

Anti-tumor Potential Ethnomedicinal Plants from Dayak Tribes in Central Kalimantan

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Submitted: 6 March 2020. Revised: 13 October 2020. Accepted: 14 December 2020

Abstract. *Hornstedtia conica* Ridl., *Microsorium pustulatum* Copel and *Rourea fulgens* Planch were medicinal plant used by people of Dayak Tribes in Central Kalimantan for anti-tumor medicines. Although these plants has been widely used in traditional medicine, however, research and scientific evidence about their potential as anti-tumor are still very limited. The research aims were to determine the qualitative content of phytochemical compounds and to study anti-tumor potential of these medicinal plants. This study used female Swiss Webster albino as a test animal. Induction of tumor cell in mice used 7,12-Dimethylbenz [a] anthracene (DMBA), was done 10 times for 5 weeks. Experiments were carried out used hexane extract from medicinal plants, every day for 7 weeks. The data obtained were analyzed descriptively. The results as follows: extracts of *Hornstedtia conica* Ridl., and *Microsorium pustulatum* Copel. contained alkaloids, while extract of *Rourea fulgens* Planch. contained flavonoids and saponins. All of these plant extracts were able to reduce the size and number of mice tumors. Hexane extract of *H. conica* was able to reduce the tumor size faster than another plants extracts. Mortality rate of mice in hexane extracts of *H. conica* and *R. fulgens* were zero- and in hexane extract of *M. pustulatum* it was 30%, meanwhile almost all mice in control group were died in days 15 of treatment. Based on this study, it can be concluded that hexane extract of *H. conica* and *R. fulgens* are potential as anti-tumor medicinal plants. These findings scientifically proved the potential of medicinal plant extracts as anti-tumor compounds. *H. conica* is the most potential one for further development as alternative drug for inhibited of tumor growth.

Key words: Anti-tumor; *Hornstedtia conica* Ridl; *Microsorium pustulatum* Copel; *Rourea fulgens* Planch

How to Cite: Neneng, L., Pujirahadju, A., Ferayani, F., & Widayat, T. (2020). Anti-tumor Potential Ethnomedicinal Plants from Dayak Tribes in Central Kalimantan. *Biosaintifika: Journal of Biology & Biology Education*, 12(3), 422-430.

DOI: <http://dx.doi.org/10.15294/biosaintifika.v12i3.23671>

INTRODUCTION

Plants are used for generations to treat numerous varieties of diseases. Many plants were used for health as a part of ancient drugs (Lichota and Gwozdziński, 2018). Herbal extracts have antioxidant compounds that can induce apoptosis and inhibit cell proliferation by the investigated mechanisms (Wesam, et. al., 2017). At present, over 60% of anti-cancer compounds that are helpful for cancer patients are obtained from herbal, marine and being sources (Prakash, et. al., 2013). A total of 84 species of medicinal plants are reported to be used for the prevention or treatment of cancer and tumors (Joabe, et. al. 2011). The big problem in cancer treatment is how to destroy of tumor cells within the presence of natural cells, without caused damaged of the normal cells. To solve the problem very important to prepare anti-cancer drugs from various natural sources such as screening raw extract of plants (Wesam, et. al., 2017).

Natural therapies, such as the use of plant-derived products in the treatment of tumors, can reduce the adverse side effects. Currently, several plants are being used to treat tumors. Plants produce a wide variety of chemical compounds that no have any direct role in the plants growth. These compounds are secondary metabolites. Secondary metabolites play an important role as anti-inflammatory, and anti-cancer. Some of the important secondary metabolite products are alkaloids, terpenoids, flavonoids, pigments, and tannins (Pagare, et al., 2016).

