



POTENCY OF SOURSOP LEAF EXTRACT AND CURCUMIN WITH MAGNETIC AND MUCUS-PENETRATING NANOPARTICLE AS COLORECTAL CANCER ALTERNATIVE THERAPY

POTENSI EKSTRAK DAUN SIRSAK DAN KURKUMIN DENGAN NANOPARTIKEL MAGNETIK DAN PENETRASI MUKUS SEBAGAI TERAPI ALTERNATIF KANKER KOLOREKTAL

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ABSTRACT

Background: Colorectal cancer is the second leading cause of death in the world. Currently, resection and adjuvant chemotherapy are the main therapies for colorectal cancer. Resection is an invasive procedure and chemotherapy often causes side effects due to non-specific work targets.

Purpose: This study examines the potential of soursop leaf extract and curcumin with magnetic and mucus-penetrating nanoparticles as an alternative therapy for colorectal cancer. **Review:** Soursop leaf extract has acetogenin agent as an anti-tumor, anti-inflammatory, and cytotoxic agent that acts specifically on target organs. Curcumin from turmeric extract has antioxidant, anti-inflammatory, antimutagenic, anti-angiogenic, and anti-cancer effects. Curcumin works molecularly on cyclooxygenase-2 (COX-2) to prevent inflammation, thereby inhibit the growth of cancer cells and reducing the risk of metastasis. Curcumin also plays a role in the inhibition of nuclear factor κ -light-chain-enhancer of activated B (NF- κ B) cells, thus inhibits carcinogenesis. For drug delivery, magnetic nanoparticles and mucus-penetrating nanoparticles could be used. Mucus-penetrating nanoparticles are more resistant to mucus degradation because they can avoid mucoadhesive effects, penetrate the mucus adherent layer, and are easily absorbed by the intestinal epithelium. **Conclusion:** Soursop leaves, curcumin, magnetic nanoparticles, and mucus-penetrating nanoparticles are potential to be an alternative therapy for colorectal cancer.

ABSTRAK

Latar belakang: Kanker kolorektal merupakan penyebab kematian kedua terbesar dengan jumlah insiden terbanyak ketiga di dunia. Saat ini, reseksi dan kemoterapi *adjuvan* merupakan terapi utama kanker kolorektal. Reseksi merupakan tindakan invasif dan kemoterapi sering menimbulkan efek samping karena target kerja yang tidak spesifik. **Tujuan:** Untuk mengetahui potensi daun sirsak dan kunyit dengan nanopartikel magnetik dan penetrasi mukus sebagai terapi alternatif kanker kolorektal. **Tinjauan pustaka:** Ekstrak daun sirsak memiliki zat asetogenin sebagai sifat anti-tumor, anti-inflamasi, dan aktivitas sitotoksik yang bekerja spesifik pada target organ. Kurkumin pada kunyit yang memiliki efek antioksidan, anti-inflamasi, antimutagenik, anti-angiogenesis, dan anti-kanker. Kurkumin bekerja secara molekuler pada siklooksigenase-2 (COX-2) untuk mencegah inflamasi sehingga menghambat pertumbuhan sel kanker dan menurunkan risiko metastasis. Kurkumin juga berperan dalam penghambatan *nuclear factor κ -light-chain-enhancer of activated B cells* (NF- κ B) sehingga menginhibisi karsinogenesis. Sebagai pengantar obat, nanopartikel magnetik dan nanopartikel penetrasi mukus dapat digunakan. Nanopartikel penetrasi mukus lebih resisten terhadap degradasi mukus karena mampu menghindari efek mukoadhesif, melakukan penetrasi hingga ke lapisan mukus adherens, serta mudah diabsorpsi oleh epitel usus. **Kesimpulan:** Ekstrak daun sirsak, kurkumin, nanopartikel magnetik, dan nanopartikel penetrasi mukus potensial sebagai terapi alternatif kanker kolorektal.

