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The Anticancer Potential of Gold Nanoparticles from Flavonoid Fractions of Soursop Leaves (*Annona muricata*) Polymerized with PLGA on HER-2 Receptor Expression in Breast Cancer: A Literature Review

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ABSTRACT

Breast cancer is a malignant disease affecting cells in the breast tissue, causing the highest mortality rate among women worldwide. As of now, the exact cause of breast cancer remains unknown, but several factors increase the risk for women, including genetics, lifestyle, direct radiation exposure, and others. In the development of breast cancer, numerous substances can influence the differentiation, adhesion, and motility of cancer cells, including the oncogene human epidermal growth factor receptor-2 (HER-2). Various treatment methods for cancer have been developed, including chemotherapy, radiotherapy, and surgery. However, due to the significant side effects and limitations of existing treatments, innovation is needed to support the success of breast cancer treatment. Recent research has explored green synthesis-based gold nanoparticles (AuNPs) as a promising alternative anticancer therapy with several advantages. The rapid growth of natural herbal plants containing anticancer compounds like flavonoids can enhance the effectiveness of modified therapies in this modern era. The polymerization of gold nanoparticles with flavonoid fractions using Poly-Lactic-co-Glycolic Acid (PLGA) can facilitate the delivery of anticancer drugs to the target site. The research method employed is a literature review using e-resources from PubMed NCBI, ScienceDirect, and Google Scholar. Keywords include Gold Nanoparticle, Breast Cancer, flavonoid, PLGA. Article criteria include full text, abstract, and publication within the last ten years (2013-2024). A total of 157 articles were obtained, and 7 articles were found to be relevant to the topic. Literature review results indicate the high anti-oncogenic effectiveness of gold nanoparticles with flavonoid-polymerized PLGA for breast cancer treatment. This finding can serve as a reference for the application of molecular therapeutic development that has proven to influence the suppression of HER-2 receptor growth expression.

Keywords: *Gold Nanoparticle, Breast Cancer, Flavonoid, PLGA, HER-2*

INTRODUCTION

In this era, Indonesia has faced various double burdens. This event is marked by the beginning of an epidemiological transition with evidence of a shift in disease patterns and causes of death in society from various infectious to non-infectious diseases. Breast

cancer is a malignant disease that causes the highest number of deaths in the world, especially in Indonesia. Breast cancer is caused by the formation of glandular tissue and breast cells that become uncontrolled and take over other healthy cells.[1]

According to the WHO, breast cancer cases are increasing each year, currently totalling 2.3 million. In more than 90% of countries worldwide, breast cancer is the leading cause of cancer-related deaths among women. This case is reinforced by the existence of 685,000 women experiencing death caused by breast cancer in 2020.[2] In Indonesia, this type of cancer accounts for 23,140 new cases each year, given a population of 200 million.[3]

Breast cancer is a type of malignancy caused by cells in breast tissue, including components from the glands (epithelium and lobules), as well as blood vessels, nerve tissue, and fatty tissue.[4] The limited technological capabilities and the difficulty of early detection of breast cancer at this time can be one of the main causes of breast cancer cases being found in the chronic or advanced stage.[3] To date, the exact cause of breast cancer has not been found, but the occurrence of breast cancer in a woman can increase if she has risk factors such as; genetics, lifestyle, direct radiation exposure, and others.[4]

Breast cancer remains a global burden that continues to increase both in morbidity and mortality. This disease is often referred to as a disparity disease because there are differences in incidence and mortality between developed and developing countries.[3] The gap that occurs between developing and developed countries could be due to differences in resources, developed countries have organised early screening programs to reduce and provide appropriate care for breast cancer cases. Furthermore, the available technology in developed countries supports the implementation of effective treatment modalities. However, in developing countries, limited resources and infrastructure make prevention and treatment programs for breast cancer limited.[5]