The ability of plants to control the activity of tumor cells is caused by their active ingredients. Several active compounds for anti-cancer in plants were included alkaloid compounds, anti-inflammatory compounds, antioxidants, and also curcumin. Vinblastine and vincristine were alkaloids compounds which derive from *Catharanthus roseus*. These compounds had ability for inhibit of tubulin polymerization and prevent formation of the mitotic spindle (Maryam, et

al., 2007). Alkaloids compounds in *Myrmecodia pendans* are also efficacious as anti-cancer (Sumarno, 2010). White turmeric contain several anti-cancer ingredients such as anti-inflammation and antioxidant compounds which is beneficial for stimulate the increase of the immune system. White turmeric also contains Ribosome-Inactivating Protein (RIP) compounds which capable of inactivating the development of cancer cells, killing cancer cells without damaging other cells or tissues around them, and also inhibiting the development of cancer cells. Antioxidants contained in white turmeric also prevent gene damage due to cancer triggers, and the anti-inflammatory agents help to overcome swelling and inflammation (Putri, 2014). *Curcuma longa* from the Zingiberaceae family, contains curcumin. The anti-cancer potential of curcumin against cancer, including leukemia, lymphoma, digestive, urinary tract, reproductive, breast, uterine, ovarian, lung, melanoma, colon cancer, and brain tumors (Shimin, et. al., 2015).

Some research revealed the potential of plants medicine as anti-tumor, such as: *Dioscorea esculenta* extract affects the growth of adenocarcinoma mammae of C3H female mice (Suprijono & Sumarno, 2012), *Carica papaya* leaf extract (Sumarny & Prisoeryanto, 2013), methanol extract of *Curcuma heyneana* rhizome (Syarifah, 2013), *Catharanthus roseus* extract (Naziya, 2006), ethanol extract of *Aglaia elliptica* Blume leaf (Wibowo, et al., 2011). As well as *Centella asiatica* and *Andrographis paniculata* extracts (Widjajakusuma, et al., 2012). Ethanol Extract of *Gynura procumbens* with dosage of 250 mg/kg of body weight had chemopreventif effect on mammae cancer (Tasmiyatun, et al., 2007).

Various types of plants have been used by traditional medicine experts of Dayak tribes, as an empirical anti-tumor in Central Kalimantan. Topah susu daro or *Hornstedtia conica* Ridl., has been used by Dayak Tomum in Lamandau Regency as an anti-tumor. Simbar or *Microsorium pustulatum* Copel., and pangarereng or *Rourea fulgens* Planch. have also been used by Dayak Taboyan in North of Barito Regency, as anti-tumor for generations. Although these plants has been widely used in traditional medicine, however, research and scientific evidence of its potential as an anti-tumor are still very limited.

Based on these reasons, The research aims were to determine the qualitative content phytochemical compounds and to study anti-tumor potency of these medicinal. the purpose of this research was to study the potential anti-tumor

activity of medicinal plants from Dayak tribes in Central Kalimantan. Research on local knowledge is very important in order to provide a database of medicinal plants, and as a basis for further research. This research was expected to provide an important information related to anti-tumor potential of plants.

METHODS

The sample of medicinal plants was collected from Delang District of Lamandau Regency and Gunung Timang area of North Barito Regency, Central Kalimantan, Indonesia. These plants were identified in Laboratory of Biology, University of Palangka Raya to certify the plant legality. These plants were then identified as *Hornstedtia conica* Ridl., *Microsorium pustulatum* Copel., and *Rourea fulgens* Planch.

Preparation of plants simplicia extract was conducted at Pharmacy Laboratory of Muhammadiyah University of Palangka Raya, Central Kalimantan, Indonesia. Experimental research for testing the effectiveness of anti-tumor activity of medicinal plants was conducted in Biology Laboratory of University of Palangka Raya. Female Swiss Webster albino mice were obtained from Faculty of Veterinary Medicine, IPB, Bogor. Extracts of *M. pustulatum* rhizoma, flower petals of *H. conica*, and *R. fulgens* leaves obtained from macerated method used hexane solvents. The chemicals used were DMBA (7,12-Dimethylbenz[a]anthracene, TCI America), corn oil, double distilled water, and hexane (Merck). This research was an experimental research. The treatment consisted of 2 factors, i.e. three species of plant simplicia (rhizoma of *M. pustulatum*, flower petals of *H. conica*, and leaves of *R. fulgens*) and hexane solvents. Double distilled water was used as a control. There were 5 treatments in total with 5 repetitions of each.