Literature Review
Study Literatur

ARTICLE INFO

Received 03 February 2021

Revised 15 April 2021

Accepted 12 March 2022

Online 28 March 2022

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Keywords:

Acetogenin, Curcumin, Magnetic nanoparticles, Mucus-penetrating nanoparticles, Colorectal cancer

Kata kunci:

Daun sirsak, Kurkumin, Nanopartikel penetrasi mukus, Nanopartikel magnetik, Kanker kolorektal



INTRODUCTION

Colorectal cancer is a disease that still becomes a problem in the world. In 2018, colorectal cancer ranks third with the highest incidence of 1.8 million cases, after lung cancer and breast cancer. This large incidence causes mortality and morbidity to the point of making colorectal cancer the second leading cause of death with an estimated 862 thousand cases in the same year (WHO, 2018). The incidence of colorectal cancer has several risk factors, including age, poor lifestyle such as low intake of fiber and calcium nutrients, and environmental factors, or a combination of the two. The incidence of colorectal cancer is not differentiated by sex (WHO, 2019). Colorectal cancer originates from the abnormal proliferation of the colon and rectum. This abnormal activity is caused by the inactivation of several genes that function in suppressing tumors and repairing damaged DNA and the activation of the oncogene. The process of tumor formation is referred to as carcinogenesis which is divided into 3 phases, the initiation phase (changes in normal cells to cells initiated by cancer cells), the promotion phase (from initiated cells to pre-neoplastic cells), and the progression phase (from pre-neoplastic cells to be a neoplastic cell). Cancer is initiated by the presence of oxidative stress and chronic inflammation. This inflammation plays an important role in the passage of normal cells into cancer cells by giving signals to cells to proliferate continuously and inhibit apoptosis. Cytokines from the inflammatory process act as growth factors and angiogenesis, causing cells to proliferate rapidly and undergo a promotion phase. Leukocytes also produce cytokines and angiogenesis factors such as matrix-degrading proteases. Tumor-infiltrating lymphocytes secrete a substance called matrix metalloproteinase-9 (MMP-9). These two matrix substances cause tumor proliferation, angiogenesis, and invasion. In a recent study, the principle was found that the inflammatory process could increase the inflammatory mediator NF- κ B which played a role in tumor growth and the progression phase of carcinogenesis (Tong *et al.*, 2016). The main therapies for colorectal cancer currently developed are resection and *adjuvant* chemotherapy. Resection is an invasive procedure and requires anaesthesia during the operation. The chemotherapy agents most commonly used are 5-fluorouracil, oxaliplatin, and irinotecan (Jabalera *et al.*, 2019). These anticancer drugs often work non-specifically, causing side effects such as hair loss, nausea, and vomiting (Cisterna *et al.*, 2016). Other side effects of chemotherapy include anorexia, changes in perception of smell and taste, constipation, stomach cramps, or even malabsorption (Indrawati and Simbolo, 2018). With so many side effects, the chemotherapy process sometimes does not give significant results because the work target is not specific and can affect the surrounding normal cells

(Indrawati and Simbolo, 2018). In further studies, long-term chemotherapy plays a role in the development of hypothyroidism and causes neuropathy (Yajid *et al.*, 2018).

According to this situation, an effort is needed to develop new drugs from nature that have been empirically tested in a disease in the hope of producing drugs that have milder side effects, especially in the chemotherapy process of colorectal cancer. This literature study aims to determine the potential of soursop leaf extract and curcumin with drug introduction in the form of magnetic and mucus-penetrating nanoparticles as an alternative therapy for colorectal cancer.

LITERATURE STUDY

Soursop (*Annona muricata* L.) is part of the *Annonaceae* family. Based on the previous research, soursop leaves contain *acetogenin*. *Acetogenin* has the potential to be biologically active as an antitumor (Indrawati *et al.*, 2017), reduces tumor size, and minimizes side effects of a disease, such as reducing pain (Sulistyoningrum *et al.*, 2017). Turmeric Extract (*Curcuma longa*) has an active constituent called curcumin. Curcumin plays a major role in being an anti-inflammatory, antimutagenic, anticancer, and antioxidant property that plays a role in inducing the apoptotic process. Curcumin activity suppresses COX 2, 5-lipoxygenase, AP-1 and NF- κ B that can make down-regulation of matrix metalloproteinase 9 (MMP 9) expression, inhibition of proinflammatory cytokines (IL-6, IL-8, IL-10), and free radicals (ROS), thus prevents mutations and inflammation that play an important role in the initiation phase of carcinogenesis.

