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Antioxidant Potential of *Usnea spp.* Extract with Lysozyme Conjugation for the Prevention of Chronic Kidney Disease Progression

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ABSTRACT

The prevalence of chronic kidney disease worldwide has been reported to increase every year with hypertension serving as the leading cause. The recommended treatment for chronic kidney disease patients with a history of hypertension is antihypertensive medications, which could cause side effects from prolonged use. Hence, the authors sought out a possible novel modality by implementing antioxidant properties from beard lichen (*Usnea spp*.) extract. Literature search was conducted on trusted scientific databases, including Google Scholar, PubMed, DOAJ, and Cochrane. The pathophysiology of hypertension in the progression of chronic kidney disease could mainly be attributed to the presence of inflammation and oxidative stress, which could be attenuated by the use of antioxidants. Lichens are a class of complex living organisms resulting from a symbiosis that allows them to synthesize various beneficial phytochemicals. Usnic and stictic acid derived from *Usnea spp*. are part of phenolic compounds that display strong antioxidant activities. In order for these antioxidants to have a focused effect on the kidneys, a kidney-targeted drug delivery system should be considered with lysozyme conjugation being the most studied method. The combination of *Usnea spp*. extract's antioxidant capabilities with lysozyme conjugation could serve as a potential novel modality in the specific prevention of chronic kidney disease progression.

Keywords: antioxidant; chronic kidney disease; lysozyme conjugation; *Usnea spp.*

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1. Introduction

Chronic kidney disease (CKD) is a disease with progressive damage to kidney function that can be assessed from a glomerular filtration rate (eGFR) of less than 60 ml/minute that has been present for three months or more. The prevalence of CKD is increasing every year and affecting >10% of the population worldwide[1,2]. Based on the data from the National Basic Health Research (*Laporan Riset Kesehatan Dasar*) in Indonesia, the prevalence of CKD reached 3.8 permil (‰) in 2018 which was a significant increase from 2.0 permil (‰) in 2013[3]. At this point, CKD is still one of the crucial issues in global health and one of the leading causes of death and morbidity in the 21st century[2,4]. CKD can be caused by various disease processes affecting the kidney, whether prerenal, intrarenal or postrenal. One of the main intrarenal etiologies that causes CKD is blood vessel pathology, namely hypertensive nephrosclerosis. Hypertensive nephrosclerosis could cause chronic damage to blood vessels, glomeruli, and tubulointerstitium[5]. The current recommended treatment for CKD patients with a history of hypertension is to use antihypertensive drugs which aim to lower blood pressure so as not to further aggravate existing CKD. Currently, the drug most frequently recommended to patients is amlodipine from the Calcium Channel Blocker group[6]. However, the use of oral antihypertensive drugs to rapidly reduce blood pressure is not without risk and could cause hypotension and subsequent morbidity. Several adverse effects that are commonly found in CKD patients who take long-term antihypertensive drugs include ankle edema, hyperkalemia, dizziness, etc[7]. The prolonged usage of antihypertensive drugs has also been associated with increased risk for the development of kidney cancer[8].

As part of their cultural heritage, Indonesians have high confidence in herbal medicines due to their effective therapeutic effects. Herbal medicines also have fewer side effects in many cases, which proves to be an advantage. Plants or products obtained from nature are preferred to be developed as pharmaceutical raw materials because of their high secondary metabolite contents[9]. One promising alternative treatment is to use active compounds from beard lichen (*Usnea spp*.) extract. *Usnea spp.* are known to have antioxidant activity capable of reducing reactive oxygen species (ROS) in the body. ROS itself plays a crucial role in the pathophysiology of hypertensive nephrosclerosis[10,11]. The unique secondary metabolites and bioactive compounds found in *Usnea spp.* are rarely found in other organisms and hold the potential of a promising source for novel drugs[9]. Therefore, the authors initiated a literature review to assess the antioxidant potential of beard lichen (*Usnea spp*.) extract with lysozyme conjugation for the prevention of CKD progression.

