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Hedyotiscorymbosa (L.) Lamk - The Potential Inhibitor Extract of Oral Cancer Cell Progressivity in Benzopyrene Induced Rattus Novergicus

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Abstract

Hedyotiscorymbosa (L.) Lamk produces ursolic acid, an anti-proliferative cancer cell agent which inhibits the progressivity of oral cancer by inhibits proliferation and angiogenesis of cancer cells thus induces cancer cell apoptosis.

To determine the potency of Hedyotiscorymbosa (L.) Lamk in different doses (375, 750, and 1500 mg/kg).

25 Rattus novergicus constituted the research sample. They were divided into four groups:

Treatment Group 1 receiving a 375mg/kg dose, Treatment Group 2 administered a 750 mg/kg dose, Treatment Group 3 given a 1500mg/kg dose and Treatment Group 4 receiving only distilled water. Oral cavities were induced intramuscularly by 8mg/kg doses of benzopyrene twice a week for four weeks to induce cancer. Hedyotiscorymbosa (L.) Lamk was administered orally for 10 days.

All samples were acclimatized to allow performance of HPA examination. HE was used to examine the proliferation of cancer cells. IHC was used to determine caspase-3. Data analyzed by ANOVA.

There were significant differences in cancer cell and capillary proliferation between the control and treatment groups. The most significant decrease in cancer cells proliferation and highest caspase-3 expression was found in the group receiving a dose of 750 mg/kg.

Hedyotiscorymbosa (L.) Lamk extract could decrease cancer cell and capillary proliferation, thereby increasing apoptosis.

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Keywords: Hedyotiscorymbosa (L.) Lamk, oral cancer, apoptosis, benzopyrene.

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Introduction

Cancer is the most common cause of mortality and morbidity around the world. In Indonesia, it ranks as the fifth largest cause of mortality.[1] In the United States, 3% of the 1 million annual cases are related to cancer of the oral cavity and oropharynx.[2] Cancer is the third leading cause of death in the United Arab Emirates (UAE). Data from the UAE ministry of health indicates that cancer accounts for approximately 500 death per year.[3]

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Head and neck cancer most common cancer worldwide. The most common type of Head and Neck cancer was Oral Squamous Carcinoma almost 90% of the cases.. In Indonesia, this type of cancer is common. The late diagnosis of cancer is about more than 14,000 cases were suffered.[4] A range of intensive cancer treatments have been undertaken including; surgery, chemotherapy, radiation therapy, immunotherapy, and pharmacotherapy. Thus, approaches of new surgical techniques, adjuvant therapy and molecular targeted therapy are urgently needed as to increase the number of cancer patient survivals. RNR has an essential role in converting ribonucleoside diphosphate to 2-deoxyribonucleoside diphosphate to maintain homeostasis of nucleotide pools. RNR in DNA synthesis and repair had found to be an attractive target for anticancer agents.[5] However, no definitive results exist, a fact rendering alternative

cancer treatments very important.[6] One of these, Hedyotiscorymbosa (L.) Lamk, is widely accepted to be a potential anti-cancer agent. Febriansah *et al.* stated that Hedyotiscorymbosa (L.) Lamk extract produces anti-proliferative effects against liver cancer cells, yet its impact on oral cavity cancer remains unknown.[7]

Free radical compounds are highly reactive to body cells causing mutations in "proto-oncogenes" and "suppressor genes" which contribute to the regulation of cell proliferation and apoptosis. This means that if there is a mutation in the gene, proliferation will be uncontrolled and apoptosis will be inhibited, thereby, increasing the likelihood of cancer occurring.[8,9,10] Cancer can also develop its own blood vessels, or angiogenesis, as a means of becoming more progressive. This results in the imbalance between cell proliferation and apoptosis, as well as the angiogenesis process, both of which accelerate cancer's progressiveness.[10,11,12]

Hedyotiscorymbosa (L.) Lamk is generally accepted to be a wild plant. It contains a group of terpenoid compounds that have potential as an herbal drug. These compounds contain ursolic acid that, at a dose of 750 mg/kg can inhibit liver cancer.[13,14] Ursolic acid has the potential to interfere with cell cycle regulation by inhibiting it between phases G to S, it restricts cell proliferation.[15] In addition, one particular piece of research posits that ursolic acid is capable of creating progressive barriers to gastric cancer by rendering cyclin/CDKS inactive. Ursolic acid also induces apoptosis in the extrinsic pathway through TRAIL or necrosis tumor factor-related apoptosis that induces ligand[16]. TRAIL works specifically in inducing apoptosis in cancer cells, but not in normal ones. Ursolic acid then activates caspase whose function is that of a pro-apoptosis enzyme[17]. In angiogenesis, the ursolic acid content of Hedyotiscorymbosa (L.) Lamk has a role in inhibiting ERK pathwayand the expressions of VEGF and bFGF.[18,19]
This research aims to determine the potency of Hedyotiscorymbosa (L.) Lamk extract as an inhibitor of oral cancer cells and in the anti-proliferation of such cells by increasing apoptosis through caspase-3 expression and decreasing the number of new blood vessels. It is hoped that the research reported here, ultimately, represents a contribution to the development of oral cancer treatment.