Curcuma longa or commonly known as turmeric is a native plant from India, including the oldest spice plant group that is widely cultivated in the Asian region, particularly in the Southeast Asian region. In everyday life, besides being used as a spice in cooking, it can also be used as medicine because of the substances contained therein (Karlłowicz-Bodalska *et al.*, 2017). Turmeric is the major source of the curcumin polyphenols (Hewlings and Kalman, 2017). Curcumin is an active constituent contained in *Curcuma longa*. Curcumin plays a major role in being an anti-inflammatory, anti-mutagenic, and anti-cancer agent (Nikmah, 2019).

Curcumin also has antioxidant properties that play a role in inducing the apoptotic process (Giordano and Tommonaro, 2019). As an antioxidant, curcumin could inhibit COX 2 enzyme and 5-lipoxygenase. When both of them were inhibited, the inflammatory process in the beginning of colorectal cancer's pathophysiology had been suppressed. Curcumin could also suppress several transcription factors such as the nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) and activator protein 1 (AP-1) (Wong *et al.*, 2019).

To reduce side effects, the dosage setting, the frequency of administration, and the duration of the drug administration cycle are based on the patient's needs. However, personalized medicine may result in different blood circulating amounts and cause resistance to cancer cells (Cisterna *et al.*, 2016; Jabalera *et al.*, 2019). Therefore, a specific drug is needed to improve colorectal cancer therapy (Cisterna *et al.*, 2016)

Magnetic nanoparticles in the form of Fe₃O₄ can be used as a diagnostic tool and a therapeutic agent. Recently research is conducted because it is reported as having minimum toxicity in human subjects (Jabalera *et al.*, 2019). Apart from magnetic nanoparticles, another nanoparticle that can be used as drug delivery in the gastroenterohepatology system and has the right mode of action for the pathophysiology of colorectal cancer is mucus-penetrating nanoparticles. Cancer treatment is a long term treatment so oral administration is preferred by the patients. Mucus-penetrating nanoparticles will help the intestine to absorb better and thus provide a more effective drug delivery (Lu *et al.*, 2016)

RESULT AND DISCUSSION

The potency of soursop leaf extract (*Annona muricata L.*) as a substitute for chemotherapy in colorectal cancer

Acetogenin, a secondary metabolite product of soursop leaf, is mostly found in soursop leaves. Soursop leaf extract has various phytochemicals, there are alkaloids, saponins, flavonoids, coumarin, lactones, anthraquinones, tannins, glycosides, phenols, and phytosterols (Sulistyoningrum *et al.*, 2017). *Acetogenin* has the potential to be an anticancer and anti-inflammatory agent which is required for colorectal cancer therapy.

Acetogenin from soursop leaves extract (*Annona muricata L.*) is an in vitro anticancer in liver cancer cells, lung cancer, breast cancer, prostate cancer, colon cancer, and spleen cancer (Setyorini *et al.*, 2016). Cancer cells need a lot of energy or ATP because of their fast growth. *Acetogenin* will attach to cell wall receptors and damage ATP in the mitochondrial wall. Energy or ATP production in cancer cells stops and ends in cancer cell death due to a lack of energy.

Acetogenin is a selective agent. *Acetogenin* only attacks cancer cells that have excess amount of ATP without disturbing normal cells and cells with normal amount of ATP. *Acetogenin* also has toxicity activity by inhibiting the mitotic phase G1, so the cancer cell proliferation will stop (Jabalera *et al.*, 2019) and trigger apoptosis in HT-29 and HCT-8 cells (Indrawati *et al.*, 2017; Qazi *et al.*, 2018; Sulistyoningrum *et al.*, 2017). This toxicity is stronger in cell tumors than in normal cells (Indrawati *et al.*, 2017; Setyorini *et al.*, 2016).

