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Research Article

Nano Transdermal Delivery Potential of Fucoidan from *Sargassum* sp. (Brown Algae) as Chemoprevention Agent for Breast Cancer Treatment

Syeftyan Muhammad Ali Hamami[1], Michelle Fai[1], Ahmad Fariduddin Aththar[1], M Nizam Zulfi Zakaria[1], Viol Dhea Kharisma[2,3], Ahmad Affan Ali Murtadlo[3], Muhammad Badrut Tamam[4], Vikash Jakhmola[5], Muhammad Hermawan Widyananda[1,3], Dora Dayu Rahma Turista[6], Maksim Rebezov[7,8,9], Nikolai Maksimiuk[10], Nataliya Kulmakova[11], Evgeniya Latynina[11], ANM Ansori[12], Rahadian Zainul[13,14,*], Riso Sari Mandeli [15], Devi Purnamasari[16], Oski Illiandri[17], Khoirun Nisyak[18], Ernarisa Fitri[19]

[1]*Department of Biology, Faculty of Mathematics and Life Sciences, Universitas Brawijaya, Malang, INDONESIA.*
[2]*Department of Biology, Faculty of Science and Technology, Universitas Airlangga, Surabaya, INDONESIA.*
[3]*Division of Molecular Biology and Genetics, Generasi Biology Indonesia Foundation, Gresik, INDONESIA.*
[4]*Department of Biology, Faculty of Sciences and Technology, Universitas Muhammadiyah Lamongan, Lamongan, INDONESIA.*
[5]*Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, INDIA.*
[6]*Department of Biology Education, Faculty of Teacher Training and Education, Mulawarman University, Samarinda, INDONESIA.*
[7]*Department of Scientific Research, V. M. Gorbatov Federal Research Center for Food Systems, Moscow, RUSSIAN FEDERATION.*
[8]*Faculty of Biotechnology and Food Engineering, Ural State Agrarian University, Yekaterinburg, RUSSIAN FEDERATION.*
[9]*Department of Scientific Research, Russian State Agrarian University Moscow Timiryazev Agricultural Academy, Moscow, RUSSIAN FEDERATION.*
[10]*Institute of Medical Education, Yaroslav-the-Wise Novgorod State University, Velikiy Novgorod, RUSSIAN FEDERATION.*
[11]*Department of Veterinary Medicine, Russian State Agrarian University - Moscow Timiryazev Agricultural Academy, Moscow, RUSSIAN FEDERATION.*
[12]*Professor Nidom Foundation, Surabaya, INDONESIA.*
[13]*Center for Advanced Material Processing, Artificial Intelligence, and Biophysic Informatics (CAMP-BIOTICS), Universitas Negeri Padang, Padang, INDONESIA.*
[14]*Department of Chemistry, Faculty of Mathematics and Natural Sciences Universitas Negeri Padang, Padang, INDONESIA.*
[15]*Environmental Science, Postgraduate Programme, Universitas Negeri Padang, INDONESIA*
[16]*Department of Radiology Engineering, Universitas Awal Bros, Pekanbaru, INDONESIA*
[17]*Department of Biomedicine, School of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia*
[18]*Department of Pharmacy, Faculty of Public Health, Universitas Anwar Medika, Sidoarjo, INDONESIA*
[19]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Andalas, Padang, INDONESIA*

Correspondence
Rahadian Zainul
Center for Advanced Material Processing, Artificial Intelligence, and Biophysic Informatics (CAMP-BIOTICS), Department of Chemistry, Faculty of Mathematics and Natural Sciences Universitas Negeri Padang, Padang, INDONESIA.
E-mail: rahadianzmsiphd@fmipa.unp.ac.id

