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SHORT COMMUNICATION

Preliminary Yeast-Based Evaluation of Medicinal Plants from Indigenous Communities in the West Coast and Northern Sabah, Malaysia, for Protein Phosphatase Inhibition

FAUZE MAHMUD[1,2,4], NURUL AIN ISMAIL[1], MISSA HARTYNIE UBOT[1], RICHARLES EDWARD[1], SIEW ENG HOW[1], ISLAM ADEL ABDELHAKIM[5], NGIT SHIN LAI[4], PING-CHIN LEE[1,2] & JUALANG AZLAN GANSAU*[1,2,3]

[1]Biotechnology Programme, Faculty of Science and Technology, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia; [2]BioAgriTech Research (BioATR) Group, Faculty of Science and Technology, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia; [3]Biotechnology Research Institute, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia; [4]Instituite for Research in Molecular Medicine, Universiti Sains Malaysia, Penang, Malaysia; [5]Pharmaceutical Department, Assiut University, Aswan, Egypt
*Corresponding author: azlanajg@ums.edu.my
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ABSTRACT

Sabah, Malaysia, is renowned for its rich biodiversity and multicultural heritage, creating a unique blend of ethnomedicinal knowledge. A total of 22 medicinal plants traditionally used by the Bajau, Dusun, and Rungus communities in Kota Belud, Kota Marudu, and Matunggong, Sabah, were collected through a direct ethnopharmacological approach. Crude extracts were prepared using methanol extraction and evaluated for their inhibitory activity against yeast Glc7, a homolog of human protein phosphatase 1 (PP1), which is considered a promising pharmaceutical target for diseases such as cancer, malaria, and fungal infections. A yeast-based assay was used to evaluate the PP1 inhibitory activity of the crude extracts with two strains: PAY704-1 (wild-type Glc7) and PAY700-4 (Glc7-10, a heat-sensitive mutant). The strains were incubated at 28 °C and 37 °C, with or without 1 M sorbitol as an osmotic stabilizer to assess cell wall integrity under Glc7-compromised conditions. This setup enabled a clear analysis of sample-induced inhibition. Notably, Sarah (*Glochidion* sp.) and Merabau (*Senna* sp.) exhibited selective Glc7/PP1 inhibitory activity as a zone of inhibition was observed only in strain PAY704-1 at 37 °C in the absence of 1 M sorbitol. This inhibitory activity has not been previously reported. Given the high conservation of PP1 across different organisms, these plants may serve as potential sources of new PP1 inhibitors, contributing to future drug development.

Keywords: Glc7/PP1, indigenous ethnomedicine, Sabah, yeast-based

Together with kinases, phosphatases play a crucial role in numerous essential pathways and cellular processes, including glycogen metabolism, apoptosis, and the cell cycle, by regulating reversible protein phosphorylation mechanisms. Protein phosphatase 1 (PP1) is one of the most significant phosphatases in humans. In addition to its role in regulating various cellular processes, PP1 is also crucial in cancer development, proliferation, and the adaptive response to anticancer drugs. Therefore, PP1 inhibitors represent promising targets for targeted cancer therapy (Felgueiras *et al*., 2020). Furthermore, PP1 has been implicated as a potential target for antiparasitic (Zeeshan *et al*., 2021) and antifungal drugs development (Loh *et al*., 2019). Despite its therapeutic potential, PP1 has received limited attention in drug development (Felgueiras *et al*., 2020).

Yeast is a valuable model organism for studying human cellular processes and diseases due to its high genetic and functional similarity to humans. In yeast, PP1 is encoded as Glc7, which is homologous to human PPP1CA and PPP1CC (Hamza *et al*., 2015). Glc7 is an essential protein involved in glycogen metabolism, meiosis, protein synthesis and

sporulation (Stark, 1996; Cannon, 2010). Using yeast strains expressing both wild-type and mutant Glc7, this study aimed to evaluate the Glc7/PP1 inhibitory activity of traditional medicinal plants used by the indigenous communities of Sabah's west coast and northern regions.

