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**RESEARCH COMMUNICATION**

## Food Biochemistry

# The first report on the *in-vitro* HDAC inhibitory potential of Sri Lankan traditional rice varieties

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**Abstract:** The objective of this investigation is to study, for the first time, the histone deacetylase (HDAC) inhibitory potential of ethanol extracts obtained from selected traditional Sri Lankan rice varieties to highlight their biochemical significance. HDACs play a key role in epigenetic-mediated gene expression. Dysregulations in the expression and activity of HDACs are seen in a wide range of diseases. The ethanolic extracts of seven rice varieties demonstrated HDAC inhibitory effects in the order of *Madathawalu* > *Pachchaperumal* > *Hangimuttan* > *Maa-wee* > *Kalu Heenati* > *Kurulu Thuda* > *Suwandel*. Our findings support the use of Sri Lankan traditional rice varieties in epigenetic research. To fully elucidate the HDAC inhibitory effects of rice extracts, profiling the composition of secondary metabolites in active extracts is crucial. This preliminary investigation demonstrates that Sri Lankan rice varieties possess the potential to inhibit the activity of HDAC in vitro.

**Keywords:** Enzyme assays, Epigenetics, HDAC, histone-modifying enzymes, rice.

## INTRODUCTION

Rice is the main staple food in Sri Lanka and other Asian countries (Samaranayake *et al*., 2022, Suresh *et al*., 2021). It is a rich source of carbohydrates, proteins, fatty acids, B vitamins and minerals such as magnesium, phosphorus and calcium (Verma & Srivastav, 2017). Studies have demonstrated that the consumption of rice is linked to a decreased risk of developing diseases and conditions such as diabetes mellitus, cancer, hypertension, cardiovascular disease, obesity and allergies (Rathna Priya *et al*., 2019). The Plant Genetics Resource Center in Gannoruwa Sri Lanka has a collection of over 2000 traditional rice varieties (Kariyawasam *et al*., 2016). Compared to improved rice varieties, the traditional Sri Lankan rice varieties are nutritionally significant and possess promising bioactivities (Goonathilaka *et al*., 2023). Research by Premakumara *et al*. (2013) found that traditional rice varieties like *Goda Heeneti*, *Masuran*, *Sudu Heeneti* and *Dik Wee* have anti-amylase and anti-glycation effects. Recent studies have characterized the fatty acid and amino acid compositions of selected traditional Sri Lankan rice varieties (Samaranayake *et al*., 2021; Liyanaarachchi *et al*., 2022;).

In epigenetics-mediated gene expression, HDACs play a key role in modifying chromatin structures. There are 18 different types of HDACs categorized into four major classes (I, II - IIa and IIb, III, and IV) identified in humans (Ediriweera *et al*., 2019). Dysregulation in the activity or expression of HDACs has been implicated in a wide range of human diseases (Ediriweera *et al*., 2019). HDAC inhibitors (such as benzamide derivatives, short and long-chain fatty acids, hydroxamic acid derivatives, and cyclic peptides) are a class of small-molecules that can reverse HDAC activity, leading to increased acetylation of histones and altered gene expression (Ediriweera *et al*., 2019).

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Food items such as broccoli, garlic, eggs, turmeric and grapes have been identified to exert epigenetic effects (Ediriweera, 2023; Stefanska *et al*., 2012). There is growing recognition of the nutritional and functional value of traditional Sri Lankan rice varieties, particularly due to their unique biochemical profile. However, no studies have assessed their HDAC inhibitory effects. This research gap motivated us to investigate the HDAC inhibition potential of selected traditional rice varieties (Figure 1). We anticipate that our findings will provide substantial additional evidence to the existing body of knowledge regarding the biochemical and nutritional significance of traditional Sri Lankan rice varieties.

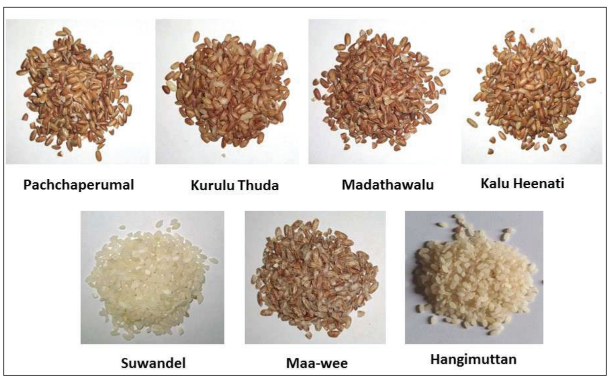


**Figure 1:** Dehusked rice seeds of Sri Lankan traditional rice varieties used in this study

## MATERIALS AND METHODS

### Chemicals and kits

The chemicals and organic solvents used in this study were purchased from Sigma-Aldrich (St. Louis, MO, USA) unless otherwise specified. The total colorimetric HDAC assay kit was purchased from Abcam, Massachusetts, USA (ab1432).

### Collection of rice samples

Seeds of the seven Sri Lankan traditional rice varieties (*Pachchaperumal, Kurulu Thuda, Madathawalu, Kalu Heenati, Suwandel, Maa-wee* and *Hangimuttan*) were purchased from a reputed vendor (*Sanstha Kulubadu* shops) and transferred to the laboratory. Rice seeds were oven dried and stored in sealed plastic bags. Each variety was given a specimen number: *Pachchaperumal* (TR-1), *Kurulu Thuda* (TR-2), *Madathawalu* (TR-3), *Kalu Heenati* (TR-4), *Suwandel* (TR-5), *Maa-wee* (TR-6), and *Hangimuttan* (TR-7). The selection of these rice varieties was based on their availability and ease of access.

