

***Ophiocordyceps sinensis*: A prominent source of bioactive components for alleviating overactive bladder**

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ABSTRACT

Ophiocordyceps sinensis is one of the most sought-after medicinal fungi used to treat various medical conditions such as respiratory diseases, liver and kidney dysfunctions. In China, it is widely used for alleviation of urinary symptoms where patients treated with *O. sinensis* have shown improvement in frequent urination and nocturia, the two most common symptoms of overactive bladder (OAB). Many studies have reported its anti-inflammatory, anti-oxidative, cytotoxic, hypoglycaemic and vasorelaxation properties. These properties are attributable to the presence of bioactive components such as polysaccharides, proteins and nucleosides. This mini-review highlights the medicinal potential of *O. sinensis* in alleviating OAB, which is a debilitating condition with a profound impact on the quality of life in a high proportion of older people. Four possible mechanisms of action of *O. sinensis* are suggested. Firstly, the relaxation of detrusor muscle through calcium dynamic, production of nitric oxide (NO) and adenosine triphosphate (ATP). A second mechanism proposed is through the suppression of micturition reflex, targeting the neurogenic OAB. The unequivocal anti-inflammation and anti-oxidative properties of *O. sinensis* are two other plausible explanations, as both chronic inflammation and accumulation of oxidative stress molecules are associated with OAB exacerbation. With the recent success in cultivation of *O. sinensis* and the positive results from toxicity studies, a better understanding of its pharmacological actions can be further substantiated, including its use for relieving OAB.

Keywords: *Ophiocordyceps sinensis*; medicinal fungi; overactive bladder; nocturia

INTRODUCTION

Overactive bladder (OAB) is a devastating condition that significantly affects the quality of life of patients in the social, occupational, domestic, physical, sexual and psychological aspects (Abrams, Kelleher, Kerr, & Rogers, 2000). According to the World Health Organisation (WHO), the prevalence of OAB reported in population-based studies ranges from 9.9% to 36.1%, and it is highly prevalent in older people aged 60 years and over (World Health Organization, 2017). OAB appears to have a multifactorial etiology that includes myogenic, neurogenic and urotheliogenic in origin (Brading, 1997; De Groat, 1997; Tyagi, 2011). Recent studies also revealed the association of metabolic syndrome with OAB as a result of inflammation and oxidative stress that arise from conditions such as atherosclerosis, diabetes and obesity (He et al., 2016). There is a deficit in knowledge on the mechanism of OAB as idiopathic OAB is seen in many patients and represents one of the main hurdles in managing this condition (Hanna-Mitchell, Kashyap, Chan, Andersson, & Tannenbaum, 2014). A summary of the pathophysiology of OAB is illustrated in Table 1. Generally, OAB involves an uninhibited elevation of intravesical pressure during the storage phase, leading to enhanced spontaneous myogenic activity and fused tetanic contractions of the bladder (Steers, 2002).

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Table 1: Pathophysiology of overactive bladder

Etiology of Overactive Bladder	Mechanism	Reference
Myogenic	Alterations in the properties and structure of detrusor cause spontaneous rises of intravesical pressure hence increase excitability and electrical coupling between cells. Innervation then spread throughout the bladder wall and result in myogenic contraction of the entire bladder.	(Brading, 1997)
	Abnormal Ca^{2+} activities mediated by extracellular calcium influx and intracellular calcium release lead to spontaneous detrusor muscle contraction.	(Sui, Fry, Malone-Lee, & Wu, 2009)
Neurogenic	Damage to the brain suppresses suprapontine inhibition and damage to axonal pathways in the spinal cord may trigger the C-fiber bladder afferent nerves, resulting in involuntary muscle contractions during the filling stage.	(De Groat, 1997)
	Upregulation of transient receptor potential vanilloid type 1 (TRPV1) receptors on the C-fiber nerve endings, following damage to the brain or spinal cord may result in involuntary micturition.	(de Groat & Yoshimura, 2012; Park, Jung, Cho, Jin, & Hong, 2018)
	Upregulation of nicotinic acetylcholine receptors in pelvic ganglion neurons may potentiate ganglionic transmission and cause detrusor overactivity.	(Chung, Lee, Park, & Jeong, 2015)
Urotheliogenic	Damage to the urothelium lining diminishes the barrier function of the urothelium causing water, urea and toxic substances to pass into underlying tissue hence causing symptoms of urinary urgency, frequency and pain.	(Apodaca et al., 2003)
	Alterations in the level of urothelial signalling molecules such as nitric oxide (NO) and adenosine triphosphate (ATP).	(Winder, Tobin, Zupančič, & Romih, 2014)
Secondary to metabolic syndrome such as atherosclerosis, obesity, insulin resistance	Upregulation of M_3 receptors and L-type calcium channels in diabetic bladder enhances muscarinic activation and influx of extracellular calcium.	(Leiria et al., 2011)
	Elevation of pro-inflammatory cytokines IL-1, IL-6, histamine and TNF- α in metabolic syndrome may directly sensitise afferent nerve terminals and result in OAB. Inhibition of these pro-inflammatory cytokines has shown to improve OAB symptoms.	(Tyagi et al., 2010; Z. Wang et al., 2012)
	Oxidative stress during disease state may lead to bladder ischaemia and reperfusion which in turn, damage and impair contractility of the detrusor.	(Nomiya, Andersson, & Yamaguchi, 2015)