Materials and methods

The research was a laboratory-based experimental investigation incorporating posttest-only control group design approved through ethical clearance from the Committee of Ethical Clearance of Health Research, Faculty of Dentistry, Universitas Airlangga (No. 127/ KKEPK.FKG/IX/2014). There were four groups: Treatment Group 1, Treatment Group 2, Treatment Group 3, and the Control Group. The research sample was a 2-3 month old, healthy, male Rattus Novergicus weighing 160-200 grams. During the investigation, each treatment was replicated on six occasions. Hedyotiscorymbosa (L.) Lamk extract was administered in three distinct doses: 375 mg/kg, 750 mg/kg, and 1500 mg/kg.

Data obtained was analyzed using the normal distribution of one sample. A Kolmogorov-Smirnovtest, Levene's homogenity test was then conducted to establish whether the variant data was homogeneous with p = 0240 (p> 0.05). The distribution of the data was confirmed as normal and homogeneous. Therefore, the data was subsequently tested using One-Way ANOVA. Based on the results, there was a significant difference to the value of p = 0.000 (p <0.05) which led to a Post Hoc Test being conducted by means of a Tukey HSD.

Preparation of Hedyotiscorymbosa (L.) Lamk extract

Hedyotiscorymbosa (L.) Lamk leaves were dried and pulverized in a blender, before being filtered to produce a powder. A large column of the resulting powder was soaked in 96% ethanol by means of a macerator tool over a period of 72 hours. The solvent was then removed and evaporated, at 40oC, within a rotary vacuum evaporator to produce its extract. The latter was then mixed with distilled water at a ratio of 1:1.

Oral cancer induction and Hedyotiscorymbosa (L.) Lamk extract treatment

The cancer was induced by administering benzopyrene to all sample groups. Benzopyrene, in the form of a powdered dose of 8 mg/kg, was dissolved in olivarum olium at a ratio of 2:11 17. The introduction of 0.7 ml benzoyrene was effected by injecting it with a syringe 2-3 mm in depth into the intraoral buccal mucosa of the rats over a period of four consecutive weeks.

After the cancer had been induced, Hedyotiscorymbosa (L.) Lamk extract was added, together with distilled water, to the treatment groups in the following approximate amounts; Treatment Group 1 - 375 mg/kg, Treatment Group 2 - 750 mg/kg, and Treatment Group 3 - 1500 mg/kg. Meanwhile, the Control Group was administered distilled water alone. The sample was injected twice a week. The extract was managed orally in the amount of 0.17ml every day for a period of 10 days18

A tissue fixation process was conducted in two stages. First, the tissue was soaked in Buffered Neutral Formalin solution (10% BNF with pH 6.5 – 7.5) at a ratio of 1:10. An auto technician processed the tissue. 4µm-thick paraffin blocks were cut. Cancer cell proliferation and capillary examination were conducted by means of HE (Hematoxyllin eosin) staining technique. Expression of caspase-3 used with caspase-3 monoclonal antibody was examined by means of immunohistochemistry staining. The counterstain was used as hematoxyllin (n=6 for each group).

Results

In this research, 24 mice developed mandibular gland cancer. The average degree of cancer cell proliferation in the control and treatment groups is shown in Figure 1. Based on the data, it seems that the average number of cancer cells in the Control Group was the highest, while that of Treatment Group 2 was lower than those of Treatment Groups 1 and 3 (Table 1).

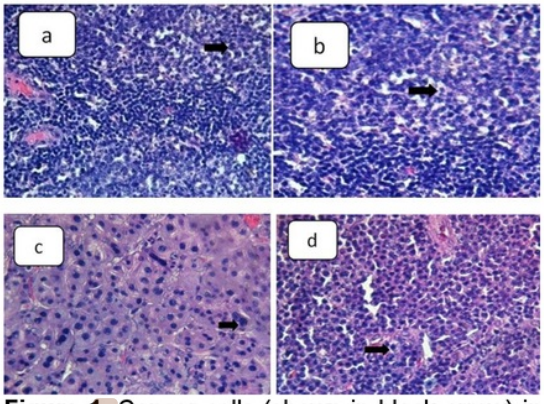

Figure 1. Cancer cells (shown in black arrow) in control (a), treatment 1 (b), treatment 2 (c), and treatment 3 (d) group.