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ABSTRACT
Conventional chemotherapy substances are associated with mild to severe side effects that affect both healthy and cancer cells. It is presumed to improve therapeutic efficacy in coexistence reducing chemotherapy's side effects. Fucoidan is an anticancer bioactive compound derived from *Sargassum* sp. that has low cytotoxic activity. The purpose of this study was to explore the effectiveness of anticancer activities of fucoidan from *Sargassum* sp. against breast cancer then analyze the suitability of nano transdermal patch of fucoidan and blueprint the long-term research design of nano transdermal patch as a chemoprevention agent in the chemotherapeutic management of breast cancer. This research was performed through a literature study and *in silico* study by imposing carbonic anhydrase IX (CA IX) as a marker of hypoxia and metastatic state of cancer cells. The results showed that the fucoidan from *Sargassum* sp. effectively induced apoptosis and prevented metastasis of breast cancer cells through the Bcl-2, Bcl-w, and bad pathways. Fucoidan, in addition, was predicted to inhibit CA IX by Glu4 Glu5, Leu7, Pro8, and Asp6 residues. Therefore, the delivery of fucoidan is favored to have a local effect on the site of breast cancer cells by nano transdermal patch preparations using fucoidan nanoparticle polymer. Further nano transdermal patch development as a treatment for breast cancer is suggested through the stages of formulation optimization, optimum formula activity testing, patent filing, and distribution in health services.
Key words: Anticancer, Breast cancer, Fucoidan, Nano transdermal, *Sargassum* sp. .

INTRODUCTION

Breast cancer is the second most common type of cancer with the most sufferers in the world in 2018 and is one of the most malignant cancers in 2020.[1] GLOBOCAN stated that breast cancer is the main cause of the incidence of cancer cases globally and has exceeded lung cancer cases by 11.7% of the total cancer cases in the world in 2020.[2] In Indonesia, it ranks first as the cause of death caused by the addition annually. According to Basic Health Research (RISKESDAS) data, the prevalence of breast cancer in Indonesia has increased significantly, in 2013 there was 1.4 per 1,000 patients and in 2018 it was 1.79 per 1,000 patients, and in 2020 based on GLOBOCAN data the number of breast cancer cases in Indonesia reached 68,858 cases.[3,4] The highest cases of breast cancer in Indonesia reached 42.1% per 100,000 population with an average case of death of 17% per 100,000 population.[5] It is estimated that in 2040 the number of breast cancer cases will increase to 0.89%.[6] These facts clearly depict that the burden of management of breast cancer treatment and care will be directly proportional to the increasing number of patients.

Uncontrolled growth of breast cells due to abnormal cell changes in genes that control cell regeneration in a person's breast tissue may develop breast cancer. The female breasts consist of several parts, namely lobules (mammary glands), ducts (milk ducts), adipose connective tissue, blood and lymph vessels.[7] The occurrence of breast cancer begins in the cells lining the ducts (ductal cancer), some in the lobules (lobular cancer), and other tissues.[8] This can be characterized by the presence of a lump or malignant tumor that enlarges and causes pain in the breast, wrinkled skin, and discharge of fluid or blood from the nipple.[9] The tumor is called carcinoma mammae which is a malignant lump that grows in breast organ tissue. Tumors in breast tissue growth in the mammary glands, gland ducts, or other breast-supporting tissues such as adipose or breast connective tissue can spread to other parts of the body, called metastases.[10]

In general, management in the treatment of breast cancer is done through surgery, radiotherapy, and chemotherapy.[11] Surgery and radiotherapy are the early steps in therapy for breast cancer patients.[12] However, the recurrence rate of patients reaches 90% after surgery and there is a risk of cancer spreading to other parts of the body.[9,13] While, chemotherapy is a pharmacological therapy for patients who have been diagnosed in stages III and IV by administering cytotoxic drugs that can cause DNA damage as a general inhibitor of cell division.[14] The agent used also has a very strong effect which not only kills cancer cells but also attacks healthy cells, especially rapidly dividing cells.[15,52,53]

Considering this phenomenon, it is essential to have a chemopreventive agent that can potentially be a

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chemotherapy companion agent in the management of breast cancer. The goal is to increase the sensitivity of cancer cells and reduce the side effects caused by chemotherapy agents. Fucoidan is a bioactive compound found in *Sargassum* sp. (brown algae) which has the ability as an anticancer with low cytotoxic activity. Fucoidan compound from *Sargassum* sp. has proven to arrest breast cancer cell metastases through the Bcl-2, Bcl-w, and Bad pathways by increasing mortality alongside decreasing transformation and malignancy of breast cancer cells.[16] In addition, fucoidan is possible to modify as a nanoparticle polymer in the delivery of active substances to breast cancer cells. For its implementation, fucoidan nano transdermal patch preparations are presumably to have a local effect on the site of action of breast cancer cells in coexistence to increase permeability, prolong bioavailability, and gradual release of active substances. The purpose of this study was formulated to examine the effectiveness of fucoidan from *Sargassum* sp. as an anticancer agent of the breast, analyze the suitability of nano transdermal patch of the bioactive compounds fucoidan *Sargassum* sp. as a chemoprevention agent for breast cancer and the long-term research design of nano transdermal patch as a chemoprevention agent in the management of breast cancer.