Therefore, regardless of the origin, patients with OAB experience similar symptoms, including urinary urgency, incontinence and most commonly, urinary frequency and nocturia. A national survey conducted in the USA showed that at least 66.8% of the OAB patients suffered from nocturia (Coyné et al., 2003). Although OAB is not a life-threatening condition, it is concerned that people with nocturia may have a higher mortality rate than the general population (Endeshaw et al., 2016).

Currently, the management of OAB consists of conservative therapy and pharmacological intervention (Srikrishna, Robinson, Cardozo, & Vella, 2007). Conservative therapy is also known as behavioural therapy, involves lifestyle modification such as limiting consumption of water, avoiding alcohol or caffeine intake, bladder retraining and/or performing pelvic floor exercise. Pharmacotherapeutic agents including antimuscarinics and β_3 -adrenoceptor agonist (mirabegron) are usually commenced if patients are unable to perform conservative therapy or if symptoms do not improve after six months (National Institute For Health and Care & Excellence, 2015). However, these medications are associated with various unpleasant effects that often lead to non-compliance and treatment failure. Dry mouth and constipation are the most common side effects experienced by antimuscarinic users due to the abundance of muscarinic M_2 and M_3 receptors at the salivary glands and gastrointestinal tract (Athanasopoulos & Giannitsas, 2011). Other side effects include blurred vision, dizziness and cognitive impairment. These effects are enhanced in those who are taking concurrent medications such as antiemetics, bronchodilators and antipsychotics as they are also blocking these muscarinic receptors. Whilst not contributing to the muscarinic burden, mirabegron may cause dizziness, back pain and cardiovascular-related adverse effects such as hypertension and tachycardia (O. Yamaguchi et al., 2015). In refractory OAB, minimally invasive treatment including botulinum toxin A (Botox A) injection and sacral neuromodulation are available (Srikrishna et al., 2007). These methods are expensive and require expert management

and they are not suitable for routine use. Furthermore, they can only provide temporary relief for up to six months.

Undoubtedly, there is a demand for alternative treatment to alleviate OAB. In this regard, herbal and natural products that represent promising sources of bioactive components are increasingly popular among patients with OAB (Chughtai et al., 2013). In China, *Ophiocordyceps sinensis* (Berk.) G.H. Sung, J.M. Sung, Hywel-Jones & Spatafora, one of the most sought-after medicinal fungi, has been used traditionally for frequent urination (Winston & Maimes, 2007). Several studies have also reported that patients treated with *O. sinensis* have shown improvement in urinary symptoms, particularly nocturia, which is the most common symptom of OAB (Bao, Wu, & Zheng, 1994; Z. J. Zhang, Luo, & Li, 1997). This mini-review aims to summarise the known bioactive components of *O. sinensis*, along with its possible mechanisms of action for alleviating OAB. These include detrusor muscle relaxation, inhibition of micturition reflex, anti-inflammation and anti-oxidation.