Flower petals of *H. conica*, rhizome of *M. pustulatum*, and leaves of *R. fulgens* were separated and dried with a drying cabinet at a temperature of 40°C - 60°C, until reached a water content of below 10%. Each dried simplicia was then crushed into a powder. The powder was macerated separately using hexane and ethanol solvents, in a ratio 1 part of powder to 10 part of solvent. The simplicia extract was then immersed in a solvent for 6 hours while occasionally stirring with an orbital shaker at room temperature every 1 hour interval, then allowed to stand for 18 hours.

The mixture was then separated using filter paper, evaporated with a rotary evaporator and freeze dryer, and concentrated in a water bath at 50°C temperature. The obtained viscous extract was dried to obtain a dry extract. The dried extract was then stored in a refrigerator of -20°C for further study. Phytochemical analysis of alkaloids, flavonoids, and saponins extracts was performed to obtain information regarding secondary metabolite dissolved in each extract with different polarities. DMBA was dissolved in 10 mL of corn oil then stirred using a magnetic stirrer. After homogeneous, corn oil was added to obtain a concentration of 1 mg DMBA / 0.2 mL of corn oil. DMBA solution was given by gavage. The given dose was determined based on the weight of the mice used for the study. For each 20 mg of mice were given 0.2 ml DMBA solution.

A total of 40 mice were acclimated for 2 weeks. Induction of tumor in mice was using DMBA solution. At the age of 10 weeks, the mice was induced with DMBA in corn oil, with dosage of 20 mg/kg body weigh, 10 times for 5 weeks. If there was a lump formed before 5 weeks, the induction with DMBA will be

stopped. Mice were then given a treatment with extract of simplicia plants. The dose used was 2 times (2n) of dose used by humans, after converted to mice using Laurent & Bacharach tables. Treatment with plants extract was done daily untill 7 weeks. Observations were carried out every five day. The data taken were the number and diameter of tumor nodes, body weight and lifetime of mice. At the end of the experiment, the mice were killed by the dislocation of neck. Data obtained in the form of an amount and diameter of tumor nodes, body weight and lifetime of mice, were analyzed descriptively.

RESULTS AND DISCUSSION

Characteristic of Medicinal Plants

Dayak Tomum and Dayak Taboyan tribes in Central Kalimantan had used some medicinal plants i.e. topah susu daro (*Hornstedtia conica* Ridl.), simbar (*Microsorium pustulatum* Copel.), and pangarereng (*Rourea fulgens* Planch.) to treat tumors and had proven their efficacy. Application of medicinal plants by Dayak Tribes is presented in Table 1.

Table 1. Anti-tumor medicinal plants used by Dayak tribes

Scientific name	Family	Vernacular name	Parts used	Preparation	Application
<i>Hornstedtia conica</i> Ridl.	Zingiberaceae	Topah susu daro	Flower petals	Decoction, baking and mixing with water	Oral, topical
<i>Rourea fulgens</i> Planch.	Connaraceae	Pangarereng	Leaves	Decoction	Oral
<i>Microsorium pustulatum</i> (G.Forst.) Copel.	Polypodiaceae	Simbar	Rhizomes	Decoction	Oral

Hornstedtia conica Ridl.

Hornstedtia conica is a plant that produces a cluster of closed shoots up to 3.5 meters from a branching rootstock growing on or just below the soil surface. *H. conica* belongs to Zingiberaceae family. The people of Dayak Tomum tribe in Lamandau Regency, of Central Kalimantan, knows *H. conica* as topah susu daro (Figure 1).



