HERBS USED AS ANALGESIC BY DAYAK TRIBE IN NORTH KALIMANTAN INDONESIA

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ABSTRACT

Traditional medicines produced from medicinal plants have played an important role in disease treatment in Dayak Tribe, North Kalimantan. Northern Kalimantan belongs to a remote area where health facilities like healthcare center (*puskesmas – pusat kesehatan masyarakat*) and hospital are not easily accessible. This research aims to investigate herbs used by Dayak tribe in North Kalimantan for treating pain. It is a descriptive research applying two research methods i.e. observation and interview. We directly observed the research object and proposed questions to respondents that were traditional healers from each village. The research was conducted in nine villages within three regencies in North Kalimantan. Meanwhile, 38 herbs collected in this research were from 26 families and 34 species. Four species were still locally named. The highest proportion of the herb family used was *Asteraceae*. The most frequently used part of the herb for medicine was the leaf (60.53%). The main serving methods were by boiling the herb and drinking it (63.15%). Bone pain and stomachache were two main illnesses mostly treated by local herb therapy involving 11 herbs. In conclusion, Dayak tribe in North Kalimantan still used herbs to treat their pain.

Keywords: analgesic; Dayak tribe; herb.

INTRODUCTION

Herbs have been processed into traditional medicine since thousands of years ago. The medicine was in the form of raw medicine such as tincture, tea, poultice, powder, and other herbal formulations (Archana *et al.*, 2011). Indonesia is known as a country with its high diversity of plants. There is 10% of global flowering plant species existing in Indonesia. It is due to natural condition in Indonesia that is different in each island even in each region (Indrawan, 2007). Herbs are plants mainly used for traditional medicine. The use of herb is one of social habits since medicine made from herbs is more natural than modern medicine (Makalalag *et al.*, 2014).

Pain is a body defense mechanism form when the body is having unpleasant emotion and sensor experiences related to potential or real tissue damage. Mediators such as interleukin-1, and TNF-α spread the synthesis, release, and acts of prostaglandin E1 (PGE2) and F2α by endothelium and brain capillary pericytes that stimulate the nerves and may cause pain. Increasing prostaglandin content in peritoneum cavity increases the capillary permeability and causes pain (Nasrin et al., 2015). Conventional therapy used to treat pain as analgesic, non-steroid anti-(NSAID), inflammatory drugs and corticosteroid have been proven to succeed (Sreekeesoon & Mahomoodally, 2014). The pain may vary from mild to severe. Some therapies such as opioid are alternated for more severe pain (Reid et al., 2015). Aloe vera (L) Burn is used as analgesic in Mauritus to treat leg pain and body pain (Sreekeesoon & Mahomoodally, 2014).

*Corresponding author: Irma Novrianti Email: *irma.novrianti@gmail.com* Most residents of Dayak tribe in North Kalimantan live in an area where they cannot easily access health facilities such as hospital and community health center due to the long distance. Living in an area next to the forest, they prefer to use herbs as medicine because of their affordability and accessibility (Yitno, 1991). This research aims to investigate herbs for pain management used by Dayak tribe in North Kalimantan.

METHODS

This research is descriptive in which the data were collected through observation and interview methods. Observation as a data collection technique was completed by the researcher by performing a direct observation towards the research object, while during interview, researchers proposed questions to respondents to investigate herbs used for pain management by Dayak tribe in North Kalimantan. The study was conducted for 3 months from March 2017 to June 2017 with permits directly addressed to customary leaders in their respective regions.

North Kalimantan is geographically located between 114°35'22"-118°03'00" east latitude and 4°24'55"-1°21'36" north latitude. North Kalimantan has a tropical climate and two seasons i.e. dry season and rainy season, which is similar to any other areas in Indonesia.

Interviews were performed to nine respondents who were traditional healers from several villages i.e. Lembudud, Long Kiwang, and Wayangung in Nunukan; Sekatak, Long Sam, and Pejalin in Bulungan; and Kaliamok, Sembuak Warod, and Tanjung Nanga in Malinau. We identified the respondents based on information given by local people. Data on characteristics of respondents and information related to the use of herbs were recorded. All interviews were conducted in the local language that was Dayak language. Meanwhile, research assistant acted as a translator of Dayak language into Indonesian.

The results of data collection including data on herb type, sample use, and the procedure of use obtained from interviews were further investigated through thorough observation.