The increasing incidence of breast cancer breast cancer cases will become a public health problem if not handled further. The average probability of three-year survival for breast cancer patients stage 1 and 2 is 99%, stage 3 86% and stage 4 31%. In this regard, the World Health Organization (WHO) has called for an intervention strategy to eliminate breast cancer cases before 2040.[4] In the development of each stage of cancer, there are many substances that can trigger it, one of which is the human epidermal growth factor receptor-2 (HER-2) oncogene which is very important for the differentiation, adhesion, and motility of cancer cells. Excessive activation of the HER-2 gene can encourage an increase in the degree of malignancy of breast cancer cells, and trigger an increase in cancer cell proliferation and extensive metastasis resulting in a worse prognosis in the future.[6]

HER-2 protein is one of the proteins found in breast cells. In breast cancer, HER-2 does not function normally and can cause breast cells to produce HER-2 receptors in large quantities (overexpression of HER-2 protein), resulting in uncontrolled growth and proliferation of breast cells, leading to malignancy.[7]

In the treatment and therapy for breast cancer, early diagnosis is essential through breast cancer screening and MRI.[8] Therapy can be tailored to the stage of breast cancer. Some treatment methods that have been developed include chemotherapy, radiotherapy, and surgery. However, not all tumors can be surgically removed, and chemotherapy can cause serious side effects.[9]

Therefore, anticancer treatment is needed to support the success of breast cancer treatment. With advancements in research, several leading studies have developed green synthesis for gold nanoparticles (AuNP) and silver (AgNP) as an alternative

anticancer therapy that has very high effectiveness with promising results.[10] Gold nanoparticles have several advantages in increasing the sensitivity and selectivity of biosensors. Gold nanoparticles (AuNP) have more complex and simple modifications, optics, properties, and biocompatibility.[11] Reflecting on the therapeutic potential of gold nanoparticles, which are widely developed in modern medicine.[12]

The variety of herbal plants with potential therapeutic compounds to combat cancer is an advantage for Indonesia, which is rich in natural herbal resources. Soursop leaves, also known as (Annona Muricata) contain flavonoids that can inhibit cancer growth in the body.[13] Flavonoids are secondary metabolites of polyphenolic plants that can exhibit chemopreventive effects and chemotherapy. Cell proliferation, survival, invasion, migration, inflammation, and angiogenesis are key aspects of carcinogenesis. Flavonoids overcome carcinogenesis by suppressing the proliferation of cancer cells and stopping the cell cycle by inhibiting the activation of several phosphorylated-mediated protein kinases, such as AMP-activated protein kinase (AMPK), protein kinase B (Akt).[14] Poor water solubility, low absorption, low stability, conversion to worse soluble derivatives in the intestine, rapid metabolism, and rapid elimination lead to low systemic availability of flavonoids. Therefore, the development of nanoparticle scale formulations, one of which is gold, has emerged as a potential strategy to overcome the problem of the delivery of therapeutic substances in the body from flavonoids to exploit their chemotherapeutic properties.[15] In cancer therapy, anticancer substances must be delivered effectively to reach the cancer cells for optimal action.[16] Modification between gold nanoparticle flavonoids based on Poly-Lactic-co-Glycolic Acid (PLGA) is a breakthrough that can be proposed in anticancer therapy. Anticancer nanoparticles using PLGA polymers can penetrate the endosomal membrane and deliver encapsulated drugs into cells so that they can increase the effectiveness of anticancer therapy.[17] Therefore, researchers are eager to assess the anti-oncogenic and anticancer effectiveness of gold flavonoid nanoparticle preparations using PLGA polymers on the expression of HER-2 as a therapy for breast cancer.[18]

MATERIALS & METHODS

This research employs a literature review approach. The study was conducted by searching the internet using various journal search engines. The search engines utilized in this study included PubMed, ScienceDirect, and Google Scholar, with the following keywords: Gold Nanoparticle, Annona Muricata, Breast Cancer, HER-2. The variables used in the selection of literature include several inclusion criteria: (1) Published in the last 10 years, (2) Language used is Indonesian or English, (3) Full text available, (4) Discussion of gold flavonoid nanoparticles of soursop leaves (Annona Muricata) on the expression of HER-2 cells in breast cancer.

