysfunctional unfolded protein response (UPR), which can be restored by antioxidant treatment[48]. These observed phenomena support

the hypothesis that ER stress is a promising target of renoprotection by anthocyanins to abolish or at least to mitigate harmful effects of UA.

Mechanisms of Anthocyanins in Preventing Renal Cell Death and Combatting Renal Inflammation

In murine model of hyperuricemia induced using potassium oxonate, purple sweet potato anthocyanins in highly acylated form has been proven to mitigate renal damage. The renoprotective effect of highly acylated anthocyanins against adverse effect of UA-rich internal milieu is established via downregulation of pro-inflammatory cytokines such as TNF-á, IL-6 and IL-1â (2). Since IL-1 â is synthesized by inflammasomes in the site of inflammation [49], the effect of PSP highly-acylated anthocyanins may be facilitated via silencing of inflammasome activity as a possible anti-inflammatory mechanism. Further studies are warranted to investigate this prediction of action mechanism.

As mentioned previously, inflammasome (specifically, NLRP3 inflammasome) is involved in the pathogenesis of UA-induced renal injury. Soluble form of UA plays a detrimental role in activating NLRP3 inflammasome, which also correlate with mitochondrial ROS biogenesis and fibrosis[50]. In line with these experimental results, UA could induce pyroptosis, a type of cell death which results in inflammation, in renal tubular epithelial cells. *In vitro* and *in vivo* studies pointed out that UA upregulated caspase-1, gasdermin D (GSDMD), IL-1â and IL-18, via the induction of NLRP3 inflammasome by involving ROS. These findings show that even though UA is not yet present in crystallized form, it is capable of triggering deterioration of renal homeostasis. Favorably, the upregulation of pyroptosis-associated biomarkers could be controlled by the administration of synthetic antioxidants. These synthetic antioxidants could also normalize mitochondrial transmembrane potential, pointing out the crucial role of mitochondria in UA-triggered pyroptosis of renal tubular epithelial cells[51].

Excessive and prolonged oxidative stress, ER stress and the concomitant inflammation of the kidney will ultimately induced cell death. This notion is supported by the findings in a study using human umbilical vein endothelial cells (HUVECs) exposed to UA. HUVECs may undergo ER stress

and apoptosis under UA exposure, which can be salvaged using direct ROS scavenger and ER stress inhibitor[46]. This UA-induced apoptosis had been shown to be facilitated by ROS biogenesis and NLRP3 inflammasome activation, specifically via NEK7-NLRP3 pathway[52]. Again, this support the notion that NLRP3 inflammasome plays an integral role in mediating harmful effects of UA to the kidney, via ROS production and pro-inflammatory responses, which are potential targets of antioxidants such as anthocyanins.

Future Directions

Several challenging issues are still open as interesting area of research regarding the development of anthocyanins as biotherapeutics to combat the negative effect of UA on kidney. We propose to classify these challenges as pharmacokinetic and pharmacodynamics challenges. Limited bioavailability of dietary anthocyanins[22] poses as an important pharmacokinetic challenge in applying them as biotherapeutics, especially in the aspects of oral drug formulation and dosing (to optimize absorption and delivery to their targets). The pharmacodynamic challenges comprise of elucidating the complex "landscape" of UA pathobiology based on comparative medicine paradigm and the exact action mechanism of individual anthocyanins as potential renoprotectors, at molecular and systemic level.

Mitochondria is crucial in facilitating pyroptosis in UA-triggered renal epithelial cells. Structurally and functionally, mitochondria is known to be associated with ER via mitochondrial-associated membrane (MAM). Other important organelle in redox communication is peroxisome, partially due to its XO content. Mitochondria, ER and peroxisomes forms a "redox triad", regulates the redox homeostasis by putting together redoxomes[41]. The role of inter-organelles crosstalk via MAM and the role as peroxisome as component of the aforementioned "redox triad" in renal cells under the exposure of UA need to be revealed, and can be potentially exploited as therapeutic target to alleviate renal injury. The effect of anthocyanins in modulating this inter-organelles communication are interesting area of future studies regarding the development of anthocyanins (specifically, PSP anthocyanins) as renoprotectors, based on

studies on renal Nox4 protein expression (5) and mitochondrial ROS .

Gut dysbiosis is also an intriguing target in hyperuricemia management[33]. The gout-specific altered composition of gut microbiota may serve as theranostic target for gout and urate nephropathy management. The biology of this specific phenotype of gut dysbiosis in UA-triggered renal injury warrants further investigations. Probiotics and agents with prebiotic activity such as purple sweet potato need to be studied as modulator of gut dysbiosis, with the expectation of correcting gut dysbiosis by enhancing potential for purine metabolism, while also establishing anti-inflammatory condition to protect kidneys from UA adverse impacts. Since XO inhibitors are not usually indicated in asymptomatic hyperuricemia management and has becoming an area of controversy since about the last 4 decades[53], anthocyanins from PSP are potential to be integrated in human diet on a daily basis, especially to maintain general health conditions and specifically to prevent the establishment of UA-instigated renal diseases.

CONCLUSION

Anthocyanins, especially from *Ipomoea batatas* L., are promising protective phytoconstituents in preventing or mitigating UA-instigated renal injury. In general, this renoprotection may be potentially achieved via several action mechanisms, i.e., antioxidants, ER stress modulation, anti-inflammation, anti-fibrosis, anti-apoptosis and restoration of gut dysbiosis. Further investigations are essential to be conducted to reveal the pharmacological profile of these anthocyanins as potential renoprotectors against the detrimental effects of UA.

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Conflict of Interest

The authors declare no potential conflicts of interest.

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