Determination of respondents using snowball sampling method started with the Head of Customary Affairs. Afterwards, he gave recommendations and led the researcher to other respondents. Each respondent would be given information about medicinal plants.

Inventory of medicinal plants in the field was carried out by field survey method based on respondent information. Every plant obtained was taken their pictures; and their regional names as well as morphological characters were recoded. Identification process of medicinal herbs was performed by referring to several books entitled *Buku Flora* (Steenis *et al.*, 2005), *Kitab Tanaman Obat Nusantara* (Widyaningrum, 2011) and *Atlas Tumbuhan Obat Indonesia Jilid 4* (Dalimartha, 2006).

RESULTS AND DISCUSSION

The findings were discussed in three subparts i.e. traditional healer, ethnobotanical flora, and type of pain.

Traditional Healer

In this research, researcher collected information about herbs used to treat pain by communicating and interviewing one or two traditional healers of each village. The age range of those traditional healers was 40 up to 70 years old. Our respondents, the traditional healers, obtained their knowledge on herbs from their ancestors. Research on herbal medicine for diabetes conducted in Northeast Iran revealed that 87% of traditional healers learned herbs from their parents or other relatives (Tag et al., 2012). In another study, traditional healers acquired their medicinal plant knowledge by inheriting from their elder lineage (father or grandfather), whereas the rest received his medicinal plant knowledge from dreams (Nasution, Aththorick and Rahayu, 2018). In this research, traditional healers admitted that they received 50-100 patients in one month. Our field observation and interview with traditional healers during survey clarified that patients preferred traditional medicine to

modern drugs due to its effectiveness, affordability, and accessibility.

Patterns of Herbs Used among Dayak Tribe

Information on herbs' scientific name, origin, family, and serving method is fully presented in Table 1. 38 herbs gathered in this research were categorized into 26 families and 34 species. Four herbs were still locally named since they could not be identified by local botanical experts. The highest proportion of the herbs was Asteraceae (five species) followed by Euphorbiaceae, Fabaceae, Lamiaceae, and Malvaceae- each with two species and other families with one species for each. Asteraceae was the largest family of herb used to reduce pain in North Kalimantan. Based on research on herbs used to reduce pain in Mauritus (2014), it was confirmed that out of 79 herbs found, there were six species from Lamiaceae family, followed by Apiaceae, Asteraceae,

Euphorbiaceae, and Poaceae with five species each (Sreekeesoon & Mahomoodally, 2014). Asteraceae was the largest family dominating plant vegetation on earth with the number of members of 24,000-30,000 species and 1,600-1,700 genera globally spread in almost all types of environment (Bisht and Purohit, 2014). Besides, herbs commonly used by eastern people in Amazon came from Asteraceae, Lamiaceae, Euphorbiaceae, Piperaceae, and Verbenaceae families (Hariyadi, 2011). Asteraceae family could be used as traditional medicine since they contained bioactive compound components such as sesquiterpene, lactone, pentacyclic triterpene, alcohol, tannin, polyphenol, saponins, and sterol that could be used as medical ingredients. Due to its bioactive property, Astereaceae family was usually used as insecticide, anthelminthic, antimalarial, antiseptic, anti-inflammation, and antioxidant (Wegeira et al., 2012).

Table 1. Types of Herbs and Serving Methods Applied by Dayak Tribe in North Kalimantan

No.	Family	Туре	Local Name	National Name	Used Part	Treated Illness	Serving Method
1.	Acanthace	ea					
		Justicia gendarussa	War	Ganda rusa	Leaf	Rheumatic	Boil ten leaves. Drink it thrice a day.
		burm	tonep	Gundu i usu		Bruise and sprain	
2.	Asteracea	e					
a.		Blumea BalsamiFera	Ipung	Sembung	Leaf	Stomachache, menstrual pain	Boil five up to seven leaves. Drink it thrice a day.
b.		Pluchea indica	Beluntas	Beluntas	Leaf	Stiffness	Boil a handful of leaves until the water decreases. Drink it thrice a day.
c.		Heliothous anuus L	Bonga mata so'o	Bunga matahari	All parts	Headache, fuzziness, toothache, menstrual pain, stomachache	Take three handfuls of flowers, add one chicken egg (do not break the egg) and three glasses of water. Boil them until the water decreases. Drink it twice a day after meal.