MATERIALS AND METHODS

Literature study

Journal articles, GLOBOCAN data, breast cancer management institutions, and cancer therapy guidelines were utilized to synthesize theoretical foundations to explore problems, describe the urgency, as well as validate the methods and approaches used in research and acquire primary data.[17] The data were analyzed using phenomenology and an inductive approach related to anticancer concepts and breast cancer management to establish the formulation of both anticancer and chemopreventive agents.

Data mining and preparation of protein and ligands

The 3D structure of the carbonic anhydrase IX (CA IX) (PDB 2HKF) was downloaded in the PDB format of the RCSB PDB database (www.rcsb.org) and prepared to remove water molecules and native ligands using the Biovia Discovery Studio version 21.1.1 (Figure 1a). Both fucoidan (CID: 92023653) and oxamide (CID: 10113) as a control that will be used as ligands were downloaded in SDF format from PubChem database (https://pubchem.ncbi.nlm.nih.gov) and prepared using the PyRx 0.8 (Figure 1b and 1c).

Druglikeness analysis and ADMET analysis of ligands

Physicochemical along with drug-likeness and pharmacokinetics of ligands were predicted using SwissADME (http://www.swissadme.ch/) to describes a molecular weight, LogP value, number of H-bond donors and H-bond acceptors, rotatable bond, and Total Polar Surface Area (TPSA) from ligands.[18,54,55] The ADMET analysis from ligands was determined using the pkCSM server (http://biosig.unimelb.edu.au/pkcsm/prediction).[19,50,51]

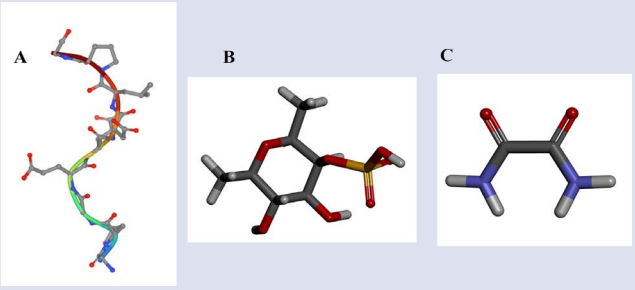

Figure 1: Target receptor and compound used in this study. A: carbonic anhydrase IX (CA IX) (PDB ID 2HKF); B: fucoidan (CID: 92023653); C: oxamide (CID: 10113).

Protein-ligand interaction and 3D molecular visualization of chemical interactions

Proteins and ligands that have been prepared were imposed based on molecular docking using VinaWizard in PyRx 0.8 software.[20,44,45] The results of docking were then stored in PDB (.pdb) format while information about energy binding is stored in text (.txt) format. Furthermore, the docking results are visualized using the Biovia Discovery Studio Visualizer application version 21.1.1. Some of the parameters analyzed from the visualization results include bond energy, bond types, and amino acid residues[46,47,53].

RESULTS AND DISCUSSION

Fucoidan effectiveness against breast cancer cell apoptosis

Fucoidan as a bioactive compound found in *Sargassum* sp. (brown algae) has proven to be effective against breast cancer cells, such as inhibiting the process of metastasis of cancer cells to other tissues or organs *in vitro* on the MCF-7 breast cancer cell line. Fucoidan, which works with interventions on the Bcl-2, Bcl-xL, Bcl-w, and Bad pathways, inflicts decreases in breast cancer cells' transformation, immortality, and malignancy. In addition, fucoidan also interplays as an immunomodulator with its ability to activate immune cells, such as T lymphocyte cells, B cells, macrophages, and NK cells. Moreover, it is also able to be a natural immunomodulator and immunoprevention agent against breast cancer by providing the main antibody response in Sheep Red Blood Cells (SRBC) and initiating the formation of breast anticancer cytokines by triggering THP-1 along with an increase in levels of IFN-γ, p53, Bax, TNF-α, IL-12 in producing IL-1 and IFN-γ.[16,48,49]