OPHIOCORDYCEPS SINENSIS AND ITS KNOWN BIOACTIVE CONSTITUENTS

O. sinensis is an entomopathogenic fungus in the family Ophiocordycipitaceae which mainly distributed on the Tibetan Plateau and its surrounding regions, namely Tibet, Gansu, Qinghai, Sichuan, Yunnan and areas above 3000 m in Bhutan, Nepal and India (Yi Li et al., 2011). It is commonly known as "Dong Chong Xia Cao" in Chinese and "yartsa gunbu" in Tibetan, which both mean *winter worm-summer grass* due to its interesting life-cycle. It parasitises the larva of ghost moth in summer, then forms a sporulating structure from the larva after overwintering (Figure 1) (Lo, Hsieh, Lin, & Hsu, 2013). According to the first official record of *O. sinensis* in the *Compendium of Materia Medica 1694* by Wang Ang, *O. sinensis* is beneficial for many conditions including respiratory diseases, liver and kidney dysfunction, as well as a general tonic to strengthen the overall health (Winkler, 2011). In recent years, it has been a focus for biochemical and pharmacological studies



Figure 1: Wild *Ophiocordyceps sinensis*. After being infected by the spores of *O. sinensis*, contents of the larva will be gradually replaced by sclerotium and become a nutrient store for the fungus. Following overwintering, the fungal fruiting body (dark brown) sporulates from the sclerotium i.e. the caterpillar body (light brown) and emerges above the soil surface.

aiming to validate and provide scientific evidence to support the claims of its efficacious traditional medicinal uses.

As a prominent source of bioactive components, *O. sinensis* has shown to elicit several pharmacological actions including anti-inflammation, anti-oxidation, cytotoxic, hypoglycaemic, and vasorelaxation (Chiou, Chang, Chou, & Chen, 2000; Ji et al., 2011; S. P. Li, Li, Dong, & Tsim, 2001; S. P. Li et al., 2006; M. L. Yang, Kuo, Hwang, & Wu, 2011). Polysaccharides are one of the major components of *O. sinensis* and they are purported to be the main contributors to the overall pharmacological effects (Y. Liu et al., 2015). These include cordyglucans, β -1,3/1,6-glucans, the acidic polysaccharide AEPS-1, which composed of glucopyranose and pyrano-glucuronic acid, and the water-soluble polysaccharide CME-1, which composed of mannose and galactose (Lu et al., 2014; Z. M. Wang et al., 2011; Yalin, Ishurd, Cuirong, & Yuanjiang, 2005). Proteins, amino acids and polypeptides also contribute to the bioactivity of *O. sinensis*. A few studies have explored the effect of cordymin and cordycedipeptide A, which are peptides purified from *O. sinensis* (Jia, Ma, Wu, Wu, & Hu, 2005; Qi et al., 2013; Qian, Pan, & Guo, 2012). In addition, 18 amino acids were detected in *O. sinensis* with glutamic acid and aspartic acid being the most abundant (Hsu, Shiao, Hsieh, & Chang, 2002; Y. Liu et al., 2015).

Nucleobases, nucleotides and nucleosides which have important roles in maintaining normal physiology are also detected in both natural and cultured *O. sinensis* using ion-pairing reversed-phase liquid chromatography-mass spectrometry (F. Q. Yang, Li, Feng, Hu, & Li, 2010). These include six nucleobases which are adenine, guanine, uracil, hypoxanthine, cytosine and thymine; three nucleotides that include uridine-5'-monophosphate (UMP), adenosine-5'-monophosphate (AMP) and guanosine-5'-monophosphate (GMP); and seven nucleosides, namely, adenosine, guanosine, uridine, inosine, thymidine, cytidine and cordycepin. Some studies suggested that the amount of cordycepin in artificially cultured *O. sinensis* is much lower than those in the wild (Khan, Parveen, Mishra, Tulsawani, & Ahmad, 2015; F. Q. Yang et al., 2010). However, a large amount of cordycepin (0.66 g per kg) has been detected in the fruiting bodies of *O. sinensis* cultivated in rice-based media (Fung, Cheong, Tan, Ng, & Tan, 2018). This contrasting outcome suggests that the different cultivation methods can affect the chemical composition of the cultivated fungi. CSDNase, an acid deoxyribonuclease, is another compound purified from the cultured mycelia of *O. sinensis* and has identical nucleolytic properties with other well-characterised acid DNases (Ye et al., 2004). Sterols that are commonly found in fungi have also been detected in *O. sinensis*. These include ergosterol and H1-A, an ergosterol-like sterol (Peng et al., 2014; L. Y. Yang, Chen, Kuo, & Lin, 1999). Other compounds include cordycepic acid, phenols, flavonoids, vitamins and microelements (Chatterjee, Srinivasan, & Maiti, 1957; Mamta et al., 2015).