Research by Indrawati (2017), showed soursop leaf extract activity in DLD-1 cells (human colorectal adenocarcinoma type C Dukes tissue), COLO 205 (Dukes

human colorectal adenocarcinoma tissue type D), and normal cell as control by using Human Embryonic Kidney (HEK) (Indrawati *et al.*, 2017). From the study, there was a decrease in DLD-1 and COLO 205 cells without decreasing the HEK cells as normal controls. Soursop leaf extract could inhibit the proliferation of colorectal cancer cells. Also, soursop leaf extract did not inhibit the activity of normal cells. This study also determined the effect of soursop leaf extract on nutrition and BMI of colorectal tumor post-resection patients. The patients were divided into 2 groups, the trial group consuming 300 mg of soursop leaf extract supplements and the control group consuming maltose as a placebo. The results of the study indicated there were no significant differences in the trial group and the control group, which means that soursop leaf extract did not affect appetite or the process of absorption of food in the body (Indrawati *et al.*, 2017).

Apart from being an anticancer agent, the soursop leaf extract is also known as an anti-inflammatory agent. The place where cancer cells grow is where cell inflammation takes place, namely cells with high amount of the enzyme cyclooxygenase. The mechanism of action of flavonoids in soursop extract leaf is inhibiting the enzyme cyclooxygenase (COX-2). This enzyme will reduce the spread of cancer cells (Soekaryo *et al.*, 2016). Flavonoid also inhibits pro-inflammatory cytokines such as the action of NSAIDs (Qazi *et al.*, 2018). Another study related to soursop leaf extract as an anti-inflammatory agent was conducted by Indrawati (2017) in which mice was used and induced by Azoxymethane (AOM) colorectal cancer cells and Dextran Sodium Sulfate (DSS) (Indrawati and Simbolo, 2018). AOM is a genotoxic colon carcinogen in the pathogenesis and carcinogenesis of colon cancer in rodents. Meanwhile, DSS is a non-genotoxic colon carcinogen that causes colonic inflammation (colitis) in rodents or ulcerative colitis in humans. Mice were divided into 2 groups, the experimental group that intervened with soursop leaf extract and the control group without intervention.

There were no specific cell abnormalities in the histopathological of the experimental group which was given soursop leaf extract at a dose of 800 mg/kg and AOM/DSS induction. The flavonoid on soursop leaves has an anti-inflammatory and antioxidant effect that can protect cells from cancer. The flavonoid also has a cytotoxic activity that can inhibit cancer cell proliferation) (Indrawati and Simbolo, 2018). There is a difference in the histopathological features of the control group that was only induced by AOM/DSS than the experimental group. In this group, there was cell inflammation that caused colorectal preneoplasia. The presence of anti-inflammatory and antioxidant effects in soursop leaf extract can reduce cancer cell proliferation and prevent the expansion of colorectal cancer due to chronic or recurrent inflammation (Indrawati and Simbolo, 2018).

The potency of curcumin as a substitute for chemotherapy in colorectal cancer

Curcumin is an active constituent contained in *Curcuma longa*. Curcumin or diferuloylmethane with the chemical formula (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a curcuminoid compound that is stable in gastric pH. It plays a major role in being an anti-inflammatory, antimutagenic, and anticancer agent (Nikmah, 2019). It also has antioxidant properties that play a role in inducing the apoptotic process (Giordano and Tommonaro, 2019). It is known for its inhibitory activity in the action of the cyclooxygenase 2 (COX-2) enzyme, which is overexpressed in cases of colorectal cancer so that if the COX-2 enzyme is inhibited, colorectal cancer cases can be suppressed. Curcumin activity suppresses COX-2 and also 5-lipoxygenase, so that it can suppress the inflammatory process which is the main actor in the three stages of the carcinogenesis process (Uzzan and Benamouziq, 2016).