The journal search process involves several steps: identification, screening, and elimination of journals that do not meet the inclusion criteria. From the identification and screening process, along with the elimination conducted by the researcher, seven articles were deemed relevant to the selected topic and in accordance with the inclusion criteria.

The data analysis employed in this literature review utilizes a simplified approach. The simplified approach involves compiling each article and summarizing the key findings from all the research.

RESULT

The resource search results on Google Scholar yielded 98 articles, while PubMed NCBI presented 12 articles, and ScienceDirect provided 47 articles. In total, there were 157 articles from the search.

After eliminating duplicate articles across the various databases and filtering by title and abstract, seven articles were identified as relevant to the research topic and meeting the inclusion criteria. The details of these seven articles have been compiled in Table 1.

Table 1. Literature Review Results

No	Source	Method	Results and Discussion
1.	Taghdisi *et al*.,2016[19]	Identification of double-targeting, controlled release, and reversible delivery of doxorubicin to cancer cells by gold nanoparticles modified with polyvalent aptamer. Using flow cytometry analysis methods and MTT assay tests.	In the study, a drug delivery system designed with gold nanoparticles can inherit the properties of efficient drug loading in tumor targeting. The release of PH-dependent drugs and controlled delivery (Dau) to tumor cells can be novel therapies in cancer drug delivery.
2.	Shipunova *et al*., 2021[20]	Identification of the development of PLGA polymer nanoparticles filled with a fluorescent photosensitive xanthene dye, Rose Bengal, and decorated with an artificial scaffolding protein that recognizes HER2, affibody $Z_{HER2:342}$.	Under radiation using an external green light, PLGA nanoparticles produce ROS for breast cancer cell apoptosis. This is supported by an increase in the specificity of targeted binding by 2.13 times quantitatively compared to other cancer cells.
3.	Chiu *et al*.,2021[21]	Analysis of physicochemical properties and biological effects of gold collagen nanoparticles with berberine alkaloid (Au-Col-BB) on BAEC and Her-2 breast cancer cell lines.	The average diameter of Au-Col-BB is about 227 nm. Au-Col-BB exhibits remarkable cytotoxicity for inducing cell apoptosis in the Her-2 cell line. Meanwhile, Au-Col-BB nanoparticles exhibit superior non-toxicity and biocompatibility properties compared to untransformed BAECs. The results of the analysis revealed that the mechanism of cell autophagy uptake and clathrin-mediated endocytosis is the main mechanism for the internalization of Au-Col-BB in both cell types. In MMP activity and cell migration tests, it was shown that Au-Col-BB (10 μg/mL) significantly inhibited cell movement in the Her-2 cell line. In addition, Au-Col-BB plays a role in inducing apoptosis-related proteins, such as Bax and p21, to be expressed.
4.	Wey *et al*.,2020[22]	Analysis of the procedure for the incorporation of ultra-small gold (2 nm) nanoparticles into PLGA nanoparticles as drug delivery agents.	Ultrafine gold nanoparticles and gold-silver alloys (2 nm) exhibit autofluorescence with a high Stokes shift (370 nm). As a result, by the water-in-water emulsion method, ultra-small gold and silver/gold nanoparticles were successfully encapsulated into PLGA nanoparticles (140 nm). Therefore, the incorporation of the material results in a high stokes shift so that additional loading with anticancer drugs is easy to add to the material.
5.	Adinew *et al*.,2021[23]	Analysis of the effect of flavonoids as anticancer through miRNA modulation in triple-negative breast cancer.	Flavonoids have a dual action related to ROS homeostasis—they act as antioxidants and anti-inflammatories under normal conditions and become powerful pro-oxidants in cancer cells.