2. Method

The objective of this study was to combine three main ideas, which included the antioxidant potentials of Usnea spp., ROS's role in the pathophysiology of CKD, and drug-lysozyme conjugation as a kidney-targeted drug delivery system to maximize the antioxidant potentials of Usnea spp. on the kidneys. Literature search was conducted on trusted scientific databases such as Google Scholar, PubMed, Directory of Open Access Journal (DOAJ), and Cochrane Central Library. The search keywords used

were antioxidant, usnic acid, stictic acid, usnea, chronic kidney disease, hypertension, pathophysiology, lysozyme, and drug delivery system. The keywords used had been checked on the Medical Subject Heading (MeSH) thesaurus prior to searching.

During the identification process, we excluded articles that were not peer-reviewed, were not written in English nor Indonesian, were not written in full text, or were ongoing. The resulting articles were then screened manually by the authors for relevant information. The inclusion criteria for this study are articles that have information regarding the therapeutic use of Usnea spp., antioxidant potentials of usnic and stictic acid contents in Usnea spp., Usnea spp.'s secondary metabolite extraction, drug-lysozyme conjugation, or pathophysiology of CKD.

3. Result and Discussion

Beard Lichen (*Usnea spp.*)

Lichens are a class of complex living organisms resulting from a symbiosis between a fungal partner (mycobiont) and one or more photosynthetic partners (phytobionts). The phytobionts are most commonly green algae or cyanobacterium[9]. This symbiosis produces a physiological and morphological state different from each component's original state[12,13]. Lichens have been evolving and thriving through extreme climate changes for centuries. This course of evolution has resulted in the ability to synthesize various beneficial phytochemicals with many different uses and advantages in treating a wide range of diseases[9,14]. Indonesia has a high potential for the exploration of lichen's natural pharmacology due to its tropical climate[15].

Usnea spp. is one of the lichens characterized by its height — spanning up to 20 cm[14]. It is classified as fruticose based on its morphology. The thallus has a structure that is shrubby; erect, vertical or trailing; radial; and attached at the base. The phytobionts of this lichen also reside in a layer inside the outer cortex. Despite the ability to live under harsh conditions, a moist environment can better contribute to *Usnea spp.*'s optimal growth and support the production of their unique secondary metabolites[16]. Known for its anti-inflammatory properties, its use has been reported in herbal medicine, Traditional Chinese Medicine (TCM), and homeopathy as a treatment for mild inflammations[9]. Some secondary metabolites in *Usnea spp.* are alkaloids, flavonoids, tannins, terpenoids, and depsides. Depsides include usnic acid which is unique to lichens and is especially abundant in *Usnea spp*. The abundance of usnic acid contributed to its pivotal role in the antioxidant activity of *Usnea spp*.[17] The following is the classification of *Usnea spp.*[18]:

Kingdom : Fungi
Division : Ascomycota
Class : Ascomycetes
Order : Lecanorales
Family : Parmeliaceae
Genus : Usnea

Usnea spp. is found widespread in Indonesia and the people have been utilizing it as herbal medicine in the form of *jamu*. The reported species found in Indonesia include *U. barbata, U. pectinata, U. intermedia, U. chaetophora, U. rubrotincta, U. flammea, U. esperantiana, U. baileyi, U. florida, U. diffracta, U. fragilescens, U. rubicunda, U. subfloridina, U. hesperina, U. trichoides* and *U. pseudogatae, U. mutabilits, and U. hirta*. These species can be found all over Java, Sulawesi, and

East Nusa Tenggara. It is commonly sold and distributed in traditional markets across Indonesia[15,16,19].

Antioxidant Component of *Usnea spp.*

Lichen extract has the potential to be used as medicine due to its antioxidant activities of its phenolic content[15,19]. It has been found that *Usnea spp.* contains stictic acid derivative (depsodoma β-orcinol) and usnic acid which has the potential as an antioxidant[9]. The study by Maulidiyah *et al.*[15] showed that by carrying out tests using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical capture method on methanol extract, the inhibitory concentration of 50% (IC_{50}) result of the usnic acid antioxidant activity test was 18.1 µg/mL. On the other hand, when a direct isolation of the lichen compound in the form of usnic acid was carried out, a high IC_{50} value of 11.7 µg/mL was acquired[15]. However, both still show very strong antioxidant capabilities by producing a value below 50.0 µg/mL[20].

