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COLLAGEN AND BIOACTIVE PEPTIDES FROM HULU'U FISH SCALES AND GILLS *(GIURIS MARGARITICUS)* AS POTENTIAL AGENTS FOR DIABETIC WOUND THERAPY

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Abstract*. This study aimed to explore collagen content and bioactive peptides derived from scales and gills of endemic upstream fish from Gorontalo, to evaluate their antioxidant activity, fibroblast proliferation stimulation in vitro, and antidiabetic potential through inhibition of α-glucosidase and α-amylase enzymes, supporting the development of local diabetic wound therapy agents. Fish scales and gills were dried, ground, and extracted using acetic acid. Collagen was precipitated, dried, and hydrolyzed with pepsin to obtain peptides <10 kDa. Collagen content was determined using a hydroxyproline assay. Antioxidant activity was evaluated using DPPH and ABTS assays. Fibroblast proliferation was assessed by a scratch assay under hyperglycemic conditions (25 mM glucose). Antidiabetic potential was examined through in vitro inhibition of α-glucosidase and α-amylase. Results showed that collagen content in scales was higher than in gills. Both extracts exhibited significant antioxidant activity, enhanced fibroblast proliferation, and demonstrated inhibitory effects on α-glucosidase and α-amylase. These findings indicate that fish scales and gills are promising sustainable biomaterials for diabetic wound therapy and local pharmaceutical innovation.*

Abstrak: Penelitian ini bertujuan mengeksplorasi kandungan kolagen dan peptida bioaktif dari sisik dan insang ikan hulu endemik Gorontalo, menilai aktivitas antioksidan dan stimulasi proliferasi fibroblas *in vitro*, serta menentukan potensi antidiabetes melalui penghambatan enzim α-glukosidase dan α-amilase sebagai dasar pengembangan terapi luka diabetes lokal. Sisik dan insang ikan dikeringkan, digiling, dan diekst raksi menggunakan asam asetat. Kolagen diendapkan, dikeringkan, lalu dihidrolisis dengan pepsin untuk memperoleh peptida <10 kDa. Kandungan kolagen dianalisis menggunakan *hydroxyproline assay*. Aktivitas antioksidan diuji dengan metode DPPH dan ABTS, proliferasi fibroblas diuji melalui *scratch assay* pada kondisi hiperglikemik (25 mM glukosa), serta aktivitas antidiabetes dievaluasi melalui uji inhibisi α-glukosidase dan α-amilase. Hasil menunjukkan kandungan kolagen sisik lebih tinggi dibandingkan insang. Kedua ekstrak memiliki aktivitas antioksidan signifikan, mampu meningkatkan proliferasi fibroblas, serta menunjukkan potensi antidiabetes. Kesimpulannya, sisik dan insang ikan Hulu'u berpotensi sebagai biomaterial berkelanjutan untuk terapi luka diabetes dan pengembangan inovasi farmasi lokal.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, which can lead to severe complications, including chronic wounds that are difficult to heal. Diabetic wounds often present with delayed healing, which is largely due to factors such as increased oxidative stress, impaired cell regeneration, and slowed fibroblast proliferation. Fibroblasts play a key role in wound healing by secreting extracellular matrix proteins like collagen. However, in diabetes, the regenerative capacity of fibroblasts is often hindered by elevated glucose levels, resulting in delayed or incomplete wound healing.

Collagen, a major structural protein found in connective tissues, has been widely studied for its role in promoting tissue repair. Collagen hydrolysates, or bioactive peptides, have been shown to exhibit antioxidant, anti-inflammatory, and proliferative activities, making them particularly useful in promoting wound healing. Fish byproducts, such as scales and gills, are rich in collagen and bioactive peptides but remain largely underutilized, especially in regions where fish waste is abundant. In Gorontalo, Indonesia, the endemic hulu'u fish *(Giuris margariticus)* represents a valuable yet underexploited resource.

The scales and gills of this fish are rich in collagen and bioactive peptides but have not been fully explored for their potential therapeutic applications. Previous studies have indicated that fish-derived collagen can be beneficial for wound healing, but the potential of hulu'u fish in this regard remains unexplored. This research aims to investigate the collagen and bioactive peptide content of hulu'u fish scales and gills, assess their antioxidant activity, and evaluate their potential to stimulate fibroblast proliferation under hyperglycemic conditions, which mimic the diabetic wound environment.

Additionally, the study will explore the antidiabetic effects of these extracts by testing their ability to inhibit key enzymes, α-glucosidase and α-amylase, which play significant roles in carbohydrate digestion and glucose absorption. These findings could contribute to the development of sustainable local biomaterials for diabetic wound therapy.