Other effects of curcumin are the ability to be a free radical scavenger, change the expression of stress genes and proteins that are at risk of angiogenesis, and can inhibit several transcription factors such as nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) and activator protein 1 (AP-1) (Wong *et al.*, 2019). Several things resulted from an inhibition of the first NF- κ B are down-regulation of matrix metalloproteinase 9 (MMP 9) expression, inhibition of proinflammatory cytokines (IL-6, IL-8, IL-10), and free radicals (ROS), thus prevent mutations and inflammation that play an important role in the initiation phase of carcinogenesis (Hashemzahi *et al.*, 2018). The second effect on inhibition of NF- κ B is the inhibition of several factors that cause angiogenesis, and the regulation of the cancer cell cycle in the promotion phase. The third effect of NF- κ B is to support apoptosis at the stage of carcinogenesis regulation. This means that inhibition of NF- κ B affects all three phases of carcinogenesis at once (Chung *et al.*, 2019; Rajitha *et al.*, 2016; Tong *et al.*, 2016). From the results of research conducted by Greil *et al.*, (2018), 300 mg/m² of liposomal curcumin given in 6 hours is the maximum dose that can be tolerated in patients with severe pre-treatment and this is the starting dose recommended for anti-cancer testing.

The way to make turmeric extract is by doing soxhletation, which is separating a component in a solid by filtering it many times in a certain solvent. Turmeric that has been powdered is oxygenated in a ratio of 1:3 to polyethylene (PE) solvent to be separated from the dregs. To separate the pulp, the turmeric powder is thinly spread with a thickness of 0.5 - 1 cm and aerated for 5–10 minutes. After the turmeric powder is free of PE, percolation (filtering) is carried out using methanol in the ratio 1:4 for 24 hours. Then, the methanol extract was concentrated on a water bath until a constant volume was obtained so that a methanol-free extract was obtained. Finally, the extract was dried with lactose to obtain a dry extract. With this procedure, the turmeric rhizome weighing 3 kg was sieved to get the powder.

The 40 g powder was dissolved and sterilized to obtain 350 ml of liquid extract. The liquid extract was then dried to obtain a dry extract weighing 7 g. Curcumin powder 2 g showed a plasma curcumin level of 10ng/mL after 1-hour consumption. If curcumin is taken together with 20mg of piperine, the bioavailability of curcumin will increase by 2000%. Concentrations of curcumin in plasma have been found to peak after 1-2 hours of intake and gradually decrease within 12 hours. Therefore, giving a dose of 8 g/day is known to produce the highest serum concentration, namely 1.75 ± 0.80 M (Shan and Iskandar, 2018)

The potency of magnetic nanoparticles as colorectal cancer therapy agent and drug delivery

Nanoparticles are less than 100 nm in size. In the gastrointestinal and hepatobiliary systems, nanoparticles are currently being studied for carrying out specific therapies. Colorectal cancer cells express carcinoembryonic antigen (CEA) as much as 98.8% than normal cells. The nanoparticles will be attached with anti-CEA, so that the drug content will work specifically on the target cells (Cisterna *et al.*, 2016). When the drug has reached the epithelial cells of the intestine, additional nanoparticles are needed to work quickly in eliminating cells that have experienced dysplasia. One type of nanoparticles that can be applied to make apoptotic cells is magnetic nanoparticles.

Magnetic nanoparticles work according to the principle of thermotherapy which utilizes magnets to move Fe₃O₄ molecules that generate energy (Chen *et al.*, 2017). To produce a cell-destroying effect, this process is called magnetic hyperthermia. Mechanical or torsional forces also result in changes in super-paramagnetic and isotropy magnetic fields.

A sufficient amount of external magnetic stimulation for a change of energy to heat energy is controlled using Electron Spin Resonance (ESR). The ESR signal intensity in tested 15 human blood samples is 3.00×10^8 a.u. (arbitrary unit). Magnetic nanoparticles can also induce lysosomal membrane permeability resulting in the production of ROS which can also lead to cancer cell apoptosis (Chen *et al.*, 2017)

Magnets have a property called the Curie temperature, which is the temperature magnet that loses its magnetic properties and returns when the temperature drops. The temperature that can make apoptotic cells without harming other body cells is 42°C. To adjust the Curie temperature of Fe₃O₄ to 42°C, it is necessary to add metallic elements such as Mn and Zn. By adding the correct proportions of Mn and Zn, research at Southeast University using Mn_xZn_{1-x}Fe₂O₄ (Mn Zn ferrite) can convert the energy generated from a magnet into heat energy before it reaches the Curie point. With this, the Mn Zn ferrite nanoparticles can control their temperature under the stimulation of an external magnetic field. Mn Zn ferrite has advantages in magnetic thermotherapy because it has good biocompatibility and can effectively kill target cells without injuring other cells (Guo *et al.*, 2018).

