

POTENTIAL OF GREEN LEAVES CINCAU (*Premna oblongifolia*, Merr) FROM INDONESIA AS ANTI CANCER

Emma Rochima^{1*}, Fransiska R. Zakaria², Maggy T. Suhartono², Nurjati C. Siregar³

¹Graduate School of Food Science, Bogor Agricultural University

²Department of Food Science and Technology, Bogor Agricultural University

³Faculty of Medicine, Indonesia University

*Corresponding author: Emma.Rochima@Gmail.com

ABSTRACT

The aim of the review were to introduce the Green Leaves Cincau *Premna oblongifolia* Merr from Indonesia which potential as anti cancer. The content of green leaves cincau fiber of 29.37%, the alkaloids of 0.98% and 2.12% total phenols. This compound is thought to provide a pharmacological effect. The alkaloids in the root *bisbenzylisoquinoline* have cytotoxic activity, chemoprotective potential and act as an antioxidant because it can inhibit lipid peroxides in nonenzimatic. The leaves extract of green jelly is as immunostimulant at low concentration stimulate cell proliferation of lymphocytes in vitro. Also reported that leaves extracts of green jelly has a cytotoxic effect on K-562 cancer cells and hela cervix cancer cell in vitro, and can inhibit proliferation of K-562 cancer cells between 61-95% and hela cervix cancer in 31%.

Keywords: green, gel, leaves, *Premna oblongifolia*, functional, food

INTRODUCTION

Cancer is a disease cause of death in the United States. In 2001 the number of cancer death of about 553,768 or 22.9% deaths caused by breast cancer for women in 2001 by 272,810 or by 15% (USA Cancer Statistics, 2004). In Indonesia, there is a tendency increasing number of cancer patients from year to year. In 1999 cancer 7,731 men (35,32%), while the women for 14,116 people, (64,49%) [1].

Breast cancer ranked second only to cervical cancer. Most cancer patients in Indonesia have gone to the doctor when the illness was in advanced stages. Difficult to handle, and require complex actions, time-consuming and expensive, while the results are disappointing the treating physicians, patients, and families. In fact, cancer is not a disease that can not be cured. Most cancers can be overcome if the steps appropriate treatment and performed at an early stage [2]

Results for last 20 years concluded that 60-90% of cancers are related to the environment, so in theory this disease can be prevented [3]. Environment here means, that all people who interact with the food consumed, drinking, smoking and sipping, radiation, drugs and other aspects of sexual behavior. Epidemiological and laboratory studies found that dietary fat and less fiber in the diet has a role to 35-50% incidence of digestive tract cancers, breast, endometrial and ovarian. Materials drunk, inhaled (e.g. alcohol, tobacco, asbestos dust) to contribute to 22-30% for the incidence of cancer in the lung, and esophagus orofaring. Besides cancer is also caused by genetic factors, and psychogenic [4].

Many attempts were made to prevent and treat cancer. Treatments such as chemotherapy, surgery and radiation is not the preferred choice of patients for expensive cost and side effects lower body immunity, hair loss, skin and teeth become damaged [5] [6]. As an alternative for the prevention and treatment of cancer is eating healthy food from natural resources. Many researchers who have successfully revealed the efficacy of the bioactive components of plants such as green tea, fruit mengkudu, turmeric, ginger, leaves, leaf parasites.

For example, carotenoids are antioxidants that anticarsinogenik [7] [8] while the compounds *genistein* contained in soybean are cytotoxic, because it can inhibit breast cancer cell proliferation in vitro [9]. *Alkaloids*, *polyphenols*, *curcumin*, *chlorophyll*, *warfarin*, *flavon* and act as an *polyphenols* antioxidants and may reduce the incidence of cancer [10]; [11]; but the number and variety is still limited. One study that was developed at the Laboratory of Food Science and Technology, Bogor

Agricultural University was the use of green leaves cincau *Cyclea barbata* L. Miers and *Premna oblongifolia* Merr. The present review details the recent evidence supporting green leaves cincau *Premna oblongifolia* Merr in cancer. Furthermore, future research directions are discussed that may enhance our understanding of the role and regulation of this plant, which could ultimately lead to the innovative design and development of new anticancer functional food.