Fucoidan induces cell apoptosis of breast cancer cells through two mechanisms, i.e., the extrinsic pathway (cytoplasmic) that triggers cell apoptosis with cell death receptors or through intrinsic pathways (mitochondria) characterized by changes in the mitochondrial membrane (MMP) and cytochrome C release.[16] The fucoidan compounds at normal doses were able to cause apoptosis in cancer cells without causing toxicity in other healthy cells on *in vitro* tests.[21] In addition, fucoidan inhibited the proliferation of breast cancer cell line cells MDA-MB-231, MCF-7, and 4T1.[22]

The advantage of fucoidan compounds from *Sargassum* sp. is its ability to act as a multitarget anticancer compound by regulating Bcl-2, Bad, Bax, caspase 8-7-3, pI3k / Akt / mTOR, MAPK pathway, MMP-2, THP-1, JKN, ERK1 / 2 and CDKs against breast cancer cells to induce apoptosis of breast cancer cells. Hence, it has the potential as an anti-metastatic agent in breast cancer cells. Considering that until now no new anti-metastatic drugs have been found in cancer cells, the use of fucoidan compounds is a breakthrough in the medical field. For its safety, fucoidan compounds can be degraded by macrophage cells and no toxic effects are found on healthy cells or tissues.[16]

In vivo tests have proven that fucoidan compounds can kill some types of cancer, especially breast cancer. Experiments with 60 Sprague Dawley mice with a fucoidan dose of 200 mg/kg BB through the oral sonde method which was able to significantly reduce tumor weight by reducing the expression of P13K and AKT proteins on the tumor surface.[23] Fucoidan extract from *Fucus vesiculosus* also showed the effect of digestion and apoptosis through the PI3K, AKT, and mTOR pathways on several female cancer cell lines (breast, endometrial, ovarian, and uterine carcinomas). Another effect is that after 24 hours

of treatment, the chromatins that were inside the nucleus fragments undergo extreme condensation and commit to the apoptotic process.[24] The induction of apoptosis by fucoidan from *Undaria pinnatifide* extract showed a decrease in intracellular GSH (glutathione) levels after 24 hours. On the contrary, reactive ROS levels were rising because GSH is a non-protein antioxidant that can suppress ROS levels. The high level of ROS affected the mitochondria through oxidative stress. The destruction of the mitochondrial membrane eventually releases cytochrome C which is the intrinsic pathway of cell apoptosis.[25]

Based on the results of predictions of physicochemical aspects, fucoidan as bioactive compound *Sargassum* sp. was evaluated using Lipinski's rule of five and Veber's rules (Table 1).[26] Fucoidan compounds do not show any violations that enable fucoidan compounds to act as druglike molecules (DLM). Oxamide is a substance that can inhibit the activity of the CA IX enzyme.[27,28] CA IX itself is classified as a glycoprotein that is on the surface of the cell membrane (cell-surface glycoprotein). This enzyme is associated with the process of occurrence of metastases in breast tumor cells. Thus, this enzyme is used as a marker of hypoxic conditions in tumor cells and is used for the diagnosis of breast cancer stages.[29]

Subsequent investigations were studied based on their pharmacokinetic characteristics, through analysis of the properties of ADMET (Table 2). The range of fucoidan absorption in water (log S) shows moderate solubility so fucoidan has a better level of solubility and permeability to the skin than oxamide. This is accompanied by a good ability to diffuse across tissues and plasma so that it can interact with target proteins (fu coefficient > 0.3). Fucoidan exhibits minimal toxic properties to the liver and risk sensitivity for transdermal applications. Another advantage of fucoidan is its non-carcinogenic properties. Based on molecular docking interactions, it is known that fucoidan and oxamide are associated with the enzyme CA IX at similar residues, such as Pro8, Leu7, Glu5, and Glu4 (Figure 2 and Table 3).