PROPOSED MECHANISMS OF ACTION OF *O. SINENSIS* IN ALLEVIATING OAB

Promoting detrusor muscle relaxation

Inhibition of extracellular calcium influx

The aberration of calcium influx and intracellular calcium release as well as upregulation of L-type calcium channels are part of the contributing factors of OAB (see Table 1). Therefore, modulation of calcium activity is recognised as one of the therapeutic targets for OAB. In a previous study, intravesical instillation of verapamil, a calcium-channel blocker, has shown to significantly increase the bladder capacity in patients with detrusor hyperreflexia (Mattiasson, Ekstrom, & Andersson, 1989). Besides, administration of amlodipine, a dihydropyridine calcium-channel blocker, decreased the bladder index and prolonged the micturition interval of rats with benign prostatic hyperplasia (H. P. Liu, Chen, Liu, & Xu, 2009). Several medicinal fungi and their polysaccharides extracts have demonstrated calcium channel inhibition property. β -glucans from *Schizophyllum commune* have shown to induce a marked relaxation in vascular smooth muscles by blocking calcium-activated chloride channels (Chen et al., 2014). Recently, high molecular weight fractions of *Lignosus rhinoceros* which contain a large amount of glucans have also exhibited airway relaxant effect in rats via blockade of calcium channels (Lee et al., 2018). Due to the abundance of polysaccharides in *O. sinensis* and the similarities in smooth muscle contraction mechanism, it is probable that *O. sinensis* induces detrusor muscle relaxation via similar pathways.

Production of NO and ATP

It is recognised that NO is an essential element in the normal physiology of smooth muscle relaxation. There is an increasing number of studies to address the role of NO in preserving the normal function of a bladder and suggest it as a therapeutic target for bladder dysfunction. Inducible form of nitric oxide synthase (iNOS) knockout mice showed that the production of NO is vital to prevent detrusor dysfunction by promoting vasodilation and reducing platelet aggregation (Lemack, Zimmermann, Vazquez, McConnell, & Lin, 2000). Furthermore, reduced nitric oxide synthase (NOS) and increased NO production were reported to enhance urinary tract symptoms in patients with benign prostatic hyperplasia and bladder outlet obstruction (McVary, 2006). Administration of phosphodiesterase type 5 (PDE5) inhibitors such as tadalafil with NO-mediated relaxant effects have found to significantly reduce the lower urinary tract symptoms in men (Giuliano et al., 2013). Chiou et al. (2000) have demonstrated the NO-releasing effect

of *O. sinensis* in their study, suggesting a possible mechanism of *O. sinensis* in promoting smooth muscle relaxation. Incubation of endothelium-intact rat thoracic aorta with *O. sinensis* mycelium protein extract produced a concentration-dependent relaxation response that can be inhibited by L-N^G-Nitro arginine methyl ester (L-NAME), a NOS inhibitor (Chiou et al., 2000). In the same study, intravenous administration of 32mg/kg of the mycelium protein extract for 45 minutes was shown to reduce the mean arterial pressure (MAP) from 107 ± 6 to 49 ± 3 mmHg, further suggesting its smooth muscle relaxation effect.

The role of ATP in the urinary bladder has been studied extensively as a therapeutic option for bladder dysfunction. ATP-induced relaxation in the urinary bladder has been documented and found to be associated with the activation of purinergic P_{2Y} receptors (Boland, Himpens, Paques, Casteels, & Gillis, 1993). Recently, with the use of vesicular nucleotide transporter (VNUT)-deficient mice, ATP has shown to play a crucial role in urine storage by maintaining bladder relaxation during the early cycle of filling (Nakagomi et al., 2016). This suggests the importance of ATP in regulating bladder smooth muscle tone via VNUT-mediated pathway. As a popular tonic and health booster, *O. sinensis* is often linked to the production of ATP (energy) in the body. Administration of methanolic extract of wild and cultured *O. sinensis* at a daily dose of 1g/kg for three days in mice has shown to enhance the myocardial mitochondrial ATP generation (Siu et al., 2004). Therefore, it is postulated that the production of ATP triggered by *O. sinensis* may also activate the purinergic P_{2Y} receptors in the bladder smooth muscle. However, further investigation is needed as ATP also binds to P_{2X} receptors in the bladder to cause muscle contraction.