Green Leaves Cincau (*Premna oblongifolia*, Merr)

Cincau means of agar gel obtained from soaking the leaves of certain plants in water. Gels formed by the leaves of plants contain carbohydrates that can bind water molecules. The word 'grass jelly' comes from the Hokkien dialect sienchau commonly pronounced among Chinese in Southeast Asia [12]. Cincau own native language is actually the name of the plant (*Messona* spp.) are the subject of making this gel.

Plants cincau has divided into two types, namely green leaves cincau and black leaves cincau. They are differentiated by color, flavor, appearance, materials and making process. Two types of green leaves cincau comes from *Cyclea barbata* L. Miers and *Premna oblongifolia* Merr. [12]. Green leaves cincau made without the heating process. Green leaves cincau *Cyclea barbata* L. Miers. has easily forming gel, which is just crushed with cold water. Meanwhile, green leaves cincau *Premna oblongifolia* Merr. which requires minerals for making gel. Black cincau is made from *M. palustris* leaves with the heating process and adding other ingredients. Both is delicious, chewy and almost like jelly.



Figure 1 Green leaves cincau *Premna oblongifolia* Merr. (personal collection)

Compositon of green leaves cincau is carbohydrates, polyphenols, saponins, flavonoids, fat, and contains elements of calcium, phosphorus, vitamin B [13] and vitamin A. It contain chlorophyll and also alkaloids. Alkaloids are compounds that are used as medicinal ingredients and anticancer [14], [15]. Composition of green leaves cincau are presented in Table 1.

Tabel 1 Nutrition Value of Green Leaves Cincau *Premna oblongifolia* Merr.

Component	Concentration (% b/b)		
	a	b	c
Protein	2,39	5,46	3,81
Hydrolised Total Carbohydrate	8,41-8,93	11,94	10,48
Water	66,33-74,54	81,00	82,62
Crude Fiber	6,23-6,70	4,33	4,96
Fat	0,45-0,51	0,94	1,11

Source: ^aSunanto (1995), ^bUntoro (1985), ^cMinawati (1985) in [14]

Cincau leaves also contain high food fiber. Fiber is a component of plants, especially in the cell wall, which can not be digested by human digestive enzymes The presence of dietary fiber important for the health of our bodies, although the fiber is not including essential nutrients. Fiber

foods include starches, polysaccharides, oligosaccharides and lignin. Dietary fiber consists of plant cell walls are mainly contains three kinds of polysaccharides are cellulose, pectin and hemicellulose. Fiber also contains substances that are not carbohydrates, namely. Lack of fiber in the daily menu are positively correlated with incidence of diseases such as obesity (obesity), constipation, atherosclerosis (hardening of the fat accumulation and blood vessels), coronary heart disease, diabetes mellitus, gallstones, hypertension (high blood pressure), hemorrhoid, hernia, appendix and colon cancer [16].

Anticancer from Natural Plant

Various are known anticancer compounds derived from plants now. From *Catharanthus roseus*, was isolated two *indole alkaloid vinblastine* and *vincristine* that are used to treat a variety of lymphoma, leukemia, and various cancer such as cell lung cancer, cervical cancer, and breast cancer. Although both compounds were similar molecular structure but have different toxic properties [17].

Several other anticancer compounds derived from plants is *elliptisin* and *9-methoxy elliptisin* of intercalation *Ochrosia elliptica* between DNA base pairs. Alkaloids from the Chinese plant, *Camptotheca acuminata* is *kamptotesin* and its derivatives have a broad-spectrum activity. From *Cephalotaxus harringtonia*, obtained two compounds, namely *harringtonin* and *homoharringtonin* that can treat leukemia and solid tumors [18].