Figure 1. Flower petals of *H. conica* (A), flower crown of *H. conica* (B), habitus of *H. conica*

H. conica is a native plant of Southeast Asia, the Himalayas, Southern China, New Guinea, Melanesia, and Queensland. In the genus *Hornstedtia*, all flowers are above ground level, with empty outer bracts forming the spiky structures of the tallest emerging flowers, 1 or 2 at a time. The seeds in the fruit are surrounded by a silvery slimy coating and taste sour. It has an ellipsoid-shaped fruit, like a red onion, about 3 cm long and 2 cm wide, which contains black seeds (Tropical Plants Database, 2020).

Rourea fulgens Planch.

R. fulgens is the member of connaraceae family. *R. fulgens* is a large climbing shrub producing vigorous stems that climb into the surrounding

vegetation (Figure 2). The plant is sometimes harvested from the wild for local medicinal use. The leaves of *R. fulgens* are used by Dayak Taboyan people for treating of tumor. The habitat of this plant is in the lowlands and rainforest edges. The place should be moist and cool with tropical climate. The distribution of these plants occurs widely in Southeast Asia, Indonesia, Myanmar, and Malaysia (Tropical Plants Database, 2020).



Figure 2. Leaves of *R. fulgens*

Microsorium pustulatum (G.Forst.) Copel.

The rhizome of *M. pustulatum* (Figure 3) was used by Dayak Taboyan tribe for tumor treatment. *M. pustulatum* is a species of fern (Mabberley, 2008) and belonging to the Polypodiaceae family. *M. pustulatum* is a native epiphytic fern from Australia and New Zealand. This species occurs widely in New Zealand and also in Queensland, New South Wales, Victoria and Tasmania in Australia. (New South Wales Flora Online, 2020)



Figure 3. *Microsorium pustulatum* (G. Forst.) Copel.

This plant is a fern that can be epiphytic by growing creeping or climbing on large shady branches of trees, and also grows on terrestrial (Brownsey & Perrie, 2014). The shape of the

leaves is shiny, bright, colored green, with various shape and size. The leaves are bright green, shiny, and rough. They spread through fragmentation of bright green and striking brown rhizomes. This plant is generally found in coastal areas to the mountains. It is often in the form of epiphytic plants tree, in a rather dry place. This plant has thick rhizomes and large round sori (spore capsules) at the bottom of the fertile leaf (Terrain Community, 2018).

The Anti-tumor Potential of Plants against Mice Tumor Growth

Results of treatment showed that extracts of *H. conica*, *M. pustulatum*, and *R. fulgens* were able to decrease the size of tumor. Meanwhile, mice in control treatment were died in day 15 of treatment (Figure 4). Hexane extract of *H. conica* was able to decrease of tumor size faster than extracts of *R. fulgens* and *M. pustulatum*.

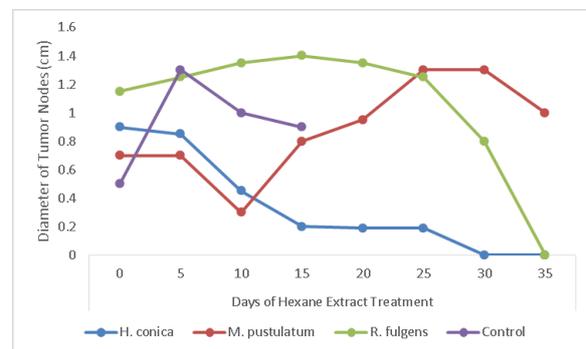


Figure 4. The effect of treatment using plants simplicial extracts on the diameter (cm) of tumor