6.	Yirankinyuki *et al*.,2020[24]	The identification of chemical compounds in soursop leaf extract (*Annona muricata L.*) was analyzed using FT-IR, UV-Vis, and GC-MS spectrophotometers. Then, the antioxidant test was carried out using the DPPH method.	The results of the study showed that soursop leaf methanol extract (*Annona muricata L.*) contained 12 compounds with a large percentage of the area, including kaempferol, hexadecanoic acid, isopulegol, 5-methyl-2-(1-methylene) cyclohexanol, octadecanoic acid.
7.	Silihe *et.al*.,2023[25]	Rats induced with DMBA breast cancer were given *A. muricata* fruit juice extract at a dose of 200 mg/kg BB (3 days/week or daily) and leaf ethanol extract (Annona muricata L.) at a dose of 200 mg/kg daily. On the 20th day, tumor incidence, tumor load, tumor volume, histopathology, protein and CA 15 − 3 levels, antioxidant status, and pro-inflammatory cytokines were assessed in the mice.	The assessment was carried out on 100% of sick mice showing grade III cribriform ductal carcinoma SBR. Administration of Annona muricata L. (leaves and fruits) and tamoxifen extracts could significantly reduce tumor mortality and incidence, tumor volume, tumor weight, total protein, and CA15-3 levels compared to the DMBA group. Anticancer compounds in (Annona muricata L.) showed antioxidant activity through increased levels of GSH and SOD as well as catalytic activity, which was characterized by decreased MDA levels compared to the DMBA group. On the other hand, the administration of treatment (Annona muricata L.) also showed a decrease in TNF-α, IL-6, and INF-γ levels.

DISCUSSION

The Role of Gold Nanoparticles In Anticancer Therapy

Nanoparticles are particles with a very small size of 1-100 nanometers. Nanoparticles are made with the aim of expanding the surface area of active substances so that they will make it easier for drugs to dissolve, improve bioavailability, modify drug delivery systems, and improve drug stability and drug absorption.[26] The use of nanoparticles has the advantage of being able to penetrate the intercellular space because of their very small size, so it is considered to be able to reach target cells well in breast cancer therapy.[27] Several studies have been conducted to explore and test the potential of nanoparticles in cancer therapy. The characteristics of nanoparticles, such as drug release, targeting, cytotoxicity, and nanoparticle-encapsulated drugs, are greatly influenced by the size, shape, and physiochemistry used.[21]

These nanoparticles are considered a potential tool to diagnose various types of cancer, one of which is breast cancer, because of their ability to go directly to the location of the target tumor. Gold nanoparticles attract the attention of researchers because of their drug carriers and SPR (Surface Plasmon Resonance) properties.[28]

Gold nanoparticles, or AuNp, can be prepared in various sizes from 1 to 150 nm, making their distribution easy to control.[29] The negative charge present in AuNp facilitates its function by adding various biomolecules such as drugs, genes, and target ligands. In addition, the low toxicity properties of these gold nanoparticles may make it a novel therapy for breast cancer.[30] Gold nanoparticles offer advantages in terms of optimal biocompatibility, ease of modification and functionalization, simple synthesis process, low toxicity level, and particle size control.[31] Smaller nanoparticles can diffuse rapidly from blood vessels to target organs, while larger ones tend to remain near blood vessels without penetrating the cell membrane.[32],[33]