Plant samples were collected from Kampung Seri Aman, Kota Marudu, Sabah, based on the ethnomedicinal knowledge obtained through interviews with the Bajau (Kota Marudu), Rungus (Matunggong) and Dusun (Kota Belud) communities (Table 1). Different parts of healthy plants, including leaves, stems, bark, and roots, were collected, cleaned, cut into smaller pieces, and air-dried at room temperature until a constant weight was achieved. The dried samples were then ground into a fine powder using a blender. Extraction was performed using methanol at a 1:10 ratio (1 g of sample in 10 ml of methanol). The mixtures were sonicated for 20 minutes and left at room temperature for 48 hours to ensure complete extraction. The resulting suspension was filtered through Whatman No. 1 filter paper to separate solid debris, yielding crude methanol extracts. The extracts were then dried using a concentrator, and re-dissolved in methanol at 100 mg/ml (Harborne, 1998).

Table 1. The list of plant samples collected from Kampung Seri Aman, Kota Marudu, Sabah

Sample code	Vernacular name	Species	Local use	Tested part
KM1L	Rumput Seriadi	*Stachytarpheta* sp.	Treat gastric	Leaves
KM2L	Kembung	*Dillenia* sp.	Treat haemorrhoids	Leaves
KM3L	Lunai	*Chromolaena* sp.	Stop bleeding	Leaves
KM4L	Bentiang	Unknown	Treat hypertension	Leaves
KM5L	Lingkong	*Lygodium* sp.	Treat hair loss and hypertension	Leaves
KM6L	Empalas	*Tertracera* sp.	Treat hypertension	Leaves
KM7L	Pelai'	*Alstonia* sp.	Treat mumps	Leaves
KM7S				Stem
KM8S	Wonod	Unknown	To stabilize body temperature	Stem
KM9Bs	Dungun	Unknown	Treat cancer, gastric, and skin problems	Branches
KM9L				Leaves
KM10R	Bangkau	*Rhizophora* sp.	Treat hypertension	Roots
KM10L				Leaves
KM11R	Rumput Pendul	*Kyllinga* sp.	Bath after giving birth[1]	Roots
KM12R	Tangkal	*Ficus* sp.	Treat mumps	Roots
KM13L	Uli-uli Semangat	*Micromelum* sp.	Bath after giving birth[1]	Leaves
KM14L	Pako-pako	*Acrostichum* sp.	Treat hypertension	Leaves
KM15L	Sarah	*Glochidion* sp.	Bath after giving birth[1]	Leaves
KM16L	Tangan-tangan	*Jatropha* sp.	Treat skin rashes	Leaves
KM16R				Roots
KM17L	Merabau	*Senna* sp.	Treat skin rashes and infections	Leaves
KM18L	Karamunsing	*Melastoma* sp.	Treat stomachache and poisoning	Leaves
KM18R				Roots
KM19L	Balik Angin	*Mallotus* sp.	Treat cancer[2]	Leaves
KM19S				Stem
KM20B	Nangka	*Artocarpus* sp.	Treat cancer[2]	Bark
KM21B	Kelempopo Batu	Unknown	Treat cancer[2]	Bark
KM22S	Unknown	Unknown	Treat cancer[2]	Stem

Note:
KM = Kota Marudu
L = Leaves, S = Stem, Bs = Branches, R = Roots, B = Barks
[1] = mixed for a bath after giving birth, [2] = consumed together for cancer treatment

Glc7/PP1 is an essential protein phosphatase in yeast, involved in numerous processes, including the maintenance of cell wall integrity at high temperatures (Andrews & Stark, 2000). The extracts were tested for Glc7/PP1 inhibitory activity using a yeast-based assay previously developed and validated (Andrews & Stark, 2000; Ong *et al*., 2007). This assay enables the identification of Glc7/PP1 inhibitors by analyzing the inhibition patterns of two yeast strains: PAY704-1 (expressing wild-type Glc7/PP1), and the PAY700-4 (expressing Glc7-

10, a heat-sensitive Glc7/PP1 mutant that cannot grow at 37 ºC). Inhibition of strain PAY704-1 served as the primary indicator of Glc7/PP1 inhibition, while strain PAY700-4 functioned as a reference strain to confirm the presence of a selective Glc7/PP1 inhibitor.

The inhibition of Glc7/PP1 was indicated by growth defects (zone of inhibition) in the PAY704-1 strain at 37 ºC only. The inhibition of Glc7/PP1 at high temperatures compromises yeast cell wall integrity; consequently, growth defects occur. In contrast, the inhibition of Glc7/PP1 should not cause yeast growth defects at 25 ºC, whether in the presence or absence of 1 M sorbitol, as cell wall stability is not compromised at low temperatures without Glc7/PP1 function (Andrews & Stark, 2000; Ong *et al*., 2007).