Results of treatment in Figure 4. show the ability of plant extracts to decrease the diameter of tumor nodes in mice. Hexane extract of *H. conica* could reduce the size of tumor nodes after fifth day of treatment, the size of the node then continued to shrink until it was finally not visible on the day 30 of treatment. The results of the treatment using ethanol extract of *R. fulgens* showed a decrease in diameter of tumor nodes on day 20 of treatment, then reduced to almost not visible on day 35. Treatments using *M. pustulatum* extract showed a trend to decrease the tumor node diameter slower. In contrast, diameter of tumor nodes of mice in control treatment tended to increase and finally the mice died on day 15. Based on these data, it was known that the extract of *H. conica* was able to decrease of tumor size faster than the other plant extracts. The ability of plant extracts to reduce the number of tumor nodes in mice was shown in Figure 5.

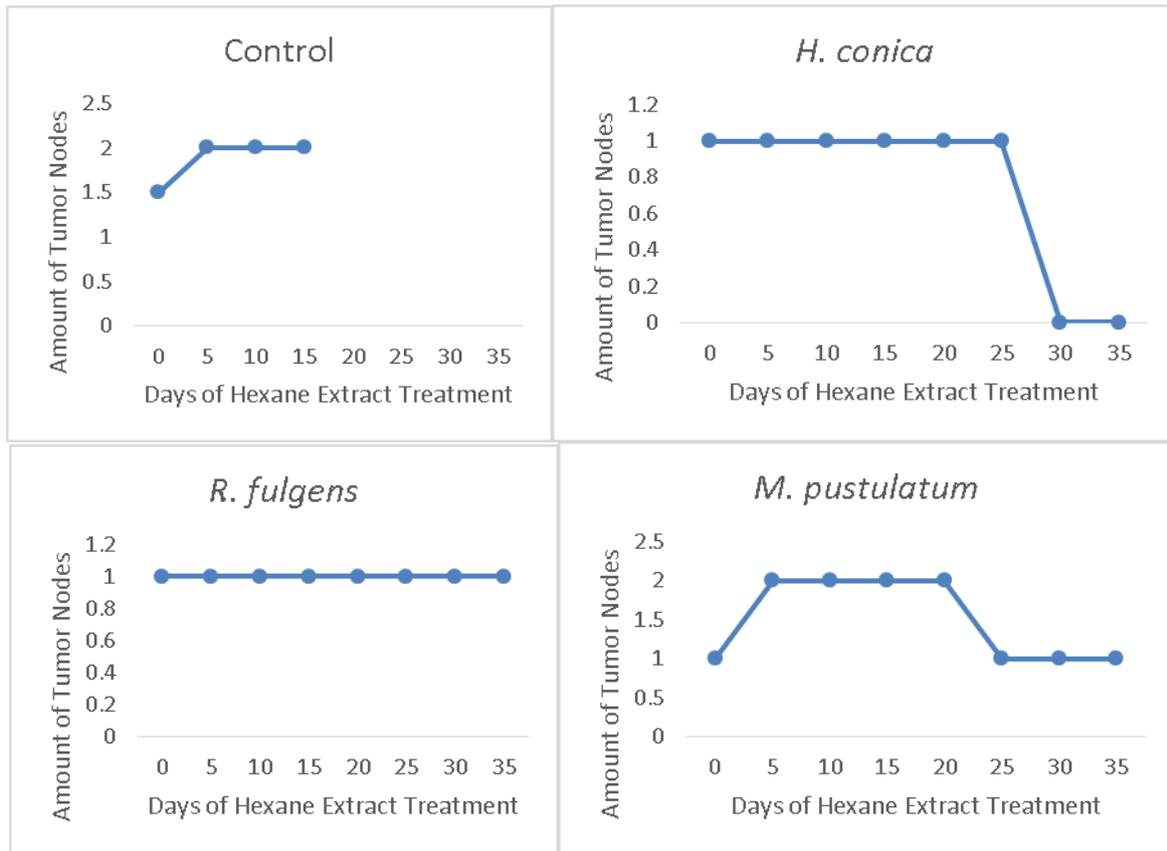


Figure 5. The effect of treatment using plants simplicia extracts on the amount of tumor nodes