Based on binding energy, the bond between fucoidan and CA IX is stronger because the lower energy represents a higher affinity and more stable conformation. The bond formed between fucoidan and CA IX includes one hydrogen bond with a binding energy of -3.5 kcal/mol in a row. It is also shown by the research of Chitra *et al.* (2021) that fucoidan from the brown algae *Turbinaria conoides* forms eight hydrogen bonds at its active site with the enzyme CA IX.[27]

Nano transdermal patches for fucoidan delivery

As sulfate groups content is positively correlated with the bioactivity of fucoidan, the evaluation of fucoidan extraction is attainable using a spectrophotometric assay for purity determination, fucose monomers, sulfation patterns and content, molecular mass, and glycosidic bonds.[30,31] The next step is the preparation of chitosan-fucoidan nanoparticles using the ionic gelation method.[32] Electrostatic interaction between positively charged amine groups due to the dissolution of chitosan in diluted acid solution will interact with NaTPP polyanion groups.[33] The availability of chitosan-fucoidan nanoparticles is visible in the formation of colloids. Quantitative evaluation was carried out comprehensively using FTIR to analyze the functional groups and mass characterization of nanoparticles using PSA.[34]

Transdermal patch preparations are arranged to have a local effect as the active substance reaches the site of action. Based on its design, there are generally 4 main components that make up the transdermal patch preparation including (1) Liner, which functions in protecting the preparation while in storage or not yet used; (2) Compartment, which is a component where the drug to be released is stored and directly attached to the liner; (3) Adhesive which functions to glue the patch preparation to the skin; (4) Permeable membrane that can release drugs in a controlled manner into the skin; and also additional components, namely (5) Backing or external protection that can minimize drug contact with the outside environment (Figure 3).[35]

Table 1: Physicochemistry analysis using SwissADME.

Compound	Lipinski's Rule of 5					Veber's Rule	
	Log P	Molecular weight (g mol^{-1})	Hydrogen donor	Hydrogen acceptor	No. of violations	Total polar surface area (Å^2)	Number of Rotatable bonds
Fucoidan	0.47	242.25	3	7	0	121.67	2
Oxamide	0.27	88.07	2	2	0	86.18	1

Table 2: Pharmacokinetic ADMET analysis using pkCSM.

Compound	Absorption			Distribution				Metabolism	Excretion	Toxicity		
	Log S	Log Papp	Log Kp	VDss	Fu	Log BB	Log PS		Total Clearance	Hepato-toxicity	AMES toxicity	Skin sensitivity
Fucoidan	-1.497	0.094	-2.735	-0.181	0.704	-0.922	-3.567	-	1.514	No	No	No
Oxamide	0.312	0.479	-4.007	-0.448	0.865	0.047	-3.473	-	0.07	No	Yes	No

Log S, Solubility (log mol/L); log Papp, Caco-2 permeabilization in 10^{-6} cm/s; log Kp, Skin permeability; VDss, volume of distribution at steady state (log L/kg); FU, Fraction Unbound; Log BB, Blood-brain barrier permeabilization; Log PS, central nervous system permeabilization; Total Clearance (log ml/min/kg)

Table 3: Molecular interaction of CA IX with fucoidan and oxamide.

Receptor-ligand	Binding energy (kcal/mol)	Interaction site	Distance (Å)	Bond Type	Interacting residues
CA IX + fucoidan	-3.5	:LIG1:H- P:LEU7:O	2.28	Hydrogen bond	Glu4 Glu5 Leu7 Pro8 Asp6
CA IX + oxamide	-2.4	P:GLU5:N :LIG1:O :LIG1:H-P:GLU5:O :LIG1:H- P:LEU7:O :LIG1:H- P:GLU5:OE1	3.07 2.26 2.40 2.90	Hydrogen bond	Pro8 Leu7 Glu5 Glu4