This data was supported by another research conducted by Oran *et al.*[21], which utilized the high-performance liquid chromatography (HPLC) method to identify the concentration of usnic and stictic acid in several species of *Usnea spp*, including *U. filipendula*, *U. fulvoragens* and *U. intermedia*. It was reported that the highest concentrations of usnic and stictic acid were found in the acetone extracts of *U. filipendula* and *U. fulvoreagens*[21].

Mechanism of Construction

Usnea spp. must first be extracted to utilize its antioxidant properties. Extraction of *Usnea spp*. could be done using solvents such as methanol, acetone, and ethanol. A study showed that acetone was the most solvent-efficient compared to methanol and ethanol in terms of usnic and stictic acid contents. The concentration of stictic and usnic acid in acetone extract of *Usnea spp.* could reach up to 9.85±0.49 mg of stictic acid/g of dried lichen and 1.19±0.01 mg of usnic acid/g of dried lichen. Using a solvent with relatively lower polarity is more efficient in extracting phenolic compounds. Acetone is a very useful solvent in extracting *Usnea spp.*'s contents, as most of the lichen substances are soluble in this solvent. The extract can be obtained by grinding air-dried and cleaned lichen, blending it with acetone, and then separating the solids through filtration[21].

Pathophysiology of Hypertension in the Progression of CKD

The pathophysiology of CKD has been associated with various pathways and hypertension being the most prominent cause. However, hypertension could not be defined solely as the cause of CKD as it acts as both the contributor and also the consequence of CKD itself[22]. The impairment of kidney functions could also lead to hypertension since the kidney is a regulator of many crucial aspects of blood pressure[23]. The relationship between the manifestation of hypertension and the progression of CKD has been very complex, interrelated, and multifactorial until now[24]. In general, the development of hypertension in CKD patients could be regulated by four mechanisms: sodium and fluid retention, Renin-Angiotensin-Aldosterone System (RAAS) activation, sympathetic nervous system activation, and endothelial dysfunction (ED). Many studies have pointed out that the development of CKD and hypertension could be attributed to the combination of oxidative stress, inflammation, and ED. High sodium intake has been found to induce a decrease in nitric oxide (NO) and an increase in inflammatory responses[25].

Aldosterone, a component in RAAS activation, has also been found to cause inflammation at the glomerular level, oxidative injuries, and inhibition of NO processes[26]. Therefore, the hallmark present in most CKD patients is the low bioavailability of NO[27].

NO is a free radical synthesized from L-arginine and oxygen mediated by Nitric Oxide Synthase (NOS). NO has properties that regulate vascular relaxation, blood pressure, kidney function, inflammatory response, and thrombosis, making it crucial in the development of ED and arterial remodeling. There are three different isoforms of NOS, one of which, in particular, is the endothelial NOS (eNOS). Under pathological conditions, eNOS could undergo a condition called eNOS coupling and produce ROS. These ROS will then combine with NO to produce peroxynitrite ($ONOO^-$), thus reducing its bioavailability. In addition, ROS could again trigger eNOS uncoupling through oxidation reactions, causing a continuous cycle[10,28–30]. The decrease in NO bioavailability will trigger more oxidative damage and inflammation on the endothelium, causing it to become vasoconstrictive, prothrombotic, and pro-apoptotic in nature. Once developed, hypertension itself could in turn induce ED, inflammation, and oxidative stress through various similar mechanisms. Hence, perpetuating the event of a vicious cycle of continuous exacerbation between CKD and hypertension[31–33].