The data in Figure 5 shows an increase in the number of tumor nodes in control treatment. The treatment using *R. fulgens* and *M. pustulatum* extract did not show a decrease in the number of tumor nodes. The different condition is shown by treatment used hexane extract of *H. conica*, showed the ability to reduce of tumor growth in mice during 35 day of treatments. Based on this data, the flower petal extract of *H. conica* is more able to decrease of tumor nodes than *R. fulgens* and *M. pustulatum* extract.

The Effect of Medicinal Plants on Body Weight and Lifetime of Mice

Result of treatment using *M. pustulatum* and *R. fulgens* extracts showed an increase in body weight of mice, ranging from 6-10%. Meanwhile the mice treated by *H. conica* extract did not show a weight gain. In contrast, the mice in the control treatment showed a weight loss of around 30% (Figure 6).

All of mice in control group were dead in day 15. Mortality rate of mice in treatments using the extracts of *H. conica* and *R. fulgens* were zero, meanwhile mortality rate in treatment using *M. pustulatum* was 30% (Figure 7).

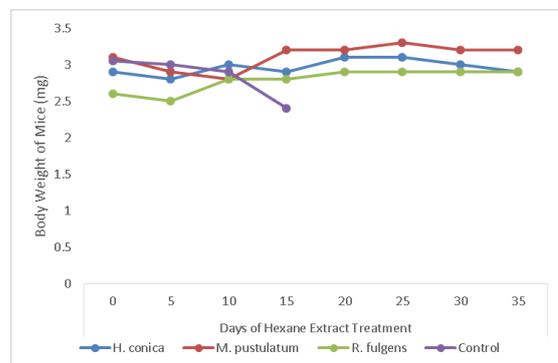


Figure 6. The effect of treatment using plants simplicia extracts on mice body weight

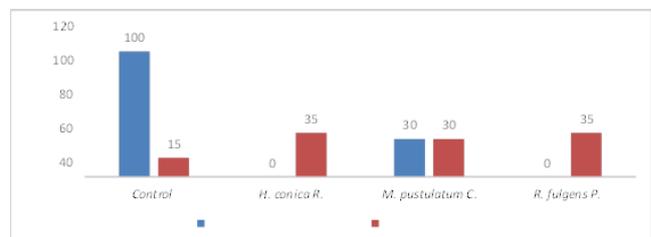


Figure 7. The effect of treatment using plants extracts on lifetime of mice

Growth and lifetime of mice treated with extract of *M. pustulatum*, *H. conica*, and *R. fulgens* were better than mice in control treatment (Figure 6-7). These facts reinforce the evidence related the ability of these plants extracts to inhibit tumor growth in mice.

Phytochemicals Compound of Medicinal Plants

Table 2 shows the results of secondary metabolites analysis in plants simplicia. Extracts of *H. conica* flower petals and of *M. pustulatum* rhizome contained alkaloid, however extract of *R. fulgens* leaves contained flavonoids and saponins.

Table 2. Phytochemicals compound of plants simplicia

Simplicia of Plant	Alkaloids	Flavonoids	Saponins
Rhizome of <i>M. pustulatum</i> Copel.	+	-	-
Flower petals of <i>H. conica</i> Ridl.	+	-	-
Leaves of <i>R. fulgens</i> Planch.	-	+	+

Some alkaloids play an important role in biological activity, such as reducing ephedrine for asthma, the analgesic action of morphine, and the anti-cancer effect of vinblastine. Alkaloids are mainly found in higher plants, such as those belonging to Ranunculaceae, Leguminosae, Papaveraceae, Menispermaceae, and Loganiaceae.