No	Group (each group n=6)	Average
1	Control	83.83
2	Treatment 1	34.67
3	Treatment 2	17.33
4	Treatment 3	43.17

Table 1. The cancer cell numbers in each group.

It seems that the average number of new blood vessels in the Control Group was far higher than that of the treatment groups, with Treatment Group 2 being the lowest (Figure 2 and Table 2).

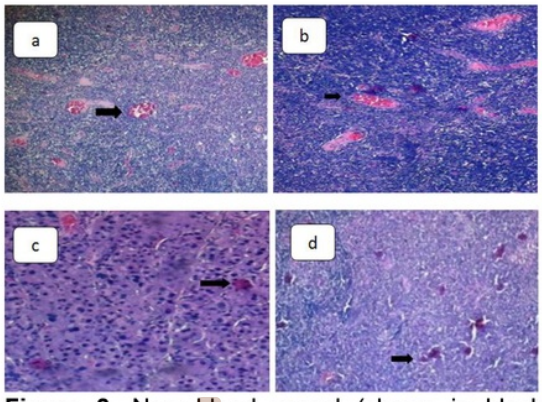

Figure 2. New blood vessel (shown in black arrow) in control (a), treatment 1 (b), treatment 2 (c), and treatment 3 (d) group.

No	Group	Average
1	Control	54.33
2	Treatment 1	32.33
3	Treatment 2	21.83
4	Treatment 3	45.67

Table 2. The number of new blood vessels in each group.

The ethanol extract of Hedyotiscorymbosa (L.) Lamk at a dose of 750 mg/kg significantly inhibited the formation of new blood vessels in Treatment Group 2. Thus, a dose of such volume could be considered to be the most effective when compared to Treatment Group 1 and 2's respective doses of 375 mg/kg and 1500 mg/kg.

The average number of cancer cells expressing caspase-3 across all groups is shown in Figure 3. Based on the data shown there, the highest average number of cancer cells expressing caspase-3 was in the apoptosis of Treatment Group 2 (see Table 3).

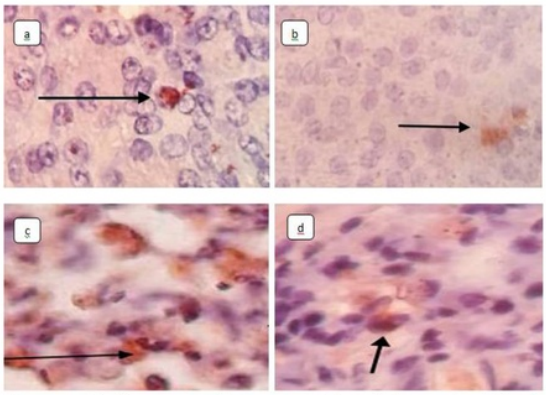

Figure 3. Caspase 3 expression (shown in black arrow) in control (a), treatment 1 (b), treatment 2 (c), and treatment 3 (d) group.

No	Group	Average
1	Control	11.67
2	Treatment 1	6.67
3	Treatment 2	24.17
4	Treatment 3	18.30

Table 3. The number of caspase-3 expression in each group.

Discussion

Cancer is considered to be the leading cause of mortality and morbidity in the world. Cancer cells can invade biological tissues by invasion and metastasis. Abnormal protein function can damage DNA and p53 gene mutation, controlling cell proliferation. Therefore, uncontrolled cell proliferation and inhibited apoptosis can lead to cancer. However, normal cells will only develop into malignant ones if the condition of the body's immune system deteriorates. In other words, the immune system tends to help the process of initiation, promotion and progression in cancer formation.[20,21,22]

The research presented here was purely experimental in nature and intended to discover the benefits of Hedyotiscorymbosa (L.) Lamk extract in preventing and curing cancer. According to Febriansah et al, Hedyotiscorymbosa (L.), Lamk extract contains ursolic acid which plays an anti-proliferative role with regard to liver cancer cells. In addition, according to Jaki et al, ursolic acid acts as an immunomodulator, anti-inflammatory, and antioxidant. Therefore, ursolic acid could potentially play a major role in the development of cancer therapies.[16]

During the research project reported here, cancer developed in the lymph gland. Informed opiniongenerally accepts that the immune system exerts a greater of lesser degree of influence on the incidence of cancer.[23] The injected benzopyrene represented a highly reactive compound potentially capable of suppressing the immune system. Therefore, it could lead to cancer in the sub-mandibular gland.[24,25].

