IFSCC 2025 full paper (IFSCC2025-1650)

"Plant-Derived Polydeoxyribonucleotide (PDRN) and Exosome Exploration from Three Indonesia Native Plants as Well-Aging Ingredients"

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1. Introduction

Skin has been demonstrated to provide a protective barrier against pathogens and prooxidants such as UVB. Antioxidants are well known for their role as agents that act against the process of aging [1]. The new concept of well-aging involves maintaining the skin in its optimal state, thereby facilitating a graceful aging process. As time passes, the skin's capacity to synthesize collagen diminishes. It is evident that the process of aging is associated with the manifestation of various physiological changes, including the appearance of skin that is characterized by a loss of smoothness and elasticity, the formation of wrinkles, and the presence of hyperpigmentation. The presence of these changes is indicative of an accumulation of prooxidant substances within the body [2]. In the current era, there is a greater awareness among individuals concerning their skin health. However, a significant challenge persists, as many lack the time necessary to commute to a medical facility for aesthetic treatments.

The utilization of plant-based skincare has been demonstrated to offer numerous benefits, including a reduction in adverse effects and an enhancement in compatibility with a wide range of skin types. In the contemporary era, the advent of sophisticated technology has given rise to a plethora of plant-based ingredients, including but not limited to extracts, exosome, and polydeoxyribonucleotide (PDRN). The extraction process was developed prior to the development of the other two methods. A significant number of skincare products utilize

plant extracts as active ingredients. As demonstrated in the research by Michalak (2023), the benefits of extract include the following: antioxidant activity, anti-aging effects, brightening, moisturization, soothing, relaxation, and coloring. It has been demonstrated that certain cutaneous concerns are not effectively managed by extract, which is intended to regulate the expression of genes in cells.

Researchers have been working to learn and develop new methods to enhance the effect and mitigate the side effects of bioactive compounds for skin. A recent innovation in the field is the PDRN method, which was developed by the researcher. According to Khan et al. (2022), PDRN contains DNA fragments with a molecular weight ranging from 50 to 500 kilodaltons. Recent studies showed the most popular PDRN product is ginseng and *Aloe vera* [6,7]. The majority of this treatment is administered by a physician at an aesthetic clinic. It has been observed that certain products developed by manufacturers do in include this substance, such as serums formulated with PDRN derived from ginseng or *Aloe vera*. PDRN has demonstrated potential as a tissue damage preventative, exhibiting wound-healing properties and the capacity to address hyperpigmentation associated with aging [8].

A recent study examined exosome and other technological advancements in this field. The utilization of exosome-derived from animal in therapeutic applications has a proven foundation that extends over a considerable duration. In order to account for the limitations of the source material and to comply with ethical standards, research is being conducted to develop methods for the isolation of exosome from plants. The demand for plant-derived exosome has increased for three primary reasons. First, there is an increasing lack of regulation in the field. Second, there are reduced side effects. Third, there is an abundance of source material [9]. The biodiversity of plant species is a hallmark of the natural sciences, and the benefits that each plant confers are subject to variation among different species. In recent years, there has been a growing trend in the skincare industry of formulating products that contain plant-derived exosome ingredients, such as apple exosome and grape exosome.

Indonesia is a country that is characterized by a high biodiversity. However, there is a notable limitation in the study of these plants, as they have yet to be utilized in a research context. A study of three species is warranted: the butterfly pea flower, the nypa flower bract, and the buah Makassar leaf. These species hold particular interest and promise to contribute to the field of study. In Indonesia, the butterfly pea flower, also known as bunga telang, is frequently utilized as a tea. A potential benefits, including antidiuretic, analgesic, antidiabetic, anti-cholesterol, antidepressant, anti-inflammatory, and antioxidant properties [10].

In Indonesia, the distribution of Nypa(*Nypa fruiticans*) is geographically diverse, including regions such as Kalimantan, Java, Sumatra, Maluku, and Papua, covering approximately 30% of the total mangrove forest area. A review of the literature reveals that the phytochemical compounds present in nypa include poliphenols, phenolics, alkaloids, tannins, flavonoids, and saponins [11].

Buah makassar is traditionally used for gastrointestinal and urinary problems [12]. Buah makassar (*Rhus javanica*) is indigenous to Asia [13]. As previously reported by Anggraini et al. (2021), the phytochemical compound of *Rhus javanica* stem extract is comprised of flavonoid, phenol, saponin, tannin, and terpenoid, which collectively possess antioxidant properties. The

same report that potential of buah makassar stem extract was examined in this study demonstrated the potential of the substance to exhibit antielastase activity. The topical gel containing buah makassar stem extract has demonstrated potential in increasing skin moisture and enhancing skin elasticity [14].