Several alkaloid compounds have been successfully developed into chemotherapy drugs, such as camptothecin (CPT), topoisomerase I (TopI) inhibitors, and vinblastine, which interact with tubulin. Alkaloids are chemical compounds that play an important role as potential ingredients for various drugs. Several alkaloids isolated from natural plants show antiproliferative and antimetastatic effects on various types of cancer in vitro and in vivo. Alkaloids, such as camptothecin and vinblastine, have been successfully developed into anti-cancer drugs (Lu et al., 2012).

Flavonoids belong to a group of plant secondary metabolites with a varied phenoplastic structure and are found in fruits, vegetables, seeds, bark, roots, stems, flowers, tea and grapes. Flavonoids play an important role in plants, including for pollination, seed dispersal, growth of plant parts, biological processes of mineral nutrition, tolerance to abiotic stress, protection against ultraviolet interactions and allelopathy, and so on (Samanta, et al., 2011). More than 8,000 different compounds of polyphenols have been known and that can be further subdivided into ten different general classes (Maheep, et al., 2011).

Flavonoids in the human diet consist of many polyphenol secondary metabolites, which have potential

as anti-cancer agents. The correlation between a diet rich in flavonoids (from vegetables and fruits) which is able to reduce the risk of colon, prostate, and breast cancer, raises suspicions regarding the role of flavonoids in mediating the protective effect as chemopreventive agents or playing a role in therapy, in collaboration with different genes and proteins. (Sharma, 2013).

The role of flavonoids in food for fighting cancer has been widely discussed. The results of laboratory studies, epidemiological investigations, and clinical trials in humans have shown that flavonoids have important effects on cancer chemoprevention and chemotherapy. Several mechanisms of action were identified, along with matter inactivation, antiproliferation, cell cycle cessation, caspase-mediated induction of cell death and differentiation, inhibition of angiogenesis, antioxidants and reversal of multidrug resistance or a mixture of these mechanisms (Ren, et al., nd).

The leaves of *R. fulgens* contain flavonoids and saponins. The presence of saponins can be found in more than one hundred plant families out of which at least one hundred and fifty types of natural saponins were found to have important anti-cancer properties (Man et al., 2010). The root decoction of *R. fulgens* is used as a treatment for stomach aches, while the tub of the leaves is used externally to soothe stomach aches. The leaves of this plant are boiled to clean wounds, heat of poultice leaves for inflammation of children's skin, leaf powder for wound healing, root juice to prevent excessive bleeding.

Comparison of Hexane and Ethanol Extract of Plants Simplicia

All of plants simplicia were extracted with hexane solvent and ethanol solvent. Comparison result of simplicia extracted with these different solvent, as showed in Table 3.

Based on the results as shown in the Table 3, all extract of plants simplicia were able to decrease of tumor growth in mice. Mortality rate of mice treated with hexane extract of *H. conica* and hexane extract and ethanol extract of *R. fulgens* were zero during the study. Extraction of of *H. conica* flower petals in hexane solvent is better than using ethanol solvent. Extract of *R. fulgens* leaves in hexane solvent give the same good effect compared with ethanol solvent in inhibiting the tumor growth.

Hexane extract of *H. conica* have a good effect in reducing and removing the tumor nodes of mice, whereas in the treatment using ethanol extract, mice suffering from tumors did not heal, even dead. Results of phytochemical tests showed that the *H. conica* flower petal contains alkaloids (Table 2). This compound is known have potential as an antioxidant

and anticancer. Some alkaloids from plants have anti-proliferative and anti-metastatic effects on various types of cancer both in vitro and in vivo. Alkaloids, such as camptothecin and vinblastine, have been shown to be successfully developed into anticancer drugs (Lu, et al., 2012). The nature of alkaloids is water soluble and can disappear in alcohol. This is thought as a cause of extraction using ethanol solvents giving unfavorable results.