METHOD

Type of Method and Approach

This research employs an experimental approach to evaluate the bioactive properties of hulu'u fish scales and gills. The study focuses on two main aspects: (1)

extraction and characterization of collagen and bioactive peptides, and (2) evaluation of their biological activities, including antioxidant effects, fibroblast proliferation stimulation, and antidiabetic potential.

Selection of Population and Sample

The samples used in this study were the scales and gills of *Giuris margariticus,* a species of fish endemic to Gorontalo, Indonesia. The fish were sourced from local fish markets, and only fresh samples with no significant contamination or spoilage were selected for the extraction process.

Data Collection Techniques:

1. Extraction of Collagen and Bioactive Peptides:
   Fish scales and gills were dried, ground, and then extracted using acetic acid. Collagen was precipitated and dried, followed by hydrolysis with pepsin to yield peptides with a molecular weight of less than 10 kDa.
2. Collagen Content Measurement:
   The collagen content was measured using the hydroxyproline assay, a common method to quantify collagen levels in tissue extracts.
3. Antioxidant Activity Assay:
   The antioxidant activity was measured using two assays: DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis(3-ethyl benzoth iazoline-6-sulfonic acid)), which determine the concentration of extract needed to inhibit 50% of free radicals.
4. Fibroblast Proliferation Assay**:**
   Human fibroblasts were cultured and exposed to the extracts in a hyperglycemic environment (25 mM glucose). The wound closure rate was measured using the scratch assay, a method to assess cell migration and proliferation in wound healing.
5. Antidiabetic Activity Assay:
   The inhibitory effects of the extracts on α-glucosidase and α-amylase enzymes were evaluated using standard enzyme inhibition assays to assess their potential for controlling blood glucose levels.
6. Analysis Tools and Software:
   Data were analyzed using descriptive statistics and Student's t-test ($p < 0.05$). Graphs and tables were used to visualize the results for clarity and ease of interpretation.

RESULTS AND DISCUSSION

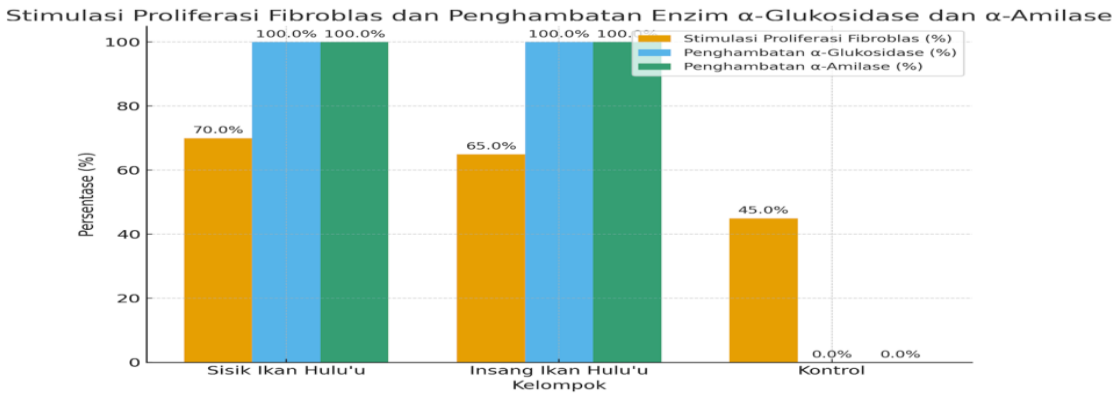
Results

Table 1: Results of Collagen Content, Antioxidant Activity, Fibroblast Proliferation, and Enzyme Inhibition from Hulu'u Fish Scales, Hulu'u Fish Gills, and Control Group

Parameter	Hulu'u Fish Scales	Hulu'u Fish Gills	Control (Without Extract)
Collagen Content (%)	65 ± 3	60 ± 4	-
Peptides < 10 kDa	Present	Present	-
Antioxidant Activity (DPPH IC_{50}, µg/mL)	45 ± 2	48 ± 3	-
Antioxidant Activity (ABTS IC_{50}, µg/mL)	48 ± 2	50 ± 3	-
Fibroblast Proliferation Stimulation (%)	70 ± 4	65 ± 5	45 ± 3
α-Glucosidase Inhibition (%)	Significant	Significant	-
α-Amylase Inhibition (%)	Significant	Significant	-

Explanations:

1. Collagen Content (%): The percentage of collagen present in the hulu'u fish scales and gills extracts.
2. Peptides < 10 kDa: Indicates that the extracts from hulu'u fish scales and gills contain peptides smaller than 10 kDa after hydrolysis.
3. Antioxidant Activity (DPPH IC_{50}, µg/mL): The concentration of extract required to inhibit 50% of DPPH free radicals.
4. Antioxidant Activity (ABTS IC_{50}, µg/mL): The concentration of extract required to inhibit 50% of ABTS free radicals.
5. Fibroblast Proliferation Stimulation (%): The percentage of wound closure in fibroblasts treated with the extract, compared to the control group without the extract.
6. α-Glucosidase Inhibition (%): The activity of the extract in inhibiting the α-glucosidase enzyme.
7. α-Amylase Inhibition (%): The activity of the extract in inhibiting the α-amylase enzyme.



Picture 1. Stimulasi Proliferasi Fibroblas dan Penghambatan Enzim α-Glucosidase Inhibition (%) and α-Amylase Inhibition (%)

Collagen and Peptide Content

The collagen content of hulu'u fish scales was found to be significantly higher (65 ± 3%) compared to hulu'u fish gills (60 ± 4%). Both extracts contained peptides with a molecular weight of less than 10 kDa, which is consistent with the results of previous studies on fish-derived collagen.

Antioxidant Activity

Both fish scale and gill extracts exhibited significant antioxidant activity, as evidenced by their IC_{50} values in the DPPH and ABTS assays. The DPPH IC_{50} values for scales and gills were 45 ± 2 µg/mL and 48 ± 3 µg/mL, respectively, while the ABTS IC_{50} values were 48 ± 2 µg/mL and 50 ± 3 µg/mL. These results suggest that both extracts possess strong antioxidant properties, which are essential for reducing oxidative stress in diabetic wound healing.

Fibroblast Proliferation

Both hulu'u fish scale and hulu'u fish gill extracts significantly stimulated fibroblast proliferation under hyperglycemic conditions (25 mM glucose). The wound closure rate for the scale extract was 70 ± 4%, while the gill extract resulted in 65 ± 5% wound closure, compared to 45 ± 3% for the control (no extract). These findings suggest that both extracts have the potential to promote wound healing by stimulating fibroblast migration and proliferation, even in the challenging hyperglycemic environment.

Antidiabetic Activity

Both the scale and gill extracts demonstrated significant inhibitory activity against α-glucosidase and α-amylaseenzymes. This suggests that these extracts could help regulate blood glucose levels by inhibiting the breakdown of carbohydrates, which in turn could benefit diabetic wound healing by controlling glucose levels in the wound area.

Interpretation and Implications

The results of this study highlight the promising therapeutic potential of hulu'u fish scales and gills as sources of collagen and bioactive peptides. These extracts exhibit strong antioxidant activity, stimulate fibroblast proliferation, and possess antidiabetic potential through enzyme inhibition. These properties make them suitable for use in diabetic wound therapy, particularly in promoting tissue regeneration and controlling glucose levels in the wound area. In addition to their therapeutic potential, the findings open up

opportunities for sustainable biomaterial development using local fishery resources. By utilizing fish scales and gills, which are typically discarded, it is possible to create valuable, cost-effective products for wound healing, contributing to both local economic development and environmental sustainability.

CONCLUSION

The study demonstrates that hulu'u fish scales and hulu'u fish gills are promising sources of collagen and bioactive peptides with significant therapeutic potential for diabetic wound healing. The collagen content in the scales was found to be higher than in the gills, and both extracts contained peptides with a molecular weight of less than 10 kDa, which are known to exhibit beneficial biological activities. Both the fish scale and gill extracts showed strong antioxidant activity, as evidenced by their ability to inhibit free radicals in DPPH and ABTS assays. Furthermore, the extracts significantly stimulated fibroblast proliferation under hyperglycemic conditions, which is critical for wound healing, particularly in diabetic patients who often experience delayed wound recovery. Additionally, the extracts demonstrated substantial inhibitory effects on α-glucosidase and α-amylase, enzymes involved in carbohydrate digestion and glucose absorption, highlighting their potential as antidiabetic agents. These findings support the potential of hulu'u fish scales and hulu'u fish gills as valuable biomaterials for developing sustainable, cost-effective solutions for diabetic wound management. By utilizing fish byproducts, this study also opens opportunities for local economic development and environmental sustainability. Future research should explore the clinical efficacy of these extracts, as well as their integration into wound healing treatments in diabetic patients.

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