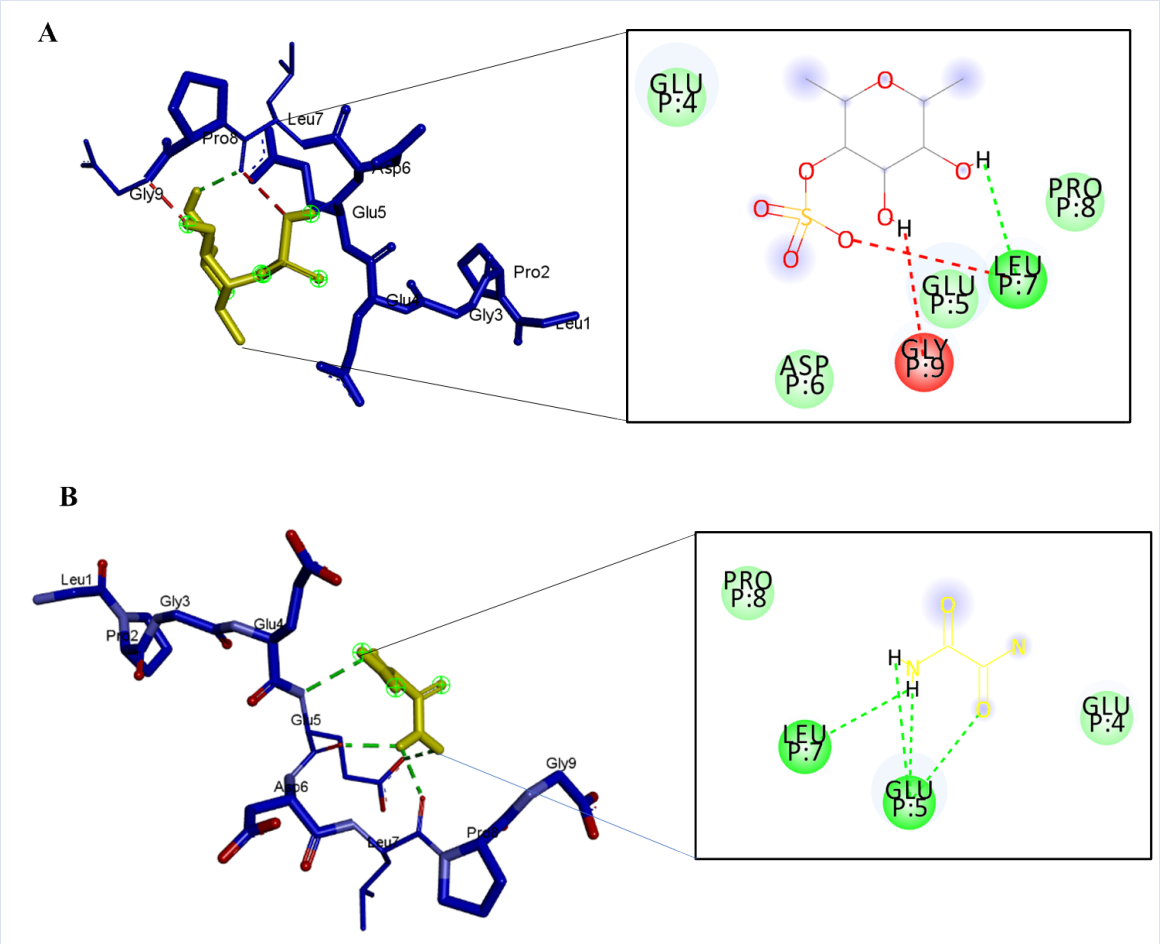

Figure 2: Molecular interaction of CA IX with fucoidan (A) and oxamide (B). CA IX, fucoidan, and/or oxamide are respectively indicated by dark blue and yellow colors.

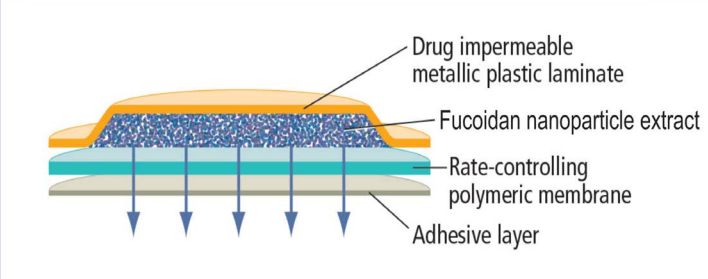

Figure 3: Nano transdermal patch design[35].

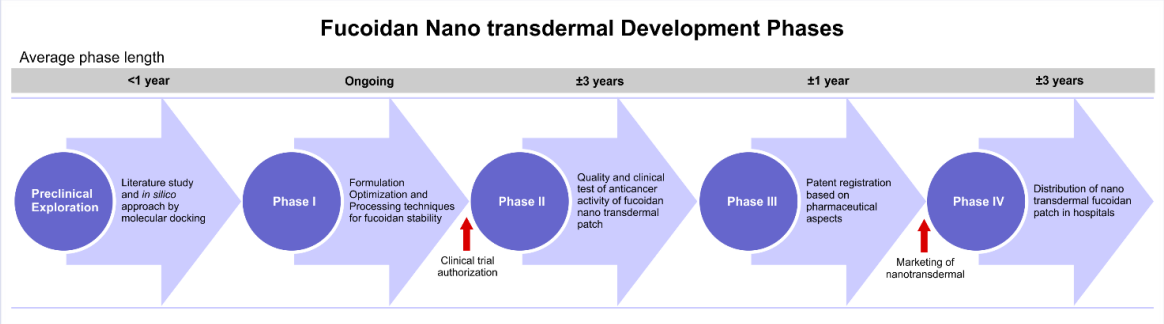

Figure 4: Schematic steps in fucoidan nano transdermal patch development.