Skin elasticity is a contributing factor to the aging process. Matrix metalloproteinase-1 (MMP-1) has been identified as a potential biomarker for measuring skin aging. MMP-1 is a member of the MMPs and collagenases family of enzymes. MMPs refer to a family of zinc-dependent extracellular matrix (ECM) remodeling endopeptidases that have the capacity to degrade almost every component of the ECM. Furthermore, the ECM plays an active role in the body's operations, such as the cell cycle, cell motility, survival, and apoptosis, as well as the distribution of growth factors and integration of signals into cells. The ECM is composed of a substantial number of molecules, including proteoglycans, glycosaminoglycans, structural proteins such as collagen and elastin, and proteases known as matrix metalloproteases [15]. Collagenases (MMP-1, MMP-8, MMP-13, and MMP-18) are a class of enzymes that are responsible for collagen degradation [16].

Advancement in science and technology evolves skincare industry rapidly, leading to innovations to enhance both efficacy and accessibility of skincare solutions. PDRN from plant and exosome which are gaining attention for their potential benefits. This study explores the potential of 3 native plants from Indonesia in supporting the skin's well-aging process, with a focus on plant-derived PDRN and exosomes through in vitro assays for future applications. The plants studied include nypa flower bract, butterfly pea and buah makassar leaf. Three of them are well known have a high concentration of antioxidants.

2. Materials and Methods

2.1 Materials

The dried plant of butterfly pea flower (*Clitoria ternatea*) was purchased from PT Karya Agro Nasional in Purworejo, Central Java, Indonesia. The dried plant of nypa flower bract (*Nypa fruiticans*) was purchased from CV. Coconut Internasional Indonesia in Makassar, South Sulawesi, and the buah makassar Leaf (*Rhus javanica*) was purchased from CV Aceh Star in Aceh, Indonesia. HDF Cell Line for in vitro assessment.

2.2 Methods

2.2.1 Extraction

Measure 10 g, 50 gr and 30 gr of dried plant butterfly flower, nypa flower bract and buah makassar leaf accurately on a scale and put it in a 2000 mL beaker. Added 700 mL of purified water accurately in a measuring cylinder and put it in a 2000 mL beaker. Added 300 mL of 1,3-Butylene Glycol accurately and put it in a 2000 mL beaker. Set the temperature to 60°C using a hot plate and extraction for 3 hours for butterfly pea flower and 6 hours for nypa flower bract and buah makassar leaf. After cooling to room temperature, filter with Advantec Quantative Filter Paper pore size 3 µm. The samples were filtered with Advantec Quantitative Filter Paper pore size 1µm. The samples were filtered with Whatman Nylon membrane NYL pore size 0.45 µm. Measured 970 mL of the filtered extract and put it in another beaker. Added

30mL of 1,2-hexanediol and stir it with a disperser. The stirred extracts were filtered with Whatman Nylon membrane NYL pore size 0.45 µm.

2.2.2. Antielastase Activity Test

The elastase enzyme activity inhibition test method was adapted Sigma-Aldrich protocols and Suwandy et al. (2023) with modifications. The sample solution of butterfly pea flower extract (*Clitoria ternatea* L) and the control sample solution, 50 and 100 µL were pipetted from the stock solution of 2000 µg/mL. Meanwhile, sample testing solutions prepared with 70% ethanol extract of nypa flower bract and buah makassar leaf to be tested at concentrations of 2000 µg/mL and added into the microplate well, resulting 150, 200, 250, and 300 µg/mL concentration. Then, Tris-HCl pH 8 buffer solution was added to the wells according to the concentrations. In each well of the test solution, 20 µL of 0.88 U/mL enzyme solution was added and incubated at 25°C for 15 minutes. Subsequently, 35 µL of 1.3 mM N-succinyl-(Ala)3-p-nitroanilide substrate solution was added to the comparison solution and control comparison, followed by incubation at 25°C for 50 minutes and measurement of absorbance at 410 nm wavelength [16]. For the blank solution testing with sample concentrations of 500 and 1000 µg/mL, 50 and 100 µL of 2% DMSO solution were added to the wells. The same process was carried out for the blank control testing, but without the use of enzyme.