To confirm the presence of a selective Glc7/PP1 inhibitor, a mutant yeast strain (PAY700-4) expressing Glc7-10, a heat-sensitive Glc7/PP1 variant, was also screened. Glc7-10 is heat-sensitive and rapidly denatures at high temperatures; therefore, strain PAY700-4 is unable to grow at 37 ºC. This adverse effect can be mitigated by adding 1 M sorbitol to the medium, which stabilizes cellular osmotic pressure and compensates for compromised Glc7-10 function. Similar to strain PAY704-1, the inhibition of Glc7-10 at 25 ºC, whether in the presence or absence of 1 M sorbitol, does not cause yeast growth defects. Therefore, a zone of inhibition that persists in the presence of sorbitol or affects strain PAY700-4 rules out selective Glc7/PP1 inhibition (Andrews & Stark, 2000; Ong *et al*., 2007).

To perform the assay, a loopful of each yeast strain was cultivated in Yeast Potato Dextrose (YPD) broth (10 g/L yeast extract, 20 g/L dextrose) at 28 °C, shaken at 220 rpm for 72 hours. Then, 400 µl of each strain was inoculated into YPD agar (maintained at approximately 40 °C to prevent premature solidification) with and without 1 M sorbitol, gently swirled, and poured into Petri dishes before solidification. Paper discs impregnated with 20 µL of plant crude extracts were placed on the solidified agar. The plates were incubated at 28 °C (permissive temperature) and 37 °C (restrictive temperature) for three days, with the zone of inhibition recorded every 24 hours (Ong *et al*., 2007).

Based on the phenotypic observations, the crude extracts from the leaves of three plants, Lunai (*Chromolaena* sp.), Sarah (*Glochidion* sp.) and Merabau (*Senna* sp.), were found to inhibit Glc7/PP1 activity (Figure 1 and Table 2). To the best of our knowledge, PP1 inhibitory activity has not been previously reported for Sarah and Merabau. Furthermore, Sarah and Merabau were shown to selectively inhibit Glc7/PP1 activity as zones of inhibition (ZOI) were only observed in yeast strain PAY704-1 at 37 ºC, in the absence of 1 M sorbitol (Table 2). However, PP1 inhibitory activity of Lunai crude extract has been previously documented (Matawali *et al.,* 2019). In addition, the leaves of Karamunsing (*Melastoma* sp.) and Balik Angin (*Mallotus* sp.) exhibited toxic activity (Table 2).

Senna sp. is traditionally used for the treatment of fungal infection in the studied areas (Yusoff *et al*., 2003). Its efficacy as an antifungal agent is also widely reported (Jeruto *et al*., 2016; Kamilah *et al*., 2022). In addition, *Senna* sp. and *Glochidion* sp. were previously reported for anticancer (Castro *et al*., 2023; Sharma *et al*., 2011) and antimalarial activities (Atanu *et al*., 2002; Hennebelle *et al*., 2009; Khairuddin *et al*., 2021). Interestingly, PP1 has been identified as a potential target for drug development of these diseases (Loh *et al*., 2019; Felgueiras *et al*., 2020; Zeeshan *et al*., 2021). Although the connection between PP1 inhibition and these bioactivities has yet to be established, the identification of Sarah (*Glochidion* sp.) and Merabau (*Senna* sp.) as new sources of PP1 inhibitors highlights their potential for future therapeutic applications in various diseases.