Inhibiting the involuntary micturition

Neurogenic OAB is often a secondary complication in patients with neurological disorders such as multiple sclerosis, Parkinson's disease, Alzheimer's disease and spinal cord injury due to impaired central inhibitory pathways or sensitisation of peripheral afferents (De Groat, 1997). In the search of new therapeutic targets in neurogenic OAB, the role of adenosine receptors in the control of detrusor neurotransmission and micturition reflex has been a major focus. It was discovered that reflex micturition can be inhibited by either activating the adenosine A₁ receptors or inhibiting the adenosine A_{2A} receptors in the brain, spinal cord or bladder (Kitta et al., 2014). Kitta et al. (2014) also showed that intravesical perfusion of 2-chloro- N⁶-cyclopentyladenosine (CCPA), a selective adenosine A₁ receptor agonist, was able to reduce bladder overactivity induced by dimethylsulfoxide in rats. Using human detrusor preparations in an isolated tissue bath system, the contractile responses to electrical field stimulation were inhibited by adenosine and selective adenosine A₁ receptor agonists in a concentration-dependent manner (Searl et al., 2016). In addition, N⁶-cyclopentyladenosine (CPA) and adenosine also reduced the amplitudes of the P_{2X} purinoceptor-mediated excitatory junctional potentials (EJP) without affecting the spontaneous EJP potentials. This suggests that the activation of prejunctional A₁ adenosine receptors may dampen detrusor neurotransmission (Searl et al., 2016). Moreover, the activation of adenosine A₁ receptor is imperative to the use of β₃-adrenoceptor agonist in increasing bladder storage capacity and prolonging intermicturition duration (Silva et al., 2017).

Purinergic active components such as adenosine and cordycepin (3'-deoxyadenosine) are major nucleosides in *O. sinensis* and they are often used as biomarkers to determine the authenticity and quality of the medicinal fungus (Hsu et al., 2002; Khan et al., 2015). In addition, cordycepin's high binding affinity at the adenosine A₁ receptor has been documented, thus enable it to induce detrusor muscle relaxation (Hu et al., 2013). It is hypothesised that other nucleosides in *O. sinensis* may also exert similar effects due to their structural similarities with cordycepin.

Anti-inflammation

Although bladder inflammation precludes the clinical diagnosis of OAB, recent studies have drawn a link between the two due to elevation of inflammation-related biomarkers such as prostaglandin E₂ (PGE₂) and pro-inflammatory cytokines within the bladder, and urine in patients with OAB and other bladder conditions (Ghoniem et al., 2011; Hegele et al., 2014). Production of PGE₂ in the bladder can be initiated by a stretch of the detrusor muscle, bladder nerve stimulation, damage of the bladder mucosa as well as inflammation mediators (Rahnama'i, van Koevrige, & Van Kerrebroeck, 2013). Bladder infusion with PGE₂ also shown to enhance micturition reflex in patients with OAB (Hegele et al., 2014). These findings have led to the suggestion of using PGE₂ as a diagnostic biomarker for OAB (Y. J. Zhang & Bai, 2014). *O. sinensis* and its bioactive components thus represent promising therapeutic options due to their well-documented anti-inflammatory property. Cordycepin, in particular, has displayed pronounced anti-inflammatory effect. Pre-treatment with cordycepin at 10, 50 or 100 μM for two hours has shown to diminish the production of PGE₂ in human osteoarthritis chondrocytes pre-stimulated with IL-1β (Ying et al., 2014). A similar procedure was carried out using lipopolysaccharide (LPS)-induced nucleus pulposus (NP) cells and showed that cordycepin at 100 μM significantly inhibited PGE₂ production (Yan Li et al., 2016). It has to be noted that these concentrations studied were very high and unlikely to be achieved *in vivo*. Other than inhibiting the production of PGE₂, cordycepin has shown to down-regulate the expression of TNF-α, IL-6, IL-17A on LPS-stimulated murine spleen cells (Seo et al., 2013). Other bioactive components of *O. sinensis* with anti-inflammatory effects include cordymin and nucleosides. Cordymin has displayed inhibitory activities against TNF-α and IL-1β, leading to suppression of inflammation (Qian et al., 2012). Nucleosides include adenine, adenosine, 2'-deoxyadenosine and thymidine isolated from *O. sinensis* has inhibited the expression of inflammatory cytokines including TNF-α, IL-6 and IL-1β in the cigarette smoke-stimulated RAW 264.7 macrophages (Sun et al., 2018).