2.2.3 Antihyaluronidase Activity Test

This method was adapted from Sigma-Aldrich protocols. The main solution of 70% ethanol extract of butterfly pea flower with all concentrations was pipetted 200 µL in each of the six test tubes for the test solution and test control to obtain the final extract concentrations were 30, 50, 70, 90, 110, and 130 µg/mL, respectively. In each test tube only the six concentration variations of the comparison and test solutions and the blank were added with the enzyme solution at the optimal concentration. Then the volume of each test tube was increased to 1 mL with enzyme diluent, homogenized using a vortex, and incubated for 10 minutes at 37ºC in an incubator.

The testing of nypa flower bract extract was conducted at 7 concentrations ranging from 25 to 175 µg/mL, requiring 7 series of pipetting (10–70 µL) from the stock solution. Next, 40 µL of bovine hyaluronidase enzyme was added to the standard solution, followed by the addition of enzyme diluent. Different volumes of enzyme diluent were added to each reaction tube to reach a final volume of 1000 µL. In the sample control solution, no enzyme was added, so the volume of enzyme diluent was adjusted to maintain a final volume of 1000 µL.

Amount 3000 µg/mL stock solution of the extract was prepared by dissolving 30 mg of buah makassar leaf extract in phosphate buffer until the volume reached 10 mL. The inhibition test of hyaluronidase activity in the extract was conducted under optimized conditions. Anti-hyaluronidase testing on the extract was performed by pipetting 500, 750, and 960 µL into reaction tubes to achieve concentrations of 750, 1125, and 1440 µg/mL. Enzyme solvent and 40 µL of hyaluronidase enzyme were added to the reaction tubes, then incubated for 10 minutes at 37°C.

After the incubation time, each of sample in tubes was added with 600 µL of hyaluronic acid substrate and 400 µL of phosphate buffer were added to each reaction tube and incubated again at 37°C for 45 minutes. In a new reaction tube, 2500 µL of albumin acid was pipetted. After 45 minutes of incubation, 500 µL was pipetted and added to the reaction tube containing albumin acid. The mixture solution was then incubated at room temperature for 10 minutes. After 10 minutes, absorbance was measured using UV-Vis spectrophotometry at a wavelength of 600 nm.

2.2.4 Isolation of PDRN

Butterfly pea flower, nypa flower bract, and buah makassar leaf were crushed into small pieces and then ground into a fine powder using a grinder. The powders were extracted with water in an amount 10 times the weight of powder. Dissolve extract in 1.25% deep-sea salt (sodium chloride). The extract was centrifuge to obtain the supernatant. The PDRN is then precipitated by adding etanol in an amount 3 times the weight of supernatant. The precipitated crude PDRN can then be collected by centrifugation. Crude PDRN were mixed with water in an amount 1 times the weight of crude PDRN. The high purity PDRN is then precipitated by adding ethanol to the crude PDRN extract. The precipitated high-purity PDRN can then be collected by centrifugation.

2.2.5 Isolation of Exosome

Butterfly pea flower, Nypa flower bract and buah makassar leaf saperately were ground with 10 times the amount of water using a grinder. Mixture was filtrate with nylon mesh to remove large fiber Each 50 mL of mixture in canonical tube was centrifugated in 2000 xg for 10 minutes, 6000 xg for 20 minutes and 10.000 xg minutes for 40 minutes. The supernatant subjected to conventional ultracentrifugation procedure 125000xg for 2 hours. Pellet was dissolved by water in 1 time the weight of pellet and filter with steril nylon filtration 0,22 um [18].

2.2.6 Particle Size Characterization

Characteristics of PDRN was conduct to measure size using electrophoresis. melt the agarose to make a gel, and add DNA ladder and PDRN to each comb. Check the DNA size using gel electrophoresis than compare with the ladder size. Exosome size was characterized by Dynamic Light Scattering (DLS) spectroscopy. Dilute the separated vesicle 100 times with water. Measuring using a DLS device. Then check the Z-Average (nm) value in software.

2.2.7 Bioactive Screening PDRN and Exosome

Antiaging assay conducted by measured protein level of MMP-1 in HDF cell using ELISA kit from Sigma Aldrich protocols and Natania et al. (2024) with modified. HDF cells were seeded with 35.000 cells in 6 well plate for 24 hours. Then PRDN, exosome, and retinoic acid from butterfly pea flower, nypa flower bract and buah makassar leaf was added to the HDF cell in separately well and incubated for 24 hours. Retinoic acid was used as a control positive. After that, HDF cells were induced with UVB irradiation approximately 30 mJ/cm^2 in PBS. After 24 hours, the medium removed from cells and added to black well plate 100 µL. Put standard

in separate well. The samples and standard were incubated approximately 2 hours in 37°C. wash the plate with washing buffer three times. Antibody was added to each well and added substrate solution. After that added stop solution. The protein was measured using a microplate reader at 450 nm, respectively.