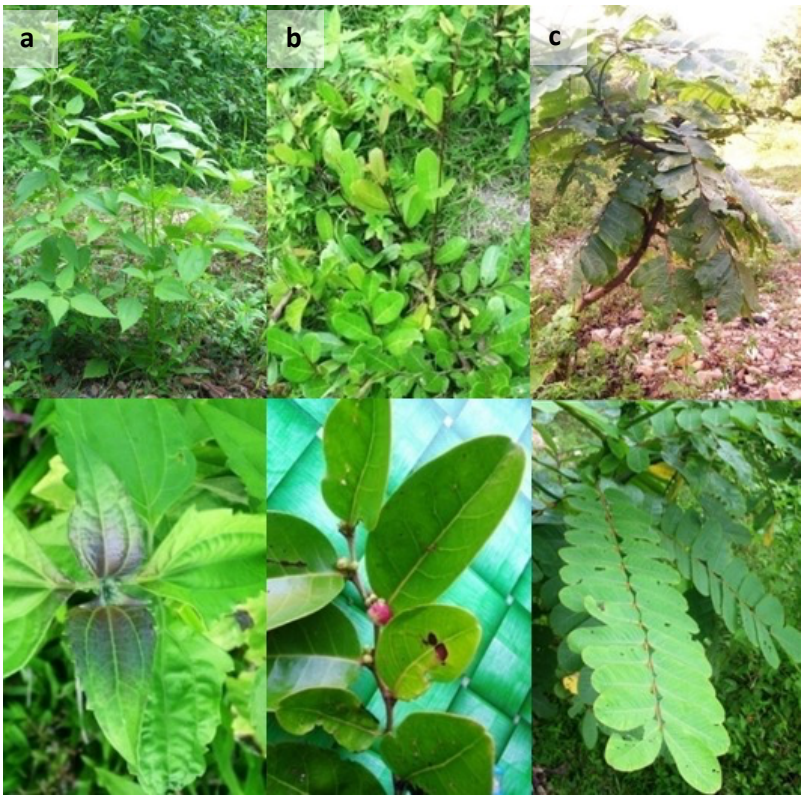

Figure 1. Traditional medicinal plants with crude leaf extracts that inhibited PP1 activity: Lunai (*Chromolaena* sp.) (a), Sarah (*Glochidion* sp.) (b), and Merabau (*Senna* sp.) (c). The top and bottom images show the whole plant and the leaves, respectively

Table 2. Inhibitory activity of plant crude extracts against Glc7/PP1 expressed in yeast cells, with KM3L (leaves of Lunai), KM15L (leaves of Sarah), and KM17L (leaves of Merabau) demonstrating inhibitory activity

Sample code	PAY700-4 (expressing GLC7-10, a heat-sensitive GLC7 mutant) (ZOI, mm)				PAY704-1 (expressing WT GLC7) (ZOI, mm)				Remarks
	YPD		YPD+1M Sorbitol		YPD		YPD+1M Sorbitol		
	25 °C	37 °C	25 °C	37 °C	25 °C	37 °C	25 °C	37 °C	
KM1L	-	No yeast growth	-	-	-	-	-	-	No activity
KM2L	-		-	-	-	-	-	-	No activity
KM3L (Lunai)	-		-	-	-	14.00	-	-	Glc7/PP1 inhibitor
KM4L	-		-	-	-	-	-	-	No activity
KM5L	-		-	-	-	-	-	-	No activity
KM6L	-		-	-	-	-	-	-	No activity
KM7L	-		-	-	-	-	-	-	No activity
KM7S	-		-	-	-	-	-	-	No activity
KM8S	-		-	-	-	-	-	-	No activity
KM9Bs	-		-	-	-	-	-	-	No activity
KM9L	-		-	-	-	-	-	-	No activity
KM10R	-		-	-	-	-	-	-	No activity
KM10L	-		-	-	-	-	-	-	No activity
KM11R	-		-	-	-	-	-	-	No activity
KM12R	-		-	-	-	-	-	-	No activity
KM13L	-		-	-	-	-	-	-	No activity
KM14L	-		-	-	-	-	-	-	No activity
KM15L (Sarah)	-		-	-	-	**8.00**	-	-	**Glc7/PP1 inhibitor**
KM16L	-		-	-	-	-	-	-	No activity
KM16R	-		-	-	-	-	-	-	No activity
KM17L (Merabau)	-		-	-	-	**8.00**	-	-	**Glc7/PP1 inhibitor**
KM18L	10.00±2.83		-	13.00±1.41	11.00±4.25	11.00±4.25	10.00	10.00±2.83	Toxic activity
KM18R	-		-	-	-	-	-	-	No activity
KM19L	10.00±2.83		10.00±1.41	17.00±4.24	10.00±2.83	10.00	10.00±2.83	10.00±2.83	Toxic activity
KM19S	-		-	-	-	-	-	-	No activity
KM20B	-		-	-	-	-	-	-	No activity
KM21B	-		-	-	-	-	-	-	No activity
KM22S	-		-	-	-	-	-	-	No activity

Note:
KM = Kota Marudu
L = Leaves, S = Stem, Bs = Branches, R = Roots, B = Bark
Values are mean ± SD (n = 3)

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