No.	Family	Туре	Local Name	National Name	Used Part	Treated Illness	Serving Method
d.		Strobilanthescrispus	Peca beling	Peca beling	Leaf	Stomachache	Boil ten leaves in three glasses of water until the water decreases. Drink it thrice a day.
3.	Arecacea	e					
		Daemonorops	Rotan sembulik	Rotan jernang	Stem	Stomachace	Boil and drink the water thrice a day.
4.	Amaryllia	daceae					
		Crynum asiaticum L	Kaber lab	Daun bakung	Leaf	Sprain	Grill the leaf and put it on the painful area once a day at night.
5.	Amarantl	hi aceae					
		Gopheruna globasa L	Bonga derem	Kenop	All parts	Headache	Grind and put it on the painful area.
6.	Apocynac	reae					
		Plumeria acuminate Ait	Kamboj a	Kamboja	Leaf, stem, root	Toothache	Pick the sap/leaf, grind it and put it on the painful area.
7.	Balsamin	aceae					
		Impatsens Balsamia	Kemban g pacar	Pacar air	Leaf	Menstrual pain	Grind the leaf and put on the lower abdomen.
8.	Crassulad	 ceae					
			Sosor	Cocor		Rheumatic	Boil seven leaves and drink the water twice a day.
		Kalanchoe pinnata	bebek	bebek	Leaf	Sprain	Pick several leaves and smear them with oil. Grill then put it on the painful area.
9.	Cycadace	ae					
		Cycas revolute thumb	Aka kabuk	Akar penawar	Stem	Pain killer	Cut one cm of the stem, divide it into two, grind it, and soak it into water. Drink the water.
10.	Euphorbi	aceae					
a.		Jatropha Curcas L	Bua jarak	Jarak pagar	Leaf	Toothache	Heat the sap and smear it on the painful area.
b.		Phyllantus niruri L	Babah anak	Meniran	All parts	Backache	Boil it and drink the water thrice a day.
11.	Eragrosti	deae					
		Eleusin indica	Unduh gelu'	Rumput carulang	Leaf	Sprain	Grind the leaf and put it on the painful area once a day.

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No.	Family	Туре	Local Name	National Name	Used Part	Treated Illness	Grind some leaves. Sn Serving: Met pat hful area twice a day.
12.	Fabaceae		Uduh		Leaf	Rheumatic	•
b. a.		Mimosa pudica Abrus precatorius L	Owat Owat dipon	Putri malu Saga rambat	Stem	and back pain Toothache	Pick 34 handful of the Grands hand Bobi Hallm the the throught sees of water. Drink it thrice a day.
13.	Gesneriac	eae					
		Cyrtandra sarawakensis	Bura kaguyad ang	Cyrtanda sarawak	The peak of the leaf	Stomachace	Soak it in hot water and drink it thrice a day.
14.	Labiatae						
		Orthosiphon stamineus	Rumput kucing	Kumis kucing	Stem, leaf	Headache	Boil it and drink the water thrice a day.
15.	Lamiacea	e					
a.		Coleus parviflorus Benth	Dikut pait	Kentang ireng	Stem, leaf	Stomachace experienced by babies	Grind it, add chili leaves then put it on the painful area.
b.		Orthosphon aristatus	Udu pa'sing	Daun kumis kucing	Stem, leaf	Backache	Pick some stems and leaves, boil them and drink the water.
16.	Loranthac	eae					
		Loranthus	Ancam	Benalu	All parts	Toothache	Burn it and mix it with oil. Put it on the painful area.
17.	Malvaceae	2					
		Grewia acuminate Juss.	Bura krotok	Akar sekapu	Stem	Stomachace	Burn it and drink the essence twice a day.
		Hibiscus rosa sinensis L	Bunga sepatu	Kembang sepatu	Leaf, flower	Headache	Chop the leaf and flower, and boil them in three glasses of water. Drink the water thrice a day.
18.	Malastom	ataceae					
					Leaf	Stomachache	Boil the leaf. Drink it while still warm.
		Melastonia sepfemnerviu	Jelemuti n	Senggani	Stem	Toothache	Peel and grind the stem. Use it as your mouthwash thrice a day.
No.	Family	Туре	Local Name	National Name	Used Part	Treated Illness	Serving Method
19.	Menispern	naceae					
		Tinospora crispa	Bundung kemamba	Brotowali	Leaf	Stomachache	Pick the stem and cut it. Boil it in three – glasses of water then
			ng		Stem	Rheumatic	C