Bark of *Taxus brevifolia* was obtained *diterpen Taxol*® (*paclitaxel*) compounds, which has 20 carbon tri or tetracyclic toxic [19]. Taxol® has a mechanism of increased mitotic index in P 388 and inhibits cell growth of HeLa cells and mouse fibroblast cells in G2 and M phases of the cell cycle. These compounds can cause depolymerization of microtubules skeleton solid tumors ovarian and breast cancer [20]

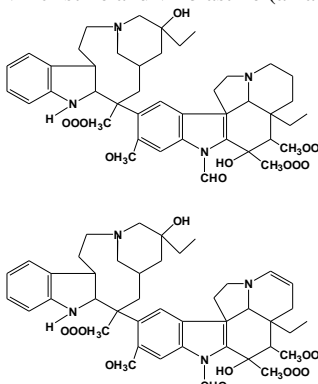
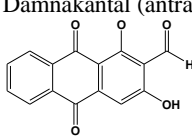
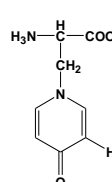
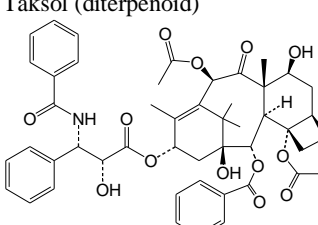
Daunomycin (daunorubicin) was isolated from *Streptomyces peucetius* in 1962 by Aurelio On Marco. Atrasiklin and adriamycin is a prototype family of antitumor antibiotics. Therefore cardiotoxic effects and other side effects, this drug is used is limited to treating solid cancer and leukemia. Antineoplastic activity of these drugs occurs due to a strong bond with the target cell's DNA. Doxorubicin and antrasiklin epirubisin are examples used to treat breast cancer and is commonly used in combination with other chemotherapy to reduce the risk of side effects [21].

Some natural anticancer compounds currently used as an effective anticancer include vinblastine, vincristine, etoposida, teniposida and paclitaxel. (Table 2).

Mechanisms of cancer

The formation of cancer cells through three stages: initiation, promotion, and progression, as shown in Figure 2 below. In the initiation phase, cells experiencing continuous stimulation or exposed to an initiator material. Initiation stage is a rapid process, and still reversible. Cells exposed to carcinogenic substances (initiators) to the initiated cells. These cells have mutations, resulting in changes in the DNA nucleotide sequence of the proto-onkogene so that there are changes in gene expression / abnormal proteins, although the network still look normal with a population of euploid cells [22]. If the basic error of the formation of genes / DNA occurs in a strain, then the system of DNA repair can still take place by way of reading, cut, remove, and replace with new. But if the DNA repair system is not running there will be a mutation of DNA in daughter cells that persist, and if continued and uncontrolled will cause neoplasms.

Table 2. Natural Anticancer Compound From Plant

No.	Sources	Bioactive compound and chemical structure	Mechanism of action
1.	<i>Catharanthus roseus</i>	Vincristine and vinblastine (alkaloids) 	Antimitosis, microtubule inhibition
2.	<i>Morinda citrifolia</i>	Damnacantal (antrakuinon) 	Inhibitor tyrosin kinase
3.	<i>Leucaena sp.</i>	Mimosin (amino acid non protein) 	Antimitosis, inhibition of cycle cell at G1 phase
4.	<i>Taxus brevifolia</i>	Taxol (diterpenoid) 	Prevention of depolymerization of microtubule skeleton

Source: [23]

The next stage is the stage of promotion. At this stage the same exposure to carcinogens or other substances cause changes in cell chromosomes and the DNA was initiated, resulting in changes in protein expression due to DNA sequence changes in cells undergoing transformation. The end result is exposure of the proto-oncogene promoter into an oncogene. Causing oncogene oncoprotein expression. Oncoprotein triggers cell growth becomes abnormal, do not follow the rules of normal growth, divide and grow in autonomy, uncoordinated and uncontrolled.

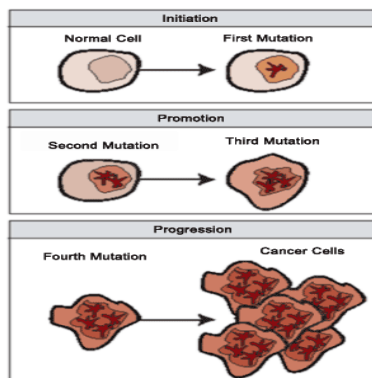


Figure 2. The process of transforming normal cells into cancer cells [24]

Stage of promotion is a process that lasts a long time, is irreversible due to exposure to the promoter material is continuously or repeatedly. Promoter is the trigger changes in expression of genetic information. This change is characterized by increased DNA synthesis and replication. Cells that initiated or transformed cells into cells of carcinoma in situ. At this stage of progression of the cancer cell phenotype changes and the clinical examination of the tumor mass was palpable in the form of a lump. At this stage, malignant neoplasm cell able to conduct infiltration, spread evenly among the cells surrounding tissues and can spread throughout the body (metastasis). Stages of progression may be a change of form of benign tumor (benign) to malignant tumors (malignant) followed by rapid cell growth that can kill the host, invasive, penetrate healthy tissues (metastasis) and increase genetic instability.