Current Management of Hypertension in CKD

The treatment of hypertension is pivotal in the overall management of CKD and significantly impacts the outcome[34]. The treatment goal for CKD patients is to achieve a systolic blood pressure (SBP) of less than 130 mmHg. It has been reported that proper control of blood pressure could decrease the incidence of cardiovascular complications and mortality rate among CKD patients[35]. The current first-line of pharmacotherapy in managing hypertension in CKD patients according to most guidelines are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)[34–36]. The most recent guideline on hypertension by the American Heart Association (AHA) and American College of Cardiology (ACC) also recommended the use of ACEIs or ARBs in stage ≥ 3 CKD patients or patients with a spot test result of albuminuria ≥ 300 mg/d or creatinine ≥ 300 mg/g[37]. The pharmacodynamics of ACEIs and ARBs work by inducing vasodilation of the efferent arteriole. The vasodilation then causes a decrease in intraglomerular pressure and a subsequent reduction in proteinuria[34,35]. However, the combined use of ACEIs and ARBs is not recommended since it increases the risk of hyperkalemia and acute kidney injury[36].

A consensus regarding the preferred second-line of antihypertensive pharmacotherapy is still lacking. Diuretics are generally considered a suitable option, especially in cases of volume overload. Loop diuretics could be considered when kidney function declines, especially when excess fluid retention is evident. Torsemide may be a more favorable choice when compared to furosemide and bumetanide from the same loop diuretics class due to its superior bioavailability and longer half-life. Non-dihydropyridine calcium channel blockers (CCBs), such as diltiazem or verapamil, could have additional benefits in reducing proteinuria in CKD patients. In cases of concomitant

In cases of concomitant heart diseases, beta blockers could be considered as an alternative antihypertensive drug based on patients' clinical requirements[35]. Spironolactone from the class of aldosterone receptor antagonists remains the standard treatment for patients with resistant hypertension[38]. Recently, Sodium-glucose cotransporter-2 (SGLT2) inhibitors from the antidiabetic drug family has been reported to show efficacy in reducing the risk of cardiovascular and kidney-related complications. Despite their nature as antidiabetic drugs, they have also been proven to exhibit antihypertensive outcomes[39].

Beneficial Effects of Antioxidant on CKD Progression

Oxidative stress is a condition of oxidative imbalance which may be due to the overproduction of free radicals, the inability of detoxification by antioxidant systems, or both[10,30]. The kidney tubule cells are abundant in mitochondria which makes the kidney more susceptible to oxidative stress-induced damage. A significant increase in the production of free radicals and prooxidants have been observed during the progression of CKD and the abundance of these products could in turn lead to more severe complications, including hypertension. Therefore, the condition of oxidative stress acts as both the cause and consequence of CKD[11]. Over the years, curative and preventive methods have been sought after as means to counter the profound adverse effects resulting from oxidative stress. One of the most promising methods is the implementation of antioxidants. Antioxidants could have both preventive and curative effects by protecting biomolecules against the adverse effects of free radicals and even repairing the resulting oxidative damages. Antioxidants' mechanism of action includes the conversion and inactivation of reactive oxidants, breaking chain reactions, and direct repair on damaged biomolecules. Antioxidants could be produced endogenously or acquired from external sources[10]. Usnic and stictic acid derived from *Usnea spp*. are a part of phenolic compounds which are one of the most prominent external antioxidants. Therefore, the administration of *Usnea spp*.'s antioxidant properties could have beneficial effects on the prevention of CKD progression.

Lysozyme Conjugation for Kidney-targeted Delivery

Kidney-targeted drug delivery should be considered in order for the beneficial phytochemicals to have a focused effect on kidneys and to reduce potential risks for extrarenal toxicity. From the various modalities studied over the past years, macromolecular carriers have been one of the most common methods. Macromolecular carriers utilized for kidney-targeted drug delivery included a wide range of possible agents, such as peptides, antibodies, viruses, and especially low molecular weight proteins (LMWPs). These LMWPs generally have small molecular weight and are active proteins in the human body in forms of enzymes, immune proteins, or peptide hormones. Drugs could be linked to the functional groups of LMWP to create a drug-LMWP conjugate. After reaching proximal tubular (HK-2) kidney cells, the conjugate will then release the linked drug through the process of hydrolysis and the LMWP will be degraded to amino acids after the fusion of endosomes with intracellular lysosomes (Figure 2). However, the synthesis of these conjugates requires intricate design and skilled execution due to the large number of active groups present in a LMWP and its vulnerability towards self-aggregation[40,41].