3. Results

3.1 Antielastase Activity Result of the Extracts

Anti-elastase assay showed percent inhibition of 20.19% at 1000 µg/mL, 30.83% at 250 µg/mL, and 66.25% at 500 µg/mL for butterfly pea flower extract (BPFE), nypa flower bract extract (NFBE), and buah makassar leaf extract (BMLE), respectively (**Table 1**).

Table 1. Anti-Elastase Activity of the Extracts

Plant	Concentration (µg /mL)	Average Inhibition (%)
BPFE	500	13.94
	1000	20.19
NFBE	150	22.79
	200	27.50
	250	30.83
	300	30.97
BMLE	200	12.71
	300	25.55
	500	66.25

3.2 Anti-Hyaluronidase Activity Result

Result for the anti-hyaluronidase assay, BPFE, NFBE, and BMLE exhibited IC_{50} values of 95.60 µg/mL, 133.25 µg/mL, and 13.12% inhibition at 750 µg/mL, respectively.

Tabel 2. Anti-Hyaluronidase Activity of the Extracts

Plant	IC_{50} (µg/mL)	Concentration (µg/mL)	Inhibition (%)
BPFE	95.60	-	-
NFBE	133.25	-	-
BMLE	-	750	13.12

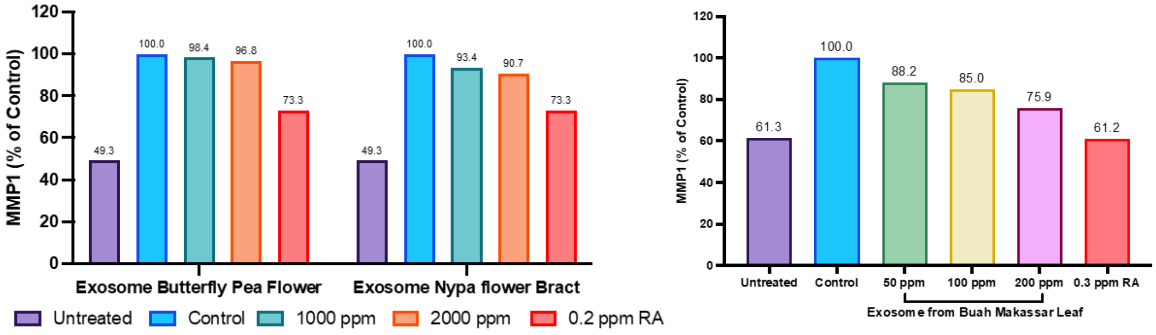
3.3 Particle Size Characterization

Isolation of exosome and PDRN from from butterfly pea flower, nypa flower bract and buah makassar leaf is confirmed by electrophoresis and DLS assessment.

Table 3. Size of PDRN and Exosome from Three Spesies

Plant	Electrophoresis	DLS
Butterfly pea	<100 bp	118.1 nm
Nypa flower bract	<50 bp	268.1 nm
Buah makassar leaf	<50 bp	144.9 nm

3.4 Bioactive Screening PDRN and Exosome



(a) **(b)**

Figure 1. Efficacy of Exosome from **(a)** Butterfly Pea Flower and Nypa Flower Bract in same concentration. (**b**) Efficacy of Exosome from Buah Makassar Leaf in Protein Level of MMP-1.