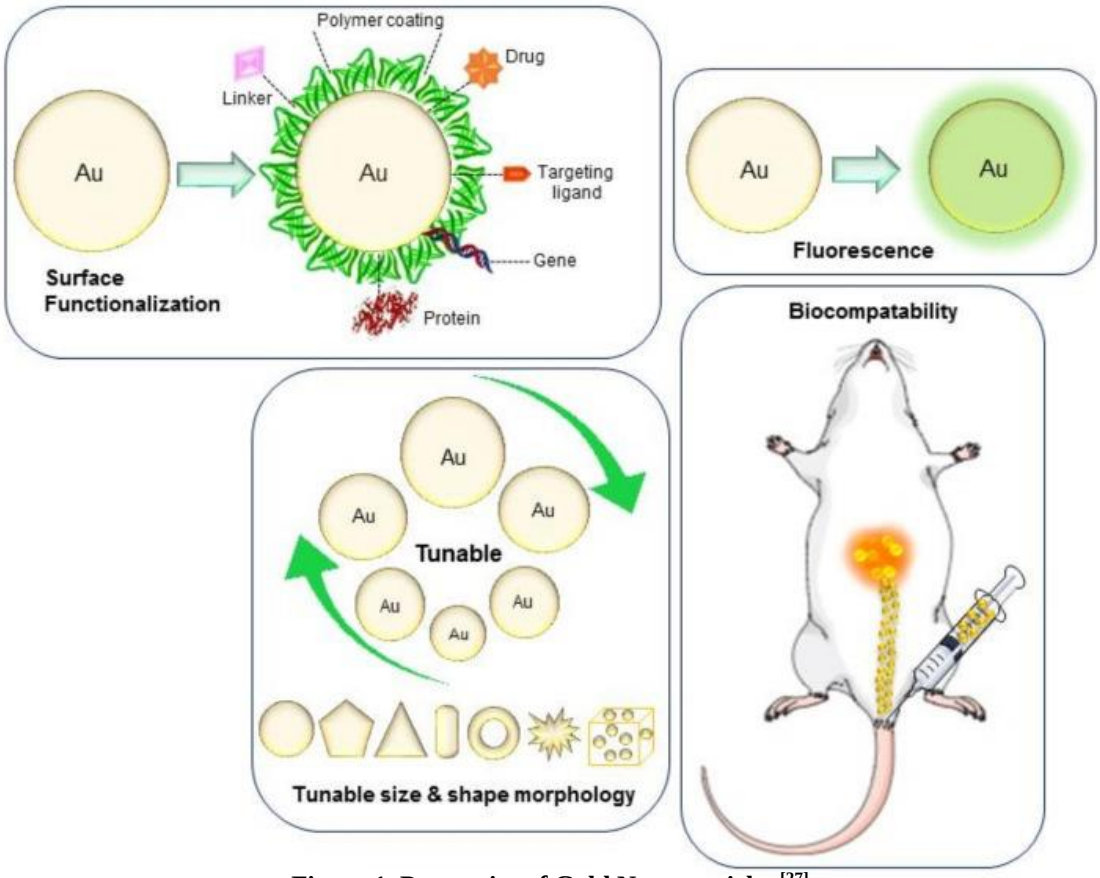

Figure 1. Properties of Gold Nanoparticles [27]

Gold nanoparticles are attracting the attention of scientists because of their potential as drug carriers, mainly thanks to their Surface Resonance Plasmon Properties (SPR), optical properties, and tunability. For example, methotrexate (MTX), a drug that has been used to treat cancer for decades after being conjugated with gold nanoparticles, showed higher levels of cytotoxicity against various tumor cell lines compared to MTX in its free form. MTX was observed to accumulate in tumor cells at a higher rate and rate when conjugated with gold nanoparticles. Doxorubicin (DOX), another drug that binds to gold nanoparticles via acid-breakable links, exhibits enhanced toxicity against multidrug-resistant MCF-7/ADR breast cancer cell lines. It overcomes multi-drug resistance to some extent due to increased uptake of drugs bound to gold nanoparticles, followed by responsive release within cells.[34]