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	Musa	Peti	Pisang	Stem	Joint pain and bone pain	Pick a stem and divide it into two. Pick the <i>umbut</i> and eat it.
Myrtaceae	2					
•	Psiatum guajava L	Libum	Jambu biji	Leaf	Stomachache	Pick and grind six leaves. Pour some water and squeeze the leaves. Drink the water.
Pandanac	eae					
	Pandanus amaryllifaius roxb	Kaber nanung	Pandan wangi	Leaf	Rheumatic and stiffness	Pick and wash three leaves. Cut them into small size and brew them with a half cup of oil. Stir it. Let it cold and smear it on the painful area.
Poaceae						
	Cymbopogon nardus L	Gisumau	Sere wangi	Root, young leaf	Rheumatic	Pick and boil some roots and young leaves in six glasses of water. Boil until the water decreases and drink it thrice a day.
Rubiaceae	2					
	Psychitria sp.	Concang abang		All parts	Pain killer	Boil and drink it thrice a day.
Solanacea	ie					
	Physalis angulate L	Latup	Ciplukan	Leaf	Toothache	Grind then use the leaves as your mouthwash thrice a day.
Zingibera	eae					
	Curcuma xanthorrhiza	Temu lawak	Temu lawak	Root	Backache	Grind the root. Filter and drink it thrice a day.
Family	Туре	Local Name	National Name	Used Part	Treated Illness	Serving Method
Unknown						
	Pandanace Solanace Caracteristics Solanace Caracterist	Myrtaceae Psiatum guajava L Pandanaceae Pandanus amaryllifaius roxb Cymbopogon nardus L Rubiaceae Psychitria sp. Solanaceae Physalis angulate L Zingiberaeae Curcuma xanthorrhiza	Myrtaceae Psiatum guajava L Pandanaceae Pandanus kaber nanung amaryllifaius roxb Kaber nanung Cymbopogon nardus L Cymbopogon nardus L Concang abang Psychitria sp. Concang abang Solanaceae Physalis angulate Latup Zingiberaee Curcuma xanthorrhiza Local	Myrtaceae Pandanaceae Pandanus amaryllifaius roxb Kaber ranung wangi Poaceae Cymbopogon rardus L Cymbopogon aradus L Concang abang Ciplukan Ciplukan Temu lawak Iawak National	Myrtaceae Psiatum guajava L Libum Jambu biji Leaf Pandanaceae Pandanus amaryllifaius roxb Raber nanung Poaceae Cymbopogon nardus L Gisumau Sere wangi leaf Root, young leaf Rubiaceae Psychitria sp. Concang abang All parts Solanaceae Latup Ciplukan Leaf Zingiberaee Curcuma xanthorrhiza Temu lawak Root National Vised	Myrtaceae Psiatum guajava L Libum Jambu biji Leaf Stomachache Pandanaceae Pandanus amaryllifaius roxb Kaber nanung Pandan wangi Leaf Rheumatic and stiffness Poaceae Cymbopogon nardus L Cymbopogon nardus L Cymbopogon nardus L Cymbopogon nardus L Psychitria sp. Concang abang All parts Pain killer Solanaceae Physalis angulate Latup Ciplukan Leaf Toothache Latup Ciplukan Root Backache Zingiberaeae Curcuma xanthorrhiza Temu lawak Root Backache Eamily Type Local National Used Treated

Unknown Unknown	Udu pejek Kelepes o	Unknown Unknown	Leaf, root Fruit	Sprain Stomachache	pejek and smash it. Twist it on the painful area, wrap the area with cloth. Pick and grate two seeds, add some water,
Unknown	Kayu pela	Unknown	Stem	Toothache	and drink it. Pick and break one stem. Wait for two minutes until the sap is out and smear it on the painful area.