The potency of mucus-penetrating nanoparticles as colorectal cancer drug delivery

Drugs pass through various environments before they reach the colon. The most challenging is the extreme pH, which is very acidic in the stomach (pH 1.3–3.5), closer to neutral in the small intestine, and slightly acidic in the colon (pH 6–8). There are also digestive enzymes, bicarbonates, and bile salts that cause the drug to degrade before reaching its target. Besides, mucus is physiologically produced to expel foreign objects. More mucus is produced during inflammation (Lu *et al.*, 2016)

Based on its histological structure, the colon has the thickest mucus among the other gastrointestinal tracts. Mucus is an adhesive gel that envelops and protects the epithelial surface from the external environment by capturing foreign bodies and pathogens through steric and adhesive interactions followed by rapid cleaning. Mucus has two layers, namely the loose mucus layer (outer) and firm mucus layer (inner). The loose mucus layer is cleaned by mucociliary cleaning every few minutes or every few hours. This has caused the mucoadhesive nanoparticles (MAP) to not work effectively. Therefore, an update is needed to improve the penetration properties of these nanoparticles and increase the duration of drug transit in the mucus adherent layer. Therefore, it takes nanoparticles that can penetrate the mucus and recognize the target cell. These nanoparticles are called mucus-penetrating nanoparticles (MPP) (Netsomboon *and* Andreas, 2016).

Mucus-penetrating nanoparticles are developed conventional nanoparticles. They can penetrate the inner mucus layer, while the conventional nanoparticles only reach the outer one. It is beneficial because one variant of the colorectal cancer cell is also producing mucin (mucinous adenocarcinoma). Mucus-penetrating nanoparticles are more resistant to mucus clearance. The drug is easily absorbed by the intestine epithelial (Popov *et al.*, 2016)

Upgrading the conventional nanoparticles to the mucus-penetrating ones is also beneficial in their hydrophilicity. Hydrophilic nanoparticles tend to be accumulated in the target tissue and are more resistant to mucin than the hydrophobic (Juliane *et al.*, 2018). Besides, the protective effect of intestinal mucus produced by mucin fiber has a negative charge due to its glycosylation. The electrostatic bond between the positive charge of the nanoparticle and the negative charge from the mucin fiber may interfere with the penetrating process. Thus, a neutral nanoparticle is known to have more penetration ability than a positively charged nanoparticle. Polyethylene glycol might be added to enhance this neutrality (Popov *et al.*, 2016)

Polyethylene glycol (PEG) is a polymer that is often used to optimize drugs in the systemic circulation and prevent macrophage opsonization. So far, PEG is known as a mucoadhesive coating agent. PEG reduces interaction between the mucin because of

its hydrophilic molecules. It also provides neutrally charged particles. However, after further investigation, PEG which has a low molecular weight can reduce the adhesion between mucus and particles because the molecular weight of the PEG is too low to adhere to the penetration. Thus, high density of PEG is expected to be coating the nanoparticle surface (Juliane *et al.*, 2018).

CONCLUSION

Acetogenin, curcumin, magnetic nanoparticles, and mucus-penetrating nanoparticles are potential to be an alternative therapy for colorectal cancer. Future perspectives, trials, and clinical data are needed to obtain more scientific evidence in this subject.

ACKNOWLEDGMENTS

The author would like to acknowledge LPPM Institut Teknologi Bandung, UPPM Poltekkes Kemenkes Bandung, and Research Center for Plant Conservation and Botanical Gardens - Cibodas Botanical Gardens (KRC) - LIPI, Cianjur, West Java for the support and the provision of facilities (there is no funding for this research).

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