Green Leaves Cincau (*Premna oblongifolia*, Merr) as Functional Food

Functional food is a term for food that can prevent and treat disease. In addition to the natural nutritional value, functional foods also contain the proper balance of composition that can help us in improving the function and effectiveness of various aspects of our lives including our direct help prevent and cure diseases. [25]

Cincau was usually used as medicine by Indonesia people for a lowering heat loss, fever, abdominal pain (stomach nausea), diarrhea, mouth sores, dysentery, cough, digestive disorders and the prevention of high blood pressure. Substances called *alkaloids bisbenzylisoquinoline* and *S, S-tetandrin* contained in the leaves of cincau was a bioactive compounds in preventing and treating heart blood vessel disease (cardiovascular), high blood pressure, and gastric diseases. Consumption of cincau jelly for patients with heart disease are highly recommended. Green leaves cincau *Premna oblongifolia* Merr. can be used to treat various diseases, ie: gastric inflammation and high blood pressure. Efficacy of green leaves cincau *Premna oblongifolia* Merr. which have been studied include allergy in mice, anticancer, increasing the number of lymphocytes (reducing the number of free radicals, increase the antioxidant capacity of lymphocytes and is not toxic to the body [16].

Cincau contains alkaloids *bisbenzylisoquinoline* and *S, S-tetandrin*. The alkaloid is a natural product derived plants that have anticancer or antitumor properties. Alkaloids are widespread in plants. Alkaloids are a large group of plant secondary metabolites composed of various types of different chemical compounds with its diversivity as a drug. In principle, the alkaloid has a ring structure with nitrogen-containing substance. Many alkaloids which have psychotropic properties, which are soothing and potential as a narcotic. Several other alkaloids are also very toxic. Most of the alkaloids are cytotoxic in inhibiting the growth of several types of cancer and leukemia. Alkaloids can also be antiviral, but alkaloid is more rarely behave as immunomodulatory [14].

Several studies in vitro on the green leaves cincau in Indonesia have been conducted since 2000 by researchers from Bogor Agricultural University. Effect of green leaves cincau on the production of free radicals of mice peritoneal macrophages [26], whereas the effect on cancer cell

proliferation and cell flow of blood lymphocytes edge of humans have been studied respectively [27] by Ananta E. et al, 2000 and [28]U.S. Pandoyo., et al, 2000.

In 2003 research of green cincau *in vivo* to C3H mice to investigate antioxidant capacity of lymphocytes [29 and antioxidant enzyme activity and tumor growth [30 and [31]. In addition, the study bioavailabilitas leaf green grass jelly on rat liver and plasma studied [32]. Effect on cytochrome P-420 content and activity in rat liver GSPx has investigated [33] too and its influence on levels of B-carotene in rat liver investigated by [34].

Research on the anticancer activity of green leaves cincau *Premna oblongifolia* Merr. have been carried out on C3H mice. Research carried out by feeding mice with a liquid extract of green grass jelly *Premna oblongifolia* Merr. dose of 7.25 g / l and 5.3 g / l per day for four weeks. Furthermore, cancer cells were injected. Observations were carried out by 57 weeks. The results showed that tumor cells which die in C3H mice as much as 37.86%. The extract of green leaves cincau in mice, shown to kill tumor cells very well. Potential green grass jelly was tested in a way described in the four types of cancer cells, the cells of blood cancer (leukemia), cervical cancer, lung cancer and breast cancer. Leaf extract of green grass jelly can kill blood cancer cells with both around 55-90%, whereas other cancer cells around 60%. This shows that green grass jelly containing bioactive components of cancer cell killer. Green grass jelly is also capable of removing harmful substances trigger cancer [35].

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