The favored type of transdermal patch in this study is minimally invasive patches to support the periodic release of active substances and extend the availability of fucoidan. The route that this preparation must take is to permeate the stratum corneum as a reservoir for the vehicular, which is where several elements in the active substance are still in contact with the skin surface, then bind to the epidermis and dermis to penetrate the hypodermis.[36] Consequently, the active substance will passively diffuse into the blood vessels. Thus, the concentration in the patch preparation is relatively in high doses to directly penetrate the skin. The active substance will diffuse regularly into the blood vessels to maintain the concentration of the active substance in the bloodstream. Hence, the permeability of this nano transdermal patch can penetrate cancer cells lining the ducts (mammary ducts) and lobules (mammary glands).

The stage of dose formulation on the patch surface area is calculated on several factors, which include the calculation flux so that the delivery of the compound can penetrate the transdermal pathway proportional to the permeability coefficient (Log Kp (cm/h)) and the concentration of the compound in the preparation. Then, this flux can be projected for compound release for up to 12 hours with precise dosing on each patch surface area.[37] The transdermal patches were fabricated using the solvent casting method consisting of solvent in the form of distilled water and methanol; permeation enhancer in the form of Tween 80 at 10% of the total weight of the compound and polymer; and plasticizer (PEG at 5% of the total volume of solvent).[38] Evaluation of transdermal patches containing nanoparticles through a series of stages, such as determination of zeta potential, polydispersity index, entrapment efficiency of nanoparticles, particle size distribution, and SEM to characterize the morphology of nanoparticles and patches that have been produced.[37] The next stage is the permeability test of the nanoparticle compound using the artificial transdermal system Franz's diffusion cells.[39]

Nanoparticle-based bioactive molecules are potential candidates in therapeutic compound delivery systems to target cells and tissues because they are permeable to cells and tissues with components that are inert to the organism's cell components. Nanoparticles also have the advantage of accelerated surface area that can increase their bioactivity compared to micro-sized particles.[40] Therefore, a transdermal patch preparation is required to deliver the fucoidan nanoparticle compound at breast cancer sites. Several advantages of transdermal preparations that are more effective than oral or intravenous administration are (1) Practical, simple, and easy to use by patients, thereby increasing patient compliance in therapy;[41] (2) Reducing the frequency of use of preparations because transdermal patches are designed to be used for a relatively long duration even up to several days;[42] and (3) Preventing unfavorable interactions between drugs and the gastrointestinal tract, such as compound degradation or digestive disorders.[43]

The long-term research design of fucoidan nano transdermal patches

Regarding the potential of fucoidan nano transdermal patches as a candidate chemoprevention agent in breast cancer management, research is required at several stages as follows, including formulation optimization, optimum formula assay, patent registration, and distribution of fucoidan nano transdermal patch. The formulation optimization stage is crucial to assess the formulation process with processing methods and techniques, the composition of appropriate additives, and maintaining the stability of active and inert compounds. Consecutively, the formula then will be assessed for quality, therapeutic effect, and clinical trial of anticancer activity in breast cancer through the procedure of identifying the mechanism of action and evaluating the synergistic effect of fucoidan as a chemoprevention agent. The establishment of fucoidan nano transdermal patch will be legalized by registering patents based on its pharmacokinetic, pharmacodynamic, and pharmacotherapeutic aspects. Thus, it will be ready for distribution in every healthcare institution as a curative measure in the management of breast cancer treatment (Figure 4).

CONCLUSION

It was concluded that the fucoidan extracted from *Sargassum* sp. works likely as an anticancer agent by inducing multitargeted apoptosis of breast cancer cells in various pathways without cytotoxic effects on normal cells. In addition, it is expected to be able to interact with enzymes related to the process of metastatic breast cancer cells. Therefore, nano transdermal preparation is the reasonable route to minimize side effects caused by chemotherapeutic agents due to the periodic release of fucoidan. Future research must concern to develop the formulation optimization of fucoidan nano transdermal and conduct clinical trials to optimize the management of breast cancer treatment.