Anti-oxidative effect

Among the elderly population and those with vascular disorders, bladder ischaemia may be an important factor in exaggerating the OAB symptoms. Accumulation of oxidative stress molecules in chronic ischaemic bladder is known to form a vicious cycle by causing further destruction on the bladder microcirculation, nerve fibres and smooth muscle cells through lipid peroxidation, protein oxidation and DNA damage (Nomiya et al., 2015). In addition, oxidative stress may amplify the muscarinic receptor activities, stimulate neurodegeneration and cause ultrastructural damage in the bladder (Azadzi, Radisavljevic, Golabek, Yalla, & Siroky, 2010). These lead to enhanced contraction of the bladder, reduced storage capacity and as a consequence incontinence. Therefore, anti-oxidants are being considered as one of the therapeutic options for OAB (Alexandre et al., 2016; Miyata et al., 2019). *O. sinensis* has displayed anti-oxidative effects in several studies, together with its anti-ageing and cytotoxic properties. Hot water extract (HWE) of *O. sinensis* has shown to inhibit lipid peroxidation and prevent accumulation of cholesteryl ester in low-density lipoprotein-induced macrophages (Y. Yamaguchi, Kagota, Nakamura, Shinozuka, & Kunitomo, 2000). It has also shown to suppress over 90% of linoleic peroxidation, surpassing α-tocopherol, an eminent natural antioxidant (Dong & Yao, 2008). Polysaccharide fraction of *O. sinensis*, CSP-1 has been found to possess a strong protective effect in rat pheochromocytoma PC12 cells by suppressing hydrogen peroxide-induced cell injury and lipid peroxidation during the ischaemic state (Shao P. Li et al., 2003). Phenols, flavonoids, nucleosides and nucleobases isolated from *O. sinensis* have also shown to neutralise free radicals in hypoxia-induced cells (Singh et al., 2013).

SAFETY PROFILE

To date, only a limited number of studies regarding its safety is available although this fungus has been used for centuries to treat many

conditions. The presence of toxic metals such as cadmium, lead and arsenic in *O. sinensis* sourced from local herbal stores across five different regions of China suggests a widespread contamination in wild *O. sinensis* (Wei et al., 2017). This, on top of its restricted geographical distribution and added effects of large-scale harvests for financial purposes, had led to the novel approaches of cultivation of the pure mycelium or fruiting bodies of *O. sinensis* in recent years using different techniques such as solid-state fermentation and submerged fermentation. Its success thus provide safer and more affordable options for consumers as well as researchers to substantiate its uses (X. Li et al., 2019). Sub-acute toxicity of cultivated *O. sinensis* has been assessed using rodent models by different groups. Overall, *O. sinensis* did not induce toxicity and behaviour change in the animals throughout the treatment period (Fung, Lee, Tan, & Pailoor, 2017; Meena, Singh, Negi, & Ahmed, 2013). Furthermore, the treatment of *O. sinensis* at 1.2 g three times per day has improved the quality of life of patients without producing any apparent adverse reaction (N. Wang, Li, Huang, Chen, & Chen, 2016).

CONCLUSION

The multifactorial etiology of OAB is a main challenge for clinicians to offer a holistic care and treatment to affected individuals. This mini review has highlighted that *O. sinensis* contains a wide range of bioactive components that may potentially alleviate OAB via different pathways. However, the exact bioactive components are currently not known as the discussed effects may be due to a particular chemical group or are the synergistic effects of several components. There are four possible mechanisms for *O. sinensis* to alleviate OAB. These include (1) promoting bladder smooth muscle relaxation, (2) preventing reflex micturition hence prolonging the filling stage, (3) suppressing inflammation, and (4) activating the anti-oxidative mechanism. The anti-inflammatory and anti-oxidative effects are thought to be particularly useful in patients with co-morbidities such as cardiovascular diseases and diabetes. Current studies suggest that artificially cultivated *O. sinensis* possesses similar bioactivities with the wild type and is a safer and cheaper alternative for consumers. Given that *O. sinensis* is used traditionally for frequent urination and nocturia, more research should be performed in this respect to substantiate its therapeutic benefits.

DISCLOSURES

The authors declare no conflicts of interest in this work.

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