Table 3. Comparison of hexane and ethanol extract in decreasing the tumor growth and mortality rate

Simplicia	Hexane Solvent	
	Growth of Tumor	Mortality Rate (%)
Rhizome of <i>M. pustulatum</i> Copel.	Decreased	33
Flower petals of <i>H. conica</i> Ridl.	Decreased	0
Leaves of <i>R. fulgens</i> Planch.	Decreased	0
Simplicia	Ethanol Solvent	
	Growth of Tumor	Mortality Rate (%)
Rhizome of <i>M. pustulatum</i> Copel.	-	-
Flower petals of <i>H. conica</i> Ridl.	No Detection	60
Leaves of <i>R. fulgens</i> Planch.	Decreased	0

H. conica belongs to zingiberaceae family. The results of several studies on the content of active ingredients zingiberaceae plant showed that its rhizomes, contain anti-inflammatory compounds, anti-cancer, anti-tumor, anti-microbial, and various properties to healing some diseases. This type of family is widely used as a traditional medicine in the form of herbal medicine that is beneficial to the health of the body (Mehdi et al., 2017). Zingiberaceae are rich in chemical molecules used in medicine or in traditional spices, but extensive information on their chemistry and pharmacology is only available for a few species (Wohlmuth, 2008).

Simplicia of *R. fulgens* leaves contain flavonoids and saponins. The results of simplicia extraction using hexane and ethanol solvents showed the potential of *R. fulgens* extract as an anti-tumor, using a dose of 2n. This is indicated by the ability of mice to survive, the process of reducing tumor cell nodes as well as the injuries due to tumor rupture which then dries and shrinks.

M. pustulatum is a species of fern belonging to the polypodiaceae family. Among all the pteridophytes

studied, taxa from Pteridaceae, Polypodiaceae, and Adiantaceae showed significant medicinal activity. Many pteridophytes are efficacious for alternative medicine, for example one type of fern i.e *Lycophyte Selaginella* sp., proven had pharmacological activities, such as antioxidants, anti-inflammatory, anti-cancer, antidiabetic, antiviral, antimicrobial, and anti-Alzheimer's (Baskaran et al., 2018). Simplicia of *M. pustulatum* also contains alkaloids and showed the ability to inhibit of tumor growth in mice (Figure 4 & 5). Several alkaloids isolated from plants have been proven to have anti-proliferative and anti-metastatic properties in various types of cancer. Alkaloids, such as camptothecin and vinblastine, have been successfully developed into anticancer drugs (Lu et al., 2012). The results of the study by (Ho, Teai, & Loquet, 2007), stated that the genus *Microsorium* sp. contains phytoecdysteroids mixture. According to Eva et al. (2007), ecdysteroid has many pharmacological influences on mammals/humans, which affect anabolic, hypoglycemic, hypocholesterol, hepatoprotective, and antidepressant properties.

The results of these medicinal plant extract above revealed that the three types of plants (*H. conica*, *R. fulgens*, and *M. pustulatum*) showed an anti-tumor potential. The potential of these plants species as an anti-tumor had never been tested and reported before. The findings of this study provide important information regarding the potential of herbal plant ingredients as anti-tumor agents, to be studied intensively in the future

CONCLUSION

Hexane extract of *H. conica* flower petals, hexane extract of *M. pustulatum* rhizomes, and hexane and ethanol extract of *R. fulgens* leaves were potential to inhibit of tumor growth in mice. Extract simplicia of *H. conica* was the most potential for further studies as alternative drug for inhibiting the tumor growth.

ACKNOWLEDGEMENT

This research was fully funded through Grant Advanced Research of RISTOJA 2016 by Central for Medicinal Plants and Traditional Medicines (B2TOOT) Tawang Mangu, Health Research and Development Agency, Health Ministry of Republic Indonesia. We also thank for Research Institute of Palangka Raya University, which has facilitated the permission and administration of research, and to management of Muhammadiyah University of Palangka Raya, for the lending of laboratory facilities and technician staff who helped us a lot.

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