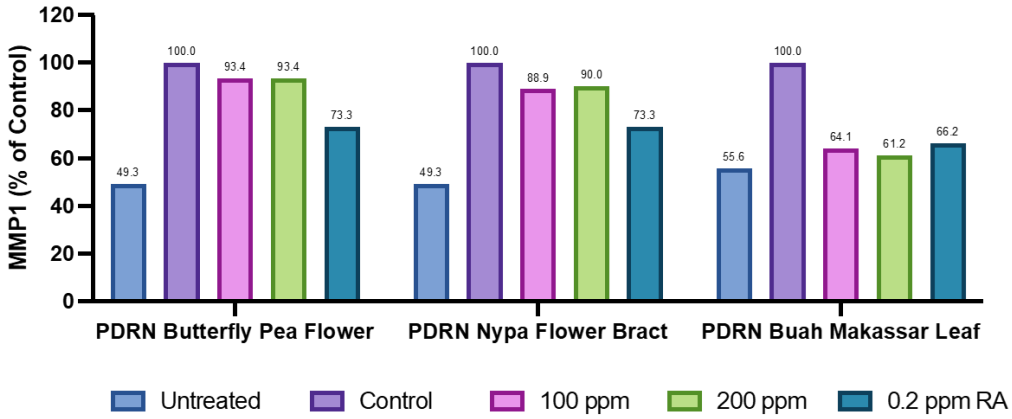


Figure 2. Efficacy of PDRN from Butterfly Pea Flower, Nypa Flower Bract and Buah Makassar Leaf in Protein Level of MMP-1.

There were decreasing MMP-1 production in HDF cell after exposure by UVB and treatment by adding exosome and PDRN from butterfly pea flower, nypa flower bract and buah makassar leaf than control after exposured by UVB but without exosome or PDRN from all species **(Figure 1 and 2)**.

4. Discussion

Preliminary tests were conducted using an anti-elastase assay and an antihyaluronidase assay to measure the anti-aging potential of the three extracts. During the maturation process, suppression of skin related enzymes such as elastase and hyaluronidase which integrate the degradation of ECM and providing good skin integrity and youthful skin [20]. The highest anti-elastase percentage 1000 µg/mL for BPFE, at 250 µg/mL NFBE, and at 500 µg/mL for BMLE, respectively (**Table 1**). There is no significancy inhibition between NFBE at concentration 250 and 300 µg/mL. The inhibition elastase of BMLE increasing more than two time at 500 µg/mL than inhibition elastase at concentration 300 µg/mL. For the anti-hyaluronidase assay, the result showed that BPFE and NFBE exhibited IC_{50} values of 95.60 and 133.25 µg/mL. However, BMLE has the lowest inhibition 13.12% at the concentration of 750 µg/mL (**Table 2**). These results showed that BPFE, NFBE and BMLE have the potential to be anti-wrinkle (anti-aging agents) and can be further studied in the form of exosomes and PDRN.

The size of PRDN from butterfly pea is less than 100 bp (**Table 3**). The molecular weight of the substance is approximately 66kDa. The PRDN sample consists of a nypa flower bract and a buah makassar leaf with a length of less than 50 bp (**Table 3**). The molecular weight is estimated to be approximately less than 33 kD. Recent studies have expanded the size of PDRN fragments from 50kDa to 1500kDa. In fact, a study by Marques et al. (2025) has demonstrated that PDRN fragments can be as small as 1 kDa and as large as 10,000 kDa. The average size of the exosome from the butterfly pea, nypa flower bract, and buah makassar leaf is 118.1 nm, 268.1 nm, and 144.9 nm, respectively (**Table 3**). The range of sizes of plant-derived exosomes is from 50 nm to 500 nm [22]. Bioactive screening confirmed the presence of PDRN and exosome in all plants.

MMP-1 is type of collagenase. It's a biomarker and responsible of skin aging. After getting UVB exposure MMP-1 commonly increasing as a sign of oxidative stress [23]. From **Figure 1.** showed that adding PDRN buah makassar leaf effectively decrease the production of MMP-1 better than control positive or retinoic acid. At protein level, 2000 µg/mL exosome from butterfly pea flower, nypa flower bract, and 100 µg/mL exosome from buah makassar leaf reduced MMP-1 expression by 3.2%, 9.3%, and 24.1%, respectively (**Figure 1**). Similarly, at 100 µg/mL, PDRN from butterfly pea flower and nypa flower bract, and 500 µg/mL PDRN from buah makassar leaf reduced MMP-1 expression by 6.6%, 11.1%, and 35.9%, respectively (**Figure 2**). These studies showed that both exosome and PDRN from from butterfly pea flower, nypa flower bract and buah makassar leaf at certain concentrations can reduce MMP-1 than control.

5. Conclusion

In conclusion, this study demonstrates the anti-aging potential of these native plants and their PDRN and exosome derivatives. Butterfly pea flower and nypa flower bract extracts exhibited strong anti-hyaluronidase activity, while buah makassar leaf showed significant elastase inhibition. The bioactive screening revealed the presence of both PDRN and exosomes, with isolated PDRN from butterfly pea flower and nypa flower bract showing superior efficacy in reducing MMP-1 expression. Overall, these plants are promising candidates for well-aging skincare products in extract, PDRN, or exosome forms.

6. References

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