Another in vitro test tested gold nanoparticles (AuNPs) that had been conjugated with the thiol-PEGylated tamoxifen, with the aim of selectively targeting breast cancer cells that have very high expression on estrogen receptors (ER).[35] PEG (polyethylene glycol) is used to improve particle stability in cell culture media and reduce nonspecific serum protein binding on the surface of conjugated particles. In addition, tamoxifen conjugated with gold nanoparticles showed higher oral bioavailability and lower hepatotoxic risk compared to tamoxifen citrate and basic tamoxifen.[36]

Flavonoid Fraction of Soursop Leaves Against Cancer Therapy

Soursop leaves have chemical content such as alkaloids, tannins, and several other ingredients that are classified as *annonaceous acetogenins* compounds. This compound is considered to have cytotoxic

potential, that is, toxic to inhibit the growth of cancer cells. In addition, soursop leaves also contain flavonoids, which function as antioxidants for cancer.[37]

Figure 2. Image of Soursop Leaves *Annona muricata*) [38]

Soursop leaves are known to contain anti-cancer substances called acetogenins, which can kill cancer cells without disrupting healthy cells in the human body. Acetogenins are polyketide compounds with a structure of 30-32 unbranched carbon chains bound to a 5-methyl-2-furanone group. One of the groups of acetogenin is phenol, causing the total phenol content in soursop leaves to be relatively high. Soursop leaf ethanol extract is found to have phenolic acid in free form, glycoside form, and ester forms are caffeic acid, p-fumaric acid, p-hydroxybenzoic acid, and vanillic acid. While ferulic acid only exists in the form of glycosides and esters. From the extraction of ethanol maceration-percolation, it was found that the most difficult flavanols in 3-O have hydroxy groups at positions 4', 5, and 7 and have glucose and one other sugar compound that is not yet known as glycone. The flavonoids found are suspected to be kaempferol.[39] The results of the identification of the flavonoid group showed that soursop leaf extract contained flavonoids of the flavonoid group: dihydroflavonol, flavonol, and flavanon. Acetogenin compounds found in soursop leaves have benefits in the treatment of various diseases. Acetogenin plays a role in supporting the immune system and preventing potentially fatal infections. Soursop leaves, which contain acetogenin, have been shown to have the ability to fight 12 types of cancer cells.[40] Flavonoids can inhibit cancer growth by regulating several protein kinases that play a role in the pathogenicity of cancer cells, such as epidermal growth factor receptors (EGFRs), platelet-derived growth factor receptors (PDGFRs), vascular endothelial growth factors (VEGFRs), and cyclin-dependent kinases (CDKs). In addition, enzymes such as cyclooxygenase (COX), lipoxygenase (LOX), and xanthine oxidase are also involved in the pathogenicity of cancer cells, which the administration of flavonoid compounds can regulate.[41] On

the other hand, flavonoids also can reduce and control all cancer pathogenic factors through their antioxidant properties. Polyphenol compounds classified as acetogenins in soursop leaves also have the potential to be anticancer because they are rich in antioxidants. The mechanism of action of this compound is the destruction of the cell wall and the precipitation (deposition) of cell proteins from microorganisms so that coagulation and malfunction occur in these microorganisms.[42]

Poly-Lactic-co-Glycolic Acid (PLGA) Polymers for Cancer Therapy

In cancer therapy, anticancer substances must reach cancer cells in order to produce maximum work. One of the efforts that can be made to reach the target cell is to use nanoparticle technology because of its ability to deliver drugs into the cell. However, an innovation shows that when we wrap these nanoparticles with PLGA-based packaging, it is considered more effective as a cancer therapy.