Benzopyrene is an organic compound with a specific molecular formula, $C_{20}H_{12}$, falling within the extremely toxic class of polycyclic aromatic hydrocarbons (PAH). In the living body, benzopyrene intercalates into Deoxyribo Nucleic Acid (DNA) that can, potentially, interfere with the process of DNA transcription. Therefore, the disruption of the transcription process could serve as a tumor initiator and mediator.[26,27]

Furthermore, Benzopyrene demonstrates structural similarities with nucleobases such as adenosine, thymine, guanine and cytosine. This, conceivably, makes it easy for benzopyrene to insert itself into DNA strands.[28,29] As a result, DNA function will be disrupted and if the damage cannot be repaired the cell will give rise to cancer.

Benzopyrene is commonly known as a hydrophobic compound lacking methyl structure or other reactive properties to be converted to a more polar compound. It is very difficult for the body to excrete this compound, causing accumulation in body tissues such as the lymph, adipose, liver and kidney tissue. As a result, exposure to high levels of benzopyrene would cause the suppression of the immune system, giving rise to cancer.[30]

In general, the result shows that the average number of cancer cells in the group treated with Hedyotiscorymbosa (L.) Lamk extract is lower than that in the control group. This contrast was due to the role of Hedyotiscorymbosa (L.) Lamk extract that acts as an anti-proliferation agent. Hedyotiscorymbosa (L.) Lamk extract contains ursolic acid that is considered to be an anti-proliferant of cancer cells through the inhibition of the STAT3 pathway (Signal Transducers and Activators of Transcription-3).[31]

Ursolic acid binds to estrogen receptors on the macrophage surface which then activates an intracellular transduction signal and causes the phosphorylation and degradation of IkB

(Inhibitor k Beta). The degradation of IkB could enable NF-kB (Nuclear Factor kappa B) to be translocated into the nucleus. Once there, NF-kB induces the transcription of genes that control various chemokines, immune receptors and cytokines such as IL-12. The induction of IL-12 stimulates the production of IFN-γ. However, it could also prevent the proliferation of Th2,which produces IL-10 through a process of homeostasis.[31,32]

IFN-γ could re-activate macrophages that give rise to the phagocytosis of cancer cells. Meanwhile, the reduction of IL-10, which is a cytokine that works on STAT3 pathways, would inhibit such pathways through JAK-2 (Janus Activated Kinase-2).[33] Ursolic acid is actually capable of inhibiting JAK-2, thereby preventing the phosphorylation of proteins used in the activation of STAT3. The inhibition of STAT3 pathways would then lead to the disruption of the regulation system of gene products (such as cyclin D1, Bcl-2, Bcl-xl, surviving, Mcl-1, and vascular endothelial growth factor) and the modulation of cell proliferation.[17,33]

STAT3 is a signal transduction that acts as a regulator of gene products such as cyclin D1. Thus, the inactivation of STAT3 pathways would lead to the disruption of the nuclear translocation rendering it unable to play a role in regulating cyclin D1 and modulating cell proliferation. Cyclin D1 is an active form of Cyclin Dependent Kinase (CDK) required by cells to perform mitosis and plays a role in the G1 phase whose purpose is to prepare for the DNA replication phase. When this phase is interrupted cell proliferation could be inhibited.[33,35]

In the G1 phase, the p53 gene was involved in the transactivation of the p21 protein. The function of the p21 gene is to suppress the activity of CDK-Cyclin complexes. A checkpoint occurred at the end of the G1 phase before entering the S phase. Its function was to create the possibility for the cells to repair themselves (apoptosis). Apoptosis is recognized by the increase of caspase-3 expression, known as the executor of dead cells. The formation of new blood vessels could be decreased by inhibiting ERK (Extra Celular Signal Regulatory Kinase), causing a reduction in HIF-α (hypoxia inducible factor). Finally, apoptosis creates VEGF barriers resulting in the newly formed blood vessels being few in number.[36]

Conclusions

The conclusion of this research is that ethanol extract of Hedyotiscorymbosa (L.) Lamk could conceivably reduce the progression of oral cancer in the lymph gland of wistar strain rats induced by benzopyrene with the most effective dose being one of 750 mg/kg.

Further research is required incorporating the use of pure ursolic acid compounds to decrease the progression of cancer in the oral cavity. Additional research also needs to be conducted, regarding to the efficacy of ursolic acid in enhancing immune system as an immunomodulator.

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Declaration of Interest

The authors would like to declare there is no conflict of interest in this research.

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PAGE 1

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PAGE 4

PAGE 5

PAGE 6