The most frequently used parts of the herbs for medicine were the leaf (60.5%) and the stem (26.3%). Meanwhile, the distribution of the herbs' parts used to treat pain is presented in Table 2. To manage pain, Dayak tribe in North Kalimantan preferred to use leaves of the selected herbs. The selection is important because the right part of herbs contains secondary metabolite that helps patients to obtain the desired therapeutic effect. In contains addition. leaf manv phytochemical pharmacologies responsible for effects (Sreekeesoon curative & Mahomoodally, 2014). Ethnobotanical research in Dayak Tribe Seberuang in Ensabang Village conveyed that leaf was mostly used because people found it easier to collect leaves than to collect other parts of herbs that existed underground. Additionally, when they dug the ground, they might destruct the herb root, thus, harmed the herb (Damianus et al., 2013). Another research declared that most traditional healers used leaf to substitute part of herb that grew underground to preserve the herb (Traore et al., 2013). Besides, leaf is the most accessible part of herb. In addition, leaf could be more easily processed and gave more benefits (Takoy, Linda & Lovadi, 2013). Herbal therapy containing many complex compounds was regarded to provide more action targets to human body (Raja Nasution, Aththorick and Rahayu, 2018).

Herbs could be used as medical treatment through several techniques like by drinking the herbs (63.2%), putting the herbs on the painful area (36.8%), and using the herbs as

mouthwash (5.26) for toothache. The fact is shown in Table 3.

Serving methods can be completed by boiling and drinking them, or by rubbing them on the painful area. Boiling was the most common and efficient method (Sreekeesoon & Mahomoodally, 2014). Methods applied to prepare the herbs were boiling (42.1%) and grinding then smearing on the painful area (36.8%), as presented in Table 4.

Types of Pain

Distribution of types of pain and number of herbs for pain management is shown in Table 5. Types of pain experienced were bone pain (rheumatic, sprain, backbone pain, and stiffness), stomachache, toothache, headache, backache, and menstrual pain. Out of those, bone pain and stomachache were two types of pain that were most frequently treated using herbs consisting of 11 herbs for each illness. Especially for headache, it could be cured with a certain therapy using nine types of herb.

One of herbs used to reduce bone pain was gandarusa. Justicia gendarussa Burm F. (Family: Acanthaceae) is widely used in Indian and Chinese traditional medicines and the leaf of the plant is recommended to treat pain such as arthritis, headache, earache, and muscle pain (Jaijesh et al., 2009). The herb could be found or cultivated in Indonesia, India, China, Malaysia, Sri Lanka, Philippine, Bangladesh. The leaf of the herb was reportedly anti-angiogenic, antioxidant, anti-bactericidal, antifungal, anti-arthritis, anti-inflammatory, anti-nociceptive, and anti-sickling, and it

showed anthelmintic, cytotoxicity, larvicidal, and adulticidal activity (Ningsih *et al.*, 2015). Additionally, *gandarusa* contained flavonoid compound (Gustina, 2017) known to cure inflammatory disorders (Wegeira *et al.*, 2012). Hence impeding Cox-2 formation and preventing prostaglandin formation.

Another herb used as a therapy for stomachache and menstrual pain was sambong (Blumea BalsamiFera). Blumea balsamifera (L.) DC. (Asteraceae), or sambong has been widely used in many countries such as Chinese, Malaysia, Thailand, Vietnam, and Philippine for years. The herb is widely used in Indonesian traditional medicines; the leaf of the plant is recommended to treat pain such as arthritis, headache, earache, and muscle pain (Rahardjo, 2016). It is the most important member in Blumea genus and the origin herb of tropical and subtropical Asia, particularly China. It grows in the edge of the forest, underneath the forest, river bed, valley, and meadow. All parts of the herb, including the leaves, were used as a traditional therapy to cure eczema, dermatitis, beriberi, backache, menorrhagia, rheumatic, and damaged skin, and as an insecticide. The main active compound contained in Sembong (Blumea BalsamiFera) is L-borneol characterized by high volatility. Besides, Sembong contained essential oil, flavonoid, and terpenoid with some different biological activities (Pang et al., 2014). It has many flavonoid compounds. There were 27 of 29 flavonoid compounds identified in Sembong (Blumea balsamifera (L.) DC) including 21 analog flavonoids, five derivative CQAs, and

one coumarin (Pang et al., 2014). Antiinflammatory activity mechanism of flavonoid is restricting eicosanoid to produce some phospholipase enzymes such as A2, cyclooxygenases, and lipoxygenase, hence, reducing both leukotriene and prostanoid concentrations. Other mechanisms histamine and phosphodiesterase restriction, protein kinase releases, and transcriptase activation. Restricted eicosanoid enzyme would restrict phospholipase A2 enzyme formation so that cyclooxygenase lipoxygenase would be unable to be formed which cancelled the production prostaglandin compound (Rathee et al., 2009).

