

## Utilization of halophytes as a potential source of pharmaceutical candidates

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(医薬品候補の潜在的供給源としての野生塩生植物の利用)  
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### Thesis Summary

Natural product research continues to play a vital role in paving the way toward the discovery of novel bioactive drug leads and has been applied in many fields of pharmaceutical and functional food industry. Recently, the scientific interest and particularly the economic significance of halophytes have been highly demanding due to the medicinal and nutraceutical potential of its bioactive compounds. The xero-halophyte herbs, *Bassia indica* and *Agathophora alopecuroides*, are deemed to be among the promising sources of natural compounds without chemical or biological investigation.

Non-communicable diseases (NCDs) greatly burden societies and national governments owing to their high mortality rates. NCDs cover a wide range of health issues, such as neurological disorders, cancer, and dermatological conditions. In Alzheimer disease (AD), the deterioration and dysfunction of the cholinergic system are accompanied by a marked decline in the main neurotransmitter, acetylcholine (ACh). Additionally, the accumulation of amyloid- $\beta$  plaques, overactivity of monoamine oxidase type B (MAO-B), and phosphorylated tau-protein in the CNS result in neuroinflammation and cognitive impairments. Hence, multi-targeting of such therapeutic targets has emerged as one of the promising strategies to develop AD treatments.

The first part of this study (Chapters 2-4) was conducted to provide a more scientific basis for the application of halophytes-derived chemicals, especially amide alkaloids, for fighting AD. Hence, the chemical investigation of *B. indica* led to the isolation of twenty-five compounds. Their structures have been determined by 1D, 2D NMR, and HR-MS analysis. Among the isolates, a novel acylated flavonol tetraglycoside and an amide alkaloid, together with a new *seco*-glycosidic oleanane saponin, were identified for the first time. Moreover, the study reports on the isolation and identification of seven amide alkaloids from the aerial parts of *B. indica* and *A. alopecuroides*, namely *N-trans*-feruloyl-3-methoxytyramine, *N-trans*-feruloyl tyramine, *S*-(-)-*N-trans*-feruloylnormetanephine, *S*-(-)-*N-trans*-feruloyloctopamine, *R*-(+)-*N-trans*-feruloyloctopamine, *N-trans*-caffeoyltyramine, and *S*-(-)-3-(4-hydroxy-3-methoxyphenyl)-*N*-[2-(4-hydroxyphenyl)methoxyethyl]acrylamide.

Interestingly, 6,7-dihydroxy coumarin, which has been isolated from *B. indica*, showed a pronounced anti-acetylcholinesterase activity. *N-trans*-feruloyl-3-methoxytyramine, *N-trans*-feruloyltyramine, and 3-(4-hydroxy-3-methoxyphenyl)-*N*-[2-(4-hydroxyphenyl)methoxyethyl]acrylamide showed potent inhibitory activity against  $\beta$ -secretase (BACE1), MAO-B, phosphorylated tau-protein, and anti-aggregation of A $\beta$ -peptides. Meanwhile, *N-trans*-caffeoyltyramine displayed a promising inhibition activity against MAO-B enzyme.

Notably, inflammation is currently known to contribute to tumor cell proliferation, angiogenesis, and inhibition of apoptosis. Recently, several studies have shown that among the effective approaches for treatment of early tumor progression is anti-inflammatory therapy. Consequently, searching for the discovery of compounds with remarkable anti-inflammatory and anti-tumor properties from halophytic plants is of great importance for developing new anti-tumor drugs. Thus, the second part of thesis (Chapter 5) was aimed to assess the anti-tumor and anti-inflammatory activity of isolated compounds from *B. indica*. The methanol extract and oleanane saponin (**23**) displayed promising anti-inflammatory activity. Additionally, *N-trans*-feruloyltyramine exhibited significant cytotoxicity against OVK-18 with  $IC_{50} = 1.74 \mu\text{g/mL}$ , while 6,7-dihydroxy coumarin exhibited a potent inhibition against MCF-7 cells with  $IC_{50} = 1.47 \mu\text{g/mL}$ . Interestingly, compounds **1** and **25** exhibited remarkable cytotoxicity against HepG2 and HCT116 with  $IC_{50} < 0.1 \mu\text{g/mL}$ . Meanwhile, compounds **2**, **4**, **5**, **6**, and **9** exerted potent cytotoxicity against HepG2.

The human skin is the body's first-line protection against environmental, chemical, and biological assaults. Aged skin and several skin diseases such as xerosis, atopic dermatitis, and psoriasis are closely linked to the disrupted skin barrier function and are associated with reduced levels of ceramides, which contribute to the epidermal barrier function as the main lipids of the skin's stratum corneum. Plant-derived compounds are perceived to be safer than synthetic chemicals and are preferable to them for therapeutic and cosmetic applications. Recently, research has been done to discover the beneficial effects of plant-derived compounds on human skin to overcome the reduced levels of natural skin ceramides in diseased and aged skin. Therefore, the third part of thesis (Chapter 6) was conducted to gain a more detailed view of the protective and beneficial health effects of *A. alopecuroides* on the skin. Consequently, the study reports on the isolation and structure elucidation of three previously undescribed compounds (glucosylceramide, flavonol triglycoside, and triterpene oleanane saponin), along with eight known ones from the methanol extract of *A. alopecuroides*. In addition, as ceramide synthase-3 (CerS3) plays a crucial role in epidermal hydration and restoration of the skin barrier function, the influence of *A. alopecuroides* extract and its isolated compounds on the mRNA expression levels of CerS3 in human keratinocyte cells (HaCaT) was evaluated. Importantly, the methanol extract significantly increased the mRNA expression levels of CerS3 by 1.2-fold. Among the isolates, isorhamnetin-3-*O*-glucoside significantly enhanced the expression levels of CerS3 by 4.3-fold. In addition,  $\beta$ -sitosterol,  $\beta$ -sitosterol-glucoside, and solysaponin A, significantly upregulated the mRNA expression levels of CerS3 by 1.9, 4.2, and 3.2-fold, respectively.

In conclusion, the area of research on halophytes is still emerging. The utilization of halophytes as a potential source of value-added products supports the concept of circular economy, in addition to their role in ecological restoration. They offer multiple opportunities as new crops, sustainable agriculture, and a promising source of candidate leads for pharmaceutical and cosmetic applications. By reviewing literature, there are no or limited studies regarding the valorization of halophytic herbs, *B. indica* and *A. alopecuroides*. Part of the findings in this study will encourage natural product researchers to utilize more halophytic plants in AD therapies. Importantly, the outcomes might be very helpful during the development of new inhibitor molecules using the scaffold of the amide alkaloids reported here. Moreover, the study results demonstrated that *A. alopecuroides* has the potential to stimulate epidermal ceramide synthesis *via* enhancing the mRNA expression levels of CerS3. Thus, *A. alopecuroides* is a promising source of bioactive compounds with the capacity to recover aged dry skin including xerosis, atopic dermatitis, and psoriasis, in addition to the ability to restore the disrupted skin barrier function, which is great potential for applications in cosmetic therapy.