ABBREVIATIONS

ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity; Asp: aspartic acid; CA IX: carbonic anhydrase IX; FTIR: Fourier-transform infrared spectroscopy; GLOBOCAN: Global Cancer Observatory; Glu: glutamic acid; GSH: glutathione; IFN-γ: interferon-gamma; IL-1: interleukin-1; IL-12: interleukin-12; Leu: leucine; NaTPP: sodium tripolyphosphate; NK: natural killer cell; PDB: Protein Data Bank; PEG: polyethylene glycol; Pro: proline; PSA: particle size analyzer; ROS: reactive oxygen species; SEM: scanning electron microscope; THP-1: Nuclear mRNA export protein THP1; TNF-α: tumor necrosis factor-alpha.

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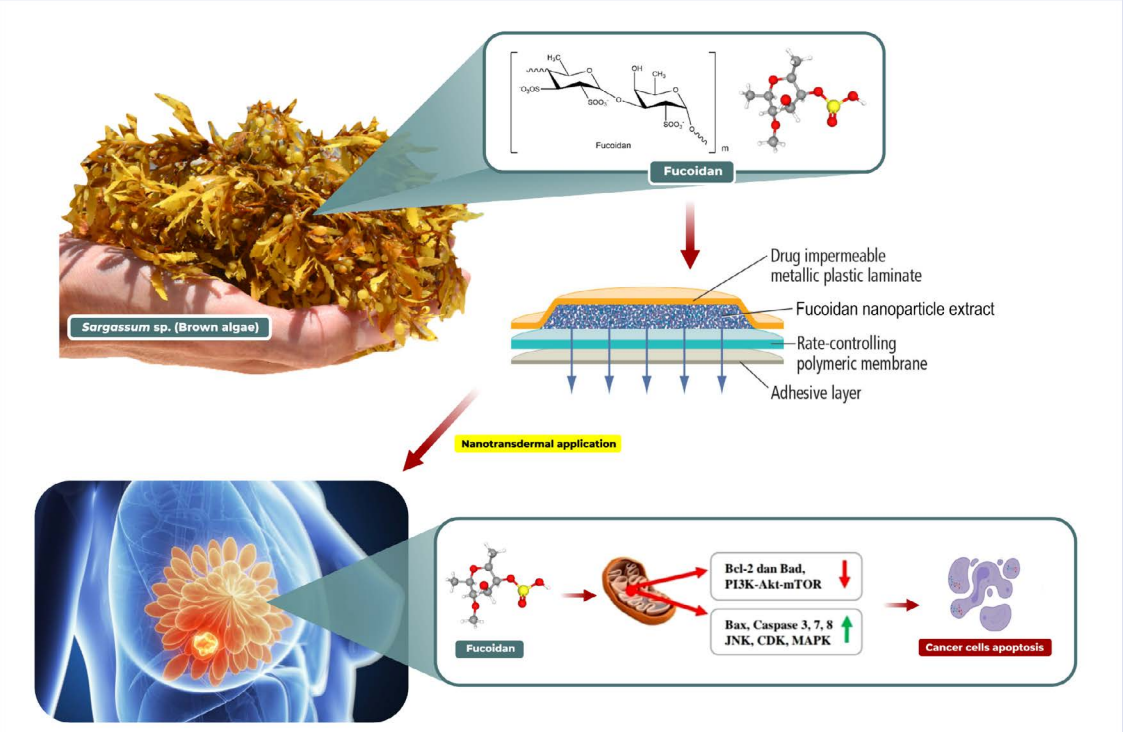
GRAPHICAL ABSTRACT



ABOUT AUTHORS

Rahadian Zainul has completed a Bachelor of Educational Chemistry in IKIP Padang, then continued his studies and obtained a Master of Chemistry at Universitas Andalas, and earned a Doctoral Chemistry degree at Universitas Andalas. He is a researcher on the design and modification of copper oxide for inactivation SARS-CoV-2 by stimulated indoor lights and a researcher on the design and modification of copper oxide by computation approach with DFTB+. He is also the Head of Cambiotics Research Center, Universitas Negeri Padang. The author has published 41 manuscripts in Scopus-indexed journals and also 8 h-index.

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