Table 2. Distribution of the Used Parts of the Herbs

No.	Part of the Herbs Used	Number	Percentage (%)
1	Leaf	23	60.5
2	Stem	10	26.3
3	Flower	1	2.6
4	Fruit	1	2.6
5	Root	2	5.3
6	Flower	1	2.6
7	All parts	2	5.3
8	Herb	1	2.6

Table 3. Distribution of the Technique in Herbs Use

No.	Technique to Use	Number	Percentage (%)
1	Oral	24	63.2
2	Topical	14	36.8
3	Mouthwash	2	5.3

Table 4. Distribution of Herbs Serving Methods

No.	Serving Method	Number	Percentage (%)
1	Boiling	16	42.1
2	Grinding and smearing on the painful area	14	36.8
3	Soaking into water	3	7.9
4	Burning	1	2.6

5	Grinding and using the herb as mouthwash	2	5.3
6	Mashing up by using a blending machine	1	2.6
7	Shredding and adding water	1	2.6
8	Brewing	1	2.6
9	Eating	1	2.6

Table 5. Types of Pain and Herbs

No.	Name of Illness	Number of Herbs	Herbs (Local Name)
1.	Bone pain (rheumatic, sprain, stiffness, backbone pain)	11	Ganda Rusa, Sere Wangi, Cocor Bebek, Putri Malu, Beluntas, leaf of Bakung, Pandan Wangi, Pisang, Brotowali, Rumput Carulan, Udu Pejek
2	Stomachache	11	Sambong, Rotan Jernang, Kentang Ireng, root of Sekapu, Cyrtanda Sarawak, Senggani, Jambu Biji, Peca Beling, Brotowali, Faling, kelepeso.
3	Toothache	9	Kamboja, Ciplukan, Senggani, Jarak Pagar, Bunga Matahari, Tahi kotok, Saga, Benalu, Kayu Pela
4	Headache	4	Kumis Kucing, Kenop, Bunga Matahari, Kembang Sepatu
5	Backache	3	Temu Lawak, Leaf of Kumis Kucing, Meniran
6	Menstrual pain	2	Pacar Air, Sembung
7	Pain killer	2	Root of Penawar, Concanga-bang

One of the herbs used by Dayak people in North Kalimantan to cure toothache was benalu (Loranthus europaeus, family: Loranthaceae). World Health Organization (WHO) estimates that more than 80% of world population relies on traditional medicines and the market is rapidly growing. Lots of medicinal plants like Loranthus europaeus are recommended to treat pain (Nasrin et al., 2015). The herb is rich of flavonoid, alkaloid, terpenoid, and polysaccharide, and shows expressed gen toxicity, cytotoxic and antioxidant properties. Flavonoid is known for its ability to impede prostaglandin synthesis involved in the final phase of acute inflammation and pain perception. It can also increase the number of endogen serotonin or interact with 5-HT2A and 5-HT3 receptors involved in central analgesic activity mechanism. Terpenoid is also reported to show a significant analgesic activity whereas alkaloid can also prevent inflammation by blocking the metabolic path of arakidonat acid.

Loranthus europaeus contains flavonoid, alkaloid, terpenoid, polysaccharide, and other phytochemicals that cause analgesic activities. All parts of herbs can be used as medicine. However, in all of our experiments, extract of the leaves gave better effect than the stems which might be due to its higher phytochemical content (Nasrin et al., 2015).

CONCLUSION

This research figured out that Dayak people in North Kalimantan still used traditional medicine to cure pain and other illnesses. Traditional healers collected herbs in the forest and processed them into medicine and gave it to their patients. The most frequently used herb by Dayak tribe in North Kalimantan was from *Asteraceae* family while the most frequently used part was leaf. Furthermore, types of pain experienced by Dayak tribe in North Kalimantan were bone pain, stomachache, toothache, headache,

backache, and menstrual pain. Effectiveness and safety of herbs reported to be potentially analgesic shall be evaluated within phytochemical and pharmacological studies to determine the dosage, minimum restriction concentration, bioactive compound, and toxicity.

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