PLGA is biodegradable because it can be decomposed into endogenous compounds, namely lactic acid and glycolic acid. The body easily metabolizes this degradation process through the Krebs cycle, so PLGA has low systemic toxicity properties. In addition, PLGA has received approval from the Food and Drug Administration (FDA) for use in therapy in humans. PLGA polymerized nanoparticles are able to penetrate endosomes and deliver encapsulated drugs into the cell.[43],[44]

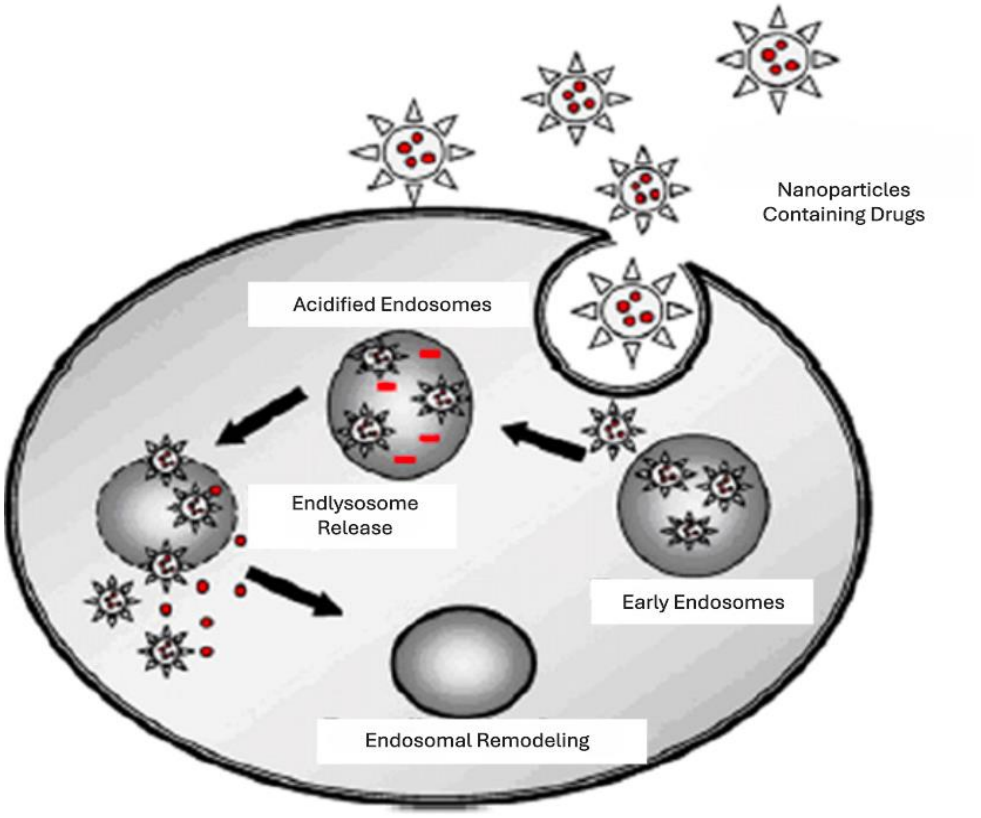

Figure 3. Ability of PLGA Polymer Nanoparticles to Penetrate Endosomes[45]

The main advantage of this PLGA polymer is that PLGA will undergo complete biodegradation in aqueous media. Also, several other advantages such as (1) biocompatible and biodegradable; (2) it has received FDA (Food Drug Administration) and EMA (European Medicine Agency) approval as a drug delivery system; (3)

modification of the surface so that foreign particles are not recognized; (5) protection of drugs from degradation; (6) can be delivered to specific organs/cells.[46]

CONCLUSION

Cases of breast cancer should be a concern because this disease causes many deaths in people who suffer from it. Moreover, there is a service gap in breast cancer treatment efforts between developed and developing countries. Developed countries tend to have better services and facilities for implementing breast cancer cases in their countries. The exact cause of Breast Cancer is still not known for sure until now, so it is a group of diseases with a high prevalence globally. This study aims to assess the effectiveness of gold flavonoid nanoparticles with PLGA polymers as an anticancer, especially in breast cancer with HER-2 receptor growth expression. The limitations of research that discuss gold flavonoid nanoparticles with PLGA polymers against breast cancer are also the reason why researchers conducted a literature review.

Declaration by Authors

Ethical Approval: Not Applicable

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