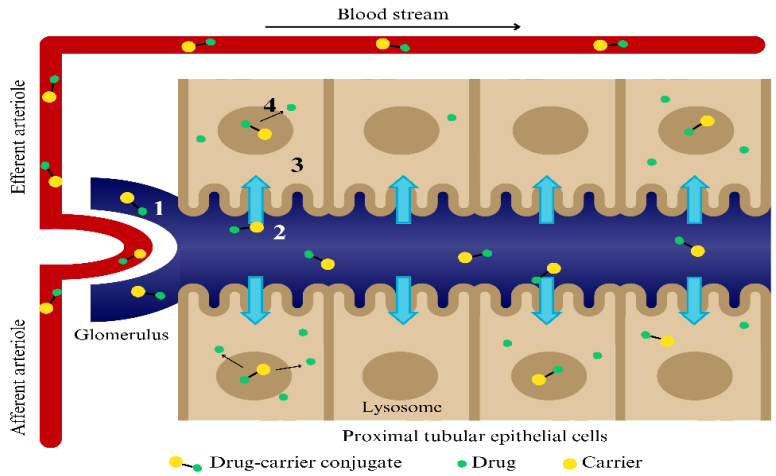

Figure 2. (1): The drug-carrier conjugates enter through glomerular filtration, (2): reabsorption of the drug-carrier conjugates by renal tubules, (3): the drug-carrier conjugates enter the renal proximal tubular cells, (4): the process of drugs release and conjugates degradation in lysosomes

One of the most studied and common choice of LMWPs is lysozyme, which has the advantage of specific renal uptake, biodegradability, and is easy to be conjugated with drugs. Until now, lysozyme has been used to create conjugates with numerous drugs including ACE inhibitor captopril, naproxen, methylprednisolone, kinase inhibitors, and even natural products of traditional medicine. A drug-lysozyme conjugate could be produced using various methods of linkage including ester, peptide, disulfide and even amide bonds[40,42]. However, each method presents its own limitations which should be considered. For instance, ester bonds were known to be unstable during their transfer to the target destination due to the presence of plasma esterase[43]. Several studies focusing on the natural products commonly used in TCM, such as curcumin, triptolide derived from *Tripterygium wilfordii* Hook F. (TWHf), and baicalin (BAI) derived from *Scutellaria baicalensis*, have utilized lysozyme conjugation to achieve the specific delivery of their phytochemicals to kidney cells[41,43–45]. The study by Wang *et al.*[41] found that curcumin-lysozyme conjugate had an enhanced cellular uptake efficiency on HK-2 cells compared to free curcumin solution. Another study by Zhang *et al.*[44] found that the targeted efficiency of 14-succinyl triptolide-lysozyme conjugate was enhanced by 83.8% and showed much less drug-induced extrarenal toxicity compared to free triptolide. Lastly, the study on BAI-lysozyme conjugate by Zheng *et al.*[45] also found that the conjugate showed better effect on the inhibition of renal fibrosis and inflammation than that of BAI-only treatment. Both the curcumin-lysozyme and triptolide-lysozyme conjugates were administered via intravenous injection in their study whereas the BAI-lysozyme conjugate was administered intragastrically[41,43–45]. Taking into account the excellent efficacy and efficiency of lysozyme conjugation in previous phytochemical studies, it may be possible to utilize this method in the administration of *Usnea spp.*'s phytochemical properties as means to achieve kidney-specific outcomes.

4. Conclusion

Usnea spp. is one of the lichen species that can be found in Indonesia and is known to display strong antioxidant capabilities from its content of usnic and stictic acid. The presence of ROS plays a crucial role in the pathophysiology of CKD progression and could be diminished using antioxidants. In order for the beneficial antioxidants of *Usnea spp*. to have a focused effect on the kidneys, lysozyme conjugation should be considered due to its advantage of specific renal uptake, biodegradability, and easier conjugation process. Therefore, the combination of *Usnea spp.* extract's antioxidant capabilities in forms of usnic and stictic acid with lysozyme conjugation could serve as a potential novel modality in the specific prevention of CKD progression. However, the findings in this literature review needs to be further investigated through in vivo studies to clinical trials to determine the safety and efficacy of the proposed novel modality.

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