### Extraction of rice seeds with ethanol

Dehusked rice seeds were ground and 3 g of flour was used for extraction with 6 mL of 99 % (v/v) ethanol at room temperature. The extracts were filtered using Whatman filter papers (grade 1) and speed-vacuumed. Stock solutions were prepared in ethanol by dissolving the dried extracts, corresponding to the seeds of each rice variety. The final concentration of each stock solution was 400 mg/mL.

### HDAC inhibitory activity assay

The HDAC colorimetric activity assay was conducted according to the protocol supplied by the kit (ab1432). For the HDAC inhibitor assay, 1 mg/mL of each rice extract was used. The absorbance was recorded at 405 nm using a microplate reader (Bioevopeak, China, MPR-A9600/MPR-A9600T) and Trichostatin A was used as the positive control. The results were presented as the percentage of enzyme activity for each rice sample tested.

### Statistical analysis

Experiments were carried out in triplicate and the results are expressed as the mean ± standard deviation (SD). GraphPad Prism version 5 (GraphPad Software, Inc., San Diego, CA, USA) software was used for statistical analysis. One-way analysis of variance (ANOVA) was used with Dunnett's post hoc test for group comparisons (control vs treated) to analyze HDAC assay results statistically. The control refers to a no-extract control containing only the enzyme. The treated groups received both the enzyme and the extract.

## RESULTS AND DISCUSSION

As shown in Figure 2, the ethanol seed extracts of the seven traditional Sri Lankan rice varieties showed HDAC inhibitory potential *in vitro*. The ethanol extracts of all rice varieties exhibited HDAC inhibition at a concentration of 1 mg/mL in the following order: *Madathawalu* > *Pachchaperumal* > *Hangimuttan*> *Maa-wee* >*Kalu Heenati* > *Kurulu Thuda* > *Suwandel*. The results from this investigation highlight the HDAC inhibitory potential of selected traditional Sri Lankan rice varieties, paving the way for further investigations into their epigenetic effects, including their impact on DNA methylation and various HDAC isoforms.

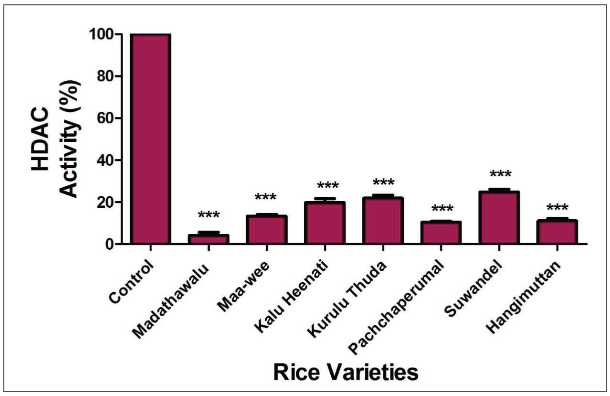


**Figure 2:** The histone deacetylase (HDAC) inhibitory potential of ethanol extracts from selected traditional rice varieties. The extracts showed HDAC inhibitory effects in the order of *Madathawalu* > *Pachchaperumal* > *Hangimuttan*> *Maa-wee* >*Kalu Heenati* > *Kurulu Thuda* > *Suwandel*. ***P<0.001 vs. control. The control refers to a no-extract control containing only the enzyme.

HDAC dysfunction is associated with various diseases (Ediriweera *et al*., 2019). This study demonstrates the HDAC inhibitory effects of specific traditional rice varieties found in Sri Lanka. Among the tested rice samples, the variety *Madathawalu* showed a high HDAC inhibitory potential (Figure 2). This investigation opens new opportunities for identifying and isolating specific secondary metabolites responsible for the observed HDAC inhibition. Benzamide derivatives, short and long-chain fatty acids, hydroxamic acid derivatives, and cyclic peptides have demonstrated encouraging clinical and pre-clinical outcomes as histone deacetylase inhibitors (HDACi) (Ediriweera *et al*. 2019). Rice contains a diverse range of phytochemicals such as phenolic compounds, flavonoids, terpenoids, steroids, fatty acids, amides, amino acids, and their derivatives, which may collectively contribute to its potent HDAC inhibitory activity (Pereira-Caro *et al*. 2013; Ravichanthiran *et al*. 2018). Fatty acids, in particular, have already been established as effective HDAC inhibitors (Ediriweera *et al*. 2019). In addition, secondary metabolites, such as ferulic acid, p-coumaric acid, and quercetin found in rice have been reported to possess HDAC inhibitory activity, further enhancing the overall HDAC inhibitory potential of these rice varieties (Apea-Bah *et al.*, 2014; Uba *et al*., 2023).

It is worth noting that *Madathawalu* has been reported to contain higher levels of polyunsaturated fatty acids/saturated fatty acids (Samaranayake *et al*., 2022), which could significantly impact its HDAC inhibitory potential as fatty acids have been shown to inhibit HDACs (Ediriweera, 2023a; Ediriweera 2023b). However, the HDAC inhibitory potential is believed to be influenced by the synergistic activity of multiple phytochemicals present in the extract, including fatty acids.

## CONCLUSION

The findings of this preliminary study demonstrate that traditional Sri Lankan rice varieties possess the ability to inhibit the activity of HDAC enzymes. Further experimental evidence is required to validate its classification as an 'epigenetic diet'. To fully elucidate the HDAC inhibitory effects of rice extracts, it is crucial to profile the composition of secondary metabolites in the active extracts.

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**Availability of the data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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